Treatment: NTT/NTT

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	肝胆道系障害／ 薬物性肝障害／ DRUG INDUCED LIVER INJURY	2017-04-26(195) /2017-04-29(198)	CONT/ MO/ R/R	No	NR	NA/ N	No	N	Y
		眼障害／ 眼乾燥／ DRY EYE	2017-04-28(197) /2017-05-12(211)	CONT/ MI/ R/R	No		NA/ DT	No	N	Y
		臨床検査／ 血中クレアチニン増加／ ELEVATED CREATININE	2017-05-01(200) /2017-05-02(201)	CONT/ MI/ R/R	No		NA/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: NTT/NTT

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	製品の問題／ 医療機器機能不良／ MALFUNCTIONING PICC LINE	2017-05-01(200) /2017-05-02(201)	CONT/ MI/ R/R	No	NR	NA/ DT	No	Y	Y
		製品の問題／ 医療機器機能不良／ PICC LINE MALFUNCTION	2017-08-16(307) /2017-08-18(309)	CONT/ MI/ R/R	No		NA/ NT	No	Y	Y
		一般・全身障害および投与部位の状態／ カテーテル留置部位分泌物／ CVC SITE DISCHARGE	2017-08-21(312) /2017-08-23(314)	CONT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: NTT/NTT

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	一般・全身障害および投与部位の状態／カテーテル留置部位出血／CVC SITE BLEEDING	2017-08-23(314) /2017-08-23(314)	CONT/ MI/ R/R	No	NR	NA/ NT	No	N	Y
		呼吸器、胸郭および縦隔障害／鼻出血／NOSE BLEED	2017-09-03(325) /2017-09-03(325)	CONT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: NTT/NTT

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	感染症および寄生虫症／上気道感染／UPPER RESPIRATORY TRACT INFECTION	2017-11-03(386) /2017-11-08(391)	CONT/ MI/ R/R	No	NR	NA/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/NTT

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	代謝および栄養障害／ 代謝性アシドーシス／ METABOLIC ACIDOSIS	2018-01-12(369) /2018-01-15(372)	CONT/ MO/ R/R	No	NR	NA/ DT	No	Y	Y
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／ 医療機器関連感染／ CENTRAL VENOUS LINE INFECTION WITH GRAM POSITIVE COAG NEG STAPH	2017-08-02(196) /2017-08-19(213)	CONT/ MO/ R/R	No	NR	NA/ DT	No	Y	Y
		感染症および寄生虫症／ 鼻咽頭炎／ COLD SYMPTOMS	2017-09-20(245) /2017-09-25(250)	CONT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／ 医療機器関連感染／ CENTRAL LINE INFECTION	2017-04-02(242) /2017-04-16(256)	CONT/ SV/ R/R	GRADE 3	NR	NC/ DT	No	Y	Y
		肝胆道系障害／ 胆石症／ GALLBLADDER SLUDGE	2017-04-06(246) /ONGOING	CONT/ MO/ NRD	No		NC/ N	No	N	Y
		感染症および寄生虫症／ 眼感染／ EYE INFECTION	2017-04-27(267) /2017-08-01(363)	CONT/ MO/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／消化管内細菌過剰増殖／SMALL BOWEL BACTERIAL OVERGROWTH INFECTION	2017-04-27(267) /2017-08-01(363)	CONT/ MO/ R/R	No	NR	NC/ DT	No	N	Y
		胃腸障害／短腸症候群／WORSENING OF SHORT BOWEL SYNDROME	2017-08-04(366) /2017-08-15(377)	CONT/ SV/ D	GRADE 4		NA/ N	Yes	Y	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-07-15(222) /2017-07-26(233)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMITING	2017-07-15(222) /2017-07-26(233)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		製品の問題／ 医療機器機能不良／ CENTRAL LINE DYSFUNCTION	2017-09-07(276) /2017-09-08(277)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	製品の問題／医療機器機能不良／MALFUNCTION OF CENTRAL LINE	2017-10-24(323) /2017-10-24(323)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		血液およびリンパ系障害／／凝血異常／COAGULAPATHY	2018-01-19(410) /2018-01-31(422)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		臨床検査／C-反応性蛋白増加／ELEVATED C REACTIVE PROTEIN	2018-01-19(410) /2018-02-02(424)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ リンパ球数増加／ ELEVATED LYMPHOCYTE COUNT	2018-01-19(410) /2018-01-25(416)	CONT/ MO/ R/R	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／ インフルエンザ／ INFLUENZA A	2018-01-23(414) /2018-02-06(428)	CONT/ MO/ R/R	No		NC/ DT	No	Y	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2018-01-23(414) /2018-02-06(428)	CONT/ MO/ R/R	No		NC/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ 血中アルブミン減少／ LOW ALBUMIN	2018-02-02(424) /2018-02-15(437)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／ 尿路感染／ URINARY TRACT INFECTION	2017-08-09(238) /2017-08-19(248)	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-10-15(305) /2017-10-19(309)	CONT/ MO/ R/R	No		NC/ N	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／ 医療機器関連感染／ LINE INFECTION	2017-10-15(305) /2017-10-19(309)	INT/ MO/ R/R	No	NR	NA/ DT	No	Y	Y
		感染症および寄生虫症／ 敗血症／ SEPSIS	2017-10-15(305) /2017-10-19(309)	INT/ MO/ R/R	No		NA/ DT	No	Y	Y
[redacted]	M/1[redacted]/WHITE	胃腸障害／ 嘔吐／ EMESIS	2017-01-15(207) /2017-01-15(207)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-02-21(244) /2017-02-23(246)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-02-21(244) /2017-02-23(246)	INT/ MO/ R/R	No		NA/ N	No	Y	Y
		神経系障害／ 頭痛／ HEADACHE	2017-02-21(244) /2017-02-22(245)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-03-02(253) /2017-03-23(274)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-03-26(277) /2017-03-30(281)	INT/ MI/ R/R	No		NC/ DT	No	N	Y
		筋骨格系および結合組織障害／ 背部痛／ BACK PAIN	2017-03-29(280) /2017-03-29(280)	INT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／クロストリジウム菌性胃腸炎／C-DIFFICILE ENTERITIS	2017-03-30(281) /2017-04-19(301)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		代謝および栄養障害／アシドーシス／ACIDOSIS	2017-04-06(288) /ONGOING	INT/ MI/ NRD	No		NC/ N	No	N	Y
		臨床検査／好中球数増加／ICREASED NEUTROPHIL COUNT	2017-04-06(288) /2017-05-01(313)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	臨床検査／ 白血球数増加／ INCREASED WHITE BLOOD CELL COUNT	2017-04-06(288) /2017-05-01(313)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMITING	2017-04-11(293) /2017-04-12(294)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 疼痛／ BODY ACHE	2017-04-12(294) /2017-04-13(295)	INT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	神経系障害／ 頭痛／ HEADACHE	2017-04-12(294) /2017-04-14(296)	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		感染症および寄生虫症／ クロストリジウム菌性胃腸炎／ C-DIFFICILE ENTERITIS	2017-04-20(302) /2017-04-22(304)	CONT/ MO/ R/R	No		NC/ DT	No	Y	Y
		感染症および寄生虫症／ クロストリジウム菌性胃腸炎／ C-DIFFICILE ENTERITIS	2017-04-23(305) /2017-06-15(358)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	神経系障害／ 浮動性めまい／ DIZZINESS	2017-06-05(348) /2017-06-08(351)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ 便潜血陽性／ POSITIVE STOOL GUDIAC	2017-06-15(358) /2017-09-07(442)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		製品の問題／ 医療機器閉塞／ CENTRAL LINE OCCLUSION	2017-06-20(363) /2017-06-21(364)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	製品の問題／ 医療機器閉塞／ CENTRAL LINE OCCLUSION	2017-07-11(384) /2017-07-11(384)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		臨床検査／ アミラーゼ増加／ ELEVATED AMYLASE	2017-07-11(384) /2017-08-11(415)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		臨床検査／ 国際標準比増加／ ELEVATED INTERNATIONAL NORMALIZED RATIO	2017-07-11(384) /2017-08-11(415)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	臨床検査／ リパーゼ増加／ ELEVATED LIPASE	2017-07-11(384) /2017-08-11(415)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ プロトロンビン時間延長 ／ ELEVATED PROTHROMBIN TIME	2017-07-11(384) /2017-08-11(415)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		神経系障害／ 頭痛／ HEADACHE	2017-07-17(390) /ONGOING	CONT/ MI/ NRD	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	臨床検査／ γ-グルタミルトランスフェラーゼ増加／ ELEVATED GGT	2017-08-11(415) /2017-09-07(442)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		傷害、中毒および処置合併症／ 皮膚擦過傷／ ROAD RASH PAIN	2017-08-15(419) /2017-08-15(419)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y
		筋骨格系および結合組織障害／ 筋痙縮／ LEG CRAMPS	2017-08-29(433) /2017-08-29(433)	INT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	代謝および栄養障害／低カリウム血症／HYPOKALEMIA	2017-09-09(444) /2017-09-13(448)	CONT/ MO/ R/R	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／クロストリジウム菌性胃腸炎／C-DIFFICILE ENTERITIS	2017-09-18(453) /2017-10-19(484)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y
		筋骨格系および結合組織障害／筋痙縮／LEG CRAMPS	2017-09-18(453) /ONGOING	INT/ MI/ NRD	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	代謝および栄養障害／ 高クロール血症／ HYPERCHLORIDEMIA	2017-10-16(481) /2017-10-24(489)	INT/ MO/ R/R	No	NR	NC/ N	No	N	Y
		代謝および栄養障害／ 低カリウム血症／ HYPOKALEMIA	2017-10-16(481) /2017-10-24(489)	CONT/ MO/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 悪心／ NAUSEA	2017-10-21(486) /2017-11	INT/ MI/ R/R	No	R	NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	血液およびリンパ系障害／貧血／SYMPTOMATIC ANEMIA	2017-11-21(517) /2017-11-30(526)	CONT/ MO/ NRD	No	NR	NC/ NT	No	N	Y
		製品の問題／医療機器閉塞／CENTRAL LINE OCCLUSION	2017-12-01(527) /2018-01-05(562)	INT/ MO/ R/R	No		NC/ NT	No	N	Y
		胃腸障害／嘔吐／VOMITING	2017-10-30(495) /2017-11	INT/ MI/ R/R	No	R	NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/WHITE	感染症および寄生虫症／ 蜂巣炎／ CELLULITIS	2018-01-20(577) /2018-01-22(579)	CONT/ MO/ R/R	No	NR	NC/ DT	No	Y	Y
[redacted]	M/[redacted]/WHITE	神経系障害／ 頭痛／ HEADACHES	2017-01-19(197) /ONGOING	INT/ MI/ NRD	No	NR	NC/ N	No	N	Y
		傷害、中毒および処置合併症／ 胃瘻管部合併症／ G-TUBE LEAKAGE	2017-02-03(212) /2017-02-16(225)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／上気道感染／UPPER RESPIRATORY INFECTION	2017-03-01(238) /2017-03-12(249)	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		代謝および栄養障害／高クロール血症／HYPERCHLOREMIA	2017-03-07(244) /2017-03-13(250)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	皮膚および皮下組織障害／ 発疹／ RASH	2017-03-21(258) /2017-03-23(260)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		傷害、中毒および処置合併症／ 胃瘻管部合併症／ G-TUBE LEAKAGE	2017-04-09(277) /2017-09-12(433)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		臨床検査／ 尿中白血球陽性／ INCREASED LEUKOCYTES IN URINE	2017-04-11(279) /2017-04-18(286)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-04-13(281) /2017-04-16(284)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ アラニンアミノトランスフェラーゼ増加／ ALT INCREASED	2017-04-18(286) /2017-05-23(321)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		感染症および寄生虫症／ 上気道感染／ UPPER RESPIRATORY INFECTION	2017-04-27(295) /2017-05-01(299)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-05-27(325) /2017-05	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-06 /2017-06-29(358)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-06-06(335) /2017-06-06(335)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	胃腸障害／ 排便回数増加／ INCREASED STOOLS FREQUENCY	2017-06-27(356) /2017-06-27(356)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻閉／ NASAL CONGESTION	2017-09-04(425) /2017-09-05(426)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	呼吸器、胸郭および縦隔障害／咳嗽／COUGH	2017-09-24(445) /2017-09	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／咳嗽／COUGH	2017-10-03(454) /2017-10-07(458)	INT/ MO/ R/R	No		NC/ DT	No	Y	Y
		一般・全身障害および投与部位の状態／発熱／FEVER	2017-10-04(455) /2017-10-07(458)	INT/ MO/ R/R	No		NC/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-10-08(459) /2017-10-15(466)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		代謝および栄養障害／ 低ナトリウム血症／ HYPONATREMIA	2017-10-17(468) /2017-11-07(489)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-10-28(479) /2017-10-31(482)	INT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	製品の問題／ 医療機器閉塞／ CENTRAL LINE OCCLUSION	2017-11-13(495) /2017-11-19(501)	INT/ MO/ R/R	No	NR	NC/ DT	No	N	Y
		感染症および寄生虫症／ 鼻咽頭炎／ COLD	2018-01-23(566) /2018-01-28(571)	INT/ MI/ R/R	No		NC/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2018-01-23(566) /2018-01-28(571)	INT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	臨床検査／ アラニンアミノトランスフェラーゼ増加／ ALT INCREASED	2017-05-18(197) /2017-05-31(210)	CONT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		胃腸障害／ 下痢／ DIAHRRHEA	2017-05-25(204) /2017-05-28(207)	INT/ MO/ R/R	No		NC/ N	No	Y	Y
		代謝および栄養障害／ 栄養補給不耐性／ INTOLERANCE OF FEEDS	2017-05-25(204) /2017-05-28(207)	CONT/ MO/ R/R	No		NC/ N	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	血管障害／ 上大静脈閉塞／ SUPERIOR VENA CAVAL OCCLUSION	2017-08 /2017-11-15(378)	INT/ MO/ R/R	No	NR	NC/ NT	No	Y	Y
		胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-09-19(321) /2017-09-20(322)	INT/ MO/ R/R	No		NC/ DT	No	N	Y
		胃腸障害／ 嘔吐／ EMESIS VOMITING	2017-09-19(321) /2017-09-20(322)	INT/ MO/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／悪心／NAUSEA	2017-09-19(321) /2017-09-20(322)	INT/ MO/ R/R	No	NR	NC/ DT	No	N	Y
		胃腸障害／鼓腸／GASSINESS	2017-12 /ONGOING	INT/ MI/ NRD	No		NC/ DT	No	N	Y
		感染症および寄生虫症／上気道感染／UPPER RESPIRATORY INFECTION	2017-12 /2018-01	CONT/ MI/ R/R	No		NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／ 腹痛／ INCREASED ABDOMINAL PAIN	2017-12-18(411) /2018-01-26(450)	INT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		臨床検査／ 体重減少／ WEIGHT LOSS	2017-12-29(422) /2018-02-13(468)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		感染症および寄生虫症／ アストルウイルス性胃腸炎／ ASTROVIRUS GASTROENTERITIS	2018-01-14(438) /2018-01-17(441)	CONT/ MO/ R/R	No		NA/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	精神障害／ 異常行動／ BEHAVIORAL PROBLEMS	2017-08 /ONGOING	INT/ MI/ NRD	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／ 尿路感染／ URINARY TRACT INFECTION WITH FEVER	2017-10-25(303) /2017-11-08(317)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	腎および尿路障害／ 腎結石症／ CALCULI WITHIN THE LEFT PELVIC KIDNEY WITH CULTURES POSITIVE FOR PROVIDENCIA, MORGANELLA, KLEBSIELLA AND STAPHYLOCOCCUS.	2017-12-05(344) /2017-12-21(360)	CONT/ MI/ R/R	No	NR	NC/ MULTIPLE	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	筋骨格系および結合組織障害／四肢痛／LOWER EXTREMITY PAIN, LEFT	2017-12-29(368) /2018-01-01(371)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／ウイルス性胃腸炎／VIRAL GASTROENTERITIS	2018-01-23(393) /2018-01-29(399)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	感染症および寄生虫症／ 上気道感染／ UPPER RESPIRATORY INFECTION	2017-09-25(251) /2017-10-04(260)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		傷害、中毒および処置合併症／ 術後イレウス／ POST ANESTHESIA ILEUS	2017-11-10(297) /2017-11-14(301)	CONT/ MI/ R/R	No		DI/ MULTIPLE	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	感染症および寄生虫症／上気道感染／UPPER RESPIRATORY INFECTION	2017-12-09(326) /2018-01	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
[redacted]	F/[redacted]/WHITE	一般・全身障害および投与部位の状態／医療機器関連合併症／CVC COMPLICATION	2017-09-16(264) /2017-09-17(265)	CONT/ MI/ R/R	No	NR	NC/ NT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	一般・全身障害および投与部位の状態／発熱／FEVER WITH CENTRAL LINE	2017-11-12(321) /2017-11-16(325)	CONT/ MI/ R/R	No	NR	NC/ DT	No	Y	Y
		皮膚および皮下組織障害／／発疹／BILATERAL WRIST RASH	2018-01-01(371) /2018-01-17(387)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	腎および尿路障害／ 腎結石症／ KIDNEY STONES	2017-07-17(243) /ONGOING	INT/ MI/ NRD	No	NR	NC/ N	No	N	Y
		代謝および栄養障害／ 代謝性アシドーシス／ D-LACTIC ACIDOSIS	2017-07-27(253) /2017-07-29(255)	CONT/ SV/ R/R	GRADE 3		DI/ DT	No	Y	Y
		代謝および栄養障害／ 代謝性アシドーシス／ D-LACTIC ACIDOSIS	2018-02-01(442) /2018-02-04(445)	CONT/ SV/ R/R	GRADE 3	R	DI/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	呼吸器、胸郭および縦隔障害／ 鼻出血／ BLOODY NOSE	2017-08-15(216) /2017-08-15(216)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-08-15(216) /2017-08-30(231)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻漏／ RUNNY NOSE	2017-08-15(216) /2017-08-30(231)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	傷害、中毒および処置合併症／ 裂傷／ LACERATION RIGHT SIDE FOREHEAD	2017-08-26(227) /2017-08-26(227)	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		胃腸障害／ 嘔吐／ EMESIS	2017-10-06(268) /2017-10-07(269)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻出血／ BLOODY NOSE	2017-10-10(272) /2017-10-12(274)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	呼吸器、胸郭および縦隔障害／鼻漏／RUNNY NOSE	2017-10-10(272) /2017-10	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／咳嗽／COUGH	2017-10-11(273) /2017-10	INT/ MI/ R/R	No		NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／咳嗽／COUGH	2017-10-31(293) /ONGOING	INT/ MI/ RCG	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	呼吸器、胸郭および縦隔障害／ 鼻漏／ RUNNY NOSE	2017-11-01(294) /ONGOING	INT/ MI/ RCG	No	NR	NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-12-11(334) /ONGOING	INT/ MI/ RCG	No		NC/ DT	No	Y	Y
[redacted]	M/[redacted]/BLACK	胃腸障害／ 裂肛／ ANAL FISSURE	2017-02 /2017-03	CONT/ MI/ R/S	No	NR	NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	感染症および寄生虫症／気道感染／MILD RESPIRATORY INFECTION	2017-03 /2017-03	CONT/ MI/ R/R	No	NR	NC/ UK	No	N	Y
		血液およびリンパ系障害／／リンパ節症／RIGHT-SIDED INGUINAL LYMPHADENOPATHY	2017-04 /2017-06-02(309)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	胃腸障害／ 胃食道逆流性疾患／ REFLUX WITH BOLUS FEEDS	2017-04-16(262) /2017-04-18(264)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／ 鼻咽頭炎／ COMMON COLD	2017-11-07(467) /ONGOING	CONT/ MI/ NRD	No		NC/ DT	No	N	Y
		製品の問題／ 医療機器破損／ HICKMAN CATHETER REPAIR	2017-11-28(488) /2017-11-29(489)	CONT/ MI/ R/R	No		NA/ N	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION	2017-12-03(493) /ONGOING	INT/ MI/ NRD	No	NR	NA/ N	No	N	Y
		胃腸障害／ 上腹部痛／ STOMACH ACHE	2017-12-18(508) /2017-12-19(509)	CONT/ MI/ R/R	No		NA/ N	No	N	Y
		臨床検査／ 尿中白血球陽性／ LEUKOCYTES PRESENT IN URINE	2017-12-20(510) /2018-02-16(568)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	臨床検査／好酸球数増加／ELEVATED ABSOLUTE EOSINOPHILS	2017-12-20(510) /2018-01-23(544)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／血中尿素増加／ELEVATED BUN	2017-12-20(510) /ONGOING	CONT/ MO/ NRD	No		NC/ N	No	N	Y
		臨床検査／好酸球数増加／ELEVATED EOSINOPHILS	2017-12-20(510) /2018-01-23(544)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	臨床検査／ 細菌検査陽性／ ELEVATED URINE BACTERIA	2017-12-20(510) /2018-01-10(531)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ 尿 pH 上昇／ ELEVATED URINE PH	2017-12-20(510) /2018-02-27(579)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		臨床検査／ ヘモグロビン減少／ LOW HEMOGLOBIN	2017-12-20(510) /ONGOING	CONT/ MI/ NRD	No		NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	臨床検査／ 赤血球数減少／ LOW RED BLOOD CELLS	2017-12-20(510) /2018-01-23(544)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		代謝および栄養障害／ 高カルシウム血症／ HYPERCALCEMIA	2018-01-03(524) /2018-02-27(579)	CONT/ MO/ R/R	No		NA/ NT	No	N	Y
		感染症および寄生虫症／ ウイルス感染／ VIRAL INFECTION	2018-01-13(534) /ONGOING	CONT/ MO/ NRD	No		NA/ DT	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/BLACK	臨床検査／ 血中クレアチニン増加／ ELEVATED CREATININE	2018-01-23(544) /2018-02-27(579)	CONT/ MO/ R/R	No	NR	NC/ NT	No	N	Y
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／ 蜂巣炎／ CELLULITIS, HOSPITALIZATION	2017-08-25(206) /2017-09-05(217)	INT/ SV/ R/R	No	NR	NA/ DT	No	Y	Y
		傷害、中毒および処置合併症／ 投薬過誤／ MEDICATION ERROR	2017-08-29(210) /2017-08-29(210)	INT/ MI/ R/R	No	R	NA/ N	No	Y	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／肺炎／PNEUMONIA	2017-09-20(232) /2017-10-09(251)	INT/ MO/ R/R	No	NR	NC/ DT	No	Y	Y
		感染症および寄生虫症／消化管内細菌過剰増殖／SMALL INTESTINAL BACTERIAL OVERGROWTH	2017-11-14(287) /2017-11-24(297)	INT/ MO/ R/R	No		NC/ DT	No	N	Y

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／消化管内細菌過剰増殖／SMALL INTESTINAL BACTERIAL OVERGROWTH	2017-12-11(314) /2017-12-15(318)	INT/ MO/ R/R	No	NR	NC/ DT	No	N	Y
[redacted]	F/[redacted]/BLACK	傷害、中毒および処置合併症／裂傷／LACERATION TO BACK OF HEAD	2017-10-21(338) /2017-10-21(338)	INT/ MI/ R/R	No	NR	NC/ MULTIPLE	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	感染症および寄生虫症／蟯虫症／PINWORMS	2017-10-28(345) /ONGOING	INT/ MI/ RCG	No	NR	NC/ DT	No	N	Y
		胃腸障害／好酸球性食道炎／EOSINOPHILIC ESOPHAGITIS	2017-11-16(364) /ONGOING	CONT/ MI/ NRD	No		NC/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／口腔咽頭痛／SORE THROAT	2017-12-04(382) /2017-12-05(383)	INT/ MI/ R/R	No		NA/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas Output: l-sae.rtf 30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	代謝および栄養障害／ 成長障害／ FAILURE TO THRIVE	2017-12-08(386) /2017-12-22(400)	INT/ SV/ R/R	GRADE 3	NR	NA/ NT	No	Y	Y
		臨床検査／ サポウイルス検査陽性／ SAPOVIRUS TEST POSITIVE	2017-12-11(389) /2017-12-22(400)	INT/ MO/ R/R	No		NA/ DT	No	N	Y
		耳および迷路障害／ 耳痛／ RIGHT EAR PAIN	2017-12-13(391) /2017-12-14(392)	INT/ MI/ R/R	No		NA/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	感染症および寄生虫症／ 急性中耳炎／ RIGHT ACUTE SEROUS OTITIS MEDIA	2018-01-19(428) /2018-01-29(438)	INT/ MI/ R/R	No	NR	NA/ DT	No	N	Y
		胃腸障害／ 嘔吐／ VOMITING	2018-01-31(440) /2018-01-31(440)	INT/ MI/ R/R	No		NA/ N	No	N	Y
[redacted]	M/[redacted]/ASIAN	臨床検査／ ヘモグロビン減少／ LOW HAEMOGLOBIN	2017-08-25(263) /2017-09-29(298)	CONT/ MO/ R/R	No	NR	NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/ASIAN	胃腸障害／ 嘔吐／ VOMIT	2017-08-25(263) /2017-10-11(310)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		傷害、中毒および処置合併症／ ストーマ部過剰肉芽／ GRANULOMA AT GASTROSTOMY SITE	2017-08-25(263) /ONGOING	CONT/ MI	No		NA/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/ASIAN	呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-10-09(308) /2018-02-14(436)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻漏／ RUNNY NOSE	2017-10-09(308) /2018-02-14(436)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMITING	2017-10-24(323) /2017-10-25(324)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/ASIAN	胃腸障害／ 嘔吐／ VOMITING	2017-11-09(339) /ONGOING	INT/ MI/ NRD	No	NR	NC/ N	No	N	Y
		胃腸障害／ 腹痛／ ABDO PAIN	2017-12-21(381) /2017-12-24(384)	CONT/ MI/ R/R	No		DI/ DT	No	N	Y
		代謝および栄養障害／ 脱水／ DEHYDRATION	2017-12-21(381) /2017-12-24(384)	CONT/ SV/ R/R	No		DI/ N	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/ASIAN	心臓障害／ 頻脈／ TACHYCARDIC	2017-12-21(381) /2017-12-23(383)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
[redacted]	M/[redacted]/NALLW	筋骨格系および結合組織障害／ 筋力低下／ LEFT LEG WEAKNESS	2017-09-07(262) /ONGOING	CONT/ MI/ NRD	No	NR	NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEBRILE, INPATIENT HOSPITALISATION	2017-09-18(273) /2017-09-27(282)	CONT/ SV/ R/R	No		NA/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/NALLW	感染症および寄生虫症／ウイルス感染／VIRAL ILLNESS	2017-11-10(326) /2017-11-21(337)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		胃腸障害／嘔吐／VOMITING	2017-11-19(335) /2017-11-20(336)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		感染症および寄生虫症／ウイルス感染／VIRAL ILLNESS	2017-11-22(338) /2017-11-27(343)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/NALLW	一般・全身障害および投与部位の状態／ 発熱／ PYREXIA	2018-01-23(400) /2018-01-26(403)	CONT/ SV/ R/R	No	NR	NA/ DT	No	Y	Y
[redacted]	F/[redacted]/WHITE	皮膚および皮下組織障害／ 発疹／ RASH (LEFT ARM)	2017-09-19(282) /2017-09-21(284)	CONT/ MI/ R/R	No	R	NC/ N	No	N	Y
		傷害、中毒および処置合併症／ ストーマ合併症／ ENLARGED STOMA	2017-09-23(286) /ONGOING	CONT/ MI/ NRD	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／ 上腹部痛／ STOMACH PAIN	2017-09-24(287) /2017-09-24(287)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ 血小板数減少／ LOW PLATELETS	2017-09-25(288) /2017-10-02(295)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMIT	2017-12-20(374) /2018-01-03(388)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	臨床検査／ 体温上昇／ INCREASED TEMPERATURE	2017-12-30(384) /2017-12-30(384)	INT/ MI/ R/R	No	NR	NC/ DT	No	N	Y
		眼障害／ 眼部腫脹／ PUFFY EYES	2017-12-30(384) /2017-12-30(384)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻漏／ RUNNY NOSE	2017-12-30(384) /2017-12-30(384)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	感染症および寄生虫症／ 医療機器関連感染／ CENTRAL VENOUS LINE INFECTION	2018-01-19(404) /2018-02-02(418)	INT/ MO/ R/R	No	NR	NC/ DT	No	Y	Y
[redacted]	M/[redacted]/WHITE	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION	2017-09-04(264) /ONGOING	CONT/ MI/ NRD	No	NR	NA/ NT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	呼吸器、胸郭および縦隔障害／ 口腔咽頭痛／ SORE THROAT	2017-09-21(281) /2017-09-23(283)	INT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		代謝および栄養障害／ 低ナトリウム血症／ HYPONATRIEMA	2017-09-23(283) /2017-09-24(284)	CONT/ SV/ R/R	No		NA/ NT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	神経系障害／ 痙攣発作／ SEIZURE	2017-09-23(283) /2017-09-23(283)	INT/ SV/ R/R	No	NR	NA/ NT	No	Y	Y
		呼吸器、胸郭および縦隔障害／ 咳嗽／ COUGH	2017-09-24(284) /2017-12	INT/ MI/ R/R	No		NA/ DT	No	N	Y
		感染症および寄生虫症／ 鼻炎／ CORYZAL SYMPTOMS	2017-11-24(345) /2017-12	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ 好中球数減少／ LOW NEUTROPHILS	2018-01-15(397) /ONGOING	INT/ MI/ NRD	No	NR	NC/ N	No	N	Y
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中マグネシウム増加／ CLINICALLY SIGNIFICANT HIGH MAGNESIUM - ELECTROLYTE IMBALANCE	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中アルブミン減少／ CLINICALLY SIGNIFICANT LOW ALBUMIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中尿酸減少／ CLINICALLY SIGNIFICANT LOW URIC ACID - UNKNOWN DIAGNOSIS	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中リン減少／ CLINICICALLY SIGNIFICANT LOW PHOSPHORUS - UNKOWN DIAGNOSIS	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ アラニンアミノトランスフェラーゼ増加／ HIGH ALT	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

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Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／アスパラギン酸アミノトランスフェラーゼ増加／HIGH AST	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／C-反応性蛋白増加／HIGH CRP	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y
		臨床検査／抱合ビリルビン増加／HIGH DIRECT BILIRUBIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中ビリルビン増加／ HIGH TOTAL BILIRUBIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中カルシウム減少／ LOW CALCIUM	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y
		肝胆道系障害／ 胆汁うっ滞／ WORSENING CHOLESTASIS	2017-05-12(106) /ONGOING	CONT/ MO/ UNK	No		NC/ N	Yes	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中ビリルビン増加／ ELEVATED BILIRUBIN	2017-09-01(218) /ONGOING	CONT/ MO/ RCG	No	NR	DW/ UK	No	Y	Y
[redacted]	M/[redacted]/WHITE	胃腸障害／ 嘔吐／ VOMIT	2017-08-19(200) /2017-08-19(200)	INT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMIT	2017-08-24(205) /2017-08-24(205)	INT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	胃腸障害／ 嘔吐／ VOMIT	2017-08-25(206) /2017-08-25(206)	INT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		臨床検査／ アラニンアミノトランスフェラーゼ増加／ ELEVATED ALT	2017-08-28(209) /2017-09-25(237)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		臨床検査／ 血中クロール増加／ ELEVATED CHLORIDE	2017-08-28(209) /2017-09-06(218)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ γ-グルタミルトランスフェラーゼ増加／ ELEVATED GGT	2017-08-28(209) /ONGOING	CONT/ MI/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中重炭酸塩減少／ LOW BICARBONATE	2017-08-28(209) /ONGOING	INT/ MI/ UNK	No		NC/ N	No	N	Y
		臨床検査／ 血小板数減少／ LOW PLATELETS	2017-08-28(209) /2018-01-08(342)	CONT/ MI/ R/R	No		NC/ UK	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ ヘマトクリット増加／ HIGH HEMATOCRIT	2017-09-06(218) /2017-09-11(223)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中クレアチニン減少／ LOW CREATININE	2017-09-06(218) /2017-09-11(223)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 嘔吐／ VOMIT	2017-09-10(222) /2017-09-10(222)	INT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／アスパラギン酸アミノトランスフェラーゼ増加／ELEVATED AST	2017-09-11(223) /2017-09-25(237)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ヘマトクリット増加／HIGH HEMATOCRIT	2017-09-25(237) /ONGOING	CONT/ MI/ UNK	No		NC/ N	No	N	Y
		臨床検査／好中球数減少／LOW ABSOLUTE NEUTROPHILS	2017-09-25(237) /ONGOING	CONT/ MI/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	臨床検査／ 赤血球数減少／ LOW RED BLOOD CELLS	2017-09-25(237) /ONGOING	CONT/ MI/ UNK	No	NR	NC/ N	No	N	Y
		感染症および寄生虫症／ 医療機器関連感染／ CENTRAL LINE INFECTION	2017-10-09(251) /2017-10-12(254)	INT/ MO/ R/R	No		NC/ UK	No	Y	Y
		感染症および寄生虫症／ 医療機器関連感染／ CENTRAL LINE INFECTION	2017-11-16(289) /2017-11-22(295)	INT/ MO/ R/R	No		NC/ UK	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／医療機器関連感染／CENTRAL LINE INFECTION	2017-11-27(300) /2017-12-17(320)	INT/ MO/ R/R	No	NR	NC/ UK	No	Y	Y
		一般・全身障害および投与部位の状態／発熱／FEVER	2018-01-26(360) /2018-01-26(360)	INT/ MI/ R/R	No		NC/ UK	No	N	Y
		胃腸障害／嘔吐／VOMIT	2018-01-26(360) /2018-01-26(360)	INT/ MI/ R/R	No		NC/ UK	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/[redacted]/WHITE	感染症および寄生虫症／医療機器関連感染／YEAST INFECTION IN CENTRAL LINE	2018-01-26(360) /2018-02-06(371)	INT/ MO/ R/R	No	NR	NC/ UK	No	Y	Y
[redacted]	M/1[redacted]/BLACK	臨床検査／γ-グルタミルトランスフェラーゼ増加／CLINICALLY SIGNIFICANT HIGH GGT	2017-02-23(205) /2017-05-17(288)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	臨床検査／ヘマトクリット増加／CLINICALLY SIGNIFICANT HIGH HCT	2017-02-23(205) /2017-03-01(211)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／国際標準比増加／CLINICALLY SIGNIFICANT HIGH INR	2017-02-23(205) /2017-03-01(211)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	臨床検査／プロトロンビン時間延長／CLINICALLY SIGNIFICANT HIGH PT	2017-02-23(205) /2017-03-01(211)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／血中尿酸増加／CLINICALLY SIGNIFICANT HIGH URIC ACID	2017-02-23(205) /2017-03-01(211)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	臨床検査／ 国際標準比増加／ CLINICALLY SIGNIFICANT HIGH INR	2017-03-08(218) /2017-04-05(246)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ プロトロンビン時間延長 ／ CLINICALLY SIGNIFICANT HIGH PT	2017-03-08(218) /2017-04-05(246)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2017-03-08(218) /2017-03-08(218)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		臨床検査／ アラニンアミノトランスフェラーゼ増加／ CLINICALLY SIGNIFICANT HIGH ALT	2017-03-22(232) /2017-04-05(246)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		傷害、中毒および処置合併症／ 裂傷／ LEFT FOOT LACERATION	2017-04-22(263) /2017-05-03(274)	CONT/ MI/ R/R	No		NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	感染症および寄生虫症／蜂巣炎／ABDOMINAL WALL CELLULITIS	2017-05-08(279) /ONGOING	CONT/ MI/ NRD	No	NR	NC/ DT	No	N	Y
		胃腸障害／下痢／DIARRHEA	2017-05-10(281) /2017-09-13(407)	CONT/ MI/ R/R	No		NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／カテーテル留置部位腫脹／BROVIAC SITE SWELLING	2017-05-30(301) /2017-05-31(302)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	一般・全身障害および投与部位の状態／カテーテル留置部位分泌物／BROVIAC SITE DRAINAGE	2017-06-10(312) /2017-06-13(315)	INT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		製品の問題／医療機器位置異常／BROVIAC DISLODGEMENT	2017-07-03(335) /2017-07-04(336)	CONT/ MO/ R/R	No		NC/ MULTIPLE	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	M/1[redacted]/BLACK	胃腸障害／ 鼓腸／ FLATULENCE	2017-09-24(418) /ONGOING	INT/ MI/ RCG	No	NR	NC/ DT	No	N	Y
		臨床検査／ 尿中血陽性／ BLOOD IN URINE	2017-09-28(422) /2017-11-16(471)	INT/ MO/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 便秘／ CONSTIPATION	2017-11-25(480) /2017-11-27(482)	INT/ MO/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	製品の問題／ 医療機器閉塞／ CENTRAL VENOUS CATHETER OCCLUSION	2017-08-27(210) /2017-08-27(210)	INT/ MO/ R/R	No	NR	NA/ N	No	N	Y
		傷害、中毒および処置合併症／ 挫傷／ LEFT ARM BRUISE	2017-08-28(211) /2017-09-11(225)	CONT/ MI/ R/R	No		NA/ N	No	N	Y
		感染症および寄生虫症／ 医療機器関連敗血症／ CENTRAL LINE INFECTION AND SEPSIS	2017-08-28(211) /2017-09-02(216)	INT/ SV/ R/R	No		NA/ NT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	免疫系障害／ アナフィラキシー反応／ VANCOMYCIN ADMINISTRATION RESULTED IN ANAPHYLAXIS.	2017-08-28(211) /2017-08-28(211)	CONT/ SV/ R/R	No	NR	NA/ N	No	Y	Y
		呼吸器、胸郭および縦隔障害／ 上気道うっ血／ UPPER RESPIRATORY CONGESTION	2017-09-11(225) /2017-09-25(239)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／ 下痢／ DIARRHEA	2017-09-16(230) /2017-09-19(233)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		製品の問題／ 医療機器破損／ BROVIAC REPAIR	2017-10-10(254) /2017-10-11(255)	INT/ MI/ R/R	No		NC/ N	No	N	Y
		胃腸障害／ 下痢／ DIARRHEA	2017-10-11(255) /2017-10-12(256)	CONT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／ 下痢／ DIARRHEA	2017-12-18(323) /2017-12-21(326)	CONT/ MI/ R/R	No	NR	NC/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-12-26(331) /2017-12-28(333)	CONT/ MI/ R/R	No		DI/ UK	No	Y	Y
		感染症および寄生虫症／ 上気道感染／ URI	2017-12-31(336) /2018-01-01(337)	CONT/ MI/ R/R	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/WHITE	胃腸障害／ 腹痛／ ABDOMINAL PAIN	2018-01-07(343) /2018-02-26(393)	CONT/ MI/ R/R	No	NR	UK/ N	No	N	Y
		胃腸障害／ イレウス／ BOWEL ILEUS	2018-01-07(343) /2018-01-11(347)	INT/ MO/ R/R	No		DI/ NT	No	Y	Y
		感染症および寄生虫症／ インフルエンザ／ INFLUENZA	2018-01-16(352) /2018-01-20(356)	INT/ MO/ R/R	No		NA/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/OTHER	胃腸障害／ 嘔吐／ VOMITING	2017-08-01(258) /2017-08-01(258)	INT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 誤嚥／ ASPIRATION	2017-08-24(281) /2017-08-24(281)	INT/ MI/ R/R	No		NA/ N	No	N	Y
		呼吸器、胸郭および縦隔障害／ 鼻閉／ NASAL CONGESTION	2017-08-25(282) /2017-09-19(307)	CONT/ MI/ R/R	No		NA/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/OTHER	感染症および寄生虫症／尿路感染／URINARY TRACT INFECTION	2017-09-14(302) /2017-09-25(313)	CONT/ MO/ R/R	No	NR	NC/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／鼻漏／NASAL DISCHARGE	2017-11-18(367) /2017-11-20(369)	CONT/ MI/ R/R	No		NA/ DT	No	N	Y
		呼吸器、胸郭および縦隔障害／呼吸困難／LABORED BREATHING	2017-11-19(368) /2017-11-19(368)	CONT/ MI/ R/R	No		NA/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas Output: l-sae.rtf 30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/OTHER	呼吸器、胸郭および縦隔障害／ 咳嗽／ MILD COUGH	2017-11-20(369) /2017-11-20(369)	CONT/ MI/ R/R	No	NR	NA/ N	No	N	Y
		一般・全身障害および投与部位の状態／ 発熱／ FEVER	2017-12-20(399) /2017-12-23(402)	CONT/ MO/ R/R	No		NC/ DT	No	Y	Y
		感染症および寄生虫症／ 膀胱炎／ FEVER COMPLICATED CYSTISIS	2017-12-30(409) /2018-01-02(412)	CONT/ MO/ R/R	No		NC/ DT	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/OTHER	呼吸器、胸郭および縦隔障害／ 鼻閉／ NASAL CONGESTION	2018-01-31(441) /2018-02-06(447)	CONT/ MI/ R/R	No	NR	NC/ DT	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　30JAN2020 20:14

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	感染症および寄生虫症／ 鼻咽頭炎／ Cold	12MAY2015 -51/ 16MAY2015 -47	5	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	No
				感染症および寄生虫症／ 帯状疱疹／ Herpes zoster	16MAY2015 -47/ 31MAY2015 -32	16	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	No
				一般・全身障害および投与部位の状態／ 発熱／ Fever	02JUL2015:19:00:00 1/ 03JUL2015 2	2	No/ Mild/ Related	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				代謝および栄養障害／ 脱水／ Dehydration	23JUL2015 22/ 23JUL2015 22	1	No/ Mild/ Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-14004¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　29JAN2020 17:13

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	一般・全身障害および投与部位の状態／ 注射部位反応／ Injection site reaction	26JUL2015 25/ 27AUG2015 57	33	No/ Mild/ Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ カテーテル留置部位感染／ Catheter site pus	06AUG2015 36/ 08AUG2015 38	3	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter infection	09AUG2015 39/ 18AUG2015 48	10	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				臨床検査／ 血小板数減少／ Plate count decreased	10AUG2015 40/ 16AUG2015 46	7	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	13AUG2015 43/ 13AUG2015 43	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-14004¥report¥adhoc¥l-sae.sas　Output: l-sae.rtf　29JAN2020 17:13

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	感染症および寄生虫症／ 鼻咽頭炎／ Common cold	01OCT2015 92/ 06OCT2015 97	6	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				皮膚および皮下組織障害／ 皮膚嚢腫／ Blepharoatheroma	19NOV2015 141/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ カテーテル留置部位炎症／ Catheter site inflammation	26NOV2015 148/ 07DEC2015 159	12	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter infection	08DEC2015 160/ 15DEC2015 167	8	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	臨床検査／ 血小板数減少／ Plate count decreased	09DEC2015 161/ 13DEC2015 165	5	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	22FEB2016 236/ 22FEB2016 236	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	14JUN2016 349/ 16JUN2016 351	3	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	01AUG2016 397/ 13OCT2016 470	74	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	08NOV2016 496/ 26NOV2016 514	19	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	筋骨格系および結合組織障害／ 関節炎／ Arthritis	02FEB2017 582/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	30APR2017 669/ 03AUG2017 764	96	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				呼吸器、胸郭および縦隔障害／ アレルギー性鼻炎／ Allergic rhinitis	02MAY2017 671/ 15MAY2017 684	14	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				代謝および栄養障害／ 脱水／ Dehydration	03AUG2017 764/ 03AUG2017 764	1	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	05DEC2017 888/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Female	4[redacted]	皮膚および皮下組織障害／ 皮膚乾燥／ Dry skin	07DEC2017 890/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				代謝および栄養障害／ 低マグネシウム血症／ Hypomagnesemia	08MAR2018 981/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				感染症および寄生虫症／ 肛門膿瘍／ Perianal abscess	05APR2018 1009/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				内分泌障害／ 甲状腺嚢腫／ Cyst of thyroid	05APR2018 1009/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/Not Resolved	Yes
				代謝および栄養障害／ 低亜鉛血症／ Hypozincemia	05APR2018 1009/ 05JUL2018 1100	92	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	神経系障害／ 頭痛／ Headache	21AUG2015:21:00:001/ 21AUG2015:22:00:001	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related blood stream infection	24AUG2015:21:00:004/ 30AUG2015:15:00:0010	7	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ カンジダ性亀頭炎／ Penis candidiasis	02SEP2015 13/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				代謝および栄養障害／ 栄養障害／ Malnutrition	02SEP2015:19:00:00 13/ - -		No/ Severe/ Not Related	Drug Interrupted/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 浮腫／ Edema	02SEP2015 13/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				胃腸障害／ 腸炎／ Enterocolitis	02SEP2015:19:00:00 13/ 18SEP2015 29	17	Yes/ Severe/ Related	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 腸閉塞／ Intestinal obstruction	02SEP2015:19:00:00 13/ 18SEP2015 29	17	Yes/ Severe/ Related	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related blood stream infection	02SEP2015 13/ 19SEP2015 30	18	No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	血液およびリンパ系障害／ 貧血／ Anemia (aggravated)	03SEP2015 14/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				血液およびリンパ系障害／ 播種性血管内凝固／ Disseminated intravascular coagulation	05SEP2015 16/ - -		No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				肝胆道系障害／ 急性肝不全／ Acute liver failure	05SEP2015 16/ 27OCT2015:12:40:0068	53	Yes/ Severe/ Related	Drug Withdrawn/ Multiple	Continuous/ Fatal	Yes
				肝胆道系障害／ 高ビリルビン血症／ High bilirubinemia	06SEP2015 17/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	感染症および寄生虫症／ 口腔ヘルペス／ Herpes labialis	07SEP2015 18/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				胃腸障害／ 膵炎／ Pancreatitis	07SEP2015 18/ 04OCT2015 45	28	No/ Moderate/ Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				皮膚および皮下組織障害／ そう痒症／ Skin pruritus	10SEP2015 21/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				代謝および栄養障害／ 高血糖／ Hyperglycemia	11SEP2015 22/ 16SEP2015 27	6	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 口腔内出血／ Bleeding mouth	16SEP2015 27/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	感染症および寄生虫症／ 敗血症／ Sepsis	20SEP2015 31/ 14OCT2015 55	25	Yes/ Severe/ Not Related	Dose Not Changed/ Multiple	Continuous/ Recovered/Resolved	Yes
				臨床検査／ 酸素飽和度低下／ Oxygen saturation low	21SEP2015 32/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter occlusion	21SEP2015 32/ 21SEP2015 32	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				代謝および栄養障害／ 低血糖症／ Hypoglycemia	21SEP2015 32/ 21SEP2015 32	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	胃腸障害／ 腸炎／ Enterocolitis	21SEP2015 32/ 13OCT2015 54	23	No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				心臓障害／ 急性心不全／ Acute heart failure	22SEP2015 33/ - -		No/ Severe/ Not Related	Dose Not Changed/ Multiple	Continuous/ -	Yes
				筋骨格系および結合組織障害／ 筋肉痛／ Muscle pain	22SEP2015 33/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				臨床検査／ 尿量減少／ Decreased urinal volume	22SEP2015 33/ - -		No/ Moderate/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	呼吸器、胸郭および縦隔障害／ 呼吸不全／ Acute lung failure	22SEP2015 33/ 13OCT2015 54	22	No/ Severe/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/Resolved	Yes
				眼障害／ 眼球浮腫／ Eye edema	23SEP2015 34/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				感染症および寄生虫症／ 口腔カンジダ症／ Oral candida	23SEP2015 34/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 低体温／ Hypothemia	24SEP2015 35/ 24SEP2015 35	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				腎および尿路障害／ 急性腎不全／ Acute renal failure	22OCT2015 63/ 27OCT2015:12:40:00 68	6	Yes/ Severe/ Not Related	Dose Not Changed/ None	Intermittent/ Fatal	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 注射部位反応／ Injection site reaction(induration)	18MAY2015 8/ 08JUN2015 29	22	No/ Mild/ Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 腹部膨満／ Abdominal distension	19MAY2015 9/ 08JUN2015 29	21	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 倦怠感／ Malaise	01OCT2015 144/ 05OCT2015 148	5	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 発熱／ Fever	24OCT2015 167/ 25OCT2015 168	2	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	胃腸障害／ 腹痛／ Abdominal pain	25OCT2015 168/ 26OCT2015 169	2	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				臨床検査／ Ｃ－反応性蛋白増加／ CRP high	26OCT2015 169/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				筋骨格系および結合組織障害／ 関節痛／ Arthralgia	11DEC2015 215/ 22FEB2016 288	74	No/ Moderate/ Not Related	Dose Not Changed/ Multiple	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 医療機器閉塞／ Occlusion of the catheter	11MAR2016 306/ 28MAR2016 323	18	No/ Moderate/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/Resolved	Yes

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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 発熱／ Fever	11MAR2016 306/ 29MAR2016 324	19	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	18MAR2016 313/ 24MAR2016 319	7	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related bloodstream infection	29MAR2016 324/ 13APR2016 339	16	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				臨床検査／ 血中クレアチニン増加／ Creatinine increased	31MAR2016 326/ 06APR2016 332	7	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	22JUL2016 439/ 23JUL2016 440	2	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 倦怠感／ Malaise	25JUL2016 442/ 22AUG2016 470	29	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				筋骨格系および結合組織障害／ 背部痛／ Back pain	24SEP2016 503/ 26SEP2016 505	3	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 気道感染／ Upper respiratory infection	23MAY2018 1109/ 24MAY2018 1110	2	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
[redacted]	Japanese	Male	3[redacted]	筋骨格系および結合組織障害／ 筋骨格系胸痛／ Right costal pain	20FEB2015 -88/ 03MAR2015 -77	12	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	No

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 発熱／ Fever	05APR2015 -44/ 06APR2015 -43	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	No
				臨床検査／ Ｃ－反応性蛋白増加／ CRP high	07APR2015 -42/ 18MAY2015 -1	42	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	No
				胃腸障害／ 腹痛／ Abonominal pain	19MAY2015 1/ 19MAY2015 1	1	No/ Mild/ Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 医療機器関連損傷／ Needle injury	19MAY2015 1/ 19MAY2015 1	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 失神寸前の状態／ Vasovagalreaction	20MAY2015:09:00:00 2/ 20MAY2015:10:30:00 2	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	臨床検査／ 癌胎児性抗原増加／ Carcinoembryonic antigen high	02JUN2015 15/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 疲労／ Fatigue	09JUN2015 22/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes
				胃腸障害／ 口内炎／ Mucositis oral	12JUN2015 25/ 23JUN2015 36	12	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter occlusion	04OCT2015:08:34:00 139/ 07OCT2015:10:00:00 142	4	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter occlusion	07OCT2015:10:00:00 142/ 09OCT2015:14:00:00 144	3	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	07DEC2015 203/ 10DEC2015 206	4	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 浮動性めまい／ Dizziness	07DEC2015 203/ 19JAN2016 246	44	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				精神障害／ うつ病／ Depression	05FEB2016 263/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				胃腸障害／ 悪心／ Nausea	28JUN2016 407/ 28JUN2016 407	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 浮動性めまい／ Dizziness	24SEP2016 495/ 18OCT2016 519	25	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[redacted]	Japanese	Male	3[redacted]	胃腸障害／ 悪心／ Nausea	25OCT2016 526/ 25OCT2016 526	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				精神障害／ 不眠症／ Insomnia	25OCT2016 526/ 02MAY2017 715	190	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter trouble	14NOV2016 546/ 06DEC2016 568	23	No/ Moderate/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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[redacted]	Japanese	Male	3[redacted]	一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter trouble	06DEC2016 568/ 07DEC2016 569	2	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	19DEC2016 581/ 31DEC2016 593	13	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ インフルエンザ／ Influenza	14FEB2017 638/ 21FEB2017 645	8	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 胸痛／ Chest pain	17FEB2017 641/ 18APR2017 701	61	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 悪心／ Nausea	30APR2017 713/ 01MAY2017 714	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

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Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	胃腸障害／ 嘔吐／ Vomiting	30APR2017 713/ 01MAY2017 714	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 下痢／ Diarrhea	30APR2017 713/ 08MAY2017 721	9	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 腹痛／ Abdominal pain	30APR2017 713/ 16MAY2017 729	17	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 口渇／ Thirst	01MAY2017 714/ 31JUL2017 805	92	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Central venous catheter related infection	25JUL2017 799/ 01AUG2017 806	8	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Central venous catheter related infection	01AUG2017 806/ 09AUG2017 814	9	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Central venous catheter related infection	09AUG2017 814/ 15AUG2017 820	7	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 口渇／ Thirst	17OCT2017 883/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/Not Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	3[redacted]	感染症および寄生虫症／ 鼻咽頭炎／ Common cold	16JUN2018 1125/ 17JUL2018 1156	32	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
[redacted]	Japanese	Female	4[redacted]	呼吸器、胸郭および縦隔障害／ 上気道の炎症／ Acute upper respiratory inflammation	15APR2015 38/ 28MAY2015 81	44	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	29MAY2015 82/ 22JUN2015 106	25	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 口唇炎／ Angular cheilitis	30MAY2015 83/ 31MAY2015 84	2	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Female	4[redacted]	臨床検査／ 血中アルカリホスファターゼ増加／ ALP increased	04JUN2015 88/ 25JUN2015 109	22	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catherter related infection	07JUL2015 121/ 30JUL2015 144	24	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				眼障害／ 硝子体混濁／ Left eye vitreous opacity	28JUL2015 142/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovering/Resolving	Yes
				胃腸障害／ 心窩部不快感／ Epigastric discomfort	13OCT2016 585/ 17NOV2016 620	36	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Female	4[redacted]	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）／ 卵巣腺腫／ Ovarian cyst	05DEC2016 638/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 発熱／ Fever up	13DEC2016 646/ 22DEC2016 655	10	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 口唇炎／ Angular Stomatitis	18MAY2017 802/ 22JUN2017 837	36	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	10SEP2017 917/ 27SEP2017 934	18	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Female	4[redacted]	一般・全身障害および投与部位の状態／ カテーテル留置部位疼痛／ Catheter site pain	27SEP2017 934/ 19OCT2017 956	23	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	27SEP2017 934/ 19OCT2017 956	23	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
[redacted]	Japanese	Male	4[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter relted infection	11FEB2015:10:00:00 -42/ 02MAR2015 -23	20	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No
				神経系障害／ 錯感覚／ Paresthesia of the hand and feet	25FEB2015 -28/ 26FEB2015 -27	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	No

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	4[redacted]	筋骨格系および結合組織障害／ 背部痛／ Low back pain	26FEB2015 -27/ 26FEB2015 -27	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	No
				傷害、中毒および処置合併症／ ストーマ部反応／ Stoma enlargement	08APR2015 15/ - -		No/ Mild/ Related	Dose Not Changed/ None	Continuous/ Recovering/Resolving	Yes
				呼吸器、胸郭および縦隔障害／ 上気道の炎症／ Acute upper respiratory inflammation	03JUL2015 101/ 15JUL2015 113	13	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 発熱／ Fever	07AUG2015 136/ 21AUG2015 150	15	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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[redacted]	Japanese	Male	4[redacted]	胃腸障害／ 腹痛／ Abdominal pain	12AUG2015 141/ 12AUG2015 141	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	24AUG2015 153/ - -		Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ カテーテル留置部位疼痛／ Catheter site pain	24AUG2015 153/ 24AUG2015 153	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 穿刺部位疼痛／ Puncture site pain	08SEP2015 168/ 15SEP2015 175	8	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[redacted]	Japanese	Male	4[redacted]	筋骨格系および結合組織障害／ 関節痛／ Arthralgia	04NOV2015 225/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				胃腸障害／ 歯痛／ Toothache	04NOV2015 225/ 04NOV2015 225	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved With Sequelae	Yes
				感染症および寄生虫症／ 蜂巣炎／ Cellulitis	09JAN2016 291/ 22JAN2016 304	14	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	23JAN2016 305/ 23JAN2016 305	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	23JAN2016:14:07:00 305/ 17FEB2016 330	26	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	4[redacted]	眼障害／ 霧視／ Vision blurred	08FEB2016 321/ 01MAR2016 343	23	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ インフルエンザ／ Influenza	24FEB2016 337/ 04MAR2016 346	10	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 発熱／ Fever up	20JUN2016 454/ 21JUN2016 455	2	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	22JUN2016 456/ 09JUL2016 473	18	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 歯肉炎／ Gingivitis	24JUN2016 458/ 08JUL2016 472	15	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

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[redacted]	Japanese	Male	4[redacted]	皮膚および皮下組織障害／ 接触性皮膚炎／ Contact dermatitis	26JUN2016 460/ 28JUN2016 462	3	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				眼障害／ 眼精疲労／ Asthenopia	01JUL2016 465/ 07JUL2016 471	7	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				呼吸器、胸郭および縦隔障害／ 喘息／ Asthma	11AUG2016 506/ 01SEP2016 527	22	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				代謝および栄養障害／ 低カリウム血症／ Hypokalemia	01SEP2016 527/ 02SEP2016 528	2	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
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[redacted]	Japanese	Male	4[redacted]	呼吸器、胸郭および縦隔障害／ 上気道の炎症／ Acute upper respiratory inflammation	03OCT2016 559/ 14OCT2016 570	12	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ 発熱／ Fever up	17OCT2016 573/ 22OCT2016 578	6	Yes/ Severe/ Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Commoncold	09DEC2016 626/ 28DEC2016 645	20	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 歯痛／ Toothache	01FEB2017 680/ 01FEB2017 680	1	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

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[redacted]	Japanese	Male	4[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Cathetel related infection	10FEB2017 689/ 23MAR2017 730	42	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				精神障害／ 不安障害／ Anxiety disorder	15FEB2017 694/ 22JUN2017 821	128	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 健忘／ Amnesia	16FEB2017 695/ 17FEB2017 696	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				血管障害／ 血管痛／ Vascular pain	19FEB2017 698/ 19FEB2017 698	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				呼吸器、胸郭および縦隔障害／ 口腔咽頭痛／ Sore throat	04MAR2017 711/ 04MAR2017 711	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				眼障害／ 眼精疲労／ Asthenopia	05MAR2017 712/ 05MAR2017 712	1	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	4[redacted]	眼障害／ 眼乾燥／ Dry eye	05MAR2017 712/ 05MAR2017 712	1	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 構音障害／ Dyslalia	11MAR2017 718/ 14MAR2017 721	4	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				一般・全身障害および投与部位の状態／ カテーテル留置部位疼痛／ Catheter site pain	21MAR2017 728/ 22MAR2017 729	2	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				腎および尿路障害／ 尿失禁／ Urine incontinence	21MAR2017 728/ 07APR2017 745	18	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	4[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	26MAR2017 733/ 26APR2017 764	32	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 傾眠／ Drowsiness	01APR2017 739/ 02APR2017 740	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 歯肉炎／ Gingivitis	01MAY2017 769/ 03MAY2017 771	3	No/ Moderate/ Not Related	Dose Not Changed/ Non-Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 歯肉痛／ Gingival pain	03MAY2017 771/ 07JUN2017 806	36	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	22JUN2017 821/ 04JUL2017 833	13	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	19SEP2017 910/ 19OCT2017 940	31	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	4[redacted]	筋骨格系および結合組織障害／ 多発性関節炎／ Polyarthritis	19OCT2017 940/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common Cold	02NOV2017 954/ 10NOV2017 962	9	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 細菌性関節炎／ Pyogenic arthritis	16NOV2017 968/ 16DEC2017 998	31	Yes/ Severe/ Not Related	Dose Not Changed/ Multiple	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 下痢／ Diarrhea	22DEC2017 1004/ 09JAN2018 1022	19	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	4[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	05MAR2018 1077/ 06APR2018 1109	33	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	18APR2018 1121/ 13MAY2018 1146	26	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	18AUG2018 1243/ 05SEP2018 1261	19	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
[redacted]	Japanese	Male	1[redacted]	感染症および寄生虫症／ 敗血症／ Blood stream infection	30MAR2015:15:36:00 -191/ 02APR2015 -188	4	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	血管障害／ 血栓性静脈炎／ Recurrence of thrombophlebitis	30MAR2015:15:36:00 -191/ 02APR2015 -188	4	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No
				肝胆道系障害／ 胆石症／ Biliary sludge	30APR2015 -160/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/Not Resolved	No
				肝胆道系障害／ 脂肪肝／ Fatty liver	30APR2015 -160/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	No
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	30APR2015:10:15:00 -160/ 04MAY2015:13:30:00 -156	5	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No
				呼吸器、胸郭および縦隔障害／ 鼻出血／ Epistaxis	04JUN2015 -125/ 16JUL2015 -83	43	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	No

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection	31JUL2015 -68/ 09AUG2015 -59	10	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No
				感染症および寄生虫症／ 医療機器関連感染／ Catherter related infection	01SEP2015 -36/ 11SEP2015 -26	11	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	No
				感染症および寄生虫症／ 医療機器関連感染／ Catherter related infection	17OCT2015 11/ 24OCT2015:10:00:00 18	8	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ おくび／ Belch	28OCT2015 22/ 13NOV2015 38	17	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 小腸炎／ Enteritis	18NOV2015:14:45:00 43/ 24NOV2015 49	7	Yes/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	代謝および栄養障害／ 脱水／ Dehydration	22DEC2015 77/ 03JAN2016 89	13	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ おくび／ Belch	04JAN2016 90/ 04JAN2016 90	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				血管障害／ 血栓性静脈炎／ Suspect of recurrence of thrombophlebitis	07JAN2016 93/ 15JAN2016 101	9	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ トリコフィトン感染症／ Trichophytosis	13JAN2016 99/ 04MAR2016 150	52	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	1[redacted]	胃腸障害／ 腹部膨満／ Abdominal distension　gaseous	28MAR2016 174/ 08APR2016 185	12	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				皮膚および皮下組織障害／ 接触性皮膚炎／ Contact dermatitis	19MAY2016 226/ 24JUN2016 262	37	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 鼻咽頭炎／ Common cold	29MAY2016 236/ 04JUN2016 242	7	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related infection susupected	04JUN2016 242/ 07JUN2016 245	4	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	代謝および栄養障害／ 脱水／ Dehydration	01JUL2016 269/ 11JUL2016 279	11	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				神経系障害／ 頭痛／ Headache	25JUL2016 293/ 25JUL2016 293	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 齲歯／ Dental caries	09AUG2016 308/ - -		No/ Mild/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ -	Yes
				筋骨格系および結合組織障害／ 顎関節症候群／ Temporomandibular arthrosis	09AUG2016 308/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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[redacted]	Japanese	Male	1[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter infection suspected	05SEP2016 335/ 11SEP2016 341	7	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ レンサ球菌感染／ Streptococal infection suspected	05SEP2016 335/ 11SEP2016 341	7	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				臨床検査／ 肝機能検査異常／ Liver Function test raised.	21SEP2016 351/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				皮膚および皮下組織障害／ ざ瘡／ Acune	26OCT2016 386/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				胃腸障害／ 消化不良／ Heart burn	26OCT2016 386/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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[redacted]	Japanese	Male	1[redacted]	傷害、中毒および処置合併症／ 処置による疼痛／ Catheter removed site pain	26DEC2016 447/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Not Recovered/Not Resolved	Yes
				筋骨格系および結合組織障害／ 関節痛／ Leg joint pain	02JAN2017 454/ 03JAN2017 455	2	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ カテーテル留置部位感染／ Catheter site infection	02JAN2017 454/ 21JAN2017 473	20	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				免疫系障害／ 過敏症／ Allergic reaction	06JAN2017 458/ 06JAN2017 458	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				血管障害／ 血管痛／ Vascular pain	06JAN2017 458/ 06JAN2017 458	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

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[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	胃腸障害／ 悪心／ Nausea	12JAN2017 464/ 12JAN2017 464	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				呼吸器、胸郭および縦隔障害／ 口腔咽頭痛／ Pain of pharynx	12JAN2017 464/ 12JAN2017 464	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				皮膚および皮下組織障害／ そう痒症／ Itching	12JAN2017 464/ 12JAN2017 464	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				神経系障害／ 傾眠／ Sleepiness	12JAN2017 464/ 12JAN2017 464	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				血管障害／ 血管痛／ Vascular pain	12JAN2017 464/ 12JAN2017 464	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	1[redacted]	胃腸障害／ 口内炎／ Stomatitis	13JAN2017 465/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/Not Resolved	Yes
				皮膚および皮下組織障害／ 紅斑／ Scrotal redness	15JAN2017 467/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/Not Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	Black	0.05 Mg/Kg/Day	Female	4[redacted]	高血圧	-897	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						カルシウム欠乏	-708	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						低カルシウム血症	-350	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						低カリウム血症	-230	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						腹痛	-175	449	Not Related	Mild	Not Serious	None	Recovered/Resolved
						筋痙縮	-175	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						振戦	-62	147	Not Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	12	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						浮動性めまい	12	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						疲労	12	74	Not Related	Mild	Not Serious	None	Recovered/Resolved
						医療機器内血栓	35	21	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						下腹部痛	51	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						乳酸アシドーシス	51	6	Not Related	Moderate	Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	Black	0.05 Mg/Kg/Day	Female	4[redacted]	下痢	51	4	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						高血圧	53	2	Not Related	Mild	Not Serious	None	Recovered/Resolved
						頚部痛	69	5	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						末梢性浮腫	169	47	Not Related	Mild	Not Serious	None	Recovered/Resolved
						結膜蒼白	169	106	Not Related	Mild	Not Serious	None	Recovered/Resolved
						末梢性浮腫	216	59	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						悪心	217	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						重感	217	58	Not Related	Mild	Not Serious	None	Recovered/Resolved
						失見当識	217	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						季節性アレルギー	248	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						関節炎	256	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						湿疹	274	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	6[redacted]	消化管ストーマ合併症	-1288	.	Related	Mild	Not Serious	None	Recovering/Resolving
						体重減少	-708	709	Not Related	Mild	Not Serious	None	Recovered/Resolved

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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	6[redacted]	下痢	.	1	Related	Mild	Not Serious	None	Recovered/Resolved
						処置後合併症	1	92	Not Related	Mild	Not Serious	None	Recovered/Resolved
						心房頻脈	133	3	Not Related	Severe	Serious	None	Recovered/Resolved
						呼吸困難	133	3	Not Related	Moderate	Serious	None	Recovered/Resolved
						急性心不全	135	4	Not Related	Moderate	Serious	None	Recovered/Resolved
						心房細動	135	63	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Recovered/Resolved
						心筋症	135	4	Not Related	Moderate	Serious	None	Recovered/Resolved
						体重減少	.	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						虚血性心筋症	192	6	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Recovered/Resolved
						中心静脈カテーテル感染	227	7	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Recovered/Resolved
						食欲減退	.	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						脱水	.	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						疲労	.	.	Not Related	Severe	Not Serious	None	Recovering/Resolving

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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	心電図 T 波振幅減少	-810	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						おくび	-809	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腎萎縮	-788	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腎動脈閉塞	-788	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						ビタミン B12 欠乏	-719	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腸骨動脈閉塞	-646	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						うつ病	-645	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						悪心	-551	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						疼痛	-501	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						高血圧	-493	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						骨粗鬆症	-479	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						ほてり	-476	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						疲労	-439	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						寝汗	-264	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						栄養障害	-73	.	Not Related	Mild	Not Serious	None	Recovering/Resolving

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Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	末梢性浮腫	-53	57	Not Related	Mild	Not Serious	None	Recovered/Resolved
						下痢	-7	9	Not Related	Mild	Not Serious	None	Recovered/Resolved
						血液量増加症	1	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						ビタミンD欠乏	1	100	Not Related	Mild	Not Serious	None	Recovered/Resolved
						うっ血性心不全	2	3	Not Related	Moderate	Serious	None	Recovered/Resolved
						肺炎	2	11	Not Related	Moderate	Serious	None	Recovered/Resolved
						嘔吐	99	101	Not Related	Mild	Not Serious	None	Recovered/Resolved
						片頭痛	99	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腎不全	101	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						季節性アレルギー	101	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						咳嗽	170	90	Not Related	Mild	Not Serious	None	Recovered/Resolved
						インフルエンザ様疾患	171	3	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						筋骨格系胸痛	192	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						末梢性浮腫	199	54	Not Related	Mild	Not Serious	None	Recovered/Resolved

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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	肝酵素上昇	199	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						末梢性浮腫	253	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						処置による疼痛	253	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						カテーテル合併症	257	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						ステント内動脈再狭窄	262	72	Not Related	Severe	Serious	Study Drug Dose Interrupted	Recovered/Resolved
						急性腎不全	262	16	Not Related	Severe	Not Serious	Study Drug Dose Interrupted	Recovered/Resolved
						呼吸不全	279	55	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						肺炎	279	14	Not Related	Severe	Serious	None	Recovered/Resolved
						呼吸困難	279	55	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						不安	318	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						背部痛	318	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						低ナトリウム血症	322	9	Not Related	Mild	Not Serious	None	Recovered/Resolved
						カテーテル菌血症	322	11	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腎動脈狭窄症	327	.	Not Related	Severe	Not Serious	None	Recovering/Resolving

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Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	高血圧	331	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
						急性肺水腫	332	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						狭心症	332	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						処置による疼痛	333	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						関節腫脹	367	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	6[redacted]	骨粗鬆症	-792	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腹部ヘルニア	-728	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						胸水	-607	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						甲状腺新生物	-550	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						大静脈血栓症	-543	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						末梢性浮腫	-47	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						平衡障害	-7	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						浮動性めまい	-7	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						体重減少	66	34	Not Related	Moderate	Not Serious	None	Recovered/Resolved

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Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	6[redacted]	汎血球減少症	73	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						下痢	84	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						尿管障害	84	18	Not Related	Mild	Not Serious	None	Recovered/Resolved
						尿路感染	84	7	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						上気道感染	.	32	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腎障害	101	62	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						腎臓痛	101	62	Not Related	Severe	Not Serious	None	Recovered/Resolved
						体重減少	101	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						貧血	101	62	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						血尿	101	62	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						下痢	104	59	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						膀胱障害	109	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						尿路感染	157	5	Not Related	Moderate	Serious	None	Recovered/Resolved
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	蛋白尿	-938	.	Not Related	Mild	Not Serious	None	Recovering/Resolving

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Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	心筋症	-572	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						憩室	-473	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						体重減少	-273	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						血中重炭酸塩減少	-273	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						血中カルシウム減少	-273	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						注射部位反応	.	.	Related	Mild	Not Serious	None	Recovering/Resolving
						末梢性浮腫	-1	179	Not Related	Mild	Not Serious	None	Recovered/Resolved
						ラ音	-1	179	Not Related	Mild	Not Serious	None	Recovered/Resolved
						上肢骨折	108	69	Not Related	Severe	Serious	None	Recovered/Resolved

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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-15-ae-sae-11001.sas

Output Generated On: 23OCT2016 1:33

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ Common Cold	07OCT2018 (-3)/ 11OCT2018 (2)	5	No/ Moderate/ Not Related	No	Not Applicable/ Drug Treatment	Continuous/ Recovered/ Resolved	
				一般・全身障害および投与部位の状態/ 注射部位反応/ Injection site reaction (flare,subcutaneous bleeding)	24OCT2018 (15)/ Ongoing		No/ Mild/ Related	No	Dose Not Changed/ None	Continuous/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ catheter related blood stream infection	10DEC2018 (62)/ 24DEC2018 (76)	15	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 湿疹/ Eczema	19DEC2018 (71)/ 04JAN2019 (87)	17	No/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	胃腸障害/ 肛門周囲痛/ anal pain	21DEC2018 (73)/ 22DEC2018 (74)	2	No/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 手足口病/ Hand-foot-and-mouth disease	03JAN2019 (86)/ 23JAN2019 (106)	21	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ Common Cold	09FEB2019 (123)/ 09APR2019 (182)	60	No/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ アデノウイルス感染/ Adenovirus infection	09APR2019 (182)/ Ongoing		Yes/ Moderate/ Not Related	No	Not Applicable/ Drug Treatment	Continuous/ Recovering/ Resolving	Yes
				感染症および寄生虫症/ 鼻炎/ Rhinitis	10APR2019 (183)/ Ongoing		No/ Moderate/ Not Related	No	Not Applicable/ Drug Treatment	Intermittent/ Recovering/ Resolving	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ [redacted]		感染症および寄生虫症/ ウイルス性上気道感染/ Common cold	05FEB2017 (5)/ 10FEB2017 (10)	6	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ fever	02MAR2017 (10:00) (30)/ 06MAR2017 (34)	5	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ おむつ皮膚炎/ diaper dermatitis	28MAR2017 (56)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				免疫系障害/ 食物アレルギー/ food allergy	28MAR2017 (56)/ 28MAR2017 (56)	1	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 便秘/ constipation	03APR2017 (62)/ Ongoing		No/ Mild/ Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	代謝および栄養障害/ 高リパーゼ血症/ Hyper lipasemia	17MAY2017 (106)/ 26MAY2017 (115)	10	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ Catheter related blood stream infection	20MAY2017 (109)/ 04JUN2017 (124)	16	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ Catheter related blood stream infection	03JUL2017 (153)/ 17JUL2017 (167)	15	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 手足口病/ hand foot mouth disease	14AUG2017 (195)/ Ongoing		Yes/ Moderate/ Not Related	No	Not Applicable/ None	Continuous/ Not Recovered/ Not Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位硬結/ Injection site reaction(induration)	10FEB2017 (3)/ 15FEB2017 (8)	6	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位血腫/ Injection site reaction(Subcutraneous hematom right lower abdomen)	10FEB2017 (3)/ 21FEB2017 (14)	12	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness)	13FEB2017 (6)/ 14FEB2017 (7)	2	No/ Mild/ Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	皮膚および皮下組織障害/ 皮膚乾燥/ dry skin	15FEB2017 (8)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding left lower abdomen)	17FEB2017 (10)/ 24FEB2017 (17)	8	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(subcutaneous bleeding right thigh)	20FEB2017 (13)/ 27FEB2017 (20)	8	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding risght lower abdomen)	23FEB2017 (16)/ 01MAR2017 (22)	7	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction redness(right arm)	25FEB2017 (18)/ 25FEB2017 (18)	1	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ tunnel infection(central venous catheter)	01MAR2017 (22)/ 25JUN2017 (138)	117	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	胃腸障害/ 小腸炎/ enteritis	15MAR2017 (36)/ 29MAR2017 (50)	15	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腸炎/ obstinate enterocolitis	29MAR2017 (50)/ 08MAY2017 (90)	41	Yes/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding right arm)	14MAY2017 (96)/ 23MAY2017 (105)	10	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ common cold	20MAY2017 (102)/ 27MAY2017 (109)	8	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness left thigh)	23MAY2017 (12:30) (105)/ 27MAY2017 (109)	5	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				免疫系障害/ アナフィラキシー反応/ Anaphylaxis	24JUN2017 (137)/ 28JUN2017 (141)	5	Yes/ Mild/ Not Related	No	Drug Withdrawn/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ tunnel infection (central venous catheter)deterioration	26JUN2017 (139)/ 09AUG2017 (183)	45	Yes/ Severe/ Not Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腹痛/ abdominal pain	08JUL2017 (151)/ 09AUG2017 (183)	33	No/ Mild/ Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1	感染症および寄生虫症/ ウイルス性胃腸炎/ Viral Gastroenteritis	31MAY2018 (-20)/ 08JUN2018 (-12)	9	No/ Mild/ Not Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction (redness)	20JUN2018 (14:00) (1)/ 20JUN2018 (16:00) (1)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位疼痛/ Injection site reaction (pain)	20JUN2018 (14:00) (1)/ 22JUN2018 (09:00) (3)	3	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleed)	22JUN2018 (3)/ 24JUN2018 (09:00) (5)	3	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1	一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleed)	26JUN2018 (7)/ 01JUL2018 (22:00) (12)	6	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 胃炎/ gastritis	02JUL2018 (02:30) (13)/ 11JUL2018 (22)	10	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位発疹/ Injection site reaction(Rush) right foot	06JUL2018 (08:00) (17)/ 21JUL2018 (32)	16	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位発疹/ Injection site reaction(Rush) left foot	07JUL2018 (18)/ 22JUL2018 (33)	16	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1[redacted]	一般・全身障害および投与部位の状態/ 注射部位発疹/ Injection site reaction(Rush) right lower abdomen	10JUL2018 (21)/ 22JUL2018 (33)	13	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位発疹/ Injection site reaction(Rush) right arm	11JUL2018 (22)/ 25JUL2018 (17:27) (36)	15	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction Subcutaneous bleed (right lower abdomen)	16JUL2018 (27)/ 22JUL2018 (33)	7	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1	一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction Subcutaneous bleed (left lower abdomen)	17JUL2018 (28)/ 22JUL2018 (33)	6	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				臨床検査/ アミラーゼ増加/ Serum amylase increased	25JUL2018 (36)/ Ongoing		No/ Mild/ Not Related	Yes/ 3	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ high fever	07AUG2018 (49)/ 13AUG2018 (55)	7	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ High Fever	15AUG2018 (57)/ 29AUG2018 (71)	15	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1	一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction right thigh (Subcutaneous bleeding)	21AUG2018 (63)/ 23AUG2018 (65)	3	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ central venous catheter insertion site infection	02SEP2018 (20:30) (75)/ 04SEP2018 (77)	3	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ Tunnel infection (central venous catheter)	05SEP2018 (78)/ 03OCT2018 (106)	29	Yes/ Severe/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ catheter related blood steam infection	10SEP2018 (83)/ 03OCT2018 (106)	24	No/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1 [redacted]	傷害、中毒および処置合併症/ 胃瘻管部合併症/ Granulation Around the gastrostomy	19SEP2018 (92)/ 09OCT2018 (112)	21	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				生殖系および乳房障害/ 亀頭包皮炎/ Posthitis	22SEP2018 (95)/ 28SEP2018 (101)	7	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness) right thigh	01OCT2018 (104)/ 03OCT2018 (106)	3	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 発疹/ Rash(whole body)	09OCT2018 (112)/ 07NOV2018 (141)	30	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1[redacted]	傷害、中毒および処置合併症/ 胃瘻管部合併症/ Skin erosion around the gastrostomy	12NOV2018 (146)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				胃腸障害/ 腹部膨満/ abdominal distention	12NOV2018 (146)/ 04JAN2019 (199)	54	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				代謝および栄養障害/ 高亜鉛血症/ Zinc excess	14NOV2018 (148)/ 19DEC2018 (183)	36	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 発疹/ Rash(both foot)	19NOV2018 (153)/ 21NOV2018 (155)	3	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 皮膚乾燥/ Dry skin(whole body)	05DEC2018 (169)/ Ongoing		No/ Mild/ Not Related	No	Not Applicable/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	1	一般・全身障害および投与部位の状態/ カテーテル留置部位肉芽腫/ Granulation(Around the centeral venous catheter insertion)	05DEC2018 (169)/ 19DEC2018 (183)	15	No/ Mild/ Not Related	No	Not Applicable/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ Tunnel infection (central venous catheter)	14DEC2018 (178)/ 24DEC2018 (188)	11	Yes/ Moderate/ Not Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 腹痛/ abdominal pain	17DEC2018 (181)/ 24DEC2018 (188)	8	Yes/ Moderate/ Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	皮膚および皮下組織障害/ 発疹/ rash (upper abdomen)	18JAN2019 (3)/ 18JAN2019 (3)	1	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 発疹/ rash (left shoulder left forearm)	18JAN2019 (14:00) (3)/ 18JAN2019 (16:00) (3)	1	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,right lower abdomen)	25JAN2019 (10)/ 25JAN2019 (10)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,left upper abdomen)	26JAN2019 (11)/ 26JAN2019 (11)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,left upper abdomen)	30JAN2019 (15)/ 30JAN2019 (15)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,right lower abdomen)	31JAN2019 (16)/ 31JAN2019 (16)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,left lower abdomen)	01FEB2019 (17)/ 01FEB2019 (17)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,right upper abdomen)	04FEB2019 (20)/ 04FEB2019 (20)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness,left upper abdomen)	05FEB2019 (21)/ 05FEB2019 (21)	1	No/ Mild/ Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器損傷/ Damaged central venous catheters	11FEB2019 (27)/ 15FEB2019 (31)	5	Yes/ Mild/ Not Related	No	Dose Not Changed/ Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ Common cold	11MAR2019 (55)/ 18MAR2019 (62)	8	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ レンサ球菌性咽頭炎/ Streptococcus infection(Pharyngitis)	01JUN2019 (137)/ 05JUN2019 (141)	5	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
	[redacted]	Asian/ Female	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ Common cold	20DEC2018 (31)/ 27DEC2018 (38)	8	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ Catheter related blood stream infection	25DEC2018 (36)/ 16JAN2019 (58)	23	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Female	[redacted]	代謝および栄養障害/ 高トリグリセリド血症/ Hypertriglyceridemia	01JAN2019 (43)/ 08JAN2019 (50)	8	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 胃腸炎/ Gastroenteritis	07JAN2019 (49)/ 16JAN2019 (58)	10	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 発疹/ eruption	28FEB2019 (101)/ 06MAR2019 (107)	7	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 歯肉炎/ Gingivitis	25MAR2019 (126)/ 27MAR2019 (128)	3	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腸炎/ Enterocolitis	04APR2019 (136)/ 12APR2019 (144)	9	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Female	[redacted]	製品の問題/ 医療機器損傷/ Cathetel damage	27MAY2019 (189)/ 27MAY2019 (189)	1	No/ Mild/ Not Related	No	Not Applicable/ Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 齲歯/ Dental caries	04JUN2019 (197)/ Ongoing		No/ Mild/ Not Related	No	Not Applicable/ None	Continuous/ Not Recovered/ Not Resolved	Yes
Infants (4 - <12 months)	[redacted]	Asian/ Female	[redacted] / 10.8	感染症および寄生虫症/ 医療機器関連感染/ Catheter related blood stream infection	10APR2019 (43)/ 24APR2019 (57)	15	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ Catheter related blood stream infection	28APR2019 (61)/ 09JUN2019 (103)	43	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants (4 - <12 months)	[redacted]	Asian/ Female	[redacted]/ 10.8	一般・全身障害および投与部位の状態/ 発熱/ Fever	05JUL2019 (129)/ 14JUL2019 (138)	10	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ Fever	31AUG2019 (186)/ 04SEP2019 (190)	5	Yes/ Moderate/ Not Related	No	Not Applicable/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
	[redacted]	Asian/ Male	[redacted]/ 9.1	胃腸障害/ 腸炎/ Enterocolitis	20JUL2019 (12)/ 26JUL2019 (18)	7	No/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 中耳炎/ Otitis media	29JUL2019 (21)/ 05AUG2019 (28)	8	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				傷害、中毒および処置合併症/ ワクチン接種合併症/ Fever by vaccination	05AUG2019 (28)/ 06AUG2019 (29)	2	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants (4 - <12 months)	[redacted]	Asian/ Male	[redacted]/ 9.1	皮膚および皮下組織障害/ おむつ皮膚炎/ Diaper rash	12AUG2019 (35)/ 20AUG2019 (43)	9	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ Common cold	07SEP2019 (61)/ 10SEP2019 (64)	4	No/ Mild/ Not Related	No	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				呼吸器、胸郭および縦隔障害/ 上気道の炎症/ Upper respiratory inflammation	14SEP2019 (68)/ 17SEP2019 (71)	4	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				呼吸器、胸郭および縦隔障害/ 上気道の炎症/ Upper respiratory inflammation	20SEP2019 (74)/ 29SEP2019 (83)	10	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 接触皮膚炎/ Contact dermatitis	21OCT2019 (105)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants (4 - <12 months)	[redacted]	Asian/ Male	[redacted]/ 9.1	呼吸器、胸郭および縦隔障害/ 上気道の炎症/ Upper respiratory inflammation	21OCT2019 (105)/ 29OCT2019 (113)	9	Yes/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 上気道感染/ Upper respiratory infection	01NOV2019 (116)/ 08NOV2019 (123)	8	Yes/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ おむつ皮膚炎/ Diaper rash	05NOV2019 (120)/ 19NOV2019 (134)	15	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ High fever	09NOV2019 (124)/ 25NOV2019 (140)	17	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ High fever	28NOV2019 (143)/ 17DEC2019 (162)	20	Yes/ Moderate/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants (4 - <12 months)	[redacted]	Asian/ Male	[redacted]/ 9.1	皮膚および皮下組織障害/ 皮膚乾燥/ Dry skin	14DEC2019 (159)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ 上気道感染/ Upper respiratory infection	10JAN2020 (186)/ 13JAN2020 (189)	4	Yes/ Mild/ Not Related	No	Not Applicable/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
Note: Study Day is calculated relative to the date of first study drug administration.

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Male	4[redacted]	感染症および寄生虫症/ 上咽頭炎/ COMMON COLD	05FEB2019 (1252)/ 09FEB2019 (1256)	5	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					腎および尿路障害/ 血尿/ HEMATURIA	09MAY2019 (1345)/ 23MAY2019 (1359)	15	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 肛門膿瘍/ PERIANAL ABSCESS	07JUL2019 (1404)/ 22AUG2019 (1450)	47	No/ Moderate/ Not Related	Dose Not Changed/ Multiple	Intermittent/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ BLOODSTREAM INFECTION OF CENTRAL VENOUS CATHETER	25DEC2019 (23:30) (1575)/ 15JAN2020 (12:30) (1596)	22	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
[redacted]	TED-C14-004	Asian	Male	3[redacted]	胃腸障害/ 腸炎/ ENTEROCOLITIS	05OCT2018 (1236)/ 23OCT2018 (1254)	19	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					胃腸障害/ 下痢/ DIARRHEA	28DEC2018 (1320)/ 28JAN2019 (1351)	32	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Male	3[redacted]	感染症および寄生虫症/ 上咽頭炎/ COMMON COLD	15JAN2019 (1338)/ 19FEB2019 (1373)	36	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL VENOUS CATHETER RELATED BLOODSTREAM INFECTION	04AUG2019 (1539)/ 10SEP2019 (1576)	38	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					血管障害/ 鎖骨下静脈閉塞/ LEFT SUBCLAVIAN VEIN OBSTRUCTION	08AUG2019 (1543)/ Ongoing		Yes/ Severe/ Not Related	Dose Not Changed/ Non-Drug Treatment Given	Intermittent/ Recovering/ Resolving	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL VENOUSCATHETER RELATED BLOODSTREAM INFECTION	06JAN2020 (1694)/ Ongoing		Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Female	4[redacted]	筋骨格系および結合組織障害/ 関節痛/ ARTHRAGIA	06JUN2019 (1551)/ Ongoing		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Not Recovered/ Not Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	22JUN2019 (20:30) (1567)/ 09JUL2019 (1584)	18	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					一般・全身障害および投与部位の状態/ カテーテル留置部位疼痛/ SPONTANEOUS PAIN AT CV PORT SITE	16JUL2019 (1591)/ 01AUG2019 (1607)	17	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	24SEP2019 (1661)/ 16OCT2019 (1683)	23	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	09NOV2019 (1707)/ 04DEC2019 (1732)	26	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Female	4[redacted]	皮膚および皮下組織障害/ 発疹/ RASH	28NOV2019 (1726)/ 04DEC2019 (1732)	7	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					一般・全身障害および投与部位の状態/ カテーテル留置部位疼痛/ SPONTANEOUS PAIN AT CV PORT SITE	03DEC2019 (1731)/ 12DEC2019 (1740)	10	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
[redacted]	TED-C14-004	Asian	Male	4[redacted]	感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	09SEP2018 (1265)/ 28SEP2018 (1284)	20	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					耳および迷路障害/ 耳鳴/ TINNITUS	22OCT2018 (1308)/ Ongoing		No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
					胃腸障害/ 腸炎/ ENTEROCOLITIS	05JAN2019 (1383)/ 07JAN2019 (1385)	3	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Male	4[redacted]	胃腸障害/ 小腸炎/ ACUTE ENTERITIS	29JAN2019 (1407)/ 07FEB2019 (1416)	10	Yes/ Severe/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					神経系障害/ 頭痛/ HEADACHE	30JAN2019 (1408)/ 11FEB2019 (1420)	13	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					眼障害/ 眼乾燥/ DRY EYE	01FEB2019 (1410)/ Ongoing		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Not Recovered/ Not Resolved	Yes
					感染症および寄生虫症/ 上気道感染/ UPPER RESPIRATORY TRACT INFECTION	01MAR2019 (1438)/ 12APR2019 (1480)	43	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ インフルエンザ/ INFULUENZA	15MAY2019 (1513)/ 30MAY2019 (1528)	16	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					神経系障害/ 頭痛/ HEADACHE	23JUL2019 (1582)/ 10AUG2019 (1600)	19	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Male	4[redacted]	感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	23JUL2019 (00:00) (1582)/ 09AUG2019 (1599)	18	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					胃腸障害/ 肛門びらん/ ANAL SKIN EROSION	24JUL2019 (1583)/ 09AUG2019 (1599)	17	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					神経系障害/ 頭痛/ HEADACHE	27AUG2019 (1617)/ 13SEP2019 (1634)	18	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOOD STREAM INFECTION	27AUG2019 (1617)/ 26SEP2019 (1647)	31	Yes/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 口腔ヘルペス/ ORAL HERPES	13DEC2019 (1725)/ 19DEC2019 (1731)	7	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	TED-C14-004	Asian	Male	4[redacted]	呼吸器、胸郭および縦隔障害/ 喘息/ BRONCHIAL ASTHMA	05JAN2020 (1748)/ 21JAN2020 (1764)	17	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
[redacted]	SHP633-306	Asian	Female	4[redacted]	胃腸障害/ 腹部膨満/ ADBMINAL BLOATING	31MAY2019 (10:30) (172)/ 27JUN2019 (14:00) (199)	28	No/ Mild/ Not Related	Not Applicable/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					一般・全身障害および投与部位の状態/ 発熱/ FEVER	01JUN2019 (13:00) (173)/ 27JUN2019 (14:00) (199)	27	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 肛門膿瘍/ PERIANAL ABSESS	15AUG2019 (248)/ 05OCT2019 (299)	52	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					皮膚および皮下組織障害/ 接触皮膚炎/ CONTACT DERMATITIS	16OCT2019 (310)/ 14NOV2019 (339)	30	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					代謝および栄養障害/ セレニウム欠乏/ HYPOSELENEMIA	12DEC2019 (367)/ Ongoing		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	SHP633-306	Asian	Female	4[redacted]	肝胆道系障害/ 胆嚢炎/ CHOLECYSTITIS	31JUL2019 (21:00) (233)/ 19SEP2019 (13:00) (283)	51	Yes/ Moderate/ Not Related	Drug Interrupted/ Multiple	Continuous/ Recovered/ Resolved	Yes
					感染症および寄生虫症/ 医療機器関連感染/ BLOODSTREAM INFECTION OF CENTRAL VENOUS CATHETER	09AUG2019 (242)/ 22AUG2019 (255)	14	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
[redacted]	SHP633-306	Asian	Male	2[redacted]	神経系障害/ てんかん/ EPILEPSY SEIZURE	24MAY2019 (03:57) (165)/ 25MAY2019 (166)	2	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
					神経系障害/ 傾眠/ SLEEPINESS	02JUL2019 (204)/ Ongoing		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/ Not Resolved	Yes
					製品の問題/ 医療機器破損/ BREAKAGE OF CENTRAL VENOUS CATHER	09SEP2019 (273)/ 11SEP2019 (275)	3	Yes/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

Site ID - Subject ID	Core Study	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	SHP633-306	Asian	Male	2[redacted]	皮膚および皮下組織障害/ 皮下出血/ SUBCUTANEOUS BLEEDING	21NOV2019 (346)/ Ongoing		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Not Recovered/ Not Resolved	Yes
					感染症および寄生虫症/ インフルエンザ/ INFLUENZA VIRUS INFECTION	28DEC2019 (383)/ 01JAN2020 (387)	5	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
					腎および尿路障害/ 血尿/ HEMATURIA	30JAN2020 (416)/ Ongoing		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment Given	Continuous/ Not Recovered/ Not Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRF.
Note: Study day is calculated relative to the date of first study drug administration in core study.
<SHIRE¥TEDUGLUTIDE¥UYA25607¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_4_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <28MAY2020>

中間解析

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害/ 嘔吐/ VOMIT*	2018-10-17(23)/ 2018-10-17(23)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		代謝および栄養障害/ 食欲減退/ LOSS OF APPETITE*	2018-10-17(23)/ 2018-10-17(23)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		臨床検査/ アラニンアミノトランスフェラーゼ増加/ ELEVATED ALT RESULT*	2018-11-13(50)/ 2018-11-19(56)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	皮膚および皮下組織障害/ おむつ皮膚炎/ NAPPY RASH*	2018-11-25(62)/ 2018-12-07(74)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		臨床検査/ 血清フェリチン減少/ LOW FERRITIN LEVEL*	2018-11-28(65)/ ONGOING	CONTINUOUS/ MODERATE/ RECOVERING/RESOLVING	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N

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Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	血液およびリンパ系障害/ 貧血/ ANAEMIA*	2018-11-30(67)/ 2018-11-30(67)	CONTINUOUS/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N
		感染症および寄生虫症/ ノロウイルス性胃腸炎/ GASTROENTERITIS NOROVIRUS*	2018-12-01(68)/ 2018-12-02(69)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害/ 腹部不快感/ ABDOMINAL DISCOMFORT*	2018-12-07(74)/ 2018-12-09(76)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		傷害、中毒および処置合併症/ 口唇損傷/ CUT LIP*	2018-12-16(83)/ 2018-12-16(83)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害/ 変色便/ BLACK STOOLS*	2018-12-16(83)/ 2018-12-17(84)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		皮膚および皮下組織障害/ おむつ皮膚炎/ WORSENING NAPPY RASH*	2019-01-16(114)/ 2019-01-18(116)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害/ 排便回数増加/ INCREASED STOOL OUTPUT (FREQUENCY)*	2019-01-16(114)/ 2019-02-05(134)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	精神障害/ 睡眠障害/ INTERRUPTED SLEEP*	2019-01-16(114)/ 2019-02-13(142)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		代謝および栄養障害/ 食欲減退/ DECREASED APPETITE*	2019-01-20(118)/ 2019-02-07(136)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	呼吸器、胸郭および縦隔障害/ 鼻漏/ RHINORRHEA*	2019-01-27(125)/ 2019-02-21(150)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害/ 腹部不快感/ ABDOMINAL DISCOMFORT*	2019-02-12(141)/ 2019-02-13(142)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	臨床検査/ アラニンアミノトランスフェラーゼ増加 / RAISED ALT*	2019-02-12(141)/ 2019-03-12(169)	CONTINUOUS/ MODERATE/ RECOVERED/RESOLVED	RELATED/ N	DOSE NOT CHANGED/ NONE	N
		製品の問題/ 医療機器機能不良/ HOLE IN CENTRAL LINE*	2019-03-14(171)/ 2019-03-15(172)	INTERMITTENT/ SEVERE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害/ 下痢/ VERY WATERY AND SMELLY STOOLS*	2019-03-20(177)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		感染症および寄生虫症/ 上気道感染/ UPPER RESPIRATORY TRACT INFECTION*	2019-03-26(183)/ 2019-03-28(185)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ UNKNOWN	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	胃腸障害/ 消化管運動障害/ VOMITING SECONDARY TO DYSMOTILITY	2019-07-16(-7)/ 2019-07-19(-4)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	Y/HOSP
		感染症および寄生虫症/ 上咽頭炎/ COMMON COLD*	2019-09-24(64)/ 2019-09-26(66)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		製品の問題/ 医療機器閉塞/ BLOCKED HICKMAN LINE*	2019-10-01(71)/ 2019-10-02(72)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	製品の問題/ 医療機器破損/ BROKEN HICKMAN LINE*	2019-10-03(73)/ 2019-10-03(73)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N
		胃腸障害/ 嘔吐/ INTERMITTENT VOMITING*	2019-10-03(73)/ 2019-11-12(113)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	一般・全身障害および投与部位の状態/ 発熱/ PYREXIA*	2019-10-06(76)/ 2019-10-15(85)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	感染症および寄生虫症/ ウイルス感染/ VIRAL ILLNESS*	2019-04-17(3)/ 2019-04-19(5)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		感染症および寄生虫症/ 医療機器関連感染/ CENTRAL LINE INFECTION*	2019-05-01(17)/ 2019-05-05(21)	INTERMITTENT/ SEVERE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP
		感染症および寄生虫症/ 上気道感染/ UPPER RESPIRITORY TRACT INFECTION*	2019-05-20(36)/ 2019-05-30(46)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ UNKNOWN	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　28APR2020 16:12

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	胃腸障害/ 生歯/ TEETHING*	2019-05-21(37)/ 2019-05-21(37)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N
		胃腸障害/ 生歯/ TEETHING*	2019-05-27(43)/ ONGOING	CONTINUOUS/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2019-interim¥report¥tables¥t-lst-sae.sas　　28APR2020 16:12

最終解析

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害／ 嘔吐／ VOMIT*	2018-10-17(23)/ 2018-10-17(23)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		代謝および栄養障害／ 食欲減退／ LOSS OF APPETITE*	2018-10-17(23)/ 2018-10-17(23)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		臨床検査／ アラニンアミノトランスフェラーゼ増加／ ELEVATED ALT RESULT*	2018-11-13(50)/ 2018-11-19(56)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	皮膚および皮下組織障害／ おむつ皮膚炎／ NAPPY RASH*	2018-11-25(62)/ 2018-12-07(74)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		臨床検査／ 血清フェリチン減少／ LOW FERRITIN LEVEL*	2018-11-28(65)/ ONGOING	CONTINUOUS/ MODERATE/ RECOVERING/RESOLVING	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	血液およびリンパ系障害／ 貧血／ ANAEMIA*	2018-11-30(67)/ 2018-11-30(67)	CONTINUOUS/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N
		感染症および寄生虫症／ ノロウイルス性胃腸炎／ GASTROENTERITIS NOROVIRUS*	2018-12-01(68)/ 2018-12-02(69)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害／ 腹部不快感／ ABDOMINAL DISCOMFORT*	2018-12-07(74)/ 2018-12-09(76)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		傷害、中毒および処置合併症／ 口唇損傷／ CUT LIP*	2018-12-16(83)/ 2018-12-16(83)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害／ 変色便／ BLACK STOOLS*	2018-12-16(83)/ 2018-12-17(84)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		皮膚および皮下組織障害／ おむつ皮膚炎／ WORSENING NAPPY RASH*	2019-01-16(114)/ 2019-01-18(116)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害／ 排便回数増加／ INCREASED STOOL OUTPUT (FREQUENCY)*	2019-01-16(114)/ 2019-02-05(134)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	精神障害／ 睡眠障害／ INTERRUPTED SLEEP*	2019-01-16(114)/ 2019-02-13(142)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		代謝および栄養障害／ 食欲減退／ DECREASED APPETITE*	2019-01-20(118)/ 2019-02-07(136)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	呼吸器、胸郭および縦隔障害／ 鼻漏／ RHINORRHEA*	2019-01-27(125)/ 2019-02-21(150)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 腹部不快感／ ABDOMINAL DISCOMFORT*	2019-02-12(141)/ 2019-02-13(142)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	臨床検査／ アラニンアミノトランスフェラーゼ増加／ RAISED ALT*	2019-02-12(141)/ 2019-03-12(169)	CONTINUOUS/ MODERATE/ RECOVERED/RESOLVED	RELATED/ N	DOSE NOT CHANGED/ NONE	N
		製品の問題／ 医療機器破損／ RUPTURED CENTRAL LINE*	2019-03-14(171)/ 2019-03-15(172)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/[redacted]/ WHITE	胃腸障害／ 下痢／ VERY WATERY AND SMELLY STOOLS*	2019-03-20(177)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		感染症および寄生虫症／ 上気道感染／ UPPER RESPIRATORY TRACT INFECTION*	2019-03-26(183)/ 2019-03-28(185)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ UNKNOWN	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIAN	一般・全身障害および投与部位の状態／発熱／PYREXIA*	2020-03-19(18)/ 2020-03-20(19)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／嘔吐／INCREASED VOMITING*	2020-03-25(24)/ 2020-04-07(37)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		胃腸障害／レッチング／RETCHING*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 嘔吐／ VOMITING IN THE MORNING*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		代謝および栄養障害／ 過小食／ REDUCED ORAL INTAKE*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 下痢／ DIARRHOEA*	2020-03-30(29)/ 2020-04-06(36)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED WITH SEQUELAE	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 粘液便／ MUCUS IN STOOLS*	2020-03-30(29)/ 2020-04-14(44)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 下痢／ WATERY STOOLS*	2020-04-06(36)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-04-08(38)/ 2020-04-14(44)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		胃腸障害／ 排便回数増加／ INCREASED STOOL FREQUENCY*	2020-04-08(38)/ 2020-04-20(50)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 異常便／ NONE SPECIFIC ABNORMAL FINDINGS IN STOOL*	2020-04-14(44)/ 2020-04-20(50)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-04-22(52)/ 2020-04-29(59)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		一般・全身障害および投与部位の状態／ 分泌物分泌／ MUCUS IN VOMIT*	2020-04-24(54)/ 2020-05-04(64)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 嘔吐／ INCREASED VOMITING*	2020-04-27(57)/ 2020-05-04(64)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 嘔吐／ BILE STAINED VOMITING*	2020-05-12(72)/ 2020-06-05(96)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 胃腸音異常／ INCREASED BOWEL SOUNDS*	2020-05-12(72)/ 2020-09-24(207)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	精神障害／ 易刺激性／ IRRITABILITY*	2020-05-12(72)/ 2020-09-24(207)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N
		胃腸障害／ 嘔吐／ INCREASED VOMITING*	2020-05-26(86)/ 2020-06-05(96)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ Y	DRUG WITHDRAWN/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	臨床検査／ 便量増加／ INCREASED STOOL VOLUME*	2020-06-05(96)/ 2020-07-14(135)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	RELATED/ Y	DRUG WITHDRAWN/ NONE	N
		胃腸障害／ 鼓腸／ GASEOUS FLATULENCE*	2020-07(-)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ASIA N	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-07(-)/ 2020-09(-)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N
		製品の問題／ 医療機器リーク／ LEAKING CENTRAL VENOUS LINE*	2020-09-04(187)/ 2020-09-05(188)	INTERMITTENT/ SEVERE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	胃腸障害／ 消化管運動障害／ VOMITING SECONDARY TO DYSMOTILITY	2019-07-16(-7)/ 2019-07-19(-4)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	Y/HOSP
		感染症および寄生虫症／ 上咽頭炎／ COMMON COLD*	2019-09-24(64)/ 2019-09-26(66)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		製品の問題／ 医療機器閉塞／ BLOCKED HICKMAN LINE*	2019-10-01(71)/ 2019-10-02(72)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	製品の問題／ 医療機器破損／ BROKEN HICKMAN LINE*	2019-10-03(73)/ 2019-10-03(73)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NON-DRUG TREATMENT	N
		胃腸障害／ 嘔吐／ INTERMITTENT VOMITING*	2019-10-03(73)/ 2019-11-12(113)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	一般・全身障害および投与部位の状態／ 発熱／ PYREXIA*	2019-10-06(76)/ 2019-10-15(85)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP
		胃腸障害／ 嘔吐／ 2 X VOMIT*	2019-12-21(152)/ 2019-12-21(152)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	呼吸器、胸郭および縦隔障害／咳嗽／COUGH*	2019-12-31(162)/ 2020-01-08(170)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		一般・全身障害および投与部位の状態／発熱／PYREXIA*	2020-01-21(183)/ 2020-01-24(186)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
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Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	感染症および寄生虫症／ 医療機器使用部位感染／ LINE SITE SKIN INFECTION*	2019-12-22(6)/ 2020-05-30(166)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		皮膚および皮下組織障害／ 湿疹／ ECZEMA*	2020-01-08(23)/ 2020-03-19(94)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		感染症および寄生虫症／ 上咽頭炎／ COMMON COLD*	2020-02-04(50)/ 2020-02-07(53)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	免疫系障害／ 免疫反応／ FEVER SECONDARY TO IMMUNIZATIONS ON RESULT OF NEGATIVE BLOOD CULTURES*	2020-05-31(167)/ 2020-06-02(169)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	感染症および寄生虫症／ ウイルス感染／ VIRAL ILLNESS*	2019-04-17(3)/ 2019-04-19(5)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		感染症および寄生虫症／ 医療機器関連感染／ CENTRAL LINE INFECTION*	2019-05-01(17)/ 2019-05-05(21)	INTERMITTENT/ SEVERE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP
		感染症および寄生虫症／ 上気道感染／ UPPER RESPIRITORY TRACT INFECTION*	2019-05-20(36)/ 2019-05-30(46)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ UNKNOWN	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/[redacted]/ WHITE	胃腸障害／ 生歯／ TEETHING*	2019-05-21(37)/ 2019-05-21(37)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N
		胃腸障害／ 生歯／ TEETHING*	2019-05-27(43)/ ONGOING	CONTINUOUS/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ WHITE	製品の問題／ 医療機器破損／ CV-CATHETER BROKEN*	2019-10-14(15)/ 2019-10-14(15)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NON-DRUG TREATMENT	N
		傷害、中毒および処置合併症／ 挫傷／ FACIAL BRUISING*	2019-11-05(37)/ 2019-11-07(39)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		臨床検査／ トランスアミナーゼ上昇／ ELEVATED TRANSAMINASIS*	2019-12-27(89)/ 2020-01-01(94)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ UNKNOWN	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	M/1[redacted]/ WHITE	臨床検査／ トランスアミナーゼ上昇／ ELEVATED TRANSAMINASIS*	2020-01-02(95)/ 2020-03-15(168)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	Y/MEDIMP
		臨床検査／ トランスアミナーゼ上昇／ ELEVATED LIVER TRANSAMINASIS*	2020-03-16(169)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/1[redacted]/ WHITE	胃腸障害／ 下痢/ DIARRHOEA	2019-12-01(-3)/ 2019-12-02(-2)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N
		製品の問題／ 医療機器閉塞／ BLOCKED CENTRAL LINE*	2019-12-17(14)/ 2019-12-18(15)	CONTINUOUS/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP
		胃腸障害／ 便秘／ CONSTIPATION*	2020-01(-)/ 2020-01(-)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
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Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/1[redacted]/ WHITE	感染症および寄生虫症／ 医療機器関連感染／ HOSPITALISATION FOR INFECTED BROVIAC LINE (CITROBACTER FREUNDII)*	2020-01-18(46)/ 2020-01-20(48)	CONTINUOUS/ SEVERE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/1[redacted]/ WHITE	感染症および寄生虫症／ 手足口病／ HAND, FOOT AND MOUTH DISEASE*	2020-02-11(70)/ 2020-02-18(77)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment: Standard of Care

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/ Reason
[redacted]	F/1[redacted]/ WHITE	代謝および栄養障害／ 代謝性アシドーシス／ D LACTIC ACIDOSIS*	2020-05-29(178)/ 2020-06-10(190)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP
		神経系障害／ 運動失調／ ATAXIA*	2020-05-29(178)/ 2020-06-10(190)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Adverse events were classified into system organ class and preferred term using version 21.0 of MedDRA.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-sae.sas　11NOV2020 10:52

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	Black	Placebo	Male	2[redacted]	耳痛	38	76	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						顎の骨折	38	.	Not Related	Moderate	Serious	None	Recovering/Resolving
						擦過傷	38	76	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						挫傷	38	6	Not Related	Moderate	Not Serious	None	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	5[redacted]	クローン病	36	10	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	3[redacted]	腹部膿瘍	8	6	Not Related	Moderate	Serious	Dose Interrupted	Recovered/Resolved
						尿路感染	29	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腸管皮膚瘻	48	13	Not Related	Moderate	Serious	Dose Interrupted	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	5[redacted]	注射部位紅斑	1	36	Related	Mild	Not Serious	None	Recovered/Resolved
						クローン病	49	8	Not Related	Severe	Serious	Dose Interrupted	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	尿路感染	1	52	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位反応	2	15	Related	Moderate	Not Serious	None	Recovered/Resolved
						便秘	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-17-ae-sae-600008.sas

Output Generated On: 22OCT2016 2:55

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	悪心	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved
						腹痛	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved
						浮動性めまい	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved
						無力症	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved
						嘔吐	52	5	Not Related	Severe	Not Serious	None	Recovered/Resolved
						頻脈	56	5	Not Related	Mild	Not Serious	None	Recovered/Resolved
						小腸閉塞	56	9	Not Related	Severe	Serious	None	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	アラニン・アミノトランスフェラーゼ増加	-16	17	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						浮動性めまい	1	3	Not Related	Severe	Not Serious	None	Recovered/Resolved
						腹部不快感	1	2	Related	Moderate	Not Serious	None	Recovered/Resolved
						腹痛	1	9	Related	Severe	Not Serious	None	Recovered/Resolved
						消化不良	2	3	Related	Mild	Not Serious	None	Recovered/Resolved
						便秘	7	2	Not Related	Severe	Serious	Dose Interrupted	Recovered/Resolved
						腹部不快感	10	32	Related	Mild	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-17-ae-sae-600008.sas

Output Generated On: 22OCT2016 2:55

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	痔瘻	15	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						消化不良	16	1	Related	Moderate	Not Serious	None	Recovered/Resolved
						腹部圧痛	56	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						悪心	56	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						腹痛	56	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
						下腹部痛	56	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	腹部圧痛	1	64	Not Related	Mild	Not Serious	None	Recovered/Resolved
						上腹部痛	1	.	Related	Moderate	Not Serious	None	Recovering/Resolving
						カンジダ症	4	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						悪心	7	.	Related	Moderate	Not Serious	None	Recovering/Resolving
						本態性血小板血症	22	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						クローン病	22	7	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						尿路感染	22	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腹部圧痛	41	24	Not Related	Mild	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-17-ae-sae-600008.sas

Output Generated On: 22OCT2016 2:55

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	急性熱性好中球性皮膚症	64	2	Not Related	Severe	Serious	None	Recovered/Resolved
						クローン病	71	8	Not Related	Severe	Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	3[redacted]	低カリウム血症	1	2	Not Related	Severe	Not Serious	None	Recovered/Resolved
						腹部膨満	2	4	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						食欲減退	2	4	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	2	3	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						低カリウム血症	3	2	Not Related	Severe	Serious	None	Recovered/Resolved
						低カリウム血症	5	7	Not Related	Moderate	Not Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Male	2[redacted]	白血球減少症	-21	70	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						悪心	19	10	Related	Moderate	Not Serious	None	Recovered/Resolved
						頭痛	19	10	Related	Moderate	Not Serious	None	Recovered/Resolved
						背部痛	20	5	Not Related	Mild	Not Serious	None	Recovered/Resolved
						排便回数増加	20	80	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						クローン病	28	14	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-17-ae-sae-600008.sas

Output Generated On: 22OCT2016 2:55

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Male	4[redacted]	注射部位不快感	2	11	Not Related	Mild	Not Serious	None	Recovered/Resolved
						栄養障害	13	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						肛門狭窄	13	1	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						直腸周囲膿瘍	13	7	Not Related	Moderate	Serious	Drug Withdrawn	Recovered/Resolved
						血中アミラーゼ増加	36	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						リパーゼ増加	36	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
Placebo	[redacted]	White	Placebo	Male	4[redacted]	腹痛	6	4	Not Related	Severe	Serious	None	Recovered/Resolved
						腹痛	11	7	Not Related	Severe	Serious	None	Recovered/Resolved
						腹痛	383	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	4[redacted]	異物による損傷	-1	85	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	4[redacted]	眼精疲労	34	97	Related	Moderate	Not Serious	None	Recovered/Resolved
						流涙増加	34	97	Related	Moderate	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-18-ae-sae-600009.sas

Output Generated On: 21OCT2016 0:54

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	4[redacted]	塞栓症	109	6	Not Related	Severe	Serious	None	Recovered/Resolved
						青趾症候群	109	87	Not Related	Severe	Not Serious	None	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	3[redacted]	注射部位出血	1	54	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位刺激感	1	54	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位疼痛	9	46	Related	Moderate	Not Serious	None	Recovered/Resolved
						関節痛	12	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	13	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						錯感覚	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						末梢性浮腫	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						末梢性浮腫	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						錯感覚	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						背部痛	51	4	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						大球性貧血	54	.	Not Related	Mild	Not Serious	None	Recovering/Resolving

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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-18-ae-sae-600009.sas

Output Generated On: 21OCT2016 0:54

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	3[redacted]	腹痛	54	4	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						背部痛	54	4	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						悪心	54	4	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	5[redacted]	失神	35	2	Not Related	Moderate	Serious	Dose Interrupted	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	5[redacted]	基底細胞癌	2	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						基底細胞癌	2	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						胃腸異形成	14	83	Not Related	Mild	Serious	Drug Withdrawn	Recovered/Resolved
						心電図異常	23	56	Not Related	Mild	Not Serious	None	Recovered/Resolved
						丘疹	23	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						血中ブドウ糖増加	23	19	Not Related	Mild	Not Serious	None	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Black	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	腹痛	7	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
						小腸閉塞	42	14	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						異物による損傷	43	1	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved

Continued next page

* Age at study informed consent date.
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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-18-ae-sae-600009.sas

Output Generated On: 21OCT2016 0:54

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Black	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	瘻孔	43	1	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Female	7[redacted]	心房細動	7	4	Not Related	Moderate	Serious	None	Recovered/Resolved
						クローン病	29	29	Related	Moderate	Not Serious	None	Recovered/Resolved
						末梢性浮腫	34	5	Not Related	Mild	Not Serious	None	Recovered/Resolved
						尿路感染	81	5	Not Related	Mild	Not Serious	None	Recovered/Resolved
						クローン病	103	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	4[redacted]	排便痛	20	4	Not Related	Severe	Not Serious	None	Recovered/Resolved
						失見当識	21	4	Not Related	Severe	Not Serious	None	Recovered/Resolved
						眼痛	21	32	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						下痢	24	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						脱水	24	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						クローン病	75	25	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						脱水	75	25	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved

Continued next page

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Note: All adverse events were coded using MedDRA version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-18-ae-sae-600009.sas

Output Generated On: 21OCT2016 0:54

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	6[redacted]	腹部不快感	6	98	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						背部痛	10	14	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						四肢痛	16	5	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						末梢性浮腫	16	5	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						背部痛	24	82	Not Related	Mild	Not Serious	None	Recovered/Resolved
						背部痛	24	81	Not Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	43	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						胆嚢障害	73	32	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						胆嚢炎	104	2	Not Related	Severe	Serious	None	Recovered/Resolved
						胆管炎	104	2	Not Related	Severe	Serious	None	Recovered/Resolved

* Age at study informed consent date.
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Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-3-18-ae-sae-600009.sas

Output Generated On: 21OCT2016 0:54

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants	[redacted]	Asian/ Female	1[redacted]/ 10.8	皮膚および皮下組織障害/ おむつ皮膚炎/ DIAPER RASH	14SEP2019 (-10)/ 30SEP2019 (7)	17	No/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 口腔カンジダ症/ ORAL CANDIDIASIS	17SEP2019 (-7)/ 17SEP2019 (-7)	1	No/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 皮膚炎/ DERMATITIS	21NOV2019 (59)/ 19DEC2019 (87)	29	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
Note: Age: chronological age and corrected gestational age at informed consent/assent of SHP633-302 study are presented. Chronological age in month are presented as actual age for subjects in Infant cohort, chronological age in year are presented as actual age for subjects in Children cohort.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants	[redacted]	Asian/ Female	1[redacted]/ 10.8	神経系障害/ 痙攣発作/ WORSENING CONVULSION	20DEC2019 (88)/ 24MAR2020 (183)	96	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved With Sequelae	Yes
				胃腸障害/ 急性膵炎/ ACUTE PANCREATITIS	30DEC2019 (98)/ 08MAY2020 (228)	131	Yes/ Severe/ Not Related	- /Grade 4	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				臨床検査/ 血中アルカリホスファターゼ増加/ ALKALINE PHOSPHATASE INCREASED	06JAN2020 (105)/ Ongoing		No/ Moderate/ Not Related	-	Not Applicable/ None	Continuous/ Not Recovered/ Not Resolved	Yes

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Note: Relationship to study treatment is based upon investigator assessment.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants	[redacted]	Asian/ Male	[redacted]/ 9.1	感染症および寄生虫症/ 上気道感染/ UPPER RESPIRATORY INFECTION	21JAN2020 (-7)/ 25JAN2020 (-3)	5	Yes/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ CVC INSERTION SITE INFECTION	03MAR2020 (36)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants	[redacted]	Asian/ Male	[redacted]/ 9.1	一般・全身障害および投与部位の状態/ 注射部位反応/ INJECTION SITE REACTION	28APR2020 (92)/ 07MAY2020 (101)	10	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 上気道感染/ UPPER RESPIRATORY INFECTION	05MAY2020 (99)/ 12MAY2020 (106)	8	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Infants	[redacted]	Asian/ Male	[redacted]/ 9.1	感染症および寄生虫症/ アデノウイルス性胃腸炎/ ADENOVIRUS ENTERITIS	24MAY2020 (118)/ 02JUN2020 (127)	10	Yes/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	06JUN2020 (131)/ 07JUL2020 (162)	32	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
Children	[redacted]	Asian/ Male	[redacted]	眼障害/ 眼脂/ EYE MUCUS	22MAY2019 (8)/ 26JUN2019 (43)	36	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	代謝および栄養障害/ 低亜鉛血症/ HYPOZINCEMIA	12JUN2019 (29)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/ Not Resolved	Yes
				皮膚および皮下組織障害/ 皮下出血/ SUBCUTANEOUS BLEEDING	12JUN2019 (29)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovering/ Resolving	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	12JUN2019 (29)/ 26JUN2019 (43)	15	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	製品の問題/ 医療機器破損/ BREAKAGE OF THE CENTRAL VENOUS CATHEHER	18JUL2019 (65)/ 21JUL2019 (68)	4	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Multiple	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	27AUG2019 (105)/ 31AUG2019 (109)	5	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器破損/ BREAKAGE OF THE CENTRAL VENOUS CATHETER	12SEP2019 (121)/ 15SEP2019 (124)	4	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	筋骨格系および結合組織障害/ 関節腫脹/ LEFT KNEE JOIN EDEMA	16OCT2019 (155)/ 30OCT2019 (169)	15	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ FEVER	28OCT2019 (167)/ 29OCT2019 (168)	2	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器破損/ BREAKAGE OF THE CENTRAL VENOUS CATHETER	14NOV2019 (184)/ 16NOV2019 (186)	3	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Multiple	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	胃腸障害/ 口唇乾燥/ DRY LIPS	15NOV2019 (185)/ 16NOV2019 (186)	2	No/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				臨床検査/ リパーゼ増加/ INCREASED BLOOD LIPASE	27NOV2019 (197)/ Ongoing		No/ Mild/ Not Related	- /Grade 3	Not Applicable/ None	Continuous/ Not Recovered/ Not Resolved	Yes
				皮膚および皮下組織障害/ 皮膚乾燥/ DRY SKIN	22JAN2020 (253)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/ Not Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Relationship to study treatment is based upon investigator assessment.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位疼痛/ PAIN AT THE SITE OF INJECTION	19FEB2020 (281)/ Ongoing		No/ Mild/ Related	-	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
Children	[redacted]	Asian/ Male	[redacted]	傷害、中毒および処置合併症/ 転倒/ FALLING	29JUN2019 (4)/ 29JUN2019 (4)	1	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	皮膚および皮下組織障害/ 皮下出血/ SUBCUTANEOUS BLEEDING(FACE)	29JUN2019 (4)/ 12JUL2019 (17)	14	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器破損/ BREAKAGE OF THE CENTRAL VENOUS CATHEHER	19AUG2019 (55)/ 22AUG2019 (58)	4	Yes/ Moderate/ Not Related	-	Drug Interrupted/ Multiple	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	呼吸器、胸郭および縦隔障害/ 咳嗽/ COUGH	30AUG2019 (66)/ 17SEP2019 (84)	19	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性咽頭炎/ ADENOVIRUS PHARYNGITIS	31OCT2019 (128)/ 03NOV2019 (131)	4	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 小腸炎/ SUSRECTAL ENTERITIS	09NOV2019 (137)/ 18NOV2019 (146)	10	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: System organ classes and preferred terms are coded using MedDRA 20.0.
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	胃腸障害/ 小腸炎/ WORSENING OF ENTERITIS	19NOV2019 (147)/ 27DEC2019 (185)	39	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				臨床検査/ トランスアミナーゼ上昇/ INCREASE TRANSAMINASE	10DEC2019 (168)/ Ongoing		No/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovering/ Resolving	Yes
				胃腸障害/ 小腸炎/ ENTERITIS	27DEC2019 (185)/ 11MAR2020 (260)	76	No/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ β溶血性レンサ球菌感染/ HEMOLYTIC STREPTCOCCAL INFECTION(GROUP A STREPTOCOCCUS)	31JAN2020 (220)/ 08FEB2020 (228)	9	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOODSTREAM INFECTION	25AUG2017 (3)/ 08SEP2017 (17)	15	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Multiple	Continuous/ Recovered/ Resolved	Yes

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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	血液およびリンパ系障害/ 貧血/ ANEMIA	13SEP2017 (22)/ Ongoing		No/ Moderate/ Not Related	-	Dose Not Changed/ None	Continuous/ Not Recovered/ Not Resolved	Yes
				胃腸障害/ 口内炎/ STOMATITIS	04OCT2017 (43)/ 08OCT2017 (47)	5	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 皮膚乾燥/ WHOLE BODY SKIN DRYNESS	25DEC2017 (125)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/ Not Resolved	Yes

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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	皮膚および皮下組織障害/ 蕁麻疹/ URTICARIA DUE TO ENVIRONMENTAL CHANGE	01JAN2018 (132)/ 01JAN2018 (132)	1	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	04FEB2018 (166)/ 07FEB2018 (169)	4	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 蕁麻疹/ URTICARIA DUE TO ENVIRONMENTAL CHANGE	05FEB2018 (167)/ 05FEB2018 (167)	1	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	26FEB2018 (188)/ 27MAR2018 (217)	30	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				免疫系障害/ 食物アレルギー/ BEEF ALLERGY	04APR2018 (225)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	15APR2018 (236)/ 20APR2018 (241)	6	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	代謝および栄養障害/ 低マグネシウム血症/ HYPOMAGNESEMIA	23MAY2018 (274)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	12JUN2018 (294)/ 15JUN2018 (297)	4	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 汗疹/ HEAT RUSH	01AUG2018 (344)/ 04SEP2018 (378)	35	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	臨床検査/ アミラーゼ増加/ SERUM AMYLASE INCREASED	08AUG2018 (351)/ Ongoing		No/ Mild/ Not Related	- /Grade 3	Dose Not Changed/ None	Continuous/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	04SEP2018 (11:30) (378)/ 05SEP2018 (13:00) (379)	2	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器関連感染/ CENTRAL CATHETER RELATED BLOODSTREAM INFECTION	18SEP2018 (392)/ 02OCT2018 (406)	15	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	免疫系障害/ 食物アレルギー/ NUTS ALLERGY	27SEP2018 (401)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
				免疫系障害/ 食物アレルギー/ ORANGE ALLERGY	27SEP2018 (08:30) (401)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	16NOV2018 (451)/ 24NOV2018 (459)	9	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ インフルエンザ/ INFLUENZA	08JAN2019 (504)/ 16JAN2019 (512)	9	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				免疫系障害/ 食物アレルギー/ WALNUT ALLERGY	28FEB2019 (555)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	20APR2019 (606)/ 29APR2019 (615)	10	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ Infected bite/ INFECTED INSECT BITE	20MAY2019 (636)/ 26MAY2019 (642)	7	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMOM COLD	22MAY2019 (638)/ MAY2019		No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	12JUN2019 (659)/ 15JUN2019 (662)	4	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: System organ classes and preferred terms are coded using MedDRA 20.0.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	08JUL2019 (685)/ 07AUG2019 (715)	31	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	13AUG2019 (721)/ 04SEP2019 (743)	23	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	22SEP2019 (761)/ 28SEP2019 (767)	7	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	皮膚および皮下組織障害/ アレルギー性皮膚炎/ ALLERGIC EIZEMA	24SEP2019 (763)/ 26SEP2019 (765)	3	No/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				傷害、中毒および処置合併症/ 角膜損傷/ CORNEAL INJURY	27OCT2019 (796)/ 30OCT2019 (799)	4	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 手足口病/ HAND-FOOT-MOUTH DISEASE	02DEC2019 (832)/ 06DEC2019 (836)	5	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	07DEC2019 (837)/ 08DEC2019 (838)	2	No/ Mild/ Not Related	-	Not Applicable/ None	Intermittent/ Recovered/ Resolved	Yes
				代謝および栄養障害/ 代謝性アシドーシス/ D-LACTIR ACIDOSIS	16DEC2019 (846)/ 19FEB2020 (911)	66	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				傷害、中毒および処置合併症/ 骨折/ FRACTURE	25DEC2019 (855)/ 15JAN2020 (876)	22	No/ Moderate/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 発熱/ FEVER	19JAN2020 (880)/ 05FEB2020 (897)	18	Yes/ Mild/ Not Related	-	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器破損/ CENTRAL CATHERTER BREAKAGE	21JAN2020 (882)/ 22JAN2020 (883)	2	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				代謝および栄養障害/ 脱水/ DEHYDRAITION	18MAR2020 (939)/ 08APR2020 (960)	22	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children*	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	20MAR2020 (941)/ 22APR2020 (974)	34	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				代謝および栄養障害/ 代謝性アシドーシス/ D-LACTIC ACIDOSIS	26MAR2020 (05:13) (947)/ 26MAR2020 (13:00) (947)	1	Yes/ Moderate/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
Children	[redacted]	Asian/ Male	[redacted]	眼障害/ アレルギー性結膜炎/ ALLERGIC RHINOCONJUNCTIVITIS	19FEB2019 (42)/ 30APR2019 (112)	71	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	皮膚および皮下組織障害/ 皮膚びらん/ SKIN EROSION AROUND THE CENTRAL VENOUS CATHETER	20FEB2019 (43)/ 25OCT2019 (290)	248	No/ Mild/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	04MAR2019 (55)/ 13MAR2019 (64)	10	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 胃腸炎/ ACUTE GASTROENTERITIS	08MAR2019 (59)/ 13MAR2019 (64)	6	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	胃腸障害/ 口唇炎/ CHEILITIS	29MAY2019 (141)/ 26JUN2019 (169)	29	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 胃障害/ GASTRIC OUTPUT DISORDER	29MAY2019 (141)/ 11SEP2019 (246)	106	No/ Mild/ Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	13JUN2019 (156)/ 18JUN2019 (161)	6	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	感染症および寄生虫症/ 医療機器使用部位感染/ TUNNEL INFECTION (CENTRAL VENOUS CATHETER)	25JUN2019 (168)/ 03AUG2019 (207)	40	Yes/ Mild/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 口内炎/ MUCOSITIS ORAL	15JUL2019 (188)/ 01AUG2019 (205)	18	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	25JUL2019 (198)/ 07AUG2019 (211)	14	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	肝胆道系障害/ 薬物性肝障害/ DRUG-INDUCED LIVER INJURY	30JUL2019 (203)/ 28AUG2019 (232)	30	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				傷害、中毒および処置合併症/ 創合併症/ WOUND PAIN	02AUG2019 (206)/ 05AUG2019 (209)	4	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				筋骨格系および結合組織障害/ 筋肉痛/ CHEST MUSCLE PAIN	26OCT2019 (291)/ 01NOV2019 (297)	7	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	傷害、中毒および処置合併症 / 胃瘻管部合併症/ SKIN EROSION(AROUND THE GASTROSTOMY)WORSNING	18DEC2019 (344)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Not Recovered/ Not Resolved	Yes
				感染症および寄生虫症/ インフルエンザ/ INFULUENZA INFECTION A	18JAN2020 (375)/ 23JAN2020 (380)	6	No/ Mild/ Not Related	-	Dose Reduced/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	1[redacted]	眼障害/ アレルギー性結膜炎/ ALLERGIC RHINOCONJUNCTIVITIS	05FEB2020 (393)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes
				胃腸障害/ 結腸血腫/ COLORECTAL SUBMUCOSAL HEMATOMA	10FEB2020 (398)/ 21FEB2020 (409)	12	Yes/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 結膜炎/ INFECTIOUS CONJUNCTIVITS	26FEB2020 (414)/ 04MAR2020 (421)	8	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
Note: Study day is calculated relative to the date of first study drug administration in SHP633-302 core study.
<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ アデノウイルス結膜炎/ EPIDEMIC KERATOCONJUNCTIVITIS	09SEP2019 (34)/ 17SEP2019 (42)	9	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 腹痛/ ABDOMINAL PAIN	15SEP2019 (40)/ 18SEP2019 (43)	4	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 発熱/ HIGH FEVER	29SEP2019 (54)/ 30SEP2019 (55)	2	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	07OCT2019 (62)/ 27OCT2019 (82)	21	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				精神障害/ 頭を激しくぶっつける/ HEAD BANGING	19NOV2019 (105)/ 19NOV2019 (105)	1	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器損傷/ DAMAGED CENTRAL VENUS CATHETER	05DEC2019 (121)/ 14DEC2019 (130)	10	Yes/ Mild/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	傷害、中毒および処置合併症/ 創合併症/ WOUND PAIN	09DEC2019 (125)/ 09DEC2019 (125)	1	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				呼吸器、胸郭および縦隔障害/ 咳嗽/ COUGH	09DEC2019 (125)/ 13DEC2019 (129)	5	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				呼吸器、胸郭および縦隔障害/ 鼻漏/ NASAL DISCHARGE	09DEC2019 (125)/ 13DEC2019 (129)	5	No/ Mild/ Not Related	-	Dose Not Changed/ None	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Male	[redacted]	感染症および寄生虫症/ ウイルス性上気道感染/ COMMON COLD	30JAN2020 (177)/ 19FEB2020 (197)	21	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
Children	[redacted]	Asian/ Female	[redacted]	感染症および寄生虫症/ 医療機器関連感染/ CENTRAL VENOUS CATHETER RELATED BLOOD STREAM INFECTION	07JUL2019 (12)/ 15JUL2019 (20)	9	Yes/ Mild/ Not Related	-	Dose Not Changed/ Multiple	Intermittent/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Female	[redacted]	呼吸器、胸郭および縦隔障害/ 喘息/ ASTHMA	12JUL2019 (17)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Intermittent/ Recovering/ Resolving	Yes
				代謝および栄養障害/ 脱水/ DEHYDRATION	16OCT2019 (113)/ 16OCT2019 (113)	1	No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 齲歯/ DENTAL CARIES	10DEC2019 (168)/ 10DEC2019 (168)	1	No/ Mild/ Not Related	-	Dose Not Changed/ Multiple	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Female	[redacted]	胃腸障害/ 腸炎/ ENTEROCOLITIS	11JAN2020 (200)/ 04MAR2020 (253)	54	Yes/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腸炎/ ENTEROCOLITIS	22JAN2020 (211)/ 04MAR2020 (253)	43	Yes/ Mild/ Not Related	-	Not Applicable/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				製品の問題/ 医療機器損傷/ DAMAGE OF GASTROSTOMY DEVICE	06FEB2020 (226)/ 06FEB2020 (226)	1	No/ Mild/ Not Related	-	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
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Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (yr/mo)/ Gestational (mo)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration (day)	Serious AE/ Severity/ Relationship	Dose Interruption Criteria Satisfied/ CTCAE Grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children	[redacted]	Asian/ Female	[redacted]	皮膚および皮下組織障害/ 発疹/ RASH	25MAR2020 (274)/ Ongoing		No/ Mild/ Not Related	-	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/ Not Resolved	Yes

Mo(s)=month(s), yr(s)=year(s).
Note: All the AEs for subjects who had at least one serious adverse event are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. Only AEs recorded in the SHP633-305 eCRF are listed.
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Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Children who began treatment before protocol amendment 2 are marked with an asterisk.
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<SHIRE¥TEDUGLUTIDE¥HYA05069¥BIOSTATISTICS¥PRODUCTION¥TABLES¥IA¥T14_3_2_12_SAE.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <22SEP2020>

付録 3. 治験薬の投与中止に至った有害事象発現症例一覧

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 5 Mg	[redacted]	White	Teduglutide 5 Mg	Male	2[redacted]	鼻咽頭炎	-2	9	Not Related	Mild	Not Serious	None	Recovered/Resolved
						浮動性めまい	1	1	Not Related	Moderate	Not Serious	Discontinued Study	Recovered/Resolved
						間代	1	1	Not Related	Moderate	Not Serious	Discontinued Study	Recovered/Resolved
						蒼白	1	1	Not Related	Moderate	Not Serious	Discontinued Study	Recovered/Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version [redacted].
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-1-ae-discon-162113.sas

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Cohort E - Teduglutide	[redacted]	White	Teduglutide 15 Mg/Dose With Formulation 50 Mg/Ml	Female	4[redacted]	注射部位疼痛	1	2	Related	Mild	Not Serious	None	Recovered/Resolved
						失神	2	1	Related	Moderate	Not Serious	Discontinued Study	Recovered/Resolved
Cohort E - Teduglutide	[redacted]	White	Teduglutide 15 Mg/Dose With Formulation 50 Mg/Ml	Male	2[redacted]	アラニン・アミノトランスフェラーゼ増加	5	19	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
						アスパラギン酸アミノトランスフェラーゼ増加	5	10	Related	Mild	Not Serious	None	Recovered/Resolved
						注射部位出血	14	.	Related	Mild	Not Serious	None	Recovering/Resolving

Notes: Teduglutide Treatment Groups: Cohort A - 20 mg qd sc 20mg/mL formulation; All other cohorts used sc 50 mg/mLformulation at following doses: Cohort AR - 20 mg qd; Cohort C - 25 mg qd; Cohort D - 10 mg qd; Cohort E - 15 mg qd;Cohort F - 30 mg qd; Cohort H - 50 mg qd; Cohort J - 80 mg qd
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 9.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-2-ae-discon-600022.sas　　Output Generated On: 23OCT2016 1:35

Treatment group sequence	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
C-D-B-A	[redacted]	White	Teduglutide 20 mg in 2.0 mL	Female	2[redacted]	鼻咽頭炎	19	19	Unlikely Related	Moderate	Not Serious	Study Discontinued	Recovered/Resolved

Note: A: Teduglutide 5 mg in 0.5 mL, B: Teduglutide 20 mg in 2.0 mL, C: Placebo, D: Moxifloxacin 400 mg
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.1.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-3-ae-discon-09001.sas

Output Generated On: 20OCT2016 23:59

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	Caucasian	Placebo	Female	2[redacted]	注射部位出血	9	4	Related	Mild	Not Serious	None	Resolved
						鼻漏	34	.	Not Related	Mild	Not Serious	None	Resolved
						疲労	42	.	Not Related	Moderate	Not Serious	None	Resolved
						カテーテル敗血症	45	15	Not Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
						カテーテル合併症	46	14	Not Related	Severe	Serious	None	Resolved
						カテーテル敗血症	90	5	Not Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
						カテーテル敗血症	149	20	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	嘔吐	-8	5	Not Related	Mild	Not Serious	None	Resolved
						背部痛	-5	.	Not Related	Mild	Not Serious	None	Resolved
						胸痛	-5	.	Not Related	Mild	Not Serious	None	Resolved
						悪心	2	2	Not Related	Mild	Not Serious	None	Resolved
						白血球数増加	2	8	Not Related	Mild	Not Serious	None	Resolved
						嘔吐	3	.	Not Related	Mild	Not Serious	None	Resolved
						上腹部痛	10	.	Not Related	Moderate	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-6-ae-discon-600004.sas

Output Generated On: 23OCT2016 21:11

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	下腹部痛	10	.	Not Related	Moderate	Not Serious	None	Resolved
						嘔吐	24	1	Not Related	Mild	Not Serious	None	Resolved
						肋骨脊柱角圧痛	26	1	Not Related	Moderate	Not Serious	None	Resolved
						下腹部痛	26	1	Not Related	Moderate	Not Serious	None	Resolved
						下腹部痛	58	1	Not Related	Moderate	Not Serious	None	Resolved
						胸痛	69	1	Not Related	Moderate	Not Serious	None	Resolved
						嘔吐	81	2	Not Related	Severe	Not Serious	None	Resolved
						腹痛	86	5	Not Related	Severe	Not Serious	Study Drug Dose Interrupted	Resolved
						無力症	132	7	Not Related	Moderate	Not Serious	None	Resolved
						短小腸症候群	157	42	Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
						痔核	159	3	Not Related	Moderate	Not Serious	None	Resolved
						痔出血	159	3	Related	Moderate	Serious	Study Drug Discontinued	Resolved
						血中カリウム減少	202	3	Not Related	Mild	Not Serious	None	Resolved
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	発疹	-5	.	Not Related	Moderate	Not Serious	None	Ongoing
						悪心	3	22	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-6-ae-discon-600004.sas

Output Generated On: 23OCT2016 21:11

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	嘔吐	3	22	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						無力症	3	22	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						味覚異常	3	22	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						直腸分泌物	68	.	Not Related	Moderate	Not Serious	None	Ongoing
						鼓腸	68	.	Not Related	Moderate	Not Serious	None	Ongoing
						上腹部痛	68	.	Not Related	Moderate	Not Serious	None	Ongoing
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	浮動性めまい	-37	1	Not Related	Mild	Not Serious	None	Resolved
						便秘	3	59	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						鼻咽頭炎	40	4	Not Related	Mild	Not Serious	None	Resolved
						カテーテル敗血症	52	8	Not Related	Severe	Serious	None	Resolved
						カテーテル敗血症	60	3	Not Related	Moderate	Not Serious	None	Resolved
						カテーテル敗血症	117	11	Not Related	Severe	Serious	None	Resolved
						カテーテル敗血症	173	14	Not Related	Moderate	Serious	None	Resolved
						カテーテル敗血症	194	11	Not Related	Moderate	Serious	None	Resolved
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	6[redacted]	転倒	-11	1	Not Related	Mild	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-6-ae-discon-600004.sas

Output Generated On: 23OCT2016 21:11

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	6[redacted]	薬物濃度増加	.	.	Related	Severe	Serious	Study Drug Discontinued	Resolved
						過眠症	8	3	Related	Severe	Serious	Study Drug Discontinued	Resolved
						昏睡	10	7	Related	Moderate	Serious	Study Drug Discontinued	Resolved
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	手首関節骨折	-27	.	Not Related	Moderate	Not Serious	None	Ongoing
						腹部膨満	3	4	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						便秘	3	4	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
Teduglutide 0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	尿路感染	-34	32	Not Related	Mild	Not Serious	None	Resolved
						子宮頚部スミア異常	85	.	Not Related	Moderate	Not Serious	None	Ongoing
						うっ血性心不全	98	7	Related	Severe	Serious	Study Drug Discontinued	Resolved
Teduglutide 0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	6[redacted]	ウイルス性胃腸炎	-65	27	Not Related	Moderate	Not Serious	None	Resolved
						卵巣嚢胞	-49	.	Not Related	Moderate	Not Serious	None	Ongoing
						膵炎	8	68	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						小腸閉塞	8	3	Related	Severe	Serious	Study Drug Discontinued	Resolved
						インフルエンザ	34	11	Not Related	Moderate	Not Serious	None	Resolved
						咽喉頭疼痛	74	.	Not Related	Moderate	Not Serious	None	Ongoing

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-6-ae-discon-600004.sas

Output Generated On: 23OCT2016 21:11

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	3[redacted]	血中アルカリホスファターゼ増加	-64	99	Not Related	Mild	Not Serious	None	Resolved
						倦怠感	-31	6	Not Related	Moderate	Not Serious	None	Resolved
						下痢	-31	6	Not Related	Moderate	Not Serious	None	Resolved
						吻合部潰瘍	.	.	Not Related	Moderate	Not Serious	None	Ongoing
						小腸狭窄	1	.	Not Related	Moderate	Not Serious	None	Ongoing
						C-反応性蛋白増加	1	36	Not Related	Mild	Not Serious	None	Resolved
						腸管ストーマ合併症	2	63	Related	Mild	Not Serious	None	Resolved
						水様便	23	3	Not Related	Moderate	Not Serious	None	Resolved
						腹痛	23	3	Not Related	Moderate	Not Serious	None	Resolved
						カテーテル敗血症	39	13	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
						カテーテル留置部位出血	47	.	Not Related	Mild	Not Serious	None	Ongoing
						静脈カテーテル留置	61	3	Not Related	Moderate	Serious	None	Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-6-ae-discon-600004.sas

Output Generated On: 23OCT2016 21:11

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Female	4[redacted]	インフルエンザ	-28	8	Not Related	Severe	Not Serious	None	Resolved
						頭痛	2	134	Related	Mild	Not Serious	None	Resolved
						処置後局所反応	5	.	Not Related	Mild	Not Serious	None	Ongoing
						遠視	64	.	Not Related	Mild	Not Serious	None	Ongoing
						眼乾燥	64	.	Not Related	Mild	Not Serious	None	Ongoing
						腸管ポリープ	79	7	Related	Moderate	Not Serious	None	Resolved
						処置後出血	79	7	Not Related	Mild	Not Serious	None	Resolved
						消化管ストーマ合併症	80	.	Related	Moderate	Not Serious	None	Ongoing
						処置後出血	87	74	Related	Severe	Not Serious	None	Resolved
						腸管ポリープ	87	74	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
Placebo	[redacted]	White	Placebo	Male	2[redacted]	鼻咽頭炎	-24	18	Not Related	Mild	Not Serious	None	Resolved
						坐骨神経痛	-22	21	Not Related	Moderate	Not Serious	None	Resolved
						感覚鈍麻	15	12	Not Related	Mild	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-4-ae-discon-600020.sas

Output Generated On: 21OCT2016 0:27

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Male	2[redacted]	直腸分泌物	26	39	Related	Moderate	Not Serious	None	Resolved
						注射部位発疹	26	8	Related	Mild	Not Serious	None	Resolved
						腹痛	36	29	Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	36	36	Related	Moderate	Not Serious	None	Resolved
						悪心	36	29	Related	Moderate	Not Serious	None	Resolved
						頭痛	42	23	Related	Moderate	Not Serious	None	Resolved
						便量増加	42	23	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						疼痛	42	23	Related	Moderate	Not Serious	None	Resolved
						発熱	42	23	Related	Mild	Not Serious	None	Resolved
						体重減少	50	15	Related	Moderate	Not Serious	None	Resolved
						嗜眠	50	15	Related	Moderate	Not Serious	None	Resolved
						中心静脈カテーテル感染	75	3	Not Related	Severe	Serious	None	Resolved
Placebo	[redacted]	White	Placebo	Female	4[redacted]	口渇	-62	35	Not Related	Mild	Not Serious	None	Resolved
						上腹部痛	-42	15	Not Related	Mild	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-4-ae-discon-600020.sas

Output Generated On: 21OCT2016 0:27

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Female	4[redacted]	疲労	-42	15	Not Related	Mild	Not Serious	None	Resolved
						頭痛	-42	15	Not Related	Mild	Not Serious	None	Resolved
						嘔吐	-42	15	Not Related	Mild	Not Serious	None	Resolved
						悪心	-42	15	Not Related	Mild	Not Serious	None	Resolved
						下痢	-31	3	Not Related	Mild	Not Serious	None	Resolved
						口腔咽頭痛	-23	10	Not Related	Mild	Not Serious	None	Resolved
						頭痛	-23	10	Not Related	Mild	Not Serious	None	Resolved
						咳嗽	-23	10	Not Related	Mild	Not Serious	None	Resolved
						鼻咽頭炎	-23	12	Not Related	Mild	Not Serious	None	Resolved
						発熱	-21	8	Not Related	Mild	Not Serious	None	Resolved
						中心静脈カテーテル感染	-16	5	Not Related	Mild	Not Serious	None	Resolved
						嘔吐	-9	1	Not Related	Mild	Not Serious	None	Resolved
						下痢	-9	6	Not Related	Moderate	Not Serious	None	Resolved
						食欲減退	-9	6	Not Related	Mild	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-4-ae-discon-600020.sas

Output Generated On: 21OCT2016 0:27

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Female	4[redacted]	浮動性めまい	-9	6	Not Related	Mild	Not Serious	None	Resolved
						腹痛	-9	6	Not Related	Moderate	Not Serious	None	Resolved
						発熱	-8	2	Not Related	Mild	Not Serious	None	Resolved
						肛門周囲痛	4	26	Not Related	Moderate	Not Serious	None	Resolved
						腹痛	4	21	Related	Moderate	Not Serious	None	Resolved
						排便回数増加	4	21	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						鼓腸	4	21	Related	Moderate	Not Serious	None	Resolved
						筋骨格痛	17	.	Not Related	Moderate	Not Serious	None	Ongoing
						インフルエンザ性肺炎	36	15	Not Related	Severe	Serious	None	Resolved
						副鼻腔炎	36	15	Not Related	Moderate	Not Serious	None	Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	関節痛	-30	5	Not Related	Severe	Serious	None	Resolved
						血中カリウム増加	1	15	Not Related	Mild	Not Serious	None	Resolved
						悪心	1	31	Related	Mild	Not Serious	None	Resolved
						腹痛	1	31	Related	Mild	Not Serious	None	Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-4-ae-discon-600020.sas

Output Generated On: 21OCT2016 0:27

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	消化管ストーマ合併症	5	27	Related	Mild	Not Serious	None	Resolved
						腹部膨満	12	11	Related	Mild	Not Serious	None	Resolved
						腹部膨満	22	10	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						嘔吐	26	3	Related	Mild	Not Serious	None	Resolved
						脱水	32	5	Not Related	Mild	Serious	None	Resolved
						尿路感染	32	5	Not Related	Moderate	Serious	None	Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	0.05 Mg/Kg/Day	Male	3[redacted]	悪心	3	6	Related	Severe	Not Serious	None	Resolved
						腹痛	3	6	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						嘔吐	3	3	Related	Severe	Not Serious	None	Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-4-ae-discon-600020.sas

Output Generated On: 21OCT2016 0:27

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
0.05/0.05	[redacted]	Caucasian	0.05 mg/kg/day	Male	5[redacted]	カテーテル敗血症	11	15	Not Related	Mild	Serious	None	Resolved
						腹痛	29	5	Not Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						カテーテル敗血症	31	7	Not Related	Mild	Serious	None	Resolved
0.05/0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	2[redacted]	頭痛	-1	.	Not Related	Moderate	Not Serious	None	Ongoing
						結腸腺腫	9	5	Not Related	Mild	Serious	Study Drug Discontinued	Resolved
0.05/0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	クローン病	-20	124	Related	Severe		None	Resolved
						腟真菌症	34	23	Not Related	Moderate	Not Serious	None	Resolved
						気管炎	55	24	Not Related	Moderate	Not Serious	None	Resolved
						急性副鼻腔炎	55	24	Not Related	Moderate	Not Serious	None	Resolved
						低アルブミン血症	56	65	Related	Moderate	Not Serious	None	Resolved
						浮腫	65	20	Related	Moderate	Not Serious	None	Resolved
						鉄欠乏性貧血	65	.	Not Related	Moderate	Not Serious	None	Ongoing
						腱炎	81	26	Not Related	Mild	Not Serious	None	Resolved
						炎症性腸疾患	104	.	Related	Moderate	Not Serious	Study Drug Discontinued	Ongoing

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Note: Placebo/0.05: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.05mg/kg/d teduglutide in Study 005
Placebo/0.10: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.10mg/kg/d teduglutide in Study 005
0.05/0.05: Subjects were randomized to 0.05mg/kg/d teduglutide in Study 004 and continued on 0.05mg/kg/d teduglutide in Study 005
0.10/0.10: Subjects were randomized to 0.10mg/kg/d teduglutide in Study 004 and continued on 0.10mg/kg/d teduglutide in Study 005
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-7-ae-discon-600005.sas

Output Generated On: 23OCT2016 21:12

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
0.05/0.05	[redacted]	Caucasian	0.05 mg/kg/day	Female	5[redacted]	カテーテル留置部位浮腫	113	.	Not Related	Moderate	Not Serious	None	Ongoing
0.10/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	5[redacted]	腹部不快感	.	.	Related	Moderate	Not Serious	None	Ongoing
						嘔吐	-3	5	Related	Moderate	Not Serious	None	Resolved
						腹痛	-3	5	Related	Moderate	Not Serious	None	Resolved
						関節捻挫	9	7	Not Related	Moderate	Not Serious	None	Resolved
						胃腸感染	42	7	Related	Moderate	Not Serious	None	Resolved
						腹部不快感	67	13	Related	Mild	Not Serious	None	Resolved
						家庭内ストレス	73	.	Not Related	Moderate	Not Serious	None	Ongoing
						倦怠感	73	.	Not Related	Moderate	Not Serious	None	Ongoing
						腹部不快感	111	23	Related	Moderate	Not Serious	None	Resolved
						嘔吐	160	.	Related	Moderate	Not Serious	Study Drug Discontinued	Ongoing
						腹痛	160	.	Related	Moderate	Not Serious	Study Drug Discontinued	Ongoing
0.10/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Male	2[redacted]	咳嗽	.	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Resolved

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Note: Placebo/0.05: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.05mg/kg/d teduglutide in Study 005
Placebo/0.10: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.10mg/kg/d teduglutide in Study 005
0.05/0.05: Subjects were randomized to 0.05mg/kg/d teduglutide in Study 004 and continued on 0.05mg/kg/d teduglutide in Study 005
0.10/0.10: Subjects were randomized to 0.10mg/kg/d teduglutide in Study 004 and continued on 0.10mg/kg/d teduglutide in Study 005
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-7-ae-discon-600005.sas

Output Generated On: 23OCT2016 21:12

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
0.10/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Male	2[redacted]	血尿	30	.	Not Related	Mild	Not Serious	None	Ongoing
						貧血	34	2	Not Related	Mild	Serious	None	Resolved
						嘔吐	58	36	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
						悪心	58	36	Related	Mild	Not Serious	Study Drug Discontinued	Resolved
0.10/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	6[redacted]	腹痛	-56	85	Related	Severe		None	Severity/Frequency Increased
						医療用具故障	3	1	Not Related	Mild	Serious	None	Resolved
						腹痛	29	.	Related	Moderate	Not Serious	Study Drug Discontinued	Ongoing
0.10/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	6[redacted]	脳血管発作	59	18	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
						心房細動	60	1	Not Related	Moderate	Not Serious	None	Resolved
Placebo/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	7[redacted]	皮膚乾燥	-1	31	Related	Severe		None	Resolved
						腸管ストーマ合併症	25	199	Related	Mild	Not Serious	None	Resolved

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Note: Placebo/0.05: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.05mg/kg/d teduglutide in Study 005
Placebo/0.10: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.10mg/kg/d teduglutide in Study 005
0.05/0.05: Subjects were randomized to 0.05mg/kg/d teduglutide in Study 004 and continued on 0.05mg/kg/d teduglutide in Study 005
0.10/0.10: Subjects were randomized to 0.10mg/kg/d teduglutide in Study 004 and continued on 0.10mg/kg/d teduglutide in Study 005
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-7-ae-discon-600005.sas

Output Generated On: 23OCT2016 21:12

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	7[redacted]	うつ病	29	.	Not Related	Moderate	Not Serious	None	Ongoing
						四肢痛	45	2	Not Related	Moderate	Not Serious	None	Resolved
						舌水疱形成	49	4	Not Related	Mild	Not Serious	None	Resolved
						悪寒	50	20	Not Related	Moderate	Not Serious	None	Resolved
						発熱	50	20	Not Related	Moderate	Not Serious	None	Resolved
						カテーテル菌血症	70	4	Not Related	Severe	Serious	None	Resolved
						発熱	100	3	Not Related	Moderate	Not Serious	None	Resolved
						悪寒	100	3	Not Related	Moderate	Not Serious	None	Resolved
						背部痛	102	1	Not Related	Moderate	Not Serious	None	Resolved
						カテーテル菌血症	103	5	Not Related	Severe	Serious	None	Resolved
						処置後痛	105	2	Not Related	Moderate	Not Serious	None	Resolved
						低マグネシウム血症	114	14	Not Related	Mild	Not Serious	None	Resolved
						坐骨神経痛	170	4	Not Related	Moderate	Not Serious	None	Resolved

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Note: Placebo/0.05: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.05mg/kg/d teduglutide in Study 005
Placebo/0.10: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.10mg/kg/d teduglutide in Study 005
0.05/0.05: Subjects were randomized to 0.05mg/kg/d teduglutide in Study 004 and continued on 0.05mg/kg/d teduglutide in Study 005
0.10/0.10: Subjects were randomized to 0.10mg/kg/d teduglutide in Study 004 and continued on 0.10mg/kg/d teduglutide in Study 005
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-7-ae-discon-600005.sas

Output Generated On: 23OCT2016 21:12

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo/0.10	[redacted]	Caucasian	0.10 mg/kg/day	Female	7[redacted]	カテーテル菌血症	171	27	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
						胸水	175	23	Not Related	Severe	Serious	None	Resolved
						胃腸出血	178	1	Not Related	Moderate	Serious	None	Resolved
						横隔膜下膿瘍	178	20	Not Related	Severe	Serious	None	Resolved
						低カリウム血症	180	12	Not Related	Moderate	Not Serious	None	Resolved
						クロストリジウム性大腸炎	186	15	Not Related	Moderate	Not Serious	None	Resolved
						胸水	198	.	Not Related	Moderate	Not Serious	None	Ongoing
						カテーテル菌血症	198	24	Not Related	Moderate	Not Serious	None	Resolved
						胃潰瘍	205	11	Not Related	Severe	Serious	None	Resolved
						低カリウム血症	208	4	Not Related	Moderate	Not Serious	None	Resolved
						消化性潰瘍	216	.	Not Related	Moderate	Not Serious	None	Ongoing

Note: Placebo/0.05: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.05mg/kg/d teduglutide in Study 005
Placebo/0.10: Subjects were randomized to placebo in Study 004 and were rerandomized to 0.10mg/kg/d teduglutide in Study 005
0.05/0.05: Subjects were randomized to 0.05mg/kg/d teduglutide in Study 004 and continued on 0.05mg/kg/d teduglutide in Study 005
0.10/0.10: Subjects were randomized to 0.10mg/kg/d teduglutide in Study 004 and continued on 0.10mg/kg/d teduglutide in Study 005
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 7.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-7-ae-discon-600005.sas

Output Generated On: 23OCT2016 21:12

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	末梢性浮腫	-148	113	Not Related	Mild	Not Serious	None	Resolved
						末梢性浮腫	4	18	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	5[redacted]	ワクチン接種部位紅斑	17	7	Not Related	Moderate	Not Serious	None	Resolved
						末梢性浮腫	29	.	Related	Mild	Not Serious	None	Ongoing
						下痢	29	.	Related	Moderate	Not Serious	None	Ongoing
						血尿	44	7	Not Related	Mild	Not Serious	None	Resolved
						電解質失調	50	4	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						敗血症	50	4	Not Related	Moderate	Serious	Study Drug Discontinued	Resolved
						無力症	50	4	Related	Severe	Not Serious	Study Drug Discontinued	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	5[redacted]	悪液質	50	4	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	3[redacted]	腹痛	-14	.	Not Related	Moderate	Not Serious	None	Ongoing
						腹痛	2	.	Related	Moderate	Not Serious	Study Drug Dose Interrupted	Ongoing
						悪心	2	.	Related	Mild	Not Serious	Study Drug Dose Interrupted	Ongoing
						体液貯留	5	.	Related	Mild	Not Serious	None	Ongoing
						消化管ストーマ合併症	20	.	Related	Moderate	Not Serious	None	Ongoing
						消化不良	49	.	Related	Moderate	Not Serious	None	Ongoing
						腹痛	62	.	Related	Severe	Not Serious	Study Drug Discontinued	Ongoing
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	5[redacted]	痔核	-8	.	Not Related	Moderate	Not Serious	None	Ongoing
						悪心	4	19	Related	Mild	Not Serious	None	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	5[redacted]	腹部膨満	6	.	Related	Moderate	Not Serious	None	Ongoing
						疲労	30	.	Not Related	Moderate	Not Serious	None	Ongoing
						腹痛	76	17	Related	Moderate	Not Serious	Study Drug Discontinued	Resolved
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	4[redacted]	腹部膨満	11	40	Related	Moderate	Not Serious	None	Resolved
						疲労	96	.	Not Related	Moderate	Not Serious	None	Ongoing
						悪心	96	.	Related	Moderate	Not Serious	None	Ongoing
						腹痛	96	.	Related	Moderate	Not Serious	Study Drug Discontinued	Ongoing
						体重減少	96	.	Related	Moderate	Not Serious	None	Ongoing
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	消化管ストーマ合併症	6	5	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						腹痛	6	5	Related	Severe	Not Serious	Study Drug Discontinued	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas　　Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	腸閉塞	6	5	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
						悪心	6	5	Related	Severe	Not Serious	Study Drug Discontinued	Resolved
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	6[redacted]	背部痛	-112	.	Not Related	Moderate	Not Serious	None	Ongoing
						胃炎	49	.	Not Related	Mild	Not Serious	None	Ongoing
						喀血	71	.	Not Related	Moderate	Not Serious	None	Ongoing
						動脈硬化症	85	.	Not Related	Mild	Not Serious	None	Ongoing
						非小細胞肺癌	85	158	Not Related	Severe	Serious	Study Drug Discontinued	Fatal
						INR 増加	87	3	Not Related	Mild	Not Serious	None	Resolved
						十二指腸ポリープ	103	.	Not Related	Mild	Not Serious	None	Ongoing
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	4[redacted]	背部痛	313	.	Not Related	Moderate	Not Serious	None	Ongoing

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	4[redacted]	腰椎骨折	323	.	Not Related	Severe	Serious	Study Drug Discontinued	Ongoing
						消化不良	323	.	Not Related	Mild	Not Serious	None	Ongoing
						転移性新生物	326	11	Related	Severe	Serious	Study Drug Discontinued	Fatal
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	肺損傷	-37	.	Not Related	Mild	Not Serious	None	Ongoing
						肋骨骨折	-37	.	Not Related	Severe	Not Serious	None	Ongoing
						胸水	-12	44	Not Related	Severe	Serious	None	Resolved
						体重減少	1	485	Not Related	Moderate	Not Serious	None	Severity/Frequency Increased
						鼓腸	9	18	Not Related	Moderate	Not Serious	None	Resolved
						血中重炭酸塩減少	15	80	Not Related	Mild	Not Serious	None	Resolved
						鼓腸	36	25	Not Related	Mild	Not Serious	None	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	異常高熱	47	1	Not Related	Mild	Not Serious	None	Resolved
						鼻咽頭炎	47	15	Not Related	Moderate	Not Serious	None	Resolved
						高血圧	92	.	Not Related	Moderate	Not Serious	None	Ongoing
						血中重炭酸塩減少	95	272	Not Related	Moderate	Not Serious	None	Resolved
						下痢	271	3	Not Related	Moderate	Not Serious	None	Resolved
						注射部位腫脹	348	3	Related	Mild	Not Serious	None	Resolved
						注射部位発疹	348	3	Related	Mild	Not Serious	None	Resolved
						注射部位発疹	354	3	Related	Mild	Not Serious	None	Resolved
						注射部位腫脹	354	3	Related	Mild	Not Serious	None	Resolved
						腎結石症	362	1	Not Related	Severe	Not Serious	None	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	血中クレアチニン増加	366	14	Not Related	Mild	Not Serious	None	Severity/Frequency Increased
						貧血	366	92	Not Related	Mild	Not Serious	None	Resolved
						血中重炭酸塩減少	380	78	Not Related	Moderate	Not Serious	None	Resolved
						急性腎不全	380	.	Not Related	Moderate	Not Serious	None	Ongoing
						血中クレアチニン増加	380	.	Not Related	Moderate	Not Serious	None	Ongoing
						尿路閉塞	380	.	Not Related	Moderate	Not Serious	None	Ongoing
						良性前立腺肥大症	437	.	Not Related	Mild	Not Serious	None	Ongoing
						下痢	457	14	Not Related	Moderate	Not Serious	None	Resolved
						体重減少	486	15	Not Related	Severe	Not Serious	None	Resolved
						血中重炭酸塩減少	500	.	Not Related	Mild	Not Serious	None	Ongoing

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	下痢	500	.	Not Related	Mild	Not Serious	None	Ongoing
						貧血	542	91	Not Related	Moderate	Not Serious	None	Resolved
						膀胱結石	586	.	Not Related	Moderate	Not Serious	None	Ongoing
						腎結石症	623	2	Not Related	Moderate	Not Serious	None	Resolved
						腎結石症	630	1	Not Related	Mild	Not Serious	None	Resolved
						慢性腎不全	688	.	Not Related	Severe	Serious	Study Drug Discontinued	Ongoing
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	便量減少	-160	324	Not Related	Moderate	Not Serious	None	Resolved
						抱合ビリルビン増加	-151	243	Not Related	Moderate	Not Serious	None	Resolved
						黄疸眼	-151	243	Not Related	Mild	Not Serious	None	Resolved
						片頭痛	-137	.	Not Related	Severe	Not Serious	None	Ongoing

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	血中ビリルビン増加	-123	187	Not Related	Moderate	Not Serious	None	Resolved
						血中アルカリホスファターゼ増加	-81	.	Not Related	Moderate	Not Serious	None	Ongoing
						γ－グルタミルトランスフェラーゼ増加	-81	.	Not Related	Moderate	Not Serious	None	Ongoing
						血小板数減少	-81	.	Not Related	Moderate	Not Serious	None	Ongoing
						悪心	-48	.	Related	Mild	Not Serious	None	Ongoing
						肝硬変	-48	.	Not Related	Severe	Not Serious	None	Ongoing
						平滑筋抗体陽性	-46	.	Not Related	Moderate	Not Serious	None	Ongoing
						胆汁うっ滞性肝炎	-20	.	Not Related	Severe	Serious	None	Ongoing
						腹痛	4	134	Related	Severe	Not Serious	None	Resolved
						消化管ストーマ合併症	5	.	Related	Moderate	Not Serious	None	Ongoing

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
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Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	消化管ストーマ合併症	5	.	Related	Mild	Not Serious	None	Ongoing
						異常高熱	9	1	Not Related	Moderate	Not Serious	None	Resolved
						嘔吐	39	1	Related	Severe	Not Serious	None	Resolved
						嘔吐	49	1	Related	Severe	Not Serious	None	Resolved
						嘔吐	58	1	Related	Severe	Not Serious	None	Resolved
						細菌性尿路感染	63	24	Not Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	64	1	Related	Moderate	Not Serious	None	Resolved
						嘔吐	75	1	Related	Moderate	Not Serious	None	Resolved
						眼部腫脹	76	4	Not Related	Moderate	Not Serious	None	Resolved
						片頭痛	76	3	Not Related	Severe	Not Serious	None	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	嘔吐	78	1	Related	Moderate	Not Serious	None	Resolved
						鼻出血	82	2	Not Related	Moderate	Not Serious	None	Resolved
						注射部位腫脹	91	122	Related	Mild	Not Serious	None	Resolved
						注射部位発疹	91	192	Related	Moderate	Not Serious	None	Resolved
						処置後出血	137	32	Not Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	146	23	Related	Moderate	Not Serious	None	Resolved
						口渇	164	6	Not Related	Moderate	Not Serious	None	Resolved
						貧血	164	19	Related	Moderate	Not Serious	None	Resolved
						便量増加	164	6	Not Related	Moderate	Not Serious	None	Resolved
						下痢	176	4	Not Related	Moderate	Not Serious	None	Resolved

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Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	異常高熱	177	2	Not Related	Moderate	Not Serious	None	Resolved
						白血球減少症	182	.	Not Related	Moderate	Not Serious	None	Ongoing
						消化管ストーマ合併症	183	12	Related	Moderate	Serious	Study Drug Discontinued	Resolved
						処置による疼痛	184	9	Not Related	Severe	Not Serious	None	Resolved
						消化管ストーマ合併症	184	1	Related	Moderate	Not Serious	None	Resolved
						術後膿瘍	191	10	Not Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	209	1	Related	Mild	Not Serious	None	Resolved
						腹痛	209	.	Related	Moderate	Not Serious	None	Ongoing
						便量増加	213	10	Not Related	Moderate	Not Serious	None	Resolved
						便量増加	224	11	Not Related	Moderate	Not Serious	None	Severity/Frequency Increased

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	消化管ストーマ合併症	225	1	Related	Mild	Not Serious	None	Resolved
						血中重炭酸塩減少	227	96	Not Related	Moderate	Not Serious	None	Resolved
						カンジダ症	228	11	Not Related	Moderate	Not Serious	None	Resolved
						便量増加	234	.	Not Related	Severe	Not Serious	None	Ongoing
						消化管ストーマ合併症	235	1	Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	241	8	Related	Severe	Not Serious	None	Resolved
						末梢性浮腫	248	15	Not Related	Moderate	Not Serious	None	Resolved
						低アルブミン血症	249	26	Not Related	Moderate	Not Serious	None	Resolved
						貧血	249	26	Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	259	2	Related	Moderate	Not Serious	Study Drug Dose Interrupted	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	異常高熱	262	6	Not Related	Moderate	Not Serious	None	Resolved
						末梢性浮腫	266	.	Not Related	Mild	Not Serious	None	Ongoing
						便量増加	274	8	Not Related	Severe	Serious	None	Resolved
						消化管ストーマ合併症	274	8	Related	Moderate	Serious	Study Drug Discontinued	Resolved
						門脈圧亢進症	276	.	Related	Moderate	Not Serious	Study Drug Dose Interrupted	Ongoing
						処置後出血	281	1	Not Related	Moderate	Not Serious	None	Resolved
						消化管ストーマ合併症	305	1	Related	Mild	Not Serious	None	Resolved
						消化管ストーマ合併症	319	1	Related	Mild	Not Serious	None	Resolved
						無力症	322	.	Not Related	Moderate	Not Serious	None	Ongoing
						筋肉痛	322	.	Not Related	Moderate	Not Serious	None	Ongoing

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Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	2[redacted]	γ-グルタミルトランスフェラーゼ増加	178	148	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Resolved
						血中ビリルビン増加	178	148	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Resolved
						アラニン・アミノトランスフェラーゼ増加	178	148	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Resolved
						アスパラギン酸アミノトランスフェラーゼ増加	178	148	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Resolved
						血中アルカリホスファターゼ増加	178	148	Not Related	Moderate	Serious	Study Drug Dose Interrupted	Resolved
						胆石症	206	101	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
						γ-グルタミルトランスフェラーゼ増加	345	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Ongoing
						アスパラギン酸アミノトランスフェラーゼ増加	345	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Ongoing
						血中アルカリホスファターゼ増加	345	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Ongoing
						血中ビリルビン増加	345	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Ongoing

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Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	2[redacted]	アラニン・アミノトランスフェラーゼ増加	345	.	Not Related	Mild	Not Serious	Study Drug Discontinued	Ongoing
Not Treated, Placebo / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	8[redacted]	消化管ストーマ合併症	16	12	Related	Severe	Serious	Study Drug Discontinued	Resolved
						胆嚢炎	16	12	Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
						腸閉塞	16	12	Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
						門脈圧亢進症	16	12	Related	Severe	Serious	Study Drug Dose Interrupted	Resolved
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	消化管ストーマ合併症	-161	.	Related	Moderate	Not Serious	None	Ongoing
						末梢性浮腫	-84	.	Related	Moderate	Not Serious	None	Ongoing
						カテーテル留置部位紅斑	-52	.	Not Related	Mild	Not Serious	None	Ongoing
						体液貯留	1	15	Related	Moderate	Not Serious	None	Resolved
						体液貯留	162	56	Not Related	Mild	Not Serious	None	Resolved

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Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	5[redacted]	脳浮腫	162	112	Not Related	Moderate	Not Serious	None	Resolved
						脳膿瘍	162	102	Not Related	Severe	Serious	Study Drug Discontinued	Resolved
						頭痛	162	102	Not Related	Moderate	Not Serious	None	Resolved
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	7[redacted]	体重減少	89	.	Not Related	Moderate	Not Serious	None	Ongoing
						カテーテル敗血症	256	22	Not Related	Moderate	Serious	None	Resolved
						鼓腸	333	.	Not Related	Mild	Not Serious	None	Ongoing
						喀血	379	.	Not Related	Moderate	Not Serious	None	Ongoing
						結核	403	110	Not Related	Moderate	Not Serious	None	Resolved
						低カリウム血症	410	2	Not Related	Mild	Not Serious	None	Resolved
						肺扁平上皮癌、病期不明	535	.	Not Related	Severe	Serious	Study Drug Discontinued	Ongoing

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Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Female	4[redacted]	体重減少	-159	217	Related	Mild	Not Serious	Study Drug Discontinued	Resolved
						末梢性浮腫	5	4	Not Related	Mild	Not Serious	None	Resolved
						口腔ヘルペス	10	7	Not Related	Mild	Not Serious	None	Resolved
						歯肉炎	10	4	Not Related	Mild	Not Serious	None	Resolved
						皮膚剥脱	22	4	Not Related	Mild	Not Serious	None	Resolved
						紅斑性皮疹	32	13	Not Related	Mild	Not Serious	None	Resolved
						低マグネシウム血症	57	35	Not Related	Mild	Not Serious	None	Resolved
						低カルシウム血症	57	35	Not Related	Mild	Not Serious	None	Resolved
						高カリウム血症	57	35	Not Related	Mild	Not Serious	None	Resolved
						結腸直腸ポリープ	91	1	Related	Moderate	Not Serious	None	Resolved

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Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas

Output Generated On: 21OCT2016 0:28

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide / Teduglutide	[redacted]	White	0.05 Mg/Kg/Day	Male	4[redacted]	直腸分泌物	121	24	Related	Mild	Not Serious	Study Drug Dose Interrupted	Resolved
						大腸炎	155	.	Related	Moderate	Not Serious	None	Ongoing
						創部分泌	158	.	Not Related	Mild	Not Serious	Study Drug Dose Interrupted	Ongoing
						血中クレアチニン増加	185	4	Not Related	Mild	Not Serious	None	Resolved
						クローン病	285	21	Related	Moderate	Serious	Study Drug Discontinued	Resolved

Note: Not Treated, Placebo/Teduglutide = subjects who were eligible for randomization in Study CL0600-020 but qualified after the enrollment number was satisfied and entered Study CL0600-021 directly, and those who participated in Study CL0600-020 and received placebo.
Teduglutide/Teduglutide = subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020
* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-5-ae-discon-600021.sas
Output Generated On: 21OCT2016 0:28

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Asian	Female	3[redacted]	一般・全身障害および投与部位の状態／発熱／Fever	15OCT2018 (-14)/ 20OCT2018 (-9)	6	No/ Mild/ Not Related	Not Applicable/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	No
				皮膚および皮下組織障害／蕁麻疹／Urticaria	29OCT2018: 12:20 (1)/ 07NOV2018 (10)	10	No/ Mild/ Not Related	Drug Interrupted/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態／発熱／Fever	11NOV2018 (14)/ 12NOV2018 (15)	2	No/ Mild/ Not Related	Not Applicable/ None	Intermittent/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態／注射部位反応／Injection Site Reaction	27NOV2018: 09:33 (30)/ 04DEC2018 (37)	8	No/ Mild/ Related	Dose Not Changed/ Drug Treatment Given	Intermittent/ Recovered/ Resolved	Yes
				呼吸器、胸郭および縦隔障害／口腔咽頭痛／Sore Throat	29NOV2018 (32)/ Ongoing		No/ Mild/ Related	Drug Withdrawn/ Drug Treatment Given	Continuous/ Recovering/ Resolving	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRFs.
<SHIRE¥TEDUGLUTIDE¥UYA25606¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_5_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <30OCT2019>

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	Duration (days)	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Asian	Female	3[redacted]	傷害、中毒および処置合併症／ 消化管ストーマ合併症／ Allergic(Stomal Edema)	29NOV2018 (32)/ 04DEC2018 (37)	6	No/ Mild/ Related	Drug Withdrawn/ Drug Treatment Given	Continuous/ Recovered/ Resolved	Yes
				胃腸障害／ 胃食道逆流性疾患／ Stomach Acid Reflux	20DEC2018 (53)/ Ongoing		No/ Mild/ Not Related	Not Applicable/ Drug Treatment Given	Continuous/ Not Recovered/ Not Resolved	Yes

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 21.0.
Note: Reported terms are collected on the eCRFs.
<SHIRE¥TEDUGLUTIDE¥UYA25606¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_5_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE, ADSL> <30OCT2019>

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中マグネシウム増加／ CLINICALLY SIGNIFICANT HIGH MAGNESIUM - ELECTROLYTE IMBALANCE	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中アルブミン減少／ CLINICALLY SIGNIFICANT LOW ALBUMIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent.　Severity: MI= Mild, MO= Moderate, SV= Severe.　Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown.　Relationship: NR = Not Related, R = Related.　Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown.　Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.　Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-ae-trt-disc.sas　30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 血中尿酸減少／ CLINICALLY SIGNIFICANT LOW URIC ACID - UNKNOWN DIAGNOSIS	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中リン減少／ CLINICICALLY SIGNIFICANT LOW PHOSPHORUS - UNKOWN DIAGNOSIS	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-ae-trt-disc.sas　30JAN2020 20:14

Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／アラニンアミノトランスフェラーゼ増加／HIGH ALT	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／アスパラギン酸アミノトランスフェラーゼ増加／HIGH AST	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y
		臨床検査／C-反応性蛋白増加／HIGH CRP	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	臨床検査／ 抱合ビリルビン増加／ HIGH DIRECT BILIRUBIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	No	N	Y
		臨床検査／ 血中ビリルビン増加／ HIGH TOTAL BILIRUBIN	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y
		臨床検査／ 血中カルシウム減少／ LOW CALCIUM	2017-02-24(29) /ONGOING	CONT/ MO/ UNK	No		NC/ N	No	N	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

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Treatment: TED/TED

Subject	Sex/Age/Race	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	Frequency/ Severity/ Outcome	CTCAE Grade	Relationship to Study Drug	Action Taken with Study Treatment / Other Action Taken	Discontinued from the Study	SAE	TEAE
[redacted]	F/[redacted]/BLACK	肝胆道系障害／胆汁うっ滞／WORSENING CHOLESTASIS	2017-05-12(106) /ONGOING	CONT/ MO/ UNK	No	NR	NC/ N	Yes	Y	Y
		臨床検査／血中ビリルビン増加／ELEVATED BILIRUBIN	2017-09-01(218) /ONGOING	CONT/ MO/ RCG	No		DW/ UK	No	Y	Y

Note: F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN = Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Note: Reasons for SAE were not collected for this study. Frequency: CONT = Continuous, INT=Intermittent. Severity: MI= Mild, MO= Moderate, SV= Severe. Outcome: R/R=Recovered/Resolved, R/S=Recovered/Resolved with sequelae, NRD=Not Recovered/Not resolved, RCG=Recovering/Resolving, D=Fatal, UNK=Unknown. Relationship: NR = Not Related, R = Related. Action: NC=Dose Not Changed, DR=Dose Reduced, DI = Drug Interrupted, DW=Drug Withdrawn, NA= Not Applicable, UK=Unknown. Other Action: N=None, DT=Drug Treatment Given, NT=Non-drug treatment given, UK=Unknown.
Note: Adverse events were coded to primary SOC and preferred term using MedDRA dictionary, Version 19.1.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative. Study day is considered to begin with the core study day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the NTT/NTT OR NTT/TED group. Study day before reference start date is negative.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-304¥report¥adhoc¥l-ae-trt-disc.sas　30JAN2020 20:14

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	4[redacted]	臨床検査／ 腸通過時間延長／ Intestinal transit time increased	31AUG2015 15/ - -		No/ Mild/ Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				臨床検査／ リパーゼ増加／ Lipase increased	31AUG2015 15/ 12OCT2015 57	43	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 上腹部痛／ Right hypochondralgia	07DEC2015 113/ 01MAR2016 198	86	No/ Mild/ Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				胃腸障害／ 嘔吐／ Vomiting	31JAN2016 168/ 08FEB2016 176	9	No/ Mild/ Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

Program: x:¥shire_s@sgattex@adhoc¥japanaelistings¥shp633-14004¥report¥adhoc¥l-ae-trt-disc.sas　29JAN2020 17:13

Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	4[redacted]	胃腸障害／ 下痢／ Diarrhea	31JAN2016 168/ 01MAR2016 198	31	No/ Mild/ Related	Drug Withdrawn/ None	Intermittent/ Recovered/Resolved	Yes
[redacted]	Japanese	Male	3[redacted]	神経系障害／ 頭痛／ Headache	21AUG2015:21:00:00 1/ 21AUG2015:22:00:00 1	1	No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/Resolved	Yes
				感染症および寄生虫症／ 医療機器関連感染／ Catheter related blood stream infection	24AUG2015:21:00:00 4/ 30AUG2015:15:00:00 10	7	Yes/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				感染症および寄生虫症／ カンジダ性亀頭炎／ Penis candidiasis	02SEP2015 13/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	代謝および栄養障害／ 栄養障害／ Malnutrition	02SEP2015:19:00:00 13/ - -		No/ Severe/ Not Related	Drug Interrupted/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				一般・全身障害および投与部位の状態／ 浮腫／ Edema	02SEP2015 13/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				胃腸障害／ 腸炎／ Enterocolitis	02SEP2015:19:00:00 13/ 18SEP2015 29	17	Yes/ Severe/ Related	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 腸閉塞／ Intestinal obstruction	02SEP2015:19:00:00 13/ 18SEP2015 29	17	Yes/ Severe/ Related	Drug Interrupted/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	感染症および寄生虫症／ 医療機器関連感染／ Catheter related blood stream infection	02SEP2015 13/ 19SEP2015 30	18	No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				血液およびリンパ系障害／ 貧血／ Anemia (aggravated)	03SEP2015 14/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				血液およびリンパ系障害／ 播種性血管内凝固／ Disseminated intravascular coagulation	05SEP2015 16/ - -		No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				肝胆道系障害／ 急性肝不全／ Acute liver failure	05SEP2015 16/ 27OCT2015:12:40:00 68	53	Yes/ Severe/ Related	Drug Withdrawn/ Multiple	Continuous/ Fatal	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	肝胆道系障害／ 高ビリルビン血症／ High bilirubinemia	06SEP2015 17/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ -	Yes
				感染症および寄生虫症／ 口腔ヘルペス／ Herpes labialis	07SEP2015 18/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Not Recovered/Not Resolved	Yes
				胃腸障害／ 膵炎／ Pancreatitis	07SEP2015 18/ 04OCT2015 45	28	No/ Moderate/ Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				皮膚および皮下組織障害／ そう痒症／ Skin pruritus	10SEP2015 21/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ -	Yes
				代謝および栄養障害／ 高血糖／ Hyperglycemia	11SEP2015 22/ 16SEP2015 27	6	No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	胃腸障害／ 口腔内出血／ Bleeding mouth	16SEP2015 27/ - -		No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes
				感染症および寄生虫症／ 敗血症／ Sepsis	20SEP2015 31/ 14OCT2015 55	25	Yes/ Severe/ Not Related	Dose Not Changed/ Multiple	Continuous/ Recovered/Resolved	Yes
				臨床検査／ 酸素飽和度低下／ Oxygen saturation low	21SEP2015 32/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 医療機器閉塞／ Central venous catheter occlusion	21SEP2015 32/ 21SEP2015 32	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	代謝および栄養障害／ 低血糖症／ Hypoglycemia	21SEP2015 32/ 21SEP2015 32	1	No/ Mild/ Not Related	Dose Not Changed/ None	Continuous/ Recovered/Resolved	Yes
				胃腸障害／ 腸炎／ Enterocolitis	21SEP2015 32/ 13OCT2015 54	23	No/ Severe/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/Resolved	Yes
				心臓障害／ 急性心不全／ Acute heart failure	22SEP2015 33/ - -		No/ Severe/ Not Related	Dose Not Changed/ Multiple	Continuous/ -	Yes
				筋骨格系および結合組織障害／ 筋肉痛／ Muscle pain	22SEP2015 33/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/Not Resolved	Yes
				臨床検査／ 尿量減少／ Decreased urinal volume	22SEP2015 33/ - -		No/ Moderate/ Not Related	Dose Not Changed/ None	Intermittent/ -	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Site ID - Subject ID	Race	Sex	Age	System Organ Class/ Preferred Term/ Reported Term[a]	Start Date and Time Relative Day/ Stop Date and Time Relative Day	Dura-tion	Serious AE/ Severity/ Relationship	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
[redacted]	Japanese	Male	3[redacted]	呼吸器、胸郭および縦隔障害／ 呼吸不全／ Acute lung failure	22SEP2015 33/ 13OCT2015 54	22	No/ Severe/ Not Related	Dose Not Changed/ Non-Drug Treatment	Continuous/ Recovered/Resolved	Yes
				眼障害／ 眼球浮腫／ Eye edema	23SEP2015 34/ - -		No/ Mild/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				感染症および寄生虫症／ 口腔カンジダ症／ Oral candida	23SEP2015 34/ - -		No/ Moderate/ Not Related	Dose Not Changed/ Drug Treatment	Continuous/ -	Yes
				一般・全身障害および投与部位の状態／ 低体温／ Hypothemia	24SEP2015 35/ 24SEP2015 35	1	No/ Mild/ Not Related	Dose Not Changed/ None	Intermittent/ Recovered/Resolved	Yes
				腎および尿路障害／ 急性腎不全／ Acute renal failure	22OCT2015 63/ 27OCT2015:12:40:00 68	6	Yes/ Severe/ Not Related	Dose Not Changed/ None	Intermittent/ Fatal	Yes

Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 17.1.
[a]: Reported terms are collected on the eCRF. Body system organ classes and preferred terms are coded using MedDRA 12.0.　Details of SAEs were not collected in this study.

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Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/[redacted] Male		一般・全身障害および投与部位の状態/ 注射部位硬結/ Injection site reaction(induration)	10FEB2017 (3)/ 15FEB2017 (8)	6	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位血腫/ Injection site reaction(Subcutraneous hematom right lower abdomen)	10FEB2017 (3)/ 21FEB2017 (14)	12	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness)	13FEB2017 (6)/ 14FEB2017 (7)	2	No/ Mild/ Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				皮膚および皮下組織障害/ 皮膚乾燥/ dry skin	15FEB2017 (8)/ Ongoing		No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Not Recovered/ Not Resolved	Yes

Note: All the AEs for subjects who had an adverse event leading to study drug discontinuation are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_14_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/[redacted] Male		一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding left lower abdomen)	17FEB2017 (10)/ 24FEB2017 (17)	8	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(subcutaneous bleeding right thigh)	20FEB2017 (13)/ 27FEB2017 (20)	8	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding risght lower abdomen)	23FEB2017 (16)/ 01MAR2017 (22)	7	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had an adverse event leading to study drug discontinuation are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_14_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/ Male	[redacted]	一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction redness(right arm)	25FEB2017 (18)/ 25FEB2017 (18)	1	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ 医療機器使用部位感染/ tunnel infection(central venous catheter)	01MAR2017 (22)/ 25JUN2017 (138)	117	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Intermittent/ Recovered/ Resolved	Yes
				胃腸障害/ 小腸炎/ enteritis	15MAR2017 (36)/ 29MAR2017 (50)	15	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腸炎/ obstinate enterocolitis	29MAR2017 (50)/ 08MAY2017 (90)	41	Yes/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had an adverse event leading to study drug discontinuation are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_14_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/[redacted] Male		一般・全身障害および投与部位の状態/ 注射部位内出血/ Injection site reaction(Subcutaneous bleeding right arm)	14MAY2017 (96)/ 23MAY2017 (105)	10	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				感染症および寄生虫症/ ウイルス性上気道感染/ common cold	20MAY2017 (102)/ 27MAY2017 (109)	8	No/ Mild/ Not Related	No	Dose Not Changed/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				一般・全身障害および投与部位の状態/ 注射部位紅斑/ Injection site reaction(Redness left thigh)	23MAY2017 (12:30) (105)/ 27MAY2017 (109)	5	No/ Mild/ Not Related	No	Dose Not Changed/ None	Continuous/ Recovered/ Resolved	Yes
				免疫系障害/ アナフィラキシー反応/ Anaphylaxis	24JUN2017 (137)/ 28JUN2017 (141)	5	Yes/ Mild/ Not Related	No	Drug Withdrawn/ Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had an adverse event leading to study drug discontinuation are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_14_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Cohort	Site ID - Subject ID	Race/ Sex	Age: Actual (years)/ Gestational (months)	System Organ Class/ Preferred Term/ Reported Term	Start Date and Time (Study Day)/ Stop Date and Time (Study Day)	AE Duration	Serious AE/ Severity/ Relationship	Dose interruption criteria satisfied/ CTCAE grade	Action Taken/ Other Action Taken	Frequency/ Outcome	TEAE?
Children (1 - 15 years)	[redacted]	Asian/[redacted] Male		感染症および寄生虫症/ 医療機器使用部位感染/ tunnel infection (central venous catheter)deterioration	26JUN2017 (139)/ 09AUG2017 (183)	45	Yes/ Severe/ Not Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes
				胃腸障害/ 腹痛/ abdominal pain	08JUL2017 (151)/ 09AUG2017 (183)	33	No/ Mild/ Related	No	Not Applicable/ Drug Treatment/Non-Drug Treatment	Continuous/ Recovered/ Resolved	Yes

Note: All the AEs for subjects who had an adverse event leading to study drug discontinuation are listed.
Note: Treatment emergent adverse events (TEAEs) are defined as any adverse events whose onset occurs, severity worsens or intensity increases during or after receiving the study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: System organ classes and preferred terms are coded using MedDRA 20.0.
Note: Reported terms are collected on the eCRF.
Note: Infants are of 4 - <12 months corrected gestational age.
Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.
<SHIRE¥TEDUGLUTIDE¥XXA39799¥BIOSTATISTICS¥PRODUCTION¥TABLES¥FINAL¥T14_3_2_14_AE_DIS.SAS> ; Source: Listing <16.2.7>; ADaM: <ADAE> <11MAY2020>

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	一般・全身障害および投与部位の状態／ 発熱／ PYREXIA*	2020-03-19(18)/ 2020-03-20(19)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 嘔吐／ INCREASED VOMITING*	2020-03-25(24)/ 2020-04-07(37)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ レッチング／ RETCHING*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 嘔吐／ VOMITING IN THE MORNING*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	No	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		代謝および栄養障害／ 過小食／ REDUCED ORAL INTAKE*	2020-03-30(29)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 下痢／ DIARRHOEA*	2020-03-30(29)/ 2020-04-06(36)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED WITH SEQUELAE	No	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 粘液便／ MUCUS IN STOOLS*	2020-03-30(29)/ 2020-04-14(44)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 下痢／ WATERY STOOLS*	2020-04-06(36)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	No	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-04-08(38)/ 2020-04-14(44)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		胃腸障害／ 排便回数増加／ INCREASED STOOL FREQUENCY*	2020-04-08(38)/ 2020-04-20(50)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 異常便／ NONE SPECIFIC ABNORMAL FINDINGS IN STOOL*	2020-04-14(44)/ 2020-04-20(50)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas　　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-04-22(52)/ 2020-04-29(59)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ DRUG TREATMENT	N
		一般・全身障害および投与部位の状態／ 分泌物分泌／ MUCUS IN VOMIT*	2020-04-24(54)/ 2020-05-04(64)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	DOSE NOT CHANGED/ NONE	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 嘔吐／ INCREASED VOMITING*	2020-04-27(57)/ 2020-05-04(64)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ N	DOSE NOT CHANGED/ NONE	N
		胃腸障害／ 嘔吐／ BILE STAINED VOMITING*	2020-05-12(72)/ 2020-06-05(96)	INTERMITTENT/ MODERATE/ RECOVERED/RESOLVED	No	RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 胃腸音異常／ INCREASED BOWEL SOUNDS*	2020-05-12(72)/ 2020-09-24(207)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas　　11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	精神障害／ 易刺激性／ IRRITABILITY*	2020-05-12(72)/ 2020-09-24(207)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ Y	DRUG WITHDRAWN/ NON-DRUG TREATMENT	N
		胃腸障害／ 嘔吐／ INCREASED VOMITING*	2020-05-26(86)/ 2020-06-05(96)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ Y	DRUG WITHDRAWN/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	臨床検査／ 便量増加／ INCREASED STOOL VOLUME*	2020-06-05(96)/ 2020-07-14(135)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	RELATED/ Y	DRUG WITHDRAWN/ NONE	N
		胃腸障害／ 鼓腸／ GASEOUS FLATULENCE*	2020-07(-)/ ONGOING	INTERMITTENT/ MILD/ NOT RECOVERED/NOT RESOLVED	No	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment: Teduglutide 0.05 mg/kg/day

Subject	Sex/Age/ Race	Body System Organ Class/ Preferred Term/ Verbatim Term	Start Datetime (Study Day)/ Stop Datetime (Study Day)	Frequency/ Severity/ Outcome	Severe (Yes /No)	Relat.to Study Drug/ Discont.Due to AE	Action Taken with Study Treatment /Other Action Taken	SAE/Reason
[redacted]	M/1[redacted]/ASIAN	胃腸障害／ 腹部膨満／ ABDOMINAL DISTENSION*	2020-07(-)/ 2020-09(-)	INTERMITTENT/ MILD/ RECOVERED/RESOLVED	No	NOT RELATED/ N	NOT APPLICABLE/ DRUG TREATMENT	N
		製品の問題／ 医療機器リーク／ LEAKING CENTRAL VENOUS LINE*	2020-09-04(187)/ 2020-09-05(188)	INTERMITTENT/ SEVERE/ RECOVERED/RESOLVED	Yes	NOT RELATED/ N	NOT APPLICABLE/ MULTIPLE: DRUG TREATMENT; NON-DRUG TREATMENT	Y/HOSP

F = Female; M = Male; AIOAN = American Indian or Alaska Native; BLACK = Black or African American; ASIAN= Asian; WHITE = White; NHOPI = Native Hawaiian or Other Pacific Islander; OTHER = Other; NALLW = Not allowed based on local regulations.
Reason: BTH= Congenital anomaly or birth defect, DIS= Persistent or significant disability or incapacity, DTH=Death, HOSP= Initial or prolonged hospitalization, LFE= Life threatening, MEDIMP= Medically important event not covered by other serious criteria.
Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.
Treatment-emergent adverse events are denoted with a * after the verbatim term.
Study day is considered to begin with the day that the subject receives the first dose of the study drug or the baseline visit for the subjects in the standard of care treatment group. Study day before reference start date is negative.
Cross-reference: Listing 16.2.7.1

Data Source: adam.adae
Program: s:¥sgattex¥shp633-301¥2020-csr¥report¥tables¥t-lst-ae-disc.sas 11NOV2020 10:52

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Female	2[redacted]	頭痛	1	.	Related	Moderate	Not Serious	None	Recovering/Resolving
						悪心	1	23	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腹部膨満	12	.	Related	Severe	Not Serious	Drug Withdrawn	Recovering/Resolving
						寝汗	20	.	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovering/Resolving
						末梢性浮腫	20	2	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位不快感	20	2	Related	Mild	Not Serious	None	Recovered/Resolved
						クローン病	21	.	Not Related	Severe	Not Serious	Drug Withdrawn	Recovering/Resolving
						注射部位血腫	21	3	Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	31	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						消化不良	33	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						嘔吐	55	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
Placebo	[redacted]	White	Placebo	Male	4[redacted]	低カリウム血症	1	2	Not Related	Mild	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Male	4[redacted]	偶発的過量投与	2	2	Related	Mild	Not Serious	None	Recovered/Resolved
						せつ	3	13	Not Related	Severe	Not Serious	None	Recovered/Resolved
						痔瘻	10	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						瘻孔分泌物	10	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						クローン病	19	.	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovering/Resolving
						嘔吐	19	1	Not Related	Moderate	Not Serious	Dose Interrupted	Recovered/Resolved
						痔瘻	56	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	5[redacted]	クローン病	36	10	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	3[redacted]	注射部位疼痛	1	.	Related	Mild	Not Serious	None	Recovering/Resolving
						腹痛	15	6	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹部膨満	15	6	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	4[redacted]	腹痛	2	11	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	5[redacted]	腹痛	1	4	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	5[redacted]	リパーゼ増加	31	9	Not Related	Mild	Not Serious	None	Recovered/Resolved
						血中アミラーゼ増加	31	9	Not Related	Mild	Not Serious	None	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	動悸	-4	11	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						粘膜変色	1	15	Not Related	Mild	Not Serious	None	Recovered/Resolved
						呼吸困難	6	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						多汗症	6	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						胸部不快感	6	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						胸痛	6	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						便秘	9	5	Related	Moderate	Not Serious	None	Recovered/Resolved
						胸部不快感	18	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						動悸	18	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						胸痛	18	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						多汗症	18	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	呼吸困難	18	2	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						腹痛	18	3	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						蒼白	28	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Black	Teduglutide 0.10 Mg/Kg/Day	Female	3[redacted]	注射部位刺激感	1	16	Related	Mild	Not Serious	Dose Interrupted	Recovered/Resolved
						易刺激性	1	.	Related	Mild	Not Serious	None	Recovering/Resolving
						うつ病	1	.	Related	Mild	Not Serious	Drug Withdrawn	Recovering/Resolving
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	4[redacted]	排便回数増加	1	6	Related	Moderate	Not Serious	Dose Interrupted	Recovered/Resolved
						腹痛	1	6	Related	Severe	Not Serious	Dose Interrupted	Recovered/Resolved
						排便回数増加	10	3	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	10	3	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						関節痛	19	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Female	4[redacted]	下気道感染	-4	15	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位発疹	1	8	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Female	4[redacted]	筋肉痛	1	8	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	2	6	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						悪心	2	5	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹部膨満	2	6	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						消化管運動障害	2	6	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						嘔吐	2	4	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						鼓腸	26	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						腸管拡張症	42	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						下腹部痛	42	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	1[redacted]	腹痛	-10	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
						上気道感染	-7	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	1	1	Related	Moderate	Not Serious	None	Recovered/Resolved
						疲労	1	1	Related	Moderate	Not Serious	None	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	1[redacted]	浮動性めまい	1	1	Related	Moderate	Not Serious	None	Recovered/Resolved
						眼痛	1	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腹部圧痛	1	3	Related	Mild	Not Serious	None	Recovered/Resolved
						アレルギー性皮膚炎	1	7	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						背部損傷	20	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	4[redacted]	注射部位紅斑	1	7	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						注射部位疼痛	1	7	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	1	5	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹部膨満	1	3	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						疲労	2	3	Related	Severe	Not Serious	None	Recovered/Resolved
						消化不良	22	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						化膿性分泌物	32	2	Not Related	Mild	Not Serious	None	Recovered/Resolved
						臍出血	32	2	Not Related	Mild	Not Serious	None	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	White	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	頭痛	1	4	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						悪心	2	3	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	2	2	Related	Severe	Not Serious	None	Recovered/Resolved
						腹痛	3	5	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	腹部圧痛	1	64	Not Related	Mild	Not Serious	None	Recovered/Resolved
						上腹部痛	1	.	Related	Moderate	Not Serious	None	Recovering/Resolving
						カンジダ症	4	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						悪心	7	.	Related	Moderate	Not Serious	None	Recovering/Resolving
						本態性血小板血症	22	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						クローン病	22	7	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						尿路感染	22	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						腹部圧痛	41	24	Not Related	Mild	Not Serious	None	Recovered/Resolved
						急性熱性好中球性皮膚症	64	2	Not Related	Severe	Serious	None	Recovered/Resolved

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Program: l-2-17-ae-discon-600008.sas

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Other	Teduglutide 0.10 Mg/Kg/Day	Female	5[redacted]	クローン病	71	8	Not Related	Severe	Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	3[redacted]	低カリウム血症	1	2	Not Related	Severe	Not Serious	None	Recovered/Resolved
						腹痛	2	3	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						食欲減退	2	4	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹部膨満	2	4	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						低カリウム血症	3	2	Not Related	Severe	Serious	None	Recovered/Resolved
						低カリウム血症	5	7	Not Related	Moderate	Not Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	6[redacted]	血中トリグリセリド増加	-14	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						悪心	1	17	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						白血球減少症	1	15	Not Related	Mild	Not Serious	None	Recovered/Resolved
						血便排泄	2	33	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						疲労	7	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						腹痛	11	2	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved

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Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	6[redacted]	腹部膨満	11	.	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovering/Resolving
						嘔吐	12	1	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						アラニン・アミノトランスフェラーゼ増加	15	67	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						肛門周囲痛	23	.	Not Related	Severe	Not Serious	None	Recovering/Resolving
						齲歯	31	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Male	3[redacted]	関節痛	-5	.	Not Related	Moderate	Not Serious	None	Recovering/Resolving
						腹部膨満	2	15	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位紅斑	8	1	Related	Mild	Not Serious	None	Recovered/Resolved
						背部痛	11	2	Not Related	Mild	Not Serious	None	Recovered/Resolved
						上気道感染	12	12	Not Related	Mild	Not Serious	None	Recovered/Resolved
						注射部位紅斑	14	4	Related	Mild	Not Serious	None	Recovered/Resolved
						下腹部痛	14	2	Not Related	Mild	Not Serious	None	Severity/Frequency Increased

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Male	3[redacted]	クローン病	15	43	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						胆石症	16	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						腹部圧痛	29	29	Not Related	Mild	Not Serious	None	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Male	2[redacted]	白血球減少症	-21	70	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						悪心	19	10	Related	Moderate	Not Serious	None	Recovered/Resolved
						頭痛	19	10	Related	Moderate	Not Serious	None	Recovered/Resolved
						背部痛	20	5	Not Related	Mild	Not Serious	None	Recovered/Resolved
						排便回数増加	20	80	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						クローン病	28	14	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-17-ae-discon-600008.sas

Output Generated On: 21OCT2016 0:17

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Male	4[redacted]	注射部位不快感	2	11	Not Related	Mild	Not Serious	None	Recovered/Resolved
						直腸周囲膿瘍	13	7	Not Related	Moderate	Serious	Drug Withdrawn	Recovered/Resolved
						肛門狭窄	13	1	Not Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						栄養障害	13	7	Not Related	Mild	Not Serious	None	Recovered/Resolved
						リパーゼ増加	36	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						血中アミラーゼ増加	36	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
Placebo	[redacted]	White	Placebo	Female	3[redacted]	下痢	15	2	Not Related	Severe	Not Serious	None	Recovered/Resolved
						アスパラギン酸アミノトランスフェラーゼ増加	28	16	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
						血中アルカリホスファターゼ増加	28	16	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
						アラニン・アミノトランスフェラーゼ増加	28	16	Related	Mild	Not Serious	Drug Withdrawn	Recovered/Resolved
Placebo	[redacted]	White	Placebo	Male	3[redacted]	悪心	1	2	Related	Mild	Not Serious	None	Recovered/Resolved
						腹部膨満	1	6	Related	Moderate	Not Serious	None	Recovered/Resolved
						食欲減退	1	6	Related	Moderate	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-18-ae-discon-600009.sas

Output Generated On: 21OCT2016 0:19

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Placebo	[redacted]	White	Placebo	Male	3[redacted]	便秘	1	6	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位疼痛	1	5	Related	Moderate	Not Serious	None	Recovered/Resolved
						体重減少	1	.	Related	Mild	Not Serious	None	Recovering/Resolving
						腹痛	1	3	Related	Severe	Not Serious	Dose Interrupted	Recovered/Resolved
						腹痛	4	3	Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
Placebo	[redacted]	White	Placebo	Female	5[redacted]	腹痛	4	25	Related	Moderate	Not Serious	Drug Withdrawn	Recovered/Resolved
						腹痛	28	.	Related	Mild	Not Serious	None	Recovering/Resolving
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	4[redacted]	異物による損傷	-1	85	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	3[redacted]	注射部位刺激感	1	54	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位出血	1	54	Related	Moderate	Not Serious	None	Recovered/Resolved
						注射部位疼痛	9	46	Related	Moderate	Not Serious	None	Recovered/Resolved
						関節痛	12	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						悪心	13	1	Not Related	Mild	Not Serious	None	Recovered/Resolved
						末梢性浮腫	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-18-ae-discon-600009.sas

Output Generated On: 21OCT2016 0:19

Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Female	3[redacted]	錯感覚	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						錯感覚	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						末梢性浮腫	15	3	Not Related	Mild	Not Serious	None	Recovered/Resolved
						背部痛	51	4	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						腹痛	54	4	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						背部痛	54	4	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						大球性貧血	54	.	Not Related	Mild	Not Serious	None	Recovering/Resolving
						悪心	54	4	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.05 Mg/Kg/Day	[redacted]	White	Teduglutide 0.05 Mg/Kg/Day	Male	5[redacted]	基底細胞癌	2	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						基底細胞癌	2	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						胃腸異形成	14	83	Not Related	Mild	Serious	Drug Withdrawn	Recovered/Resolved
						血中ブドウ糖増加	23	19	Not Related	Mild	Not Serious	None	Recovered/Resolved
						丘疹	23	8	Not Related	Mild	Not Serious	None	Recovered/Resolved
						心電図異常	23	56	Not Related	Mild	Not Serious	None	Recovered/Resolved

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* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-18-ae-discon-600009.sas

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Treatment group	Subject ID	Race	Dose	Sex	Age*	Adverse event	Day of onset	Duration (Days)	Causality	Severity	Serious /Not serious	Action taken	Outcome
Teduglutide 0.10 Mg/Kg/Day	[redacted]	Black	Teduglutide 0.10 Mg/Kg/Day	Male	3[redacted]	腹痛	7	1	Not Related	Severe	Not Serious	None	Recovered/Resolved
						小腸閉塞	42	14	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						瘻孔	43	1	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
						異物による損傷	43	1	Not Related	Severe	Not Serious	Drug Withdrawn	Recovered/Resolved
Teduglutide 0.20 Mg/Kg/Day	[redacted]	White	Teduglutide 0.20 Mg/Kg/Day	Female	4[redacted]	排便痛	20	4	Not Related	Severe	Not Serious	None	Recovered/Resolved
						失見当識	21	4	Not Related	Severe	Not Serious	None	Recovered/Resolved
						眼痛	21	32	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						下痢	24	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						脱水	24	1	Not Related	Moderate	Not Serious	None	Recovered/Resolved
						脱水	75	25	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved
						クローン病	75	25	Not Related	Severe	Serious	Drug Withdrawn	Recovered/Resolved

* Age at study informed consent date.
Note: All adverse events were coded using MedDRA preferred term version 12.0.
Note: Day of onset is counted from the day of the first administration inclusive.
Program: l-2-18-ae-discon-600009.sas

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付録 4. 併合データ

Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
Extent of Exposure (Days)	n	18	14	18
	Mean (SD)	787.1 (721.11)	989.4 (693.17)	787.1 (721.11)
	Median	407.5	1013.0	407.5
	Min, Max	15, 1709	161, 1709	15, 1709
Extent of Exposure (Weeks)	n	18	14	18
	Mean (SD)	112.4 (103.02)	141.3 (99.02)	112.4 (103.02)
	Median	58.2	144.7	58.2
	Min, Max	2, 244	23, 244	2, 244
Extent of Exposure Category (Months)				
< 3 Months	n (%)	2 (11.1)	0	2 (11.1)
>= 3 Months and < 6 Months	n (%)	4 (22.2)	2 (14.3)	4 (22.2)
>= 6 Months and < 9 Months	n (%)	0	0	0
>= 9 Months and < 12 Months	n (%)	1 (5.6)	1 (7.1)	1 (5.6)
>= 12 Months and < 15 Months	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 15 Months and < 18 Months	n (%)	0	0	0

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.
[2] Exposure of duration is sum of treatment duration in core study + extension study.
[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

Program: s:¥sgattex¥gattex pooled japan¥2020-jnda-three-studies¥report¥tables¥t-ex.sas 17JUN2020 10:53

Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
>= 18 Months and < 21 Months	n (%)	0	0	0
>= 21 Months and < 24 Months	n (%)	0	0	0
>= 24 Months and < 27 Months	n (%)	0	0	0
>= 27 Months and < 30 Months	n (%)	0	0	0
>= 30 Months and < 33 Months	n (%)	0	0	0
>= 33 Months and < 36 Months	n (%)	0	0	0
>= 36 Months and < 39 Months	n (%)	0	0	0
>= 39 Months and < 42 Months	n (%)	0	0	0
>= 42 Months and < 45 Months	n (%)	0	0	0
>= 45 Months and < 48 Months	n (%)	0	0	0
>= 48 Months and < 51 Months	n (%)	0	0	0
>= 51 Months and < 54 Months	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 54 Months and < 57 Months	n (%)	3 (16.7)	3 (21.4)	3 (16.7)
Extent of Exposure (Months)	n	18	14	18
	Mean (SD)	25.86 (23.692)	32.51 (22.773)	25.86 (23.692)
	Median	13.39	33.28	13.39
	Min, Max	0.5, 56.1	5.3, 56.1	0.5, 56.1

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
Extent of Exposure Category (Semi-yearly)				
< 6 Months	n (%)	6 (33.3)	2 (14.3)	6 (33.3)
>= 6 Months and < 12 Months	n (%)	1 (5.6)	1 (7.1)	1 (5.6)
>= 12 Months and < 18 Months	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 18 Months and < 24 Months	n (%)	0	0	0
>= 24 Months and < 30 Months	n (%)	0	0	0
>= 30 Months and < 36 Months	n (%)	0	0	0
>= 36 Months and < 42 Months	n (%)	0	0	0
>= 42 Months and < 48 Months	n (%)	0	0	0
>= 48 Months and < 54 Months	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 54 Months and < 60 Months	n (%)	3 (16.7)	3 (21.4)	3 (16.7)
Extent of Exposure Category (Years)				
< 1 Year	n (%)	7 (38.9)	3 (21.4)	7 (38.9)
>= 1 Year and < 2 Years	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 2 Year and < 3 Years	n (%)	0	0	0
>= 3 Year and < 4 Years	n (%)	0	0	0
>= 4 Year and < 5 Years	n (%)	7 (38.9)	7 (50.0)	7 (38.9)

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
Extent of Exposure (Years)	n	18	14	18
	Mean (SD)	2.15 (1.974)	2.71 (1.898)	2.15 (1.974)
	Median	1.12	2.77	1.12
	Min, Max	0.0, 4.7	0.4, 4.7	0.0, 4.7
Extent of Observation Category (Months)				
< 3 Months	n (%)	2 (11.1)	0	2 (11.1)
>= 3 Months and < 6 Months	n (%)	2 (11.1)	0	2 (11.1)
>= 6 Months and < 9 Months	n (%)	2 (11.1)	2 (14.3)	2 (11.1)
>= 9 Months and < 12 Months	n (%)	1 (5.6)	1 (7.1)	1 (5.6)
>= 12 Months and < 15 Months	n (%)	3 (16.7)	3 (21.4)	3 (16.7)
>= 15 Months and < 18 Months	n (%)	1 (5.6)	1 (7.1)	1 (5.6)
>= 18 Months and < 21 Months	n (%)	0	0	0
>= 21 Months and < 24 Months	n (%)	0	0	0
>= 24 Months and < 27 Months	n (%)	0	0	0
>= 27 Months and < 30 Months	n (%)	0	0	0
>= 30 Months and < 33 Months	n (%)	0	0	0

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
>= 33 Months and < 36 Months	n (%)	0	0	0
>= 36 Months and < 39 Months	n (%)	0	0	0
>= 39 Months and < 42 Months	n (%)	0	0	0
>= 42 Months and < 45 Months	n (%)	0	0	0
>= 45 Months and < 48 Months	n (%)	0	0	0
>= 48 Months and < 51 Months	n (%)	0	0	0
>= 51 Months and < 54 Months	n (%)	2 (11.1)	2 (14.3)	2 (11.1)
>= 54 Months and < 57 Months	n (%)	3 (16.7)	3 (21.4)	3 (16.7)
>= 57 Months and < 60 Months	n (%)	2 (11.1)	2 (14.3)	2 (11.1)
Extent of Observation (Months)	n	18	14	18
	Mean (SD)	27.06 (24.235)	33.86 (23.302)	27.06 (24.235)
	Median	13.83	34.30	13.83
	Min, Max	1.9, 58.9	6.3, 58.9	1.9, 58.9

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.1
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307, TED-C14-004)

		Total Teduglutide		
	Statistic	ITT (N=18)	PP (N=14)	Safety (N=18)
Extent of Observation Category (Years)				
< 1 Year	n (%)	7 (38.9)	3 (21.4)	7 (38.9)
>= 1 Year and < 2 Years	n (%)	4 (22.2)	4 (28.6)	4 (22.2)
>= 2 Year and < 3 Years	n (%)	0	0	0
>= 3 Year and < 4 Years	n (%)	0	0	0
>= 4 Year and < 5 Years	n (%)	7 (38.9)	7 (50.0)	7 (38.9)
Extent of Observation (Years)	n	18	14	18
	Mean (SD)	2.25 (2.020)	2.82 (1.942)	2.25 (2.020)
	Median	1.15	2.86	1.15
	Min, Max	0.2, 4.9	0.5, 4.9	0.2, 4.9

[1] All subjects that participated in either SHP633-306, SHP633-307, or TED-c14-004 are accounted for in this table. SHP633-306 and TED-c14-004 are completed core studies. Subjects from both core studies had the option to participate in the SHP633-307 extension study. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core studies. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.2
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307)

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)
Extent of Exposure (Days)	n	7	6	7
	Mean (SD)	271.6 (149.76)	311.5 (116.28)	271.6 (149.76)
	Median	345.0	362.5	345.0
	Min, Max	32, 415	161, 415	32, 415
Extent of Exposure (Weeks)	n	7	6	7
	Mean (SD)	38.8 (21.39)	44.5 (16.61)	38.8 (21.39)
	Median	49.3	51.8	49.3
	Min, Max	5, 59	23, 59	5, 59
Extent of Exposure Category (Months)				
< 3 Months	n (%)	1 (14.3)	0	1 (14.3)
>= 3 Months and < 6 Months	n (%)	2 (28.6)	2 (33.3)	2 (28.6)
>= 6 Months and < 9 Months	n (%)	0	0	0
>= 9 Months and < 12 Months	n (%)	1 (14.3)	1 (16.7)	1 (14.3)
>= 12 Months and < 15 Months	n (%)	3 (42.9)	3 (50.0)	3 (42.9)

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)

[1] All subjects that participated in either SHP633-306 only or continued onto SHP633-307 are accounted for in this table. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.
[2] Exposure of duration is sum of treatment duration in core study + extension study.
[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.2
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307)

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)
Extent of Exposure (Months)	n	7	6	7
	Mean (SD)	8.92 (4.920)	10.23 (3.820)	8.92 (4.920)
	Median	11.33	11.91	11.33
	Min, Max	1.1, 13.6	5.3, 13.6	1.1, 13.6
Extent of Exposure Category (Semi-yearly)				
< 6 Months	n (%)	3 (42.9)	2 (33.3)	3 (42.9)
>= 6 Months and < 12 Months	n (%)	1 (14.3)	1 (16.7)	1 (14.3)
>= 12 Months and < 18 Months	n (%)	3 (42.9)	3 (50.0)	3 (42.9)
Extent of Exposure Category (Years)				
< 1 Year	n (%)	4 (57.1)	3 (50.0)	4 (57.1)
>= 1 Year and < 2 Years	n (%)	3 (42.9)	3 (50.0)	3 (42.9)

[1] All subjects that participated in either SHP633-306 only or continued onto SHP633-307 are accounted for in this table. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.
[2] Exposure of duration is sum of treatment duration in core study + extension study.
[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.2
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307)

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)
Extent of Exposure (Years)	n	7	6	7
	Mean (SD)	0.74 (0.410)	0.85 (0.318)	0.74 (0.410)
	Median	0.94	0.99	0.94
	Min, Max	0.1, 1.1	0.4, 1.1	0.1, 1.1
Extent of Observation Category (Months)				
< 3 Months	n (%)	1 (14.3)	0	1 (14.3)
>= 3 Months and < 6 Months	n (%)	0	0	0
>= 6 Months and < 9 Months	n (%)	2 (28.6)	2 (33.3)	2 (28.6)
>= 9 Months and < 12 Months	n (%)	1 (14.3)	1 (16.7)	1 (14.3)
>= 12 Months and < 15 Months	n (%)	3 (42.9)	3 (50.0)	3 (42.9)
Extent of Observation (Months)	n	7	6	7
	Mean (SD)	9.65 (4.753)	10.93 (3.651)	9.65 (4.753)
	Median	11.33	12.58	11.33
	Min, Max	2.0, 13.8	6.3, 13.8	2.0, 13.8

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)

[1] All subjects that participated in either SHP633-306 only or continued onto SHP633-307 are accounted for in this table. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.
[2] Exposure of duration is sum of treatment duration in core study + extension study.
[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 1.2
Extent of Exposure
ITT Population, PP Population and Safety Population (Studies SHP633-306, SHP633-307)

		Total Teduglutide		
	Statistic	ITT (N=7)	PP (N=6)	Safety (N=7)
Extent of Observation Category (Years)				
< 1 Year	n (%)	4 (57.1)	3 (50.0)	4 (57.1)
>= 1 Year and < 2 Years	n (%)	3 (42.9)	3 (50.0)	3 (42.9)
Extent of Observation (Years)	n	7	6	7
	Mean (SD)	0.80 (0.396)	0.91 (0.304)	0.80 (0.396)
	Median	0.94	1.05	0.94
	Min, Max	0.2, 1.2	0.5, 1.2	0.2, 1.2

[1] All subjects that participated in either SHP633-306 only or continued onto SHP633-307 are accounted for in this table. ITT=Intent to Treat, PP=Per Protocol. The population definition is from core study.
[2] Exposure of duration is sum of treatment duration in core study + extension study.
[3] Extent of Observation is defined as [(last follow-up date) - (first dose in core study)+1] /365.25, last may follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-307 extension study, the last follow-up date is Feb 4, 2020, inclusive.

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
Number of subjects evaluated	18	18	16	14	12	11	8
All AEs	18 (100.0)	16 (88.9)	11 (68.8)	11 (78.6)	6 (50.0)	8 (72.7)	7 (87.5)
Number of deaths	1 (5.6)	1 (5.6)	0	0	0	0	0
Number of subjects with SAEs other than deaths	11 (61.1)	5 (27.8)	7 (43.8)	3 (21.4)	3 (25.0)	2 (18.2)	0
Number of subjects who discontinued	3 (16.7)	2 (11.1)	1 (6.3)	0	0	0	0
血液およびリンパ系障害	3 (16.7)	2 (11.1)	0	1 (7.1)	0	0	0
貧血	2 (11.1)	2 (11.1)	0	0	0	0	0
播種性血管内凝固	1 (5.6)	1 (5.6)	0	0	0	0	0
赤血球増加症	1 (5.6)	0	0	1 (7.1)	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
Number of subjects evaluated	7	7	7	7	7	7	7
All AEs	5 (71.4)	5 (71.4)	4 (57.1)	4 (57.1)	5 (71.4)	2 (28.6)	3 (42.9)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	2 (28.6)	1 (14.3)	2 (28.6)	0	2 (28.6)	1 (14.3)	1 (14.3)
Number of subjects who discontinued	0	0	0	0	0	0	0
血液およびリンパ系障害	0	0	0	0	0	0	0
貧血	0	0	0	0	0	0	0
播種性血管内凝固	0	0	0	0	0	0	0
赤血球増加症	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
Number of subjects evaluated	7	7	7	7	7	5	2
All AEs	5 (71.4)	5 (71.4)	2 (28.6)	4 (57.1)	4 (57.1)	5 (100.0)	1 (50.0)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	1 (14.3)	0	1 (14.3)	1 (14.3)	3 (42.9)	2 (40.0)	0
Number of subjects who discontinued	0	0	0	0	0	0	0
血液およびリンパ系障害	0	0	0	0	0	0	0
貧血	0	0	0	0	0	0	0
播種性血管内凝固	0	0	0	0	0	0	0
赤血球増加症	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
心臓障害	1 (5.6)	1 (5.6)	0	0	0	0	0
急性心不全	1 (5.6)	1 (5.6)	0	0	0	0	0
耳および迷路障害	1 (5.6)	0	0	0	0	0	0
耳鳴	1 (5.6)	0	0	0	0	0	0
内分泌障害	1 (5.6)	0	0	0	0	0	0
甲状腺嚢腫	1 (5.6)	0	0	0	0	0	0
眼障害	3 (16.7)	1 (5.6)	1 (6.3)	0	1 (8.3)	0	1 (12.5)
眼精疲労	1 (5.6)	0	0	0	0	0	1 (12.5)
眼乾燥	1 (5.6)	0	0	0	0	0	0
眼球浮腫	1 (5.6)	1 (5.6)	0	0	0	0	0
霧視	1 (5.6)	0	0	0	1 (8.3)	0	0
硝子体混濁	1 (5.6)	0	1 (6.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
心臓障害	0	0	0	0	0	0	0
急性心不全	0	0	0	0	0	0	0
耳および迷路障害	0	0	0	0	0	0	0
耳鳴	0	0	0	0	0	0	0
内分泌障害	0	0	0	0	0	1 (14.3)	0
甲状腺嚢腫	0	0	0	0	0	1 (14.3)	0
眼障害	0	1 (14.3)	0	0	0	0	0
眼精疲労	0	1 (14.3)	0	0	0	0	0
眼乾燥	0	1 (14.3)	0	0	0	0	0
眼球浮腫	0	0	0	0	0	0	0
霧視	0	0	0	0	0	0	0
硝子体混濁	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
心臓障害	0	0	0	0	0	0	0
急性心不全	0	0	0	0	0	0	0
耳および迷路障害	0	1 (14.3)	0	0	0	0	0
耳鳴	0	1 (14.3)	0	0	0	0	0
内分泌障害	0	0	0	0	0	0	0
甲状腺嚢腫	0	0	0	0	0	0	0
眼障害	0	0	1 (14.3)	0	0	0	0
眼精疲労	0	0	0	0	0	0	0
眼乾燥	0	0	1 (14.3)	0	0	0	0
眼球浮腫	0	0	0	0	0	0	0
霧視	0	0	0	0	0	0	0
硝子体混濁	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
胃腸障害	15 (83.3)	9 (50.0)	7 (43.8)	2 (14.3)	1 (8.3)	3 (27.3)	3 (37.5)
腹部膨満	6 (33.3)	4 (22.2)	2 (12.5)	0	0	0	0
腹痛	5 (27.8)	2 (11.1)	3 (18.8)	0	0	0	0
下腹部痛	1 (5.6)	0	1 (6.3)	0	0	0	0
上腹部痛	1 (5.6)	0	1 (6.3)	0	0	0	0
腹部圧痛	1 (5.6)	1 (5.6)	0	0	0	0	0
肛門びらん	1 (5.6)	0	0	0	0	0	0
口角口唇炎	1 (5.6)	1 (5.6)	0	0	0	0	0
便秘	1 (5.6)	0	0	0	0	1 (9.1)	0
齲歯	1 (5.6)	0	0	0	1 (8.3)	0	0
下痢	4 (22.2)	0	1 (6.3)	0	0	0	0
十二指腸炎	1 (5.6)	0	0	0	0	0	0
消化不良	1 (5.6)	0	0	0	0	1 (9.1)	0
小腸炎	2 (11.1)	1 (5.6)	0	0	0	0	0
腸炎	3 (16.7)	1 (5.6)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
胃腸障害	1 (14.3)	2 (28.6)	2 (28.6)	1 (14.3)	2 (28.6)	0	1 (14.3)
腹部膨満	0	0	0	0	0	0	0
腹痛	0	1 (14.3)	0	0	0	0	0
下腹部痛	0	0	0	0	0	0	0
上腹部痛	0	0	0	0	0	0	0
腹部圧痛	0	0	0	0	0	0	0
肛門びらん	0	0	0	0	0	0	0
口角口唇炎	0	0	1 (14.3)	0	0	0	0
便秘	0	0	0	0	0	0	0
齲歯	0	0	0	0	0	0	0
下痢	0	1 (14.3)	0	0	1 (14.3)	0	0
十二指腸炎	0	0	0	0	0	0	1 (14.3)
消化不良	0	0	0	0	0	0	0
小腸炎	0	0	0	0	0	0	0
腸炎	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
胃腸障害	1 (14.3)	1 (14.3)	1 (14.3)	0	1 (14.3)	1 (20.0)	0
腹部膨満	0	0	0	0	0	0	0
腹痛	0	0	0	0	0	0	0
下腹部痛	0	0	0	0	0	0	0
上腹部痛	0	0	0	0	0	0	0
腹部圧痛	0	0	0	0	0	0	0
肛門びらん	0	0	0	0	1 (14.3)	0	0
口角口唇炎	0	0	0	0	0	0	0
便秘	0	0	0	0	0	0	0
齲歯	0	0	0	0	0	0	0
下痢	0	1 (14.3)	0	0	0	1 (20.0)	0
十二指腸炎	0	0	0	0	0	0	0
消化不良	0	0	0	0	0	0	0
小腸炎	0	0	1 (14.3)	0	0	0	0
腸炎	1 (14.3)	0	1 (14.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
胃腸障害（続き）							
心窩部不快感	1 (5.6)	0	0	0	0	0	0
おくび	1 (5.6)	1 (5.6)	0	0	0	0	0
胃食道逆流性疾患	1 (5.6)	1 (5.6)	0	0	0	0	0
歯肉痛	1 (5.6)	0	0	0	0	0	0
腸閉塞	1 (5.6)	1 (5.6)	0	0	0	0	0
口腔内出血	1 (5.6)	1 (5.6)	0	0	0	0	0
悪心	4 (22.2)	1 (5.6)	0	0	0	2 (18.2)	3 (37.5)
膵管拡張	1 (5.6)	0	0	0	0	0	0
膵炎	1 (5.6)	1 (5.6)	0	0	0	0	0
肛門周囲痛	1 (5.6)	0	0	1 (7.1)	0	0	0
口内炎	4 (22.2)	1 (5.6)	0	0	0	0	1 (12.5)
歯痛	1 (5.6)	0	0	1 (7.1)	0	0	0
嘔吐	3 (16.7)	1 (5.6)	1 (6.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.

Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
胃腸障害（続き）							
心窩部不快感	1 (14.3)	0	0	0	0	0	0
おくび	0	0	0	0	0	0	0
胃食道逆流性疾患	0	0	0	0	0	0	0
歯肉痛	0	0	1 (14.3)	0	0	0	0
腸閉塞	0	0	0	0	0	0	0
口腔内出血	0	0	0	0	0	0	0
悪心	0	1 (14.3)	0	0	1 (14.3)	0	0
膵管拡張	0	0	0	1 (14.3)	0	0	0
膵炎	0	0	0	0	0	0	0
肛門周囲痛	0	0	0	0	0	0	0
口内炎	0	0	0	0	1 (14.3)	0	0
歯痛	0	1 (14.3)	0	0	0	0	0
嘔吐	0	1 (14.3)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
胃腸障害（続き）							
心窩部不快感	0	0	0	0	0	0	0
おくび	0	0	0	0	0	0	0
胃食道逆流性疾患	0	0	0	0	0	0	0
歯肉痛	0	0	0	0	0	0	0
腸閉塞	0	0	0	0	0	0	0
口腔内出血	0	0	0	0	0	0	0
悪心	0	0	0	0	0	0	0
膵管拡張	0	0	0	0	0	0	0
膵炎	0	0	0	0	0	0	0
肛門周囲痛	0	0	0	0	0	0	0
口内炎	0	0	0	0	0	1 (20.0)	0
歯痛	0	0	0	0	0	0	0
嘔吐	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
一般・全身障害および投与部位の状態	10 (55.6)	8 (44.4)	5 (31.3)	0	1 (8.3)	2 (18.2)	1 (12.5)
カテーテル留置部位炎症	1 (5.6)	0	1 (6.3)	0	0	0	0
カテーテル留置部位疼痛	2 (11.1)	0	1 (6.3)	0	0	0	0
胸痛	1 (5.6)	0	0	0	0	0	0
医療機器閉塞	3 (16.7)	1 (5.6)	1 (6.3)	0	1 (8.3)	0	1 (12.5)
疲労	1 (5.6)	1 (5.6)	0	0	0	0	0
低体温	1 (5.6)	1 (5.6)	0	0	0	0	0
注射部位反応	4 (22.2)	4 (22.2)	0	0	0	0	0
医療機器関連損傷	1 (5.6)	1 (5.6)	0	0	0	0	0
倦怠感	1 (5.6)	0	1 (6.3)	0	0	1 (9.1)	0
浮腫	1 (5.6)	1 (5.6)	0	0	0	0	0
穿刺部位疼痛	1 (5.6)	0	1 (6.3)	0	0	0	0
発熱	8 (44.4)	4 (22.2)	3 (18.8)	0	1 (8.3)	1 (9.1)	0
口渇	1 (5.6)	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.

Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
一般・全身障害および投与部位の状態	2 (28.6)	3 (42.9)	0	1 (14.3)	1 (14.3)	0	0
カテーテル留置部位炎症	0	0	0	0	0	0	0
カテーテル留置部位疼痛	0	1 (14.3)	0	0	1 (14.3)	0	0
胸痛	0	1 (14.3)	0	0	0	0	0
医療機器閉塞	1 (14.3)	0	0	0	0	0	0
疲労	0	0	0	0	0	0	0
低体温	0	0	0	0	0	0	0
注射部位反応	0	0	0	0	0	0	0
医療機器関連損傷	0	0	0	0	0	0	0
倦怠感	0	0	0	0	0	0	0
浮腫	0	0	0	0	0	0	0
穿刺部位疼痛	0	0	0	0	0	0	0
発熱	1 (14.3)	1 (14.3)	0	0	0	0	0
口渇	0	1 (14.3)	0	1 (14.3)	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
一般・全身障害および投与部位の状態	0	0	0	0	1 (14.3)	1 (20.0)	0
カテーテル留置部位炎症	0	0	0	0	0	0	0
カテーテル留置部位疼痛	0	0	0	0	1 (14.3)	1 (20.0)	0
胸痛	0	0	0	0	0	0	0
医療機器閉塞	0	0	0	0	0	0	0
疲労	0	0	0	0	0	0	0
低体温	0	0	0	0	0	0	0
注射部位反応	0	0	0	0	0	0	0
医療機器関連損傷	0	0	0	0	0	0	0
倦怠感	0	0	0	0	0	0	0
浮腫	0	0	0	0	0	0	0
穿刺部位疼痛	0	0	0	0	0	0	0
発熱	0	0	0	0	0	0	0
口渇	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
肝胆道系障害	4 (22.2)	2 (11.1)	0	1 (7.1)	0	0	0
急性肝不全	1 (5.6)	1 (5.6)	0	0	0	0	0
胆嚢炎	1 (5.6)	0	0	1 (7.1)	0	0	0
胆石症	1 (5.6)	1 (5.6)	0	0	0	0	0
高ビリルビン血症	1 (5.6)	1 (5.6)	0	0	0	0	0
過形成性胆嚢症	1 (5.6)	0	0	0	0	0	0
免疫系障害	2 (11.1)	0	0	0	0	0	1 (12.5)
過敏症	2 (11.1)	0	0	0	0	0	1 (12.5)
感染症および寄生虫症	12 (66.7)	6 (33.3)	5 (31.3)	4 (28.6)	4 (33.3)	3 (27.3)	3 (37.5)
肛門膿瘍	3 (16.7)	0	0	1 (7.1)	0	0	0
細菌性関節炎	1 (5.6)	0	0	0	0	0	0
カンジダ性亀頭炎	1 (5.6)	1 (5.6)	0	0	0	0	0
カテーテル留置部位感染	2 (11.1)	1 (5.6)	0	0	0	1 (9.1)	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
肝胆道系障害	0	0	0	1 (14.3)	0	0	0
急性肝不全	0	0	0	0	0	0	0
胆嚢炎	0	0	0	0	0	0	0
胆石症	0	0	0	0	0	0	0
高ビリルビン血症	0	0	0	0	0	0	0
過形成性胆嚢症	0	0	0	1 (14.3)	0	0	0
免疫系障害	0	0	0	0	0	0	0
過敏症	0	0	0	0	0	0	0
感染症および寄生虫症	3 (42.9)	2 (28.6)	2 (28.6)	1 (14.3)	3 (42.9)	2 (28.6)	3 (42.9)
肛門膿瘍	0	0	0	0	0	1 (14.3)	0
細菌性関節炎	0	0	0	0	1 (14.3)	0	0
カンジダ性亀頭炎	0	0	0	0	0	0	0
カテーテル留置部位感染	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
肝胆道系障害	0	0	0	0	0	0	0
急性肝不全	0	0	0	0	0	0	0
胆嚢炎	0	0	0	0	0	0	0
胆石症	0	0	0	0	0	0	0
高ビリルビン血症	0	0	0	0	0	0	0
過形成性胆嚢症	0	0	0	0	0	0	0
免疫系障害	0	0	0	0	0	1 (20.0)	0
過敏症	0	0	0	0	0	1 (20.0)	0
感染症および寄生虫症	2 (28.6)	3 (42.9)	2 (28.6)	3 (42.9)	4 (57.1)	5 (100.0)	0
肛門膿瘍	0	0	1 (14.3)	0	0	0	0
細菌性関節炎	0	0	0	0	0	0	0
カンジダ性亀頭炎	0	0	0	0	0	0	0
カテーテル留置部位感染	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
感染症および寄生虫症（続き）							
蜂巣炎	1 (5.6)	0	0	0	1 (8.3)	0	0
医療機器関連感染	10 (55.6)	5 (27.8)	3 (18.8)	2 (14.3)	3 (25.0)	1 (9.1)	0
歯肉炎	1 (5.6)	0	0	0	0	0	1 (12.5)
インフルエンザ	5 (27.8)	0	0	0	1 (8.3)	1 (9.1)	0
医療機器使用部位感染	1 (5.6)	1 (5.6)	0	0	0	0	0
上咽頭炎	7 (38.9)	1 (5.6)	2 (12.5)	2 (14.3)	1 (8.3)	0	2 (25.0)
爪真菌症	1 (5.6)	0	0	0	0	0	0
口腔カンジダ症	1 (5.6)	1 (5.6)	0	0	0	0	0
口腔ヘルペス	2 (11.1)	1 (5.6)	0	0	0	0	0
咽頭炎	1 (5.6)	0	0	0	0	0	0
気道感染	1 (5.6)	0	0	0	0	0	0
敗血症	1 (5.6)	1 (5.6)	0	0	0	0	0
レンサ球菌感染	1 (5.6)	0	0	0	1 (8.3)	0	0
トリコフィトン感染症	1 (5.6)	0	1 (6.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
感染症および寄生虫症（続き）							
蜂巣炎	0	0	0	0	0	0	0
医療機器関連感染	0	1 (14.3)	2 (28.6)	0	1 (14.3)	1 (14.3)	1 (14.3)
歯肉炎	0	0	1 (14.3)	0	0	0	0
インフルエンザ	1 (14.3)	0	0	0	0	0	0
医療機器使用部位感染	0	0	0	0	0	0	0
上咽頭炎	3 (42.9)	1 (14.3)	1 (14.3)	1 (14.3)	2 (28.6)	0	1 (14.3)
爪真菌症	0	0	0	0	0	0	0
口腔カンジダ症	0	0	0	0	0	0	0
口腔ヘルペス	0	0	0	0	0	0	0
咽頭炎	0	0	0	0	0	0	0
気道感染	0	0	0	0	0	0	1 (14.3)
敗血症	0	0	0	0	0	0	0
レンサ球菌感染	0	0	0	0	0	0	0
トリコフィトン感染症	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
感染症および寄生虫症（続き）							
蜂巣炎	0	0	0	0	0	0	0
医療機器関連感染	1 (14.3)	0	0	1 (14.3)	3 (42.9)	2 (40.0)	0
歯肉炎	0	0	0	0	0	0	0
インフルエンザ	0	0	0	1 (14.3)	0	2 (40.0)	0
医療機器使用部位感染	0	0	0	0	0	0	0
上咽頭炎	1 (14.3)	2 (28.6)	0	0	1 (14.3)	0	0
爪真菌症	0	0	0	1 (14.3)	0	0	0
口腔カンジダ症	0	0	0	0	0	0	0
口腔ヘルペス	0	0	0	0	0	1 (20.0)	0
咽頭炎	0	1 (14.3)	0	0	0	0	0
気道感染	0	0	0	0	0	0	0
敗血症	0	0	0	0	0	0	0
レンサ球菌感染	0	0	0	0	0	0	0
トリコフィトン感染症	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
感染症および寄生虫症（続き）							
上気道感染	1 (5.6)	0	0	0	0	0	0
傷害、中毒および処置合併症	5 (27.8)	3 (16.7)	2 (12.5)	0	0	1 (9.1)	0
消化管ストーマ合併症	1 (5.6)	1 (5.6)	0	0	0	0	0
筋挫傷	1 (5.6)	0	1 (6.3)	0	0	0	0
処置による疼痛	1 (5.6)	0	0	0	0	1 (9.1)	0
肋骨骨折	1 (5.6)	1 (5.6)	0	0	0	0	0
脊椎圧迫骨折	1 (5.6)	0	1 (6.3)	0	0	0	0
ストーマ部反応	1 (5.6)	1 (5.6)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
感染症および寄生虫症（続き）							
上気道感染	0	0	0	0	0	0	0
傷害、中毒および処置合併症	0	0	0	0	0	0	0
消化管ストーマ合併症	0	0	0	0	0	0	0
筋挫傷	0	0	0	0	0	0	0
処置による疼痛	0	0	0	0	0	0	0
肋骨骨折	0	0	0	0	0	0	0
脊椎圧迫骨折	0	0	0	0	0	0	0
ストーマ部反応	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
感染症および寄生虫症（続き）							
上気道感染	0	0	1 (14.3)	0	0	0	0
傷害、中毒および処置合併症	0	0	0	0	0	0	0
消化管ストーマ合併症	0	0	0	0	0	0	0
筋挫傷	0	0	0	0	0	0	0
処置による疼痛	0	0	0	0	0	0	0
肋骨骨折	0	0	0	0	0	0	0
脊椎圧迫骨折	0	0	0	0	0	0	0
ストーマ部反応	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
臨床検査	7 (38.9)	5 (27.8)	2 (12.5)	0	2 (16.7)	0	0
血中アルカリホスファターゼ増加	1 (5.6)	1 (5.6)	0	0	0	0	0
血中クレアチニン増加	1 (5.6)	0	0	0	1 (8.3)	0	0
Ｃ－反応性蛋白増加	1 (5.6)	0	1 (6.3)	0	0	0	0
癌胎児性抗原増加	1 (5.6)	1 (5.6)	0	0	0	0	0
腸通過時間延長	1 (5.6)	1 (5.6)	0	0	0	0	0
リパーゼ増加	1 (5.6)	1 (5.6)	0	0	0	0	0
肝機能検査値上昇	1 (5.6)	0	0	0	1 (8.3)	0	0
好中球数減少	1 (5.6)	0	0	0	0	0	0
酸素飽和度低下	1 (5.6)	1 (5.6)	0	0	0	0	0
血小板数減少	1 (5.6)	1 (5.6)	1 (6.3)	0	0	0	0
尿量減少	1 (5.6)	1 (5.6)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
臨床検査	0	0	0	0	0	0	0
血中アルカリホスファターゼ増加	0	0	0	0	0	0	0
血中クレアチニン増加	0	0	0	0	0	0	0
Ｃ－反応性蛋白増加	0	0	0	0	0	0	0
癌胎児性抗原増加	0	0	0	0	0	0	0
腸通過時間延長	0	0	0	0	0	0	0
リパーゼ増加	0	0	0	0	0	0	0
肝機能検査値上昇	0	0	0	0	0	0	0
好中球数減少	0	0	0	0	0	0	0
酸素飽和度低下	0	0	0	0	0	0	0
血小板数減少	0	0	0	0	0	0	0
尿量減少	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
臨床検査	0	1 (14.3)	0	0	0	1 (20.0)	0
血中アルカリホスファターゼ増加	0	0	0	0	0	0	0
血中クレアチニン増加	0	0	0	0	0	0	0
Ｃ－反応性蛋白増加	0	1 (14.3)	0	0	0	0	0
癌胎児性抗原増加	0	0	0	0	0	0	0
腸通過時間延長	0	0	0	0	0	0	0
リパーゼ増加	0	0	0	0	0	0	0
肝機能検査値上昇	0	0	0	0	0	0	0
好中球数減少	0	0	0	0	0	1 (20.0)	0
酸素飽和度低下	0	0	0	0	0	0	0
血小板数減少	0	0	0	0	0	0	0
尿量減少	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
臨床検査（続き）							
白血球数減少	1 (5.6)	0	0	0	0	0	0
代謝および栄養障害	7 (38.9)	4 (22.2)	0	1 (7.1)	0	2 (18.2)	1 (12.5)
食欲減退	1 (5.6)	0	0	0	0	1 (9.1)	0
脱水	2 (11.1)	2 (11.1)	0	1 (7.1)	0	0	0
高血糖	1 (5.6)	1 (5.6)	0	0	0	0	0
低血糖	1 (5.6)	1 (5.6)	0	0	0	0	0
低カリウム血症	1 (5.6)	0	0	0	0	0	1 (12.5)
低マグネシウム血症	1 (5.6)	0	0	0	0	0	0
低亜鉛血症	2 (11.1)	1 (5.6)	0	0	0	0	0
栄養障害	1 (5.6)	1 (5.6)	0	0	0	0	0
セレニウム欠乏	1 (5.6)	0	0	0	0	1 (9.1)	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.

Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
臨床検査（続き）							
白血球数減少	0	0	0	0	0	0	0
代謝および栄養障害	0	0	1 (14.3)	0	1 (14.3)	1 (14.3)	0
食欲減退	0	0	0	0	0	0	0
脱水	0	0	1 (14.3)	0	0	0	0
高血糖	0	0	0	0	0	0	0
低血糖	0	0	0	0	0	0	0
低カリウム血症	0	0	0	0	0	0	0
低マグネシウム血症	0	0	0	0	1 (14.3)	0	0
低亜鉛血症	0	0	0	0	0	1 (14.3)	0
栄養障害	0	0	0	0	0	0	0
セレニウム欠乏	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
臨床検査（続き）							
白血球数減少	0	0	0	0	0	1 (20.0)	0
代謝および栄養障害	0	0	0	0	0	0	0
食欲減退	0	0	0	0	0	0	0
脱水	0	0	0	0	0	0	0
高血糖	0	0	0	0	0	0	0
低血糖	0	0	0	0	0	0	0
低カリウム血症	0	0	0	0	0	0	0
低マグネシウム血症	0	0	0	0	0	0	0
低亜鉛血症	0	0	0	0	0	0	0
栄養障害	0	0	0	0	0	0	0
セレニウム欠乏	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
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Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
筋骨格系および結合組織障害	8 (44.4)	2 (11.1)	0	3 (21.4)	1 (8.3)	1 (9.1)	1 (12.5)
関節痛	5 (27.8)	0	0	2 (14.3)	0	1 (9.1)	0
関節炎	1 (5.6)	0	0	0	0	0	0
背部痛	2 (11.1)	1 (5.6)	0	0	0	0	1 (12.5)
筋痙縮	1 (5.6)	0	0	1 (7.1)	0	0	0
筋肉痛	1 (5.6)	1 (5.6)	0	0	0	0	0
多発性関節炎	1 (5.6)	0	0	0	0	0	0
顎関節症候群	1 (5.6)	0	0	0	1 (8.3)	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (5.6)	0	0	0	0	0	0
卵巣腺腫	1 (5.6)	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
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(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
筋骨格系および結合組織障害	1 (14.3)	1 (14.3)	0	0	1 (14.3)	0	0
関節痛	0	1 (14.3)	0	0	0	0	0
関節炎	1 (14.3)	0	0	0	0	0	0
背部痛	0	0	0	0	0	0	0
筋痙縮	0	0	0	0	0	0	0
筋肉痛	0	0	0	0	0	0	0
多発性関節炎	0	0	0	0	1 (14.3)	0	0
顎関節症候群	0	0	0	0	0	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (14.3)	0	0	0	0	0	0
卵巣腺腫	1 (14.3)	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
筋骨格系および結合組織障害	0	0	0	1 (14.3)	0	0	0
関節痛	0	0	0	1 (14.3)	0	0	0
関節炎	0	0	0	0	0	0	0
背部痛	0	0	0	0	0	0	0
筋痙縮	0	0	0	0	0	0	0
筋肉痛	0	0	0	0	0	0	0
多発性関節炎	0	0	0	0	0	0	0
顎関節症候群	0	0	0	0	0	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0	0	0	0	0	0	0
卵巣腺腫	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
神経系障害	8 (44.4)	3 (16.7)	1 (6.3)	3 (21.4)	3 (25.0)	2 (18.2)	2 (25.0)
健忘	1 (5.6)	0	0	0	0	0	0
浮動性めまい	1 (5.6)	0	0	1 (7.1)	0	0	1 (12.5)
構音障害	1 (5.6)	0	0	0	0	0	0
てんかん	1 (5.6)	0	1 (6.3)	0	0	0	0
頭痛	7 (38.9)	2 (11.1)	1 (6.3)	1 (7.1)	3 (25.0)	2 (18.2)	0
失神寸前の状態	1 (5.6)	1 (5.6)	0	0	0	0	0
傾眠	3 (16.7)	0	0	1 (7.1)	0	0	1 (12.5)
製品の問題	1 (5.6)	0	0	1 (7.1)	0	0	0
医療機器破損	1 (5.6)	0	0	1 (7.1)	0	0	0
精神障害	3 (16.7)	0	0	2 (14.3)	0	0	1 (12.5)
不安障害	1 (5.6)	0	0	0	0	0	0
うつ病	1 (5.6)	0	0	1 (7.1)	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
神経系障害	0	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)	0	0
健忘	0	1 (14.3)	0	0	0	0	0
浮動性めまい	0	0	0	0	0	0	0
構音障害	0	1 (14.3)	0	0	0	0	0
てんかん	0	0	0	0	0	0	0
頭痛	0	0	0	1 (14.3)	1 (14.3)	0	0
失神寸前の状態	0	0	0	0	0	0	0
傾眠	0	0	1 (14.3)	0	0	0	0
製品の問題	0	0	0	0	0	0	0
医療機器破損	0	0	0	0	0	0	0
精神障害	0	1 (14.3)	0	0	0	0	0
不安障害	0	1 (14.3)	0	0	0	0	0
うつ病	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
神経系障害	0	0	1 (14.3)	0	1 (14.3)	0	0
健忘	0	0	0	0	0	0	0
浮動性めまい	0	0	0	0	0	0	0
構音障害	0	0	0	0	0	0	0
てんかん	0	0	0	0	0	0	0
頭痛	0	0	1 (14.3)	0	1 (14.3)	0	0
失神寸前の状態	0	0	0	0	0	0	0
傾眠	0	0	0	0	0	0	0
製品の問題	0	0	0	0	0	0	0
医療機器破損	0	0	0	0	0	0	0
精神障害	0	0	0	0	0	0	0
不安障害	0	0	0	0	0	0	0
うつ病	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
精神障害（続き）							
不眠症	2 (11.1)	0	0	1 (7.1)	0	0	1 (12.5)
腎および尿路障害	5 (27.8)	2 (11.1)	0	0	0	1 (9.1)	0
急性腎障害	1 (5.6)	1 (5.6)	0	0	0	0	0
血尿	3 (16.7)	1 (5.6)	0	0	0	1 (9.1)	0
腎嚢胞	1 (5.6)	0	0	0	0	0	0
尿失禁	1 (5.6)	0	0	0	0	0	0
生殖系および乳房障害	1 (5.6)	1 (5.6)	0	0	0	0	0
月経過多	1 (5.6)	1 (5.6)	0	0	0	0	0
呼吸器、胸郭および縦隔障害	7 (38.9)	4 (22.2)	1 (6.3)	0	0	0	2 (25.0)
喘息	1 (5.6)	0	0	0	0	0	1 (12.5)
鼻出血	1 (5.6)	1 (5.6)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
精神障害（続き）							
不眠症	0	0	0	0	0	0	0
腎および尿路障害	0	1 (14.3)	0	1 (14.3)	0	0	0
急性腎障害	0	0	0	0	0	0	0
血尿	0	0	0	0	0	0	0
腎嚢胞	0	0	0	1 (14.3)	0	0	0
尿失禁	0	1 (14.3)	0	0	0	0	0
生殖系および乳房障害	0	0	0	0	0	0	0
月経過多	0	0	0	0	0	0	0
呼吸器、胸郭および縦隔障害	1 (14.3)	2 (28.6)	0	0	0	0	0
喘息	0	0	0	0	0	0	0
鼻出血	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
精神障害（続き）							
不眠症	0	0	0	0	0	0	0
腎および尿路障害	0	1 (14.3)	0	0	0	0	0
急性腎障害	0	0	0	0	0	0	0
血尿	0	1 (14.3)	0	0	0	0	0
腎嚢胞	0	0	0	0	0	0	0
尿失禁	0	0	0	0	0	0	0
生殖系および乳房障害	0	0	0	0	0	0	0
月経過多	0	0	0	0	0	0	0
呼吸器、胸郭および縦隔障害	0	1 (14.3)	0	0	1 (14.3)	0	1 (50.0)
喘息	0	0	0	0	0	0	1 (50.0)
鼻出血	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
呼吸器、胸郭および縦隔障害（続き）							
口腔咽頭痛	4 (22.2)	1 (5.6)	0	0	0	0	1 (12.5)
呼吸不全	1 (5.6)	1 (5.6)	0	0	0	0	0
アレルギー性鼻炎	1 (5.6)	0	0	0	0	0	0
上気道の炎症	2 (11.1)	1 (5.6)	1 (6.3)	0	0	0	0
皮膚および皮下組織障害	9 (50.0)	3 (16.7)	1 (6.3)	1 (7.1)	2 (16.7)	1 (9.1)	2 (25.0)
ざ瘡	1 (5.6)	0	0	0	0	1 (9.1)	0
皮膚嚢腫	1 (5.6)	0	1 (6.3)	0	0	0	0
接触皮膚炎	4 (22.2)	0	0	1 (7.1)	1 (8.3)	0	1 (12.5)
皮膚乾燥	2 (11.1)	1 (5.6)	0	0	0	0	0
湿疹	1 (5.6)	0	0	0	0	0	0
貨幣状湿疹	1 (5.6)	0	0	0	0	0	0
紅斑	1 (5.6)	0	0	0	0	0	1 (12.5)

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
呼吸器、胸郭および縦隔障害（続き）							
口腔咽頭痛	0	1 (14.3)	0	0	0	0	0
呼吸不全	0	0	0	0	0	0	0
アレルギー性鼻炎	0	1 (14.3)	0	0	0	0	0
上気道の炎症	1 (14.3)	0	0	0	0	0	0
皮膚および皮下組織障害	0	0	0	1 (14.3)	0	0	0
ざ瘡	0	0	0	0	0	0	0
皮膚嚢腫	0	0	0	0	0	0	0
接触皮膚炎	0	0	0	0	0	0	0
皮膚乾燥	0	0	0	1 (14.3)	0	0	0
湿疹	0	0	0	0	0	0	0
貨幣状湿疹	0	0	0	0	0	0	0
紅斑	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
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Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
呼吸器、胸郭および縦隔障害（続き）							
口腔咽頭痛	0	0	0	0	1 (14.3)	0	0
呼吸不全	0	0	0	0	0	0	0
アレルギー性鼻炎	0	1 (14.3)	0	0	0	0	0
上気道の炎症	0	0	0	0	0	0	0
皮膚および皮下組織障害	2 (28.6)	0	0	1 (14.3)	0	1 (20.0)	0
ざ瘡	0	0	0	0	0	0	0
皮膚嚢腫	0	0	0	0	0	0	0
接触皮膚炎	1 (14.3)	0	0	0	0	0	0
皮膚乾燥	0	0	0	0	0	0	0
湿疹	0	0	0	1 (14.3)	0	0	0
貨幣状湿疹	1 (14.3)	0	0	0	0	0	0
紅斑	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
皮膚および皮下組織障害（続き）							
皮下出血	2 (11.1)	1 (5.6)	0	0	1 (8.3)	0	0
そう痒症	2 (11.1)	1 (5.6)	0	0	0	0	1 (12.5)
発疹	1 (5.6)	0	0	0	0	0	0
蕁麻疹	1 (5.6)	1 (5.6)	0	0	0	0	0
血管障害	4 (22.2)	1 (5.6)	1 (6.3)	0	0	0	1 (12.5)
静脈炎	1 (5.6)	1 (5.6)	0	0	0	0	0
鎖骨下静脈閉塞	1 (5.6)	0	0	0	0	0	0
血栓性静脈炎	1 (5.6)	0	1 (6.3)	0	0	0	0
血管痛	2 (11.1)	0	0	0	0	0	1 (12.5)

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
皮膚および皮下組織障害（続き）							
皮下出血	0	0	0	0	0	0	0
そう痒症	0	0	0	0	0	0	0
発疹	0	0	0	0	0	0	0
蕁麻疹	0	0	0	0	0	0	0
血管障害	0	1 (14.3)	0	0	0	0	0
静脈炎	0	0	0	0	0	0	0
鎖骨下静脈閉塞	0	0	0	0	0	0	0
血栓性静脈炎	0	0	0	0	0	0	0
血管痛	0	1 (14.3)	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307, TED-C14-004)

	Teduglutide						
Day of Onset	Month 39 to 42	Month 42 to 45	Month 45 to 48	Month 48 to 51	Month 51 to 54	Month 54 to 57	Month 57 to 60
皮膚および皮下組織障害（続き）							
皮下出血	0	0	0	1 (14.3)	0	0	0
そう痒症	0	0	0	0	0	0	0
発疹	0	0	0	0	0	1 (20.0)	0
蕁麻疹	0	0	0	0	0	0	0
血管障害	0	0	0	1 (14.3)	0	0	0
静脈炎	0	0	0	0	0	0	0
鎖骨下静脈閉塞	0	0	0	1 (14.3)	0	0	0
血栓性静脈炎	0	0	0	0	0	0	0
血管痛	0	0	0	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".

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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
Number of subjects evaluated	7	7	6	6	4	3
All AEs	7 (100.0)	6 (85.7)	4 (66.7)	4 (66.7)	2 (50.0)	2 (66.7)
Number of deaths	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	4 (57.1)	2 (28.6)	2 (33.3)	2 (33.3)	0	0
Number of subjects who discontinued	1 (14.3)	1 (14.3)	0	0	0	0
血液およびリンパ系障害	2 (28.6)	1 (14.3)	0	1 (16.7)	0	0
貧血	1 (14.3)	1 (14.3)	0	0	0	0
赤血球増加症	1 (14.3)	0	0	1 (16.7)	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
胃腸障害	5 (71.4)	3 (42.9)	3 (50.0)	0	0	0
腹部膨満	3 (42.9)	2 (28.6)	1 (16.7)	0	0	0
腹痛	1 (14.3)	0	1 (16.7)	0	0	0
下腹部痛	1 (14.3)	0	1 (16.7)	0	0	0
胃食道逆流性疾患	1 (14.3)	1 (14.3)	0	0	0	0
悪心	1 (14.3)	1 (14.3)	0	0	0	0
一般・全身障害および投与部位の状態	3 (42.9)	3 (42.9)	1 (16.7)	0	0	0
注射部位反応	2 (28.6)	2 (28.6)	0	0	0	0
発熱	3 (42.9)	2 (28.6)	1 (16.7)	0	0	0
肝胆道系障害	2 (28.6)	1 (14.3)	0	1 (16.7)	0	0
胆嚢炎	1 (14.3)	0	0	1 (16.7)	0	0
胆石症	1 (14.3)	1 (14.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
感染症および寄生虫症	4 (57.1)	2 (28.6)	1 (16.7)	2 (33.3)	0	1 (33.3)
肛門膿瘍	1 (14.3)	0	0	1 (16.7)	0	0
医療機器関連感染	2 (28.6)	1 (14.3)	0	1 (16.7)	0	0
インフルエンザ	1 (14.3)	0	0	0	0	1 (33.3)
医療機器使用部位感染	1 (14.3)	1 (14.3)	0	0	0	0
上咽頭炎	2 (28.6)	1 (14.3)	1 (16.7)	0	0	0
傷害、中毒および処置合併症	3 (42.9)	2 (28.6)	2 (33.3)	0	0	0
消化管ストーマ合併症	1 (14.3)	1 (14.3)	0	0	0	0
筋挫傷	1 (14.3)	0	1 (16.7)	0	0	0
肋骨骨折	1 (14.3)	1 (14.3)	0	0	0	0
脊椎圧迫骨折	1 (14.3)	0	1 (16.7)	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
代謝および栄養障害	2 (28.6)	1 (14.3)	0	0	0	1 (33.3)
低亜鉛血症	1 (14.3)	1 (14.3)	0	0	0	0
セレニウム欠乏	1 (14.3)	0	0	0	0	1 (33.3)
筋骨格系および結合組織障害	1 (14.3)	1 (14.3)	0	0	0	0
背部痛	1 (14.3)	1 (14.3)	0	0	0	0
神経系障害	1 (14.3)	0	1 (16.7)	1 (16.7)	0	0
てんかん	1 (14.3)	0	1 (16.7)	0	0	0
頭痛	1 (14.3)	0	1 (16.7)	0	0	0
傾眠	1 (14.3)	0	0	1 (16.7)	0	0
製品の問題	1 (14.3)	0	0	1 (16.7)	0	0
医療機器破損	1 (14.3)	0	0	1 (16.7)	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
腎および尿路障害	1 (14.3)	0	0	0	0	1 (33.3)
血尿	1 (14.3)	0	0	0	0	1 (33.3)
生殖系および乳房障害	1 (14.3)	1 (14.3)	0	0	0	0
月経過多	1 (14.3)	1 (14.3)	0	0	0	0
呼吸器、胸郭および縦隔障害	2 (28.6)	2 (28.6)	0	0	0	0
鼻出血	1 (14.3)	1 (14.3)	0	0	0	0
口腔咽頭痛	1 (14.3)	1 (14.3)	0	0	0	0
皮膚および皮下組織障害	3 (42.9)	2 (28.6)	0	0	2 (50.0)	0
接触皮膚炎	1 (14.3)	0	0	0	1 (25.0)	0
皮膚乾燥	1 (14.3)	1 (14.3)	0	0	0	0
皮下出血	1 (14.3)	1 (14.3)	0	0	1 (25.0)	0
蕁麻疹	1 (14.3)	1 (14.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 3.2
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-306, SHP633-307)

		Teduglutide				
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15
血管障害	1 (14.3)	1 (14.3)	0	0	0	0
静脈炎	1 (14.3)	1 (14.3)	0	0	0	0

Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence but can be counted multiple times for the number of events.
Note: Number of Deaths is based on AEs with a Fatal outcome or have an SAE reason of Death. Number of subjects with SAEs other than deaths is based on Serious AEs that wasn't Fatal. Number of Subjects who discontinued based on AEs with "Drug Withdrawn".
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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

		Children			
	Statistic	All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
Extent of Exposure (Days)	n	8	6	2	10
	Mean (SD)	475.1 (314.46)	421.3 (157.31)	300.5 (51.62)	440.2 (287.45)
	Median	442.5	442.5	300.5	380.0
	Min, Max	137, 1136	168, 631	264, 337	137, 1136
Extent of Exposure (Weeks)	n	8	6	2	10
	Mean (SD)	67.9 (44.92)	60.2 (22.47)	42.9 (7.37)	62.9 (41.06)
	Median	63.2	63.2	42.9	54.3
	Min, Max	20, 162	24, 90	38, 48	20, 162
Extent of Exposure Category (Months)					
< 3 Months	n (%)	0	0	0	0
>= 3 Months and < 6 Months	n (%)	2 (25.0)	1 (16.7)	0	2 (20.0)
>= 6 Months and < 9 Months	n (%)	0	0	1 (50.0)	1 (10.0)
>= 9 Months and < 12 Months	n (%)	1 (12.5)	1 (16.7)	1 (50.0)	2 (20.0)
>= 12 Months and < 15 Months	n (%)	1 (12.5)	1 (16.7)	0	1 (10.0)
>= 15 Months and < 18 Months	n (%)	2 (25.0)	2 (33.3)	0	2 (20.0)

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

		Children			
	Statistic	All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
>= 18 Months and < 21 Months	n (%)	1 (12.5)	1 (16.7)	0	1 (10.0)
>= 21 Months and < 24 Months	n (%)	0	0	0	0
>= 24 Months and < 27 Months	n (%)	0	0	0	0
>= 27 Months and < 30 Months	n (%)	0	0	0	0
>= 30 Months and < 33 Months	n (%)	0	0	0	0
>= 33 Months and < 36 Months	n (%)	0	0	0	0
>= 36 Months and < 39 Months	n (%)	1 (12.5)	0	0	1 (10.0)
>= 39 Months and < 42 Months	n (%)	0	0	0	0
Extent of Exposure (Months)	n	8	6	2	10
	Mean (SD)	15.61 (10.331)	13.84 (5.168)	9.87 (1.696)	14.46 (9.444)
	Median	14.54	14.54	9.87	12.48
	Min, Max	4.5, 37.3	5.5, 20.7	8.7, 11.1	4.5, 37.3

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

	Statistic	Children			
		All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
Extent of Exposure Category (Semi-yearly)					
< 6 Months	n (%)	2 (25.0)	1 (16.7)	0	2 (20.0)
>= 6 Months and < 12 Months	n (%)	1 (12.5)	1 (16.7)	2 (100.0)	3 (30.0)
>= 12 Months and < 18 Months	n (%)	3 (37.5)	3 (50.0)	0	3 (30.0)
>= 18 Months and < 24 Months	n (%)	1 (12.5)	1 (16.7)	0	1 (10.0)
>= 24 Months and < 30 Months	n (%)	0	0	0	0
>= 30 Months and < 36 Months	n (%)	0	0	0	0
>= 36 Months and < 42 Months	n (%)	1 (12.5)	0	0	1 (10.0)
Extent of Exposure Category (Years)					
< 1 Year	n (%)	3 (37.5)	2 (33.3)	2 (100.0)	5 (50.0)
>= 1 Year and < 2 Years	n (%)	4 (50.0)	4 (66.7)	0	4 (40.0)
>= 2 Year and < 3 Years	n (%)	0	0	0	0
>= 3 Year and < 4 Years	n (%)	1 (12.5)	0	0	1 (10.0)

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

		Children			
	Statistic	All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
Extent of Exposure (Years)	n	8	6	2	10
	Mean (SD)	1.30 (0.861)	1.15 (0.431)	0.82 (0.141)	1.21 (0.787)
	Median	1.21	1.21	0.82	1.04
	Min, Max	0.4, 3.1	0.5, 1.7	0.7, 0.9	0.4, 3.1
Extent of Observation Category (Months)					
< 3 Months	n (%)	0	0	0	0
>= 3 Months and < 6 Months	n (%)	0	0	0	0
>= 6 Months and < 9 Months	n (%)	1 (12.5)	0	0	1 (10.0)
>= 9 Months and < 12 Months	n (%)	0	0	0	0
>= 12 Months and < 15 Months	n (%)	1 (12.5)	1 (16.7)	1 (50.0)	2 (20.0)
>= 15 Months and < 18 Months	n (%)	3 (37.5)	3 (50.0)	1 (50.0)	4 (40.0)
>= 18 Months and < 21 Months	n (%)	1 (12.5)	1 (16.7)	0	1 (10.0)
>= 21 Months and < 24 Months	n (%)	1 (12.5)	1 (16.7)	0	1 (10.0)
>= 24 Months and < 27 Months	n (%)	0	0	0	0
>= 27 Months and < 30 Months	n (%)	0	0	0	0
>= 30 Months and < 33 Months	n (%)	0	0	0	0

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

		Children			
	Statistic	All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
>= 33 Months and < 36 Months	n (%)	0	0	0	0
>= 36 Months and < 39 Months	n (%)	1 (12.5)	0	0	1 (10.0)
Extent of Observation (Months)	n	8	6	2	10
	Mean (SD)	18.64 (9.175)	17.44 (2.413)	14.42 (3.067)	17.79 (8.347)
	Median	16.72	16.72	14.42	16.59
	Min, Max	6.0, 38.4	15.0, 21.9	12.3, 16.6	6.0, 38.4

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 10.1
Extent of Exposure
(Studies SHP633-302, SHP633-305)

		Children			
	Statistic	All Children (N=8)	After Amendent 3 (N=6)	Infants (N=2)	Children + Infants (N=10)
Extent of Observation Category (Years)					
< 1 Year	n (%)	1 (12.5)	0	0	1 (10.0)
>= 1 Year and < 2 Years	n (%)	6 (75.0)	6 (100.0)	2 (100.0)	8 (80.0)
>= 2 Year and < 3 Years	n (%)	0	0	0	0
>= 3 Year and < 4 Years	n (%)	1 (12.5)	0	0	1 (10.0)
Extent of Observation (Years)	n	8	6	2	10
	Mean (SD)	1.55 (0.765)	1.45 (0.201)	1.20 (0.256)	1.48 (0.696)
	Median	1.39	1.39	1.20	1.38
	Min, Max	0.5, 3.2	1.2, 1.8	1.0, 1.4	0.5, 3.2

[1] All subjects that participated in either SHP633-302 of SHP633-305 are accounted for in this table. Protocol Amendment 3 uses vial adaptors. All infants were enrolled after Protocol Amendment 3. In the 305 extension study, the use of vial adaptors are aligned with what was used in the core study.

[2] Exposure of duration is sum of treatment duration in core study + extension study.

[3] Extent of Observation in years is defined as [(last follow-up date) - (first dose in core study) + 1] /365.25, Extent of Observation in months is defined as [(last follow-up date) - (first dose in core study) + 1] /30.4375, last follow-up date may be in core or extension study. Last follow-up date is defined as EOS date if subjects only participated in core study. If subjects continued to SHP633-305 extension study, the last follow-up date is April 15, 2020, inclusive for Children and July 15, 2020, inclusive for Infants.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
Number of subjects evaluated	8	8	8	8	7	7	6
All AEs	8 (100.0)	8 (100.0)	6 (75.0)	6 (75.0)	7 (100.0)	7 (100.0)	4 (66.7)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	7 (87.5)	5 (62.5)	5 (62.5)	3 (37.5)	3 (42.9)	4 (57.1)	0
Number of subjects who discontinued	1 (12.5)	0	1 (12.5)	0	0	0	0
血液およびリンパ系障害	1 (12.5)	0	0	1 (12.5)	0	0	0
貧血	1 (12.5)	0	0	1 (12.5)	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
Number of subjects evaluated	3	2	1	1	1	1	1
All AEs	2 (66.7)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	2 (66.7)	0	0	0	0	1 (100.0)	1 (100.0)
Number of subjects who discontinued	0	0	0	0	0	0	0
血液およびリンパ系障害	0	0	0	0	0	0	0
貧血	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
眼障害	2 (25.0)	0	0	2 (25.0)	0	0	0
アレルギー性結膜炎	1 (12.5)	0	0	1 (12.5)	0	0	0
眼脂	1 (12.5)	0	0	1 (12.5)	0	0	0
胃腸障害	8 (100.0)	5 (62.5)	3 (37.5)	3 (37.5)	3 (42.9)	5 (71.4)	0
腹部膨満	2 (25.0)	0	1 (12.5)	0	1 (14.3)	0	0
腹痛	3 (37.5)	0	2 (25.0)	1 (12.5)	0	0	0
口唇炎	1 (12.5)	0	0	0	1 (14.3)	0	0
結腸血腫	1 (12.5)	0	0	0	0	0	0
便秘	2 (25.0)	2 (25.0)	0	0	0	0	0
齲歯	2 (25.0)	0	0	1 (12.5)	0	2 (28.6)	0
小腸炎	2 (25.0)	1 (12.5)	0	0	1 (14.3)	1 (14.3)	0
腸炎	2 (25.0)	1 (12.5)	1 (12.5)	0	0	1 (14.3)	0
胃障害	1 (12.5)	0	0	0	1 (14.3)	0	0
胃炎	1 (12.5)	1 (12.5)	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
眼障害	1 (33.3)	0	0	0	0	0	0
アレルギー性結膜炎	1 (33.3)	0	0	0	0	0	0
眼脂	0	0	0	0	0	0	0
胃腸障害	1 (33.3)	0	0	0	0	0	0
腹部膨満	0	0	0	0	0	0	0
腹痛	0	0	0	0	0	0	0
口唇炎	0	0	0	0	0	0	0
結腸血腫	1 (33.3)	0	0	0	0	0	0
便秘	0	0	0	0	0	0	0
齲歯	0	0	0	0	0	0	0
小腸炎	0	0	0	0	0	0	0
腸炎	0	0	0	0	0	0	0
胃障害	0	0	0	0	0	0	0
胃炎	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
胃腸障害（続き）							
口唇乾燥	1 (12.5)	0	0	0	0	1 (14.3)	0
肛門周囲痛	1 (12.5)	1 (12.5)	0	0	0	0	0
口内炎	2 (25.0)	0	0	1 (12.5)	0	1 (14.3)	0
一般・全身障害および投与部位の状態	5 (62.5)	5 (62.5)	2 (25.0)	1 (12.5)	0	1 (14.3)	1 (16.7)
カテーテル留置部位肉芽腫	1 (12.5)	0	1 (12.5)	0	0	0	0
注射部位内出血	2 (25.0)	2 (25.0)	1 (12.5)	0	0	0	0
注射部位紅斑	3 (37.5)	3 (37.5)	2 (25.0)	0	0	0	0
注射部位血腫	1 (12.5)	1 (12.5)	0	0	0	0	0
注射部位硬結	1 (12.5)	1 (12.5)	0	0	0	0	0
注射部位疼痛	2 (25.0)	1 (12.5)	0	0	0	0	1 (16.7)
注射部位発疹	1 (12.5)	1 (12.5)	0	0	0	0	0
注射部位反応	1 (12.5)	1 (12.5)	0	0	0	0	0
発熱	4 (50.0)	2 (25.0)	0	1 (12.5)	0	1 (14.3)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
胃腸障害（続き）							
口唇乾燥	0	0	0	0	0	0	0
肛門周囲痛	0	0	0	0	0	0	0
口内炎	0	0	0	0	0	0	0
一般・全身障害および投与部位の状態	0	0	0	0	0	1 (100.0)	0
カテーテル留置部位肉芽腫	0	0	0	0	0	0	0
注射部位内出血	0	0	0	0	0	0	0
注射部位紅斑	0	0	0	0	0	0	0
注射部位血腫	0	0	0	0	0	0	0
注射部位硬結	0	0	0	0	0	0	0
注射部位疼痛	0	0	0	0	0	0	0
注射部位発疹	0	0	0	0	0	0	0
注射部位反応	0	0	0	0	0	0	0
発熱	0	0	0	0	0	1 (100.0)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
肝胆道系障害	1 (12.5)	0	0	0	0	1 (14.3)	0
薬物性肝障害	1 (12.5)	0	0	0	0	1 (14.3)	0
免疫系障害	2 (25.0)	1 (12.5)	1 (12.5)	0	0	1 (14.3)	0
アナフィラキシー反応	1 (12.5)	0	1 (12.5)	0	0	0	0
食物アレルギー	1 (12.5)	1 (12.5)	0	0	0	1 (14.3)	0
感染症および寄生虫症	8 (100.0)	7 (87.5)	6 (75.0)	5 (62.5)	3 (42.9)	4 (57.1)	1 (16.7)
アデノウイルス結膜炎	1 (12.5)	0	0	1 (12.5)	0	0	0
アデノウイルス感染	1 (12.5)	0	1 (12.5)	0	0	0	0
β溶血性レンサ球菌感染	1 (12.5)	0	0	0	0	1 (14.3)	0
結膜炎	1 (12.5)	0	0	0	0	0	0
医療機器関連感染	4 (50.0)	3 (37.5)	1 (12.5)	2 (25.0)	0	0	0
胃腸炎	2 (25.0)	1 (12.5)	0	1 (12.5)	0	0	0
歯肉炎	1 (12.5)	0	1 (12.5)	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
肝胆道系障害	0	0	0	0	0	0	0
薬物性肝障害	0	0	0	0	0	0	0
免疫系障害	1 (33.3)	0	1 (100.0)	0	0	0	0
アナフィラキシー反応	0	0	0	0	0	0	0
食物アレルギー	1 (33.3)	0	1 (100.0)	0	0	0	0
感染症および寄生虫症	2 (66.7)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
アデノウイルス結膜炎	0	0	0	0	0	0	0
アデノウイルス感染	0	0	0	0	0	0	0
β溶血性レンサ球菌感染	0	0	0	0	0	0	0
結膜炎	1 (33.3)	0	0	0	0	0	0
医療機器関連感染	1 (33.3)	0	0	0	0	0	0
胃腸炎	0	0	0	0	0	0	0
歯肉炎	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
感染症および寄生虫症（続き）							
手足口病	2 (25.0)	1 (12.5)	0	1 (12.5)	0	0	0
咬傷感染	1 (12.5)	0	0	0	0	0	0
インフルエンザ	3 (37.5)	1 (12.5)	0	0	0	0	0
医療機器使用部位感染	2 (25.0)	2 (25.0)	2 (25.0)	0	0	1 (14.3)	0
レンサ球菌性咽頭炎	1 (12.5)	0	1 (12.5)	0	0	0	0
鼻炎	1 (12.5)	0	0	1 (12.5)	0	0	0
ウイルス性咽頭炎	1 (12.5)	0	0	0	1 (14.3)	0	0
ウイルス性上気道感染	7 (87.5)	4 (50.0)	2 (25.0)	3 (37.5)	2 (28.6)	3 (42.9)	1 (16.7)
傷害、中毒および処置合併症	4 (50.0)	1 (12.5)	1 (12.5)	1 (12.5)	1 (14.3)	1 (14.3)	1 (16.7)
転倒	1 (12.5)	0	0	1 (12.5)	0	0	0
骨折	1 (12.5)	0	0	0	0	0	0
凍傷	1 (12.5)	1 (12.5)	0	0	0	0	0
胃瘻管部合併症	1 (12.5)	0	1 (12.5)	0	0	0	1 (16.7)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
感染症および寄生虫症（続き）							
手足口病	0	0	0	0	0	1 (100.0)	0
咬傷感染	0	0	0	1 (100.0)	0	0	0
インフルエンザ	1 (33.3)	1 (50.0)	0	0	0	0	0
医療機器使用部位感染	0	0	0	0	0	0	0
レンサ球菌性咽頭炎	0	0	0	0	0	0	0
鼻炎	0	0	0	0	0	0	0
ウイルス性咽頭炎	0	0	0	0	0	0	0
ウイルス性上気道感染	1 (33.3)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
傷害、中毒および処置合併症	0	0	0	0	1 (100.0)	1 (100.0)	0
転倒	0	0	0	0	0	0	0
骨折	0	0	0	0	0	1 (100.0)	0
凍傷	0	0	0	0	0	0	0
胃瘻管部合併症	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
傷害、中毒および処置合併症（続き）							
角膜損傷	1 (12.5)	0	0	0	0	0	0
創合併症	2 (25.0)	0	0	0	1 (14.3)	1 (14.3)	0
臨床検査	4 (50.0)	1 (12.5)	0	0	0	2 (28.6)	0
アミラーゼ増加	2 (25.0)	1 (12.5)	0	0	0	0	0
リパーゼ増加	1 (12.5)	0	0	0	0	1 (14.3)	0
トランスアミナーゼ上昇	1 (12.5)	0	0	0	0	1 (14.3)	0
代謝および栄養障害	5 (62.5)	2 (25.0)	2 (25.0)	1 (12.5)	1 (14.3)	0	1 (16.7)
脱水	3 (37.5)	1 (12.5)	0	0	1 (14.3)	0	0
高リパーゼ血症	1 (12.5)	0	1 (12.5)	0	0	0	0
高トリグリセリド血症	1 (12.5)	1 (12.5)	0	0	0	0	0
高亜鉛血症	1 (12.5)	0	1 (12.5)	0	0	0	0
低マグネシウム血症	1 (12.5)	0	0	0	0	0	1 (16.7)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
傷害、中毒および処置合併症（続き）							
角膜損傷	0	0	0	0	1 (100.0)	0	0
創合併症	0	0	0	0	0	0	0
臨床検査	1 (33.3)	0	0	0	0	0	0
アミラーゼ増加	1 (33.3)	0	0	0	0	0	0
リパーゼ増加	0	0	0	0	0	0	0
トランスアミナーゼ上昇	0	0	0	0	0	0	0
代謝および栄養障害	0	0	0	0	0	1 (100.0)	1 (100.0)
脱水	0	0	0	0	0	0	1 (100.0)
高リパーゼ血症	0	0	0	0	0	0	0
高トリグリセリド血症	0	0	0	0	0	0	0
高亜鉛血症	0	0	0	0	0	0	0
低マグネシウム血症	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
代謝および栄養障害（続き）							
低亜鉛血症	1 (12.5)	0	0	1 (12.5)	0	0	0
代謝性アシドーシス	1 (12.5)	0	0	0	0	0	0
筋骨格系および結合組織障害	2 (25.0)	0	0	0	0	1 (14.3)	1 (16.7)
関節腫脹	1 (12.5)	0	0	0	0	1 (14.3)	0
筋肉痛	1 (12.5)	0	0	0	0	0	1 (16.7)
神経系障害	1 (12.5)	1 (12.5)	0	0	0	0	0
頭痛	1 (12.5)	1 (12.5)	0	0	0	0	0
製品の問題	6 (75.0)	2 (25.0)	0	2 (25.0)	2 (28.6)	2 (28.6)	0
医療機器破損	3 (37.5)	0	0	1 (12.5)	1 (14.3)	1 (14.3)	0
医療機器損傷	3 (37.5)	2 (25.0)	0	1 (12.5)	1 (14.3)	1 (14.3)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
代謝および栄養障害（続き）							
低亜鉛血症	0	0	0	0	0	0	0
代謝性アシドーシス	0	0	0	0	0	1 (100.0)	1 (100.0)
筋骨格系および結合組織障害	0	0	0	0	0	0	0
関節腫脹	0	0	0	0	0	0	0
筋肉痛	0	0	0	0	0	0	0
神経系障害	0	0	0	0	0	0	0
頭痛	0	0	0	0	0	0	0
製品の問題	0	0	0	0	0	1 (100.0)	0
医療機器破損	0	0	0	0	0	1 (100.0)	0
医療機器損傷	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
精神障害	1 (12.5)	0	0	0	1 (14.3)	0	0
頭を激しくぶっつける	1 (12.5)	0	0	0	1 (14.3)	0	0
生殖系および乳房障害	1 (12.5)	0	1 (12.5)	0	0	0	0
亀頭包皮炎	1 (12.5)	0	1 (12.5)	0	0	0	0
呼吸器、胸郭および縦隔障害	3 (37.5)	0	0	1 (12.5)	2 (28.6)	0	0
喘息	1 (12.5)	0	0	1 (12.5)	0	0	0
咳嗽	2 (25.0)	0	0	0	2 (28.6)	0	0
鼻漏	1 (12.5)	0	0	0	1 (14.3)	0	0
皮膚および皮下組織障害	7 (87.5)	5 (62.5)	2 (25.0)	3 (37.5)	1 (14.3)	1 (14.3)	3 (50.0)
アレルギー性皮膚炎	1 (12.5)	0	0	0	0	0	0
おむつ皮膚炎	1 (12.5)	1 (12.5)	0	0	0	0	0
皮膚乾燥	4 (50.0)	1 (12.5)	1 (12.5)	0	1 (14.3)	0	1 (16.7)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
精神障害	0	0	0	0	0	0	0
頭を激しくぶっつける	0	0	0	0	0	0	0
生殖系および乳房障害	0	0	0	0	0	0	0
亀頭包皮炎	0	0	0	0	0	0	0
呼吸器、胸郭および縦隔障害	0	0	0	0	0	0	0
喘息	0	0	0	0	0	0	0
咳嗽	0	0	0	0	0	0	0
鼻漏	0	0	0	0	0	0	0
皮膚および皮下組織障害	0	0	0	0	1 (100.0)	0	0
アレルギー性皮膚炎	0	0	0	0	1 (100.0)	0	0
おむつ皮膚炎	0	0	0	0	0	0	0
皮膚乾燥	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
皮膚および皮下組織障害（続き）							
湿疹	1 (12.5)	1 (12.5)	0	0	0	0	0
皮下出血	2 (25.0)	0	0	2 (25.0)	0	0	0
汗疹	1 (12.5)	0	0	0	0	0	1 (16.7)
発疹	4 (50.0)	2 (25.0)	2 (25.0)	0	0	0	1 (16.7)
皮膚びらん	1 (12.5)	0	0	1 (12.5)	0	0	0
蕁麻疹	1 (12.5)	0	0	0	1 (14.3)	1 (14.3)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

All Children

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
皮膚および皮下組織障害（続き）							
湿疹	0	0	0	0	0	0	0
皮下出血	0	0	0	0	0	0	0
汗疹	0	0	0	0	0	0	0
発疹	0	0	0	0	0	0	0
皮膚びらん	0	0	0	0	0	0	0
蕁麻疹	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
Number of subjects evaluated	6	6	6	6	6
All AEs	6 (100.0)	6 (100.0)	4 (66.7)	5 (83.3)	6 (100.0)
Number of deaths	0	0	0	0	0
Number of subjects with SAEs other than deaths	5 (83.3)	4 (66.7)	3 (50.0)	2 (33.3)	3 (50.0)
Number of subjects who discontinued	0	0	0	0	0
眼障害	2 (33.3)	0	0	2 (33.3)	0
アレルギー性結膜炎	1 (16.7)	0	0	1 (16.7)	0
眼脂	1 (16.7)	0	0	1 (16.7)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
Number of subjects evaluated	6	5	2	1
All AEs	6 (100.0)	3 (60.0)	1 (50.0)	0
Number of deaths	0	0	0	0
Number of subjects with SAEs other than deaths	4 (66.7)	0	1 (50.0)	0
Number of subjects who discontinued	0	0	0	0
眼障害	0	0	1 (50.0)	0
アレルギー性結膜炎	0	0	1 (50.0)	0
眼脂	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
胃腸障害	6 (100.0)	3 (50.0)	2 (33.3)	2 (33.3)	3 (50.0)
腹部膨満	2 (33.3)	0	1 (16.7)	0	1 (16.7)
腹痛	2 (33.3)	0	1 (16.7)	1 (16.7)	0
口唇炎	1 (16.7)	0	0	0	1 (16.7)
結腸血腫	1 (16.7)	0	0	0	0
便秘	1 (16.7)	1 (16.7)	0	0	0
齲歯	2 (33.3)	0	0	1 (16.7)	0
小腸炎	1 (16.7)	0	0	0	1 (16.7)
腸炎	1 (16.7)	0	1 (16.7)	0	0
胃障害	1 (16.7)	0	0	0	1 (16.7)
胃炎	1 (16.7)	1 (16.7)	0	0	0
口唇乾燥	1 (16.7)	0	0	0	0
肛門周囲痛	1 (16.7)	1 (16.7)	0	0	0
口内炎	1 (16.7)	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
胃腸障害	5 (83.3)	0	1 (50.0)	0
腹部膨満	0	0	0	0
腹痛	0	0	0	0
口唇炎	0	0	0	0
結腸血腫	0	0	1 (50.0)	0
便秘	0	0	0	0
齲歯	2 (33.3)	0	0	0
小腸炎	1 (16.7)	0	0	0
腸炎	1 (16.7)	0	0	0
胃障害	0	0	0	0
胃炎	0	0	0	0
口唇乾燥	1 (16.7)	0	0	0
肛門周囲痛	0	0	0	0
口内炎	1 (16.7)	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
一般・全身障害および投与部位の状態	3 (50.0)	3 (50.0)	1 (16.7)	1 (16.7)	0
カテーテル留置部位肉芽腫	1 (16.7)	0	1 (16.7)	0	0
注射部位内出血	1 (16.7)	1 (16.7)	0	0	0
注射部位紅斑	2 (33.3)	2 (33.3)	1 (16.7)	0	0
注射部位疼痛	2 (33.3)	1 (16.7)	0	0	0
注射部位発疹	1 (16.7)	1 (16.7)	0	0	0
注射部位反応	1 (16.7)	1 (16.7)	0	0	0
発熱	3 (50.0)	1 (16.7)	0	1 (16.7)	0
肝胆道系障害	1 (16.7)	0	0	0	0
薬物性肝障害	1 (16.7)	0	0	0	0
感染症および寄生虫症	6 (100.0)	5 (83.3)	4 (66.7)	4 (66.7)	3 (50.0)
アデノウイルス結膜炎	1 (16.7)	0	0	1 (16.7)	0
アデノウイルス感染	1 (16.7)	0	1 (16.7)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
一般・全身障害および投与部位の状態	1 (16.7)	1 (20.0)	0	0
カテーテル留置部位肉芽腫	0	0	0	0
注射部位内出血	0	0	0	0
注射部位紅斑	0	0	0	0
注射部位疼痛	0	1 (20.0)	0	0
注射部位発疹	0	0	0	0
注射部位反応	0	0	0	0
発熱	1 (16.7)	0	0	0
肝胆道系障害	1 (16.7)	0	0	0
薬物性肝障害	1 (16.7)	0	0	0
感染症および寄生虫症	3 (50.0)	0	1 (50.0)	0
アデノウイルス結膜炎	0	0	0	0
アデノウイルス感染	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
感染症および寄生虫症（続き）					
β溶血性レンサ球菌感染	1 (16.7)	0	0	0	0
結膜炎	1 (16.7)	0	0	0	0
医療機器関連感染	3 (50.0)	3 (50.0)	0	1 (16.7)	0
胃腸炎	2 (33.3)	1 (16.7)	0	1 (16.7)	0
歯肉炎	1 (16.7)	0	1 (16.7)	0	0
手足口病	1 (16.7)	1 (16.7)	0	0	0
インフルエンザ	2 (33.3)	1 (16.7)	0	0	0
医療機器使用部位感染	1 (16.7)	1 (16.7)	1 (16.7)	0	0
レンサ球菌性咽頭炎	1 (16.7)	0	1 (16.7)	0	0
鼻炎	1 (16.7)	0	0	1 (16.7)	0
ウイルス性咽頭炎	1 (16.7)	0	0	0	1 (16.7)
ウイルス性上気道感染	5 (83.3)	3 (50.0)	1 (16.7)	3 (50.0)	2 (33.3)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
感染症および寄生虫症（続き）				
β溶血性レンサ球菌感染	1 (16.7)	0	0	0
結膜炎	0	0	1 (50.0)	0
医療機器関連感染	0	0	0	0
胃腸炎	0	0	0	0
歯肉炎	0	0	0	0
手足口病	0	0	0	0
インフルエンザ	0	0	1 (50.0)	0
医療機器使用部位感染	1 (16.7)	0	0	0
レンサ球菌性咽頭炎	0	0	0	0
鼻炎	0	0	0	0
ウイルス性咽頭炎	0	0	0	0
ウイルス性上気道感染	2 (33.3)	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
傷害、中毒および処置合併症	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
転倒	1 (16.7)	0	0	1 (16.7)	0
凍傷	1 (16.7)	1 (16.7)	0	0	0
胃瘻管部合併症	1 (16.7)	0	1 (16.7)	0	0
創合併症	2 (33.3)	0	0	0	1 (16.7)
臨床検査	3 (50.0)	1 (16.7)	0	0	0
アミラーゼ増加	1 (16.7)	1 (16.7)	0	0	0
リパーゼ増加	1 (16.7)	0	0	0	0
トランスアミナーゼ上昇	1 (16.7)	0	0	0	0
代謝および栄養障害	4 (66.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
脱水	2 (33.3)	1 (16.7)	0	0	1 (16.7)
高トリグリセリド血症	1 (16.7)	1 (16.7)	0	0	0
高亜鉛血症	1 (16.7)	0	1 (16.7)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
傷害、中毒および処置合併症	1 (16.7)	1 (20.0)	0	0
転倒	0	0	0	0
凍傷	0	0	0	0
胃瘻管部合併症	0	1 (20.0)	0	0
創合併症	1 (16.7)	0	0	0
臨床検査	2 (33.3)	0	0	0
アミラーゼ増加	0	0	0	0
リパーゼ増加	1 (16.7)	0	0	0
トランスアミナーゼ上昇	1 (16.7)	0	0	0
代謝および栄養障害	0	0	0	0
脱水	0	0	0	0
高トリグリセリド血症	0	0	0	0
高亜鉛血症	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
代謝および栄養障害（続き）					
低亜鉛血症	1 (16.7)	0	0	1 (16.7)	0
筋骨格系および結合組織障害	2 (33.3)	0	0	0	0
関節腫脹	1 (16.7)	0	0	0	0
筋肉痛	1 (16.7)	0	0	0	0
神経系障害	1 (16.7)	1 (16.7)	0	0	0
頭痛	1 (16.7)	1 (16.7)	0	0	0
製品の問題	5 (83.3)	2 (33.3)	0	2 (33.3)	2 (33.3)
医療機器破損	2 (33.3)	0	0	1 (16.7)	1 (16.7)
医療機器損傷	3 (50.0)	2 (33.3)	0	1 (16.7)	1 (16.7)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
代謝および栄養障害（続き）				
低亜鉛血症	0	0	0	0
筋骨格系および結合組織障害	1 (16.7)	1 (20.0)	0	0
関節腫脹	1 (16.7)	0	0	0
筋肉痛	0	1 (20.0)	0	0
神経系障害	0	0	0	0
頭痛	0	0	0	0
製品の問題	2 (33.3)	0	0	0
医療機器破損	1 (16.7)	0	0	0
医療機器損傷	1 (16.7)	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
精神障害	1 (16.7)	0	0	0	1 (16.7)
頭を激しくぶっつける	1 (16.7)	0	0	0	1 (16.7)
生殖系および乳房障害	1 (16.7)	0	1 (16.7)	0	0
亀頭包皮炎	1 (16.7)	0	1 (16.7)	0	0
呼吸器、胸郭および縦隔障害	3 (50.0)	0	0	1 (16.7)	2 (33.3)
喘息	1 (16.7)	0	0	1 (16.7)	0
咳嗽	2 (33.3)	0	0	0	2 (33.3)
鼻漏	1 (16.7)	0	0	0	1 (16.7)
皮膚および皮下組織障害	5 (83.3)	3 (50.0)	2 (33.3)	3 (50.0)	0
皮膚乾燥	2 (33.3)	0	1 (16.7)	0	0
湿疹	1 (16.7)	1 (16.7)	0	0	0
皮下出血	2 (33.3)	0	0	2 (33.3)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
精神障害	0	0	0	0
頭を激しくぶっつける	0	0	0	0
生殖系および乳房障害	0	0	0	0
亀頭包皮炎	0	0	0	0
呼吸器、胸郭および縦隔障害	0	0	0	0
喘息	0	0	0	0
咳嗽	0	0	0	0
鼻漏	0	0	0	0
皮膚および皮下組織障害	0	2 (40.0)	0	0
皮膚乾燥	0	1 (20.0)	0	0
湿疹	0	0	0	0
皮下出血	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

		Teduglutide			
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12
皮膚および皮下組織障害（続き）					
発疹	4 (66.7)	2 (33.3)	2 (33.3)	0	0
皮膚びらん	1 (16.7)	0	0	1 (16.7)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children After Amendment 3

	Teduglutide			
Day of Onset	Month 12 to 15	Month 15 to 18	Month 18 to 21	Month 21 to 24
皮膚および皮下組織障害（続き）				
発疹	0	1 (20.0)	0	0
皮膚びらん	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
Number of subjects evaluated	2	2	2	2	2	2	1
All AEs	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0	0
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	0	0
Number of subjects who discontinued	0	0	0	0	0	0	0
胃腸障害	2 (100.0)	1 (50.0)	0	0	1 (50.0)	0	0
腸炎	1 (50.0)	1 (50.0)	0	0	0	0	0
急性膵炎	1 (50.0)	0	0	0	1 (50.0)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
一般・全身障害および投与部位の状態	2 (100.0)	0	2 (100.0)	1 (50.0)	1 (50.0)	0	0
注射部位反応	1 (50.0)	0	0	0	1 (50.0)	0	0
発熱	2 (100.0)	0	2 (100.0)	1 (50.0)	0	0	0
感染症および寄生虫症	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	1 (50.0)	0	0
医療機器関連感染	1 (50.0)	1 (50.0)	0	0	0	0	0
アデノウイルス性胃腸炎	1 (50.0)	0	0	0	1 (50.0)	0	0
医療機器使用部位感染	1 (50.0)	0	0	1 (50.0)	0	0	0
口腔カンジダ症	1 (50.0)	0	0	1 (50.0)	0	0	0
中耳炎	1 (50.0)	1 (50.0)	0	0	0	0	0
上気道感染	1 (50.0)	0	1 (50.0)	1 (50.0)	1 (50.0)	0	0
ウイルス性上気道感染	1 (50.0)	1 (50.0)	0	0	1 (50.0)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
傷害、中毒および処置合併症	1 (50.0)	1 (50.0)	0	0	0	0	0
ワクチン接種合併症	1 (50.0)	1 (50.0)	0	0	0	0	0
臨床検査	1 (50.0)	0	0	0	1 (50.0)	0	0
血中アルカリホスファターゼ増加	1 (50.0)	0	0	0	1 (50.0)	0	0
神経系障害	1 (50.0)	0	0	0	1 (50.0)	0	0
痙攣発作	1 (50.0)	0	0	0	1 (50.0)	0	0
呼吸器、胸郭および縦隔障害	1 (50.0)	1 (50.0)	1 (50.0)	0	0	0	0
上気道の炎症	1 (50.0)	1 (50.0)	1 (50.0)	0	0	0	0
皮膚および皮下組織障害	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	0	0	0
皮膚炎	1 (50.0)	0	0	1 (50.0)	0	0	0
接触皮膚炎	1 (50.0)	0	1 (50.0)	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
皮膚および皮下組織障害（続き）							
おむつ皮膚炎	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	0	0	0
皮膚乾燥	1 (50.0)	0	1 (50.0)	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
Number of subjects evaluated	10	10	10	10	9	9	7
All AEs	10 (100.0)	10 (100.0)	8 (80.0)	8 (80.0)	9 (100.0)	7 (77.8)	4 (57.1)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	9 (90.0)	6 (60.0)	7 (70.0)	5 (50.0)	5 (55.6)	4 (44.4)	0
Number of subjects who discontinued	1 (10.0)	0	1 (10.0)	0	0	0	0
血液およびリンパ系障害	1 (10.0)	0	0	1 (10.0)	0	0	0
貧血	1 (10.0)	0	0	1 (10.0)	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
Number of subjects evaluated	3	2	1	1	1	1	1
All AEs	2 (66.7)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
Number of deaths	0	0	0	0	0	0	0
Number of subjects with SAEs other than deaths	2 (66.7)	0	0	0	0	1 (100.0)	1 (100.0)
Number of subjects who discontinued	0	0	0	0	0	0	0
血液およびリンパ系障害	0	0	0	0	0	0	0
貧血	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
眼障害	2 (20.0)	0	0	2 (20.0)	0	0	0
アレルギー性結膜炎	1 (10.0)	0	0	1 (10.0)	0	0	0
眼脂	1 (10.0)	0	0	1 (10.0)	0	0	0
胃腸障害	10 (100.0)	6 (60.0)	3 (30.0)	3 (30.0)	4 (44.4)	5 (55.6)	0
腹部膨満	2 (20.0)	0	1 (10.0)	0	1 (11.1)	0	0
腹痛	3 (30.0)	0	2 (20.0)	1 (10.0)	0	0	0
口唇炎	1 (10.0)	0	0	0	1 (11.1)	0	0
結腸血腫	1 (10.0)	0	0	0	0	0	0
便秘	2 (20.0)	2 (20.0)	0	0	0	0	0
齲歯	2 (20.0)	0	0	1 (10.0)	0	2 (22.2)	0
小腸炎	2 (20.0)	1 (10.0)	0	0	1 (11.1)	1 (11.1)	0
腸炎	3 (30.0)	2 (20.0)	1 (10.0)	0	0	1 (11.1)	0
胃障害	1 (10.0)	0	0	0	1 (11.1)	0	0
胃炎	1 (10.0)	1 (10.0)	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
眼障害	1 (33.3)	0	0	0	0	0	0
アレルギー性結膜炎	1 (33.3)	0	0	0	0	0	0
眼脂	0	0	0	0	0	0	0
胃腸障害	1 (33.3)	0	0	0	0	0	0
腹部膨満	0	0	0	0	0	0	0
腹痛	0	0	0	0	0	0	0
口唇炎	0	0	0	0	0	0	0
結腸血腫	1 (33.3)	0	0	0	0	0	0
便秘	0	0	0	0	0	0	0
齲歯	0	0	0	0	0	0	0
小腸炎	0	0	0	0	0	0	0
腸炎	0	0	0	0	0	0	0
胃障害	0	0	0	0	0	0	0
胃炎	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
胃腸障害（続き）							
口唇乾燥	1 (10.0)	0	0	0	0	1 (11.1)	0
急性膵炎	1 (10.0)	0	0	0	1 (11.1)	0	0
肛門周囲痛	1 (10.0)	1 (10.0)	0	0	0	0	0
口内炎	2 (20.0)	0	0	1 (10.0)	0	1 (11.1)	0
一般・全身障害および投与部位の状態	7 (70.0)	5 (50.0)	4 (40.0)	2 (20.0)	1 (11.1)	1 (11.1)	1 (14.3)
カテーテル留置部位肉芽腫	1 (10.0)	0	1 (10.0)	0	0	0	0
注射部位内出血	2 (20.0)	2 (20.0)	1 (10.0)	0	0	0	0
注射部位紅斑	3 (30.0)	3 (30.0)	2 (20.0)	0	0	0	0
注射部位血腫	1 (10.0)	1 (10.0)	0	0	0	0	0
注射部位硬結	1 (10.0)	1 (10.0)	0	0	0	0	0
注射部位疼痛	2 (20.0)	1 (10.0)	0	0	0	0	1 (14.3)
注射部位発疹	1 (10.0)	1 (10.0)	0	0	0	0	0
注射部位反応	2 (20.0)	1 (10.0)	0	0	1 (11.1)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
胃腸障害（続き）							
口唇乾燥	0	0	0	0	0	0	0
急性膵炎	0	0	0	0	0	0	0
肛門周囲痛	0	0	0	0	0	0	0
口内炎	0	0	0	0	0	0	0
一般・全身障害および投与部位の状態	0	0	0	0	0	1 (100.0)	0
カテーテル留置部位肉芽腫	0	0	0	0	0	0	0
注射部位内出血	0	0	0	0	0	0	0
注射部位紅斑	0	0	0	0	0	0	0
注射部位血腫	0	0	0	0	0	0	0
注射部位硬結	0	0	0	0	0	0	0
注射部位疼痛	0	0	0	0	0	0	0
注射部位発疹	0	0	0	0	0	0	0
注射部位反応	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
一般・全身障害および投与部位の状態（続き）							
発熱	6 (60.0)	2 (20.0)	2 (20.0)	2 (20.0)	0	1 (11.1)	0
肝胆道系障害	1 (10.0)	0	0	0	0	1 (11.1)	0
薬物性肝障害	1 (10.0)	0	0	0	0	1 (11.1)	0
免疫系障害	2 (20.0)	1 (10.0)	1 (10.0)	0	0	1 (11.1)	0
アナフィラキシー反応	1 (10.0)	0	1 (10.0)	0	0	0	0
食物アレルギー	1 (10.0)	1 (10.0)	0	0	0	1 (11.1)	0
感染症および寄生虫症	10 (100.0)	9 (90.0)	7 (70.0)	7 (70.0)	4 (44.4)	4 (44.4)	1 (14.3)
アデノウイルス結膜炎	1 (10.0)	0	0	1 (10.0)	0	0	0
アデノウイルス感染	1 (10.0)	0	1 (10.0)	0	0	0	0
β溶血性レンサ球菌感染	1 (10.0)	0	0	0	0	1 (11.1)	0
結膜炎	1 (10.0)	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
一般・全身障害および投与部位の状態（続き）							
発熱	0	0	0	0	0	1 (100.0)	0
肝胆道系障害	0	0	0	0	0	0	0
薬物性肝障害	0	0	0	0	0	0	0
免疫系障害	1 (33.3)	0	1 (100.0)	0	0	0	0
アナフィラキシー反応	0	0	0	0	0	0	0
食物アレルギー	1 (33.3)	0	1 (100.0)	0	0	0	0
感染症および寄生虫症	2 (66.7)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
アデノウイルス結膜炎	0	0	0	0	0	0	0
アデノウイルス感染	0	0	0	0	0	0	0
β溶血性レンサ球菌感染	0	0	0	0	0	0	0
結膜炎	1 (33.3)	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
感染症および寄生虫症（続き）							
医療機器関連感染	5 (50.0)	4 (40.0)	1 (10.0)	2 (20.0)	0	0	0
胃腸炎	2 (20.0)	1 (10.0)	0	1 (10.0)	0	0	0
アデノウイルス性胃腸炎	1 (10.0)	0	0	0	1 (11.1)	0	0
歯肉炎	1 (10.0)	0	1 (10.0)	0	0	0	0
手足口病	2 (20.0)	1 (10.0)	0	1 (10.0)	0	0	0
咬傷感染	1 (10.0)	0	0	0	0	0	0
インフルエンザ	3 (30.0)	1 (10.0)	0	0	0	0	0
医療機器使用部位感染	3 (30.0)	2 (20.0)	2 (20.0)	1 (10.0)	0	1 (11.1)	0
口腔カンジダ症	1 (10.0)	0	0	1 (10.0)	0	0	0
中耳炎	1 (10.0)	1 (10.0)	0	0	0	0	0
レンサ球菌性咽頭炎	1 (10.0)	0	1 (10.0)	0	0	0	0
鼻炎	1 (10.0)	0	0	1 (10.0)	0	0	0
上気道感染	1 (10.0)	0	1 (10.0)	1 (10.0)	1 (11.1)	0	0
ウイルス性咽頭炎	1 (10.0)	0	0	0	1 (11.1)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
感染症および寄生虫症（続き）							
医療機器関連感染	1 (33.3)	0	0	0	0	0	0
胃腸炎	0	0	0	0	0	0	0
アデノウイルス性胃腸炎	0	0	0	0	0	0	0
歯肉炎	0	0	0	0	0	0	0
手足口病	0	0	0	0	0	1 (100.0)	0
咬傷感染	0	0	0	1 (100.0)	0	0	0
インフルエンザ	1 (33.3)	1 (50.0)	0	0	0	0	0
医療機器使用部位感染	0	0	0	0	0	0	0
口腔カンジダ症	0	0	0	0	0	0	0
中耳炎	0	0	0	0	0	0	0
レンサ球菌性咽頭炎	0	0	0	0	0	0	0
鼻炎	0	0	0	0	0	0	0
上気道感染	0	0	0	0	0	0	0
ウイルス性咽頭炎	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
感染症および寄生虫症（続き）							
ウイルス性上気道感染	8 (80.0)	5 (50.0)	2 (20.0)	3 (30.0)	3 (33.3)	3 (33.3)	1 (14.3)
傷害、中毒および処置合併症	5 (50.0)	2 (20.0)	1 (10.0)	1 (10.0)	1 (11.1)	1 (11.1)	1 (14.3)
転倒	1 (10.0)	0	0	1 (10.0)	0	0	0
骨折	1 (10.0)	0	0	0	0	0	0
凍傷	1 (10.0)	1 (10.0)	0	0	0	0	0
胃瘻管部合併症	1 (10.0)	0	1 (10.0)	0	0	0	1 (14.3)
角膜損傷	1 (10.0)	0	0	0	0	0	0
ワクチン接種合併症	1 (10.0)	1 (10.0)	0	0	0	0	0
創合併症	2 (20.0)	0	0	0	1 (11.1)	1 (11.1)	0
臨床検査	5 (50.0)	1 (10.0)	0	0	1 (11.1)	2 (22.2)	0
アミラーゼ増加	2 (20.0)	1 (10.0)	0	0	0	0	0
血中アルカリホスファターゼ増加	1 (10.0)	0	0	0	1 (11.1)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
感染症および寄生虫症（続き）							
ウイルス性上気道感染	1 (33.3)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
傷害、中毒および処置合併症	0	0	0	0	1 (100.0)	1 (100.0)	0
転倒	0	0	0	0	0	0	0
骨折	0	0	0	0	0	1 (100.0)	0
凍傷	0	0	0	0	0	0	0
胃瘻管部合併症	0	0	0	0	0	0	0
角膜損傷	0	0	0	0	1 (100.0)	0	0
ワクチン接種合併症	0	0	0	0	0	0	0
創合併症	0	0	0	0	0	0	0
臨床検査	1 (33.3)	0	0	0	0	0	0
アミラーゼ増加	1 (33.3)	0	0	0	0	0	0
血中アルカリホスファターゼ増加	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
臨床検査（続き）							
リパーゼ増加	1 (10.0)	0	0	0	0	1 (11.1)	0
トランスアミナーゼ上昇	1 (10.0)	0	0	0	0	1 (11.1)	0
代謝および栄養障害	5 (50.0)	2 (20.0)	2 (20.0)	1 (10.0)	1 (11.1)	0	1 (14.3)
脱水	3 (30.0)	1 (10.0)	0	0	1 (11.1)	0	0
高リパーゼ血症	1 (10.0)	0	1 (10.0)	0	0	0	0
高トリグリセリド血症	1 (10.0)	1 (10.0)	0	0	0	0	0
高亜鉛血症	1 (10.0)	0	1 (10.0)	0	0	0	0
低マグネシウム血症	1 (10.0)	0	0	0	0	0	1 (14.3)
低亜鉛血症	1 (10.0)	0	0	1 (10.0)	0	0	0
代謝性アシドーシス	1 (10.0)	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
臨床検査（続き）							
リパーゼ増加	0	0	0	0	0	0	0
トランスアミナーゼ上昇	0	0	0	0	0	0	0
代謝および栄養障害	0	0	0	0	0	1 (100.0)	1 (100.0)
脱水	0	0	0	0	0	0	1 (100.0)
高リパーゼ血症	0	0	0	0	0	0	0
高トリグリセリド血症	0	0	0	0	0	0	0
高亜鉛血症	0	0	0	0	0	0	0
低マグネシウム血症	0	0	0	0	0	0	0
低亜鉛血症	0	0	0	0	0	0	0
代謝性アシドーシス	0	0	0	0	0	1 (100.0)	1 (100.0)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
筋骨格系および結合組織障害	2 (20.0)	0	0	0	0	1 (11.1)	1 (14.3)
関節腫脹	1 (10.0)	0	0	0	0	1 (11.1)	0
筋肉痛	1 (10.0)	0	0	0	0	0	1 (14.3)
神経系障害	2 (20.0)	1 (10.0)	0	0	1 (11.1)	0	0
頭痛	1 (10.0)	1 (10.0)	0	0	0	0	0
痙攣発作	1 (10.0)	0	0	0	1 (11.1)	0	0
製品の問題	6 (60.0)	2 (20.0)	0	2 (20.0)	2 (22.2)	2 (22.2)	0
医療機器破損	3 (30.0)	0	0	1 (10.0)	1 (11.1)	1 (11.1)	0
医療機器損傷	3 (30.0)	2 (20.0)	0	1 (10.0)	1 (11.1)	1 (11.1)	0
精神障害	1 (10.0)	0	0	0	1 (11.1)	0	0
頭を激しくぶっつける	1 (10.0)	0	0	0	1 (11.1)	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
筋骨格系および結合組織障害	0	0	0	0	0	0	0
関節腫脹	0	0	0	0	0	0	0
筋肉痛	0	0	0	0	0	0	0
神経系障害	0	0	0	0	0	0	0
頭痛	0	0	0	0	0	0	0
痙攣発作	0	0	0	0	0	0	0
製品の問題	0	0	0	0	0	1 (100.0)	0
医療機器破損	0	0	0	0	0	1 (100.0)	0
医療機器損傷	0	0	0	0	0	0	0
精神障害	0	0	0	0	0	0	0
頭を激しくぶっつける	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
生殖系および乳房障害	1 (10.0)	0	1 (10.0)	0	0	0	0
亀頭包皮炎	1 (10.0)	0	1 (10.0)	0	0	0	0
呼吸器、胸郭および縦隔障害	4 (40.0)	1 (10.0)	1 (10.0)	1 (10.0)	2 (22.2)	0	0
喘息	1 (10.0)	0	0	1 (10.0)	0	0	0
咳嗽	2 (20.0)	0	0	0	2 (22.2)	0	0
鼻漏	1 (10.0)	0	0	0	1 (11.1)	0	0
上気道の炎症	1 (10.0)	1 (10.0)	1 (10.0)	0	0	0	0
皮膚および皮下組織障害	9 (90.0)	6 (60.0)	3 (30.0)	4 (40.0)	1 (11.1)	1 (11.1)	3 (42.9)
皮膚炎	1 (10.0)	0	0	1 (10.0)	0	0	0
アレルギー性皮膚炎	1 (10.0)	0	0	0	0	0	0
接触皮膚炎	1 (10.0)	0	1 (10.0)	0	0	0	0
おむつ皮膚炎	3 (30.0)	2 (20.0)	1 (10.0)	1 (10.0)	0	0	0
皮膚乾燥	5 (50.0)	1 (10.0)	2 (20.0)	0	1 (11.1)	0	1 (14.3)

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
生殖系および乳房障害	0	0	0	0	0	0	0
亀頭包皮炎	0	0	0	0	0	0	0
呼吸器、胸郭および縦隔障害	0	0	0	0	0	0	0
喘息	0	0	0	0	0	0	0
咳嗽	0	0	0	0	0	0	0
鼻漏	0	0	0	0	0	0	0
上気道の炎症	0	0	0	0	0	0	0
皮膚および皮下組織障害	0	0	0	0	1 (100.0)	0	0
皮膚炎	0	0	0	0	0	0	0
アレルギー性皮膚炎	0	0	0	0	1 (100.0)	0	0
接触皮膚炎	0	0	0	0	0	0	0
おむつ皮膚炎	0	0	0	0	0	0	0
皮膚乾燥	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

		Teduglutide					
Day of Onset	Total	To Month 3	Month 3 to 6	Month 6 to 9	Month 9 to 12	Month 12 to 15	Month 15 to 18
皮膚および皮下組織障害（続き）							
湿疹	1 (10.0)	1 (10.0)	0	0	0	0	0
皮下出血	2 (20.0)	0	0	2 (20.0)	0	0	0
汗疹	1 (10.0)	0	0	0	0	0	1 (14.3)
発疹	4 (40.0)	2 (20.0)	2 (20.0)	0	0	0	1 (14.3)
皮膚びらん	1 (10.0)	0	0	1 (10.0)	0	0	0
蕁麻疹	1 (10.0)	0	0	0	1 (11.1)	1 (11.1)	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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Table 13.1
Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and AE Onset Time
(Safety Population: SHP633-302, SHP633-305)

Children + Infants

	Teduglutide						
Day of Onset	Month 18 to 21	Month 21 to 24	Month 24 to 27	Month 27 to 30	Month 30 to 33	Month 33 to 36	Month 36 to 39
皮膚および皮下組織障害（続き）							
湿疹	0	0	0	0	0	0	0
皮下出血	0	0	0	0	0	0	0
汗疹	0	0	0	0	0	0	0
発疹	0	0	0	0	0	0	0
皮膚びらん	0	0	0	0	0	0	0
蕁麻疹	0	0	0	0	0	0	0

Note: All AEs refers to the number of subjects who had at least 1 AE.
Note: AE onset time is calculated based on AE start date and first dose date in core study. Percentages are based on the number of subjects in the Safety population, who reach each the observation interval. This could include follow-up periods after discontinuation of treatment.
Note: Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study treatment. Within each AE onset category, subjects are counted no more than once for incidence.

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参考文献	添付資料番号
Burrin DG, Stoll B, Guan X, Cui L, Chang X, Hadsell D. GLP-2 rapidly activates divergent intracellular signaling pathways involved in intestinal cell survival and proliferation in neonatal piglets. Am J Physiol Endocrinol Metab. 2007;292(1):E281-91.	5.4.12
Burrin DG, Stoll B, Guan X, Cui L, Chang X, Holst JJ. Glucagon-like peptide 2 dose-dependently activates intestinal cell survival and proliferation in neonatal piglets. Endocrinology. 2005;146(1):22-32.	5.4.13
Burrin DG, Stoll B, Jiang R, Petersen Y, Elnif J, Buddington RK, et al. GLP-2 stimulates intestinal growth in premature TPN-fed pigs by suppressing proteolysis and apoptosis. Am J Physiol Gastrointest Liver Physiol. 2000;279(6):G1249-56.	5.4.14
Crenn P, Coudray–Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology. 2000;119(6):1496-505.	5.4.17
Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut. 2005;54(9):1224-31.	5.4.35
Lovshin JA, Huang Q, Seaberg R, Brubaker PL, Drucker DJ. Extrahypothalamic expression of the glucagon-like peptide-2 receptor is coupled to reduction of glutamate-induced cell death in cultured hippocampal cells. Endocrinology. 2004;145(7):3495-506.	5.4.41
Marier J, Kassir N, Martin P, Wang Y. Population pharmacokinetic modeling of teduglutide to support dosing in pediatric patients with short bowel syndrome. Clin Pharmacol Ther. 2017;101(1):S91.	5.4.43
Petersen YM, Burrin DG, Sangild PT. GLP-2 has differential effects on small intestine growth and function in fetal and neonatal pigs. Am J Physiol Regul Integr Comp Physiol. 2001;281(6):R1986-93.	5.4.56
Takagi Y, Okada A, Sato T, Fukushima T, Shirotani N, Osawa Y, et al. Report on the first annual survey of home parenteral nutrition in Japan. Surg Today. 1995;25(3):193-201.	5.4.69
Ukleja A, Romano MM. Complications of parenteral nutrition. Gastroenterol Clin North Am. 2007;36(1):23-46.	5.4.72
嵩原裕夫，在宅栄養療法の現況 小児での在宅静脈栄養．日本臨床．2001;59(5):848-51	5.4.89

1　臨床試験一覧

テデュグルチドの臨床試験一覧 [a]

試験の種類	試験 ID	実施国	試験の状況	試験の目的	試験デザイン	投与群及び被験者数（安全性解析対象集団）	健康被験者又は患者の診断名	投与期間	総括報告書添付場所評価／参考
バイオアベイラビリティ（BA）	CL0600-006	海外	完了	BA 皮下注対 1 時間点滴静注	第 1 相、単施設、無作為化、非盲検、2-way クロスオーバー試験	テデュグルチド：14 例 （0.12 mg/kg/dose IV 及び 0.12mg/kg/dose SC）	健康被験者	2 回の単回投与	Module 5.3.1.1 参考資料
BA	CL0600-015	海外	完了	BA 投与部位	第 1 相、単施設、無作為化、非盲検、3-way クロスオーバー試験	テデュグルチド：18 例 （0.1 mg/kg/dose SC）	健康被験者	3 回の単回投与	Module 5.3.1.2 参考資料
安全性、忍容性、薬物動態	1621/13	海外	完了	単回投与時の安全性、忍容性、薬物動態	第 1 相、単施設、単盲検、プラセボ対照、用量漸増単回投与試験	テデュグルチド：24 例 （4 用量のうちのいずれか：2.5 mg、5.0 mg、7.0 mg 又は 10 mg SC） プラセボ：8 例	健康被験者	単回投与	Module 5.3.3.1 評価資料
安全性、忍容性、薬物動態	CL0600-022	海外	完了	反復投与時の安全性、忍容性、薬物動態	第 1 相、単施設、無作為化、二重盲検、プラセボ対照、用量漸増反復投与試験	テデュグルチド：71 例 （7 用量のうちいずれか：10、15、20、25、30、50 又は 80 mg/日　SC） プラセボ：24 例	健康被験者	8 日間	Module 5.3.3.1 評価資料
内因性要因 薬物動態	CL0600-017	海外	完了	肝機能障害患者における薬物動態	第 1 相、単施設、非盲検、並行群間、前向き、健康人対照試験	テデュグルチド：24 例 （20 mg SC）	健康被験者 肝機能障害患者	単回投与	Module 5.3.3.3 参考資料
内因性要因 薬物動態	CL0600-018	海外	完了	腎機能障害患者における薬物動態	第 1 相、単施設、非盲検、並行群間、前向き、健康人対照試験	テデュグルチド：36 例 （10 mg SC）	健康被験者 腎機能障害患者	単回投与	Module 5.3.3.3 参考資料

テデュグルチドの臨床試験一覧 [a]

試験の種類	試験 ID	実施国	試験の状況	試験の目的	試験デザイン	投与群及び被験者数（安全性解析対象集団）	健康被験者又は患者の診断名	投与期間	総括報告書添付場所評価／参考
QT/QTc	C09-001	海外	完了	QT/QTc	第 1 相、単施設、無作為化、二重盲検（テデュグルチド投与につき）、単回投与、プラセボ及び陽性対照、4 期、チェンジオーバー試験	72 例 （全例：テデュグルチド 5 mg SC、20 mg SC、プラセボ SC、モキシフロキサシン 400 mg oral）	健康被験者	4 回の単回投与	Module 5.3.4.1 評価資料
薬物動態、PD	C10-003	海外	完了	胃内容排出に対する影響の検討	第 1 相、無作為化、二重盲検、プラセボ対照、反復投与試験	テデュグルチド：23 例 （4 mg SC） プラセボ：13 例	健康被験者	10 日間	Module 5.3.4.1 参考資料
薬物動態、PD	TED-C10-004	海外	完了	胆嚢運動及び胆道内腔径に対する影響	第 1 相、無作為化、二重盲検、プラセボ対照、反復投与試験	テデュグルチド：29 例 （4 mg SC） プラセボ：31 例	健康被験者	5 日間	Module 5.3.4.1 参考資料
薬物動態、PD	ALX-0600-92001	海外	完了	安全性及び忍容性、残存腸の水及び主要栄養素の吸収能に対する影響を測定、薬物動態	第 2 相、多施設共同、非盲検、用量漸増パイロット試験	テデュグルチド： 3 例（0.03 mg/kg/日 QD SC） 10 例（0.10 mg/kg/日 QD SC） 4 例（0.15 mg/kg/日 QD SC） 5 例（0.10 又は 0.15 mg/kg/日 BID SC）	SBS 患者	21 日間	Module 5.3.4.2 参考資料
有効性、安全性	CL0600-004	海外	完了	有効性、安全性、忍容性、及び薬物動態をプラセボと比較検討	第 3 相、多施設共同、無作為化、二重盲検、並行群間比較、プラセボ対照試験	プラセボ：16 例 テデュグルチド： 35 例（0.05 mg/kg/日　SC）、 32 例（0.10 mg/kg/日　SC）	SBS 患者	24 週間	Module 5.3.5.1 評価資料
有効性、安全性	CL0600-020	海外	完了	有効性、安全性及び忍容性をプラセボと比較検討	第 3 相、多施設共同、無作為化、二重盲検、並行群間比較、プラセボ対照試験	テデュグルチド： 42 例（0.05 mg/kg/日　SC） プラセボ：43 例	SBS 患者	24 週間	Module 5.3.5.1 評価資料
継続投与試験	CL0600-005	海外	完了	長期の安全性及び有効性の検討	第 3 相、多施設共同、無作為化、二重盲検、CL0600-004 試験からの継続投与試験	テデュグルチド： 31 例（0.05 mg/kg/日　SC）、 34 例（0.10 mg/kg/日　SC）	SBS 患者	28 週間	Module 5.3.5.2 評価資料

テデュグルチドの臨床試験一覧 [a]

試験の種類	試験 ID	実施国	試験の状況	試験の目的	試験デザイン	投与群及び被験者数（安全性解析対象集団）	健康被験者又は患者の診断名	投与期間	総括報告書添付場所評価／参考
継続投与試験	CL0600-021	海外	完了	長期の安全性及び有効性の検討	第 3 相、多施設共同、非盲検、CL0600-020 試験からの継続投与試験	テデュグルチド： 88 例（0.05 mg/kg/日　SC）	SBS 患者	最長 2 年間	Module 5.3.5.2 評価資料
安全性、有効性	SHP633-306	日本	完了	日本人における安全性、有効性、及び薬物動態の検討	第 3 相、多施設共同、非盲検試験	テデュグルチド：7 例 （0.05 mg/kg/日　SC）	SBS 患者	24 週間	Module 5.3.5.2 評価資料
安全性、薬物動態、PD	TED-C13-003	海外	完了	小児における薬物動態、安全性、及び忍容性、薬力学的効果を標準治療と比較検討	第 3 相、多施設共同、非盲検試験	テデュグルチド： 8 例（0.0125 mg/kg/日　SC）、 14 例（0.025 mg/kg/日　SC）、 15 例（0.05 mg/kg/日　SC） 標準治療：5 例	SBS 患者	12 週間	Module 5.3.5.2 評価資料
安全性、有効性、PD	TED-C14-006	海外	完了	小児における安全性、忍容性、薬物動態、及び有効性／PD の検討	第 3 相、多施設共同、二重盲検試験 非盲検下でテデュグルチド群又は標準治療群を選択 テデュグルチド用量群は二重盲検下で割付	テデュグルチド： 24 例（0.025 mg/kg/日　SC）、 26 例（0.05 mg/kg/日　SC） 標準治療：9 例	SBS 患者	24 週間	Module 5.3.5.2 評価資料
継続投与試験	SHP633-303	海外	実施中 [1]	小児における長期の安全性及び有効性の検討	第 3 相、後向き及び前向き、非盲検、TED-C13-003 試験からの継続投与試験	テデュグルチド：16 例 [b] （0.05 mg/kg/日　SC） TED/NTT：8 例	SBS 患者	長期継続投与 [c]	Module 5.3.5.2 Module 5.3.5.2 (final) 評価資料

テデュグルチドの臨床試験一覧 [a]

試験の種類	試験 ID	実施国	試験の状況	試験の目的	試験デザイン	投与群及び被験者数（安全性解析対象集団）	健康被験者又は患者の診断名	投与期間	総括報告書添付場所評価／参考
継続投与試験	SHP633-304	海外	実施中 [2]	小児における長期の安全性及び有効性の検討	第 3 相、非盲検、TED-C14-006 試験及び SHP633-301 試験からの継続投与試験	テデュグルチド：49 例 [d] （0.05 mg/kg/日　SC） NTT/NTT：6 例 （中間解析時に SHP633-301 試験からの移行例は含まれない）	SBS 患者	長期継続投与 [c]	Module 5.3.5.2 Module 5.3.5.2 (final) 評価資料
安全性、有効性	TED-C14-004	日本	完了	日本人における安全性、有効性、及び薬物動態の検討	長期継続投与期間を含む、第 3 相、非盲検、多施設共同、4 ステージ試験	テデュグルチド：11 例 （0.05 mg/kg/日　SC）	SBS 患者	24 週間+長期継続投与期間	Module 5.3.5.2 参考資料
継続投与試験	TED-C11-001	海外	完了	長期の安全性及び有効性の検討	第 3 相、多施設共同、非盲検、CL0600-021 試験からの継続投与試験	テデュグルチド：14 例 （0.05 mg/kg/日　SC）	SBS 患者	最長 1 年間	Module 5.3.5.2 参考資料
安全性、有効性	SHP633-302	日本	完了	日本人小児における安全性、有効性、及び薬物動態の検討	第 3 相、多施設共同、非盲検試験	テデュグルチド：10 例 （0.05 mg/kg/日　SC）	SBS 患者	24 週間	Module 5.3.5.2 評価資料
継続投与試験	SHP633-307	日本	実施中 中間解析完了	日本人における長期の安全性、有効性の検討	第 3 相、多施設共同、非盲検、SHP633-306 試験及び TED-C14-004 試験からの継続投与試験	テデュグルチド：11 例 （0.05 mg/kg/日　SC）	SBS 患者	長期継続投与	Module 5.3.5.2 評価資料
安全性、有効性及び薬物動態	SHP633-301	海外	完了 [3] 中間解析完了 最終解析完了	乳児における安全性、有効性／PD 及び薬物動態の検討	第 3 相、無作為化、非盲検試験	中間解析時： テデュグルチド：3 例 （0.05 mg/kg/日　SC） 標準治療：3 例 最終解析時： テデュグルチド：5 例 （0.05 mg/kg/日　SC） 標準治療：5 例	SBS 患者	24 週間	Module 5.3.5.2 Module 5.3.5.2 (final) 参考資料

テデュグルチドの臨床試験一覧 [a]

試験の種類	試験 ID	実施国	試験の状況	試験の目的	試験デザイン	投与群及び被験者数（安全性解析対象集団）	健康被験者又は患者の診断名	投与期間	総括報告書添付場所評価／参考
継続投与試験	SHP633-305	日本	実施中 中間解析完了	日本人小児における長期の安全性及び有効性の検討	第 3 相、非盲検、SHP633-302 試験からの継続投与試験	テデュグルチド：9 例（小児 7 例及び乳児 2 例） （0.05 mg/kg/日　SC）	SBS 患者	長期継続投与 [c]	Module 5.3.5.2 評価資料
その他の臨床試験	CL0600-008	海外	完了	クローン病患者を対象とする安全性及び有効性試験	第 2 相、多施設共同、無作為化、二重盲検、プラセボ対照、パイロット試験	テデュグルチド： 24 例（0.05 mg/kg/日　SC） 26 例（0.10 mg/kg/日　SC） 25 例（0.20 mg/kg/日　SC） プラセボ：25 例	クローン病患者	8 週間	Module 5.3.5.4 参考資料
その他の臨床試験	CL0600-009	海外	完了	クローン病患者を対象とする継続投与試験	第 2 相、多施設共同、非盲検、CL0600-008 試験からの継続投与試験	テデュグルチド：67 例 （0.10 mg/kg/日　SC）	クローン病患者	12 週間	Module 5.3.5.4 参考資料

IV=静脈内投与；SC=皮下投与；PD=薬力学；QD=1 日 1 回；BID=1 日 2 回

1. 本試験は 2020 年 10 月申請時には実施中であった。本概括評価には 2018 年 1 月のデータカットオフ時点のデータを示す。最終の総括報告書は照会事項回答別添（[redacted]_別添資料）として 20[redacted]年[redacted]月[redacted]日に機構へ提出し、5.3.5.2.6 項（final）に格納。最終の総括報告書において結論の変更はなかった。
2. 本試験は 2020 年 10 月申請時には実施中であった。本概括評価には 2018 年 2 月のデータカットオフ時点のデータを示す。その後、2020 年 11 月に最終被験者の最終来院を実施し、試験は完了した。最終の総括報告書は 5.3.5.2.7 項（final）に格納。
3. 本試験は 2020 年 10 月申請時には実施中であった。本概括評価には 2019 年 10 月 9 日のデータカットオフ時点のデータ及び最終の総括報告書のデータを示す。最終の総括報告書は照会事項回答別添（[redacted]_別添資料）として 20[redacted]年[redacted]月[redacted]日に機構へ提出した。最終の総括報告書において結論の変更はなかった。最終の総括報告書は 5.3.5.2.12 項（final）に格納。

a　TED-R13-002 試験は実施中のレジストリ試験であり、この表に示さない。テデュグルチド投与の有無に関わらず SBS を有する患者を組み入れた。
b　前向き期間で、治験薬を 1 回以上投与され（安全性解析対象集団）、中間解析に含めた被験者数。
c　本試験では、疾患の経過に応じて無投与期間及び 24 週間投与を繰り返す。
d　先行試験及び／又は本試験でテデュグルチドを 1 回以上投与された被験者数（Any TED）。

2　CL0600-006 試験

（参考資料：5.3.1.1 項）

CL0600-006 試験の概要を表 2.7.6.2 - 1 に示す。

表 2.7.6.2 - 1　　CL0600-006 試験：試験の概要

試験識別番号	CL0600-006
試験の標題	健康被験者を対象とする、ALX-0600 0.12 mg/kg の第 1 相、無作為化、2-way クロスオーバーバイオアベイラビリティ試験
試験の相	1
目的	主要目的： 1)　健康男性及び女性被験者を対象とし、ALX-0600（テデュグルチド）0.12 mg/kg の空腹時における皮下注のバイオアベイラビリティを 1 時間点滴静注と比較して評価すること。 2)　健康男性及び女性被験者を対象とし、テデュグルチド 0.12 mg/kg の空腹時における皮下注と 1 時間点滴静注の安全性及び忍容性を評価すること。 副次目的： 健康男性及び女性被験者を対象として、テデュグルチド 0.12 mg/kg を空腹時に点滴静注した際のその薬物動態を評価すること。
方法	本試験は、テデュグルチド 0.12 mg/kg の皮下注と 1 時間点滴静注を比較する、単一施設、非盲検、無作為化、2-way クロスオーバー（2 種類の投与、2 種類の投与順［1：A/B 又は 2：B/A］）バイオアベイラビリティ試験である。 試験組入れ（第 1 期、Day −1 の入院）前 28 日以内に候補被験者をスクリーニングした。被験者は、各投与期間中、点滴静注／皮下注（午前中）の約 24 時間前から点滴静注／皮下注開始後 24 時間以上実施医療機関に入院した。その後、被験者は次の投与まで 5 日間以上の休薬期間を取った。試験完了手順は、Day 13 の追跡調査来院時（最終／2 回目の投与から約 7 日後）に実施した。身体所見、12 誘導心電図、バイタルサイン、問診、及び臨床検査値の評価については、スクリーニング時、試験期間中の特定の時点、及び試験完了時に行った。 テデュグルチドの薬物動態解析用血液検体は、各期間中、次に示す時点に採取した：0 時間（点滴静注又は皮下注の前）、0.5 時間（1 時間点滴静注の中間時点［投与 A］、又は皮下注の 0.5 時間後［投与 B］）；1.0 時間（1 時間点滴静注の終了直前［投与 A］又は皮下注から 1.0 時間後［投与 B］）；点滴静注開始から 1.083、1.167、及び 1.33 時間後（1 時間点滴静注終了から 5、10、及び 20 分後［投与 A のみ］）；並びに点滴静注開始時又は皮下注から 1.5、2.0、2.5、3、3.5、4、5、6、8、10、12、及び 24 時間後。
診断及び主な選択基準	18 歳～45 歳で体重が身長及び体格に基づく理想体重の±20%以内の健康な男性及び女性被験者
予定症例数及び解析対象例数（合計及び投与群ごと）	解析対象集団：14 例（男性 12 例、女性 2 例）

表 2.7.6.2 - 1　　CL0600-006 試験：試験の概要

被験薬、用法・用量、バッチ番号	ALX-0600（テデュグルチド）：9 mg/バイアル、無菌粉末 ロット番号：[redacted] ● 投与 A：一晩、8 時間以上絶食した後、テデュグルチド 0.12 mg/kg を 1 時間かけて単回静脈内投与（点滴静注）。 ● 投与 B：一晩、8 時間以上絶食した後、テデュグルチド 0.12 mg/kg を単回投与（皮下）。 投与と投与の間に少なくとも 5 日間の休薬期間を設定した。
対照薬、用法・用量、バッチ番号	なし
投与期間	単回投与
評価基準	薬物動態パラメータ： • C_{max}：観察された最高血漿中濃度。 • T_{max}：最高血漿中濃度到達時間。 • AUC_{0-t}：0 時間から最終血漿中濃度測定可能時間までの血漿中濃度－時間曲線下面積、線形台形則に基づき算出。 • AUC_{0-inf}：無限大まで外挿した血漿中濃度－時間曲線下面積、以下の式を用いて算出。 o $AUC_{0-inf} = AUC_{0-t} + (C_t / K_e)$、ここで C_t は最終の測定可能血漿中濃度、K_e は見かけの終末相速度定数を表す。 • K_e：見かけの終末相速度定数、ここで K_e は、終末相における対数変換した濃度－時間プロファイルの線形回帰の傾きの大きさを表す。 • $t_{1/2}$：見かけの終末相半減期（可能な場合）、ここでは、$t_{1/2} = (\ln 2) / K_e$ • F（%）：テデュグルチドの絶対的バイオアベイラビリティ、計算法は以下のとおり。 o $F = (AUC_{0-t\ (sc)} / AUC_{0-t\ (IV)}) \times (Dose_{IV}/Dose_{SC}) \times 100$ さらに、投与 A（点滴静注）に限り、可能な場合、以下のパラメータを算出した。 • CL：総血漿クリアランス、ここでは、$CL = Dose_{IV} / AUC_{0-inf\ IV}$ • Vd_β：終末相における分布容積、ここでは、$Vd_\beta = CL/K_e$ • Vd_{ss}：定常状態における分布容積、ここでは、$Vd_{ss} = CL*MRT$ • MRT：平均滞留時間、以下の式を用いて算出した。 o $MRT = (AUMC_{0-inf\ IV}/AUC_{0-inf\ IV}) - (Ti/2)$、ここで $AUMC_{0-inf}$ は 1 次モーメント曲線下面積（標準手法を用いて決定）、Ti は点滴静注に費やす時間。 安全性： • 有害事象（AE） • 臨床検査値 • バイタルサイン • 12 誘導心電図（ECG） • 身体所見
統計手法	データが利用できる場合、投与 A（1 時間点滴静注；対照群）と投与 B（皮下注；被験群）を比較して分散分析を行い、バイオアベイラビリティを検討した。C_{max}、AUC_{0-t}、AUC_{0-inf}、及び $t_{1/2}$ に関するデータは、解析前に自然対数（ln）に変換した。対照群の平均値と比較したときの被験群の平均値の 90%信頼区間については、対数目盛上における平均間の差の対応する 90%信頼区間の逆対数を求めることで算出した。C_{max}、AUC_{0-t}、及び AUC_{0-inf} について、被験群の平均値と対照群の平均値

表 2.7.6.2 - 1　　CL0600-006 試験：試験の概要

	の比率の90%信頼区間を検討することによりバイオアベイラビリティを評価した。表に提示したp値は、検定した正規仮説（normal hypothesis）に基づいた値である（生物学的同等性には、この仮説とは異なる区間仮説［interval hypothesis］を利用）。具体的には、このp値は、平均は等しいとする帰無仮説及び平均は等しくないとする対立仮説の検定に基づいた値である。これらのp値は情報として提示するものであり、解析から何らかの結論を引き出すためには用いなかった。本試験は生物学的同等性試験ではないため、正式な統計学的結論（80～125%信頼区間法を利用）は下さなかった。
治験責任医師及び実施医療機関	1施設（米国）
試験期間	最初の被験者への投与：20[redacted]年[redacted]月[redacted]日 最終追跡調査完了：20[redacted]年[redacted]月[redacted]日

要約及び結論

薬物動態：

テデュグルチドの薬物動態パラメータ（平均値）を以下の表に示す。

表：テデュグルチドの薬物動態パラメータ（平均値）の概要

Parameter	Subcutaneous Injection	N (SC)	Intravenous Infusion	N (IV)
C_{max} (ng/mL)	112 (± 18)	14	841 (± 123)	14
T_{max} (hr)	4 (1.50-8.00)	14	0.961 (0.941-1.27)	14
AUC_{0-t}	872 (± 202)	14	1003 (± 161)	14
AUC_{0-inf}	886 (± 200)	14	1004 (± 175)	12[b]
$T_{1/2}$ (hr)	2.23 (± 0.68)	14	5.17 (± 2.79)	12[b]
CL (mL/hr/kg)	NC	NC	123 (± 22)	12[b]
Vd_{β}	NC	NC	878 (± 391)	12[b]
Vd_{ss}	NC	NC	122 (± 30)	12[b]
MRT	NC	NC	1.02 (± 0.33)	12[b]
F(%)[a]	87.1 (± 14.0)	14	NC	NC

Source: M5.3.1.1 CL0600-006 CSR, Table 11.4-1
Note: Arithmetic mean (± standard deviation) is presented. For T_{max}, the median values (range) are presented.
NC=not calculated
[a] Mean F(%) determined by calculating the F(%) after subcutaneous administration for all 14 individuals and taking the arithmetic mean.
[b] Subject Nos. [redacted] and [redacted] not included in these calculations.

安全性：

本試験でみられた有害事象は21件であり、そのうち10件は投与A（テデュグルチド 0.12 mg/kg 点滴静注）の後でみられ、11件は投与B（テデュグルチド0.12 mg/kg皮下注）の後でみられた。有害事象はいずれも軽度と判断された。発現した有害事象21件のうち、治験薬投与との関連なし（none）は11件、治験薬投与との関連はないと思われる（improbable）が1件、治験薬と関連の可能性あり（possible）が9件であった。関連ありとされた有害事象は、悪心（nausea）（50%）、浮動性めまい（dizziness）（20%）、頭痛NOS（headache NOS）（20%）、及び流涙増加（lacrimation increased）（10%）で、悪心が最も頻度の高い治験薬と関連がある有害事象であった*。全般的に、テデュグルチド0.12 mg/kgの1時間点滴静注（投与A）と皮下注（投与B）との間で、有害事象の発現件数、又はこれら有害事象の特性及び重症度に意味のある差は認められなかった。本試験で死亡、その他の重篤な有害事象及び治験薬の投与中止に至った有害事象はみられなかった。

生化学的検査、血液学的検査、尿検査、バイタルサイン、12誘導心電図、及び身体所見を評価した結果、1時間点滴静注又は皮下注のいずれの方法で投与してもテデュグルチド0.12 mg/kgは安全で

表 2.7.6.2 - 1　　CL0600-006 試験：試験の概要

あり、忍容性は良好であることが示された。

*本試験で報告された有害事象は国際医薬用語集（MedDRA®）Version.[redacted] を用いてコード化し、有害事象用語の翻訳には version18.1 を使用した。

結論：

点滴静注終了後、テデュグルチドの濃度は、概して双指数関数的に着実に低下し、終末相の $t_{1/2}$（平均値）は 5.17 時間であった。終末相における血漿中テデュグルチド濃度の変動は、分析時にテデュグルチドに加えてその他の内因性 GLP-2 関連ペプチドも検出されるという事実と関連している可能性があった。ベースラインで補正した $t_{1/2}$（平均値）は 3.20（± 1.67）時間であり、この結果から、ベースラインで補正することにより、終末相における血漿中濃度の変動の一部を除去できる可能性が示唆された。被験者 12 例に静脈内投与したときの $AUC_{0\text{-}t}$ 及び $AUC_{0\text{-}inf}$（平均値）については、両パラメータの計算が可能であり、それぞれの値は 996 ng•hr/ml 及び 1004 ng•hr/ml であった。この結果から、$AUC_{0\text{-}t}$ は $AUC_{0\text{-}inf}$ にほぼ一致（99%）することが示された。Vd_{ss}（平均値）は総体重の約 12%であり、テデュグルチドが、少なくとも部分的には、細胞外液に分布する可能性が示された。皮下投与後、テデュグルチドは直ちに吸収され、その血漿中からの消失は速やかで、$t_{1/2}$（平均値）は 2.23 時間であった。

被験者 14 例に皮下投与したときの $AUC_{0\text{-}t}$ 及び $AUC_{0\text{-}inf}$（平均値）はそれぞれ、872 ng•hr/mL 及び 886 ng•hr/mL であり、この結果から、$AUC_{0\text{-}t}$ は $AUC_{0\text{-}inf}$ にほぼ一致（98%）することが示された。皮下投与後のテデュグルチドのバイオアベイラビリティ（平均値）は 87.1%（±14%）であった。

$AUC_{0\text{-}t}$ は $AUC_{0\text{-}inf}$ とほぼ一致（98%～99%）したこと、並びに被験者番号：[redacted] 及び[redacted] では $t_{1/2}$ が推定不能で、両者を $AUC_{0\text{-}inf}$ の計算対象から除外したため、$AUC_{0\text{-}inf}$ 値はバイオアベイラビリティの算出に利用しなかった。有害事象、生化学的検査、血液学的検査、尿検査、バイタルサイン、12 誘導心電図、及び身体所見を評価した結果、点滴静注又は皮下注のいずれの方法で投与してもテデュグルチド 0.12 mg/kg は安全で、その忍容性は良好であることが示された。

3　CL0600-015 試験

（参考資料：5.3.1.2 項）

CL0600-015 試験の概要を表 2.7.6.3 - 1 に示す。

表 2.7.6.3 - 1　　CL0600-015 試験：試験の概要

試験識別番号	CL0600-015
試験の標題	健康成人を対象とするテデュグルチド 10 mg の第 1 相、無作為化、非盲検、3-way クロスオーバーバイオアベイラビリティ試験
試験の相	1
目的	腹部を対照とし、大腿及び上腕にテデュグルチド 10 mg を皮下投与したときの相対的バイオアベイラビリティを確認すること、並びにテデュグルチド 10 mg を上腕、大腿、及び腹部に皮下投与したときの薬物動態及び安全性を評価すること
方法	本試験は、単一施設、非盲検、無作為化、3-way クロスオーバー（投与は 3 種類、投与順は 6 種類）バイオアベイラビリティ試験である。テデュグルチドの投与について以下に示す。 投与 A：テデュグルチド 10 mg の下腹部皮下への単回投与。 投与 B：テデュグルチド 10 mg の大腿上部皮下への単回投与。 投与 C：テデュグルチド 10 mg の上腕皮下への単回投与。 投与と投与の間隔は 3 日間とした。6 種類の投与順を以下に示す。 シーケンス I：A、B、C シーケンス II：A、C、B シーケンス III：B、A、C シーケンス IV：B、C、A シーケンス V：C、A、B シーケンス VI：C、B、A
診断及び主な選択基準	被験者は、18 歳から 45 歳、体格指数 18～30 kg/m^2 の健康な男性及び女性
予定症例数及び解析対象例数（合計及び投与群ごと）	予定症例数：18 例 解析対象例数：16 例
被験薬、用法・用量、バッチ番号	テデュグルチド（10 mg）は皮下投与した。 テデュグルチド（20 mg/バイアル、凍結乾燥粉末） ロット番号：[redacted]
対照薬、用法・用量、バッチ番号	なし
投与期間	3 回の単回投与、投与と投与の間隔は 3 日間とした。

表 2.7.6.3 - 1　　CL0600-015 試験：試験の概要

評価基準	薬物動態： 薬物動態検体採取スケジュール：全ての被験者を対象とし、各投与日の次の時点に採血した 7 mL の血液検体を用い、テデュグルチドの血漿中プロファイルを評価した：0 時間（投与前）、及び投与後 0.5、1、1.5、2、2.5、3、3.5、4、5、6、8、10、12、及び 24 時間。さらに、Day 1 及び Day 4 の投与 48 時間後の検体を採血した。 薬物動態解析：単回投与に適した、モデルに依存しない方法に基づき、各被験者のテデュグルチドの血漿中プロファイルを用いて、全ての投与について次に示す薬物動態パラメータを算出した：C_{max}、T_{max}、AUC_{0-t}、AUC_{0-inf}、$t_{1/2}$、及び k_e。投与 B 及び投与 C については、それぞれ F_{thigh} 及び F_{arm} を算出した。 安全性： 安全性の測定項目は、有害事象、バイタルサイン、心電図、身体所見、体重、及び臨床検査値の評価とした。 薬力学： ベースラインデータ（平均値）からの変化量（絶対値）にノンコンパートメント解析を適用し、次のパラメータを算出した：AUC_{all}、C_{max}、ベースライン（平均値）からの最大変化量、及び T_{max}。
統計手法	要約と統計モデルの対象は、バイオアベイラビリティ評価可能集団の被験者とした。被験注射部位（大腿及び上腕）と対照注射部位（腹部）を比較してバイオアベイラビリティを検討した。共分散分析（ANCOVA）を用い、解析前に C_{max}、AUC_{0-t}、及び AUC_{0-inf} の各データを自然対数に変換した。Ke のデータについては解析前の変換を行わなかった。投与、期、シーケンス、及びシーケンス内の被験者のそれぞれの効果について、パラメータごとに評価した。 被験部位ごとの相対的バイオアベイラビリティを推測するため、AUC_{0-inf} のデータを自然対数に変換して用いた。上腕及び大腿の注射部位と、腹部の対照注射部位とのペアワイズ・コントラスト比較（pairwise contrast comparison）を行い、それぞれの相対的バイオアベイラビリティの 90%信頼区間（CI）を推定した。対照群の平均値と比較したときの被験群の平均値の 90% CI については、自然対数目盛上における平均間の差の対応する 90%CI の逆対数を求めることで算出した。この手順は、有意水準を 0.05 とする Schuirmann の 2 つの片側検定（2 one-sided tests）に相当する。
治験責任医師及び実施医療機関	1 施設（米国）
試験期間	最初の被験者の組入れ：20[redacted]年 [redacted]月 [redacted]日 最終被験者の完了：20[redacted]年 [redacted]月 [redacted]日

表 2.7.6.3 - 1 CL0600-015 試験：試験の概要

要約及び結論

薬物動態の結果：

a）薬物動態パラメータ結果：

全ての投与から得られたテデュグルチド薬物動態パラメータの要約を以下の表に示す。

表：テデュグルチド薬物動態パラメータの要約

		PK Parameter							
Treatment (Injection Site)		**C_{max} (ng/mL)**	**T_{max}[a] (hr)**	**AUC_{0-t} (ng·hr/mL)**	**AUC_{0-inf} (ng·hr/mL)**	**$t_{1/2}$ (hr)**	**AUC_{0-inf} /dose (ng·hr/mL/mg/kg)**	**$F_{AUC0-inf}$**	**$F_{AUC0-inf}$**
A (Abdomen)	Mean	144	3.50	846	930	2.09	6788	NA	NA
	SD	59	(2.50, 5.03)	202	200	1.07	1479	NA	NA
	N	16	16	16	16	16	16	NA	NA
B (Thigh)	Mean	118	4.00	731	816	2.22	5955	0.865	0.877
	SD	35	(2.50, 6.00)	200	214	0.98	1456	0.120	0.133
	N	16	16	16	16	16	16	16	16
C (Arm)	Mean	113	4.50	754	863	2.12	6251	0.892	0.914
	SD	52	(3.00, 6.08)	227	256	1.26	1933	0.141	0.153
	N	16	16	16	15	15	15	15	16

Source: M5.3.1.2 CL0600-015 CSR, Table 14.2.2.-1a, Table 14.2.2-1b

異なる 3 部位に皮下投与したとき、テデュグルチドは直ちに吸収され、速やかに消失した。$t_{1/2}$（平均値）は 2.09～2.22 時間であり、全般的に 3 部位間で大きな差はみられなかった。テデュグルチドの C_{max}（平均値）は、腹部（対照投与 A）への皮下注が最も高く、これに大腿部及び上腕部が続いた（それぞれ、投与 B 及び投与 C）。総曝露量（AUC_{0-t} 及び AUC_{0-inf}）は、腹部投与後が最も高く、これに上腕及び大腿部が続いた。用量で補正した AUC_{0-inf} についても類似の傾向が認められた。腹部投与と比較したとき、テデュグルチド AUC_{0-inf} の相対的バイオアベイラビリティは、大腿部が 86.5%、上腕部が 89.2%であった。

b）薬物動態パラメータの統計学的比較：

相対的バイオアベイラビリティを確認するための統計解析結果の要約を以下の表に示す。

表：テデュグルチドの相対的バイオアベイラビリティに関する統計解析結果の要約

		Mean[a]					**90% Confidence Interval[b]**
Parameter	**Units**	**Thigh**	**Arm**	**Abdomen**	**Comparison**	**Ratio**	
C_{max}	ng/mL	118	NA	143	Thigh vs Abdomen	82.7	(74.0, 92.4)
		NA	114	143	Arm vs Abdomen	79.7	(71.4, 89.1)
AUC_{0-t}	ng·hr/mL	745	NA	851	Thigh vs Abdomen	87.5	(82.6, 92.8)
		NA	768	851	Arm vs Abdomen	90.3	(85.1, 95.7)
AUC_{0-inf}	ng·hr/mL	836	NA	943	Thigh vs Abdomen	88.6	(82.2, 95.5)
		NA	869	941	Arm vs Abdomen	92.4	(85.3, 100)

[a] Geometric least squares mean from ANCOVA.

[b] 90% confidence interval of geometric least squares mean ratio from ANCOVA

Source: M5.3.1.2 CL0600-015 CSR Table 11-3

表 2.7.6.3 - 1　　CL0600-015 試験：試験の概要

テデュグルチドの相対的バイオアベイラビリティについて統計解析した結果、AUC_{0-t} 及び AUC_{0-inf} の 90%信頼区間は、80%～125%の範囲に完全に収まった。しかしながら、テデュグルチドの C_{max} については、90%信頼区間の下限がこの範囲からわずかに外れた。相対的バイオアベイラビリティの点推定値によると、テデュグルチドを大腿及び上腕に投与したときの総曝露量は、腹部投与の 88%～92%であった。C_{max} の相対曝露量は、大腿が 83%、上腕が 80%であった。

安全性の結果：

全体では被験者 18 例のうち 13 例に有害事象が 42 件（試験治療下：39 件）発現した。内訳は、投与 A が 16 件、投与 B が 18 件、投与 C が 5 件、及び投与開始前に発現した 3 件であった。治験薬と有害事象との因果関係は、関連ありが 39 件、関連なしが 3 件であった。42 件の有害事象はいずれも軽度であった。

有害事象の発現頻度が高かった器官別大分類は、全身障害および投与局所様態（注射部位疼痛など）、治験薬投与下に発現した有害事象 17 件；胃腸障害（腹部不快感など）、治験薬投与下に発現した有害事象 7 件；神経系障害（浮動性めまいなど）、治験薬投与下に発現した有害事象 5 件；臨床検査（リパーゼ増加など）、治験薬投与下に発現した有害事象 3 件；皮膚および皮下組織障害（ざ瘡など）、治験薬投与下に発現した有害事象 2 件；眼障害（眼そう痒症など）、治験薬投与下に発現した有害事象 2 件；筋骨格系および結合組織障害（筋緊張など）、治験薬投与下に発現した有害事象 2 件であった。

本試験期間中には死亡、重篤な有害事象又は治験薬の投与中止に至った有害事象の発現はなかった。

本試験では、臨床検査値の評価、バイタルサイン測定値、身体所見、又は 12 誘導心電図に臨床的に問題となる変化又は所見はみられなかった。

全体的に見て、臨床安全性評価項目の変化に注目すべきものはなかった。

薬力学の結果：

下表に薬力学パラメータ（平均値）を示す。

表：LC-MS/MS による血漿中シトルリン濃度の薬力学パラメータ（平均値）

Treatment		**Δ_{max} (ng/mL)**	**$t_{\Delta max}$ [a] (hr)**	**AUC_{all} (µmol•hr/L)**	**Maximum Percent Change from Mean Baseline (%)**
A (Abdomen)	Mean	-11.8	6.00	162	-37.4
	SD	-4.3	(1.00, 10.0)	66	-8.5
	N	16	16	16	16
B (Thigh)	Mean	-13.5	6.00	183	-43.3
	SD	-4.8	(2.00, 12.0)	56.4	-9.2
	N	17	17	17	17
C (Arm)	Mean	-11.7	5.00	155	-38.4
	SD	-3.6	(1.00, 12.0)	49	-9.5
	N	17	17	17	17

[a] Mean Plasma Pharmacodynamic Data for Citrulline Using LC-MS/MS
Source: M5.3.1.2 CL0600-015 CSR, Table 11-4.

テデュグルチド投与後に血漿中シトルリン濃度（平均値）は低下を示したが、この原因がシトルリン濃度の日内変動、食事の影響、又はテデュグルチド投与による反応であるのかは明らかではない。プラセボ群がないので、シトルリン循環に対する薬物の効果について決定的な証拠は得られなかった。

ベースラインからの最大変化率（平均値）は 3 群で概して類似しており、範囲は−37.4%～−43.3%で

表 2.7.6.3 - 1　　CL0600-015 試験：試験の概要

あった。血漿中シトルリン濃度のプロファイルについて、投与群間で 2 倍を超える顕著な差は認められなかった。大腿上部に投与した（投与 B）場合が最も血漿中シトルリン濃度変化が大きかった。血漿中シトルリン濃度低下が最大になるまでの時間（中央値）の範囲は投与後 5.00～6.00 時間であった。
結論： 薬物動態の結論： 異なる 3 部位に皮下投与したとき、テデュグルチドは直ちに吸収され、速やかに消失した。全般的に、3 注射部位間では T_{max}（中央値）及び $t_{1/2}$（平均値）に大きな差はみられなかった。腹部投与と比較したときの相対的バイオアベイラビリティ（平均値）は、大腿が 88.6%、上腕が 92.4%であった。AUC_{0-t} 又は AUC_{0-inf} の 90%信頼区間は、80%～125%の範囲に完全に収まり、この結果から、3 部位間で皮下投与後の曝露量に大きな差はないことが示された。 安全性の結論： 有害事象、臨床検査、バイタルサイン測定値、12 誘導心電図、及び身体所見の評価から、上腕、大腿、及び腹部それぞれにテデュグルチド 10 mg を 1 回皮下投与したとき、その安全性及び忍容性はいずれも良好であることが示された。

4　1621/13 試験

（評価資料：5.3.3.1 項）

1621/13 試験の概要を表 2.7.6.4 - 1 に示す。本項で使用している ALX-0600 はテデュグルチドのコード名であった。

表 2.7.6.4 - 1　　1621/13 試験：試験の概要

試験識別番号	1621/13
試験の標題	ALX-0600 –健康男性被験者を対象とし単回漸増皮下投与したときの安全性、忍容性、及び薬物動態を検討する第 1 相、単盲検、プラセボ対照試験
試験の相	1
目的	• 健康男性被験者を対象として ALX-0600 を単回漸増皮下投与したときの安全性及び忍容性を検討すること。 • 健康男性被験者を対象として ALX-0600 の単回投与薬物動態を検討すること。
方法	本試験は、第 1 相、単盲検、プラセボ対照、単回皮下漸増投与試験であった。ALX-0600 の 4 用量（2.5 mg、5.0 mg、7.0 mg、及び 10 mg）を検討した。
診断及び主な選択基準	選択基準 以下に示す基準を全て満たす者を適格とした。 • 年齢 18～45 歳、体格指数（BMI）19～29 の白人男性被験者。 • 病歴、診察、心電図、血清生化学検査、血液学的検査、尿検査、及び血清学的検査に基づいて健康状態が良好と判断された者（先天性非溶血性高ビリルビン血症は組入れ不可とした）。 • 排便回数が 3 回／日から 3 回／週の者。 • 非喫煙者、又は 6 ヵ月以上喫煙していない元喫煙者。 • 試験に参加するため同意書を提出した者。同意書は、被験者による署名と日付、及び立会人による署名と日付が記入されたものとする。 除外基準 以下の基準のいずれかに合致する者は除外した。 • 投与開始前 14 日以内に全身性又は局所性の処方箋薬の投与を受けた者。 • 投与開始前 7 日以内に全身性又は局所性の非処方箋薬を使用した者（全身性又は局所性の非処方箋薬を使用した者であっても、当該薬が試験手順の妨げになったり安全性を損なったりすることはないと治験責任／分担医師が判断した場合は、試験への組入れを可とした）。 • 投与開始前 30 日以内に、バルビツール系薬剤や、フェノチアジン系薬剤、シメチジンといった、主要な臓器や組織系に影響を及ぼすことが知られている薬剤の投与を受けた者。 • 投与開始前 1 ヵ月以内に献血又は血漿献血を行った者、又は投与開始前 12 ヵ月以内に 1300 mL を超える献血を行った者。 • 投与開始前 4 ヵ月以内（新規化学物質）又は 3 ヵ月以内（既承認薬）に他の治験薬の投与を受けた者。 • 複数の薬物アレルギーの既往歴を有する被験者、若しくは本治験薬そのもの又は本治験薬と化学的に関連のある薬剤に対するアレルギーが知られている者。 • 臨床的に問題となるアレルギー性疾患（非活性の花粉症は除く）を有する者。 • スクリーニング時に 5 分間安静を保持した後に仰臥位で測定した血圧が

表 2.7.6.4 - 1　1621/13 試験：試験の概要

	150/90 mmHg を超える、又は 100/50 mmHg 未満の者。 • スクリーニング時に 5 分間安静を保持した後に仰臥位で測定した脈拍数が 40～90 bpm の範囲外であった者。 • アルコール摂取量が 28 単位／週を超える者、あるいは、重度のアルコール依存症又は薬物／化学物質乱用の既往歴を有する者（アルコール 1 単位は、ビール又はラガービール 1/2 パイント、ワイン 1 グラス、又は蒸留酒 1/6 ジルに相当する）。 • 臨床的に問題となる、神経、消化器、腎臓、肝臓、循環器、精神、肺、代謝、内分泌、血液の障害又は疾患、若しくは他の重要な障害又は疾患の既往歴又は現病歴を有する者。 • 胆石症、及び消化管（胆嚢を含む）関連手術の既往歴又は現病歴を有する者。なお、虫垂切除は組入れを認めた。 • 結腸直腸癌の既往歴、現病歴、又は家族歴を有する者。 • 吸収不良、膵疾患、及び過敏性腸症候群のような胃腸障害の既往歴又は現病歴を有する者。 • 試験開始前 4 週間以内に臨床的に問題となる疾患がみられた者。 • 血清肝炎であることが判明している、あるいは B 型肝炎表面抗原又は C 型肝炎（非 A、非 B）抗体のキャリアであることが判明している者、又は HIV-1 及び HIV-2 抗体陽性の者、又は HIV 感染の「高リスク」群に属する者。 • かかりつけの一般開業医又は治験責任医師が、試験に参加すべきではないと判断した者。
予定症例数及び解析対象例数（合計及び投与群ごと）	計画どおり 32 例が組み入れられた。被験者 1 例が、有害事象（血管迷走神経性失神）により ALX-0600 5 mg 投与の約 15 分後に採血手順から脱落した（被験者番号：[redacted]、B 群）。本被験者の血漿中濃度データは一覧化されたが、血漿中濃度の要約表及び図からは除外されており、本被験者の薬物動態データは報告していない。なお、本被験者は、安全性及び忍容性の全評価に参加した。他の全ての被験者は、治験実施計画書及び Amendment 1 に従って試験を完了し、解析が行われた。 予定した投与群 **Group** / **A** / **B** / **C** / **D** Subjects / 1-8 / 9-16 / 17-24 / 25-32 Dose level of ALX-0600 / 2.5 mg or placebo / 5.0 mg or placebo / 7.0 mg or placebo / 10.0 mg or placebo Source: M5.3.3.1 1621/13 CSR Appendix 10.1.1
被験薬、用法・用量、バッチ番号	ALX-0600 溶液（3.5 mg/mL）含有バイアル：バッチ番号 [redacted] 各群、ALX-0600 又はプラセボを腹部皮下に単回投与した。ALX-0600 の各用量 2.5、5.0、7.0、及び 10.0 mg が達成されるよう、3.5 mg/mL 溶液の適切な容量を投与した。
対照薬、用法・用量、バッチ番号	プラセボ溶液含有バイアル：バッチ番号 [redacted]
投与期間	単回投与

表 2.7.6.4 - 1　　1621/13 試験：試験の概要

評価基準	安全性及び忍容性： 試験期間を通じて有害事象のモニタリングを行い、特定の時点において徴候を観察しオープンクエスチョンにより症状を調査した。また、試験中の特定の時点において、バイタルサイン、12 誘導心電図、臨床検査、体重、及び身体所見を評価した。 薬物動態： 各群、血液検体を投与前及び投与 12 時間後まで採取し、血漿中の ALX-0600 を解析した。
統計手法	人口統計、有害事象、バイタルサイン、12 誘導心電図、臨床検査、及び薬物動態の各データについて記述統計量を算出した。 パラメータ及び用量を自然対数変換して回帰分析を行い、$AUC_{0\text{-}tz}$、$AUC_{0\text{-}inf}$、及び C_{max} について用量比例性の検定を行った。パラメータごとに傾きと 95%信頼区間を算出した。CL/F の解析は分散分析（ANOVA）を用いて行った。ANOVA から得られた残差の二乗平均誤差（residual mean square error）を用い、ALX-0600 の用量ごとに最小二乗平均値と 95%信頼区間を算出した。Kruskal-Wallis 検定法を用いノンパラメトリックに T_{max} を解析した。ALX-0600 の用量ごとに中央値を算出した。
治験責任医師及び実施医療機関	1 実施医療機関（英国）
試験期間	初回のスクリーニング観察：19[redacted]年[redacted]月[redacted]日 初回投与の前日：19[redacted]年[redacted]月[redacted]日 最終投与の前日：19[redacted]年[redacted]月[redacted]日 最終の試験後来院：19[redacted]年[redacted]月[redacted]日

4.1　被験者の内訳、人口統計学的特性、及びベースライン特性

Covance CRU Volunteer Panel から募集した白人男性被験者 32 例を試験に組み入れた。被験者番号：[redacted] は、ALX-0600 5 mg 投与 15 分後に血管迷走神経性失神が発現し、採血スケジュールから脱落したが、安全性及び忍容性評価は全て完了した。他の被験者はいずれも、治験実施計画書及び Amendment 1 に従って試験を完了した。

本試験の投与群を表 2.7.6.4 - 2 に示す。

表 2.7.6.4 - 2　　1621/13 試験：投与の詳細

Group	Treatment	Subject numbers	Dosing date
A	2.5 mg ALX-0600 Placebo	[redacted]	[redacted]
B	5 mg ALX-0600 Placebo	[redacted]	[redacted]
C	7 mg ALX-0600 Placebo	[redacted]	[redacted]
D	10 mg ALX-0600 Placebo	[redacted]	[redacted]

Source: M5.3.3.1 1621/13 CSR Table E

被験者はいずれも白人男性で、年齢は 19 歳～44 歳であった。体重は 62.6～101.2 kg、身長は 165～191 cm であった。被験者に喫煙者はおらず、アルコールを嗜む（頻度：時折［occasional］～24 単位/週）被験者は 30 例であった。

各群の被験者間で、年齢、体重、身長、及び BMI の平均値は同様であった。各投与群の被験者データを表 2.7.6.4 - 3 に示す。

表 2.7.6.4 - 3　　1621/13 試験：人口統計学的データ（平均値［SD］）

	Treatment				
	Placebo	**2.5 mg ALX-0600**	**5 mg ALX-0600**	**7 mg ALX-0600**	**10 mg ALX-0600**
Age (years)	26 [4.5]	25 [6.3]	29 [5.9]	28 [6.9]	34 [8.2]
Body weight (kg)	79.2 [9.56]	78.0 [6.84]	72.8 [6.96]	80.8 [11.57]	81.7 [4.98]
Height (cm)	179 [7.0]	178 [6.2]	179 [2.6]	181 [5.7]	182 [6.3]
Body mass index (kg/m^2)	24.6 [2.15]	24.6 [2.51]	22.6 [1.72]	24.6 [2.26]	24.8 [2.05]

Source: M5.3.3.1 1621/13 CSR Table F

4.2　有効性の結果

本試験では有効性の評価は行わなかった。

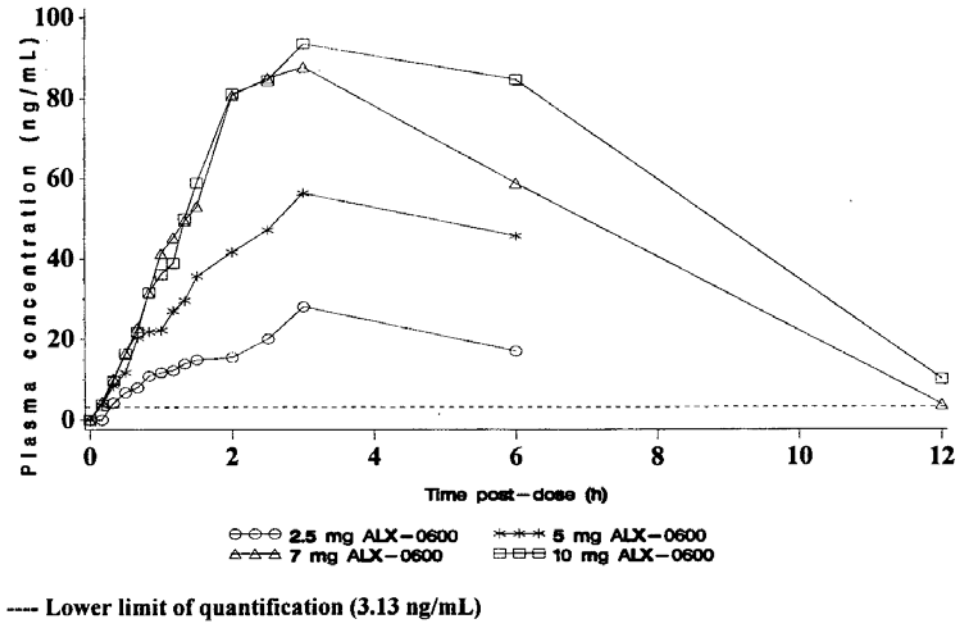
4.3　薬物動態

被験者番号：[redacted] は、血管迷走神経性失神が発現した結果、投与から約 15 分後に採血手順から脱落した。本被験者の血漿中濃度データは個別データの一覧表に記載したが、血漿中濃度を要約した表及び図からは除外されており、本被験者の薬物動態データは報告していない。残る全被験

者のデータは個別データの一覧表に提示しており、また、全データを要約した表及び図の集計対象とされている。

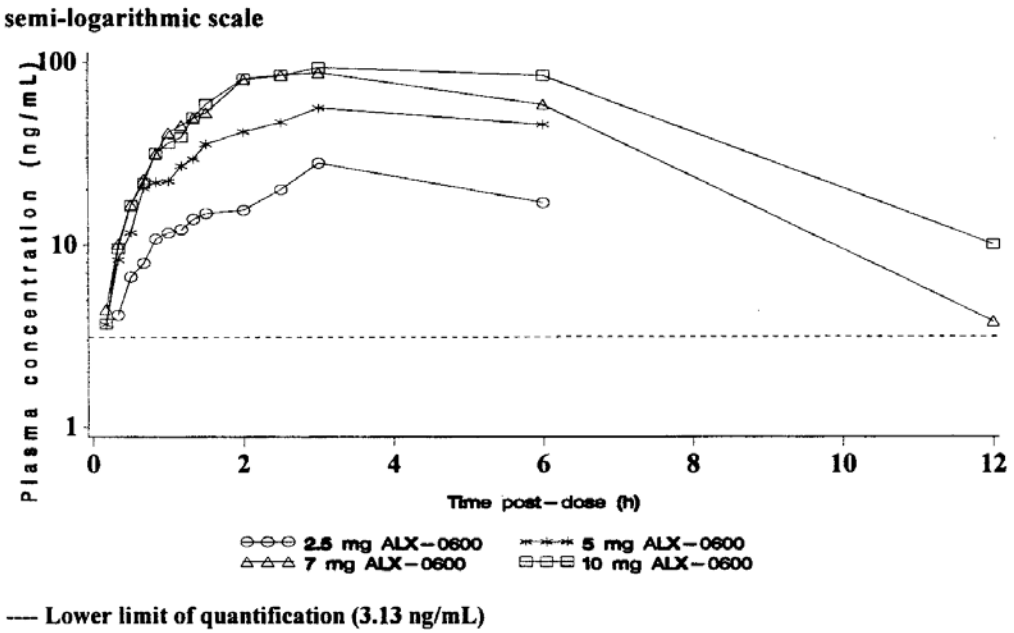
ALX-0600 の血漿中濃度を図 2.7.6.4 - 1 及び図 2.7.6.4 - 2 に示す。

図 2.7.6.4 - 1　1621/13 試験：ALX-0600 血漿中濃度（中央値、均等目盛）



Source: M5.3.3.1 1621/13 CSR Figure 1

図 2.7.6.4 - 2　1621/13 試験：ALX-0600 の血漿中濃度（中央値、片対数目盛）



Source: M5.3.3.1 1621/13 CSR Figure 2

プラセボ投与被験者の投与前及び投与後 3 時間の血漿検体を分析した結果、ALX-0600 の濃度は定量下限未満であり、投与無作為化の遵守が確認された。

2.5 mg 群と 5 mg 群の血漿中濃度–時間プロファイルは 2 段階の吸収パターンを特徴としたが、7 mg 群及び 10 mg 群ではそのような特徴はみられず、ALX-0600 の最高血漿中濃度（中央値）には、ALX-0600 の 2.5、5、7、及び 10 mg 投与から 3 時間後に到達し、それぞれ、28.03、56.43、87.77、及び 93.55 ng/mL であった。ALX-0600 の 2.5、5、7、及び 10 mg の投与から 12 時間後に血漿中濃度が定量下限を下回った被験者はそれぞれ、5/6 例、3/5 例、2/6 例、及び 1/6 例であった。

大部分の被験者では終末相を確定することができなかったが、5.3.3.1 項 1621/13 CSR Section 3.8.1.2 に示すとおり消失半減期を推定した。この方法により算出した消失半減期（調和平均）はいずれの用量でも同様であり、その範囲は 1.40～1.90 時間であった。なお、これらのデータは、開始時点と終了時点の近似値を用いて算出しており、そのため取扱いには慎重さが求められる。

ALX-0600 の血漿薬物動態パラメータと対応する用量標準化パラメータを表 2.7.6.4 - 4 に示す。

表 2.7.6.4 - 4　　1621/13 試験：ALX-0600 の血漿中薬物動態パラメータ

	Dose of ALX-0600			
Parameter	**2.5 mg**	**5 mg**	**7 mg**	**10 mg**
AUC(0-inf)* (ng.h/mL)	169 (132-217)	411 (320-528)	521 (392-692)	732 (587-913)
AUC(0-t_z)* (ng.h/mL)	122 (89.1-167)	312 (231-422)	452 (355-576)	612 (470-797)
C_{max}* (ng/mL)	27.1 (17.3-42.5)	63.3 (41.6-96.5)	95.7 (70.6-130)	101 (82.1-125)
T_{max}† (h)	3.00 (2.50-6.00)	3.00 (2.50-6.00)	2.75 (2.00-6.00)	2.75 (2.00-6.00)
AUC(0-∞)* (norm)	67.8 (52.8-86.9)	82.1 (63.9-106)	74.4 (56.0-98.8)	73.2 (58.7-91.3)
AUC(0-t_z)* (norm)	48.8 (35.6-66.7)	62.4 (46.1-84.5)	64.6 (50.7-82.3)	61.2 (47.0-79.7)
C_{max}* (norm)	10.8 (6.92-17.0)	12.7 (8.31-19.3)	13.7 (10.1-18.5)	10.1 (8.21-12.5)
$t_{1/2}$‡ (h)	1.90 (1.51-3.51)	1.40 (1.23-1.97)	1.72 (1.19-2.43)	1.75 (1.03-2.98)
CL/F$ (mL/min)	251 (53.6)	206 (38.3)	231 (64.5)	232 (46.0)

*　Geometric mean (95% confidence interval)
†　Median (min-max)
‡　Harmonic mean (min-max)
$　Arithmetic mean (SD)
norm=Normalised to 1 mg
Source: M5.3.3.1 1621/13 CSR Table K

終末相が確定できた被験者は 1 例のみであり、そのため、薬物動態パラメータの平均滞留時間（MRT）、V_z/F、及び V_{ss}/F を決定することはできなかった。また、終末相の $t_{1/2}$ 及び λz は開始時点と終了時点の推定値を用いて算出したため、これらは統計解析の対象とはしていない。

$AUC_{0\text{-}tz}$ から外挿した $AUC_{0\text{-}inf}$ の算術平均の割合（%AUCex）は、2.5 mg 群及び 5 mg 群では高く、それぞれ 27.2%及び 23.5%であった。高用量群の%AUCex は低く、7 mg 群及び 10 mg 群の値はそれぞれ、13.0%及び 15.6%であり、この結果から、$AUC_{0\text{-}tz}$ を基にして信頼性のある $AUC_{0\text{-}inf}$ が推定できるのは高用量の 2 群のみであることが示唆された。ALX-0600 薬物動態パラメータの被験者間のばらつきはいずれの投与群でも中等度であり、ALX-0600 の用量範囲 2.5～10 mg における変動係数（CV%）の幅は、$AUC_{0\text{-}inf}$ が 21.8%～26.5%、$AUC_{0\text{-}tz}$ が 22.7%～29.7%、C_{max} が 22.3%～42.2%であった。

データを視覚的に検討した結果、AUC 及び C_{max} は用量に比例して増加することが示唆された。$\log_e$ AUC 及び $\log_e$ C_{max} 対 $\log_e$ 用量を回帰分析した結果、傾きの推定値（及びその 95%信頼区間）は、$AUC_{0\text{–}inf}$ が 1.05（0.86～1.24）、$AUC_{0\text{-}tz}$ が 1.18（0.97～1.39）、及び C_{max} が 1.00（0.73～1.28）であった。対応する p 値はそれぞれ約 0.57、0.09、及び 0.98 であり、この結果から、$AUC_{0\text{-}inf}$、$AUC_{0\text{-}tz}$、及び C_{max} の傾きと 1.00 との差異は有意ではないことが示され、ALX-0600 の用量範囲 2.5～10 mg では、AUC 及び C_{max} が用量に比例して増加することが示唆された。なお、2.5、5、7 及び 10 mg の各用量における t はそれぞれ、7.00、8.40、10.0、及び 11.0 時間であり、用量の増加に伴って増加していることから、$AUC_{0\text{-}tz}$ の用量比例性に関する解析の取扱いには慎重さが求められる。ALX-0600 の用量範囲 2.5～10 mg では、$t_{1/2}$、T_{max}、及び CL/F の各パラメータは同様であった。

4.4　安全性の結果

4.4.1　曝露状況

各被験者に対し ALX-0600 又はプラセボを単回投与した。
表 2.7.6.4 - 2 に示すとおりに投与群の検討を行った。

4.4.2　有害事象

本項では特に断りのない限り、有害事象とは試験治療下に発現した有害事象（TEAE）であり、重篤な有害事象とは試験治療下の重篤な有害事象を示す。

4.4.2.1　有害事象の概要

13 例に計 23 件の有害事象が発現したが、大部分（91%）は軽度であり、中等度に分類された事象は 2 件のみであった。

プラセボ又は ALX-0600 2.5 及び 5 mg 投与後に治験薬に関連する有害事象はみられなかった。7 mg 群及び 10 mg 群で、治験薬に関連する有害事象が発現した被験者はそれぞれ 4 例（66.7%）及び 2 例（33.3%）であり、治験薬と関連する事象はそれぞれ 4/7 件及び 2/5 件であった。治験薬に関連する有害事象はいずれも軽度であった。2.5 群及び 5 mg 群の各群に中等度の有害事象が 1 件ずつ発現した。これらは治験責任医師により治験薬と関連なしと判断された。

重症度別因果関係別の有害事象の発現頻度を表 2.7.6.4 - 5 に示す。

表 2.7.6.4 - 5　　1621/13 試験：有害事象の発現頻度（重症度別因果関係別）

Treatment	Number of Subjects Studied	Subjects [%] with adverse events (all causalities)	Subjects [%] with adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related*)	Subjects [%] with adverse events and severity (drug-related*)	
Placebo	8	3 [37.5%]	Mild	3	0 [0%]	Mild	0
			Moderate	0		Moderate	0
			Severe	0		Severe	0
			Total	3		Total	0
2.5 mg teduglutide	6	3 [50%]	Mild	4	0 [0%]	Mild	0
			Moderate	1		Moderate	0
			Severe	0		Severe	0
			Total	5		Total	0
5 mg teduglutide	6	1 [16.7%]	Mild	0	0 [0%]	Mild	0
			Moderate	1		Moderate	0
			Severe	0		Severe	0
			Total	1		Total	0
7 mg teduglutide	6	4 [66.7%]	Mild	7	4 [66.7%]	Mild	4
			Moderate	0		Moderate	0
			Severe	0		Severe	0
			Total	7		Total	4
10 mg teduglutide	6	2 [33.3%]	Mild	5	2 [33.3%]	Mild	2
			Moderate	0		Moderate	0
			Severe	0		Severe	0
			Total	5		Total	2

Source: Module 5.3.3.1 1621/13 CSR , Section 9.2.1 (Tables 3.1 and 3.2)
*Adverse events considered possibly, probably, or definitely-related to administration of study drug.

ALX-0600 2.5 mg 投与群に頭痛が 2 件（うち 1 件は中等度）認められた。これらは、いずれも被験者番号：[redacted] で発現した事象であった。また、ALX-0600 7 mg 投与群の被験者番号：[redacted] 及び被験者番号：[redacted] でも頭痛が認められた。これらの頭痛の発現時期は、投与後約 5～16 時間で、その持続時間は約 15 分～1 日であった。治験薬と関連ありと判断されたものはなく、おそらく、被験者が絶食下に置かれたために生じたものと思われた。中等度の頭痛では、投与 18 時間後にパラセタモール 1 g の併用（単回経口投与）が必要とされたが、その他の頭痛は自然に回復した。有害事象発現頻度を表 2.7.6.4 - 6 に示す（当該表は、CSR 作成時の COSTART による集計表である。MedDRA による集計表を表 2.7.6.4 - 9 に示す）。

表 2.7.6.4 - 6　　1621/13 試験：有害事象一覧

COSTART Body system COSTART term	Placebo (N=8)	2.5 mg ALX-0600 (N=6)	5 mg ALX-0600 (N=6)	7 mg ALX-0600 (N=6)	10 mg ALX-0600 (N=6)
Body as a whole					
Headache		2 [1]		2 [2]	
Injection site reaction	1 [1]	1 [1]		1 [1]	1 [1]
Injection site pain				2 [2]	1 [1]
Abdominal pain		1 [1]		1 [1]	
Digestive system					
Eructation					1 [1]
Flatulence					1 [1]
Nausea		1 [1]			
Skin & appendages					
Rash				1 [1]	
Sweating	1 [1]				
Cardiovascular system					
Syncope			1 [1]		
Nervous system					
Dizziness					1 [1]
Respiratory system					
Rhinitis	1 [1]				
Total	**3 [3]**	**5 [3]**	**1 [1]**	**7 [4]**	**5 [2]**

N=Number of subjects studied
Source: M5.3.3.1 1621/13 CSR Table 4.1

4.4.2.2　　有害事象の分析

被験者番号：[redacted] に ALX-0600 2.5 mg 投与から約 16 時間後に頭痛が発現し、約 1 日持続した。また、被験者番号：[redacted] では ALX-0600 5 mg の投与から 15 分後に血管迷走神経性失神の単一エピソードが発現し 3 分間持続した。2 件とも中等度であり、治験薬との関連なしと判断された。

治験薬に関連する有害事象はいずれも高用量群（ALX-0600 7 mg 及び 10 mg）に発現した。報告された有害事象 6 件のうち 5 件は注射部位関連の事象であった。この内訳は、注射部位疼痛が 3 件、注射部位反応が 2 件であった。また、発疹が 1 件あったが、これは被験者 1 例で ALX-0600 7 mg 投与後にみられたものであった。治験薬と関連ありと判断された有害事象の一覧を表 2.7.6.4 - 7 に示す（当該表は、CSR 作成時の COSTART による集計表である。MedDRA による集計表を表 2.7.6.4 - 8 に示す）。

表 2.7.6.4 - 7　　1621/13 試験：治験薬と関連ありと判断された有害事象一覧

COSTART Body system **COSTART term**	**Placebo (N=8)**	**2.5 mg ALX-0600 (N=6)**	**5 mg ALX-0600 (N=6)**	**7 mg ALX-0600 (N=6)**	**10 mg ALX-0600 (N=6)**
Body as a whole					
Injection site pain				2 [2]	1 [1]
Injection site reaction				1 [1]	1 [1]
Skin & appendages					
Rash				1 [1]	
Total	**0 [0]**	**0 [0]**	**0 [0]**	**4 [4]**	**2 [2]**

Adverse events with possible, probable or definite relationship to the study drug
N=Number of subjects studied
Source: M5.3.3.1 1621/13 CSR Table4.2

表 2.7.6.4 - 8　　1621/13 試験：有害事象一覧（MedDRA SOC 及び PT）

System Organ Class (SOC)/ Preferred Term (PT)		All-causality TEAEs					Treatment-related AEs				
		Placebo (N = 8) n (%)	Teduglutide 2.5 mg (N = 6) n (%)	Teduglutide 5 mg (N = 6) n (%)	Teduglutide 7 mg (N = 6) n (%)	Teduglutide 10 mg - Normal (N = 6) n (%)	Placebo (N = 8) n (%)	Teduglutide 2.5 mg (N = 6) n (%)	Teduglutide 5 mg (N = 6) n (%)	Teduglutide 7 mg (N = 6) n (%)	Teduglutide 10 mg - Normal (N = 6) n (%)
Number of subjects with at least one TEAE	有害事象発現例数（%）	3 (37.5)	3 (50.0)	1 (16.7)	4 (66.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (66.7)	2 (33.3)
Gastrointestinal Disorders	胃腸障害	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Discomfort	腹部不快感	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain Upper	上腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eructation	おくび	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	鼓腸	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	悪心	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders And Administration Site Conditions	全身障害および投与局所様態	1 (12.5)	1 (16.7)	0 (0.0)	3 (50.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	2 (33.3)
Injection Site Discomfort	注射部位不快感	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Injection Site Erythema	注射部位紅斑	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Injection Site Haematoma	注射部位血腫	1 (12.5)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Pain	注射部位疼痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)
Injection Site Pruritus	注射部位そう痒感	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Infections And Infestations	感染症および寄生虫症	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	鼻咽頭炎	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	神経系障害	0 (0.0)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clonus	間代	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	浮動性めまい	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.4 - 8　1621/13 試験：有害事象一覧（MedDRA SOC 及び PT）

System Organ Class (SOC)/ Preferred Term (PT)		All-causality TEAEs: Placebo (N = 8) n (%)	Teduglutide 2.5 mg (N = 6) n (%)	Teduglutide 5 mg (N = 6) n (%)	Teduglutide 7 mg (N = 6) n (%)	Teduglutide 10 mg - Normal (N = 6) n (%)	Treatment-related AEs: Placebo (N = 8) n (%)	Teduglutide 2.5 mg (N = 6) n (%)	Teduglutide 5 mg (N = 6) n (%)	Teduglutide 7 mg (N = 6) n (%)	Teduglutide 10 mg - Normal (N = 6) n (%)
Headache	頭痛	0 (0.0)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	皮膚および皮下組織障害	1 (12.5)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Hyperhidrosis	多汗症	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash Erythematous	紅斑性皮疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Vascular Disorders	血管障害	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pallor	蒼白	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based upon the number of subjects in the Safety Population for each treatment arm.
Note: Treatment emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within thirty days after discontinuation of study drug.
Note: Related AEs include AEs that were 'possibly related', 'probably related', 'related' or with relationship missing.
Note: Subjects are counted no more than once for incidence of System Organ Class and Preferred Term.
Note: All adverse events were coded using MedDRA version [redacted].
Program: t-1-1-ae-socpt-162113.sas　　Output Generated On: 20OCT2016 23:21

4.4.3　死亡、その他の重篤な有害事象及び他の重要な有害事象

本試験期間中に死亡、重篤な有害事象、投与中止に至った有害事象及び特に注目すべき有害事象はみられなかった。

4.4.4　バイタルサイン、身体所見、及び安全性に関連するその他の所見

口腔体温、仰臥位血圧、及び脈拍数の各平均値に、臨床的に問題となる、治験薬又は用量に関連した何らかの傾向は認められなかった。また、個別被験者から得られたこれらのデータについても臨床的に問題となる、治験薬又は用量に関連した何らかの傾向は認められなかった。

12 誘導心電図データの平均値、又は個別被験者の 12 誘導心電図データに、臨床的に問題となる、治験薬又は用量に関連した何らかの傾向は認められず、個別被験者の心電図トレース上の波形で臨床的に問題となる異常は認められなかった。

臨床的に問題となる臨床検査値異常はなかったが、試験期間中、数例の被験者に基準範囲外の臨床検査値がみられた。また、臨床検査データの平均値を検討した結果、治験薬又は用量に関連した何らかの傾向は認められなかった。

試験後に認められたスクリーニングからの変化は、被験者 1 例でみられた右下腹部注射部位の軽度出血のみで、臨床的に問題なしと判断された。

4.5　結論：

- 健康男性被験者に空腹下で ALX-0600 を用量範囲 2.5～10 mg を皮下投与したとき、ALX-0600 の忍容性は良好であった。
- ALX-0600 は安全で、バイタルサイン、12 誘導心電図、臨床検査、及び身体所見に臨床的に問題となる、治験薬又は用量関連性の変化は認められなかった。
- ALX-0600 は速やかに吸収され、ALX-0600 2.5～10 mg の用量範囲では、$AUC_{0\text{-}inf}$、$AUC_{0\text{-}tz}$、及び C_{max} に用量比例性のあることが示唆された。

5　CL0600-022 試験

（評価資料：5.3.3.1 項）

CL0600-022 試験の概要を表 2.7.6.5 - 1 に示す。

表 2.7.6.5 - 1　　CL0600-022 試験：試験の概要

試験識別番号	CL0600-022
試験の標題	テデュグルチドの忍容性及び薬物動態を検討した二重盲検反復投与試験
試験の相	1
目的	主要目的は、健康被験者を対象とし、テデュグルチドを 1 日 1 回又は場合により 1 日 2 回、8 日間皮下投与したときの安全性及び忍容性を検討することとした。副次目的は、健康被験者を対象とし、テデュグルチドを 1 日 1 回又は 1 日 2 回、8 日間皮下投与したときのテデュグルチドの薬物動態を検討することとした。
方法	本試験は、単一施設、二重盲検、無作為化、プラセボ対照試験である。テデュグルチドの忍容性及び薬物動態を検討するためテデュグルチド又はプラセボを健康被験者の独立したコホートに反復投与した。あるコホートにおいて 8 日間の投与完了後、かつ次に予定するコホートの開始前、Independent Safety Review Panel（ISRP）が安全性及び忍容性をレビューし、その評価を行った。 予定した被験者の分布及びコホート決定図を下図に示す。 試験は、スクリーニング（Day −28～−2）、入院（Day −1）、投与（Day 1～8）、退院（Day 9）、及び追跡調査（Day 14～16）の各期から構成された。被験者は、治験薬投与前の夕方（Day 1）における投与の 12 時間以上前に入院し（Day −1）、約 8.5 日間、実施医療機関に滞在した。Day −1 の入院後、診察及び臨床検査が行われ、適格基準を全て満たす被験者に対し Day 1 に投与が行われた。Day 9 の午前中、被験者はクリニックから退院した。 各コホートは新たな 12 例の被験者からなるセットで構成された。投与期間は約 8 日間であった。コホート F からコホート J では、ISRP の勧告及び治験依頼者と治験責任医師の承認に基づき、投与スキーム（最大テデュグルチド 80 mg まで）の記載と対比して、隔日投与及び／又は反復投与、又は 1 日 2 回投与が選択できることとした。（その後、高用量での安全性が許容可能であったため 1 日 2 回コホートは不要とした）コホート A を除く全てのコホートでは 50 mg/mL 製剤を用いた。

表 2.7.6.5 - 1　　CL0600-022 試験：試験の概要

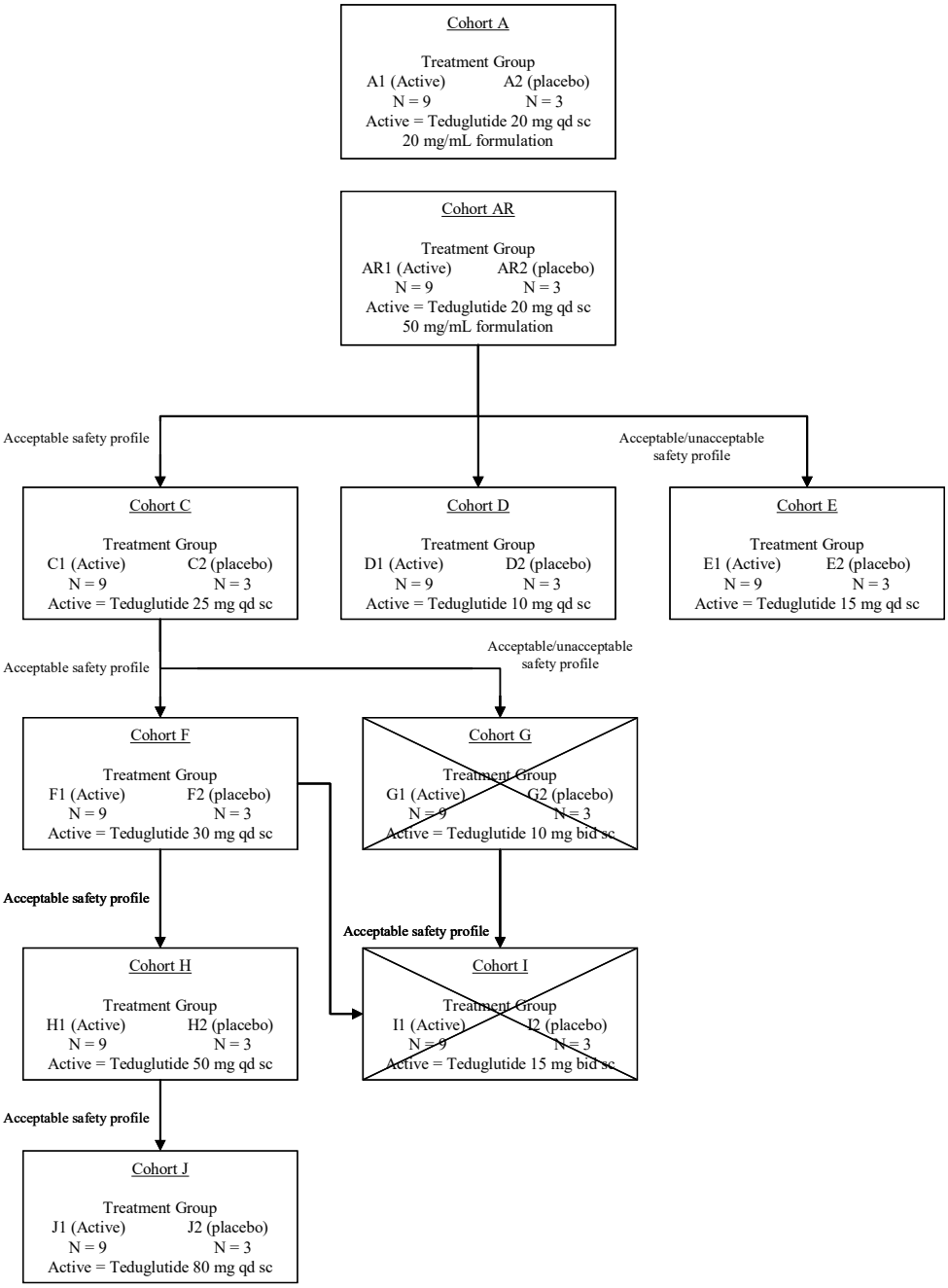
	図　　コホート決定図 
診断及び主な選択基準	選択基準 以下に示す基準を全て満たす者を本試験の組入れ対象とした。 1. スクリーニング時の年齢が 20 歳以上 55 歳以下の成人男性及び女性（妊娠中又は授乳中ではない）。 2. 体格指数（BMI）18 以上 35 以下の者。 3. 同意説明文書（ICF）を理解する能力があり、これに自らの意思で署名した者。 4. 8.5 日間の実施医療機関への入所に自らの意思で参加できる者。 5. 閉経後の女性（月経が 1 年以上ない）又は不妊手術を受けた女性。妊娠可能

表 2.7.6.5 - 1　CL0600-022 試験：試験の概要

	な女性の場合は、授乳中ではなく、試験スクリーニング前 30 日以上、試験期間中、及び投与終了後 30 日以上にわたり有効な避妊法を実行することに同意する者。有効な避妊法とは、エストロゲン成分量を 30 μg 以上含有する二相性又は三相性ピルによる経口療法；経皮、注射、又は植え込み式の避妊薬；子宮内避妊具；又は二重遮断法（ペッサリー及びコンドーム）とした。禁欲法は受け入れ可能な避妊法とはみなさなかった。 6. 妊娠可能な女性の場合、スクリーニング時（Day −28～Day −2）及び入院時（Day−1）に、尿 β-hCG 検査結果が陰性であること。 7. スクリーニング時（Day −28～Day −2）及び入院時（Day −1）に、特定の薬物及びアルコールに関する尿検査結果が陰性である者。 8. スクリーニング時（Day −28～Day −2）及び入院時（Day −1）に、診療結果（臨床検査プロファイル、既往歴、心電図、及び身体所見）が正常もしくは臨床的に大きな問題がなく、医学的に健康である者。 <u>除外基準</u> スクリーニング来院中、以下に示す除外基準のいずれかに合致した者は本試験への組入れに不適格とした。 1. 試験開始前 56 日以内に 1 パイント以上の血液又は血液製剤の献血を行った、又は試験開始前 7 日以内に血漿成分献血を行った者。 2. 妊娠中又は妊娠予定の者。 3. 試験組入れ前 30 日以内及び試験完了までに別の治験薬の試験に参加した者。 4. 治験責任医師又は分担医師により、診察結果又は既往歴から、被験者が試験に不適となる臨床症状又は合併症が懸念される者。 5. 臨床的に問題となる心血管系、肺、肝、腎、血液系、消化器系、内分泌系、免疫系、皮膚（乾癬、湿疹、アトピー性皮膚炎など）、神経系、又は精神系の疾患を有する又はその既往歴を有する者。 6. 先天性非溶血性高ビリルビン血症を有する又はその既往歴を有する者。 7. 胆石症又は胃腸の手術（虫垂切除術は除く）の既往歴又はエビデンスを有する者。 8. 結腸直腸癌の既往歴又はエビデンスを有する者。 9. 吸収不良、膵疾患、消化管ポリープ、又は胃腸障害（過敏性腸症候群、クローン病、又は潰瘍性大腸炎など）の既往歴又はエビデンスを有する者。 10. 皮疹又は皮膚炎の既往歴又はエビデンスを有する者。 11. 治験実施医療機関入院前の 7 日間に、経口避妊法を除く、処方箋薬又は OTC 薬（ビタミン剤［非治療適応を目的に栄養補助食品として摂取したもので、治験責任医師が許容可能と判断したもの以外］、ミネラル、及び植物療法剤／生薬製剤を含む）を服用していた場合、及び／又は試験期間中に処方箋薬又は OTC 薬を使用する必要があると予想された場合。
予定症例数及び解析対象例数（合計及び投与群ごと）	計画時　：各コホート 12 例（プラセボ 3 例、テデュグルチド 9 例；8 コホート） 無作為化　：95 例 PK 解析対象例　：71 例 安全性解析対象例：95 例（プラセボ 24 例、テデュグルチド 71 例）

表 2.7.6.5 - 1　CL0600-022 試験：試験の概要

被験薬、用法・用量、バッチ番号

テデュグルチドは、1 日 1 回、連続 8 日間、皮下投与された。注射部位は、腹部の 4 分割のうちの 1 ヵ所とし、ローテーションを行った。テデュグルチドの投与は以下のとおり実施した。

Cohort	Teduglutide (mg/dose)	Dosing Frequency	Daily Dose (mg)	Formulation (mg/mL)	Volume per Injection (mL)
A	20	qd	20	20	1.0
AR[a]	20	qd	20	50	0.4
C	25	qd	25	50	0.5
D	10	qd	10	50	0.2
E	15	qd	15	50	0.3
F	30	qd	30	50	0.6
H	50	qd	50	50	1.0
J	80	qd	80	50	0.8 (2X)[b]

[a] AR (repeat) cohort used additional randomization numbers from cohort A, and randomization numbers for cohort B were not used.

[b] Each 80 mg dose will be administered as 2 injections of 0.8 mL each administered 3 to 4 cm apart within a single quadrant of the abdomen

実薬のロット番号：[redacted]（20 mg）、[redacted]（30 mg：使用せず）、[redacted]（50 mg）

対照薬、用法・用量、バッチ番号

マッチさせたプラセボ(バッチ番号[redacted]［20 mg］及び[redacted]［30 又は 50 mg］)は、腹部の 4 分割のうちの 1 ヵ所に 1 日 1 回皮下投与した。

投与期間

連続 8 日間

評価基準

有効性：

本試験では有効性の評価は行わなかった。

安全性：

安全性の評価項目は、有害事象、バイタルサイン、心電図、身体所見、体重、及び臨床検査値とした。

薬物動態：

血液検体の採取は、Day 1 及び Day 8 の複数時点（0 時間［投与前］、投与後 0.5、1、1.5、2、2.5、3、3.5、4、6、8、10、12、及び 24 時間）に行った。血漿検体の分析は、バリデーション済みの LC-MS/MS アッセイ法を用いて行い、ノンコンパートメント法を用いて次に示すテデュグルチドの薬物動態パラメータを算出した：$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、C_{max}、T_{max}、及び $t_{1/2}$。

統計手法

薬物動態：

Day 1 及び Day 8 における個々のテデュグルチドの血漿中濃度及び薬物動態パラメータについては、記述統計量［平均値、SD、中央値、最小値、最大値、及び CV（%）］を用い、コホート別及び各コホート内の男女別に要約した。

反復皮下投与後のテデュグルチドの蓄積の程度を評価するため、Day 8 と Day 1 の薬物動態パラメータ（$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$ 及び C_{max}）の比率を算出した。これらの比率の幾何平均値と 90%信頼区間については、コホート別及び各コホート内の男女別に算出した。

テデュグルチドの薬物動態パラメータ（$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$ 及び C_{max}）を自然対数に変換し、ANOVA（分散分析）モデルを用いて、Day 1 及び Day 8 において、コホート A とコホート AR とを比較した（20 mg/mL 製剤と 50 mg/mL 製剤の比較）。本 ANOVA モデルでは、製剤及び Day を固定効果、被験者を変量効果とした。ま

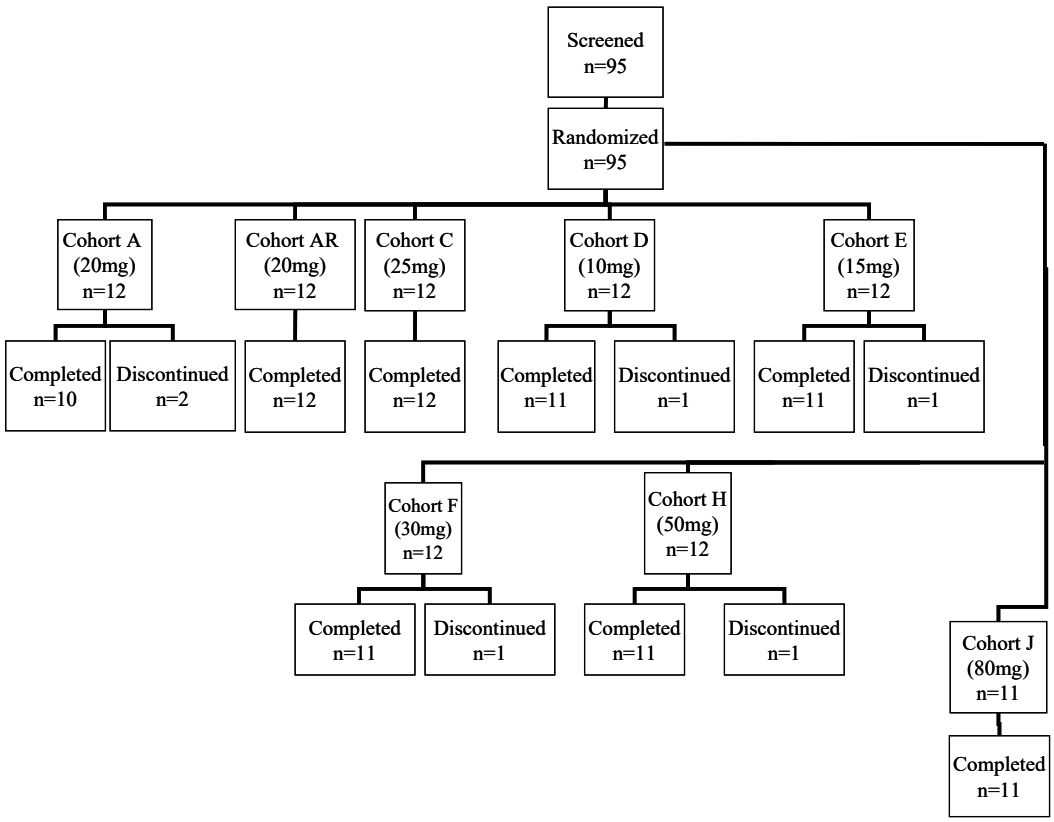
表 2.7.6.5 - 1　　CL0600-022 試験：試験の概要

	た、本 ANOVA モデルには、最小二乗平均値（LSM）、LSM の差、及びこの差の標準誤差が含まれた。上述した統計解析は SAS® MIXED 手順を用いて行った。LSM の比率（A/AR）を算出し、ANOVA を用いて 90%信頼区間を求めた。 Day 1 及び Day 8 においてテデュグルチドの薬物動態パラメータ（$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$ 及び C_{max}）を自然対数に変換し、パワーモデル法を用いて用量比例性を評価した。線形関係が統計学的に成立し、薬物動態パラメータの勾配推定値の 95%信頼区間が 1 を跨ぐ場合、用量比例性が成立するものとした。用量比例性の評価は SAS® MIXED 手順を用いて行った。 統計学的外れ値を検出するためテデュグルチドの薬物動態パラメータに対しスチューデント化残差検定を実施した。統計学的外れ値を含む場合と含まない場合について、薬物動態パラメータの記述統計量を算出した。 安全性： 臨床検査結果については記述統計量を用いて要約した。正常値から高値といった値の変化を表すため、臨床検査値のシフト表（各予定来院時における、ベースラインから、基準範囲下限未満［BNL］、基準範囲内［WNL］、及び基準範囲上限超［ANL］への変化のクロス集計表）を用いた。バイタルサインについては、各時点における絶対値を要約するため、記述統計量（被験者数、平均値、SD、中央値、最小値及び最大値）を用いた。各時点におけるバイタルサインを要約するため、ベースラインからの変化量も用いた。心電図については、臨床的に重要な所見、及び／又は臨床的に問題とはならない所見を、投与群別及びテデュグルチド投与被験者全例で要約するため、記述統計量（被験者数及びその割合［%］など）を用いた。
治験責任医師及び実施医療機関	米国（1 施設）
試験期間	試験開始日：2006 年 9 月 6 日（最初の被験者の組入れ） 試験完了日：2007 年 4 月 18 日（最終被験者の最終来院）

5.1　被験者の内訳、人口統計学的特性、及びベースライン特性

組み入れられた被験者 95 例のうち 89 例が試験を完了した。試験を完了しなかった被験者は 6 例であったが、有害事象発現が直接の原因とされたのは 1 例のみであった。3 例は直接的に同意を撤回し、2 例は別の理由（家族に緊急の用件ができた、又は別の試験中止理由）により試験を完了しなかった。被験者の内訳を図 2.7.6.5 - 1 に示す。

図 2.7.6.5 - 1　CL0600-022 試験：被験者の内訳



Source: M5.3.3.1 CL0600-022 CSR Figure 10-1

総じて、プラセボ群とテデュグルチド群における被験者の、年齢、体重、身長、BMI、及び性別に関する人口統計学的特性は同様であった。プラセボ群の被験者の年齢、体重、身長、及び BMI の各平均値は、テデュグルチド群の各平均値の 10%以内であり、プラセボ及びテデュグルチドの投与を受けた男女の割合（%）は同程度であった。

プラセボの投与を受けた黒人（又はアフリカ系米国人）と白人の割合（それぞれ、4.2%及び 83.3%）と、テデュグルチドの投与を受けた黒人と白人の割合（それぞれ、33.8%及び 59.2%）との間に大きな差がみられた。テデュグルチドの投与を受けた黒人（又はアフリカ系米国人）の例数は、コホート A、AR、C、D、E、F、H、及び J（それぞれ、4、1、4、3、4、4、2、2 例）で均等に分布した。

プラセボ投与被験者及びテデュグルチド投与被験者の人口統計学的特性をコホートごとに表 2.7.6.5 - 2 に示す。

表 2.7.6.5 - 2　　CL0600-022 試験：人口統計学的特性

Demographic Variable	Placebo (N=24)	Teduglutide (N=71)
Mean Age in years (SD)	34.4 (10.56)	32.1 (9.75)
Check–in Weight in kg (SD)	80.28 (17.01)	82.03 (15.15)
Height in cm (SD)	173.75 (7.10)	172.93 (10.84)
BMI in kg/m^2 (SD)	26.53 (4.95)	27.52 (5.28)
Gender [n(%)]		
Male	17 (70.8%)	52 (73.2%)
Female	7 (29.2%)	19 (26.8%)
Race [n(%)]		
Asian	2 (8.3%)	2 (2.8%)
Black or African American	1 (4.2%)	24 (33.8%)
Native American or Alaska native	0 (0%)	2 (2.8%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1.4%)
Other: Native American/White	1 (4.2%)	0 (0.0%)
White	20 (83.3%)	42 (59.2%)
Ethnicity [n(%)]		
Hispanic or Latino	2 (8.3%)	10 (14.1%)
Not Hispanic or Latino	22 (91.7%)	61 (85.9%)

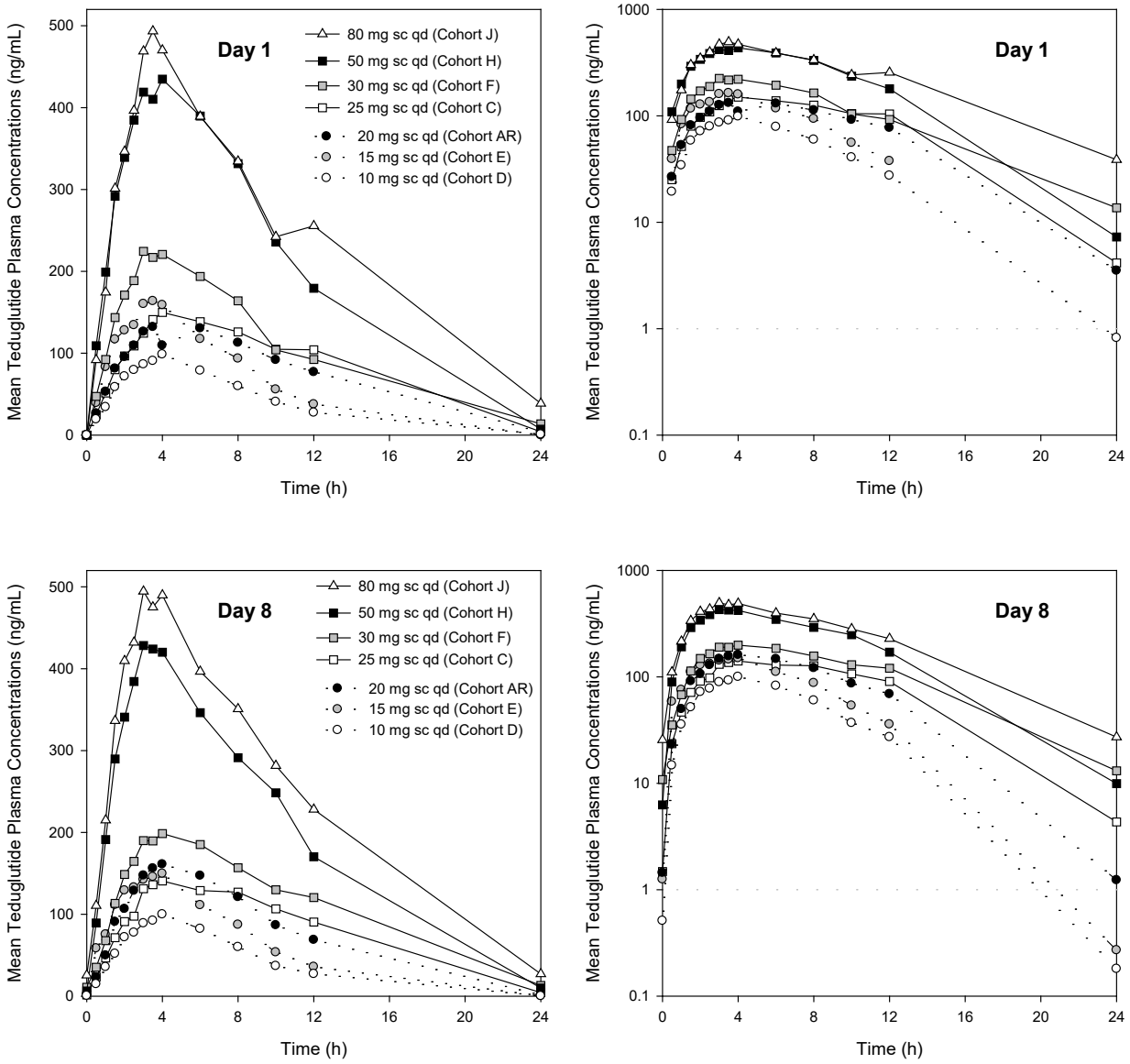
Source: M5.3.3.1 CL0600-022 CSR Table 11-1

5.2　薬物動態成績

5.2.1　　テデュグルチドの濃度

Day 1 及び Day 8 に 50 mg/mL 製剤を皮下投与したときのテデュグルチドの血漿中濃度－時間プロファイル（平均値）を、均等目盛及び片対数目盛で図 2.7.6.5 - 2 に示す。

図 2.7.6.5 - 2　CL0600-022 試験：Day 1 及び Day 8 に 50 mg/mL 製剤を皮下投与したときのテデュグルチドの薬物動態プロファイル（男女併合値）

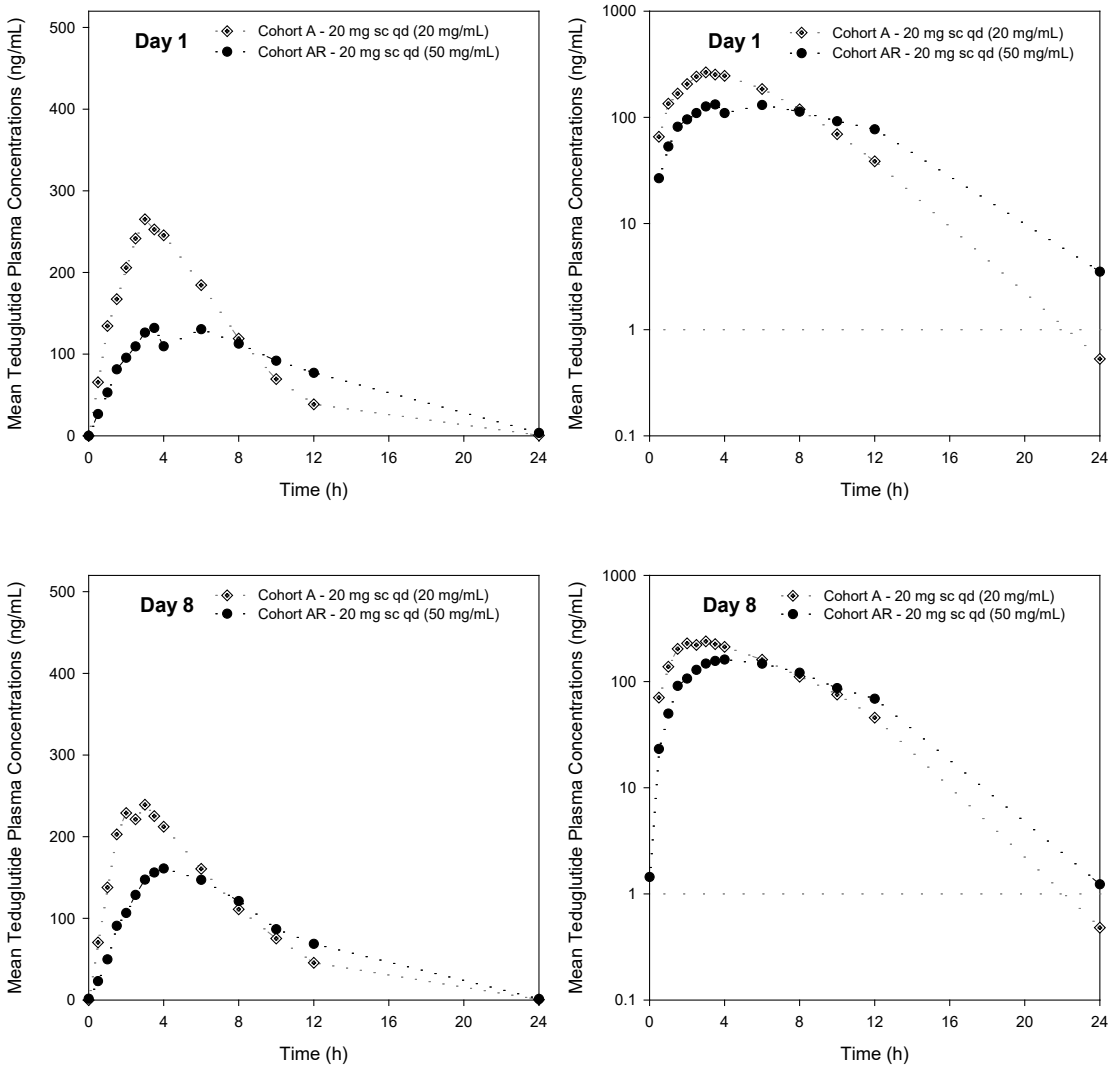


Source: M5.3.3.1 CL0600-022 CSR Figure 11-1

Day 1 及び Day 8 においてテデュグルチドの血漿中濃度がピークに達したのは皮下投与から約 4 時間後であった。テデュグルチドの血漿中濃度（平均値）は単一指数関数的に低下した。投与 24 時間後のテデュグルチド濃度（平均値）については、測定値が LOQ 未満の場合、0 と見なしたことから、その解釈には慎重さが求められる。血漿中濃度のピークは LOQ の 20 倍を上回っており、総合的に見て、Day 1 及び Day 8 におけるテデュグルチドの薬物動態については、特性がよく解明されている。Day 8 におけるテデュグルチドの投与前血漿中濃度（平均値）は極めて低く、この結果から反復皮下投与時における薬剤の蓄積性は最小限であることが示唆された。

Day 1 及び Day 8 にコホート A（20 mg/mL 製剤を 20 mg 皮下投与）及びコホート AR（50 mg/mL 製剤を 20 mg 皮下投与）で得られたテデュグルチドの血漿中濃度－時間プロファイル（平均値）を均等目盛及び片対数目盛で図 2.7.6.5 - 3 に示す。

図 2.7.6.5 - 3　CL0600-022 試験： Day 1 及び Day 8 にコホート A 及びコホート AR で得られたテデュグルチドの血漿中濃度（平均値）プロファイル（男女併合値）



Source: M5.3.3.1 CL0600-022 CSR Figure 11-2

5.2.2　　薬物動態パラメータの結果

テデュグルチドの薬物動態パラメータはノンコンパートメント法を用いて算出した。Day 1（表 2.7.6.5 - 3）及び Day 8（表 2.7.6.5 - 4）に 50 mg/mL 製剤を皮下投与したときのテデュグルチドの薬物動態パラメータに関する記述統計量を以下に示す。

表 2.7.6.5 - 3 CL0600-022 試験：Day 1 に濃度 50 mg/mL で投与したときのテデュグルチドの薬物動態パラメータに関する記述統計量（男女併合値）

Parameters Day 1	Arithmetic Mean (SD)						
	AR 20 mg qd	C 25 mg qd	D 10 mg qd	E 15 mg qd	F 30 mg qd	H 50 mg qd	J 80 mg qd
AUC_{0-last} (ng•hr/mL)	1430 (162.2)	1658 (310.0)	774 (128.3)	1172 (444.4)	2189 (628.2)	4166 (864.6)	5113 (1002.1)
AUC_{0-inf} (ng•hr/mL)	1528 (213.2)	1784 (653.1)	857 (146.1)	1423 (483.2)	2634 (1295.3)	4526 (1020.3)	5707 (972.2)
C_{max} (ng/mL)	152 (54.5)	162 (51.3)	101 (38.1)	175 (89.3)	250 (169.3)	456 (96.5)	562 (355.1)
T_{max} * (hr)	4.00 (3.00 – 12.0)	6.00 (3.50 – 12.0)	4.00 (3.00 – 6.00)	3.50 (1.50 – 12.0)	6.00 (3.00 – 8.00)	4.00 (2.50 – 8.00)	6.00 (3.00 – 12.0)
$t_{1/2}$ (hr)	3.38 (2.31)	3.60 (1.70)	3.20 (1.300)	3.17 (1.774)	5.53 (6.970)	3.33 (1.029)	5.41 (4.992)

* Median (Min, Max)
Subject [redacted] is an outlier, summary statistics in this table is calculated with this subject.
Source: M5.3.3.1 CL0600-022 CSR Table 14.2.3

表 2.7.6.5 - 4 CL0600-022 試験：Day 8 に濃度 50 mg/mL で投与したときのテデュグルチドの薬物動態パラメータに関する記述統計量（男女併合値）

Parameters Day 8	Arithmetic Mean (SD)						
	AR 20 mg qd	C 25 mg qd	D 10 mg qd	E 15 mg qd	F 30 mg qd	H 50 mg qd	J 80 mg qd
AUC_{0-last} (ng•hr/mL)	1418 (288)	1529 (290.3)	740 (144.7)	1135 (565.8)	2266 (679.3)	4057 (987.8)	5088 (1209)
AUC_{0-inf} (ng•hr/mL)	1790 (364.1)	1924 (928.7)	863 (140.1)	1289 (663.1)	2433 (651.4)	4316 (894.8)	5377 (910.0)
C_{max} (ng/mL)	165 (57.4)	150 (47.8)	104 (36.2)	186 (105.4)	211 (101.6)	454 (156.6)	555 (329.8)
T_{max} * (hr)	4.00 (2.50, 6.00)	4.00 (3.00, 10.0)	4.00 (3.00, 6.00)	2.75 (0.52, 4.00)	5.00 (3.00, 6.02)	3.75 (2.50, 6.00)	4.00 (3.00, 8.00)
$t_{1/2}$ (hr)	4.50 (2.513)	4.63 (2.681)	3.40 (1.535)	2.99 (1.147)	4.61 (1.930)	3.25 (1.753)	4.49 (3.348)

* Median (Min, Max)
Subject [redacted] is an outlier, summary statistics in this table is calculated with this subject.
Source: M5.3.3.1 CL0600-022 CSR Table 14.2.3

総合的に見て、テデュグルチドのパラメータである AUC_{0-last}、AUC_{0-inf}、及び C_{max}（平均値）は、Day 1 と Day 8 の値が極めて近く、この結果から反復皮下投与時の薬剤蓄積性が最小限であることが示唆された。テデュグルチドは直ちに吸収され、消失も速やかで、$t_{1/2}$（平均値）は、Day 1 が 3.17～5.53 時間、Day 8 が 2.99～4.63 時間であった。単回皮下投与と反復皮下投与後の消失半減期が極めて近い値を示したことから、テデュグルチドの薬物動態は線形であることが示唆された。

Day 1 及び Day 8 の $AUC_{0\text{-last}}$ 及び $AUC_{0\text{-inf}}$（平均値）は、全般的にテデュグルチドの用量の増加に伴って増加した。一方、テデュグルチドの C_{max}（平均値）は、高用量の 2 用量である、50 mg 及び 80 mg 1 日 1 回では、用量比例性を下回る上昇を示した。Day 1 及び Day 8 における T_{max} は、用量段階が上昇しても比較的一定であった。

コホート E において、その中央値（Day 1 : 158.0 ng/mL、Day 8 : 178.5 ng/mL）と比較したとき、1 例のテデュグルチドの C_{max} が Day 1 及び Day 8 で予想外の低値（それぞれ、71.1 ng/mL 及び 5.05 ng/mL）を示したことから、コホート E では外れ値の統計学的検定を行った。本被験者が Day 1 及び Day 8 におけるコホート E の総平均値の計算に大きく影響を及ぼすかどうか検討するため、スチューデント化残差法を用い、外れ値の統計学的検定を行った。統計解析の結果、Day 1 及び Day 8 において、被験者番号：[redacted] が最も高いスチューデント化残差を示した（それぞれ>2 及び>8）。その結果、コホート E の統計学的外れ値として被験者番号：[redacted] が特定された。本被験者を除外した上で、コホート E*として新しいグループの記述統計量を算出した。コホート E*のテデュグルチドの $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、及び C_{max}（平均）はそれぞれ、1295 ng•hr/mL、1470 ng•hr/mL、及び 212 ng/mL であった。

5.2.3　コホート AR とコホート A の統計学的比較（ANOVA）

Day 1 及び Day 8 において 20 mg を投与したときのテデュグルチドの薬物動態パラメータ（$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$及びC_{max}）を自然対数に変換し、ANOVA モデルを用いて、コホート A（20 mg/mL 製剤を 1.0 mL 注射）とコホート AR（50 mg/mL 製剤を 0.4 mL 注射）とを比較した。投与日と製剤の交互作用はいずれの薬物動態パラメータについても統計学的に有意ではなかったことから、相対的バイオアベイラビリティの評価は、Day 1 と Day 8 のデータをプールして行った。結果については表 2.7.6.5 - 5 に示す。

表 2.7.6.5 - 5　CL0600-022 試験：テデュグルチド 20 mg/mL 製剤と 50 mg/mL 製剤の薬物動態パラメータの比較（男女併合値）

Parameters	Geometric LSM (%CV)		ANOVA		
	A 20 mg qd (20 mg/mL)	AR 20 mg qd (50 mg/mL)	Ratio of LSM (A/AR)	90% CI for Ratio	P– Value
$AUC_{0\text{–last}}$ (ng•hr/mL)	1723 (15.2)	1408 (15.3)	122.6	108.8 – 138.1	0.0091
$AUC_{0\text{–inf}}$ (ng•hr/mL)	1861 (13.0)	1637 (19.6)	115.1	102.1 – 129.7	0.0573
C_{max} (ng/mL)	266 (36.5)	151 (32.5)	177.7	136.9 – 230.7	0.0015

Source: M5.3.3.1 CL0600-022 CSR Table 11-4

テデュグルチドの $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、及び C_{max} の最小二乗平均（LSM）の比率（比率：A/AR）は、122.6%、115.1%、及び 177.7%であり、90%信頼区間は 80.0%～125.0%の範囲に収まらなかっ

た。この結果から、テデュグルチド 20 mg/mL 製剤を 1.0 mL 投与する場合（コホート A）、治験薬の総曝露量及び C_{max} がそれぞれ約 15%及び 78%上昇することが示唆された。各コホート内の女性被験者数が相対的に少なかったことを考慮し、性別に特化した ANOVA は実施しなかった。

5.2.4　蓄積性の評価（Day 8 と Day 1 の比較）

テデュグルチドを反復皮下投与したときの蓄積性を評価するため、ANOVA モデルを用い、各コホート内で Day 8 の $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$ 及び C_{max} を Day 1 の値と比較した。蓄積指数の幾何平均値及び 90%信頼区間を表 2.7.6.5 - 6 に示す。

表 2.7.6.5 - 6　CL0600-022 試験：テデュグルチドの蓄積性の評価（男女併合値）

Day 8 / Day 1	Geometric Mean (90% Confidence Intervals) – Cohorts*							
	A 20 mg qd	**AR** 20 mg qd	**C** 25 mg qd	**D** 10 mg qd	**E** 15 mg qd	**F** 30 mg qd	**H** 50 mg qd	**J** 80 mg qd
$AUC_{0\text{–last}}$	1.01 (0.94 – 1.09)	1.16 (1.02 – 1.33)	0.94 (0.83 – 1.06)	1.01 (0.91 – 1.12)	1.05 (0.88 – 1.25)	0.94 (0.81 – 1.10)	0.96 (0.85 – 1.08)	0.99 (0.83 – 1.18)
$AUC_{0\text{–inf}}$	0.95 (0.90 – 1.00)	0.98 (0.91 – 1.06)	0.92 (0.85 – 1.00)	0.96 (0.88 – 1.05)	0.68 (0.27 – 1.70)	1.01 (0.97 – 1.06)	0.95 (0.87 – 1.03)	0.99 (0.87 – 1.12)
C_{max}	0.93 (0.78 – 1.11)	1.07 (0.91 – 1.27)	0.92 (0.84 – 1.01)	1.02 (0.87 – 1.20)	0.86 (0.41 – 1.78)	0.89 (0.71 – 1.12)	0.96 (0.86 – 1.08)	0.99 (0.81 – 1.20)

*　Teduglutide was administered as 50 mg/mL in all cohorts, with the exception of Cohort A (20 mg/mL)
Subject [redacted] is an outlier, summary statistics in this table is calculated with this subject.
Source: M5.3.3.1 CL0600-022 CSR Table 11-5

いずれのコホートにおいても $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、及び C_{max} の比率は 1.00 に近いことから、テデュグルチドの 1 日 1 回反復皮下投与による蓄積はないことが示唆された。$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、及び C_{max} の Day 8 と Day 1 の比の信頼区間は、コホート AR の $AUC_{0\text{-last}}$ を除いて、いずれも 1.00 を含んでいた。

5.2.5　用量比例性の評価（パワーモデル）

パワーモデルを用いて用量比例性を評価した。コホート AR とコホート A を比較すると製剤の影響が認められたため、コホート A は用量依存性の評価に含めず、50 mg/mL の製剤のみで評価した。$AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$ 及び C_{max} のいずれも、投与日間の交互作用は統計学的に有意ではなかったことから、用量依存性の評価は、Day 1 と Day 8 のデータをプールして実施した。自然対数変換した PK パラメータの傾き及び 95%信頼区間を表 2.7.6.5 - 7 に示す。

表 2.7.6.5 - 7　　CL0600-022 試験：テデュグルチドの用量比例性の評価（男女併合値）

Ln–Transformed Parameters	Slope Estimate	95% CI of Slope
AUC_{0-last}	0.95	0.86, 1.04
AUC_{0-inf}	0.91	0.81, 1.01
C_{max}	0.80	0.64, 0.96

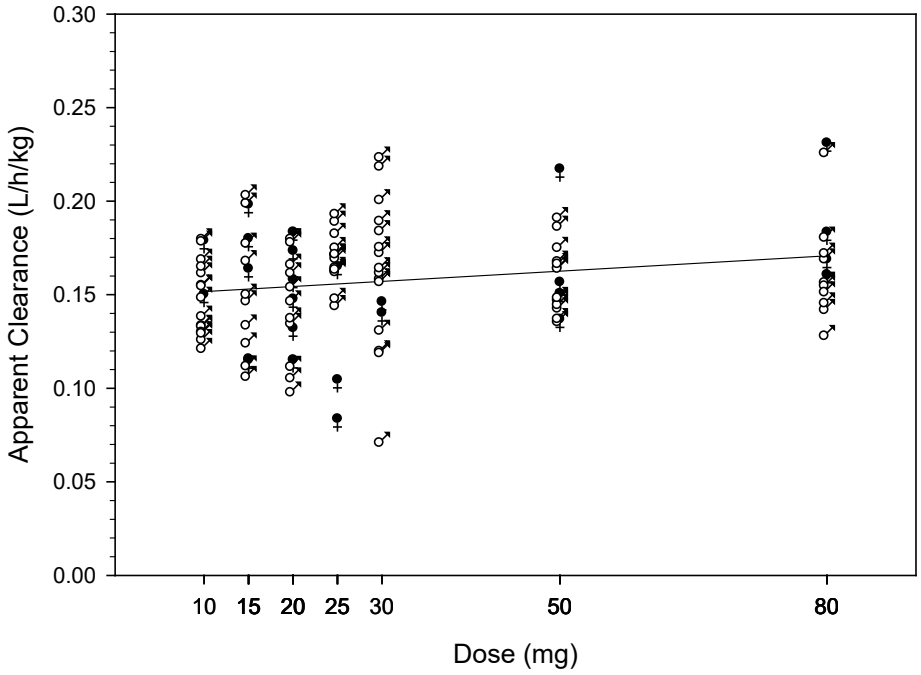
*　Administered as 50 mg/mL
Source: M5.3.3.1 CL0600-022 CSR Appendix 16.1.9.2

AUC_{0-last} 及び AUC_{0-inf} の傾きの 95%信頼区間はいずれも 1 を含み、10～80 mg の範囲で用量比例性が確認された。一方、C_{max} の傾きの信頼区間上限が 1.00 未満であり、10～80 mg の範囲ではその上昇は用量比を下回ったが、80 mg（0.8 mL を 2 回投与する唯一の用量）を除外すると 95%信頼区間は 0.61～1.04 となり 1.00 を含むことから、用量比例性が確認された。

5.2.6　　性別の評価

個々の被験者について体重補正した見かけのクリアランス（CL/F）値とテデュグルチドの用量段階との関係を図 2.7.6.5 - 4 に示す。

図 2.7.6.5 - 4　　CL0600-022 試験：男女別被験者別の投与量と CL/F 値との関係

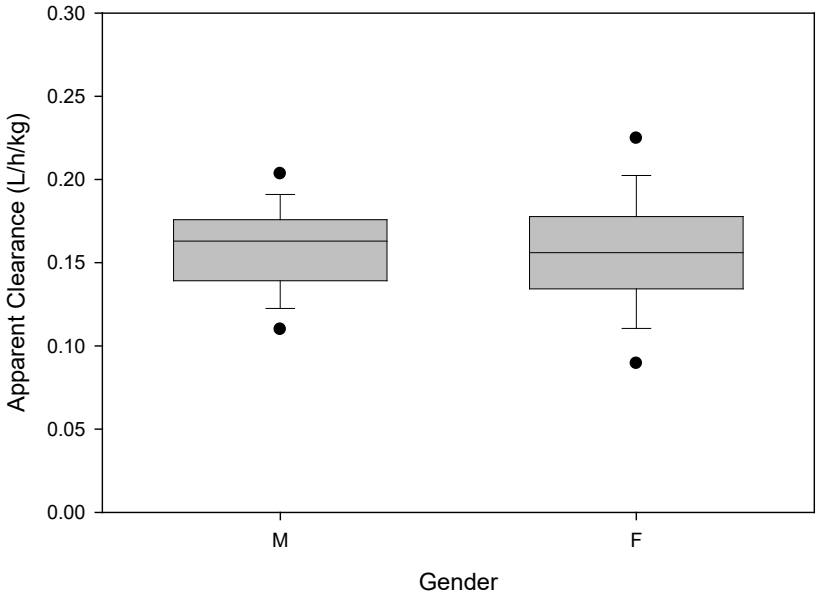


Source: M5.3.3.1 CL0600-022 CSR Figure 11-3

総合的に見て、男女別被験者別の CL/F 値は、検討した用量範囲内では相対的に一定であった。この結果は、テデュグルチドの AUC_{0-inf} が用量に比例して増加することを示した、以前の用量比

例性の評価結果と一致した。この結果を受け、性別に関連する傾向を検討するため、CL/F 値を男女別にコホート全体で併合した。CL/F の男女の比較を図 2.7.6.5 - 5 に示す。

図 2.7.6.5 - 5　CL0600-022 試験：男性被験者及び女性被験者の CL/F の比較（コホートを併合）



Note: Median and 5th/95th percentile are represented in the above Whisker Plot.
Values from individual cohorts (Source: M5.3.3.1 CL0600-022 CSR Figure 11-3) were pooled.
Source: M5.3.3.1 CL0600-022 CSR Figure 11-4.

男性被験者及び女性被験者の CL/F（平均値）はそれぞれ、0.155 及び 0.159 L/h/kg であった。全体的に、CL/F 値に性差はみられず、男性被験者と女性被験者のデータは類似の分布を示した。

5.3　安全性の結果

5.3.1　　曝露状況

無作為化された被験者はいずれも二重盲検下で治験薬の投与を受け、安全性解析の対象とされた。本集団には、プラセボの投与を受けた被験者 24 例及びテデュグルチドの漸増投与を受けた被験者 71 例（7 コホートに各 9 例、1 コホートに 8 例）が含まれた。

曝露量とは、投与した薬剤の合計と規定した（投与回数×固定用量）。プラセボ群の被験者はいずれも必要とされた用量の投与を受けたが、テデュグルチド群の被験者の投与量は予定用量の 91.5%であった。コホート AR（20 mg）、コホート C（25 mg）、及びコホート J（80 mg）における投与量は予定用量の 100%であったが、コホート A の投与量は Day 3 までは予定用量の 100%（9/9 例）で、その後の試験期間は予定用量の 77.8%（7/9 例）であった。

5.3.2　有害事象

本項では特に断りのない限り、有害事象とは試験治療下に発現した有害事象（TEAE）であり、重篤な有害事象とは試験治療下の重篤な有害事象を示す。

5.3.2.1　有害事象の概要

有害事象は、86/95 例（プラセボ群：17/24 例、テデュグルチド群：69/71 例）に 409 件（プラセボ群：70 件、テデュグルチド群：339 件）発現した。有害事象の総発現例数及び総発現件数はいずれの投与群でも類似の分布を示した。総じて各投与群の有害事象の大部分は軽度又は中等度であった。治験薬との因果関係有無別の事象数もいずれの投与群でも同様であった。投与及び試験の中止に至った有害事象が 1 例に 1 件発現した（血管迷走神経性失神、テデュグルチドコホート E）。試験期間中に重篤な有害事象は 1 例に 1 件発現した（顔面骨骨折、テデュグルチドコホート AR）。この重篤な有害事象は、治験責任医師により治験薬との関連なしと評価された。試験期間中の死亡例はなかった。有害事象の概要について表 2.7.6.5 - 8 に示す。

表 2.7.6.5 - 8　CL0600-022 試験：有害事象の概要（安全性解析対象集団）

Demographic Variable	**Placebo (N=24)**	**Teduglutide (N=71)**
Any AE Reported		
Yes	17 (70.8%)	69 (97.2%)
No	7 (29.2%)	2 (2.8%)
AE Severity		
Mild	17 (70.8%)	69 (97.2%)
Moderate	1 (4.2%)	6 (8.5%)
Severe	0 (0.0%)	1 (1.4%)
AE Highest Severity (for a subject)		
Mild	16 (66.7%)	62 (87.3%)
Moderate	1 (4.2%)	6 (8.5%)
Severe	0 (0.0%)	1 (1.4%)
AE Relationship		
Related	16 (66.7%)	64 (90.1%)
Not Related	6 (25.0%)	38 (53.5%)
AE Highest Relationship (for a subject)		
Related	16 (66.7%)	62 (87.3%)
Not Related	1 (4.2%)	7 (9.9%)
AE Leading to Treatment Discontinuation	**0 (0.0%)**	**1 (1.4%)**
AE Leading to Study Discontinuation	**0 (0.0%)**	**1 (1.4%)**
Any SAE	**0 (0.0%)**	**1 (1.4%)**
Death	**0 (0.0%)**	**0(0.0%)**

Source: M5.3.3.1 CL0600-022 CSR Table 12-1

5.3.2.2　　有害事象の分析

有害事象は、プラセボ群では 17 例（70.8%）に 70 件、テデュグルチド群では 69 例（97.2%）に 339 件発現した（表 2.7.6.5 - 9）。投与群全体で最も発現頻度の高かった有害事象を基本語別に示すと、腹部膨満（プラセボ群：16.7%、テデュグルチド群：29.6%）、悪心（プラセボ群：8.3%、テデュグルチド群：14.1%）、注射部位疼痛（プラセボ群：4.2%、テデュグルチド群：35.2%）、注射部位出血（プラセボ群：12.5%、テデュグルチド群：8.5%）、及び頭痛（プラセボ群：25.0%、テデュグルチド群：23.9%）であった。テデュグルチド群では、便秘（22.5%）、アラニン・アミノトランスフェラーゼ増加（18.3%）、腹痛（16.9%）、注射部位紅斑（15.5%）、及びアスパラギン酸アミノトランスフェラーゼ増加（14.1%）の発現頻度も高かった。また、プラセボ群では、鼻出血（12.5%）及び筋挫傷（8.3%）の発現頻度も高かった。

その他の事象はいずれもその発現頻度が各群の 10%未満であった。「胃腸障害」及び「一般・全身障害」のテデュグルチド群での発現頻度はプラセボ群より高かったが、テデュグルチドの用量との関連性は明瞭ではなかった。その他の事象については、プラセボ群とテデュグルチド群の発現頻度は同様であった。いずれの場合もテデュグルチドの用量との関連性は明確ではなかった。

表 2.7.6.5 - 9　CL0600-022 試験：有害事象一覧（器官別大分類及び基本語別、いずれかの投与群で発現率 5%以上）（安全性解析対象集団）

MedDRA System Organ Class / Preferred Term		Placebo (N=24)		Teduglutide (N=71)	
Gastrointestinal Disorders	**胃腸障害**	**10**	**(41.7%)**	**54**	**(76.1%)**
Abdominal Discomfort	腹部不快感	1	(4.2%)	5	(7.0%)
Abdominal Distension	腹部膨満	4	(16.7%)	21	(29.6%)
Abdominal Pain	腹痛	1	(4.2%)	12	(16.9%)
Constipation	便秘	1	(4.2%)	16	(22.5%)
Diarrhoea	下痢	2	(8.3%)	6	(8.5%)
Dyspepsia	消化不良	0	(0.0%)	5	(7.0%)
Flatulence	鼓腸	0	(0.0%)	7	(9.9%)
Nausea	悪心	2	(8.3%)	10	(14.1%)
General Disorders and Administration Site Conditions	**全身障害および投与局所様態**	**7**	**(29.2%)**	**42**	**(59.2%)**
Injection Site Bruising	注射部位内出血	1	(4.2%)	7	(9.9%)
Injection Site Erythema	注射部位紅斑	0	(0.0%)	11	(15.5%)
Injection Site Haemorrhage	注射部位出血	3	(12.5%)	6	(8.5%)
Injection Site Pain	注射部位疼痛	1	(4.2%)	25	(35.2%)
Infections and Infestations	感染症および寄生虫症	2	(8.3%)	4	(5.6%)
Injury, Poisoning and Procedural Complications	**傷害、中毒および処置合併症**	**3**	**(12.5%)**	**5**	**(7.0%)**
Muscle Strain	筋挫傷	2	(8.3%)	0	(0.0%)
Investigations	**臨床検査**	**2**	**(8.3%)**	**18**	**(25.4%)**
Alanine Aminotransferase Increased	アラニン・アミノトランスフェラーゼ増加	0	(0.0%)	13	(18.3%)

表 2.7.6.5 - 9　CL0600-022 試験：有害事象一覧（器官別大分類及び基本語別、いずれかの投与群で発現率 5%以上）（安全性解析対象集団）

MedDRA System Organ Class Preferred Term		Placebo (N=24)		Teduglutide (N=71)	
Aspartate Aminotransferase Increased	アスパラギン酸アミノトランスフェラーゼ増加	0	(0.0%)	10	(14.1%)
Musculoskeletal and Connective Tissue Disorders	**筋骨格系および結合組織障害**	**3**	**(12.5%)**	**13**	**(18.3%)**
Myalgia	筋痛	0	(0.0%)	4	(5.6%)
Nervous System Disorders	**神経系障害**	**9**	**(37.5%)**	**25**	**(35.2%)**
Dizziness	浮動性めまい	1	(4.2%)	7	(9.9%)
Headache	頭痛	6	(25.0%)	17	(23.9%)
Respiratory, Thoracic and Mediastinal Disorders	**呼吸器、胸郭および縦隔障害**	**4**	**(16.7%)**	**5**	**(7.0%)**
Epistaxis	鼻出血	3	(12.5%)	0	(0.0%)
Skin and Subcutaneous Tissue Disorders	**皮膚および皮下組織障害**	**2**	**(8.3%)**	**9**	**(12.7%)**
Dermatitis Contact	接触性皮膚炎	1	(4.2%)	4	(5.6%)

Source: M5.3.3.1 CL0600-022 CSR Table 12-2
Pooled data was used to increase power of detection.

治験責任医師により治験薬と関連ありと判断された有害事象の発現例数は 80 例（プラセボ群：16 例、テデュグルチド群：64 例）で、発現件数は 312 件（プラセボ群：43 件、テデュグルチド群：269 件）であった。いずれの投与群においても、治験薬と関連のある有害事象の発現頻度が最も高かった器官別大分類は、1）胃腸障害、2）一般・全身障害および投与部位の状態、及び 3）神経系障害であった（表 2.7.6.5 - 10）。

テデュグルチド群で最も発現頻度の高かった治験薬と関連のある有害事象を基本語別に示すと、注射部位疼痛（22 例；31.0%）、腹部膨満（20 例、28.2%）、便秘及び頭痛（15 例、21.1%）、アラニン･アミノトランスフェラーゼ増加（12 例、16.9%）、腹痛、悪心及び注射部位紅斑（10 例、14.1%）、並びにアスパラギン酸アミノトランスフェラーゼ増加（9 例、12.7%）であった。その他の治験薬と関連のある有害事象の発現例数は 7 例（10%）以下であった。

プラセボ群で最も発現頻度の高かった治験薬と関連のある有害事象を基本語別に示すと、頭痛（6 例、25.0%）、腹部膨満（4 例、16.7%）、注射部位出血（3 例、12.5%）、及び鼻出血（2 例、8.3%）であった。その他の治験薬と関連のある有害事象の発現例数はいずれも 1 例（4.2%）以下であった。プラセボ群における治験薬と関連のある有害事象の発現頻度は総じてテデュグルチド群より低かった。

いずれの器官別大分類についても用量との明確な関連性は認められなかったが、コホート A（20 mg/mL 製剤で 20 mg 投与）と比較したとき、コホート AR（50 mg/mL 製剤で 20 mg 投与）では「一般・全身障害および投与部位の状態」分類に関係する有害事象の発現頻度に顕著な低下がみられた。その他の有害事象の発現頻度には 50 mg/mL 製剤と 20 mg/mL 製剤間で大きな差はみられなかった。

本試験で認められた全有害事象及び治験薬と関連のある有害事象（コホート別）をそれぞれ表 2.7.6.5 - 11 及び表 2.7.6.5 - 12 に示す。

表 2.7.6.5 - 10 CL0600-022 試験：治験薬と関連のある有害事象一覧（器官別大分類及び基本語別）（安全性解析対象集団）

MedDRA System Organ Class Preferred Term		Placebo (N=24)		Teduglutide (N=71)	
Gastrointestinal Disorders	**胃腸障害**	**9**	**(37.5%)**	**50**	**(70.4%)**
Abdominal Discomfort	腹部不快感	1	(4.2%)	5	(7.0%)
Abdominal Distension	腹部膨満	4	(16.7%)	20	(28.2%)
Abdominal Pain	腹痛	1	(4.2%)	10	(14.1%)
Constipation	便秘	1	(4.2%)	15	(21.1%)
Diarrhoea	下痢	1	(4.2%)	6	(8.5%)
Dyspepsia	消化不良	0	(0.0%)	4	(5.6%)
Flatulence	鼓腸	0	(0.0%)	6	(8.5%)
Nausea	悪心	1	(4.2%)	10	(14.1%)
General Disorders and Administration Site Conditions	**全身障害および投与局所様態**	**7**	**(29.2%)**	**37**	**(52.1%)**
Injection Site Bruising	注射部位内出血	1	(4.2%)	7	(9.9%)
Injection Site Erythema	注射部位紅斑	0	(0.0%)	10	(14.1%)
Injection Site Haemorrhage	注射部位出血	3	(12.5%)	6	(8.5%)
Injection Site Pain	注射部位疼痛	1	(4.2%)	22	(31.0%)
Investigations	**臨床検査**	**1**	**(8.3%)**	**12**	**(16.9%)**
Alanine Aminotransferase Increased	アラニン・アミノトランスフェラーゼ増加	0	(0.0%)	12	(16.9%)
Aspartate Aminotransferase Increased	アスパラギン酸アミノトランスフェラーゼ増加	0	(0.0%)	9	(12.7%)
Musculoskeletal and Connective Tissue Disorders	**筋骨格系および結合組織障害**	**1**	**(4.2%)**	**11**	**(15.5%)**
Myalgia	筋痛	0	(0.0%)	4	(5.6%)
Nervous System Disorders	**神経系障害**	**8**	**(33.3%)**	**19**	**(26.8%)**
Dizziness	浮動性めまい	1	(4.2%)	4	(5.6%)
Headache	頭痛	6	(25.0%)	15	(21.1%)
Respiratory, Thoracic and Mediastinal Disorders	**呼吸器、胸郭および縦隔障害**	**2**	**(8.3%)**	**3**	**(4.2%)**
Epistaxis	鼻出血	2	(8.3%)	0	(0.0%)

Source: M5.3.3.1 CL0600-022 CSR Table 14.3.1.7. Pooled data was used to increase power of detection.

5.3.3　死亡、その他の重篤な有害事象及び他の重要な有害事象

死亡

試験期間中に死亡例の報告はなかった。

その他の重篤な有害事象

重篤な有害事象（顔面骨骨折）が 1 例（コホート AR）に認められた（叙述を 5.5.2 に示す）。本事象は、その特性及び発現時期により治験薬との関連なしと判断された。

他の重要な有害事象

テデュグルチド群の被験者 1 例（テデュグルチド　コホート E）が有害事象（中等度の血管迷走神経性失神）により治験薬の投与及び試験を中止した。当該事象は事象の特性により、治験薬と関連ありと判断された。

5.3.4　　バイタルサイン、身体所見、及び安全性に関連するその他の所見

ベースライン時及び最終測定時（Day 8）におけるバイタルサインの平均値に投与群間で大きな差はみられなかった。プラセボ群とテデュグルチド群との差、及びベースラインからの変化量はいずれも小さく、臨床的に意味のある差は認められなかった。

総合的に見て、心電図は、試験期間を通じていずれの時点においても大部分（> 64.0%）が正常と評価された。正常からの逸脱で臨床的に問題と判断されたものはなかった。ベースラインの心電図に異常がみられた被験者の割合は、プラセボ群が 12.5%、テデュグルチド群が 19.7%であった。最終来院時の心電図に異常がみられた被験者の割合は、プラセボ群が 20.8%、テデュグルチド群が 15.5%であった。

全般的に各血液学的検査パラメータの平均値は比較的一定かつ基準範囲内であり、試験終了時の値のベースラインに対する変化は相対的に小さかった。例外は、総ヘマトクリット、ヘモグロビン、赤血球数、及び好中球（%）であり、テデュグルチド群で試験開始時に正常レベルであったが試験終了時には正常レベルを下回った被験者の割合はそれぞれ、6.0、10.9、7.4、及び 6.2%であった。プラセボ群では、赤血球数が試験終了時にベースラインから減少した被験者の割合は 8.0%であった。

その他の例外としては活性化部分トロンボプラスチン時間があげられ、テデュグルチド群で試験開始時に正常レベルであったが試験終了時には正常値を上回った被験者の割合が 5.6%であった。プラセボ群又はテデュグルチド群内においてみられたその他のベースラインからの変動は、いずれも頻度 5%未満であった。

血液学的検査パラメータにベースラインから臨床的に差のある変化がみられ、治験薬と関連ありとされた被験者は極めて少なかった。全体では、臨床的に重要な有害事象に分類されたベースラインからの変化の発現頻度は、全被験者の 5%未満であり、白血球数増加との関連性が認められた。

全般的に、各生化学検査の平均値は比較的一定かつ基準範囲内であり、試験終了時の値のベースラインに対する変化は相対的に小さかった。例外は、血中尿素窒素（BUN）、グルコース、鉄、及び尿酸であり、テデュグルチド群で試験開始時に正常レベルであったが試験終了時には正常レベルを下回った被験者の割合はそれぞれ、5.6、10.4、45.5、及び 8.7%であった。鉄で頻度が高かったが、これは、少ないサンプル数（投与前に正常レベル内を示した値の数はわずか 11 であった）

に基づく推測であることから、解釈に際しては慎重さが求められる。グルコースが試験開始時に正常レベルであったが試験終了時には正常レベルを上回った被験者の割合は計 16.4%であった。プラセボ群でも同様の結果が観察された（試験終了時にベースラインから値の低下がみられた被験者の割合は、コレステロールが 9.1%、鉄が 33.3%であり、鉄についてはやはりサンプル数が少なかった)。

その他の例外は、アラニン・アミノトランスフェラーゼ、アスパラギン酸アミノトランスフェラーゼ、リン、及びトリグリセリドで試験開始時に正常レベルであったが、試験終了時には正常レベルを上回ったテデュグルチド群の被験者の割合はそれぞれ、9.6、5.5、10.3、及び 8.6%であった。プラセボ群でも同様の結果が観察された（試験終了時にベースラインから値の上昇がみられた被験者の割合は、グルコースが 9.5%、リンが 8.7%、トリグリセリドが 5.6%であった)。

プラセボ群又はテデュグルチド群内においてみられた、その他の生化学検査のベースラインからのシフトは、いずれも頻度 5%未満であった。

ベースラインから臨床的に差があり、臨床的に問題ありと分類され、治験薬と関連ありとされた生化学検査値を呈した被験者は極めて少なかった。生化学検査パラメータのうち、ベースラインからの増加がみられたのは、アラニン・アミノトランスフェラーゼが 13 例（18.3%）及びアスパラギン酸アミノトランスフェラーゼが 10 例（14.1%）であった。その他のベースラインからの変化は、いずれも被験者の 5%未満であった。

全般的に、尿検査の各項目については、いずれの投与群でも、大部分の被験者の結果は正常であった。臨床的に重要な所見（潜血陽性、グルコース濃度、又は白血球エステラーゼアッセイ陽性を含む）がみられたのは、テデュグルチド群内では 1 又は 2 例に限られ、本群での発現頻度は 5%未満であった。

5.4　結論：

本試験の主要目的は、健康被験者を対象とし、テデュグルチドを 1 日 1 回又は場合により 1 日 2 回、8 日間皮下投与したときの安全性及び忍容性を検討することであった。副次目的は、健康被験者を対象とし、テデュグルチドを 1 日 1 回又は 1 日 2 回、8 日間皮下投与したときのテデュグルチドの薬物動態を検討することであった。

有害事象、臨床検査値、バイタルサイン、12 誘導心電図、及び身体所見の評価から、テデュグルチド 10～80 mg の腹部皮下投与は安全で忍容性も良好であることが示唆された。テデュグルチドの 20 mg/mL 製剤に比べ 50 mg/mL 製剤の投与時には注射部位に関連した有害事象の頻度が低かった。

検討した用量範囲において、テデュグルチドは直ちに吸収され、血漿中濃度は単一指数関数的に低下し、$t_{1/2}$（平均値）は 2.99～4.63 時間であった。20 mg/mL 製剤を 20 mg 皮下投与したとき、テデュグルチドの C_{max} は、50 mg/mL 製剤で観察された濃度より約 78%高かった。反復皮下投与後、テデュグルチドの蓄積は観察されなかった。Day 1 及び Day 8 において、テデュグルチドの総曝露量は用量段階に沿って用量比例性に増加したが、テデュグルチドの C_{max} が用量比例性に増加したのは 10～50 mg の範囲であった。テデュグルチドの CL/F に性差はみられなかった。

5.5 付録

5.5.1 有害事象表

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
全有害事象	9 (100.0)	0 (0.0)	9 (100.0)	3 (100.0)	9 (100.0)	3 (100.0)	6 (66.7)	1 (33.3)	9 (100.0)	3 (100.0)	9 (100.0)	1 (33.3)	9 (100.0)	3 (100.0)	8 (100.0)	3 (100.0)
血液およびリンパ系障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
リンパ節症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
好中球減少症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
鼓膜障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
眼障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (25.0)	0 (0.0)
眼瞼痙攣	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
結膜充血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
眼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
強膜充血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
胃腸障害	7 (77.8)	0 (0.0)	7 (77.8)	2 (66.7)	8 (88.9)	2 (66.7)	6 (66.7)	0 (0.0)	7 (77.8)	1 (33.3)	5 (55.6)	1 (33.3)	6 (66.7)	1 (33.3)	7 (87.5)	3 (100.0)
腹部不快感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (33.3)
腹部膨満	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	1 (33.3)	2 (22.2)	0 (0.0)	2 (22.2)	1 (33.3)	2 (22.2)	1 (33.3)	4 (44.4)	0 (0.0)	3 (37.5)	1 (33.3)
腹痛	3 (33.3)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (12.5)	0 (0.0)
下腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
上腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
腹部圧痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
便秘	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	4 (44.4)	1 (33.3)	2 (22.2)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	2 (25.0)	0 (0.0)
下痢	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)
消化不良	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
おくび	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
白色便	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
鼓腸	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (25.0)	0 (0.0)
消化管運動障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
胃食道逆流性疾患	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
口の感覚鈍麻	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
悪心	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	1 (33.3)
歯痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
嘔吐	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
全身障害および投与局所様態	7 (77.8)	0 (0.0)	4 (44.4)	1 (33.3)	5 (55.6)	2 (66.7)	2 (22.2)	0 (0.0)	8 (88.9)	2 (66.7)	4 (44.4)	1 (33.3)	6 (66.7)	0 (0.0)	6 (75.0)	1 (33.3)
適用部位刺激感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
無力症	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
疲労	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
硬結	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
注入部位静脈炎	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位内出血	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
注射部位紅斑	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	0 (0.0)	2 (25.0)	0 (0.0)
注射部位出血	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位刺激感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位浮腫	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位疼痛	5 (55.6)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)	1 (33.3)	3 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	4 (50.0)	0 (0.0)
注射部位知覚異常	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
注射部位そう痒感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位熱感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (33.3)
血管穿刺部位疼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管穿刺部位反応	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
肝胆道系障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
高ビリルビン血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (66.7)	1 (12.5)	0 (0.0)
単純ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
麦粒腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
口腔ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
咽頭炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)
傷害、中毒および処置合併症	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	3 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)
挫傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)
顔面骨骨折	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋挫傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚損傷	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
臨床検査	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	2 (22.2)	1 (33.3)	2 (25.0)	1 (33.3)
アラニン・アミノトランスフェラーゼ増加	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
アスパラギン酸アミノトランスフェラーゼ増加	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
尿中細菌	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
血中ビリルビン増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
血中ブドウ糖増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
血中乳酸脱水素酵素増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血中カリウム増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
尿中血陽性	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
γ-グルタミルトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
代謝および栄養障害	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
食欲亢進	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	5 (55.6)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (33.3)	2 (22.2)	1 (33.3)	1 (12.5)	0 (0.0)
背部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
側腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋緊張	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)
筋痛	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頚部痛	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
四肢痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	5 (55.6)	0 (0.0)	4 (44.4)	1 (33.3)	2 (22.2)	1 (33.3)	3 (33.3)	1 (33.3)	3 (33.3)	1 (33.3)	3 (33.3)	1 (33.3)	2 (22.2)	1 (33.3)	2 (25.0)	2 (66.7)
平衡障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注意力障害	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
浮動性めまい	4 (44.4)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
味覚異常	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頭痛	1 (11.1)	0 (0.0)	3 (33.3)	1 (33.3)	1 (11.1)	1 (33.3)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	3 (33.3)	1 (33.3)	2 (22.2)	1 (33.3)	2 (25.0)	2 (66.7)
錯感覚	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
副鼻腔炎に伴う頭痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傾眠	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管迷走神経性失神	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
精神障害	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
激越	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
睡眠障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎および尿路障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
排尿困難	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
糖尿	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
排尿躊躇	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
生殖系および乳房障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
月経困難症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
外陰腟不快感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	2 (25.0)	1 (33.3)
咳嗽	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
鼻出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
鼻閉	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)
湿性咳嗽	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
ラ音	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
鼻漏	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)
副鼻腔うっ血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
くしゃみ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
咽喉刺激感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	1 (33.3)	4 (44.4)	1 (33.3)	1 (12.5)	0 (0.0)
皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
接触性皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)
斑状出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 11 CL0600-022 試験：全有害事象一覧（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
毛髪成長異常	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
多汗症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
潮紅	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ほてり	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)

Notes: Teduglutide Treatment Groups: Cohort A - 20 mg qd sc 20mg/mL formulation; All other cohorts used sc 50 mg/mLformulation at following doses: Cohort AR - 20 mg qd; Cohort C - 25 mg qd; Cohort D - 10 mg qd; Cohort E - 15 mg qd;Cohort F - 30 mg qd; Cohort H - 50 mg qd; Cohort J - 80 mg qd
Note: Treatment emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within thirty days after discontinuation of study drug.
Note: Related AEs include AEs that were 'possibly related', 'probably related', 'related' or with relationship missing.
Note: Subjects are counted no more than once for incidence of System Organ Class and Preferred Term.
Note: All adverse events were coded using MedDRA version 9.0.
Program: t-1-2-ae-socpt-600022.sas　　Output Generated On: 23OCT2016 1:50

表 2.7.6.5 - 12 CL0600-022 試験：治験薬と関連のある有害事象発現頻度（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
治験薬と関連のある有害事象	7 (77.8)	0 (0.0)	9 (100.0)	3 (100.0)	9 (100.0)	3 (100.0)	6 (66.7)	1 (33.3)	9 (100.0)	3 (100.0)	7 (77.8)	1 (33.3)	8 (88.9)	2 (66.7)	8 (100.0)	3 (100.0)
血液およびリンパ系障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
リンパ節症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
好中球減少症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
鼓膜障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (25.0)	0 (0.0)
眼瞼痙攣	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
結膜充血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
強膜充血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
胃腸障害	5 (55.6)	0 (0.0)	6 (66.7)	2 (66.7)	8 (88.9)	2 (66.7)	6 (66.7)	0 (0.0)	7 (77.8)	1 (33.3)	5 (55.6)	1 (33.3)	5 (55.6)	0 (0.0)	7 (87.5)	3 (100.0)
腹部不快感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (33.3)
腹部膨満	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	1 (33.3)	2 (22.2)	0 (0.0)	2 (22.2)	1 (33.3)	2 (22.2)	1 (33.3)	4 (44.4)	0 (0.0)	3 (37.5)	1 (33.3)
腹痛	2 (22.2)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
下腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
上腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
腹部圧痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
便秘	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	3 (33.3)	1 (33.3)	2 (22.2)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	2 (25.0)	0 (0.0)
下痢	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
消化不良	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
おくび	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)

表 2.7.6.5 - 12 CL0600-022 試験：治験薬と関連のある有害事象発現頻度（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
白色便	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
鼓腸	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
消化管運動障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
胃食道逆流性疾患	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
口の感覚鈍麻	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
悪心	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (33.3)
歯痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
嘔吐	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
全身障害および投与局所様態	4 (44.4)	0 (0.0)	4 (44.4)	1 (33.3)	5 (55.6)	2 (66.7)	1 (11.1)	0 (0.0)	8 (88.9)	2 (66.7)	4 (44.4)	1 (33.3)	6 (66.7)	0 (0.0)	5 (62.5)	1 (33.3)
適用部位刺激感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
無力症	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
疲労	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
硬結	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
注入部位静脈炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位内出血	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
注射部位紅斑	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	0 (0.0)	2 (25.0)	0 (0.0)
注射部位出血	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位刺激感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位浮腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位疼痛	2 (22.2)	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)	1 (33.3)	3 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	4 (50.0)	0 (0.0)
注射部位知覚異常	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位そう痒感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注射部位熱感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (33.3)
血管穿刺部位疼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管穿刺部位反応	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 12 CL0600-022 試験：治験薬と関連のある有害事象発現頻度（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
肝胆道系障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
高ビリルビン血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
単純ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
麦粒腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
口腔ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
咽頭炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
挫傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
顔面骨骨折	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋挫傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚損傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
臨床検査	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (33.3)
アラニン・アミノトランスフェラーゼ増加	1 (11.1)	0 (0.0)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
アスパラギン酸アミノトランスフェラーゼ増加	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
尿中細菌	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血中ビリルビン増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
血中ブドウ糖増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血中乳酸脱水素酵素増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血中カリウム増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
尿中血陽性	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
γ-グルタミルトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
代謝および栄養障害	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
食欲亢進	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	4 (44.4)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)	1 (33.3)	1 (12.5)	0 (0.0)
背部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
側腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋緊張	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	1 (33.3)	0 (0.0)	0 (0.0)
筋痛	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頚部痛	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
四肢痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	2 (22.2)	0 (0.0)	4 (44.4)	1 (33.3)	1 (11.1)	1 (33.3)	3 (33.3)	1 (33.3)	3 (33.3)	1 (33.3)	3 (33.3)	1 (33.3)	1 (11.1)	1 (33.3)	2 (25.0)	2 (66.7)
平衡障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
注意力障害	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
浮動性めまい	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
味覚異常	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頭痛	1 (11.1)	0 (0.0)	3 (33.3)	1 (33.3)	1 (11.1)	1 (33.3)	2 (22.2)	0 (0.0)	2 (22.2)	0 (0.0)	3 (33.3)	1 (33.3)	1 (11.1)	1 (33.3)	2 (25.0)	2 (66.7)
錯感覚	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
副鼻腔炎に伴う頭痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傾眠	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管迷走神経性失神	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
精神障害	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
激越	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
睡眠障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎および尿路障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 12 CL0600-022 試験：治験薬と関連のある有害事象発現頻度（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Tedugludide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
排尿困難	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
糖尿	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
排尿躊躇	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
生殖系および乳房障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
月経困難症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
外陰腟不快感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
咳嗽	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
鼻出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
鼻閉	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
湿性咳嗽	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ラ音	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
鼻漏	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
副鼻腔うっ血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
くしゃみ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
咽喉刺激感	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (33.3)	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
接触性皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
斑状出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
毛髪成長異常	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
多汗症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.5 - 12 CL0600-022 試験：治験薬と関連のある有害事象発現頻度（コホート別）

System Organ Class (SOC)/ Preferred Term (PT)	Cohort A		Cohort AR		Cohort C		Cohort D		Cohort E		Cohort F		Cohort H		Cohort J	
	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)	Teduglutide (N = 9) n (%)	Placebo (N = 3) n (%)
血管障害	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
潮紅	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ほてり	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)

Notes: Teduglutide Treatment Groups: Cohort A - 20 mg qd sc 20mg/mL formulation; All other cohorts used sc 50 mg/mLformulation at following doses: Cohort AR - 20 mg qd; Cohort C - 25 mg qd; Cohort D - 10 mg qd; Cohort E - 15 mg qd;Cohort F - 30 mg qd; Cohort H - 50 mg qd; Cohort J - 80 mg qd
Note: Treatment emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within thirty days after discontinuation of study drug.
Note: Related AEs include AEs that were 'possibly related', 'probably related', 'related' or with relationship missing.
Note: Subjects are counted no more than once for incidence of System Organ Class and Preferred Term.
Note: All adverse events were coded using MedDRA version 9.0.
Program: t-1-2-ae-socpt-600022.sas Output Generated On: 23OCT2016 1:50

5.5.2 死亡、その他の重篤な有害事象の叙述

本試験に組み入れられ、試験参加中に死亡した被験者はいなかった。

重篤な有害事象がみられたのはコホート AR の被験者 1 例のみであり、左眼窩骨折であった。この重篤な有害事象は治験薬と関連なしと判断された。他に重篤な有害事象はみられなかった。以下に簡略な叙述を示す。

被験者番号：[redacted]

治験実施計画書 CL0600-022 に参加した 2[redacted]歳の白人男性がテデュグルチド 20 mg/日投与に無作為化され、初回投与日は 2006 年 9 月 28 日、最終投与日は同年 10 月 05 日であった。追跡調査期間中の同年 10 月 07 日（Day 10）、被験者は暴行を受け、試験組入れ中に左眼窩骨折のため入院した。身体の挫傷及び引っかき傷に加え、骨折の外科的修復が行われ、被験者は同年 10 月 10 日に退院した。既往歴の報告はなく、骨折治療のためモルヒネ、Anzemet®（ドラセトロンメシル酸塩）、及びキシロカイン 0.5%の投与が行われた。本事象は被験者の退院日に回復、治験薬との関連なしと判断された。

6　CL0600-017 試験

（参考資料：5.3.3.3 項）

CL0600-017 試験の概要を表 2.7.6.6 - 1 に示す。

表 2.7.6.6 - 1　　CL0600-017 試験：試験の概要

試験識別番号	CL0600-017
試験の標題	健康被験者と比較したときの中等度肝機能障害患者におけるテデュグルチド 20 mg の薬物動態
試験の相	1
目的	主要目的は、テデュグルチド 20 mg を皮下投与したときのテデュグルチドの薬物動態に対する中等度肝機能障害の影響を評価することとした。副次的目的は、全ての被験者を対象としてテデュグルチド 20 mg の安全性及び忍容性を検討することとした。
方法	本試験は非盲検試験であり、臨床センター1～3 施設に計 24 例を組み入れるものとした。性別、年齢、腎機能、及び体格指数（BMI）の分布が類似するよう、可能な限り、中等度肝機能障害患者（Child-Pugh 分類、グレード B）と健康被験者の背景を揃えた。 試験の構成は、スクリーニング来院（Visit 1、Day –28～–2）、入院日来院（Visit 2、Day –1）、投与日（Visit 2、Day 1）、及び追跡調査来院（Visit 3、Day 7～9）とした。適格な被験者を Day –1（Day 1 における投与の 12 時間以上前）に医療機関に入院させた。Day –1 の入院後、診察と臨床検査を実施し、選択基準を全て満たす被験者に対し Day 1 に投与を行った。投与約 2 日後に（Day 3）、被験者は退院した。
診断及び主な選択基準	年齢 18 歳以上 85 歳以下の肝機能正常者又は中等度肝機能障害患者（悪性腫瘍とは関係のない、Child-Pugh 分類グレード B の肝機能）
予定症例数及び解析対象例数（合計及び投与群ごと）	被験者計 33 例（肝機能障害患者：15 例、背景を一致させた対照健康被験者：18 例）が本試験のスクリーニングを受け、24 例（肝機能障害患者：12 例、背景を一致させた対照健康被験者：12 例）が本試験に組み入れられ、試験を完了した。被験者 24 例が安全性及び薬物動態（PK）解析の対象とされた。
被験薬、用法・用量、バッチ番号	テデュグルチド 20 mg（ロット番号：[redacted]）の固定用量を腹部皮下に単回投与した。
対照薬、用法・用量、バッチ番号	なし
投与期間	単回投与
評価基準	薬物動態：ノンコンパートメント法を用い、20 mg 単回皮下投与後のテデュグルチドの血漿中薬物動態パラメータ（$AUC_{0\text{-}t}$、$AUC_{0\text{-}inf}$、C_{max}、T_{max}、$t_{1/2}$、Kel、CL/F、及び V_d/F）を算出し、中等度肝機能障害患者のパラメータと、背景を一致させた対照健康被験者のパラメータを比較した。 安全性：安全性の評価は、同意説明文書への署名時から最終試験評価まで実施した、有害事象、臨床検査値（血液学的検査、生化学的検査、凝固、及び尿検査など）、バイタルサイン、心電図、身体所見、及び注射部位反応のモニタリングに基づいて行った。

表 2.7.6.6 - 1　CL0600-017 試験：試験の概要

統計手法	薬物動態：記述統計量（算術平均、標準偏差［SD］、パーセント変動係数［%CV］、平均値の標準誤差［SEM］、観察回数［N］、最小値、最大値、及び中央値）を用いて、濃度及び薬物動態パラメータを要約した。また、C_{max}、AUC_{0-t}、及び AUC_{0-inf} については幾何平均値（Geo. Mean）を提示した。自然対数に変換した主要パラメータ（C_{max}、AUC_{0-inf}、及び AUC_{0-t}）を対象として共分散分析（ANCOVA）を実施した。肝機能群（肝機能正常、肝機能障害）を固定効果、肝機能群内のネストした被験者を変量効果、総体重を共変量として、SAS（PROC MIXED）の混合モデル手順を用いた。テデュグルチドの薬物動態に対する肝機能障害の影響を評価するため、幾何平均値、幾何平均比（障害/正常）（%GMR）、及び%GMR の 90%信頼区間を算出した。標準的な%GMR の 90%信頼区間の 80%～125%を、「影響なし（no effect）」の境界の評価に用いた。 安全性：試験期間中に使用した併用薬はいずれも WHO Drug Dictionary, Version 2007, Quarter 1 を用いてコード化した。発現した有害事象は国際医薬用語集（MedDRA®）Version 7.0 を用いてコード化した。試験治療下に発現した有害事象（被験者数及び件数）については、肝機能群ごと及び全体で、器官別大分類及び基本語別に要約した。 安全性データについては、時点ごとに肝機能群別及び全体で要約した。安全性に関する定量データについて、記述統計量（平均値、SD、最小値、中央値、最大値、及び N）を算出し、安全性に関する定性データを分類するため、頻度を集計した。 実際の成績及びそのベースラインからの変化量を示す要約表を臨床検査値及びバイタルサインについて提示した。基準範囲から外れた臨床検査値及び全ての再検査値を一覧表にした。さらに、臨床検査値、身体所見、及び心電図について、投与前から投与後へのシフト状況を示すシフト表を作成した。
治験責任医師及び実施医療機関	1 施設（米国）
試験期間	初回組入れ日：2007 年 7 月 26 日 最終完了日：2007 年 8 月 23 日

表 2.7.6.6 - 1 CL0600-017 試験：試験の概要

要約及び結論

薬物動態成績：

中等度肝機能障害患者及び背景を一致させた対照健康被験者にテデュグルチドを 20 mg を単回皮下投与したときのテデュグルチドの血漿中薬物動態パラメータ算術平均及び SD を以下の表に示す。

表：肝機能障害患者及び対照健康被験者におけるテデュグルチド 20 mg 単回皮下投与時の血漿中薬物動態パラメータの要約

Pharmacokinetic Parameters	**Impaired Mean ± SD (N)**	**Normal Mean ± SD (N)**	**% GMR (90% CI)***
C_{max} (ng/mL)	215 ± 95.6 (12)	244 ± 76.7 (12)	90.46 (75.93-107.77)
T_{max} (hr)	5.00 (2.00, 8.00) (12)	4.00 (2.50, 6.00) (12)	
$AUC_{(0-t)}$ (ng*hr/mL)	1676.8 ± 705.62 (12)	1993.6 ± 554.16 (12)	85.12 (70.58-102.67)
$AUC_{(0-inf)}$ (ng*hr/mL)	1948.9 ± 654.65 (11)	2177.0 ± 639.26 (12)	89.40 (75.08-106.45)
$T_{1/2}$ (hr)	3.05 ± 0.890 (11)	2.95 ± 0.813 (12)	
Kel (1/hr)	0.254 ± 0.112 (11)	0.252 ± 0.0706 (12)	
CL/F (hr/mL)	11.20 ± 3.311 (11)	10.10 ± 3.789 (12)	
Vd/F (mL)	50.35 ± 23.04 (11)	43.24 ± 19.94 (12)	
$ln(C_{max})$	5.290 ± 0.4126 (12)	5.445 ± 0.3609 (12)	
$ln(AUC_{(0-t)})$	7.356 ± 0.3762 (12)	7.558 ± 0.3078 (12)	
$ln(AUC_{(0-inf)})$	7.529 ± 0.3111 (11)	7.642 ± 0.3207 (12)	

T_{max} is presented as Median (Min, Max) as T_{max} is not a continuous variable but depends on discrete sampling times.
Impaired = the administration of 20 mg teduglutide in Hepatically Impaired Subjects (test)
Normal = the administration of 20 mg teduglutide in Healthy Matched Control Subjects (reference)
* = 90% CI and % Geometric Mean Ratios (% GMR) were calculated based on exponentiated LSMEANS from the ANCOVA on ln-transformed parameters.
%GMR = (impaired/normal) * 100
Weight was used as the covariate in the ANCOVA.
Source: M5.3.3.3 CL0600-017 CSR, Table 11.4.1.2.:1

%平均比に基づくと、テデュグルチドの C_{max} 及び AUC_{0-t} は、肝機能障害患者が、背景を一致させた対照健康被験者よりそれぞれ約 10%及び 15%少なかった。T_{max}（中央値）は肝機能障害患者が 1 時間長かった。しかしながら、濃度－時間プロットに基づくと、肝機能障害患者が、背景を一致させた対照健康被験者より約 3 時間早く最高濃度（平均値）に到達した。$t_{1/2}$、CL/F、及び Vd/F の平均値はいずれも肝機能障害患者が、背景を一致させた対照健康被験者よりわずかに大きかったが、各群のパラメータの平均値はそれぞれ 1 標準偏差内にあった。

安全性の結果：

本試験では死亡及びその他の重篤な有害事象の発現はなく、有害事象により中止した被験者もいなかった。投与を受けた被験者 5 例（21%）に有害事象が 5 件発現した。この 5 例のうち 4 例は肝機能障害患者、1 例は背景を一致させた対照健康被験者であった。5 件の有害事象はいずれも軽度であった。有害事象 4 件は、治験責任医師により治験薬と関連あり、1 件は関連なしと判断された。本

表 2.7.6.6 - 1　CL0600-017 試験：試験の概要

試験で最も発現頻度の高かった有害事象は腹痛であった。 有害事象、臨床検査、バイタルサイン、及び身体所見に関して投与に関連した傾向は特にみられなかった。 本試験の期間中、中等度又は重度の臨床的に意味のある注射部位反応はみられなかった。
結論： テデュグルチド 20 mg を単回皮下投与したときの C_{max} 及び AUC_{0-t} は、中等度肝機能障害患者が、背景を一致させた対照健康被験者よりわずかに低かった（10%～15%）。C_{max}、AUC_{0-inf}、及び AUC_{0-t} の%GMR に関する 90%信頼区間は影響なし（no effect）の境界 80%～125%に収まらなかったが、本試験の結果から、テデュグルチドを肝機能障害患者へ投与する際に、異常蓄積による問題が生じる可能性は低く、また、用量調節が必要となる可能性も低いことが示された。 男性及び女性の肝機能正常被験者及び中等度肝機能障害患者に対するテデュグルチド 20 mg の単回皮下投与は安全であり、総じて忍容性も良好であった。

7　CL0600-018 試験

（参考資料：5.3.3.3 項）

CL0600-018 試験の概要を表 2.7.6.7 - 1 に示す。

表 2.7.6.7 - 1　　CL0600-018 試験：試験の概要

試験識別番号	CL0600-018
試験の標題	腎機能が正常な健康被験者と比較したときの腎障害患者におけるテデュグルチド 10 mg の薬物動態
試験の相	1
目的	主要目的： テデュグルチド 10 mg を皮下投与したときのテデュグルチドの薬物動態に及ぼす腎機能障害の影響を評価する。 副次的目的： テデュグルチド 10 mg に関する安全性及び忍容性を身体所見、バイタルサイン、臨床検査、心電図、及び有害事象に基づいて評価する。 さらに、高齢（65 歳以上）の健康被験者にテデュグルチド 10 mg を皮下投与したときの薬物動態を非高齢健康被験者と比較すること。
方法	本試験は、ドイツの 1 施設で実施した、1 種類の投与を用いた非盲検試験である。本薬物動態試験は、各群が腎機能障害患者 6 例から構成される 3 群（第 1 群：中等度腎機能障害、第 3 群：重度腎機能障害、及び第 5 群：末期腎不全［透析を必要とする］）と、腎機能障害患者に性別、体格指数、及び年齢を一致させた腎機能が正常な健康被験者 6 例から構成される 3 並行群（第 2、4、6 群）とを比較するプロスペクティブ試験である。 試験の構成は、スクリーニング（Day–28～–2）、入院（Day–1）、入院投与（Day 1）、退院（Day 2）、及び追跡調査（Day7～9）とした。 被験者全例に対して Day 1 に治験責任医師又は治験スタッフが腹部皮下にテデュグルチド 10 mg を単回投与した。テデュグルチドの血漿中濃度を測定するため、投与前及び投与後 24 時間までの規定された時点において血液検体を採取した。安全性の評価は、有害事象モニタリング、臨床検査値、バイタルサイン、心電図、及び身体所見をもとに行った。有害事象は、同意説明文書への署名時から追跡調査時まで記録した。
診断及び主な選択基準	以下に示す腎機能障害患者 18 例、及び性別、BMI（±10%）、並びに年齢（年齢が 50 歳以下の場合は±5 歳、年齢が 50 歳を超える場合は±10%）を一致させた腎機能が正常な健康被験者 18 例を組み入れるように計画した。 • スクリーニング時（Day–28～–2）の年齢が 18 歳以上 75 歳以下の成人男性または女性 • BMI 18 kg/m^2 以上 34 kg/m^2 以下 性別及び年齢の分布を類似させるため、各群には、男性及び女性被験者をそれぞれ 2 例以上、及び高齢被験者を 2 例以上組み入れた。

	Renal Function	**Creatinine Clearance**
Group 1	Moderate renal impairment	30 – 50 mL/min
Group 2 (Control group to Group 1)	Normal renal function	≥80 mL/min
Group 3	Severe renal impairment	<30 mL/min

表 2.7.6.7 - 1　CL0600-018 試験：試験の概要

	Group 4 (Control group to Group 3) / Normal renal function / ≥80 mL/min Group 5 / End stage renal disease (requiring dialysis) / Group 6 (Control group to Group 5) / Normal renal function / ≥80 mL/min
予定症例数及び解析対象例数（合計及び投与群ごと）	計画時：36 例 組入れ：36 例（中等度腎機能障害患者：6 例、重度腎機能障害患者：6 例、末期腎不全：6 例、対応させた健康被験者：18 例）。 安全性解析対象集団：36 例（中等度腎機能障害患者：6 例、重度腎機能障害患者：6 例、末期腎不全：6 例、対応させた健康被験者：18 例）。 ITT 集団：36 例（中等度腎機能障害患者：6 例、重度腎機能障害患者：6 例、末期腎不全：6 例、対応させた健康被験者：18 例）。 Per-Protocol 解析対象集団：36 例（中等度腎機能障害患者：6 例、重度腎機能障害患者：6 例、末期腎不全：6 例、対応させた健康被験者：18 例）。
被験薬、用法・用量、バッチ番号	皮下注射用テデュグルチドは、凍結乾燥粉末として提供された。各バイアルはテデュグルチド 5 mg を含有し、注射用蒸留水 0.5 mL に溶解したとき、抽出可能な容量として 0.42 mL が得られた。溶解後の濃度は 10 mg/mL であった。用量 10 mg/1 mL を確保するには、一被験者当たり 3 バイアルを必要とした。溶解した治験薬は直ちに使用するものとした。 投与経路：皮下投与 用量：10 mg/1 mL バッチ番号：[redacted]
対照薬、用法・用量、バッチ番号	なし
投与期間	単回投与
評価基準	薬物動態 テデュグルチドの血漿中薬物動態パラメータとして AUC_{inf}、AUC_{last}、C_{max}、CL/F、V_d/F、T_{max}、及び $t_{1/2}$ を推定した。 主要解析は AUC_{inf} 及び C_{max} に基づいて行った。 安全性 有害事象、臨床検査値、バイタルサイン、心電図、及び身体所見
統計手法	薬物動態 薬物動態パラメータの計算は、WinNonlin Version 5.2 を用いて行った。血漿中濃度の要約は、記述統計量を用いて行った。 薬物動態パラメータについては、適切な場合、ノンコンパートメント法を用いて個々の血漿中濃度から計算し、記述統計量を用いて要約した。 腎機能障害患者の薬物動態パラメータについては、比率分析を用いて、対応した健康被験者のパラメータと比較した。解析前に薬物動態パラメータ（AUC_{inf}、AUC_{last}、及び C_{max}）を対数変換した。各腎機能グループの平均値、及びグループ間の差の 90%信頼区間を算出した。幾何平均値、比、及び比の 90%信頼区間を得るため、対数変換した結果をべき乗することで元のスケールに戻し、腎機能が正常な被験者を対照群として利用した。

表 2.7.6.7 - 1　　CL0600-018 試験：試験の概要

	さらに、テデュグルチド 10 mg を皮下投与し、高齢健康被験者と非高齢健康被験者におけるテデュグルチドの薬物動態を記述的に比較した。 安全性 安全性は記述的に評価した。
治験責任医師及び実施医療機関	1 施設（ドイツ）
試験期間	最初の被験者の組入れ：2009 年 10 月 15 日 最終被験者の完了：2010 年 1 月 29 日

要約及び結論

表：人口統計学及びベースライン特性

		Group					
		1	**2**	**3**	**4**	**5**	**6**
	n	6	6	6	6	6	6
Sex (n)	Male/Female	4/2	4/2	4/2	4/2	4/2	4/2
Elderly (n)	≥ 65 years	4	3	3	3	2	2
Age (years)	Mean (SD)	61.7 (13.74)	59.8 (12.25)	60.8 (13.08)	57.7 (11.86)	51.0 (17.12)	49.3 (16.49)
BMI (kg/m^2)	Mean (SD)	26.15 (4.227)	26.48 (4.352)	26.02 (3.956)	26.58 (4.282)	27.65 (3.906)	28.38 (3.401)
Body weight (kg)	Mean (SD)	76.57 (12.083)	84.82 (12.697)	76.72 (9.284)	78.90 (12.799)	81.02 (11.390)	87.30 (9.014)
Creatinine clearance (mL/min)	Mean (SD)	43.408 (4.59)	90.665 (6.4299)	27.315 (3.3701)	92.607 (8.7016)	17.720 (4.9958)	114.808 (29.9776)

Source: M5.3.3.3 CL0600-018 CSR, Table 11.2.2

薬物動態：

バイオアナリシスは GLP に準拠して行い、テデュグルチドの定量下限（LLOQ）は 1.0 µg/L であった。総合的に見て、腎機能障害患者と被験者背景を一致させた健康対照群との間で、テデュグルチドの血漿中濃度推移に大きな差は認められなかった。しかしながら、血漿中濃度（平均値）は腎機能障害患者が高かった。主要なテデュグルチド薬物動態パラメータの幾何平均値を以下に示す。

表：テデュグルチド 10 mg 皮下投与後の薬物動態パラメータの幾何平均値（68%の範囲）

	Group					
	1	**2**	**3**	**4**	**5**	**6**
AUC_{inf} (µg*h/l)	1333 (1064; 1668)	875.5 (795.2; 963.9)	1610 (1219; 2126)	934.1 (821.5; 1062)	2073 (1627; 2642)	800.4 (652.9; 981.3)
C_{max} (µg/l)	160 (112;229)	101 (85.5, 120)	192 (121; 306)	136 (103; 181)	213 (140; 324)	102 (67.3; 155)

Group 1: Moderate renal impairment, Group 2 (Control group healthy subjects to Group 1)
Group 3: Severe renal impairment; Group 4 (Control group healthy subjects to Group 3)
Group 5: End stage renal disease (requiring dialysis); Group 6 (Control group healthy subjects to Group 5)
Source:　M5.3.3.3 CL0600-018 CSR, Table 2-2

表 2.7.6.7 - 1　　CL0600-018 試験：試験の概要

表：テデュグルチド 10 mg 皮下投与後の AUC_{inf} 及び C_{max} の統計学的比較

Test	Reference		Ratio [%]	90% CI [%]
Group 1	Group 2	AUC_{inf}	152	127-182
		C_{max}	158	118-212
Group 3	Group 4	AUC_{inf}	172	137-216
		C_{max}	141	94-211
Group 5	Group 6	AUC_{inf}	259	205-327
		C_{max}	208	134-323

Source: M5.3.3.3 CL0600-018 CSR, Table 2-3

65 歳未満の健康被験者（本試験の非高齢者）と 65 歳以上の健康被験者（高齢者）の間にテデュグルチドの AUC_{inf} 又は C_{max} に差はみられなかった。

安全性の結果：

死亡、重篤な有害事象、及び重要な有害事象はいずれもみられず、有害事象による中止もなかった。大部分の被験者では、投与後に CRP の増加が認められた。治験責任医師は、CRP 増加が 24 mg/mL（施設基準値上限の 3 倍）を超えた場合、全て有害事象とした。いずれの投与群でも投与後に CRP（平均値）の増加がみられた。

投与後、被験者 36 例のうち 6 例に有害事象が発現した。内訳は、24 mg/ml を超える CRP 増加が 4 例、悪心が 1 例、頭痛、悪心、及び嘔吐を発現した被験者が 1 例であった。事象は軽度又は中等度であり、試験終了時には回復した。治験責任医師は、いずれの有害事象も治験薬との関連の可能性あり（likely）と判断した。

CRP の増加については、増加の程度、関連する臨床所見がないこと、及び持続期間が短く一過性であることから、医学的に懸念すべき点はないと判断された。また、その他の安全性臨床検査パラメータ、バイタルサイン、又は心電図検査に対する影響はみられなかった。

結論：

腎機能障害の重症化に伴い、テデュグルチドの主要な薬物動態パラメータは増加し、健康被験者と比較した場合、末期腎不全患者では、AUC_{inf} 及び C_{max} がそれぞれ最高 2.6 倍及び 2.1 倍まで上昇した。健康被験者においては、年齢はテデュグルチドの薬物動態に影響を及ぼさないものと考えられる。中等度又は重度の腎機能障害を有する、又は末期腎不全を有する被験者、及び被験者背景を一致させた健康被験者に対するテデュグルチド 10 mg の単回皮下投与は安全であり、忍容性も良好であった。

死亡、重篤な有害事象、及び重要な有害事象はいずれもみられず、有害事象による中止も認められなかった。

8　C09-001 試験

（評価資料：5.3.4.1 項）

C09-001 試験の概要を表 2.7.6.8 - 1 に示す。

表 2.7.6.8 - 1　　C09-001 試験：試験の概要

試験識別番号	C09-001
試験の標題	男性及び女性の健康被験者を対象とし、心室再分極及び心伝導に対するテデュグルチドの影響を評価する、無作為化、4 期、プラセボ及び陽性対照、単回投与、チェンジオーバー試験
試験の相	1
目的	主要目的： • 心室再分極（QT、QTc 間隔）にテデュグルチドの単回投与が及ぼす影響を検討すること。 副次目的： • 心室再分極、心拍数、及び心伝導に、陽性対照としたモキシフロキサシンの単回投与が及ぼす影響を検討すること。 • 心拍数及び心伝導（RR 間隔、PR 間隔、QRS 時間）に、テデュグルチドの単回投与が及ぼす影響を検討すること。 • テデュグルチドの血漿中薬物動態を検討すること。 • QT/QTc 間隔に対する濃度－効果の関係を探索的に検討すること。 • テデュグルチドの安全性及び忍容性。
方法	本試験は、単回投与、プラセボ及び陽性対照、4 期、チェンジオーバーデザインに従い、単一実施医療機関で実施した。 被験者に対し、それぞれの期において以下の投与を実施した。 • テデュグルチド 5 mg 皮下注射（投与 A）。 • テデュグルチド 20 mg 皮下注射（投与 B）。 • テデュグルチドに対応するプラセボ皮下注射（投与 C）。 • モキシフロキサシン 400 mg 経口（投与 D、陽性対照）。 プラセボ及びテデュグルチド（5 mg、20 mg）については、治験責任医師及び被験者は盲検下に置かれた。両者は、モキシフロキサシンの投与については非盲検とした。いずれの被験者に対しても、テデュグルチド 5 mg、20 mg、及びプラセボを腹部に単回皮下投与し、また、モキシフロキサシンを単回経口投与した。盲検確保のため、ダブルダミー法を用いた。 投与日には、被験者に対し、皮下注を 2 回（一方は 0.5 mL、もう一方は 2.0 mL）又はモキシフロキサシンの経口投与を行った。投与 A 及び B の場合、一方の注射はテデュグルチドを含有せず、もう一方はテデュグルチドを含有した。投与 C（プラセボ）の場合、両注射ともテデュグルチドを含有しなかった。 中央機関で心電図評価に関わる個人は投与及び心電図記録時点について盲検下に置かれた。 試験の構成を以下に示す。 • 治験薬初回投与の 21 日前から 2 日前までに外来で行うスクリーニング期。ここでは、試験参加の適格性を判定した。 • 投与相は 4 回の投与期から構成され、各投与期の長さは 3 日間（Day -1～Day

表 2.7.6.8 - 1　C09-001 試験：試験の概要

	2）とした。治験薬投与は Day 1 の朝に行い、投与 24 時間後まで規定の時間に安全性（心臓の安全性を含む）の評価と薬物動態の測定を実施した。投与期と投与期の間に 7 日以上（最長 4 週間）のウォッシュアウト期を設定した。各投与期の Day -1 から Day 2 まで、被験者を入院させた。 • 治験薬最終投与の 7～14 日後に外来で、試験終了時追跡調査を実施した。
診断及び主な選択基準	選択基準 以下の選択基準を満たす全ての被験者を本試験の投与相への参加に適格とした。 1. 本臨床試験の目的、方法、予想されるベネフィットと潜在的リスク、及び被験者が被る可能性のある不快感について口頭及び文書で説明を受け、試験及び試験関連手順の開始に先立って、試験への参加同意を書面で提出した者。 2. 民族は不問とし、年齢 18 歳以上 45 歳以下の、スクリーニング検査（病歴、身体所見、血圧、脈拍数、心電図評価、及び臨床検査結果を含む）に基づき健康と評価された健康な男性又は女性。 3. 体格指数（BMI）が 18 kg/m²以上 29 kg/m²以下、体重は女性の場合 50 kg を男性の場合 60 kg を超える者。 4. 女性のみ：妊娠可能な女性（閉経からの経過期間が 2 年未満、又は不妊手術を受けていない）は、スクリーニング前の少なくとも 30 日間、試験期間中、及び治験薬最終投与後少なくとも 30 日間、ホルモン避妊薬（経口避妊配合剤、既承認の植込み避妊薬又は注射用避妊薬、子宮内ホルモン避妊薬など）による確立した治療法と遮断避妊法を併用し、極めて有効な避妊法を実行する者。極めて有効な避妊法とは、単独又は併用により、継続的に正しく使用した場合、失敗する確率が低いもの（年間 1%未満）と規定した（改訂第 1 版）。 5. 非喫煙者、又は元喫煙者の場合は本臨床試験の開始前 6 ヵ月以上にわたって禁煙していた者。 除外基準 以下に示す除外基準のいずれかに合致した被験者は本試験の投与相への組入れに不適格とした。 1. 薬物又は食物に対し、臨床的に問題となるアレルギー若しくは特異体質である又はその既往歴がある。 2. テデュグルチド、モキシフロキサシン、又は治験薬の成分のいずれかに対するアレルギー反応の既往歴がある。 3. 過去 2 年以内に臨床的に問題となる肺、肝臓、腎臓、消化器系、血液系、内分泌系、代謝系、神経系、精神系、若しくはその他の疾患を有する又はその既往歴がある。 4. 心血管系疾患を有する又はその既往歴がある。 5. 心不全、低カリウム血症、QT 延長症候群の家族歴といった、トルサード ド ポアントの追加リスクファクターの既往歴がある。 6. 臨床的に問題となる心電図異常（Bazett 法による QTc が 450 ミリ秒を超える［男女とも］、PR≧210 ミリ秒；又は QRS≧120 ミリ秒）。 7. 安静時心拍数 50 拍/分未満、収縮期血圧 90 mmHg 未満、拡張期血圧 50 mmHg 未満の者。 8. 起立性調節障害、失神、又は黒くらみの傾向。 9. 過去 5 年以内に悪性腫瘍の既往歴がある。 10. 生化学検査、血液学的検査、又は他の臨床検査値に臨床的に問題となる異常がある。 11. 慢性又は臨床的に問題となる急性感染症。

表 2.7.6.8 - 1　C09-001 試験：試験の概要

	12. 急性又は慢性のヒト免疫不全ウイルス（HIV）感染症及び肝炎ウイルス感染症のウイルス検査結果が陽性。 13. 薬物スクリーニング陽性。 14. アルコール又は薬物乱用。 15. β-ヒト絨毛性ゴナドトロピン（β-hCG）妊娠検査陽性。 16. 妊婦又は授乳中の女性。 17. 治験薬初回投与前 30 日以内又は試験中に既知の酵素誘導剤又は酵素阻害剤（セント・ジョーンズ・ワート［Johanniskraut］、バルビツール系薬剤、フェノチアジン系薬剤、シメチジン、ケトコナゾールなど）を投与した者。 18. 治験薬初回投与前 2 週間以内（生物製剤は 6 ヵ月）、又は当該薬の消失半減期の 10 倍が経過する前、又は薬力学効果の持続期間のいずれか長い方の期間が経過する前に、併用が認められた薬剤以外の薬剤（生薬などの OTC 薬）を使用した、又は投与期に併用薬の使用が予想された（治験責任医師により臨床的関連がなく、試験目的に関連がないと判断された場合、1 剤の単回服用は容認されることあり）。 19. 治験薬初回投与前 14 日以内又は試験中に、酵素誘導又は酵素阻害作用のある食物及び飲料（ブロッコリー、芽キャベツ、グレープフルーツ、グレープフルーツジュース、スターフルーツなど）を摂取。 20. 治験薬初回投与の 48 時間前にカフェイン又はテオフィリン含有物を摂取。 21. 標準食の受け入れを妨げる菜食主義やその他の変わった食習慣。 22. 薬剤の吸収を阻害する可能性のある消化管手術（注：本基準は、虫垂切除術やヘルニア切開術のようなそれほど重大ではない腹部手術には適用しなかった）。 23. 試験期間中に生殖細胞、血液、臓器、又は骨髄を提供する予定があった。 24. 本試験組入れ前 1 ヵ月以内（単回投与の場合）及び 3 ヵ月以内（反復投与の場合）、又は当該薬の半減期の 10 倍のいずれか長い方の期間が経過する前に、別の治験薬又は器具の臨床試験に参加した。生物製剤の場合、最短期間は、本試験組入れ前 6 ヵ月以上、又は薬力学的効果の持続期間、又は当該薬の半減期の 10 倍のいずれか長い方の期間とした。 25. スクリーニング前 30 日以内に献血した。 26. 同意能力の欠如、又は自発的に同意する意思がない。 27. 試験の来院／手順が守れないと予想された。 28. 適切に協力する能力又は自発的な意思に欠けると予想された。 29. 弱い立場の被験者（拘留中の個人など）。 30. その他の理由。 31. 本試験に過去に参加した。 32. 実施医療機関の被雇用者、治験責任医師の血縁者又は配偶者。 33. キノロン療法により腱に障害が生じた。 34. 電解質平衡状態の失調（高カリウム血症、低カリウム血症、及びその他）。
予定症例数及び解析対象例数（合計及び投与群ごと）	• 計画時：最大 80 例 • スクリーニング：97 例 • 組入れ：72 例 • 早期中止：5 例 • 全試験期間を完了：67 例 • 安全性解析対象集団：72 例 • 薬物動態解析対象集団：72 例（最大の解析対象集団）

表 2.7.6.8 - 1　C09-001 試験：試験の概要

	• 薬力学解析対象集団：72 例（最大の解析対象集団）
被験薬、用法・用量、バッチ番号	皮下注用テデュグルチドは凍結乾燥粉末として提供された。 各バイアルはテデュグルチド 5 mg を含有し、これを 0.5 mL の無菌注射用水で溶解したとき、抽出可能な容量は 0.42 mL であった。溶解後の濃度は 10 mg/mL であった。5 mg の用量を得るためには 2 バイアルを必要とした。20 mg の用量を得るためには 5 バイアルを必要とした。 有効成分：テデュグルチド 添加成分：L-ヒスチジン、マンニトール、第一リン酸ナトリウム及び第二リン酸ナトリウム（リン酸二水素ナトリウム一水和物［欧州薬局方］、及びリン酸水素二ナトリウム七水和物［欧州薬局方］） 投与経路：皮下注 用量：5 mg（低用量：投与 A）及び 20 mg（高用量：投与 B） バッチ番号：[redacted]（製造バッチ） [redacted]（ラベリングバッチ）
対照薬、用法・用量、バッチ番号	皮下注用プラセボ（溶媒：投与 C）は凍結乾燥粉末として提供し、無菌注射用水を用いて溶解した。各バイアルはプラセボを含有し、これを 0.5 mL の無菌注射用水で溶解したとき、抽出可能な容量は 0.42 mL であった。 有効成分：なし 添加成分：L-ヒスチジン、マンニトール、第一リン酸ナトリウム及び第二リン酸ナトリウム（リン酸二水素ナトリウム一水和物［欧州薬局方］、及びリン酸水素ジナトリウム 7 水和物［欧州薬局方］） 投与経路：皮下注 用量：該当せず バッチ番号：[redacted]（製造バッチ） [redacted]（ラベリングバッチ）
投与期間	4 回の投与期それぞれにおいて単回投与を行った（Day 1）。
評価基準	<u>薬力学</u> QT/QTc 間隔の、ベースライン（投与前）との比較、及び時間を一致させたときのプラセボとの差（Δ Δ QTc）。 12 誘導心電図：心拍数並びに PQ（=PR）、QRS、及び QT/QTc の各間隔を評価した。 <u>薬物動態</u> 血漿中テデュグルチドの AUC_{inf}、AUC_{last}、C_{max}、T_{max} 及び $t_{1/2}$。 <u>安全性</u> 有害事象、人口統計学的変数及びベースライン変数、心電図（RR、QRS、PQ）、バイタルサイン、安全性臨床検査値、及び身体所見。
統計手法	**統計手法** 安全性解析対象集団は、治験薬（テデュグルチド、モキシフロキサシン、及びプラセボ）の投与を 1 回以上受け、投与後の安全性評価が 1 回以上利用できる全ての被験者を対象とした。 薬力学解析対象集団は、治験実施計画書からの重大な逸脱がなく、テデュグルチド、モキシフロキサシン、又はプラセボの投与期 1 回において、投与前と投与後の両時点にそれぞれ 1 回以上の評価可能な QT 測定値が得られた、安全性解析対象集団の被験者全てを対象とした。 薬力学解析対象集団を対象として QTc 関連心電図の解析を行った。薬物動態解析

表 2.7.6.8 - 1　C09-001 試験：試験の概要

	対象集団は、テデュグルチドの投与を 1 回以上受け、少なくとも一プロファイルに対し評価可能な薬物動態測定値が得られた被験者全てを対象とした。 統計仮説 本試験の検証的解析では、テデュグルチドに関する比較とモキシフロキサシンに関する比較の収集とを合せて、ファミリーワイズエラー率を 0.05 に強力に制御する階層的多重比較手順に使用した。比較（検証的）の順序について以下のステップ 1～4 で説明する。 1. 全ての時点における投与 A（低用量のテデュグルチド）とプラセボとの比較。両側 90%信頼区間（CI）の一つが 10 ミリ秒をまたいだ場合は検証的検定を中止することとした。 2. 投与後 3 時間におけるモキシフロキサシン／プラセボの比較。信頼区間が 0 ミリ秒をまたいだ場合は検証的検定を中止することとした。 3. 全ての時点における投与 B（高用量のテデュグルチド）とプラセボとの比較。信頼区間の一つが 10 ミリ秒をまたいだ場合は検証的検定を中止することとした。 4. 残るモキシフロキサシン／プラセボの比較は次に示す時点 i の順に従い実行した：i＝2、4、1、5、6、8、12、24 時間。信頼区間が最初に 0 ミリ秒をまたいだときに検証的検定を中止することとした。 統計解析 3 回測定した心電図の算術平均に基づいて統計解析を行った。心電図の変数は QT パラメータの QTcF（主要）及び QTcB とした。 以下に示すとおり、各投与について心電図の変数のベースライン（投与前）からの変化量を算出した。 ベースラインからの変化量＝投与後データ － ベースラインデータ（各投与期の投与前データ） 以下に示すとおり、各投与について時間を一致させた心電図変数のプラセボとの差を算出した。 プラセボとの差＝実薬のベースラインからの変化量 － プラセボのベースラインからの変化量 ベースラインからの変化量（ΔQTcF）のテデュグルチドの各用量とプラセボ間の差（主要解析）及びベースラインからの変化量のモキシフロキサシンとプラセボ間の差について、点推定値及び片側 95%信頼区間を算出した。被験者の変量効果及び固定効果（ベースライン、期、投与［レジメン］、時点、時点と期の交互作用、及び時点と投与の交互作用）を説明する反復測定データについて、分散分析（ANOVA）モデルを用いて統計解析を実施した。 さらに、ΔQTcB データについても分散分析を実施した。 薬物動態／薬力学の関係 実行可能な場合は線形回帰を用い、QTc 及び心拍数のベースラインからの変化量に対しテデュグルチドの C_{max} 及び AUC が及ぼす影響について検討した。
治験責任医師及び実施医療機関	1 施設（ドイツ）
試験期間	試験開始日：2009 年 11 月 17 日（最初の被験者組入れ） 試験完了日：2010 年 2 月 24 日（最終被験者のデータ収集）

8.1　被験者の内訳、人口統計学的特性、及びベースライン特性

全体で 72 例が投与相に組み入れられ、24 の投与シーケンスの一つに無作為化された。

- 女性被験者 32 例
- 男性被験者 40 例

5 例が早期に試験を中止した。

- 被験者番号：[redacted]（A-D-B-C シーケンス群）、被験者の要請／継続する意志がなくなったため 2009 年 11 月 29 日に中止。
- 被験者番号：[redacted]（A-D-B-C シーケンス群）、被験者の不遵守のためコンプライアンスプロトコールに従い 2010 年 2 月 05 日に中止。
- 被験者番号：[redacted]（C-A-B-D シーケンス群）、被験者の要請／継続する意志がなくなったため 2010 年 2 月 01 日に中止。
- 被験者番号：[redacted]（C-D-B-A シーケンス群）、有害事象により 2010 年 2 月 05 日に中止。
- 被験者番号：[redacted]（D-B-C-A シーケンス群）、被験者の要請／継続する意志がなくなったため 2010 年 2 月 04 日に中止。

被験者 67 例が試験全体を完了した（表 2.7.6.8 - 2）。

表 2.7.6.8 - 2　　C09-001 試験：被験者の内訳（安全性解析対象集団）

Status	All	Female	Male
Included(randomized)	**72**	**32**	**40**
in compliance with the protocol	72	32	40
with a protocol deviation at inclusion	0	0	0
Treated with IMP	**72**	**32**	**40**
Lost to follow-up	0	0	0
Withdrawn due to	**5**	**3**	**2**
adverse event	1	1	0
non-medical reason	3	2	1
non-compliance	1	0	1
Completed	**67**	**29**	**38**
Completed Period 1	72	32	40
Completed Period 2	71	31	40
Completed Period 3	69	30	39
Completed Period 4	67	29	38

Source: M5.3.4.1 C09-001 CSR Table 10.1.1

本試験は、健康な白人女性被験者 32 例（44.4%）及び健康な白人男性被験者 40 例（55.6%）、年齢 18～45 歳（平均値：35.4 歳）を対象として実施した。被験者の体重は標準的であり、BMI

の範囲は 19.0～28.9 kg/m^2（平均値：24.8 kg/m^2）であった。体重の範囲は 51.0～108.4 kg（平均値：73.9 kg）であった。人口統計学的データを表 2.7.6.8 - 3 に示す。

表 2.7.6.8 - 3　　C09-001 試験：人口統計学的データ（安全性解析対象集団）

		All	Female	Male
Age (years)	n	72	32	40
	Mean ± SD	35.4 ± 7.73	35.3 ± 6.64	35.5 ± 8.59
	Min - Max	18 - 45	24 - 45	18 - 45
Body height (cm)	n	72	32	40
	Mean ± SD	172.0 ± 9.57	163.7 ± 5.68	178.7 ± 6.27
	Min - Max	152 - 194	152 - 174	168 - 194
Body weight (kg)	n	72	32	40
	Mean ± SD	73.9 ± 12.82	63.3 ± 7.00	82.4 ± 9.69
	Min - Max	51.0 - 108.4	51.0 - 76.5	62.5 - 108.4
BMI (kg/m^2)	n	72	32	40
	Mean ± SD	24.8 ± 2.54	23.6 ± 2.30	25.8 ± 2.32
	Min - Max	19.0 - 28.9	19.0 - 28.9	21.4 - 28.9

Source: M5.3.4.1 C09-001 CSR Table 11.2.1

8.2　薬物動態及び薬力学の評価

8.2.1　　薬物動態の結果

8.2.1.1　　薬物動態パラメータ

液体クロマトグラフィー・質量分析計を用いた、定量下限が 1 µg/L のバリデーションされた生物分析法を用い、血漿検体を分析した。テデュグルチド 5 mg 及び 20 mg の投与を受けた大部分の症例から 24 時間後までの完全な薬物動態プロファイルが得られた。主要な薬物動態パラメータ（AUC 及び C_{max}）を表 2.7.6.8 - 4 に示す。用量比例性は明らかであり、生物学的同等性手法を用いてその確認を行った。

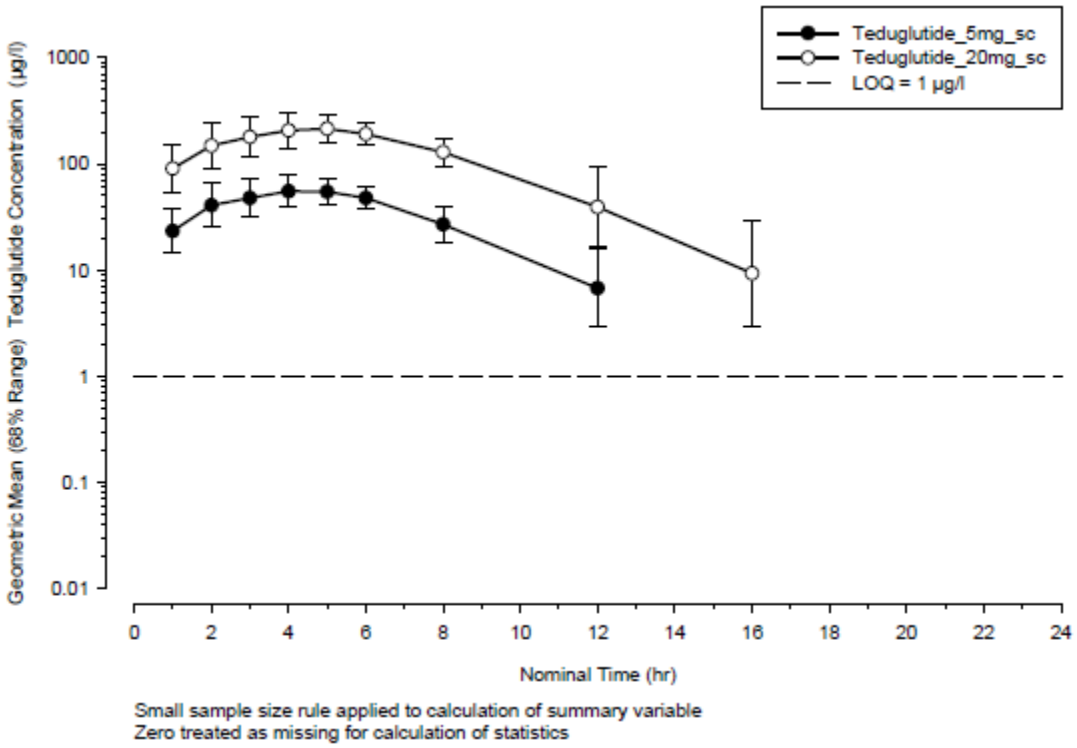
表 2.7.6.8 - 4　C09-001 試験：テデュグルチド 5 mg 及び 20 mg 皮下投与後の主要な薬物動態パラメータ幾何平均値（68%範囲）

	Teduglutide 5 mg sc	Teduglutide 20 mg sc
AUC_{inf} (µg•h/L)	438.9 (359.6; 535.7)	1885 (1589; 2237)
C_{max} (µg/L)	60.8 (44.1; 84.0)	231 (170; 314)

Source: M5.3.4.1 C09-001 CSR Table 2.3

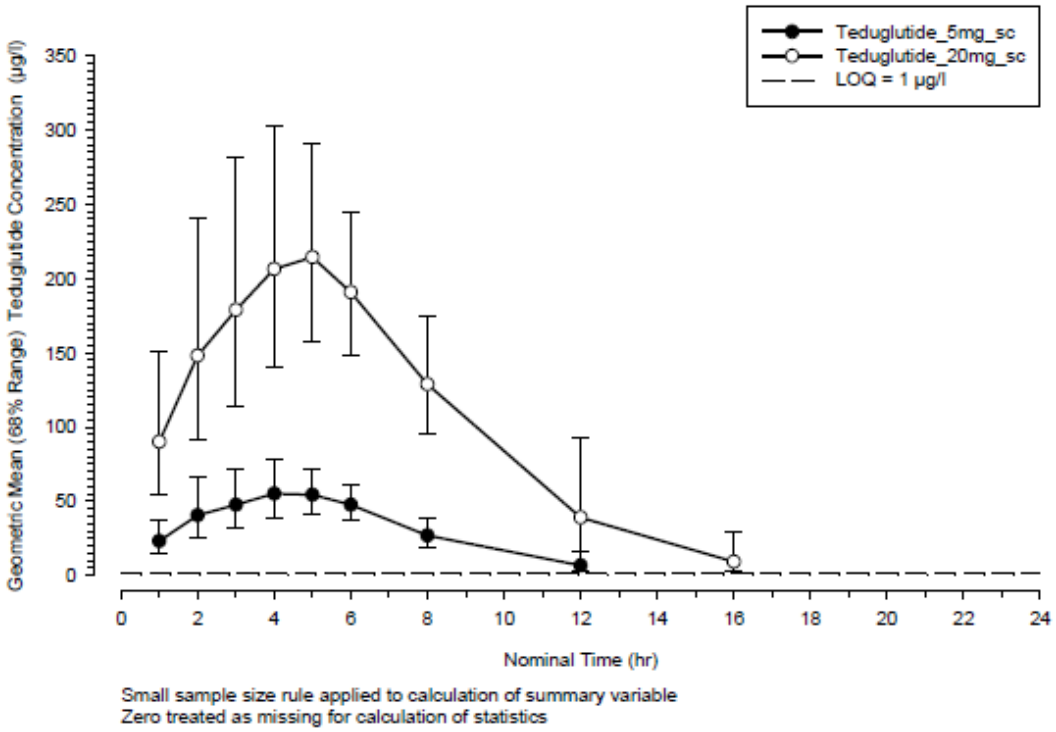
テデュグルチド濃度（平均値）を図 2.7.6.8 - 1（対数目盛）及び図 2.7.6.8 - 2（均等目盛）に示す。

図 2.7.6.8 - 1　C09-001 試験 : テデュグルチドの血漿中濃度（幾何平均値、68%範囲、対数目盛）



Source: M5.3.4.1 C09-001 CSR Figure 11.4-1

図 2.7.6.8 - 2　C09-001 試験 : テデュグルチドの血漿中濃度（幾何平均値、68%範囲、均等目盛）



Source: M5.3.4.1 C09-001 CSR Figure 11.4-2

テデュグルチドの薬物動態パラメータについては表 2.7.6.8 - 5 に示す。テデュグルチド 5 mg 及び 20 mg 投与群における T_{max} の中央値はそれぞれ 4.16 及び 5.07 時間であった。さらに、$t_{1/2}$ の中央値は約 1.8 時間であった。

表 2.7.6.8 - 5　C09-001 試験：テデュグルチド 5 mg 及び 20 mg 皮下投与後の主要な薬物動態パラメータ幾何平均値（68%範囲）

	AUC_{Inf}	**C_{max}**	**AUC_t**	**T_{max}**	**$t_{1/2}$**
	(µg･h/l)	**(µg/l)**	**(µg･h/l)**	**(h)**	**(h)**
	Treatment A (5 mg Teduglutide)				
N	67	70	70	70	67
Mean(SEM)	447.6 (11.01)	64.2 (2.80)	428 (11.0)	4.50 (0.12)	1.98 (0.10)
Median	448.4	61.0	432	4.16	1.81
Min/Max	268.2/742.1	30.3/189	261/738	2.07/8.07	0.92/4.85
Geom. Mean (68% range)	438.9 (359.6; 535.7)	60.8 (44.1; 84.0)	419 (339; 517)	-	1.86 (1.30; 2.65)
	Treatment B (20 mg Teduglutide)				
N	70	70	70	70	70
Mean(SEM)	1913 (39.75)	242 (8.84)	1860 (41.8)	4.81 (0.14)	2.16 (0.12)
Median	1884	227	1820	5.07	1.87
Min/Max	1361/2844	114/398	1300/2810	2.08/8.20	1.11/5.60
Geom. Mean (68% range)	1885 (1589; 2237)	231 (170; 314)	1830 (1520; 2200)	-	1.99 (1.35; 2.93)

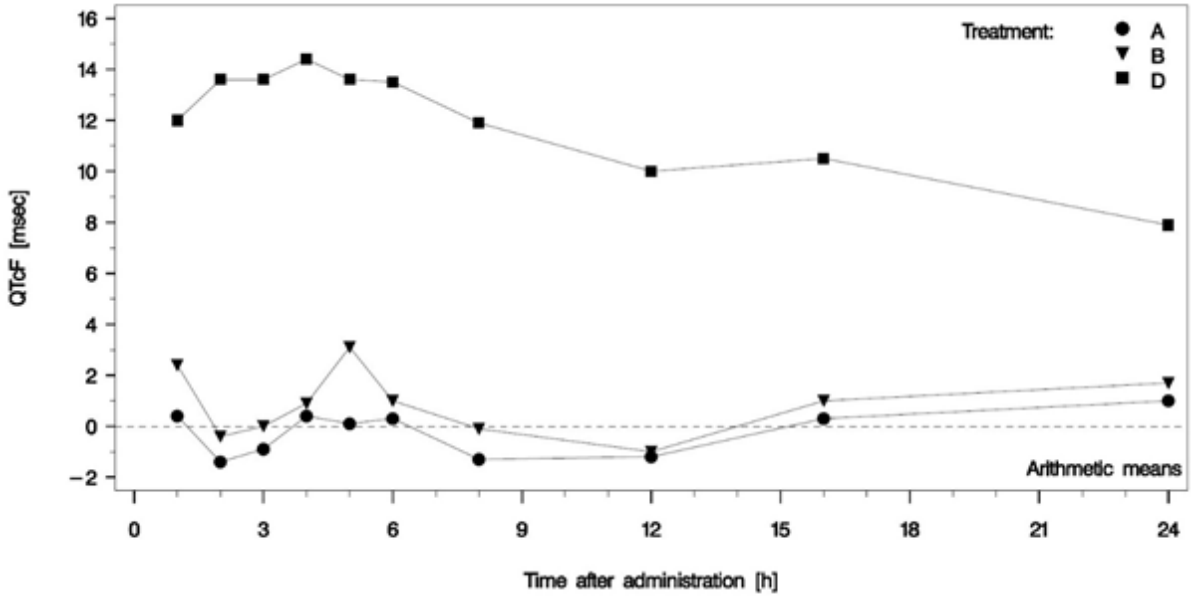
N=Number of observations; SEM: Standard Error of the Mean
Source: M5.3.4.1 C09-001 CSR Table 11.4.1

8.2.2　薬力学の結果

8.2.2.1　QTcF 間隔の推移

テデュグルチド 5 mg 及び 20 mg 投与後の、時間を一致させたときのプラセボとの差は、5 mg が−1.38 ミリ秒（投与 2 時間後）～0.98 ミリ秒（投与 24 時間後）、20 mg が−0.96 ミリ秒（投与 12 時間後）～3.12 ミリ秒（投与 5 時間後）であった。モキシフロキサシン 400 mg 投与後の、時間を一致させたときのプラセボとの差の算術平均値（Δ Δ QTcF）は、7.91 ミリ秒（投与 24 時間後）～14.37 ミリ秒（投与 4 時間後）であった（図 2.7.6.8 - 3）。

図 2.7.6.8 - 3　C09-001 試験 : ΔΔQTcF 間隔 ― ベースラインからの変化量に関する時間を一致させたときのプラセボとの差



A: Teduglutide 5 mg in 0.5 mL, B: Teduglutide 20 mg in 2.0 mL, D: Moxifloxacin 400 mg
Source: M5.3.4.1 C09-001 CSR Figure 11.5-3

QTcF 間隔を解析した結果、Thorough QT（TQT）試験はテデュグルチドの用量 5 mg 及び 20 mg について陰性であった。95%片側信頼区間上限の最大値は、用量 5 mg が 3.0 ミリ秒、用量 20 mg が 4.5 ミリ秒であり、これらは薬事規制上の閾値（10 ミリ秒）を大きく下回る値であった。したがって、心臓の脱分極及び再分極に対する治験薬の影響は極めて小さいものと思われる（表 2.7.6.8 - 6）。

陽性対照モキシフロキサシン 400 mg とプラセボを比較した結果は試験の感度を示しており、信頼区間の下限はいずれも 5 ミリ秒を上回った。実際に、3 時間目の信頼下限（本試験におけるファミリーワイズエラーの制御に必要とされた）は 11.3 ミリ秒であった。

表 2.7.6.8 - 6　C09-001 試験：QTcF（ミリ秒）のベースラインからの変化量に関する、混合モデル法に基づいた、時間を一致させたときのプラセボとの投与間差の点推定値

Time [h] after administration	Low dose teduglutide (5mg)		High dose teduglutide (20mg)		Moxifloxacin (400mg)	
	Estimate	95%UCL	Estimate	95%UCL	Estimate	95%LCL
1	0.7	2.4	2.0	3.7	11.2	9.5
2	-1.2	0.5	-0.6	1.1	13.0	11.3
3	-0.8	0.9	-0.2	1.5	13.0	11.3
4	0.4	2.1	0.7	2.4	13.8	12.1
5	0.3	2.0	2.8	4.5	12.9	11.2
6	0.4	2.1	0.6	2.2	13.1	11.4
8	-1.0	0.7	-0.5	1.2	11.3	9.7
12	-1.3	0.4	-1.1	0.6	9.5	7.8
16	0.5	2.2	0.8	2.5	9.8	8.1
24	1.3	3.0	1.5	3.2	7.3	5.6

UCL:upper confidence limit (one-sided)
LCL:lower confidence limit
Source: M5.3.4.1 C09-001, CSR Table 11.5.3

8.2.2.2　ECG

8.2.2.2.1　形態の変化

T/U 波の形態に変化はみられなかった。T 波はいずれも正常であり、何らかの所見は他にみられなかった。U 波は認められなかった。

8.2.2.2.2　心電図の解釈的所見

全体では、治験薬投与下に発現した異常所見が、72 例中 39 例に 246 件みられた。

最も頻度の高かった所見は、異常洞調律（32 例に 84 件の所見［22 例に 59 件発現した洞性不整脈を含む］）及び異常伝導（7 例に 39 件の所見）であった。大部分の所見はプラセボ投与下で観察され（104 件の所見）、テデュグルチド（5 mg 及び 20 mg）とモキシフロキサシン投与下でみられた所見はそれぞれ 48、56、及び 38 件であり、頻度は同程度であった。

8.2.2.2.3　その他の心電図パラメータ：心拍数、PQ、及び QRS

テデュグルチドの両用量（5、20 mg）投与下で、心拍数に増加がみられた（図 2.7.6.8 - 4）。しかしながら、個々の値は大部分が正常範囲内であった（45～99 拍/分）。投与前の心拍数はいずれの被験者でも 99 拍/分以下であった。

テデュグルチド投与から約 8 時間後に心拍数平均値の一過性の増加が観察されたが、臨床的な意義はないと判断された。

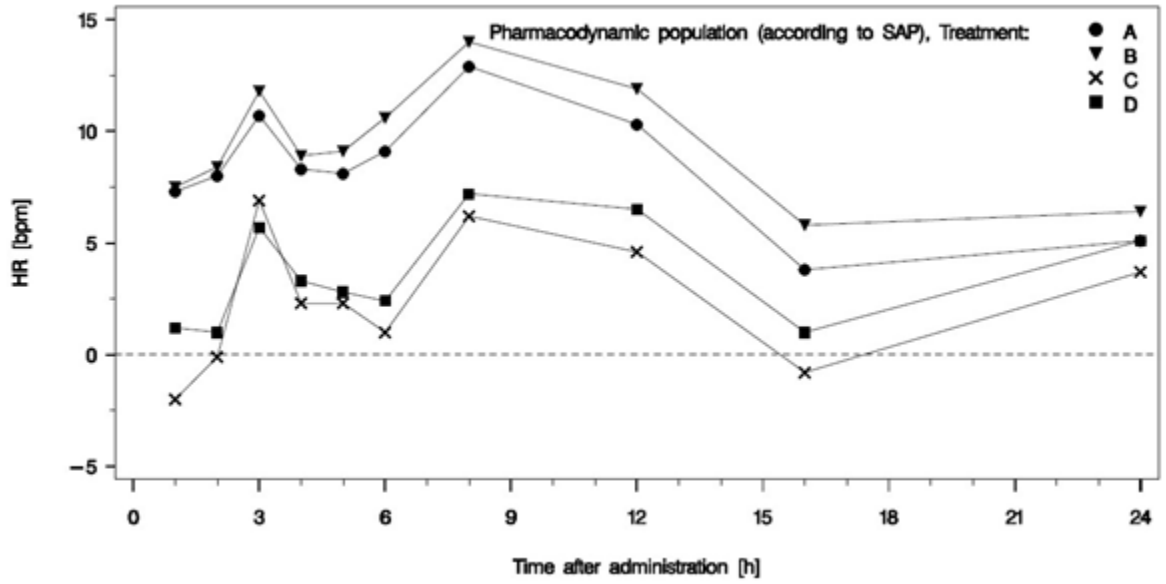
QT 値は心拍数に応じて変わるため、心拍数の変化が QT 間隔の長さに直接的に影響する。

QT の最大値は、485.0 ミリ秒（テデュグルチド 5 mg）、485.7 ミリ秒（テデュグルチド 20 mg）、478.3 ミリ秒（プラセボ）、及び 487.3 ミリ秒（モキシフロキサシン 400 mg）であった。

このように、投与群間で QT の最大値に大きな差はみられなかった。懸念事項は特にみられなかった。

投与前からの変化量の最大値はプラセボ及びモキシフロキサシンの投与中に観察され、その値はそれぞれ 42.6 ミリ秒及び 42.4 ミリ秒であった。4 種類の投与間でその他の心電図間隔（PQ 及び QRS）に意義のある差はみられなかった。正常範囲外の値が偶発的に観察されたが、投与に関連したパターンは認められなかった。

図 2.7.6.8 - 4　C09-001 試験：心拍数の推移、ベースラインからの変化量の算術平均値



A: Teduglutide 5 mg in 0.5 mL, B: Teduglutide 20 mg in 2.0 mL, C: Placebo, D: Moxifloxacin 400 mg
Source: M5.3.4.1 C09-001 CSR Figure 11.5-4

8.3　安全性の結果

8.3.1　　曝露状況

組み入れられた 72 例のうち、4 回の投与期を完了し、テデュグルチドの総用量 25 mg 及びモキシフロキサシン 400 mg の投与を受けた被験者は 67 例であった。

8.3.2　　有害事象

本項では特に断りのない限り、有害事象とは試験治療下に発現した有害事象（TEAE）であり、重篤な有害事象とは試験治療下の重篤な有害事象を示す。

8.3.2.1　　有害事象の概要

総合的にみて、健康被験者に対するテデュグルチド 5 mg 及び 20 mg の単回皮下投与は安全であり、その忍容性は良好であった。

試験中に死亡又はその他の重篤な有害事象の発現はなかった。

当該被験者の試験中止に至った有害事象の発現件数は 1 件であった（中等度の鼻咽頭炎、治験薬と関連の可能性は低いと判断された）。

投与後、72 例のうち 40 例に計 99 件の有害事象が発現し、その大部分（43 件）は器官別大分類「胃腸障害」に属する事象であった。

有害事象はいずれも軽度又は中等度であり、重度の有害事象はみられなかった。全ての有害事象は症状を残すことなく試験終了時には回復した。有害事象 99 件のうち 78 件（79%）は副作用（治験責任医師により治験薬と関連の可能性が高いと判断された事象）であった。

用量との関連性を明確に否定することはできなかった。

胃腸障害（主に腹痛）はテデュグルチド（5 mg 及び 20 mg）の投与後に発現し、発現例数は各 14 例で、それぞれの用量での発現頻度は同様であった。

有害事象とされた頭痛は、テデュグルチド、モキシフロキサシン、及びプラセボのいずれの投与群でも同程度の発現頻度であった。

試験期間中にみられた治験薬投与下に発現した有害事象の特性を表 2.7.6.8 - 7 に示す。

表 2.7.6.8 - 7　C09-001 試験：試験期間中にみられた治験薬投与下に発現した有害事象の特性

		5 mg Teduglutide (N=70)			**20mg Teduglutide (N=70)**			**Placebo (N=69)**			**400mg Moxifloxacin (N=70)**			**Overall (N=72)**		
		n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Causality*	Likely relation	15	21.4	30	22	31.4	31	9	13.0	9	7	10.0	8	32	44.4	78
	No relation	4	5.7	4				3	4.3	3	3	4.3	3	10	13.9	10
	Unlikely relation	3	4.3	3	4	5.7	4	1	1.4	1	3	4.3	3	9	12.5	11
Serious	No	21	30.0	37	26	37.1	35	12	17.4	13	13	18.6	14	40	55.6	99
Intensity	Mild	19	27.1	30	24	34.3	32	8	11.6	8	11	15.7	12	37	51.4	82
	Moderate	4	5.7	7	3	4.3	3	5	7.2	5	2	2.9	2	9	12.5	17
No. of AEs		21	30.0	37	26	37.1	35	12	17.4	13	13	18.6	14	40	55.6	99

N=number of subjects in each treatment group, n=number of subjects with event, E=number of events
* Causality assessment by investigator
Source: M5.3.4.1 C09-001 CSR Table 12.2.2

8.3.2.2　　有害事象の分析

スクリーニング相では有害事象の発現はなかった。試験期間中にみられた有害事象を表 2.7.6.8 - 8 に示す。投与後、72 例のうち 40 例に 99 件の有害事象が発現した。投与後 3 時間以内に発現した有害事象は 29 件、投与 3 時間以後 24 時間以内に発現した有害事象は 50 件、投与から 24 時間超経過後に発現した有害事象は 20 件であった。器官別大分類で有害事象の発現頻度が最も高かったのは胃腸障害（43 件）であり、これに神経系障害（32 件）及び臨床検査（7 件）が続いた。

胃腸障害は主としてテデュグルチド（5 mg 及び 20 mg）の投与後に発現し、それぞれの用量での発現頻度は同様であった。有害事象とされた頭痛は、いずれの投与群でも同程度の発現頻度であった。

いずれの有害事象も軽度又は中等度であり、重度の有害事象の発現はなかった。全ての有害事象は試験終了時に症状を残すことなく回復した。テデュグルチド 5 mg の投与を受けた被験者 21 例に有害事象が 37 件発現し、テデュグルチド 20 mg の投与を受けた被験者 26 例に有害事象が 35 件発現した。有害事象の 79%（78/99 件）は副作用（治験責任医師により治験薬と関連の可能性が高いと判断された事象）であった。テデュグルチド 5 mg の投与を受けた被験者 15 例に副作用が 30 件発現し、テデュグルチド 20 mg の投与を受けた被験者 22 例に副作用が 31 件発現した（表 2.7.6.8 - 9）。以上より、用量との関連性を明確に否定することはできなかった。

被験者 4 例で有害事象として CRP 増加がみられた（テデュグルチド：3 例、関連あり、プラセボ：1 例、関連なし）。治験責任医師は、閾値 24 mg/L を超える CRP 増加の全てを有害事象として報告した。

有害事象による中止が 1 例みられた（第 3 期の Day 5 に中等度の鼻咽頭炎が発現、治験薬と関連の可能性は低い）。有害事象 17 件に併用薬による治療が行われた。

表 2.7.6.8 - 8　C09-001 試験：有害事象の発現頻度

System Organ Class Preferred Term		5 mg Teduglutide (N=70)			20 mg Teduglutide (N=70)			Placebo (N=69)			400 mg Moxifloxacin (N=70)		
		n	%	E	n	%	E	n	%	E	n	%	E
Gastrointestinal Disorders	**胃腸障害**	**14**	**20.0**	**21**	**14**	**20.0**	**19**	**2**	**2.9**	**2**	**1**	**1.4**	**1**
Abdominal pain upper	上腹部痛	7	10.0	7	8	11.4	9	0	0	0	0	0	0
Nausea	悪心	7	10.0	7	4	5.7	4	0	0	0	0	0	0
Flatulence	鼓腸	2	2.9	2	1	1.4	1	0	0	0	0	0	0
Vomiting	嘔吐	3	4.3	3	0	0	0	0	0	0	0	0	0
Abdominal discomfort	腹部不快感	1	1.4	1	1	1.4	1	0	0	0	0	0	0
Diarrhoea	下痢	1	1.4	1	1	1.4	1	0	0	0	0	0	0
Abdominal pain lower	下腹部痛	0	0	0	1	1.4	1	0	0	0	0	0	0
Dry Mouth	口内乾燥	0	0	0	0	0	0	0	0	0	1	1.4	1
Dyspepsia	消化不良	0	0	0	1	1.4	1	0	0	0	0	0	0
Gastric disorder	胃障害	0	0	0	0	0	0	1	1.4	1	0	0	0
Gastrointestinal disorder	胃腸障害	0	0	0	1	1.4	1	0	0	0	0	0	0
Gastrointestinal pain	消化器痛	0	0	0	0	0	0	1	1.4	1	0	0	0
Nervous System Disorders	**神経系障害**	**8**	**11.4**	**9**	**8**	**11.4**	**9**	**8**	**11.6**	**8**	**6**	**8.6**	**6**
Headache	頭痛	7	10.0	7	7	10.0	7	8	11.6	8	5	7.1	5
Dizziness	浮動性めまい	2	2.9	2	1	1.4	1	0	0	0	1	1.4	1
Hyperaesthesia	知覚過敏	0	0	0	1	1.4	1	0	0	0	0	0	0
Investigations	**臨床検査**	**4**	**5.7**	**4**	**2**	**2.9**	**2**	**1**	**1.4**	**1**	**0**	**0**	**0**
C-reactive protein increased	Ｃ－反応性蛋白増加	2	2.9	2	2	2.9	2	1	1.4	1	0	0	0
Blood creatinine phosphaokinase increased	血中クレアチンホスホキナーゼ増加	1	1.4	1	0	0	0	0	0	0	0	0	0
Body temperature increased	体温上昇	1	1.4	1	0	0	0	0	0	0	0	0	0

表 2.7.6.8 - 8　C09-001 試験：有害事象の発現頻度

System Organ Class Preferred Term		5 mg Teduglutide (N=70)			20 mg Teduglutide (N=70)			Placebo (N=69)			400 mg Moxifloxacin (N=70)		
		n	%	E	n	%	E	n	%	E	n	%	E
General Disorders and Administration Site Conditions	**全身障害および投与局所様態**	**1**	**1.4**	**1**	**3**	**4.3**	**3**	**0**	**0**	**0**	**2**	**2.9**	**2**
Fatigue	疲労	1	1.4	1	2	2.9	2	0	0	0	2	2.9	2
Injection site erythema	注射部位紅斑	0	0	0	1	1.4	1	0	0	0	0	0	0
Infections and Infestations	**感染症および寄生虫症**	**0**	**0**	**0**	**1**	**1.4**	**1**	**1**	**1.4**	**1**	**1**	**1.4**	**1**
Nasopharyngitis	鼻咽頭炎	0	0	0	1	1.4	1	1	1.4	1	1	1.4	1
Vascular Disorders	**血管障害**	**1**	**1.4**	**1**	**1**	**1.4**	**1**	**1**	**1.4**	**1**	**0**	**0**	**0**
Hypotension	低血圧	1	1.4	1	1	1.4	1	1	1.4	1	0	0	0
Renal and Urinary Disorders	**腎および尿路障害**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**2.9**	**2**
Pollakiuria	頻尿	0	0	0	0	0	0	0	0	0	2	2.9	2
Blood and Lymphatic Disorders	**血液およびリンパ系障害**	**1**	**1.4**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Eosinophilia	好酸球増加症	1	1.4	1	0	0	0	0	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	**筋骨格系および結合組織障害**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1.4**	**1**
Musculoskeletal pain	筋骨格痛	0	0	0	0	0	0	0	0	0	1	1.4	1
Reproductive System and Breast Disorders	**生殖系および乳房障害**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1.4**	**1**
Dysmenorrhoea	月経困難症	0	0	0	0	0	0	0	0	0	1	1.4	1

N=Number of subjects in each treatment group; n=number of subjects with event; E=number of events
Source M5.3.4.1 C09-001 CSR Table 12.2.1

表 2.7.6.8 - 9 C09-001 試験：重症度別治験薬と関連のある有害事象の発現頻度

Parameter		5 mg Teduglutide (N=70)						20 mg Teduglutide (N=70)						Placebo (N=69)						400 mg Moxifloxacin (N=70)					
		Mild			Moderate			Mild			Moderate			Mild			Moderate			Mild			Moderate		
		E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%
Gastrointestinal Disorders	**胃腸障害**	**17**	**11**	**15.7**	**3**	**2**	**2.9**	**17**	**13**	**18.6**	**1**	**1**	**1.4**	**1**	**1**	**1.4**	**0**	**0**	**0**	**1**	**1**	**1.4**	**0**	**0**	**0**
Nausea	悪心	6	6	8.6	1	1	1.4	2	2	2.9	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain upper	上腹部痛	4	4	5.7	2	2	2.9	9	8	11.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vomiting	嘔吐	3	3	4.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Flatulence	鼓腸	2	2	2.9	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Abdominal discomfort	腹部不快感	1	1	1.4	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhoea	下痢	1	1	1.4	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain lower	下腹部痛	0	0	0	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dyspepsia	消化不良	0	0	0	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorder	胃腸障害	0	0	0	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal pain	消化器痛	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0
Dry Mouth	口内乾燥	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1.4	0	0	0
Nervous System Disorders	**神経系障害**	**4**	**4**	**5.7**	**3**	**3**	**4.3**	**7**	**6**	**8.6**	**1**	**1**	**1.4**	**4**	**4**	**5.8**	**4**	**4**	**5.8**	**3**	**3**	**4.3**	**2**	**2**	**2.9**
Headache	頭痛	2	2	2.9	3	3	4.3	6	6	8.6	1	1	1.4	4	4	5.8	4	4	5.8	2	2	2.9	2	2	2.9
Dizziness	浮動性めまい	2	2	2.9	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	1	1	1.4	0	0	0
Investigations	**臨床検査**	**2**	**2**	**2.9**	**0**	**0**	**0**	**2**	**2**	**2.9**	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0
Body temperature increased	体温上昇	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C-reactive protein increased	C-反応性蛋白増加	1	1	1.4	0	0	0	2	2	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
General Disorders and Administration Site Conditions	**全身障害および投与局所様態**	**1**	**1**	**1.4**	**0**	**0**	**0**	**3**	**3**	**4.3**	**0**	**0**	**0**	0	0	0	0	0	0	**2**	**2**	**2.9**	**0**	**0**	**0**
Fatigue	疲労	1	1	1.4	0	0	0	2	2	2.9	0	0	0	0	0	0	0	0	0	2	2	2.9	0	0	0
Injection site erythema	注射部位紅斑	0	0	0	0	0	0	1	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

8.3.3 死亡、その他の重篤な有害事象及び他の重要な有害事象

試験期間中、死亡やその他の重篤な有害事象の発現はなかった。被験者 1 例が、テデュグルチド 20 mg 皮下投与後に有害事象（鼻咽頭炎、中等度）がみられ、試験を中止した。治験薬との因果関係はおそらく関連なしと判断された。

8.3.4 バイタルサイン、身体所見、及び安全性に関連するその他の所見

バイタルサイン、身体所見、体重、体温、及び心電図パラメータに意義のある又は顕著な変化はみられなかった。

CRP 増加がテデュグルチド 5 mg 及び 20 mg 皮下投与後にみられたが、上昇の程度、関連する臨床所見の欠如、及び持続期間が短く一過性であったことから、臨床的に懸念される点はなかった。

モキシフロキサシン又はプラセボの投与を受けた被験者ではCRP値について同様のパターンはみられなかった。皮下注用に溶解した治験薬の成分又は注射手順そのものと関連の可能性が高いと思われる。本試験で得られたデータからは、これら CRP 増加の原因について結論を下すことはできない。

本試験では、テデュグルチドの投与後に、安全性臨床検査パラメータにこれ以外の意義のある変化はみられなかった。

8.4 結論：

- QTcF 間隔を解析した結果、テデュグルチドの用量 5 mg 及び 20 mg ともに TQT 試験は陰性と判断された。心室再分極（QTcF 間隔）に対するテデュグルチドの影響はプラセボと同程度であった。95%片側信頼区間の上限は、用量 5 mg が 3.0 ミリ秒、用量 20 mg が 4.5 ミリ秒であり、両用量ともに時間を一致させた平均効果の最大値は 10 ミリ秒を下回った。
- テデュグルチド（5 mg 及び 20 mg）及びプラセボのそれぞれを投与したときの QTcF 間隔（算術平均）の曲線は同様の推移を示し、ほぼ重ね合わせることができた。モキシフロキサシンも類似の QTcF－時間曲線を示したが、予想されるとおり QTcF の高値方向に平行移動が認められた。
- モキシフロキサシンは、陽性対照として予想された QTcF 延長を示した（検出感度があった）。
- 薬物動態に関しては、健康被験者を対象としてテデュグルチド 5 mg 皮下投与と 20 mg 皮下投与間に明瞭な用量比例性が示され、吸収の速度及び程度（C_{max} 及び AUC）は、用量に比例して上昇した。さらに、生物学的同等性手法を追加実施し、薬物動態の用量比例性が統計学的に確認された。
- 総合的にみて、健康被験者に対するテデュグルチド 5 mg 及び 20 mg 単回皮下投与は安全であり、その忍容性は良好であった。

- 有害事象の発現件数は、テデュグルチド 20 mg の投与を受けた被験者の方がテデュグルチド 5 mg の投与を受けた被験者より多かった。そのため、用量との関連性を明確に否定することはできなかった。なお、テデュグルチドの両用量群における有害事象の発現件数は同程度であった。
- テデュグルチド投与下で最も頻度の高かった有害事象は胃腸障害であった。
- 試験期間中、死亡やその他の重篤な有害事象の発現はなかった。
- 有害事象はいずれも軽度又は中等度であり、重度の有害事象はみられなかった。全ての有害事象は症状を残すことなく試験終了時には回復した。
- 有害事象（鼻咽頭炎）により試験を中止した被験者は 1 例で、治験責任医師により治験薬との関連性は低いと判断された。

9　C10-003 試験

（参考資料：5.3.4.1 項）

C10-003 試験の概要を表 2.7.6.9 - 1 に示す。

表 2.7.6.9 - 1　　C10-003 試験：試験の概要

試験識別番号	C10-003
試験の標題	健康被験者を対象とし、胃内容排出に対するテデュグルチド（ALX-0600）の影響を評価する、無作為化、二重盲検、プラセボ対照、反復投与、並行群間試験
試験の相	1
目的	主要目的は、健康被験者を対象とし、プラセボと比較して、テデュグルチド 4 mg を連日 10 日間皮下投与したときの胃内容排出に対する影響を、アセトアミノフェン吸収動態に基づき評価することとした。 副次的目的は、テデュグルチド 4 mg を 1 日 1 回、連日皮下投与したときの、テデュグルチドの薬物動態／薬力学（PK/PD）、食前・食後の消化管（GI）血中バイオマーカー（インスリン、グルカゴン、及びグルコース）、及び C 反応性タンパク（CRP）に対する影響を評価することとした。
方法	本試験は、単施設、二重盲検試験であり、健康な定住被験者 36 例を、テデュグルチド 4 mg 又はプラセボの 1 日 1 回、10 日間、連日皮下投与に無作為化した。試験期間全体、及び 7 日後の追跡調査来院時において、PK/PD、安全性及び忍容性を評価した。
診断及び主な選択基準	18 歳から 45 歳の健康成人男性又は女性を適格とした。消化管運動に影響する消化管異常の既往歴又は現病歴、肝炎又は膵炎の既往歴、又は肝臓の炎症を示すエビデンスがある被験者は除外とした。
予定症例数及び解析対象例数（合計及び投与群ごと）	計画時症例数：最大 36 例。評価可能な被験者を少なくとも 30 例（テデュグルチド：20 例、プラセボ：10 例） • 無作為化対象例数：36 例（テデュグルチド：23 例、プラセボ：13 例） • 安全性解析対象例数：36 例 • PK/PD 解析対象例数：36 例
被験薬、用法・用量、バッチ番号	テデュグルチド 4 mg、皮下投与、 バッチ番号 [redacted]
対照薬、用法・用量、バッチ番号	プラセボ、皮下投与、 バッチ番号 [redacted]
投与期間	連日 10 日間
評価基準	薬力学：主要な薬力学評価項目は、健康被験者での胃内容排出に対するテデュグルチドの影響とし、アセトアミノフェン吸収動態に基づいて評価を行った。他の副次的評価項目は、テデュグルチドの薬物動態、食前・食後の消化管血中バイオマーカー、及び CRP 値とした。 安全性：安全性評価項目は、バイタルサイン及び身体所見、臨床検査値、有害事象、CRP 値、及び心電図とした。
統計手法	アセトアミノフェンの吸収については、アセトアミノフェンの血漿中濃度（Day 0 及び Day 10）に基づき、薬物動態パラメータとして血漿中濃度–時間曲線下面積

表 2.7.6.9 - 1　C10-003 試験：試験の概要

	（AUC）、最高血漿中濃度（C_{max}）、最高血漿中濃度到達時間（T_{max}）、及び消失半減期（$t_{1/2}$）を推定した。薬物動態パラメータの推定は、検体の実採取時間を基に行い、ノンコンパートメント解析法を用いて計算した。胃内容排出のテデュグルチドとプラセボ間の差については、AUC 及び C_{max} パラメータに共分散分析（ANCOVA）を用い、また、T_{max} にはランク調整したノンパラメトリック共分散分析（ANCOVA）を使用した。 CRP、インスリン、グルカゴン及びグルコースの各値については記述統計量を提示し、必要に応じ、ANOVA の計算結果を適用した。 臨床検査値、身体所見、有害事象、心電図モニタリング、及びバイタルサイン測定値を含む安全性データについては、投与、来院、及び時点別に要約した。各時点における安全性の定量データ及びそのベースラインとの差については、該当する場合、記述統計量を用いて要約した。安全性の定性データについては頻度数を用いて要約した。
治験責任医師及び実施医療機関	1 施設（米国）
試験期間	最初の被験者組入れ：2010 年 9 月 28 日 最終被験者の完了：2010 年 11 月 08 日

要約及び結論

<u>薬力学及び薬物動態の結果：</u>

健康被験者を対象に、アセトアミノフェン吸収動態を用いて得られた薬物動態プロファイルに基づくと、テデュグルチドは胃内容排出に対し臨床的に意味のある影響を及ぼさなかった。Day 10 に、テデュグルチドを併用した場合とプラセボを併用した場合を比較したとき、アセトアミノフェンの血漿中濃度に統計学的有意差はみられなかった。ANCOVA を用いて算出した P 値は、アセトアミノフェンの $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、及び C_{max} のいずれについても統計学的に有意ではなかった（$p > 0.05$）。テデュグルチドとプラセボとの間でアセトアミノフェンの T_{max} に統計学的有意差はみられなかった（$p > 0.05$）。テデュグルチドは血清インスリン値に臨床的に意味のある影響を及ぼさなかった。テデュグルチドとプラセボとの間で、食前又は食後インスリンの $AUC_{0\text{-last}}$、$AUC_{0\text{-inf}}$、$AUC_{0\text{-3}}$、C_{max}、又は $C_{max\ 0\text{-3}}$ に、統計学的な有意差はみられなかった（$p > 0.05$）。テデュグルチドにより食後のグルカゴン濃度（$AUC_{0\text{-3}}$）は 6.2%上昇し（$p = 0.152$、食前を共変量とした）、食前のグルカゴン濃度（AUC_{last}）は約 16.9%上昇した（$p = 0.007$、投与前を共変量とした）。これらは臨床的に意味のある変化とは判断されなかった。テデュグルチド投与後、食事から 3 時間後までのグルコース曝露量（$AUC_{0\text{-3}}$）に約 9%～10%の増加がみられ、プラセボと比較したとき、テデュグルチド投与前のグルコース値を共変量とした場合も食前のグルコース値を共変量とした場合も統計学的に有意であった。食直前に測定したグルコース値を共変量としたとき、テデュグルチド投与後、食事から 10 時間後までのグルコース曝露量（$AUC_{0\text{-10}}$）に、わずかではあるが（約 6%）統計学的に有意な増加がみられた。影響は限定的で、臨床的な意味はないと判断された。テデュグルチドを連日投与している間、CRP は Day 3 に最高値を示し（平均値 6.15 mg/L；基準値の上限［ULN］= 3 mg/L）、投与終了後 1 週間以内にベースラインレベルまで回復した。CRP 値は、テデュグルチドの投与を受けた男性被験者が女性被験者より高かった。全ての被験者を対象としたとき、CRP 値の投与群間の差は、Day 1 と Day 17 を除く全ての Study Day において統計学的に有意であった（$p < 0.05$）。本試験において測定したテデュグルチドの薬物動態パラメータは、健康被験者を対象として実施したテデュグルチドの先行する薬物動態試験（C09-001 試験）と同様であった。正常な胃内容排出という薬力学の結果も、健康被験者を対象に GLP-2 を用いて実施した先行試験及び結腸損傷のない被験者を対象とした試験の成績と一貫していた。

<u>安全性の結果：</u>

試験治療下に発現した有害事象（以下、有害事象）は、被験者 23/36 例（63.9%）に 64 件発現した。内訳は、プラセボ投与を受けた被験者が 9/13 例（69.2%）、14 件、テデュグルチド投与を受けた被

表 2.7.6.9 - 1　　C10-003 試験：試験の概要

験者が 14/23 例（60.9%）、50 件であった。テデュグルチドの投与を受けた被験者で最も発現頻度が高かった有害事象は、腹部膨満（8/23 例、34.8%）、腹痛、便秘、悪心、及び頭痛（それぞれ 5/23 例、21.7%）であった。プラセボの投与を受けた被験者で最も発現頻度が高かった有害事象は、腹部膨満、便秘、及び頭痛（それぞれ 2/13 例、15.4%）であった。CRP 増加に関連した有害事象はみられなかった。大部分の有害事象は軽度であった。中等度の有害事象を発現した被験者数は、テデュグルチドの投与を受けた被験者に計 3/23 例（13.0%）、プラセボの投与を受けた被験者にはみられなかった。重度の有害事象を発現した被験者はいなかった。試験期間中の死亡又は重篤な有害事象の発現はなく、有害事象により試験を中止した被験者もいなかった。通常の臨床検査パラメータ、バイタルサイン、身体所見、及び心電図に、臨床的に問題となるベースラインからの変化はみられなかった。以上をまとめると、予期しない安全性シグナルは認められなかった。

結論：

本試験の主要目的は、健康被験者を対象とし、プラセボと比較して、テデュグルチド 4 mg を連日 10 日間皮下投与したときの胃内容排出に対する影響を、アセトアミノフェン吸収動態に基づき評価することであった。プラセボと比較したとき、テデュグルチドとの併用下での Day 10 における AUC 及び C_{max} に統計学的有意差はみられず、またアセトアミノフェンの T_{max} にも統計学的有意差はみられなかった。これらのデータから、テデュグルチドは健康被験者の胃内容排出に臨床的に意味のある影響を及ぼさないことが示唆された。

インスリン、グルカゴン、及びグルコースに対するテデュグルチドの影響についても評価した。

テデュグルチド群とプラセボ群との間で食前又は食後のインスリン曝露に関するパラメータに臨床的に意味のある差はみられなかった。テデュグルチドの投与により食前及び食後のグルカゴン濃度が中等度に上昇した。血清グルコースへの影響が小さかったことに基づき、これらの変化に臨床的な意味はないと判断された。テデュグルチドによる食後グルコースへの影響は小さかった（6%の上昇）。GLP-2 を用いて以前観察されたようなグルコース値又はインスリン値の臨床的に問題となる影響はみられなかった。GLP-2 介在性の食後グルカゴン上昇がこれまでに報告されているが、テデュグルチド投与ではみられなかった。

以前、健康被験者を対象とした試験で報告されているように、テデュグルチドを投与した結果、投与初期の数日間、CRP が一過性に上昇した。テデュグルチドを連日投与している間、Day 3 に CRP が最高値を示し（平均値 6.15 mg/L ; ULN = 3 mg/L）、投与中止後 1 週間以内にベースラインレベルまで回復した。

予期しない安全性シグナルは観察されなかった。テデュグルチドの投与を受けた被験者で最も発現頻度が高かった有害事象は、腹部膨満（8/23 例、34.8%）、腹痛、便秘、悪心、及び頭痛（それぞれ 5/23 例、21.7%）であった。大部分の有害事象は軽度であった。試験期間中には死亡又は重篤な有害事象の発現はなく有害事象により中止した被験者もいなかった。臨床検査パラメータ、バイタルサイン、身体所見、又は心電図に、臨床的に問題となるベースラインからの変化はみられなかった。

10　TED-C10-004 試験

（参考資料：5.3.4.1 項）

TED-C10-004 試験の概要を表 2.7.6.10 - 1 に示す。

表 2.7.6.10 - 1　　TED-C10-004 試験：試験の概要

試験識別番号	TED-C10-004
試験の標題	健康被験者の食後の胆嚢運動及び胆道内腔径に対するテデュグルチドの影響
試験の相	1
目的	主要目的は、健康被験者を対象とし、プラセボを対照として、テデュグルチド 4 mg を連日 5 日間、皮下投与し、超音波検査に基づいて食後の胆嚢運動に対するテデュグルチドの影響を評価すること。 副次的目的は、健康被験者を対象とし、プラセボを対照として、テデュグルチド 4 mg を連日 5 日間、皮下投与し、以下に対する影響を評価すること。 • 超音波検査に基づく、食後の総肝管及び総胆管の内腔径 • テデュグルチド濃度との関連における食後の胆嚢運動パラメータ及び総肝管並びに総胆管の内腔径 • テデュグルチド濃度との関連における食後のコレシストキニン（CCK）血中濃度及びグルカゴン血中濃度 • CCK 血中濃度及びグルカゴン血中濃度との関連における食後の胆嚢運動パラメータ、総肝管及び総胆管の内腔径 探索的目的を以下に示す。 • 薬力学評価項目（食後の総肝管及び総胆管の内腔径、食後の胆嚢運動パラメータ、並びに食後の CCK 濃度及びグルカゴン濃度）とテデュグルチドの曝露量との関連性、並びに反応の時間的推移について、その特性を明らかにするためグラフ化して薬力学評価項目を検討する。 • テデュグルチド濃度のノンコンパートメント薬物動態解析を行うこと。

表 2.7.6.10 - 1 TED-C10-004 試験：試験の概要

方法

本試験は、無作為化、単施設、二重盲検、反復投与、並行群間試験であり、健康被験者 60 例を対象として、腹部にテデュグルチド 4 mg 又はプラセボを連日 5 日間、皮下投与した。標準食に順応するため、被験者はベースライン（Day 0）来院の 3 日前に実施医療機関に入院した。排出率並びに総肝管及び総胆管の内腔径を含む胆嚢運動を検討するため、ベースライン時及び投与期の Day 5 において、食前・食後の胆管超音波検査を実施した。Day 5 の Boost Plus™食（流動食）摂取後に、近位、中位、及び遠位の総肝管及び総胆管の内腔径のベースラインからの変化量を計算し、間接的にオディ括約筋機能を評価した。ベースライン及び Day 5 に食前・食後の CCK 濃度及びグルカゴン濃度測定用血液検体を採取した。テデュグルチドの血中濃度は Day 5 のみ測定した。安全性及び忍容性は試験期間を通じて評価した。

Screening	Admission to Clinic	Check-in	Baseline	Double-blind Treatment		Discharge	Follow-up[a] (Phone)
Day -28 (± 2) to -4	Day -3	Day -2	Day 0	Day 1−Day 4	Day 5	Day 6	Day 35
Eligibility including lab, ECG, ultrasound	Admission to clinic, begin 8-hour fast	Re-assess I/E, lab, start standard diet	GB Motility, CCK and glucagon levels	TED/ Pbo	TED/ Pbo, GB Motility, CCK, glucagon, and TED levels	Safety labs, ECG	Safety

GB：胆嚢、I/E：組入れ／除外基準、Pbo：プラセボ、TED：テデュグルチド投与

[a] 治験薬の最終投与後 30 日に、被験者に対し電話で追跡調査として新規又は継続中の重篤な有害事象の有無を確認した。

診断及び主な選択基準

選択基準

- スクリーニング前に、同意説明文書を読んで理解し、署名する能力を有しており、試験について説明を受けて同意した者。
- 投与前 28 日以内にスクリーニングを完了した者。
- 既往歴、身体所見、及び臨床検査値に基づき判断した 18 歳～45 歳の健康な成人男性又は女性。
- スクリーニングと入院の間に性的活動を行う場合、遮断式の避妊法（非ホルモン性）の実行に同意した者。
- 試験の入院期間中、性的活動を行わないことに同意した者。
- 治験薬の最終投与後 4 週間、認められた避妊法を実行することに同意した者。

除外基準

- スクリーニング時の超音波検査で、胆管に構造的異常又は病的変化（総胆管 >7 mm、胆石、胆泥）が確認された者。
- 胆管の疾患又は病態の既往歴、若しくは砕石術等の外科的、内視鏡的、又は他の胆管への治療歴がある者。
- 消化管の構造的異常又は病的変化の既往歴、若しくは以下のような消化管運動に影響を及ぼす疾患／病状の既往歴を有する者：
  - 胃、小腸、又は結腸の切除。なお、虫垂切除、ヘルニア修復及び良性ポリープ切除は除く
  - 膵炎
  - 結腸癌又は他の消化管悪性腫瘍
  - 炎症性腸疾患
  - 過敏性腸疾患
  - 糖尿病
- 臨床的に問題となる臨床検査パラメータを有する者（治験責任医師が治験依

表 2.7.6.10 - 1 TED-C10-004 試験：試験の概要

	頼者と相談の上、判断した） • 体重が 80 kg を超える者。 • 重大な心血管系、呼吸器系、腎臓、消化管、血液系、神経系、精神系の疾患、又は試験目的や被験者の試験完了の妨げとなり得る別の疾患に関する、臨床所見又は既往歴を有する者（病歴・薬剤歴、身体所見、臨床検査、心電図検査、及び画像検査の結果など利用可能な検査所見含む） • 入院前 30 日以内に処方薬を使用した者。 • 入院前 1 週間以内にビタミン、薬草、又は栄養補助食品（アセトアミノフェンを除く）等の一般市販薬（OTC）を使用した者。 • 薬物又はアルコール乱用の現病歴又は最近の病歴を有する者（12 ヵ月以内） • 薬物又はアルコールのスクリーニング検査が陽性である者。 • タバコ製品の現使用歴又は最近の使用歴を有する者（3 ヵ月以内） • 尿中ニコチンスクリーニング検査が陽性である者。 • 生化学的検査、血液学的検査、尿検査、又は他の臨床検査での臨床的に意味のある異常を有する者。 • 急性又は慢性の感染性ヒト免疫不全ウイルス（HIV）及び肝炎ウイルス感染症に関するウイルス検査が陽性である者。 • 妊娠中又は授乳中の女性 ; 女性に限り、β ヒト絨毛性ゴナドトロピン（β HCG）妊娠検査が陽性である者。 • 高脂肪、標準食受け入れの妨げとなる特別食が必要である者。 • 入院日前 4 週間以内に献血した者。 • スクリーニング検査前 1 ヵ月以内（単回投与の場合）及び最短 3 ヵ月以内（反復投与の場合）、又は当該薬の半減期の 10 倍以内のいずれか長い期間に、治験薬又は治験用医療機器を用いる別の臨床試験に参加した者。生物製剤の場合、最短期間はスクリーニング検査前 6 ヵ月以上、又は薬力学効果持続期間、又は当該薬の半減期の 10 倍のいずれか長い期間とした • 過去にテデュグルチドを使用した者。 • 同意能力又は同意の意思が欠如している者。
予定症例数及び解析対象例数（合計及び投与群ごと）	治験実施計画書で計画したとおり、治験実施医療機関 1 施設で 60 例を組み入れた。 無作為化された被験者：60 例（プラセボ群 31 例、テデュグルチド群 29 例） ITT 集団：58 例（プラセボ群 30 例、テデュグルチド群 28 例） 安全性解析対象集団：60 例（プラセボ群 31 例、テデュグルチド群 29 例）
被験薬、用法・用量、バッチ番号	本試験では、テデュグルチド 4 mg、皮下注、バッチ番号 [redacted] を使用した。
対照薬、用法・用量、バッチ番号	本試験では、プラセボ、皮下注、バッチ番号 [redacted] を使用した。
投与期間	1 日 1 回（5 日間）
評価基準	薬力学 統計解析計画書（SAP）に定めた主要な薬力学評価項目は、Boost Plus 食（刺激）摂取前の胆嚢平均容積から刺激後の最小容積への変化量に基づいて算出した、Day 5 における食後の胆嚢最大排出率とした。

表 2.7.6.10 - 1 TED-C10-004 試験：試験の概要

	副次的評価項目は、食後 30 分時点における胆嚢排出速度、15 分から 120 分までのいずれかの時点における胆嚢最大排出速度、胆嚢最大排出量、並びに 90 分及び 120 分時点における胆嚢再充満量とした。他の副次的評価項目は、オディ括約筋機能の間接評価としての近位、中位、及び遠位の総肝管及び総胆管の内腔径の Day 5 におけるベースラインからの変化量とした。 テデュグルチドの血漿中濃度と胆嚢運動パラメータである、総肝管及び総胆管の内腔径、又は CCK 又はグルカゴンの血漿中濃度との関連性を検討するため、探索的統計解析を実施した。 薬物動態 SAP にはテデュグルチド濃度の探索的ノンコンパートメント薬物動態解析の実施を含めた。血漿中テデュグルチドの薬物動態パラメータの計算は、Day 5 に収集した血漿中濃度時間データを基に行った。これらのパラメータを次に示す : 最高血漿中薬物濃度（C_{max}）、最高血漿中薬物濃度到達時間（T_{max}）、0 時間から最終濃度測定可能時間までの血漿中濃度－時間曲線下面積（$AUC_{0\text{-}tlast}$）、最終濃度測定可能時間（t_{last}）、食後 15 分から最終濃度測定可能時間までの血漿中濃度－時間曲線下面積（$AUC_{15\ min\text{-}tlast}$）、0 時間から τ までの血漿中濃度－時間曲線下面積（AUC_{τ}）、見かけの終末相一次消失速度定数（k_{e1}）、終末相半減期（$t_{1/2}$）、見かけのクリアランス（CLss/F）、及び終末相に基づく見かけの分布容積（Vz/F）。 安全性 安全性評価項目は、有害事象及び重篤な有害事象、臨床検査結果（血液学的検査、血清生化学検査）、バイタルサイン、身体所見、及び心電図にて評価した。
統計手法	解析対象集団 薬力学解析は ITT 集団を対象として行った。ITT 集団は無作為割付け後に治験薬の投与を 1 回以上受け、ベースライン後の薬力学評価が 1 回以上行われた全被験者とした。ノンコンパートメント薬物動態解析は、テデュグルチドの投与を受け、血液検体を Day 5 に採取して血漿中テデュグルチド濃度の解析が行われた被験者を対象とした。 安全性解析は安全性解析対象集団を対象として行った。安全性解析集団は無作為割付け後、治験薬の投与を 1 回以上受けた全ての被験者とした。 薬力学の主要評価項目：Day 0 及び Day 5 の最大排出率 Day 5 の最大排出率について、テデュグルチド群とプラセボ群との差を検定するため、共分散分析（ANCOVA）モデルを用いた。本モデルでは、Boost Plus 食摂取時間における群間差を考慮せず群間差を評価した。すなわち、食事とは関係のない群間差が検出された可能性がある。本モデルは、対応するベースラインの最大排出率及び性別を共変量として評価した。さらに、投与と性別の交互作用も評価した。水準 0.10 で交互作用が有意であれば、男女別のサブグループ解析を行うものとした。 薬力学の副次的評価項目 副次的評価項目とした胆嚢運動について Day 0 及び Day 5 の要約統計量を算出した。 • 30 分時点における排出速度 • 最大排出速度 • 最大排出量 • 90 分及び 120 分時点における再充満量 算出した胆嚢運動パラメータについてテデュグルチド群とプラセボ群間の差を検定するため二つの ANCOVA モデルを用いた。第一の ANCOVA モデルでは、Boost Plus 食摂取時間の群間差を考慮せず群間差を評価した。第二の ANCOVA モデルでは、当該食の摂取時にみられた差について調整した上で群間差を評価した。本モデルで検出された群間差は、テデュグルチドと食事の交互作用によるものと推定され

表 2.7.6.10 - 1 TED-C10-004 試験：試験の概要

	た。いずれのモデルにおいても、対応するベースライン値及び性別を共変量として用いた。さらに、投与と性別の交互作用も評価した。水準 0.10 で交互作用が有意であれば、男女別のサブグループ解析を行うものとした。 食後における近位、中位、及び遠位の総肝管及び総胆管の内腔径についてテデュグルチド群とプラセボ群との差を検定するため、線形混合モデルを用いた。本モデルでは、食事摂取時にみられた差について調整した上で群間差を評価しており、本モデルで検出された群間差は、テデュグルチドと食事の交互作用によるものと推定された。さらに、投与と時点の交互作用についても評価した。 探索的な統計学的評価項目 胆嚢運動パラメータ、総肝管及び総胆管の内腔径、CCK、及びグルカゴンと、テデュグルチドの血漿中濃度との薬力学的関連性を検討するため、薬力学評価項目のグラフによるレビューを行った。 薬物動態解析 統計解析には、被験者ごとに薬物動態パラメータを算出する探索的ノンコンパートメント薬物動態解析を含めた。テデュグルチドの血漿中薬物動態パラメータはテデュグルチドの血漿中濃度-時間データに基づき推定した。 安全性解析 有害事象、重篤な有害事象、臨床検査値、身体所見、心電図モニタリング、及びバイタルサイン測定値を含む安全性データの要約は、投与、来院、及び時点別に要約した。統計学的比較検定は実施しなかった。
治験責任医師及び実施医療機関	1 施設（米国）
試験期間	最初の被験者のスクリーニング：20[redacted]年[redacted]月[redacted]日 最終被験者の完了：20[redacted]年[redacted]月[redacted]日

要約及び結論

薬力学の結果：

薬力学の主要評価項目

ベースラインにおける最大排出率及び性別の影響を考慮した解析で、Day 5 における最大排出率は、テデュグルチド群がプラセボ群より有意に低いことが示された（p <0.0001）。投与と性別の交互作用は統計学的に有意ではなかった。

薬力学の副次的評価項目

次に示す副次的評価項目の解析に際し、ベースライン及び性別の効果を考慮した：30 分時点における胆嚢排出速度、最大排出速度、胆嚢最大排出量、90 分時点における胆嚢再充満量、及び 120 分時点における胆嚢再充満量。

プラセボ投与と比較したとき、テデュグルチド群の 30 分時点における胆嚢排出速度が有意に低かった（p = 0.0037）。投与と性別の交互作用は統計学的に有意ではなかった。

テデュグルチド群とプラセボ群との間で Day 5 の最大排出速度に統計学的有意差はみられなかった。投与と性別の交互作用は統計学的に有意ではなかった。

プラセボ群と比較したときテデュグルチド群における Day 5 の胆嚢最大排出量は有意に低かった（p = 0.0452）。投与と性別の交互作用は統計学的に有意ではなかった。

プラセボ群と比較したときテデュグルチド群における Day 5 の 90 分時点における胆嚢再充満量は有意に低かった（p < 0.0001）。投与と性別の交互作用は統計学的に有意ではなかった。

プラセボ群と比較したときテデュグルチド群における Day 5 の 120 分時点における胆嚢再充満量は有意に低かった（p < 0.0001）。投与と性別の交互作用は統計学的に有意ではなかった。

性別、人種、時間、投与と時間の交互作用、及び Boost Plus 食に関して考慮した解析で、Day 5 における近位、中位、又は遠位の総管腔測定値（総肝管及び総胆管を含む）の変化にテデュグルチド群

表 2.7.6.10 - 1　TED-C10-004 試験：試験の概要

とプラセボ群との間で有意な差はみられなかった。

テデュグルチド群における食前・食後の CCK 濃度（平均値）はプラセボ群と並行に推移した。Day 0 の血漿中グルカゴン濃度（平均値）にプラセボ群とテデュグルチド群との間で明らかな差はみられなかった。しかし、Day 5 における食前・食後の血漿中グルカゴン濃度（平均値）は、テデュグルチド群がプラセボ群より高かった。Day 5 におけるグルカゴンの食前 AUC、食後 AUC、及び $AUC_{0\text{-tlast}}$ の各平均値は、いずれもテデュグルチド群がプラセボ群より 15%高かった。

薬物動態の結果

Day 5 の投与後、血漿中テデュグルチド濃度（平均値）に上昇がみられ、血漿中テデュグルチド濃度（平均値）が最高に到達したのはテデュグルチドの投与から約 3 時間後であった。薬物動態用検体採取時間の最後の 2 時間に、血漿中テデュグルチド濃度は低下し続けた。

5 時間にわたる検体採取時間における C_{max} 及び $AUC_{0\text{-tlast}}$ の幾何平均値はそれぞれ、66.2 ng/mL 及び 227 ng × h/mL であった。$t_{1/2}$（n = 23）の幾何平均値は 2.02 時間であった。

安全性の結果：

全体では、被験者 60 例中 36 例（60.0%）に試験治療下の有害事象（以下、有害事象）が 118 件発現した。60 例中 27 例（45.0%）に軽度、9 例（15.0%）には中等度の有害事象が発現した。テデュグルチド群では、被験者 29 例中 21 例（72.4%）に有害事象が 75 件発現し、29 例中 16 例（55.2%）に軽度、5 例（17.2%）に中等度の有害事象が発現した。プラセボ群では、被験者 31 例中 15 例（48.4%）に有害事象が 43 件発現し、31 例中 11 例（35.5%）に軽度、4 例（12.9%）に中等度の有害事象が発現した。いずれの投与群でも重度の有害事象が発現した被験者はいなかった。

全体では、被験者 60 例中 33 例（55.0%）に、治験薬と関連ありとされた有害事象が 105 件発現した。テデュグルチド群では 29 例中 20 例（69.0%）に 66 件発現し、プラセボ群では 31 例中 13 例（41.9%）に 39 件発現した。

本試験期間中に死亡又は重篤な有害事象の発現はなかった。しかしながら、テデュグルチド群の被験者 1 例が、Day 2 に胃のむかつき、悪心及び頭痛の発現、並びに提供した全ての食事と飲み物の拒否により同意を撤回した。頭痛は治験責任医師により治験薬と関連なしとされたが、他の消化管の有害事象はいずれも関連ありとされた。頭痛は持続中であったが、消化管の有害事象はいずれも治療を行うことなく回復した。

全ての被験者で最も頻度の高かった有害事象は、器官別大分類「胃腸障害」に属する事象であった（31/60 例［51.7%］）。

発現例数が 3 例以上で、テデュグルチド投与群の発現頻度が上回った消化管の有害事象は、腹痛（11/29；37.9%）、腹部膨満（9/29；31.0%）、嘔吐（4/29；13.8%）、及び便秘（3/29；10.3%）であった。発現例数が 3 例以上で、テデュグルチド投与群の発現頻度が上回った、その他の有害事象は頭痛（6/29；20.7%）及び浮動性めまい（3/29；10.3%）であった。

発現例数が 3 例以上のその他の有害事象については、悪心がテデュグルチド群の 29 例中 8 例（27.6%）、プラセボ群の 31 例中 9 例（29.0%）に発現し、食欲減退がテデュグルチド群の 29 例中 2 例（6.9%）、プラセボ群の 31 例中 3 例（9.7%）に発現した。

本試験では重度の有害事象はみられなかった。全体では、60 例中 27 例（45.0%）に軽度、9 例（15.0%）に中等度の有害事象が発現した。プラセボ投与群では、31 例中 11 例（35.5%）に軽度、4 例（12.9%）に中等度の有害事象が発現した。テデュグルチド投与群では、29 例中 16 例（55.2%）に軽度、5 例（17.2%）に中等度の有害事象が発現した。

いずれの投与群においても、臨床検査値又はバイタルサインの各平均値のベースラインから Day 6 までの変化量に明らかな傾向はみられず、投与前後で臨床的に問題となる身体所見もみられなかった。

結論：

本試験結果から、テデュグルチド 4 mg の連日 5 日間投与は健康被験者の胆汁動態に影響を及ぼすことが示唆された。プラセボ投与時に比し、このレジメンによる投与では胆嚢運動が低下したが、管径変化の測定よりオディ括約筋機能に対する閉塞作用はみられなかった。健康被験者へのテデュグルチドの投与では、CCK 濃度に影響はみられず、グルカゴン濃度にも大きな影響はみられなかった。

表 2.7.6.10 - 1　TED-C10-004 試験：試験の概要

テデュグルチド投与被験者の胆管に構造的な変化はみられなかった。全体的に、テデュグルチド群とプラセボ群の有害事象プロファイルに大きな差はみられなかったが、消化管に特異的な事象はテデュグルチド群がわずかに多かった。本試験の健康被験者においては予期しない安全性シグナルは確認されず、テデュグルチドの総合的な安全性プロファイルは、テデュグルチドの臨床試験で確立された海外の添付文書に記載されたプロファイルと同様であった。本試験の結果から、テデュグルチドの投与を受けた被験者には、胆嚢の運動不全が生じる可能性のあることが示唆された。以上より、海外の添付文書に記載のとおり、胆嚢疾患及び胆管疾患については綿密なモニタリング実施の必要性が示唆された。

11　ALX-0600-92001 試験

（参考資料：5.3.4.2 項）

ALX-0600-92001 試験の概要を表 2.7.6.11 - 1 に示す。

表 2.7.6.11 - 1　　ALX-0600-92001 試験：試験の概要

試験識別番号	ALX-0600-92001
試験の標題	短腸症候群患者を対象とし、ALX-0600 の用量を漸増して、21 日間反復皮下投与したときの安全性、忍容性、及び効果を検討する非盲検、多施設共同、用量検討、パイロット試験
試験の相	2a
目的	主要目的：短腸症候群（SBS）患者を対象とし ALX-0600（テデュグルチド）の 21 日間皮下投与レジメンの安全性及び忍容性を検討する。 副次目的：テデュグルチドを 21 日間投与し、残存腸の水及び主要栄養素の吸収能に対する影響を測定する。 その他の目的として、SBS 患者にテデュグルチドを単回及び反復投与したときの薬物動態（PK）及びテデュグルチド投与後の腸管粘膜の組織学的変化を検討する。
方法	本試験は、SBS 患者を対象とする非盲検、用量漸増、反復投与試験である。結腸を有さない被験者から成る 3 群、この 3 群のうち 2 群の被験者を用いるリチャレンジ群、及び結腸と小腸の連続性があり結腸の 50%以上が残存する群、の計 5 群を対象とした。用量は、第 1 群、0.03 mg/kg 1 日 1 回；第 2 群、0.10 mg/kg 1 日 1 回；第 3 群、0.15 mg/kg 1 日 1 回；第 4 群（リチャレンジ）、0.05 又は 0.075 mg/kg 1 日 2 回；第 5 群、0.10 mg/kg 1 日 1 回（結腸連続性群）とした。試験の構成は、スクリーニング相（Day −14～−1）、投与前相（Day −3～−1）、21 日間投与相、及び 21 日間追跡調査相の計 4 相とした。安全性の評価は、有害事象、バイタルサイン、心電図、及び臨床検査値（全血球血算、生化学的検査、肝機能、テデュグルチド及び大腸菌タンパク質（ECP）に対する抗体産生、並びに臨床病理学的検査）のモニタリングに基づいて行った。テデュグルチドの腸管機能に対する作用は、72 時間栄養分吸収試験（脂質、窒素、電解質、総エネルギー、及び消化管水分の絶対吸収量及び相対吸収量）、72 時間排泄（ストーマ／便）容量、陰窩絨毛高、分裂指数、組成及び機能解析、並びに D-キシロース濃度に基づいて評価した。
診断及び主な選択基準	全ての被験者：男性及び女性、18 歳以上、SBS 患者（虚血性血管疾患に続発した SBS、回転異常又は腸軸捻転を含む）。内視鏡検査により静止期の炎症性腸疾患（IBD）と確認された被験者もスクリーニング対象とした。残存小腸が 150 cm 以下の SBS 患者、及びカロリー必要量の 50%以上を満たすため中心静脈栄養を必要とする SBS 患者。直近の腸切除は組み入れの 12 ヵ月以上前。理想体重の 90%～120%である体重を維持している者、生化学的検査値、腎機能及び肝機能の検査値、及び運動調節薬がいずれも安定している者。 なお、活動性 IBD、その他の重大な全身性疾患（腎疾患、肝疾患、又は心疾患）又は放射線性腸炎の既往歴を有する患者、瘻孔又はスプルーの発現した患者、過去 3 ヵ月以内に成長ホルモン、増殖因子、又は治験薬を使用した患者（テデュグルチド投与後にリチャレンジ群に組み入れられた患者を除く）は除外とした。 SBS を有し、結腸を有さない被験者とは、上述した基準に加え、結腸を有さない患者を指す。第 4 群（リチャレンジ）に参加するには、被験者は第 2 群又は第 3 群への参加を完了していること。 SBS を有し、結腸と小腸の連続性があり、結腸が約 50%以上残存している被験者とは、いずれの被験者についても上述した基準に加え、結腸と小腸の連続性があ

表 2.7.6.11 - 1　ALX-0600-92001 試験：試験の概要

	り、結腸が 50%以上残存し、かつ便重量>1 kg/日、及び便からのエネルギーロスが 2.0 MJ/日（又は便からの脂質ロス>50 g/日）の患者を指す。
予定症例数及び解析対象例数（合計及び投与群ごと）	予定症例数：約 24 例。実際の組入れ例数：22 例。重複していない被験者の合計：17 例。 第 1 群：0.03 mg/kg 1 日 1 回（n=3） 第 2 群：0.10 mg/kg 1 日 1 回（n=5） 第 3 群：0.15 mg/kg 1 日 1 回（n=4） 第 4 群：0.05 又は 0.075 mg/kg 1 日 2 回（n=5）；第 2 群及び第 3 群の被験者のリチャレンジ 第 5 群：0.10 mg/kg1 日 1 回（結腸連続性群）（n=5）；結腸と小腸の連続性があり、結腸が 50%以上残存している被験者 併合群： 第 1 併合群：第 2 群及び第 3 群（8 例） 第 2 併合群：第 2 群、第 3 群及び第 5 群（13 例） 第 3 併合群：第 2 群及び第 5 群（9 例） 第 4 併合群：第 1 群、第 2 群、第 3 群、第 4 群及び第 5 群（17 例、5 例は 2 群重複）
被験薬、用法・用量、バッチ番号	テデュグルチドの用量は、0.03 mg/kg/日、0.10 mg/kg/日、0.15 mg/kg/日の 3 段階を用いた。 投与レジメンは、1 日 1 回（0.03 mg/kg/日、0.10 mg/kg/日、0.15 mg/kg/日）及び 1 日 2 回（0.1 mg/kg/日及び 0.15 mg/kg/日）の 2 種類を用いた。 ロット番号 [redacted]。 被験者は、テデュグルチドを腹部、大腿部、又は腕部皮下に 1 日 1 回又は 1 日 2 回自己投与した。1 日 1 回投与の場合、被験者は朝、治験薬を自己投与した。1 日 2 回投与の場合、被験者は 12 時間ごとに治験薬を自己投与した。
対照薬、用法・用量、バッチ番号	なし
投与期間	テデュグルチドの投与は、21 日間、連日（1 日 1 回又は 1 日 2 回）行った。被験者の参加期間は約 7 週間であった。第 4 群の被験者には新たに被験者番号を割り当て、被験者は 2 回目の 7 週間の相に参加した。
評価基準	有効性：評価と手順は、ベースライン（Day −3～Day 1 の投与前）、投与終了時（Day 18～Day 21）、及び追跡調査（Day 39～Day 42）の計 3 回実施した。 • 脂質、窒素、ナトリウム、カリウム、カロリー、及び消化管水分の絶対吸収量及び相対吸収量に対するテデュグルチドの作用を評価するため、72 時間栄養分吸収試験を実施した。また、本試験からは、脂質、窒素、ナトリウム、カリウム、カロリー、及び水分のストーマ排泄量又は便排泄量に関する情報が得られる。 • いずれの群でも、吸収不良の尺度として、D-キシロース吸収検査を実施した。 • 小腸（第 1、2、及び 3 群）あるいは大腸又は直腸（第 5 群）の状態を評価すること、絨毛高、陰窩の深度、及び分裂指数を病理組織学的に検討するための生検検体を採取すること、並びに組成及び機能解析を含む生物学的パラメータを検討することを目的として、内視鏡検査を実施した。 PK：C_{max}、T_{max}、及び AUC を含む標準的な PK パラメータを算出するため、投与相の Day 1 及び Day 21 に血液検体を採取した。

表 2.7.6.11 - 1　ALX-0600-92001 試験：試験の概要

	安全性：安全性パラメータを以下に示す。 • 有害事象 • バイタルサイン（血圧、脈拍数、口腔温） • 心電図（PR、QT、QTc 間隔、QRS 持続時間、心拍数） • 臨床検査安全性データ［全血球計算値、生化学的検査、肝機能、テデュグルチド及び ECP に対する抗体］
統計手法	Intent-To-Treat（ITT）集団は、組入れ被験者全例（22 例）を対象とした。ベースライン、被験者背景、及び安全性に関する全ての解析に ITT 集団を用いた。Per-Protocol（PP）集団は、治験薬の投与を 1 回以上受けた全被験者（21 例）を対象とし、これは、ITT 集団から、治験薬とは関係のない長期発熱事象が発現した被験者 1 例を除外した集団であった。完了集団（19 例）とは、試験手順を全て完了した PP 集団の被験者と規定した。有効性の解析には PP 集団及び完了集団を用いた。
治験責任医師及び実施医療機関	5 施設（米国）及び 1 施設（デンマーク）
試験期間	最初の被験者の組入れ：20[redacted] 年 [redacted] 月 [redacted] 日 最終被験者の完了：20[redacted] 年 [redacted] 月 [redacted] 日

要約及び結論

被験者背景：重複していない男性被験者 8 例（47%）及び女性被験者 9 例（53%）。白人 16 例（94%）及びアフリカ系米国人 1 例（6%）。重複していない被験者における年齢（平均値）は 49 歳、体重（平均値）は 59 kg、身長（平均値）は 168 cm、直近の切除術からの期間は 0.8～20 年、及び残存空腸の長さは 25～200 cm であった。

有効性の結果：

群別：投与終了時に最も目を引いた所見は消化管内の水分吸収増加であった（第 2、3、4、5 群）。投与終了時における絶対値はおよそ 3000 g/72 時間、相対的な増加は約 30%であった。通常、追跡調査時において、改善に反転がみられた。投与終了時におけるその他の重要で臨床的に意味のある変化は、窒素及びカロリー（第 2、4、5 群）、脂質（第 1、2、4、5 群）、ナトリウム（第 2、3、4、5 群）、及びカリウム（第 1、2、4 群）の絶対吸収量及び／又は相対吸収量の増加であった。便中脂質、便中窒素、便中ナトリウム（第 2、3、4 群）、及び便中カロリー（第 2、4、5 群）；便中カリウム（第 2、5 群）；ストーマ又は便中の水分（第 2、3、4、5 群）；及び尿中窒素（第 3 群）に臨床的に意味のある減少が認められた。また、テデュグルチドにより、尿中ナトリウム（第 2、3、4、5 群）；尿中カリウム（第 2、3 群）；及び尿重量（第 2、3、4、5 群）に臨床的に意味のある増加が生じた。第 1 群では、脂質及び消化管水分の絶対吸収量を除き、栄養分吸収について、テデュグルチドによる臨床的に意味のある増加はみられなかった。第 3 群でみられた臨床的に意味のある所見は多様であり、改善に関しては、消化管水分の絶対吸収量及び相対吸収量についてみられただけであった。栄養分、水分、及び電解質の各吸収の臨床的に意味のある増加は、生検検体の組成、機能、及び組織学的（形態学的）変化として現れた。投与終了時、小腸（第 2 群）では、絨毛高、陰窩の深度、及び分裂指数に増加が、また結腸直腸検体（第 5 群）では陰窩の深度に増加がみられた。

併合群：投与終了時、併合群において最も顕著であったのは消化管水分の吸収増加であった。4 併合群いずれにおいても、水分の絶対吸収量及び相対吸収量の増加は統計学的に有意であった。個々の群でみられた所見と同じく、投与終了時にみられたその他の重要で臨床的に意味のある変化は、脂質（第 3 併合群、第 4 併合群）；窒素（第 3 併合群）；カロリー（第 2 併合群、第 3 併合群、第 4 併合群）；ナトリウム（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）；及びカリウム（第 3 併合群、第 4 併合群）の絶対吸収量及び／又は相対吸収量であった。便中脂質（第 3 併合群、第 4 併合群）；窒素（第 2 併合群、第 3 併合群、第 4 併合群）；ナトリウム（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）；カリウム（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）；カロリー（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）；及びストーマ又は便中の水分（第

表 2.7.6.11 - 1　ALX-0600-92001 試験：試験の概要

1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）に臨床的に意味のある又は統計学的に有意な減少がみられた。また、テデュグルチドにより、尿中ナトリウム（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）；尿中カリウム（第 1 併合群、第 2 併合群）；及び尿重量（第 1 併合群、第 2 併合群、第 3 併合群、第 4 併合群）に、臨床的に意味のある又は統計学的に有意な増加が生じた。第 2 併合群及び第 4 併合群では、ストーマ又は便排泄中の消化管水分に減少がみられ、統計学的に有意であった。第 2 併合群及び第 4 併合群では尿中ナトリウムに、また第 3 併合群及び第 4 併合群では尿重量に増加がみられ、いずれも統計学的に有意であった。

安全性の結果：

死亡は認められなかった。有害事象*により中止した被験者はいなかった。治験薬の投与を受けた被験者 4 例に重篤な有害事象 5 件が発現した。各群の有害事象発現頻度は同程度であり、各群の有害事象発現被験者の割合は 80%～100%であった。最も頻度の高い有害事象は、オストミーニップルの限局性浮腫（localized edema）で、重複していない被験者 17 例のうち 7 例（41.2%）及び第 4 群（リチャレンジ）の 5 例（100%）全例でみられ、重複していない／リチャレンジ被験者 22 例のうち 12 例（54.5%）を占めた。全被験者の 10%以上に発現したその他の有害事象の発現例数は、頭痛（headache）が重複していない被験者として 4 例（重複していない被験者 17 例の 23.5%；重複していない／リチャレンジ被験者 22 例の 18.2%）、下肢の浮腫（edema of the lower limb）が重複していない被験者として 3 例（重複していない被験者 17 例の 17.6%、重複していない／リチャレンジ被験者 22 例の 13.6%）、及び腹痛 NOS（abdominal pain NOS）が重複していない被験者として 3 例（重複していない被験者 17 例の 17.6%、重複していない／リチャレンジ被験者 22 例の 13.6%）であった。臨床検査値異常もみられたが、明らかな治験薬又は投与量の濃度による影響は認められなかった。バイタルサイン測定値や心電図には安全性に関する懸念は認められなかった。大部分の被験者では注射部位反応はみられなかった。テデュグルチド投与後にテデュグルチドに対する抗体は検出されなかった。ECP に対する相対抗体価は、1624 を示した被験者が 1 例、107～228 の範囲を示した被験者が 6 例みられた。

投与終了時、いずれの群でも D-キシロースの血漿レベルに数値上の改善がみられ、第 4 群では有意であった。また、D-キシロースの尿中排泄量の増加は、第 4 群では統計学的に有意、第 5 群では有意水準に迫る値であった。投与期間中、ITT 集団では、第 2、3、4、及び 5 群において、体重の軽微な増加傾向がみられた。体重増加は一過性であり、Day 21（第 5 群）又は追跡調査相までにベースライン値に近い値に戻った。

*本試験で報告された有害事象は国際医薬用語集（MedDRA®）Version.[redacted]を用いてコード化し、有害事象用語の翻訳には Version18.1 を使用した。

PK：テデュグルチドの PK の被験者間変動は中等度から高度であった。用量 0.03～0.15 mg/kg/日の範囲において、テデュグルチドの PK は用量比例性及び線形性であった。21 日間の連日投与は、テデュグルチドの PK に影響を及ぼさなかった。抗体産生がテデュグルチドの PK に影響する可能性は低いと思われた。1 日 1 回投与から 1 日 2 回投与に変更すると、用量で補正した曝露量がわずかに高くなったが、被験者数が少なく明確な結論を下すことは困難であった。SBS 被験者では、結腸の存在はテデュグルチドの PK に影響を及ぼさなかった。これらの結果は健康被験者の成績と類似しており、SBS の状態がテデュグルチドの PK に影響を及ぼすことはない。

表 2.7.6.11 - 1　ALX-0600-92001 試験：試験の概要

表：PK パラメータ

Pharmacokinetic Parameter	**Estimate of the Pharmacokinetic Parameter**					
	0.03 mg/kg (n=3)		**0.10 mg/kg (n=5)**		**0.15 mg/kg (n=4)**	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21
C_{max} (ng/ mL)	39.7	43.4	122.5	111.9	179.4	138.5
T_{max} (h)	3.3	2.7	3.1	2.7	3.3	3.5
$AUC_{(0\text{-}inf)}$ (ng*h/mL)	236.9	NA	565.6	NA	825.0	NA
$AUC_{(0\text{-}r)}$ (ng*h/mL)	139.7	148.5	539.0	533.0	792.3	698.8
$t_{1/2}$ (h)	2.0	1.2	1.6	1.2	2.0	1.5
Note: all results in both tables shown as the Mean						
	0.15 mg/kg given as 0.075 mg/kg/dose bid (n=2)		**0.10 mg/kg given as 0.05 mg/kg/dose bid (n=3)**		**Colon group 0.10 mg/kg (n=5)**	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21
C_{max} (ng/ mL)	94.2	79.4	78.4	88.8	99.8	114.9
T_{max} (h)	2.8	2.8	3.7	3.0	3.2	3.6
$AUC_{(0\text{-}inf)}$ (ng*h/mL)	504.6	NA	452.3	NA	521.5	NA
$AUC_{(0\text{-}r)}$ (ng*h/mL)	502.6	379.9	437.0	353.2	507.8	583.6
$t_{1/2}$ (h)	1.1	1.3	1.6	2.5	1.6	1.2

Source:　M5.3.4.2 ALX-0600-92001 CSR Tables 12.1.3A, 12.1.3B, 12.1.3C

結論：

全般的に、本被験者集団において、テデュグルチドは安全で、その忍容性は良好であり、PK は用量比例性を示し、健康被験者の PK との乖離は認められなかった。投与終了時にテデュグルチドにより、栄養分、電解質、及び水分の各吸収に関する測定値に、臨床的に意味のある、統計学的に有意な改善がみられたが、これらの改善は多くの場合、追跡調査時に投与開始前の状態に戻った。最も重要な所見は、第 2、3、4、及び 5 群でみられた、消化管内の水分の約 1000 mL/日の吸収増加であった。補液依存のみの患者であれば、この水分吸収の増加により、静脈内輸液への依存から離脱できる、あるいは依存度を大きく下げる可能性がある。その他の重要な所見は、脂質、窒素、及びカロリーの各吸収の増加、便中の脂質、窒素、ナトリウム、カリウム、カロリー、及びストーマ又は便中の水分のそれぞれの減少、並びに尿重量及び尿中ナトリウムの増加であった。併合群でみられた最も重要な所見は、消化管内の水分吸収、尿中ナトリウム、及び尿重量のそれぞれの増加、並びにストーマ又は便中の水分の減少であった。併合群でみられた、その他の臨床的に意味のある所見は、脂質、窒素、カロリー、及びナトリウムの各吸収の増加、便中の脂質、窒素、ナトリウム、カリウム、カロリー、及びストーマ又は便中の水分のそれぞれの減少、並びに尿重量、尿中ナトリウム、及び尿中カリウムのそれぞれの増加であった。

本試験において、結腸の有無に関わらず有効性（特に水分とエネルギーの吸収の増加）が示されたことから、SBS 患者を対象としてテデュグルチドの検討を更に進めることは妥当と考えた。

12　CL0600-004 試験

（評価資料：5.3.5.1 項）

CL0600-004 試験の概要を表 2.7.6.12 - 1 に示す。（本項で経静脈サポート［PS］とは経静脈栄養［PN］及び経静脈栄養／補液［PN/I.V.］を示す。）

表 2.7.6.12 - 1　　CL0600-004 試験：試験の概要

試験識別番号	CL0600-004
試験の標題	経静脈栄養を必要とする短腸症候群患者を対象としテデュグルチドの有効性及び安全性を検討する試験
試験の相	3
目的	PS を必要とする短腸症候群（SBS）患者を対象とし、テデュグルチドの有効性、安全性、忍容性、及び薬物動態をプラセボと比較検討すること。 主要目的は、24 週間の投与期間終了時における奏効の程度及び持続期間をカテゴリー化したうえで各カテゴリーを点数化し、「奏効スコア」という指標を使用した。テデュグルチド投与被験者とプラセボ投与被験者とを比較することとした。 • 奏効の程度は、ベースラインからの週間 PS 量の減少により定義する。治験実施計画書では、ベースラインからの週間 PS 量の減少について最小値を 20%、最大値を 100%と定めた。 • 奏効の持続期間は、Week 16 から Week 20、及び Week 20 から Week 24 の間にみられた奏効を対象とした。 有効性の副次目的は、レスポンダーの割合（Week 20 に奏効を示し、Week 24 にその奏効を維持していた被験者の割合）とした。奏効とは、ベースラインからの週間 PS 量の減少が 20%以上に達することと規定した（プロトコル初版の主要評価項目）。 • その他の副次目的は、血漿中シトルリン濃度、並びに水分及び主要栄養素の腸管吸収の改善により生じる直接的な変化に基づく変数とした。 • 生活の質（QOL）及び医療リソースの利用についても評価した。 • 探索的評価項目は、副甲状腺ホルモン（PTH）、骨マーカー、血漿中シトルリン濃度、生検による腸管粘膜の絨毛高及び陰窩深度のベースラインからの変化量、骨密度、体脂肪、及び除脂肪体重の変化とした。 特定の実施医療機関では、胃腸液の経腸吸収（湿重量）、熱量、窒素、脂肪、炭水化物、ナトリウム、マグネシウム、カルシウム、及びカリウムの各変化を評価するため、追加データを収集した。 さらに、プラセボと比較してテデュグルチドを投与したときの安全性及び忍容性を評価した。 テデュグルチドの母集団薬物動態についても評価した。
方法	本試験は 24 週間の二重盲検、無作為化、並行群、プラセボ対照、多施設、国際共同試験であり、被験者をテデュグルチド群（0.05 又は 0.10 mg/kg/日）又はプラセボ群に無作為化した。試験の構成は、スクリーニング来院、PS 最適化期、安定化期（4 週間にわたって PS 投与の安定を維持するようデザインされた）、これに続く 24 週間の投与期、及び継続投与試験に移行しない被験者の場合は 4 週間の追跡調査期とした。本試験を完了した被験者は、継続投与試験（CL0600-005 試験）に参加し、更に 28 週間の投与を受けることができた。

表 2.7.6.12 - 1　　CL0600-004 試験：試験の概要

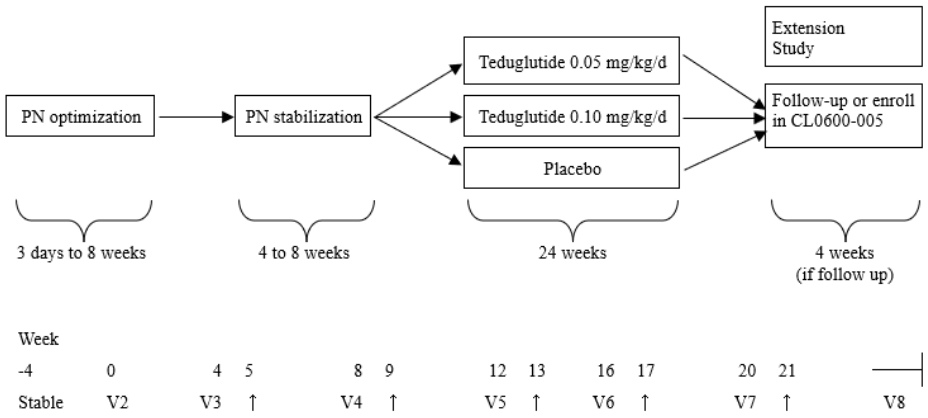
	図：試験ダイアグラム  Abbreviations: V = clinic visit number; ↑ = safety labs 3-4 days after reduction and again at 6-7 days. Notes: Study Visit 1 occurred at Week – 4 labeled “stable” above. When the total weekly PN was administered on only two days, it was in the subject’s best interest to be weaned off PN completely and this was to be done under the supervision of the investigator.
診断及び主な選択基準	選択基準 以下に示す基準を全て満たす者を適格とした。 1. 本試験に関する全ての手順に先立ち、同意文書へ日付入りの署名が得られている者。 2. 同意取得時の年齢が 18 歳以上の男性及び女性。 3. 外傷、腸軸捻、血管病変、悪性腫瘍、クローン病などによる小腸広範切除により SBS となった者。 　a. 悪性腫瘍の既往を有する被験者の場合（5.3.5.1 項 Protocol Section 4.3 Exclusion Criteria [Appendix 16.1.1]に例外の一覧あり）、無病期間が少なくとも 5 年間あること。 　b. クローン病の既往を有する者の場合、臨床評価に基づく臨床的寛解が得られていること。 4. 組入れ時の体重が 90 kg 未満である者。 5. 小腸広範切除に起因する PS 使用が、同意取得前 12 ヵ月以上持続している者（この間に行われた瘻再建の小手術は容認した）。 6. ベースライン時に、持続的な吸収不良により、必要エネルギー又は電解質の必要量を満たすため PS 療法を週 3 回以上必要とした者。 7. 無作為割付け前に連続して 4 週間以上、以下が安定している者。 　a. PS の使用状況及び投与量。 　b. 48 時間尿量（1.0～2.0 L/日）。 　c. 尿中ナトリウム（20 mmol/日超）。 　d. 腎機能（血清クレアチニン及び血中尿素窒素［BUN］1.5×基準範囲上限［ULN］以下）。 　e. ヘマトクリット（Hct）が十分な水分補給を示している（ULN 以下）。 　f. 腸運動を変化させる薬剤。 8. 体格指数（BMI）が 18～27 kg/m^2 である者。 9. 肝機能が正常である者（アラニンアミノトランスフェラーゼ［ALT］及びアスパラギン酸アミノトランスフェラーゼ［AST］のいずれも 2.0 × ULN 未満；総ビリルビン 1.25 × ULN 未満；及びアルカリホスファターゼ 2.5 × ULN 未満）

表 2.7.6.12 - 1　CL0600-004 試験：試験の概要

10. 不妊手術を受けていない、又は閉経前の女性の場合、投与期間中及び投与期間終了後 30 日間、医学的に容認される避妊法を実行できる者。閉経後とは、年齢 60 歳以上、かつ最終月経から 2 年以上経過している場合と規定した。
11. 試験来院スケジュール及びその他の治験実施計画書の要件について、理解能力があり、これを自発的に遵守する意思がある者。

除外基準

以下の基準のいずれかに該当する者は除外した。

1. 悪性腫瘍又は臨床的に問題となるリンパ増殖性疾患の既往歴を有し、無病期間が 5 年未満の者。なお、切除された皮膚の基底細胞癌又は有棘細胞癌、又は上皮内子宮頸癌は例外とした。
2. アルコール又は薬物乱用の既往歴（1 年以内）を持つ者。
3. 同意取得前 30 日以内に臨床試験に参加に同意した、又は何らかの臨床試験に参加中である者。
4. 無作為割付け時に臨床的に問題となる臨床検査値異常がある者。
5. テデュグルチド（ALX-0600）の投与経験を持つ者。
6. スクリーニング来院前 3 ヵ月以内に天然 GLP-2 を使用した者。
7. スクリーニング来院前 1 ヵ月以内に入院した者。
8. 妊婦又は授乳中の女性。
9. 過度の危険がある、試験完了の妨げになる、又は試験結果の解析に影響を与えると治験責任医師が治験への参加を不適当と判断した者。
10. 体組織別に下表に示すいずれかの疾患を有する者。

器官分類	除外となる疾患
SBS 関連	放射線性腸炎
	強皮症
	セリアック病
	熱帯性スプルー、難治性スプルー
	偽性腸閉塞
消化器系	活動性の炎症性腸疾患（IBD）
	大腸内視鏡生検又はポリープ切除時における前悪性又は悪性病変の所見
	治験期間中の待機手術
免疫系	ヒト免疫不全ウイルス検査陽性
	免疫不全
	テデュグルチド又は製剤中のいずれかの成分に対するアレルギーの可能性
心血管、呼吸器、腎臓、内分泌、肝臓、又は中枢神経系	コントロール不良かつ未治療の重要な活動性全身性疾患

11. 必要な休薬期間を取得できない者。本試験でテデュグルチドの初回投与前に確保すべき休薬期間別に薬剤の一覧を下表に示す。インスリンの静脈内投与は除外対象とはしなかった。

表 2.7.6.12 - 1　CL0600-004 試験：試験の概要

	Day 1 前の休薬期間	
	休薬期間が 12 週間必要な薬剤： モノクローナル抗体治療薬 例：インフリキシマブ（レミケード®） 成長ホルモン又は成長因子	**休薬期間が 30 日間必要な薬剤**： 全身性副腎皮質ステロイド（短期間の漸減投与は可能、依頼者と検討する） 他の生物製剤 メトトレキサート シクロスポリン タクロリムス（FK506） シロリムス オクトレオチド IV グルタミン 他の治験薬
予定症例数及び解析対象例数（合計及び投与群ごと）	計画時：無作為割付け例を 80 例（プラセボ、0.05 mg/kg/日、0.10 mg/kg/日への割付け比率は 1：2：2）確保するため、約 125 例をスクリーニングすることとした。 解析時：スクリーニング 139 例、無作為化 84 例；無作為割付けされ治験薬の投与を 1 回以上受けた被験者 83 例（無作為割付けされた被験者のうち 1 例は治験薬の投与を受けなかった）。治験薬の投与を受けた被験者全てを有効性及び安全性の解析対象とした。	
被験薬、用法・用量、バッチ番号	本試験では、テデュグルチドの 2 用量（0.05mg/kg/日及び 0.10 mg/kg/日）を用いた。ロット番号は以下のとおり。 • テデュグルチド 0.05 mg/kg/日 － 21003011、21004011、21004021、21004031 • テデュグルチド 0.10 mg/kg/日 － 08403011、08403021、08404021、08404031 被験者は、腹部の 4 分割のうちの 1 ヵ所、又はどちらかの大腿部にテデュグルチドを 1 日 1 回皮下投与することとした。	
対照薬、用法・用量、バッチ番号	プラセボ ロット番号：08303011、08305011 被験者は、腹部の 4 分割のうちの 1 ヵ所、又はどちらかの大腿部にプラセボを 1 日 1 回皮下投与することとした。	
投与期間	1 日 1 回、24 週間	

表 2.7.6.12 - 1　CL0600-004 試験：試験の概要

評価基準	有効性 有効性の主要評価項目は、24 週間の投与期間終了時における奏効の程度及び持続期間をカテゴリー化した上で各カテゴリーを点数化した「奏効スコア」という指標を使用した。 • 奏効の程度は、ベースラインからの週間 PS 量の減少により規定する。治験実施計画書では、ベースラインからの週間 PS 量の減少について最小値を 20%、最大値を 100%と定めた。 • 奏効の持続期間は、Week 16 から Week 20、及び Week 20 から Week 24 の間にみられた奏効を対象とした。 副次的評価項目（レスポンダーの割合）は、Week 20 に奏効を示し、Week 24 にその奏効を維持していた被験者の割合とした。奏効とは、週間 PS 量がベースラインから 20%以上減少することと規定した。 • その他の副次的評価項目は、水分及び主要栄養素の腸管吸収の改善による直接的な変化に基づく変数とした。 • QOL 及び医療リソースの利用についても評価した。 安全性 有害事象、12 誘導心電図、バイタルサイン、臨床検査安全性データ、テデュグルチド及び大腸菌タンパク質（ECP）に対する抗体、静脈内（IV）カテーテル合併症、及び尿量の変化、及び体重を評価することとした。 薬物動態 本試験では、ベースライン、Week 8、Week 16、及び Week 24 に薬物動態を測定した。薬力学マーカーとして血漿中シトルリン濃度を評価した。
統計手法	有効性の解析は、Intent-to-Treat（ITT）集団及び Per-Protocol（PP）集団を対象として実施した。ITT 集団及び安全性解析対象集団は、治験薬の投与を 1 回以上受けた全ての被験者とした。各群及び全体のベースライン特性及び人口統計学的特性を要約するため、記述統計量（被験者数、平均値、標準偏差、中央値、最小値及び最大値、及び特定のカテゴリーに属する被験者数とその割合［%］）を用いた。 有効性評価項目 • 有効性の主要評価項目については、記述統計量を用い、投与群ごとに奏効スコアを要約した。 • 全投与群の比較は、ランク共分散分析を用い、無作為割付けの層別に用いたベースラインの PS 量及び投与群を層とし、ベースラインの週間 PS 量を共変量として行うこととした。 • 治療効果に関する複数の仮説を検定する場合、多重比較の調整にステップダウン手順を用いることとした。この手順では、まず高用量とプラセボとを比較し、有意水準 0.05 で有意差が認められた場合にのみ低用量とプラセボの比較検定を行うこととした。 • 副次的評価項目（Week 20 から Week 24 まで奏効が維持されること。奏効とは、ベースラインからの週間 PS 量の減少が 20%以上に達することと規定）については、レスポンダー例数とその割合（%）、及び各投与群におけるレスポンダーの割合（%）の 95%信頼区間（CI）により要約した。 • 対比較（pairwise comparisons）による、レスポンダーの割合のプラセボとの差及び対応する 95%信頼区間についても提示した。投与群間の対比較は Fisher の直接確率法を用いて行った。

表 2.7.6.12 - 1　CL0600-004 試験：試験の概要

	• ランクを用いた共分散分析（ANCOVA）を用い、ベースライン PS 量及び投与群を層として割合に関する投与群間の比較を行った。 • その他の有効性副次的評価項目については、投与群ごとに各時点における記述統計量（被験者数、平均値、標準偏差、連続変数の場合は中央値、最小値、及び最大値、離散変数の場合は特定のカテゴリーに属する被験者の数とその割合［%］及び対応する 95%信頼区間）を用いて要約した。 • ベースラインからの変化量については、投与群間の pairwise differences と対応する 95%信頼区間に、2 元配置反復測定共分散分析（ANCOVA）による推定値を用いた。このモデルでは、ベースラインの PS による無作為割付けの層別、投与群、来院の効果を用い、ベースラインの週間 PS 量を共変量とした。 <u>安全性評価項目</u> • 試験治療下に発現した有害事象を表にした。 • その他の安全性データ（バイタルサイン、体重、心電図、及び IV カテーテル合併症）については、投与群ごとに記述統計量で要約した。 • 安全性臨床検査値のシフト表については投与群別に提示した。 • テデュグルチド及び ECP に対する特異抗体陽性被験者の例数とその割合（%）については、CL0600-005 試験のデータも含む独立した報告書に報告した。 <u>薬物動態変数及び薬力学変数</u> • SBS 患者を対象とするテデュグルチドの薬物動態母集団モデルで最適な集団モデルを特定するため、標準的な薬物動態（PK）構造モデル手法を用いた。 • テデュグルチドの薬物動態と消化管活動との関係を評価する試みに際し、薬剤濃度と有効性との関係について、有効性評価項目に関係する本治験実施計画書の全データを精査した。 • 薬力学（PD）関係が認められない場合であっても探索的解析について報告することとした。
治験責任医師及び実施医療機関	9 ヵ国、32 施設（米国 15 施設、カナダ 4 施設、ベルギー1 施設、デンマーク 1 施設、ドイツ 3 施設、フランス 3 施設、英国 1 施設、オランダ 1 施設、ポーランド 3 施設）
試験期間	最初の被験者の組入れ：2004 年 5 月 25 日 最終被験者の完了時：2007 年 7 月 06 日

12.1 被験者の内訳、人口統計学的特性、及びベースライン特性

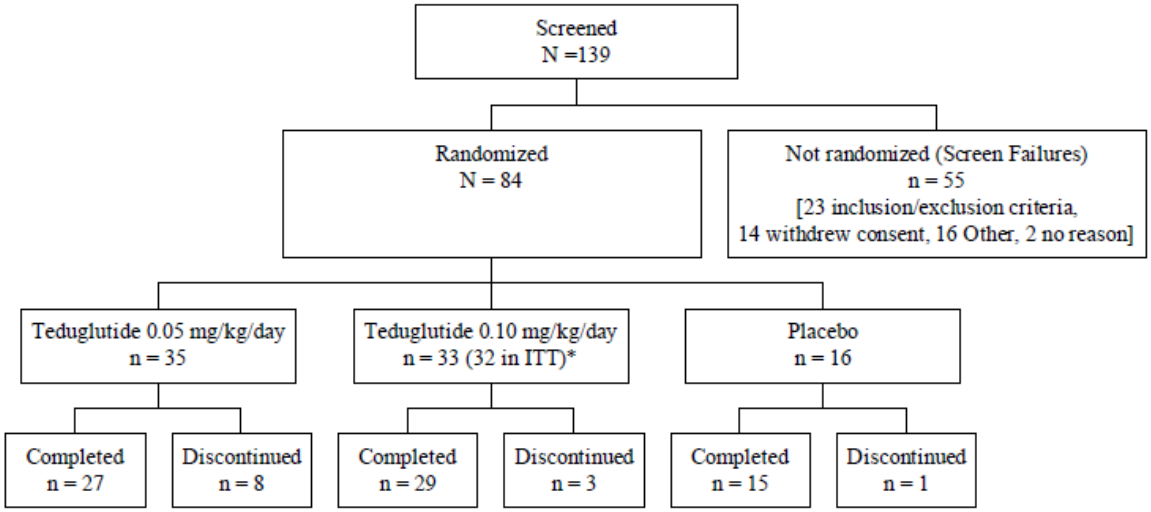
無作為化された被験者 84 例のうち 71 例が 24 週間の試験を完了した。無作為化された被験者 1 例（被験者番号 [redacted]）が治験薬の投与を受けなかった。したがって、無作為化され治験薬を投与された被験者は計 83 例であった（ITT 集団：プラセボ群 16 例、テデュグルチド 0.05 mg/kg/日群 35 例、テデュグルチド 0.10 mg/kg/日群 32 例）。

無作為割付けは、72 時間栄養分吸収検査への参加、及び 3 段階の PS 量（IV 輸液及び電解質のみ毎週 3～7 回、PS を毎週 3～5 回、及び PS を毎週 6～7 回）に基づいて層別した。そのため、被

験者は、一実施医療機関内ではなく実施医療機関全体で無作為化された。最初の被験者のスクリーニングは 2004 年 5 月 25 日に実施され、最終被験者の評価は 2007 年 7 月 6 日に行われた。

被験者の試験組入れから完了までを図 2.7.6.12 - 1 に示す。

図 2.7.6.12 - 1　CL0600-004 試験：被験者の内訳



*A total of 83 subjects were randomized and received study drug. One subject (#[redacted]) who was randomized to teduglutide 0.10 mg/kg/day group did not receive the study drug.

Source: M5.3.5.1 CL0600-004 CSR Figure 10-1

各解析対象集団の被験者の内訳を表 2.7.6.12 - 2 に示す。

表 2.7.6.12 - 2　　CL0600-004 試験：解析対象集団

Population[a]	Treatment Group, n (%) of subjects			
		Teduglutide		
	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 33	All Subjects N = 84
Randomized population	16 (100)	35 (100)	33 (100)	84 (100)
Intent-to-treat population (ITT)	16 (100)	35 (100)	32 (97.0)	83 (98.8)
Per-protocol population (PP)	15 (93.8)	26 (74.3)	29 (87.9)	70 (83.3)
Continued to Extension Study – (0600-005)	13 (81.3)	25 (71.4)	27 (81.8)	65 (77.4)

[a] Note: ITT population includes all subjects who were randomized and received at least one dose of study drug. Per protocol population includes all subjects who were randomized, received study drug, and had no significant protocol violations. One subject (#[redacted]) in the 0.05 mg/kg/day teduglutide treatment group completed the study but was not compliant with study drug doses and was not included in PP population.

Source: M5.3.5.1 CL0600-004 CSR Table 11-1

ベースラインの人口統計学的特性を表 2.7.6.12 - 3 に示す。概して、投与群間でベースラインの人口統計学的特性に大きな違いはみられなかった。本試験に組入れられた被験者の大部分は、白人（92.8%）で、年齢 19～79 歳（平均値：48.8 歳、中央値：52.0 歳）であり、被験者の 38.6%は

55 歳であった。本試験に参加した被験者は、女性（55.4%）が男性（44.6%）より多かった。高用量群では、低用量群及びプラセボ群と比較したとき、PS を 6～7 回/週使用する被験者が多く（34.4%）、IV 輸液の投与のみを受けている被験者は少なかった（9.4%）が、いずれの投与群及びいずれの PS 量レベルにおいてもその差は有意ではなかった。ベースラインの人口統計学的特性について、いずれの投与群間でも有意差はみられなかった。

また、ITT 集団のいずれの投与群でも、喫煙経験、現喫煙者、及びアルコール摂取のパターンに大きな違いはみられなかった。

表 2.7.6.12 - 3 CL0600-004 試験：人口統計学的特性及びベースライン特性（ITT 集団）

	Treatment Group			
		Teduglutide		
Variable	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	All Subjects N = 83
Age (years)				
N	16	35	32	83
Mean (SD)	49.4 (15.1)	47.1 (14.2)	50.3 (14.0)	48.8 (14.2)
Median (Range)	53.5 (20, 72)	51.0 (20, 68)	52.5 (19, 79)	52.0 (19, 79)
Gender n (%)				
Female	9 (56.3)	18 (51.4)	19 (59.4)	46 (55.4)
Male	7 (43.8)	17 (48.6)	13 (40.6)	37 (44.6)
Race n (%)				
Caucasian	15 (93.8)	32 (91.4)	30 (93.8)	77 (92.8)
Black	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)
PN consumption level n (%) *				
Level 1: IV fluids 3-7 x weekly	4 (25.0)	8 (22.9)	3 (9.4)	15 (18.1)
Level 2: PN 3-5 x weekly	8 (50.0)	19 (54.3)	18 (56.3)	45 (54.2)
Level 3: PN 6-7 x weekly	4 (25.0)	8 (22.9)	11 (34.4)	23 (27.7)
Height (cm)				
N	16	35	32	83
Mean (SD)	167.5 (9.4)	167.5 (10.8)	165.2 (7.1)	166.6 (9.2)
Median (Range)	169 (144, 180)	164 (144, 190)	165 (150, 179)	165 (144, 190)
Weight (kg)				
N	16	35	32	83
Mean (SD)	61.5 (8.6)	59.2 (8.7)	59.6 (10.0)	59.8 (9.1)
Median (Range)	60.8 (42, 79)	59.6 (42, 78)	58.3 (44, 80)	59.0 (42, 80)
BMI (kg/m^2)				
N	16	35	32	83
Mean (SD)	22.0 (2.9)	21.2 (3.0)	21.7 (2.6)	21.5 (2.8)
Median (Range)	21.3 (17, 28)	20.8 (16, 27)	21.0 (17, 26)	21.0 (16, 28)
Ever smoked n (%)				
Yes	8 (50.0)	19 (54.3)	17 (53.1)	44 (53.0)
No	8 (50.0)	16 (45.7)	15 (46.9)	39 (47.0)

表 2.7.6.12 - 3 CL0600-004 試験：人口統計学的特性及びベースライン特性（ITT 集団）

Variable	Treatment Group: Placebo N = 16	Teduglutide 0.05 mg/kg/d N = 35	Teduglutide 0.10 mg/kg/d N = 32	All Subjects N = 83
If, Yes, current smokers	5 (62.5)	11 (57.9)	6 (35.3)	22 (50.0)
Alcohol use n (%)				
Yes	10 (62.5)	20 (57.1)	17 (53.1)	47 (56.6)
No	6 (37.5)	15 (42.9)	15 (46.9)	36 (43.4)

* PN consumption level at entry into study, before optimization and stabilization
Note: p-values for overall treatment comparisons are based on the Fisher's exact test for categorical variables and on a one-way ANOVA with effect for treatment for continuous variables. The results for p-values were ≥ 0.518 for all treatment comparisons.
Source: M5.3.5.1 CL0600-004 CSR Table 11-2

腸切除の主な原因はクローン病（36.1%）又は血管病変（30.1%）であった。ストーマのある被験者の割合は 34.9%であった。残存小腸の長さ（平均値±SD）は、65.8±45.4 cm（範囲：6～200 cm）であった。切除対象に結腸も含まれていた被験者は 27 例（32.5%）であった。結腸の連続性をある程度保っている被験者 56 例（67.5%）のうち、20 例（35.7%）は、結腸の 75%超～100%が残存していたが、19 例（33.9%）は、残存結腸がわずかに 25%超～50%であった。残る 17 例（30.4%）の残存結腸は、50%超～75%であった。回腸遠位部／終末部が残存する被験者 17 例（20.5%）のうち、回盲弁を有する被験者は 9 例（52.9%）、有しない被験者は 8 例（47.1%）であった。被験者の大部分（53 例［63.9%］）では、残存小腸の長さは手術により測定された。ITT 集団の各群における SBS の既往歴を表 2.7.6.12 - 4 に示す。

表 2.7.6.12 - 4 CL0600-004 試験：人口統計学的特性及びベースライン特性、短腸症候群の既往歴（ITT 集団）

Variable	Treatment Group: Placebo N = 16	Teduglutide 0.05 mg/kg/d N = 35	Teduglutide 0.10 mg/kg/d N = 32	All Subjects N = 83
Cause of major intestinal resection, n (%)				
Crohn's disease	7 (43.8)	10 (28.6)	13 (40.6)	30 (36.1)
Vascular disease	3 (18.8)	14 (40.0)	8 (25.0)	25 (30.1)
Injury	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)
Volvulus	2 (12.5)	5 (14.3)	4 (12.5)	11 (13.3)
Other	3 (18.8)	3 (8.6)	5 (15.6)	11 (13.3)
Stoma, n (%)				
Yes	5 (31.3)	10 (28.6)	14 (43.8)	29 (34.9)
No	11 (68.8)	25 (71.4)	18 (56.3)	54 (65.1)
If yes, type				
Jejunostomy	4 (80.0)	6 (60.0)	4 (28.6)	14 (48.3)
Ileostomy	1 (20.0)	2 (20.0)	7 (50.0)	10 (34.5)

表 2.7.6.12 - 4 CL0600-004 試験：人口統計学的特性及びベースライン特性、短腸症候群の既往歴（ITT 集団）

Variable	Treatment Group			
		Teduglutide		
	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	All Subjects N = 83
Colostomy	0	2 (20.0)	3 (21.4)	5 (17.2)
Colon in continuity, n (%)				
Yes	11 (68.8)	26 (74.3)	19 (59.4)	56 (67.5)
No	5 (31.3)	9 (25.7)	13 (40.6)	27 (32.5)
If yes, remaining amount				
>25% - 50% Colon Remaining	4 (36.4)	7 (26.9)	8 (42.1)	19 (33.9)
>50% - 75% Colon Remaining	4 (36.4)	9 (34.6)	4 (21.1)	17 (30.4)
>75% - 100% Colon Remaining	3 (27.3)	10 (38.5)	7 (36.8)	20 (35.7)
Remaining small intestinal length (cm)				
N	15	31	27	73
Mean (SD)	77.3 (52.9)	58.3 (43.6)	68.1 (43.1)	65.8 (45.4)
Median (Range)	60 (15, 200)	50 (6, 200)	60(10,200)	60 (6, 200)
Not known n (%)	1 (6.3)	4 (11.4)	5 (15.6)	10 (12.0)
Distal/terminal ileum, n (%)				
Yes	3 (18.8)	6 (17.1)	8 (25.0)	17 (20.5)
No	13 (81.3)	28 (80.0)	23 (71.9)	64 (77.1)
If yes, ileocecal valve present				
Yes	1 (33.3)	5 (83.3)	3 (37.5)	9 (52.9)
No	2 (66.7)	1 (16.7)	5 (62.5)	8 (47.1)
Remaining anatomy length determined by, n (%)				
Surgery	11 (68.8)	20 (57.1)	22 (68.8)	53 (63.9)
Radiology	3 (18.8)	8 (22.9)	3 (9.4)	14 (16.9)
Surgery & Radiology	1 (6.3)	4 (11.4)	3 (9.4)	8 (9.6)
Other	0	0	2 (6.3)	2 (2.4)
Not applicable (N/A)	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)

Source：M5.3.5.1 CL0600-004 CSR Table 11-3

ベースラインの週間 PS 量（平均値±SD）は 11.7±5.96 L であり、被験者の大部分（71 例［85.5%］）は、中心静脈カテーテルの静脈内留置例であった。過去 6 ヵ月以内に、静脈カテーテル感染症、血栓症、又は閉塞症に対する治療を受けた被験者の割合は約 1/4（23 例［27.7%］）であった。静脈カテーテル感染による入院回数（平均値±SD）は 1.0±1.04 であった。血栓症及び／又は閉塞症発症回数（平均値±SD）は 0.5± 0.67 であった。PP 集団でも、ベースラインで同様の観察結果が得られた。

12.2 有効性の結果

12.2.1　有効性の主要評価項目

治療に対する奏効の程度及び持続期間を総合的にグレード化した指標（奏効スコア）を表 2.7.6.12 - 5 に示す。奏効スコアは、プラセボ群よりも実薬群が、また高用量群より低用量群が数字の上では高かった。

本試験における有効性の主要評価項目は奏効スコアとした。治験実施計画書では、ステップダウン手順を行うこととし、0.10 mg/kg/日群が統計学的に有意にプラセボ群を上回らなかった場合、それ以上の統計学的検定は行わないものとした。プラセボ群と 0.10 mg/kg/日群との間には、統計学的有意差は認められなかった。

しかし、PS 量が 20%減少した被験者や PS から離脱した被験者などの有効性を示す臨床的エビデンスがみられたことから、0.05 mg/kg/日群について検定を行うことが決定された。テデュグルチド 0.05 mg/kg/日投与群とプラセボ群との比較について検定した結果、奏効スコアに統計学的有意差が認められた（p=0.007、ランクを用いた ANCOVA）（表 2.7.6.12 - 6）。

表 2.7.6.12 - 5 CL0600-004 試験：奏効スコア別被験者数及び割合（ITT 集団）

	Response Category ITT Population				
Treatment Group (n, %)	0 No Response	1	2	4	5 Off-PN
Placebo	15 (93.8)	0	1 (6.3)	0	0
Teduglutide 0.05 mg/kg/day	19 (54.3)	6 (17.1)	6 (17.1)	2 (5.7)	2 (5.7)
Teduglutide 0.10 mg/kg/day	24 (75.0)	2 (6.3)	4 (12.5)	2 (6.3)	0
Total: (0.05 + 0.10 mg/kg/day)	43 (64.2)	8 (11.9)	10 (14.9)	4 (6.0)	2 (3.0)

Note: Subject # [redacted] is missing the Baseline value and cannot be ranked.
Source: M5.3.5.1 CL0600-004 CSR Table 11-6

表 2.7.6.12 - 6 CL0600-004 試験：奏効スコア統計量（ITT 集団）

	Test Statistic	Degrees of Freedom	p-Value	p-Value (adjusted)
	Primary Efficacy Analysis: ANCOVA Test*			
Comparison	ITT Population			
0.10 mg/kg/day teduglutide vs. Placebo	1.96	1	0.161	0.161
0.05 mg/kg/day teduglutide vs. Placebo	7.32	1	0.007	
0.10 mg/kg/day teduglutide vs. 0.05 mg/kg/day teduglutide	3.06	1	0.080	

* Test statistic is based on pairwise ANCOVA test after adjustment for the Baseline PN consumption level and Baseline PN volume as a covariate.
Subject # [redacted] is missing the Baseline value and cannot be ranked. Therefore, this subject is not included in the calculation of the test statistic for Rank ANCOVA 0.05 mg/kg/day – Placebo and 0.10 mg/kg/day – 0.05 mg/kg/day teduglutide.
p-value is adjusted for multiple comparisons in the primary efficacy analysis.
Source: M5.3.5.1 CL0600-004 CSR Table 11-7

12.2.2　副次的有効性及び有効性のその他の評価項目／アウトカム

Week 20 と Week 24 の両時点において PS 量の 20%減少を達成した被験者（レスポンダー）の割合は、テデュグルチド 0.05 mg/kg/日群がプラセボ群を上回った（16/35 例[45.7%]vs. 1/16 例[6.3%]、p=0.005）。テデュグルチド 0.10 mg/kg/日群とプラセボ群との間には有意差はみられなかった（表 2.7.6.12 - 7、8/32 例；25% vs. 1/16 例；6.3%、p=0.172）。

表 2.7.6.12 - 7 CL0600-004 試験：レスポンダー数とその割合（%）（ITT 集団）

	Treatment Group, n (%) of subjects			
		Teduglutide		
Binary Responder Status	**Placebo N=16**	**0.05 mg/kg/d N=35**	**0.10 mg/kg/d N=32**	**Total N=67**
Response ≥ 20% PN Reduction from Baseline to Week 20 and maintained to Week 24.				
Responders	1 (6.3)	16 (45.7)	8 (25.0)	24 (35.8)
Non-Responders	15 (93.8)	19 (54.3)	24 (75.0)	43 (64.2)
95% CI of % Responders	0, 18.1	29.2, 62.2	10.0, 40.0	
Difference from Placebo for % Responders		39.5	18.8	
p-value for Treatment Comparison		0.009	0.238	
ANCOVA (on the rank) test:			**p-value***	
0.10 mg/kg/d teduglutide vs. Placebo			0.172	
0.05 mg/kg/d teduglutide vs. Placebo			0.005	
0.10 mg/kg/d teduglutide vs. 0.05 mg/kg/d teduglutide			0.053	

Note: Treatment comparisons for difference from placebo are based on Fisher's Exact test
* Test Statistic is based on Pairwise rank ANCOVA after adjustment for the Baseline PN consumption level and Baseline PN volume as a covariate. Subject #[redacted] is missing Baseline and cannot be ranked. Therefore, this subject is not included in the calculation of the test statistic for Rank ANCOVA 0.05 mg/kg/day – Placebo and 0.10 mg/kg/day – 0.05 mg/kg/day.
Source: M5.3.5.1 CL0600-004 CSR Table 11-9

ITT 集団におけるその他の有効性に関わる副次的評価項目／アウトカムを以下に示す。

- 週間 PS 施行日数が 1 日以上減少した被験者の割合は、テデュグルチド 0.05 mg/kg/日群が 11/35 例（31.4%）、テデュグルチド 0.10 mg/kg/日群が 3/32 例（9.4%）であった。これらはプラセボ群（4/16 例；25%減少）と比較して統計学的に有意ではなかった（表 2.7.6.12 - 8）。

表 2.7.6.12 - 8 CL0600-004 試験 : 週間 PS 施行日数が 1 日以上減少した被験者数とその割合（%）（ITT 集団）

	Treatment Group, n (%) of subjects			
		Teduglutide		
Response Status	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	Total N = 67
Yes	4 (25.0)	11 (31.4)	3 (9.4)	14 (20.9)
No	12 (75.0)	24 (68.6)	29 (90.6)	53 (79.1)
95% CI of % Responders	3.8, 46.2	16.0, 46.8	0.0, 19.5	
Difference from Placebo for %Achievers		6.4%	– 15.6%	
p-value for Treatment Comparison		0.749	0.201	
ANCOVA (on the rank) test:			**p-value**	
0.10 mg/kg/day teduglutide vs. Placebo			0.120	
0.05 mg/kg/day teduglutide vs. Placebo			0.684	
0.10 mg/kg/day teduglutide vs. 0.05 mg/kg/day teduglutide			0.031	

Note: Treatment comparisons for difference from placebo are based on Fisher's Exact test.
* Test statistic is based on Pairwise rank ANCOVA after adjustment for the Baseline PN consumption level and Baseline PN volume as a covariate.
Source: M5.3.5.1 CL0600-004 CSR Table 11-10

- Week 24 及び最終投与来院時におけるベースラインからの週間 PS エネルギー摂取量（キロジュール）の変化量（平均値）はプラセボと比較して、統計学的に有意な差はみられなかった。
- 週間 PS 量はベースラインから Week 24 までに、両実薬群では 2.5 L の減少、プラセボ群では 0.9 L の減少し（いずれも平均値）（プラセボと各実薬群の比較、p=0.08）、この結果から両実薬群の有効性に大きな差はないことが示された（p=0.98）。前述した実薬群間におけるレスポンダーの割合（%）の差は、ベースラインの PS 量に、2 つの実薬群間で 32%の差があったことに起因すると考えられた（9.6 L/週 vs. 12.7 L/週）（表 2.7.6.12 - 9）。

表 2.7.6.12 - 9 CL0600-004 試験 : ベースラインからの週間 PS 量の減少（ITT 集団）

	Weekly PN Volume (L)			
		Teduglutide		
Visit	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	Total N = 67
Baseline*				
N	16	34	32	66
Mean (SD)	10.72 (6.12)	9.62 (4.47)	12.71 (7.06)	11.12 (6.03)
Median (Range)	8.98 (5.2, 27.0)	9.65 (2.3, 17.5)	11.60 (3.3, 32.5)	10.27 (2.3, 32.5)
Change from Baseline to Dosing Week 24				
N	15	27	29	56
Mean (SD)	–0.90 (1.41)	–2.48 (2.34)	–2.47 (3.33)	–2.47 (2.87)
Median (Range)	–0.53 (–3.5, 1.5)	–1.66 (–7.2, 0.8)	–1.93 (–15.0, 3.3)	–1.75 (–15.0, 3.3)

表 2.7.6.12 - 9 CL0600-004 試験：ベースラインからの週間 PS 量の減少（ITT 集団）

	Weekly PN Volume (L)			
		Teduglutide		
Visit	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	Total N = 67
Difference from placebo		–1.408	–1.426	
Difference from placebo p-value		0.0768	0.0755	
Difference from 0.05 mg/kg/d p-value			0.9776	
Change from Baseline to Last Dosing Visit				
N	16	34	32	66
Mean (SD)	–0.84 (1.38)	–1.83 (2.97)	–2.29 (3.22)	–2.05 (3.08)
Median (Range)	–0.43 (–3.5, 1.5)	–1.53 (–7.2, 9.2)	–1.57 (–15.0, 3.3)	–1.53 (–15.0, 9.2)
Overall N**	94	176	178	
Mean	–0.603	–1.353	–1.569	
Difference from placebo p-value		0.1794	0.1618	
Difference from 0.05mg/kg/d p-value			0.9188	

Actual Weekly PN volume = (sum of last 14 days prior to next visit/14) x 7
* PN volume at Baseline after Optimization and Stabilization
** In each treatment group, the Overall N represents the sum of the subjects at each visit. A repeated measures model (Proc Mixed) was used with effects for treatment, visit, and treatment by visit interaction, and Baseline PN and Baseline PN consumption level as covariates.
Source: M5.3.5.1 CL0600-004 CSR Table 11-12

- テデュグルチド投与被験者では、経口による水分摂取量が減少し、尿量が増加した（正味の効果は合計で約 500 mL/48 時間）。プラセボ投与被験者では Week 24 時に、水分摂取量（400 mL）が増加し、尿量は 200 mL 増加し、48 時間測定時の総水分増加量（中央値）は 200 mL であった。
- Week 24 に ITT 集団を対象として、テデュグルチドの両投与群における血漿中シトルリン濃度の変化量はプラセボ群と比較して統計学的に有意に大きかった（p<0.0001）。
- Week 24 の小腸及び大腸内部の陰窩－絨毛構造及び細胞構成を検討した結果、テデュグルチド投与により、成人 SBS 患者では腸管粘膜に顕著な構造順応が誘発されることが示された。テデュグルチドの両群は、小腸絨毛高の伸長を介して吸収上皮の拡張を誘発した。低用量群では大腸の陰窩深度に変化はみられなかったが、高用量群では顕著な変化が観察された。粘膜量ベースでの粘膜組成はテデュグルチド投与群もプラセボ群も同様であり、したがって腸粘膜の構造的変化には既存の組織と細胞のサイズも組成も変わらない新たな組織が産生されたことが示唆される。腸組織検体の病理組織学的検査結果では異形成変化の発生は認められなかった。

一部の実施医療機関において、SBS 患者を対象として、72 時間栄養吸収に対するテデュグルチドの効果を評価しようと試みた。しかし、技術的及びロジスティック上の理由により成功に至らず、極めて少数のデータが得られたに過ぎなかった。データ量が少ないためこれを解釈することは困難若しくは不可能である。

- 探索的有効性アウトカムである、週間 PS 量（平均値）が 20%減少するまでの期間（平均値）は、プラセボ群では 19.5 週間、テデュグルチド 0.05 mg/kg/日群では 14.4 週間であり、その差は統計学的に有意であった。テデュグルチド 0.10 mg/kg/日群では（18.8 週間）とプラセボ群の間に統計学的有意差はみられなかった。
- PK/PD を解析した結果、テデュグルチドの AUC はレスポンダーと非レスポンダーの間で相関はなかった。テデュグルチドの曝露量（AUC）と、週間 PS 量のベースラインからの変化量（絶対値）との間に明らかな関係はみられなかった。
- ベースライン、Week 24、及び最終投与来院時の投与群間には、IV カテーテルアクセスに統計学的有意差はみられなかった。ベースラインと比較したとき、Week 24 に IV カテーテルアクセスが減少した被験者の割合は、テデュグルチド 0.05 mg/kg/日群が 55.6%、テデュグルチド 0.10 mg/kg/日群が 44.8%、プラセボ群が 31.3%であった。最終投与来院時にも同様の結果が観察された。
- 骨マーカーの骨型アルカリホスファターゼ（BSAP）又はピリジノリン架橋 N テロペプチド（NTx）について、テデュグルチド 0.10 mg/kg/日群及び 0.05 mg/kg/日群と、プラセボ群との間、又はテデュグルチド 0.05 mg/kg/日群とテデュグルチド 0.10 mg/kg/日群との間に、統計学的有意差はみられなかった。
- 全身骨塩量（BMC）について、プラセボ群とテデュグルチド 0.10 mg/kg/日投与群との差（平均値）に統計学的に有意な増加がみられたが（p=0.046）、プラセボ群とテデュグルチド 0.05 mg/kg/日投与群との差は有意ではなかった（p=0.065）。検討した他の脊椎及び全身領域並びに BMC については、投与群間に統計学的有意差はみられなかった。総除脂肪組織及び体幹の除脂肪組織について、プラセボ群とテデュグルチド群との差（平均値）に、統計学的に有意な増加がみられた。
- 3 種類の QOL 評価（SF-36、EuroQol EQ-5D、及び IBDQ）から得られた総合成績によると、QOL に重要な効果は認められなかった。

12.3 母集団薬物動態／薬力学解析

非線形混合効果母集団モデル法を用い、テデュグルチド薬物動態パラメータの平均値及び個別被験者の値について、その特性を検討した。

- 典型的な被験者におけるテデュグルチドのクリアランス（CL/F）は 12.2 L/hr（範囲：10.2～13.9 L/hr）、V/F は約 65.3 L と推定された。

- C_{max}（ng/mL）の平均値±SD は、0.05 mg/kg/日群が 36.4±13.6、0.1 mg/kg/日群が 70.5±26.07 であった。
- 年齢はテデュグルチドの薬物動態に顕著な影響を及ぼさなかった。そのため、65 歳以上の被験者と 65 歳未満の被験者間で、年齢の違いのみの理由から、テデュグルチドの曝露量に差が生じることは予測されない。

テデュグルチドの曝露量と PS 量への反応性との関係、及び血漿中シトルリン濃度と PS 量への反応性との関係を評価するため、探索的な PK/PD 解析を実施した。その結果、テデュグルチドの AUC はレスポンダーと非レスポンダーとの間で大きく異なるものではなかった。また、テデュグルチドの AUC と、週間 PS 量のベースラインからの変化量との間に明らかな関連はみられなかった。Week 24 において、テデュグルチドの AUC と血漿中シトルリン濃度との間に明らかな関連はみられなかった。同様に、PS 量のベースラインからの減少と血漿中シトルリン濃度との間にも関連はみられなかった。

テデュグルチド 1 日 1 回 24 週間投与後の血漿中シトルリン濃度の変化に関する母集団 PD モデルを開発した。最大効果の 50%に到達するまでの時間（血漿中シトルリン濃度の最大変化の 50%達成に要する時間）は 2.43 週間であり、95%信頼区間の上限は 4 週間未満であった。両群とも、Week 4 までに最大効果（血漿中シトルリン濃度の最大変化）の 62%に到達し、Week 8 までには最大効果の 78%に到達した。用量を増加すると最大薬理効果（E_{max}）推定値も増加し、最大効果は、0.05 mg/kg/日群が 9.32 µmol/L、0.10 mg/kg/日群が 15.2 µmol/L であった。以上より、SBS 患者にテデュグルチドを 1 日 1 回投与することで、血漿中シトルリン濃度が約 25～31 µmol/L に上昇するものと思われる。これらの値は、正常な健康被験者を対象としてこれまでに報告された血漿中シトルリン濃度と同様もしくはそれに近い値である。

12.4 安全性の結果

12.4.1　曝露状況

安全性解析対象集団は、無作為化され治験薬の投与を受けた被験者 83 例を対象とした。これは ITT 集団と同一の集団であった。

テデュグルチド又はプラセボの曝露期間を表 2.7.6.12 - 10 に示す。

表 2.7.6.12 - 10　CL0600-004 試験：治験薬への曝露（ITT 集団）

Number of Weeks on Study Drug [a]	Treatment Group			
		Teduglutide		
	Placebo	0.05 mg/kg/d	0.10 mg/kg/d	Total
N	16	35	32	67
Mean (SD)	24.3 (1.3)	20.7 (8.0)	23.2 (5.6)	21.9 (7.0)
Median (Range)	24.1 (21.1, 28.0)	24.1 (0.6, 27.6)	24.4 (0.9, 29.7)	24.1 (0.6, 29.7)
Weeks on Study Drug	**Number (%) of Subjects Dosed**			
< 1	0	1 (2.9)	1 (3.1)	2 (3.0)
≥ 1 - < 4	0	3 (8.6)	0	3 (4.5)
≥ 4 - < 8	0	1 (2.9)	1 (3.1)	2 (3.0)
≥ 12 - < 16	0	2 (5.7)	1 (3.1)	3 (4.5)
≥ 20 - < 24	2 (12.5)	5 (14.3)	1 (3.1)	6 (9.0)
≥ 24 - < 28	13 (81.3)	23 (65.7)	27 (84.4)	50 (74.6)
≥ 28	1 (6.3)	0	1 (3.1)	1 (1.5)

[a] Number of weeks on study drug = (Date of last dose – Date of first dose + 1) divided by 7 without taking into account the missed doses

Source: M5.3.5.1 CL0600-004 CSR Table 12-1

12.4.2　有害事象

本項では特に断りのない限り、有害事象とは試験治療下に発現した有害事象（TEAE）であり、重篤な有害事象とは試験治療下の重篤な有害事象を示す。

12.4.2.1　有害事象の概要

本試験で発現した有害事象の概要を表 2.7.6.12 - 11 に示す。有害事象はプラセボ群 15 例（93.8%）及びテデュグルチド群 64 例（95.5%）に発現した。これは投与群全体で同程度であった。有害事象の大部分は軽度（プラセボ群 13 例［81.3%］、テデュグルチド群 52 例［77.6%］）、又は中等度（プラセボ群 9 例［56.3%］、テデュグルチド群 47 例［70.1%］）であり、重度の事象が発現した被験者はプラセボ群 3 例（18.8%）、テデュグルチド群 15 例（22.4%）であった。治験責任医師によって治験薬と関連ありと判断された事象は、プラセボ群 2 例（12.5%）、テデュグルチド群 34 例（50.7%）に発現した。

本試験では、治験薬の投与を受けた被験者の死亡はなかったが、無作為割付け前のスクリーニング期に死亡が 1 例みられた。この被験者は、5[redacted]歳の白人女性で、クローン病及び肺炎の既往歴があり、2005 年 1 月 20 日に試験に組み入れられた。2005 年 3 月 10 日（Day 50）午前 5：30、被験者が大量の血液中に横たわって死亡しているのが発見された。治験責任医師の意見によると、被験者の死亡と治験薬に関連はなく、大量の上部消化管出血が原因と判断された。

重篤な有害事象の発現頻度はいずれの投与群でも同程度であった。試験期間中に重篤な有害事象の発現した被験者数は 29 例であった（プラセボ群 5 例［31.3%］、テデュグルチド 0.05 mg/kg/

日群 13 例［37.1%］、テデュグルチド 0.10 mg/kg/日群 11 例［34.4%］）。試験中止に至った有害事象の発現頻度は、テデュグルチド 0.05 mg/kg/日群（6 例［17.1%］）がプラセボ群（1 例［6.3%］）及びテデュグルチド 0.10 mg/kg/日群（2 例［6.3%］）より高かった。

表 2.7.6.12 - 11　CL0600-004 試験：有害事象の概要（安全性解析対象集団）

Seriousness, Severity, Relationship, and Discontinuation	Treatment Group							
	Placebo N = 16		Teduglutide 0.05 mg/kg/d N = 35		Teduglutide 0.10 mg/kg/d N = 32		Teduglutide Total N = 67	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any AE	15 (93.8)	91	33 (94.3)	279	31 (96.9)	250	64 (95.5)	529
AE severity								
Mild	13 (81.3)	50	26 (74.3)	172	26 (81.3)	157	52 (77.6)	329
Moderate	9 (56.3)	30	23 (65.7)	75	24 (75.0)	86	47 (70.1)	161
Severe	3 (18.8)	11	9 (25.7)	32	6 (18.8)	7	15 (22.4)	39
AE relationship								
Not Related	15 (93.8)	84	31 (88.6)	234	31 (96.9)	187	62 (92.5)	421
Related	2 (12.5)	7	15 (42.9)	45	19 (59.4)	63	34 (50.7)	108
AE leading to study discontinuation	1 (6.3)	1	6 (17.1)	12	2 (6.3)	3	8 (11.9)	15
Any SAE	5 (31.3)	12	13 (37.1)	43	11 (34.4)	16	24 (35.8)	59
SAE severity								
Mild	2 (12.5)	2	3 (8.6)	5	7 (21.9)	9	10 (14.9)	14
Moderate	1 (6.3)	2	8 (22.9)	14	2 (6.3)	3	10 (14.9)	17
Severe	2 (12.5)	8	7 (20.0)	24	4 (12.5)	4	11 (16.4)	28
SAE relationship								
Not Related	5 (31.3)	12	9 (25.7)	33	9 (28.1)	14	18 (26.9)	47
Related	0	0	6 (17.1)	10	2 (6.3)	2	8 (11.9)	12
Death	0	0	0	0	0	0	0	0

Note: This table contains counts of subjects and events. If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event is counted. Subject [redacted] in the 0.05 mg/kg/day Teduglutide treatment group who discontinued due to an adverse event (Table 14.3.1.1 and Table 14.3.2.8) is not included as discontinuing due to an adverse event in (Table 14.1.1.7) but is included as discontinuing due to Subject Decision only.

Source: M5.3.5.1 CL0600-004 CSR Table 12-2

12.4.2.2　　有害事象の分析

有害事象を MedDRA 器官別大分類別に表 2.7.6.12 - 12 に示す。有害事象の発現頻度が高かった器官別大分類は（いずれかの投与群で 3 例以上発現）、胃腸障害（プラセボ群 31.3%、テデュグルチド群 59.7%）、一般・全身障害及び投与部位の状態（プラセボ群 43.8%、テデュグルチド群 53.7%）、感染症及び寄生虫症（プラセボ群：62.5%、テデュグルチド群 64.2%）、傷害、中毒及び処置合併症（プラセボ群 18.8%、テデュグルチド群 20.9%）、筋骨格系及び結合組織障害（プラセボ群 25.0%、テデュグルチド群 28.4%）、神経系障害（プラセボ群 6.3%、テデュグルチド群 34.3%）、並びに呼吸器、胸郭及び縦隔障害（プラセボ群 37.5%、テデュグルチド群 16.4%）であった。

有害事象の発現頻度は高くはないが、テデュグルチド群の発現頻度がプラセボ群を 5%以上上回った SOC は、「胃腸障害」、「一般・全身障害及び投与部位の状態」、「臨床検査」、「神経系障害」、「精神障害」、並びに「皮膚及び皮下組織障害」の 6 分類であった。

高位グループ語を用いて、カテーテル合併症及びカテーテル感染を集計した。カテーテル合併症を発現した被験者は 23 例（プラセボ群 6 例、0.05 mg/kg/日テデュグルチド群 7 例、テデュグルチド 0.10 mg/kg/日群 10 例）であった。注入部位反応（カテーテル関連、注射部位ではない）を発現した被験者は 7 例（プラセボ群 3 例、0.05 mg/kg/日テデュグルチド群 1 例、テデュグルチド 0.10 mg/kg/日群 3 例）であった。感染（病原体の種類は特定されていない）が認められた被験者は 16 例（プラセボ群 3 例、0.05 mg/kg/日テデュグルチド群 7 例、テデュグルチド 0.10 mg/kg/日群 6 例）であった。感染の内訳は、カテーテル菌血症、カテーテル敗血症、及びカテーテル留置部位感染であった。医療用具故障がみられた被験者は、プラセボ群 1 例及びテデュグルチド 0.10 mg/kg/日群 1 例の計 2 例であった。カテーテル関連血流感染（カテーテル敗血症）がみられた割合（%）は、プラセボ群が 12.5%、テデュグルチド 0.05 mg/kg/日群が 11.4%、テデュグルチド 0.10 mg/kg/日群が 12.5%であった。

表 2.7.6.12 - 12　CL0600-004 試験：有害事象の発現頻度（発現例数が 3 例以上）（安全性解析対象集団）

MedDRA SOC / PT		Treatment Group							
				Teduglutide					
		Placebo N = 16		0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any AE		**15 (93.8)**	**91**	**33 (94.3)**	**279**	**31 (96.9)**	**250**	**64 (95.5)**	**529**
Gastrointestinal disorders	**胃腸障害**	**5 (31.3)**	**15**	**21 (60.0)**	**71**	**19 (59.4)**	**70**	**40 (59.7)**	**141**
Abdominal distension	腹部膨満	0	0	6 (17.1)	7	3 (9.4)	4	9 (13.4)	11
Abdominal pain	腹痛	2 (12.5)	2	7 (20.0)	12	9 (28.1)	11	16 (23.9)	23
Abdominal pain upper	上腹部痛	0	0	4 (11.4)	5	2 (6.3)	4	6 (9.0)	9
Diarrhoea	下痢	0	0	0	0	3 (9.4)	3	3 (4.5)	3
Dyspepsia	消化不良	1 (6.3)	1	0	0	3 (9.4)	4	3 (4.5)	4
Nausea	悪心	4 (25.0)	4	5 (14.3)	7	10 (31.3)	13	15 (22.4)	20
Vomiting	嘔吐	2 (12.5)	2	4 (11.4)	8	6 (18.8)	7	10 (14.9)	15
General disorders and Administration site conditions	**全身障害および投与局所様態**	**7 (43.8)**	**15**	**13 (37.1)**	**20**	**23 (71.9)**	**52**	**36 (53.7)**	**72**
Asthenia	無力症	0	0	3 (8.6)	3	2 (6.3)	2	5 (7.5)	5
Catheter related complications	カテーテル合併症	3 (18.8)	3	1 (2.9)	1	3 (9.4)	3	4 (6.0)	4
Fatigue	疲労	2 (12.5)	2	1 (2.9)	1	5 (15.6)	7	6 (9.0)	8
Injection site bruising	注射部位挫傷	0	0	1 (2.9)	1	7 (21.9)	8	8 (11.9)	9
Injection site erythema	注射部位紅斑	0	0	1 (2.9)	1	6 (18.8)	6	7 (10.4)	7
Injection site pain	注射部位疼痛	0	0	0	0	4 (12.5)	5	4 (6.0)	5
Pain	疼痛	1 (6.3)	1	0	0	4 (12.5)	4	4 (6.0)	4
Pyrexia	発熱	1 (6.3)	1	3 (8.6)	3	3 (9.4)	3	6 (9.0)	6

表 2.7.6.12 - 12 CL0600-004 試験：有害事象の発現頻度（発現例数が 3 例以上）（安全性解析対象集団）

MedDRA SOC / PT		Treatment Group							
				Teduglutide					
		Placebo N = 16		0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Infections and Infestations	**感染症および寄生虫症**	**10 (62.5)**	**14**	**23 (65.7)**	**60**	**20 (62.5)**	**40**	**43 (64.2)**	**100**
Catheter sepsis	カテーテル敗血症	2 (12.5)	4	4 (11.4)	12	4 (12.5)	5	8 (11.9)	17
Catheter site infection	カテーテル留置部位感染	0	0	3 (8.6)	3	1 (3.1)	1	4 (6.0)	4
Influenza	インフルエンザ	1 (6.3)	1	3 (8.6)	3	4 (12.5)	4	7 (10.4)	7
Nasopharyngitis	鼻咽頭炎	2 (12.5)	2	6 (17.1)	9	5 (15.6)	7	11 (16.4)	16
Urinary tract infection	尿路感染	3 (18.8)	3	3 (8.6)	7	5 (15.6)	6	8 (11.9)	13
Injury, Poisoning and Procedural Complications	**傷害、中毒および処置合併症**	**3 (18.8)**	**5**	**6 (17.1)**	**9**	**8 (25.0)**	**13**	**14 (20.9)**	**22**
Intestinal stoma complications	腸管ストーマ合併症	0	0	1 (2.9)	1	5 (15.6)	5	6 (9.0)	6
Musculoskeletal and Connective tissue disorders	**筋骨格系および結合組織障害**	**4 (25.0)**	**10**	**6 (17.1)**	**9**	**13 (40.6)**	**15**	**19 (28.4)**	**24**
Arthralgia	関節痛	1 (6.3)	1	2 (5.7)	4	3 (9.4)	3	5 (7.5)	7
Back pain	背部痛	1 (6.3)	2	0	0	3 (9.4)	3	3 (4.5)	3
Nervous system disorders	**神経系障害**	**1 (6.3)**	**3**	**13 (37.1)**	**36**	**10 (31.3)**	**20**	**23 (34.3)**	**56**
Headache	頭痛	1 (6.3)	1	9 (25.7)	29	7 (21.9)	12	16 (23.9)	41
Respiratory, thoracic and mediastinal disorders	**呼吸器、胸郭および縦隔障害**	**6 (37.5)**	**8**	**8 (22.9)**	**13**	**3 (9.4)**	**4**	**11 (16.4)**	**17**

表 2.7.6.12 - 12 CL0600-004 試験：有害事象の発現頻度（発現例数が 3 例以上）（安全性解析対象集団）

MedDRA SOC / PT		Treatment Group							
				Teduglutide					
		Placebo N = 16		0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Cough	咳嗽	0	0	3 (8.6)	3	1 (3.1)	1	4 (6.0)	4

MedDRA = Medical Dictionary for Regulatory Activities V. 7.0; SOC = system organ class; PT = preferred term.
Note: This table contains counts of subjects and events. If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event was counted.
Source: M5.3.5.1 CL0600-004 CSR Table 12-3

治験責任医師により治験薬と関連ありと判断された有害事象を表 2.7.6.12 - 13 に示す。

治験責任医師により治験薬と関連ありと判断された有害事象は、36 例に 115 件（プラセボ群 2 例 7 件、テデュグルチド 0.05 mg/kg/日群 15 例 45 件、テデュグルチド 0.10 mg/kg/日群 19 例 63 件）認められた。いずれかの投与群で被験者の 10%以上に発現した関連ありの有害事象は、悪心、注射部位挫傷、注射部位紅斑、注射部位疼痛、及び腸管ストーマ合併症であった。

本試験で認められた全有害事象を因果関係別に表 2.7.6.12 - 16 に示す。

表 2.7.6.12 - 13　CL0600-004 試験：治験責任医師により治験薬と関連ありとされた有害事象一覧（安全性解析対象集団）

		Treatment Group							
		Placebo N = 16		Teduglutide					
				0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
MedDRA SOC / PT		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any AE		**2 (12.5)**	**7**	**15 (42.9)**	**45**	**19 (59.4)**	**63**	**34 (50.7)**	**108**
Cardiac disorders	**心臓障害**	**0**	**0**	**1 (2.9)**	**1**	**0**	**0**	**1 (1.5)**	**1**
Cardiac failure congestive	うっ血性心不全	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Eye disorders	**眼障害**	**0**	**0**	**0**	**0**	**1 (3.1)**	**1**	**1 (1.5)**	**1**
Lacrimation increased	流涙増加	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Gastrointestinal disorders	**胃腸障害**	**1 (6.3)**	**5**	**10 (28.6)**	**22**	**9 (28.1)**	**22**	**19 (28.4)**	**44**
Abdominal discomfort	腹部不快感	0	0	0	0	1 (3.1)	2	1 (1.5)	2
Abdominal distension	腹部膨満	0	0	3 (8.6)	3	1 (3.1)	2	4 (6.0)	5
Abdominal hernia	腹部ヘルニア	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Abdominal pain	腹痛	1 (6.3)	1	2 (5.7)	4	1 (3.1)	2	3 (4.5)	6
Abdominal rigidity	腹部硬直	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Abdominal tenderness	腹部圧痛	0	0	0	0	2 (6.3)	2	2 (3.0)	2
Abnormal faeces	異常便	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Colonic polyp	結腸ポリープ	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Constipation	便秘	0	0	2 (5.7)	2	0	0	2 (3.0)	2
Crohn’s disease	クローン病	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Dyspepsia	消化不良	1 (6.3)	1	0	0	0	0	0	0
Flatulence	鼓腸	1 (6.3)	1	0	0	0	0	0	0
Gastrointestinal pain	消化器痛	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Hemorrhoidal hemorrhage	痔出血	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Intestinal obstruction	腸管閉塞	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Loose stools	軟便	1 (6.3)	1	0	0	0	0	0	0
Nausea	悪心	1 (6.3)	1	4 (11.4)	4	3 (9.4)	5	7 (10.4)	9
Pancreatitis	膵炎	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Retching	レッチング	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Short-bowel syndrome	短小腸症候群	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Small intestinal obstruction	小腸閉塞	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
Vomiting	嘔吐	0	0	2 (5.7)	2	2 (6.3)	3	4 (6.0)	5

表 2.7.6.12 - 13 CL0600-004 試験：治験責任医師により治験薬と関連ありとされた有害事象一覧（安全性解析対象集団）

MedDRA SOC / PT		Treatment Group							
		Placebo N = 16		Teduglutide					
				0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
General disorders and Administration site conditions	**全身障害および投与局所様態**	**2 (12.5)**	**2**	**6 (17.1)**	**9**	**15 (46.9)**	**25**	**21 (31.3)**	**34**
Asthenia	無力症	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
Discomfort	不快感	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Edema	浮腫	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Edema peripheral	末梢性浮腫	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
Fatigue	疲労	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Injection site bruising	注射部位挫傷	0	0	1 (2.9)	1	6 (18.8)	7	7 (10.4)	8
Injection site dermatitis	注射部位皮膚炎	1 (6.3)	1	0	0	0	0	0	0
Injection site erythema	注射部位紅斑	0	0	1 (2.9)	1	5 (15.6)	5	6 (9.0)	6
Injection site hemorrhage	注射部位出血	1 (6.3)	1	0	0	0	0	0	0
Injection site induration	注射部位硬結	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Injection site pain	注射部位疼痛	0	0	0	0	4 (12.5)	4	4 (6.0)	4
Injection site pruritus	注射部位そう痒感	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Injection site reaction	注射部位反応	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Injection site swelling	注射部位腫脹	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
Pain	疼痛	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Thirst decreased	口渇感減少	0	0	2 (5.7)	2	0	0	2 (3.0)	2
Venipuncture site bruise	静脈穿刺部位挫傷	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Injury, poisoning and procedural complications	**傷害、中毒および処置合併症**	**0**	**0**	**3 (8.6)**	**3**	**5 (15.6)**	**6**	**8 (11.9)**	**9**
Intestinal stoma complication	腸管ストーマ合併症	0	0	1 (2.9)	1	4 (12.5)	4	5 (7.5)	5
Joint sprain	関節捻挫	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Post procedural hemorrhage	処置後出血	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Stoma site reaction	ストーマ部反応	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
Hepatobiliary disorders	**肝胆道系障害**	**0**	**0**	**1 (2.9)**	**3**	**0**	**0**	**1 (1.5)**	**3**
Cholecystitis	胆嚢炎	0	0	1 (2.9)	3	0	0	1 (1.5)	3
Investigations	**臨床検査**	**0**	**0**	**1 (2.9)**	**1**	**3 (9.4)**	**4**	**4 (6.0)**	**5**
Blood alkaline phosphatase inc	血中アルカリホスファターゼ増加	0	0	0	0	1 (3.1)	1	1 (1.5)	1

表 2.7.6.12 - 13 CL0600-004 試験：治験責任医師により治験薬と関連ありとされた有害事象一覧（安全性解析対象集団）

		Treatment Group							
		Placebo N = 16		Teduglutide					
				0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
MedDRA SOC / PT		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Drug level increased	薬物濃度増加	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Gamma-glutamyl transferase inc.	γ－グルタミルトランスフェラーゼ増加	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Hepatic enzyme inc.	肝酵素上昇	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Weight decreased	体重減少	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Metabolism and nutrition disorders	**代謝および栄養障害**	**0**	**0**	**1 (2.9)**	**1**	**2 (6.3)**	**2**	**3 (4.5)**	**3**
Anorexia	食欲不振	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Decreased appetite	食欲減退	0	0	0	0	2 (6.3)	2	2 (3.0)	2
Nervous system disorders	**神経系障害**	**0**	**0**	**2 (5.7)**	**3**	**1 (3.1)**	**1**	**3 (4.5)**	**4**
Coma	昏睡	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Dysgeusia	味覚異常	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Headache	頭痛	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Hypersomnia	過眠症	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Skin and subcutaneous tissue disorders	**皮膚および皮下組織障害**	**0**	**0**	**2 (5.7)**	**2**	**1 (3.1)**	**1**	**3 (4.5)**	**3**
Erythema	紅斑	0	0	2 (5.7)	2	1 (3.1)	1	3 (4.5)	3
Vascular disorders	**血管障害**	**0**	**0**	**0**	**0**	**1 (3.1)**	**1**	**1 (1.5)**	**1**
Hypertension	高血圧	0	0	0	0	1 (3.1)	1	1 (1.5)	1

MedDRA = Medical Dictionary for Regulatory Activities V. 7.0; PT = preferred term; SOC = system organ class; inc. = increased.
Note: This table contains counts of subjects and events. If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event was counted.
Source: M5.3.5.1 CL0600-004 CSR Table 12-6

12.4.3　死亡、その他の重篤な有害事象及び他の重要な有害事象

死亡

試験期間中、安全性解析対象集団では死亡例はなかった。しかし、無作為割付け前のスクリーニング期に死亡が 1 例みられた。この被験者（被験者番号：[redacted]）は、5[redacted]歳の白人女性で、クローン病及び肺炎の既往歴があり、2005 年 1 月 20 日に試験に組み入れられた。本被験者は無作為化される予定であったが、本事象発現時には治験薬の投与は受けていなかった。被験者には、結腸連続性、ストーマなし、残存小腸長 70 cm、及び抗リン脂質症候群に伴う血栓症による小腸広範切除の小腸に関する既往歴があった。2005 年 3 月 10 日（Day 50）午前 5：30、被験者が大量の血液中に横たわって死亡しているのが発見された。治験責任医師の意見によると、大量の上部消化管出血に起因する死亡であった。

その他の重篤な有害事象

試験期間中に発現した重篤な有害事象は、29 例（プラセボ群 5 例、テデュグルチド 0.05 mg/kg/日群：13 例、テデュグルチド 0.10 mg/kg/日群：11 例）に 71 件（プラセボ群 12 件、テデュグルチド群全体 59 件）認められた（表 2.7.6.12 - 14）。あるカテゴリーに属する重篤な有害事象が同一被験者に 2 件以上発現した場合、そのカテゴリーについて当該被験者を 1 回のみカウントした。大部分の重篤な有害事象は器官別大分類で、感染症及び寄生虫症（35 件）、胃腸障害（8 件）、及び一般・全身障害及び投与部位の状態（8 件）に属する事象であった。最も発現頻度の高かった重篤な有害事象（基本語）は、カテーテル敗血症 18 件（プラセボ群 3 件、テデュグルチド 0.05 mg/kg/日群 10 件、テデュグルチド 0.10 mg/kg/日群 5 件）、カテーテル合併症 6 件（プラセボ群 3 件、テデュグルチド 0.10 mg/kg/日群 3 件）、及び尿路感染 4 件（全てテデュグルチド 0.05 mg/kg/日群）であった。重篤な有害事象が発現した全ての被験者について表 2.7.6.12 - 15 に示す。重篤な有害事象の発現した全ての被験者に関する叙述は 12.6.2 項に示す。

表 2.7.6.12 - 14 CL0600-004 試験：重篤な有害事象一覧（ITT 集団）

MedDRA SOC / PT		Treatment Group							
				Teduglutide					
		Placebo N = 16		0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any SAE		**5 (31.3)**	**12**	**13 (37.1)**	**43**	**11 (34.4)**	**16**	**24 (35.8)**	**59**
Cardiac disorders	**心臓障害**	**0**	**0**	**1 (2.9)**	**1**	**0**	**0**	**1 (1.50)**	**1**
Cardiac failure congestive	うっ血性心不全	0	0	1 (2.9)	1	0	0	1 (1.50)	1
Gastrointestinal disorders	**胃腸障害**	**0**	**0**	**4 (11.4)**	**6**	**2 (6.3)**	**2**	**6 (9.0)**	**8**
Abdominal pain*	腹痛	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Colonic stenosis	結腸狭窄	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Hemorrhoidal hemorrhage	痔出血	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Intestinal obstruction	腸管閉塞	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Pancreatitis	膵炎	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Short-bowel syndrome	短小腸症候群	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Small intestinal obstruction	小腸閉塞	0	0	1 (2.9)	1	1 (3.1)	1	2 (3.0)	2
General disorders & administration site conditions	**全身障害および投与局所様態**	**3 (18.8)**	**3**	**2 (5.7)**	**2**	**3 (9.4)**	**3**	**5 (7.5)**	**5**
Catheter related complication	カテーテル合併症	3 (18.8)	3	0	0	3 (9.4)	3	3 (4.5)	3
Pyrexia	発熱	0	0	2 (5.7)	2	0	0	2 (3.0)	2
Hepatobiliary disorders	**肝胆道系障害**	**0**	**0**	**2 (5.7)**	**4**	**0**	**0**	**2 (3.0)**	**4**
Cholecystitis	胆嚢炎	0	0	1 (2.9)	2	0	0	1 (1.5)	2
Cholecystitis acute	急性胆嚢炎	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Gallbladder perforation	胆嚢穿孔	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Infections and infestations	**感染症および寄生虫症**	**2 (12.5)**	**4**	**7 (20.0)**	**24**	**5 (15.6)**	**7**	**12 (17.9)**	**31**
Bronchitis	気管支炎	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Catheter bacteraemia	カテーテル菌血症	1 (6.3)	1	1 (2.9)	2	0	0	1 (1.5)	2
Catheter related infection	カテーテル関連感染	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Catheter sepsis	カテーテル敗血症	1 (6.3)	3	3 (8.6)	10	4 (12.5)	5	7 (10.4)	15
Catheter site infection	カテーテル留置部位感染	0	0	2 (5.7)	2	0	0	2 (3.0)	2
Fungemia	真菌血症	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Infectious mononucleosis	伝染性単核症		0	1 (2.9)	1	0	0	1 (1.5)	1
Meningitis	髄膜炎	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Pneumonia	肺炎	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Sepsis	敗血症	0	0	1 (2.9)	2	0	0	1 (1.5)	2
Urinary tract infection	尿路感染	0	0	1 (2.9)	4	0	0	1 (1.5)	4

表 2.7.6.12 - 14 CL0600-004 試験：重篤な有害事象一覧（ITT 集団）

		Treatment Group							
				Teduglutide					
		Placebo N = 16		0.05 mg/kg/d N = 35		0.10 mg/kg/d N = 32		Total N = 67	
MedDRA SOC / PT		Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Injury, poisoning and procedural complications	**傷害、中毒および処置合併症**	**2 (12.5)**	**2**	**1 (2.9)**	**1**	**2 (6.3)**	**2**	**3 (4.5)**	**3**
Device failure	医療用具故障	1 (6.3)	1	0	0	1 (3.1)	1	1 (1.5)	1
Eye Injury	眼外傷	1 (6.3)	1	0	0	0	0	0	0
Intestinal stoma complication	腸管ストーマ合併症	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Medical device complication	医療用具合併症	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Investigations	**臨床検査**	**0**	**0**	**2 (5.7)**	**2**	**0**	**0**	**2 (3.0)**	**2**
Drug level increased	薬物濃度増加	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Heart rate increased	心拍数増加	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Musculoskeletal and connective tissue disorders	**筋骨格系および結合組織障害**	**1 (6.3)**	**2**	**0**	**0**	**1 (3.1)**	**1**	**1 (1.5)**	**1**
Back pain	背部痛	1 (6.3)	1	0	0	0	0	0	0
Intervertebral discitis	椎間板炎	1 (6.3)	1	0	0	0	0	0	0
Pain in extremity	四肢痛	0	0	0	0	1 (3.1)	1	1 (1.5)	1
Nervous system disorders	**神経系障害**	**0**	**0**	**2 (5.7)**	**3**	**0**	**0**	**2 (3.0)**	**3**
Coma	昏睡	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Dizziness	浮動性めまい	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Hypersomnia	過眠症	0	0	1 (2.9)	1	0	0	1 (1.5)	1
Respiratory, thoracic and mediastinal disorders	**呼吸器、胸郭および縦隔障害**	**1 (6.3)**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Pneumothorax	気胸	1 (6.3)	1	0	0	0	0	0	0
Surgical and medical procedures	**外科および内科処置**	**0**	**0**	**0**	**0**	**1 (3.1)**	**1**	**1 (1.5)**	**1**
Catheterization venous	静脈カテーテル留置	0	0	0	0	1 (3.1)	1	1 (1.5)	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Note: This table contains counts of subjects and events. If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event was counted

***Upon review of case report forms, subject [redacted] was found to have an SAE of abdominal pain. This SAE is not reflected in the current in text tables (Tables 12-7 and Table 12-8) and end text listings (16.2.7.1) because it was not coded as a serious adverse event in the database.**

Source: M5.3.5.1 CL0600-004 CSR Table 12-7

表 2.7.6.12 - 15 CL0600-004 試験：重篤な有害事象一覧

Subject Number	Treatment group	Age/ Race/Gender	First Dose Date / Last Dose Date	SAE Start Date (Day)[a] / SAE Stop Date (Day)[a]	Serious Adverse Event(s)[b]	Relationship[c]
[redacted]	Placebo	2[redacted]/W/F	10 Aug 06 / 04 Jan 07	24 Sep 2006 (46)/07 Oct 2006 (59) 23 Sep 2006 (45)/07 Oct 2006 (59) 07 Nov 2006 (90)/11 Nov 2006 (94) 05 Jan 2007 (149)/ 24 Jan 2007 (168)	カテーテル合併症 カテーテル敗血症[d] カテーテル敗血症[d] カテーテル敗血症[e]	Not related Not related Not related Not related
[redacted]	Placebo	7[redacted]/W/F	23 Aug 06 / 07 Feb 07	31 Oct 2006 (70)/03 Nov 2006 (73) 16 Nov 2006 (86)/22 Nov 2006 (92) 28 Aug 2006 (6)/ 29 Aug 2006 (7) 16 Nov 2006 (86)/ 22 Nov 2006 (92)	背部痛 カテーテル菌血症 眼外傷 椎間板炎	Not related Not related Not related Not related
[redacted]	Placebo	5[redacted]/W/F	18 Nov 04 / 03 May 05	06 Dec 2004 (19)/08 Dec 2004 (21)	医療用具故障	Not related
[redacted]	Placebo	5[redacted]/W/M	31 Oct 06 / 19 Apr 07	23 Jan 2007 (85)/ 28 Jan 2007 (88)	カテーテル合併症	Not related
[redacted]	Placebo	3[redacted]/W/F	30 Aug 06 / 14 Feb 07	10 Oct 2006 (42)/ 25 Oct 2006 (57) 13 Oct 2006 (45)/ 18 Oct 2006 (50)	カテーテル合併症 気胸	Not related Not related
[redacted]	0.05 mg/kg/d	3[redacted]/W/F	28 Feb 06 / 15 Aug 06	12 Apr 2006 (44)/ 18 Apr 2006 (50)	発熱	Not related
[redacted]	0.05 mg/kg/d	3[redacted]/W/M	18 Dec 06 / 05 Jun 07	01 Apr 2007 (105)/ 10 Apr 2007 (114) 01 Apr 2007 (105)/ 10 Apr 2007 (114) 22 May 2007 (156)/ 29 May 2007(163)	急性胆嚢炎 胆嚢穿孔 小腸閉塞[d]	Not related Not related Related
[redacted]	0.05 mg/kg/d	2[redacted]/W/M	03 Feb 05 / 13 May 05	Unk Apr 2005 (XX)/ 26 May 2005 (113)	伝染性単核症	Not related
[redacted]*	0.05 mg/kg/d	5[redacted]/W/F	21 Dec 05 / 16 Mar 06 22 Mar 06 / 28 May 06	28 May 2006 (159)/ 30 May 2006 (161) 26 May 2006 (157)/ 06 Jul 2006 (199)	痔出血[e] 短小腸症候群[d]	Related Related

表 2.7.6.12 - 15 CL0600-004 試験：重篤な有害事象一覧

Subject Number	Treatment group	Age/ Race/Gender	First Dose Date / Last Dose Date	SAE Start Date (Day)[a] / SAE Stop Date (Day)[a]	Serious Adverse Event(s)[b]	Relationship[c]
[redacted]	0.05 mg/kg/d	5[redacted]/W/F	22 Dec 06 / 21 Jun 07	31 Dec 2006 (10)/ 03 Jan 2007 (13)	カテーテル菌血症[d]	Not related
				06 Jan 2007 (16)/ 18 Jan 2007 (28)	カテーテル菌血症[d]	Not related
				31 Dec 2006 (10)/ 03 Jan 2007 (13)	カテーテル敗血症[d]	Not related
				06 Jan 2007 (16)/ 18 Jan 2007 (28)	カテーテル敗血症[d]	Not related
				17 Apr 2007 (117)/ 25 Apr 2007 (125)	カテーテル敗血症[d]	Not related
				31 May 2007 (161)/ 12 Jun 2007 (173)		Not related
				18 Mar 2007 (87)/ 28 Mar 2007 (97)	真菌血症[d]	Not related
				31 May 2007 (161)/ 12 Jun 2007 (173)	髄膜炎[d]	Not related
				18 Mar 2007 (87)/ 28 Mar 2007 (97)	発熱[d]	Not related
				31 May 2007 (161)/ 12 Jun 2007 (173)	敗血症[d]	Not related
				17 Apr 2007 (117)/ 25 Apr 2007 (125)	敗血症[d]	Not related
				31 Dec 2006 (10)/ 03 Jan 2007 (13)	尿路感染[d]	Not related
				06 Jan 2007 (16)/ 18 Jan 2007 (28)	尿路感染[d]	Not related
				18 Mar 2007 (87)/ 28 Mar 2007 (97)	尿路感染[d]	Not related
					尿路感染[d]	
[redacted]	0.05 mg/kg/d	5[redacted]/W/F	01 Mar 06 / 08 Apr 06	21 Apr 2006 (52)/ 28 Apr 2006 (59)	カテーテル敗血症	Not related
				25 Jun 2006 (117)/ 05 Jul 2006 (127)	カテーテル敗血症	Not related
				20 Aug 2006 (173)/ 02 Sep 2006 (186)	カテーテル敗血症	Not related
				10 Sep 2006 (194)/20 Sep 2006 (204)	カテーテル敗血症	Not related
[redacted]	0.05 mg/kg/d	3[redacted]/W/M	07 Jun 06 / 22 Nov 06	29 Oct 2006 (145)/ 06 Nov 2006 (153)	胆嚢炎	Related
				06 Nov 2006 (153)/ 20 Nov 2006 (167)	胆嚢炎	Related
[redacted]	0.05 mg/kg/d	5[redacted]/B/F	06 Jun 06 / 21 Nov 06	26 Jul 2006 (51)/ 21 Aug 2006 (77)	カテーテル留置部位感染	Not related
[redacted]	0.05 mg/kg/d	6[redacted]/W/F	06 Nov 06 / 15 Nov 06	15 Nov 2006 (10)/ 21 Nov 2006 (16)	昏睡[e]	Related
				Unk Nov 2006/ Unk Dec 2006[f]	薬物濃度増加（ベンゾジアゼピン）[e]	Related
				13 Nov 2006 (8)/15 Nov 2006 (10)	過眠症[e]	Related
[redacted]	0.05 mg/kg/d	5[redacted]/W/M	02 Feb 05 / 20 Jul 05	09 Feb 2005 (8)/ 20 Feb 2005 (19)	カテーテル敗血症	Not related
				18 Mar 2005 (45)/26 Mar 2005 (53)	カテーテル敗血症	Not related
				13 Jun 2005 (132)/ 20 Jun 2005 (139)	カテーテル敗血症	Not related

表 2.7.6.12 - 15 CL0600-004 試験：重篤な有害事象一覧

Subject Number	Treatment group	Age/ Race/Gender	First Dose Date / Last Dose Date	SAE Start Date (Day)[a] / SAE Stop Date (Day)[a]	Serious Adverse Event(s)[b]	Relationship[c]
[redacted]	0.05 mg/kg/d	5[redacted]/W/F	13 Jan 06 / 19 Apr 06	20 Apr 2006 (98)/ 26 Apr 2006 (104)	うっ血性心不全[e]	Related
[redacted]	0.05 mg/kg/d	4[redacted]/W/M	02 Aug 06 / 25 Jan 07	02-Aug-06 (1)/29-Aug-06 (28) 24 Jan 2007 (176)/ 02 Feb 2007 (185) 25 Jan 2007 (177)/ Ongoing 22 Nov 2006 (113)/ Ongoing	カテーテル留置部位感染 結腸狭窄 医療用具合併症 膵炎	Not related Not related Not related Not related
[redacted]	0.05 mg/kg/d	4[redacted]/W/F	19 Nov 04/03 May 05	19 Apr 2005 (152)/ 21 Apr 2005 (154) 04 Dec 2004 (16)/ 05 Dec 2004 (17) 04 Dec 2004 (16)/ 05 Dec 2004 (17) 17 May 2005 (180)/ 24 May 2005 (187)	腹痛 浮動性めまい 心拍数増加 肺炎	Related Not related Not related Not related
[redacted]	0.10 mg/kg/d	7[redacted]/W/M	05 Apr 05 /23 Sep 05	06 Jul 2005 (93)/ 15 Jul 2005 (102)	カテーテル敗血症	Not related
[redacted]	0.10 mg/kg/d	6[redacted]/W/F	28 Dec 06 / 18 Jun 07	01 Feb 2007 (36)/ 02 Feb 2007 (37)	医療用具故障	Not related
[redacted]	0.10 mg/kg/d	6[redacted]/W/F	11 Dec 06 / 16 Dec 06	18 Dec 2006 (8)/ 20 Dec 2006 (10)	小腸閉塞[e]	Related
[redacted]	0.10 mg/kg/d	5[redacted]/W/F	02 Nov 04 / 03 May 05	20 Dec 2004 (49)/ 21 Dec 2004 (50)	腸管閉塞[d]	Related
[redacted]	0.10 mg/kg/d	5[redacted]/W/F	20 Jan 05 / 19 Jul 05	16 Mar 2005 (56)/13 May 2005 (115)	カテーテル関連感染	Not related
[redacted]	0.10 mg/kg/d	5[redacted]/W/M	06 Jun 05 / 18 Nov 05	04 Jul 2005 (29)/07 Jul 2005 (32)	カテーテル合併症	Not related
[redacted]	0.10 mg/kg/d	2[redacted]/W/M	09 Dec 04 / 25 May 05	23 Feb 2005 (77)/ 02 Mar 2005 (84) 13 Apr 2005 (126)/ 25 Apr 2005 (138) 03 Mar 2005 (85)/ 07 Mar 2005 (89)	カテーテル敗血症 カテーテル敗血症 四肢痛	Not related Not related Not related
[redacted]	0.10 mg/kg/d	6[redacted]/W/F	17 Mar 05 / 31 Aug 05	23 Mar 2005 (7)/ 24 Mar 2005 (8) 12 Jul 2005 (118)/ 22 Jul 2005 (128) 08 Jun 2005 (84)/ 09 Jun 2005 (85)	気管支炎 カテーテル敗血症 腸管ストーマ合併症	Not related Not related Not related
[redacted]	0.10 mg/kg/d	3[redacted]/W/M	10 Nov 06 / 27 Apr 07	28 Jan 2007 (80)/ 30 Jan 2007 (82)	カテーテル合併症	Not related
[redacted]	0.10 mg/kg/d	6[redacted]/W/F	15 Nov 06 / 04 May 07	18 Nov 2006 (4)/ 22 Nov 2006 (8)	カテーテル合併症	Not related

表 2.7.6.12 - 15 CL0600-004 試験：重篤な有害事象一覧

Subject Number	Treatment group	Age/ Race/Gender	First Dose Date / Last Dose Date	SAE Start Date (Day)[a] / SAE Stop Date (Day)[a]	Serious Adverse Event(s)[b]	Relationship[c]
[redacted]	0.10 mg/kg/d	3[redacted]/W/F	24 Aug 06 / 01 Oct 06	01 Oct 2006 (39)/ 13 Oct 2006 (51)	カテーテル敗血症 [e]	Not related
				23 Oct 2006 (61)/ 25 Oct 2006 (63)	静脈カテーテル留置	Not related

B = Black; H = Hispanic; W = White; O = Other; Unk = Unknown

[a] Baseline was the last time point prior to administration of study drug

[b] Preferred term

[c] Causal relationship to study drug as assessed by the investigator; events assessed as related include those that were possibly related.

[d] Study drug dose interrupted

[e] Study drug discontinued

[f] Follow-up information in the safety database [eg, indicates that the event was considered resolved in December 2006 with no specific date]

Source: M5.3.5.1 CL6000-004 CSR Table 12-8

SAEs referenced with Case Report Forms

*** Upon review of case report forms, subject [redacted] was found to have an SAE of abdominal pain. This SAE is not reflected in the current in text tables (Tables 12-7 and Table 12-8) and end text listings (16.2.7.1) because it was not coded as a serious adverse event in the database.**

他の重要な有害事象

有害事象により治験薬の投与を中止した被験者は 9 例（16 件の事象）であり、各投与群のうち頻度が高かったのはテデュグルチド 0.05 mg/kg/日群であった（プラセボ群 1 例［6.3%］、0.05 mg/kg/日群 6 例［17.1%］、0.10 mg/kg/日群 2 例［6.3%］）。

投与中止に至った有害事象は、痔出血、無力症、味覚異常、悪心、嘔吐、便秘、小腸閉塞、昏睡、薬物濃度増加（ベンゾジアゼピン）、過眠症、腹部膨満、うっ血性心不全、膵炎及びカテーテル敗血症であった。便秘は 2 例（いずれも 0.05 mg/kg/日群）に発現し、カテーテル敗血症も 2 例（プラセボ群及び 0.10 mg/kg/日群に各 1 例）に発現した。その他の事象は 1 例に発現した単発の事象であった。カテーテル敗血症を除いた全ての事象は治験薬との関連ありと判断された。

12.4.4　バイタルサイン、身体所見、及び安全性に関連するその他の所見

試験期間中に臨床的に問題となる臨床検査所見がみられた被験者は、プラセボ群が 6/16 例（37.5%）、テデュグルチド 0.05 mg/kg/日群が 11/35 例（31.4%）、テデュグルチド 0.10 mg/kg/日群が 12/32 例（37.5%）であった。臨床的に問題となる臨床検査異常所見の大部分は、アルカリホスファターゼ増加、ALT 増加、AST 増加、GGT 増加、尿酸増加、マグネシウム低値、プレアルブミン低値、総ビリルビン増加、ヘマトクリット低値、ヘモグロビン低値、及び C-反応タンパク高値であった。これらの臨床検査異常所見は本試験の早期に（スクリーニング来院／ベースライン来院）高頻度にみられ、Week 4～24 まで期間をとおして持続した。試験期間の早期（スクリーニング来院／ベースライン来院など）にみられた臨床検査異常所見の一部は、治験薬の投与継続中に回復し、この結果から臨床検査値異常と治験薬との間に関連のないことが示唆された。臨床検査値が正常範囲下限未満から正常範囲上限を超える値へシフト、又は正常範囲上限を超える値から正常範囲下限未満へシフトした被験者は極めてわずかであった。

試験期間中、バイタルサイン及び心電図検査には比較的変化がみられなかった。

臨床的に問題となる心電図所見は、テデュグルチド 0.05 mg/kg/日群で Week 16 にみられた 1 例（被験者番号：[redacted]）のみで、治験薬との関連なしと判断された。本被験者は試験参加を継続し、これを完了したが、Week 24 における心電図は正常であった。

12.5 結論

以上より、テデュグルチドには PS 量を減少させる臨床効果があり、その効果は低用量の 0.05 mg/kg/日では統計学的に有意であった。0.05 mg/kg/日及び 0.10 mg/kg/日共に、最長 24 週間まで安全で忍容性も良好であることが示された。本試験において、24 週間のテデュグルチド投与が PS 量を減少させ栄養状態を改善することが示された。つまり、PS を必要とする SBS の治療に対するテデュグルチドの効果が示された。良好な安全性プロファイルは、ポジティブなベネフィット・リスク比に寄与しており、これよりテデュグルチドが SBS 患者の限られた治療選択肢に大きく貢献できることが示唆された。

12.6 付録

12.6.1 有害事象表

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Number of subjects with at least one TEAE		15 (93.8)	33 (94.3)	31 (96.9)	2 (12.5)	15 (42.9)	19 (59.4)
Blood And Lymphatic System Disorders	血液およびリンパ系障害	1 (6.3)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	貧血	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Iron Deficiency Anaemia	鉄欠乏性貧血	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphadenopathy	リンパ節症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders	心臓障害	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Bundle Branch Block Right	右脚ブロック	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Failure Congestive	うっ血性心不全	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Tachycardia	頻脈	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorders	眼障害	1 (6.3)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	1 (3.1)
Eye Discharge	眼脂	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Haemorrhage	眼出血	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Inflammation	眼の炎症	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Pain	眼痛	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Keratoconjunctivitis Sicca	乾性角結膜炎	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Lacrimation Increased	流涙増加	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Photophobia	羞明	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	胃腸障害	5 (31.3)	21 (60.0)	19 (59.4)	1 (6.3)	10 (28.6)	9 (28.1)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Abdominal Discomfort	腹部不快感	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Abdominal Distension	腹部膨満	0 (0.0)	6 (17.1)	3 (9.4)	0 (0.0)	3 (8.6)	1 (3.1)
Abdominal Hernia	腹部ヘルニア	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Abdominal Pain	腹痛	2 (12.5)	7 (20.0)	9 (28.1)	1 (6.3)	2 (5.7)	1 (3.1)
Abdominal Pain Lower	下腹部痛	0 (0.0)	1 (2.9)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain Upper	上腹部痛	0 (0.0)	4 (11.4)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Rigidity	腹部硬直	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Abdominal Tenderness	腹部圧痛	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	2 (6.3)
Abnormal Faeces	異常便	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Colonic Polyp	結腸ポリープ	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Colonic Stenosis	結腸狭窄	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	便秘	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	2 (5.7)	0 (0.0)
Crohn's Disease	クローン病	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Diarrhoea	下痢	0 (0.0)	0 (0.0)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	消化不良	1 (6.3)	0 (0.0)	3 (9.4)	1 (6.3)	0 (0.0)	0 (0.0)
Dysphagia	嚥下障害	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Enterocutaneous Fistula	腸管皮膚瘻	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	鼓腸	1 (6.3)	2 (5.7)	2 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)
Frequent Bowel Movements	排便回数増加	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastro-Intestinal Fistula	胃腸管瘻	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Discomfort	胃腸不快感	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Pain	消化器痛	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Haematochezia	血便排泄	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Haemorrhoidal Haemorrhage	痔出血	1 (6.3)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Haemorrhoids	痔核	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal Obstruction	腸管閉塞	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Loose Stools	軟便	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
Nausea	悪心	4 (25.0)	5 (14.3)	10 (31.3)	1 (6.3)	4 (11.4)	3 (9.4)
Pancreatitis	膵炎	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Parotid Gland Enlargement	耳下腺腫大	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal Discharge	直腸分泌物	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retching	レッチング	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Short-Bowel Syndrome	短小腸症候群	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Small Intestinal Obstruction	小腸閉塞	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	1 (3.1)
Small Intestinal Stenosis	小腸狭窄	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stomach Discomfort	胃不快感	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stools Watery	水様便	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	歯痛	1 (6.3)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	嘔吐	2 (12.5)	4 (11.4)	6 (18.8)	0 (0.0)	2 (5.7)	2 (6.3)
General Disorders And Administration Site Conditions	全身障害および投与局所様態	7 (43.8)	13 (37.1)	23 (71.9)	2 (12.5)	6 (17.1)	15 (46.9)
Asthenia	無力症	0 (0.0)	3 (8.6)	2 (6.3)	0 (0.0)	1 (2.9)	1 (3.1)
Catheter Related Complication	カテーテル合併症	3 (18.8)	1 (2.9)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Site Discharge	カテーテル留置部位分泌物	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Site Erythema	カテーテル留置部位紅斑	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Site Haemorrhage	カテーテル留置部位出血	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

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		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Catheter Site Pain	カテーテル留置部位疼痛	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Site Related Reaction	カテーテル留置部位関連反応	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest Pain	胸痛	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Discomfort	不快感	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Drug Intolerance	薬物不耐性	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	疲労	2 (12.5)	1 (2.9)	5 (15.6)	0 (0.0)	0 (0.0)	1 (3.1)
Injection Site Bruising	注射部位挫傷	0 (0.0)	1 (2.9)	7 (21.9)	0 (0.0)	1 (2.9)	6 (18.8)
Injection Site Dermatitis	注射部位皮膚炎	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
Injection Site Erythema	注射部位紅斑	0 (0.0)	1 (2.9)	6 (18.8)	0 (0.0)	1 (2.9)	5 (15.6)
Injection Site Haemorrhage	注射部位出血	1 (6.3)	0 (0.0)	1 (3.1)	1 (6.3)	0 (0.0)	0 (0.0)
Injection Site Induration	注射部位硬結	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Injection Site Pain	注射部位疼痛	0 (0.0)	0 (0.0)	4 (12.5)	0 (0.0)	0 (0.0)	4 (12.5)
Injection Site Pruritus	注射部位そう痒感	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Injection Site Reaction	注射部位反応	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Injection Site Swelling	注射部位腫脹	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	1 (3.1)
Malaise	倦怠感	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Cardiac Chest Pain	非心臓性胸痛	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Oedema	浮腫	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Oedema Peripheral	末梢性浮腫	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	1 (3.1)
Pain	疼痛	1 (6.3)	0 (0.0)	4 (12.5)	0 (0.0)	0 (0.0)	1 (3.1)
Pyrexia	発熱	1 (6.3)	3 (8.6)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rigors	悪寒	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tenderness	圧痛	1 (6.3)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

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		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Thirst	口渇	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thirst Decreased	口渇感減少	1 (6.3)	2 (5.7)	0 (0.0)	0 (0.0)	2 (5.7)	0 (0.0)
Venipuncture Site Bruise	静脈穿刺部位挫傷	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Hepatobiliary Disorders	肝胆道系障害	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Cholecystitis	胆嚢炎	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Cholecystitis Acute	急性胆嚢炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gallbladder Perforation	胆嚢穿孔	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune System Disorders	免疫系障害	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Seasonal Allergy	季節性アレルギー	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections And Infestations	感染症および寄生虫症	10 (62.5)	23 (65.7)	20 (62.5)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	気管支炎	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Bacteraemia	カテーテル菌血症	1 (6.3)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Related Infection	カテーテル関連感染	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Sepsis	カテーテル敗血症	2 (12.5)	4 (11.4)	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Catheter Site Infection	カテーテル留置部位感染	0 (0.0)	3 (8.6)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	膀胱炎	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dental Caries	齲歯	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fungaemia	真菌血症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gingival Infection	歯肉感染	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes Simplex	単純ヘルペス	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infectious Mononucleosis	伝染性単核症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	インフルエンザ	1 (6.3)	3 (8.6)	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Klebsiella Infection	クレブシエラ感染	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

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System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
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Laryngitis	喉頭炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lower Respiratory Tract Infection	下気道感染	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis	髄膜炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	鼻咽頭炎	2 (12.5)	6 (17.1)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Oral Candidiasis	口腔カンジダ症	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Oral Fungal Infection	口腔真菌感染	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis Externa	外耳炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreas Infection	膵感染	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	咽頭炎	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	肺炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative Infection	術後感染	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis	腎盂腎炎	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	敗血症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	副鼻腔炎	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth Abscess	歯膿瘍	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper Respiratory Tract Infection	上気道感染	1 (6.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary Tract Infection	尿路感染	3 (18.8)	3 (8.6)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginitis	腟炎	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Viral Upper Respiratory Tract Infection	ウイルス性上気道感染	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	傷害、中毒および処置合併症	3 (18.8)	6 (17.1)	8 (25.0)	0 (0.0)	3 (8.6)	5 (15.6)
Anastomotic Ulcer	吻合部潰瘍	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Blister	血性水疱	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Contusion	挫傷	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Device Failure	医療用具故障	1 (6.3)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Excoriation	擦過傷	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Injury	眼外傷	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal Stoma Complication	腸管ストーマ合併症	0 (0.0)	1 (2.9)	5 (15.6)	0 (0.0)	1 (2.9)	4 (12.5)
Joint Sprain	関節捻挫	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Limb Injury	四肢損傷	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medical Device Complication	医療用具合併症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Overdose	過量投与	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Complication	処置後合併症	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Haemorrhage	処置後出血	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Post Procedural Pain	処置後痛	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Laceration	皮膚裂傷	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stoma Site Reaction	ストーマ部反応	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	1 (2.9)	1 (3.1)
Superficial Injury Of Eye	眼の擦過傷	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound	創傷	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	臨床検査	3 (18.8)	11 (31.4)	5 (15.6)	0 (0.0)	1 (2.9)	3 (9.4)
Alanine Aminotransferase Increased	アラニン・アミノトランスフェラーゼ増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Alkaline Phosphatase Increased	血中アルカリホスファターゼ増加	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Blood Bicarbonate Increased	血中重炭酸塩増加	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	血中クレアチニン増加	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Blood Glucose Increased	血中ブドウ糖増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Magnesium Decreased	血中マグネシウム減少	1 (6.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Potassium Decreased	血中カリウム減少	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	体温上昇	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
C-Reactive Protein Increased	C-反応性蛋白増加	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Drug Level Increased	薬物濃度増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Electrocardiogram Abnormal	心電図異常	1 (6.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-Glutamyltransferase Increased	γ-グルタミルトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Haematocrit Decreased	ヘマトクリット減少	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin Decreased	ヘモグロビン減少	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Rate Increased	心拍数増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic Enzyme Increased	肝酵素上昇	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Liver Function Test Abnormal	肝機能検査値異常	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prealbumin Decreased	プレアルブミン減少	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Smear Cervix Abnormal	子宮頚部スミア異常	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight Decreased	体重減少	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Weight Increased	体重増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White Blood Cell Count Increased	白血球数増加	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White Blood Cells Urine Positive	尿中白血球陽性	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	代謝および栄養障害	3 (18.8)	4 (11.4)	5 (15.6)	0 (0.0)	1 (2.9)	2 (6.3)
Anorexia	食欲不振	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)
Decreased Appetite	食欲減退	1 (6.3)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	2 (6.3)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Dehydration	脱水	2 (12.5)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Glucose Tolerance Impaired	耐糖能障害	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertriglyceridaemia	高トリグリセリド血症	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalaemia	低カリウム血症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypomagnesaemia	低マグネシウム血症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitamin D Deficiency	ビタミン D 欠乏	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitamin K Deficiency	ビタミン K 欠乏	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders	筋骨格系および結合組織障害	4 (25.0)	6 (17.1)	13 (40.6)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	関節痛	1 (6.3)	2 (5.7)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Back Pain	背部痛	1 (6.3)	0 (0.0)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Chest Wall Pain	胸壁痛	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Facial Pain	顔面痛	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Groin Pain	鼠径部痛	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral Discitis	椎間板炎	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint Effusion	関節滲出液	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint Swelling	関節腫脹	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle Cramp	筋痙攣	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle Spasms	筋痙縮	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	筋痛	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neck Pain	頚部痛	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	骨関節炎	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain In Extremity	四肢痛	1 (6.3)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Sensation Of Heaviness	重感	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tendonitis	腱炎	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Papilloma	皮膚乳頭腫	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	神経系障害	1 (6.3)	13 (37.1)	10 (31.3)	0 (0.0)	2 (5.7)	1 (3.1)
Balance Disorder	平衡障害	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coma	昏睡	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Dizziness	浮動性めまい	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	味覚異常	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Headache	頭痛	1 (6.3)	9 (25.7)	7 (21.9)	0 (0.0)	0 (0.0)	1 (3.1)
Hypersomnia	過眠症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Hypoaesthesia	感覚減退	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mental Impairment	精神的機能障害	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine	片頭痛	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	錯感覚	0 (0.0)	1 (2.9)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Disorders	精神障害	0 (0.0)	4 (11.4)	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	不安	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	うつ病	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	不眠症	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Irritability	易刺激性	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nightmare	悪夢	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Sleep Disorder	睡眠障害	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Renal And Urinary Disorders	腎および尿路障害	3 (18.8)	2 (5.7)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder Discomfort	膀胱不快感	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Costovertebral Angle Tenderness	肋骨脊柱角圧痛	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrolithiasis	腎結石症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pollakiuria	頻尿	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal Colic	腎仙痛	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Renal Cyst	腎嚢胞	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive System And Breast Disorders	生殖系および乳房障害	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genital Pruritus Female	女性陰部そう痒症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovulation Pain	排卵痛	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders	呼吸器、胸郭および縦隔障害	6 (37.5)	8 (22.9)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	咳嗽	0 (0.0)	3 (8.6)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	鼻出血	1 (6.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoptysis	喀血	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Congestion	鼻閉	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngolaryngeal Pain	咽喉頭疼痛	1 (6.3)	2 (5.7)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	気胸	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary Embolism	肺塞栓症	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rales	ラ音	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	鼻漏	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhonchi	低音性連続性ラ音	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 2.7.6.12 - 16 CL0600-004 試験：治験薬との因果関係別有害事象の発現頻度（安全性解析対象集団）

System Organ Class (SOC)/ Preferred Term (PT)		有害事象			治験薬と関連のある有害事象		
		Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)	Placebo (N = 16) n (%)	Teduglutide 0.05 mg/kg/day (N = 35) n (%)	Teduglutide 0.10 mg/kg/day (N = 32) n (%)
Sinus Pain	副鼻腔痛	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Throat Irritation	咽喉刺激感	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper Respiratory Tract Congestion	上気道うっ血	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	喘鳴音	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	皮膚および皮下組織障害	2 (12.5)	7 (20.0)	5 (15.6)	0 (0.0)	2 (5.7)	1 (3.1)
Dermatitis Allergic	アレルギー性皮膚炎	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Skin	皮膚乾燥	1 (6.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	紅斑	0 (0.0)	2 (5.7)	1 (3.1)	0 (0.0)	2 (5.7)	1 (3.1)
Night Sweats	寝汗	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	そう痒症	1 (6.3)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	発疹	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash Erythematous	紅斑性皮疹	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash Generalised	全身性皮疹	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash Macular	斑状皮疹	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Chapped	ひび・あかぎれ	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Reaction	皮膚反応	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical And Medical Procedures	外科および内科処置	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Catheterisation Venous	静脈カテーテル留置	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders	血管障害	1 (6.3)	2 (5.7)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Deep Vein Thrombosis	深部静脈血栓症	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	高血圧	0 (0.0)	1 (2.9)	1 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)
Hypotension	低血圧	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based upon the number of subjects randomized who received dose in the Safety Population for each treatment arm.

Note: Treatment emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within thirty days after discontinuation of study drug.
Note: Related AEs include AEs that were 'possibly related', 'probably related', 'related' or with relationship missing.
Note: Subjects are counted no more than once for incidence of System Organ Class and Preferred Term.
Note: All adverse events were coded using MedDRA version 7.0.
M5.3.5.1 CL600-004 CSR Table 14.3.1.2, Table 14.3.1.7　　Output Generated On: 20OCT2016 23:26