2.7.4.2.2 個別有害事象の文章による説明

20 試験及び 40 試験での死亡及びその他の重篤な有害事象の詳細をそれぞれの 2.7.6 項（2.7.6.9 項及び 2.7.6.10 項）に記載した。

2.7.4.3 臨床検査値の評価

2.7.4.3.1 治験期間を通しての臨床検査

20 試験の二重盲検治療期の臨床検査項目のうち、糖関連（血糖、HbA1c）、脂質関連（トリグリセリド、コレステロール）及びプロラクチンは、ランクを用いた共分散分析でベースラインからの Week 6（LOCF）の変化量を解析した。血糖値はいずれの群でもベースラインからの変動はみられなかった。HbA1c 値の Week 6（LOCF）のベースラインからの変化量（mean±SD）は、プラセボ群、40 mg 群及び 80 mg 群（以下、同順）でそれぞれ−0.06±0.248%、0.01±0.228%、0.00±0.256%で、プラセボ群との変化量の差［LS mean（SE）］が 40 mg 群で 0.1（0.02）%、80 mg 群で 0.1（0.02）%となりプラセボ群との間に統計学的差が示された。トリグリセリド（空腹時）の Week 6（LOCF）のベースラインからの変化量（mean±SD）はそれぞれ−2.8±68.85 mg/dL、8.8±59.31 mg/dL、3.5±58.35 mg/dL、コレステロール（空腹時）の Week 6（LOCF）のベースラインからの変化量（mean±SD）はそれぞれ 1.2±28.87 mg/dL、−3.3±34.19 mg/dL、0.6±30.04 mg/dL であった。トリグリセリド（空腹時）はロナセンテープ貼付後に上昇したものの、プラセボ群との間に統計学的な差はみられなかった。プロラクチンの Week 6（LOCF）のベースラインからの変化量（mean±SD）は、プラセボ群で −2.3±18.81 ng/mL、40 mg 群で 5.3±14.62 ng/mL、80 mg 群で 8.1±17.34 ng/mL で、Week 6（LOCF）のプラセボ群との変化量の差［LS mean（SE）］は 40 mg 群で 7.7（1.61）ng/mL、80 mg 群で 10.2（1.61）ng/mL となり、プラセボ群との間に統計学的差が示された（5.3.5.1.01 参照）。HbA1c 値はプラセボ群と比較して実薬群で統計学的に有意な上昇がみられたが、変化量としては臨床的に問題となる変動ではないと考えられた。プロラクチンはロナセンテープ貼付により上昇する傾向を示した。その他の臨床検査項目では臨床的に問題となる変動はみられなかった。

20 試験のロナセンテープ貼付期ではトリグリセリド（mean±SD）は、プラセボ-FLEX 群ではベースラインで 132.7±72.33 mg/dL、Week 28 に 148.1±100.33 mg/dL、実薬-FLEX 群ではベースラインで 124.1±69.96 mg/dL、Week 34 に 150.3±111.91 mg/dL、DSP-5423P dosed population 合計ではベースラインで 126.3±70.60 mg/dL、On-treatment（LOCF）に 138.5±92.78 mg/dL と、いずれも長期間のロナセンテープ貼付により高くなる傾向を示した。プロラクチン（mean±SD）は、プラセボ-FLEX 群ではベースラインで 9.0±8.92 ng/mL、Week 28 に 17.1±27.10 ng/mL、実薬-FLEX 群ではベースラインで 12.9±19.57 ng/mL、Week 34 に 17.5±13.51 ng/mL、DSP-5423P dosed population 合計ではベースラインで 11.9±17.59 mg/dL、On-treatment（LOCF）に 17.9±21.40 mg/dL と、いずれも長期間のロナセンテープ貼付により高くなる傾向を示した。トリグリセリド及びプロラクチン以外の臨床検査値では治験薬貼付前後で臨床的に問題となる変動はなかった（5.3.5.1.01 参照）。

40 試験では、プロラクチンのベースラインからの変化量（mean±SD）は Week 52（LOCF）で−2.1±15.63 ng/mL で大きな変動はみられなかった。その他の臨床検査項目（糖関連、脂質関連を含む）でもロナセンテープ貼付後に臨床的に問題となる変動はなかった（5.3.5.2.01 参照）。

2.7.4.3.2 個々の臨床的に重要な異常

(1) 20 試験

二重盲検治療期

治験依頼者が臨床検査（血液生化学的検査、血液学的検査）ごとに設定した基準を超える値を顕著な異常値として、顕著な異常値を示した被験者の割合を表 2.7.4.3-1 及び表 2.7.4.3-2 に示す。

ナトリウムは平均値では臨床的に問題となる変動はみられなかったが、ナトリウム 130 mEq/L 未満の被験者はプラセボ群（0.5%、1/184 名）に比べ、40 mg 群（2.6%、5/194 名）、80 mg 群（3.1%、6/193 名）で高かった。ナトリウム 130 mEq/L 未満を示したそれぞれの被験者の二重盲検治療期中のナトリウムの測定値及び推移から、いずれも臨床的に意義のある低値ではないと考えられた。その他、3 群の顕著な異常値を示した被験者の割合に大きな違いはなかった。

表 2.7.4.3-1 臨床検査（血液生化学的検査）の顕著な異常値を示した被験者の割合（20 試験・二重盲検治療期）

Safety population

Parameter	Criteria	PLCB (N = 190) n/Tested (%)	40MG (N = 196) n/Tested (%)	80MG (N = 194) n/Tested (%)	Active (N = 390) n/Tested (%)
Alanine Aminotransferase	>=3 x ULN	3/184 (1.6)	5/194 (2.6)	0/193	5/387 (1.3)
Aspartate Aminotransferase	>=3 x ULN	2/184 (1.1)	3/194 (1.5)	0/191	3/385 (0.8)
Alkaline Phosphatase	>=1.5 x ULN	2/184 (1.1)	1/194 (0.5)	0/193	1/387 (0.3)
Sodium	<130 mEq/L	1/184 (0.5)	5/194 (2.6)	6/193 (3.1)	11/387 (2.8)
	>150 mEq/L	0/184	0/194	0/193	0/387
Potassium	<3 mEq/L	1/184 (0.5)	0/194	1/193 (0.5)	1/387 (0.3)
	>5.5 mEq/L	0/184	2/194 (1.0)	1/193 (0.5)	3/387 (0.8)
Chloride	<90 mEq/L	1/184 (0.5)	2/194 (1.0)	3/193 (1.6)	5/387 (1.3)
	>115 mEq/L	0/184	0/194	0/193	0/387
Glucose (fasting)	<50 mg/dL	1/180 (0.6)	0/188	1/188 (0.5)	1/376 (0.3)
	>250 mg/dL	1/180 (0.6)	0/188	1/188 (0.5)	1/376 (0.3)

Parameter	Criteria	PLCB (N = 190) n/Tested (%)	40MG (N = 196) n/Tested (%)	80MG (N = 194) n/Tested (%)	Active (N = 390) n/Tested (%)
Hemoglobin A1C	>=7.5 %	0/184	2/194 (1.0)	3/193 (1.6)	5/387 (1.3)
Bilirubin	>2 x ULN	0/184	1/194 (0.5)	0/193	1/387 (0.3)
Blood Urea Nitrogen	>30 mg/dL	0/184	0/194	0/193	0/387
Creatinine	>2.0 mg/dL	0/184	0/194	0/193	0/387
Creatine Kinase	>3 x ULN	10/184 (5.4)	5/194 (2.6)	4/193 (2.1)	9/387 (2.3)
Prolactin	>=5 x ULN	0/183	4/193 (2.1)	0/193	4/386 (1.0)
Triglycerides (fasting)	>300 mg/dL	10/180 (5.6)	9/188 (4.8)	11/188 (5.9)	20/376 (5.3)
Cholesterol (fasting)	>300 mg/dL	0/180	3/188 (1.6)	1/188 (0.5)	4/376 (1.1)

ULN, upper limit of normal range. Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup.

表 2.7.4.3-2　臨床検査（血液学的検査）の顕著な異常値を示した被験者の割合（20 試験・二重盲検治療期）

Safety population

Parameter	Criteria	PLCB (N = 190) n/Tested (%)	40MG (N = 196) n/Tested (%)	80MG (N = 194) n/Tested (%)	Active (N = 390) n/Tested (%)
Hemoglobin	Male: =<11.5 g/dL	2/110 (1.8)	5/114 (4.4)	4/113 (3.5)	9/227 (4.0)
	Female: =<9.5 g/dL	0/74	0/79	0/79	0/158
Hematocrit	Male: =<37 %	8/110 (7.3)	6/114 (5.3)	7/112 (6.3)	13/226 (5.8)
	Female: =<32 %	2/73 (2.7)	0/79	3/79 (3.8)	3/158 (1.9)
Leukocytes	=<2.8 x 10^3/uL	1/184 (0.5)	0/193	4/192 (2.1)	4/385 (1.0)
	>=16 x 10^3/uL	1/184 (0.5)	1/193 (0.5)	1/192 (0.5)	2/385 (0.5)
Platelets	=<75 x 10^3/uL	0/183	0/191	0/192	0/383
	>=700 x 10^3/uL	0/183	0/191	0/192	0/383

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup.

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

治験依頼者が臨床検査（血液生化学的検査、血液学的検査）ごとに設定した基準を超える値を顕著な異常値として、顕著な異常値を示した被験者の割合を表 2.7.4.3-5 及び表 2.7.4.3-6 に示す。

顕著な異常値を示した被験者の割合が DSP-5423P dosed population 合計で 3%以上となっ

た臨床検査項目は、ナトリウム（130 mEq/L 未満）が 3.1%（16/515 名）、クレアチンキナーゼ（基準値上限の 3 倍超）が 4.7%（24/514 名）、ヘモグロビン（男性 11.5 g/dL 以下）が 3.6%（11/309 名）、ヘマトクリット（男性 37%以下）が 8.1%（25/308 名）、ヘマトクリット（女性 32%以下）が 4.4%（9/203 名）であった。

糖関連では、血糖値（空腹時）（50 mg/dL 未満）が 0.4%（2/501 名）、血糖値（空腹時）（250 mg/dL 超）が 0.4%（2/501 名）、HbA1c（7.5%以上）が 1.7%（9/515 名）であった。プロラクチン（基準値上限の 5 倍以上）は 1.0%（5/514 名）であった。脂質関連では、トリグリセリド（300 mg/dL 超）が 10.0%（50/501 名）で、コレステロール（空腹時）（300 mg/dL 超）は 2.0%（10/501 名）であった。

いずれも二重盲検治療期の実薬群での割合と比較して著しく高くなったものはなかった。

表 2.7.4.3-3　臨床検査（血液生化学的検査）の顕著な異常値を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Alanine Aminotransferase	>=3 x ULN	4/127 (3.1)	8/194 (4.1)	1/193 (0.5)	9/387 (2.3)	13/514 (2.5)
Aspartate Aminotransferase	>=3 x ULN	1/127 (0.8)	4/194 (2.1)	1/192 (0.5)	5/386 (1.3)	6/513 (1.2)
Alkaline Phosphatase	>=1.5 x ULN	1/127 (0.8)	2/194 (1.0)	1/193 (0.5)	3/387 (0.8)	4/514 (0.8)
Sodium	<130 mEq/L	3/128 (2.3)	7/194 (3.6)	6/193 (3.1)	13/387 (3.4)	16/515 (3.1)
	>150 mEq/L	1/128 (0.8)	0/194	0/193	0/387	1/515 (0.2)
Potassium	<3 mEq/L	1/127 (0.8)	0/194	1/193 (0.5)	1/387 (0.3)	2/514 (0.4)
	>5.5 mEq/L	1/127 (0.8)	7/194 (3.6)	2/193 (1.0)	9/387 (2.3)	10/514 (1.9)
Chloride	<90 mEq/L	2/128 (1.6)	4/194 (2.1)	3/193 (1.6)	7/387 (1.8)	9/515 (1.7)
	>115 mEq/L	0/128	0/194	0/193	0/387	0/515
Glucose (fasting)	<50 mg/dL	0/125	0/188	2/188 (1.1)	2/376 (0.5)	2/501 (0.4)
	>250 mg/dL	0/125	0/188	2/188 (1.1)	2/376 (0.5)	2/501 (0.4)
Hemoglobin A1C	>=7.5 %	2/128 (1.6)	2/194 (1.0)	5/193 (2.6)	7/387 (1.8)	9/515 (1.7)
Bilirubin	>2 x ULN	0/128	1/194 (0.5)	0/193	1/387 (0.3)	1/515 (0.2)
Blood Urea Nitrogen	>30 mg/dL	0/128	0/194	1/193 (0.5)	1/387 (0.3)	1/515 (0.2)
Creatinine	>2.0 mg/dL	0/128	0/194	0/193	0/387	0/515
Creatine Kinase	>3 x ULN	5/127 (3.9)	10/194 (5.2)	9/193 (4.7)	19/387 (4.9)	24/514 (4.7)

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Prolactin	>=5 x ULN	0/128	5/193 (2.6)	0/193	5/386 (1.3)	5/514 (1.0)
Triglycerides (fasting)	>300 mg/dL	10/125 (8.0)	20/188 (10.6)	20/188 (10.6)	40/376 (10.6)	50/501 (10.0)
Cholesterol (fasting)	>300 mg/dL	2/125 (1.6)	5/188 (2.7)	3/188 (1.6)	8/376 (2.1)	10/501 (2.0)

ULN, upper limit of normal range. Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The data cut-off at Open-Week 24 was used.

表 2.7.4.3-4　臨床検査（血液学的検査）の顕著な異常値を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Hemoglobin	Male: =<11.5 g/dL	0/82	6/114 (5.3)	5/113 (4.4)	11/227 (4.8)	11/309 (3.6)
	Female: =<9.5 g/dL	0/46	0/79	2/79 (2.5)	2/158 (1.3)	2/204 (1.0)
Hematocrit	Male: =<37 %	3/82 (3.7)	11/114 (9.6)	11/112 (9.8)	22/226 (9.7)	25/308 (8.1)
	Female: =<32 %	1/45 (2.2)	1/79 (1.3)	7/79 (8.9)	8/158 (5.1)	9/203 (4.4)
Leukocytes	=<2.8 x 10^3/uL	1/128 (0.8)	2/193 (1.0)	5/192 (2.6)	7/385 (1.8)	8/513 (1.6)
	>=16 x 10^3/uL	1/128 (0.8)	1/193 (0.5)	2/192 (1.0)	3/385 (0.8)	4/513 (0.8)
Platelets	=<75 x 10^3/uL	0/128	0/191	0/192	0/383	0/511
	>=700 x 10^3/uL	0/128	0/191	0/192	0/383	0/511

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

治験依頼者が臨床検査（血液生化学的検査、血液学的検査）ごとに設定した基準を超える値を顕著な異常値として、顕著な異常値を示した被験者の割合を表 2.7.4.3-5 及び表 2.7.4.3-6 に示す。

顕著な異常値を示した被験者の割合が DSP-5423P dosed population 合計で 3%以上となった臨床検査項目は、ナトリウム（130 mEq/L 未満）が 3.5%（18/515 名）、クレアチンキナーゼ（基準値上限の 3 倍超）が 5.3%（27/514 名）、ヘモグロビン（男性 11.5 g/dL 以下）が 4.5%（14/309 名）、ヘマトクリット（男性 37%以下）が 10.1%（31/308 名）、ヘマトクリット（女性 32%以下）が 5.4%（11/203 名）であった。

糖関連では、血糖値（空腹時）（50 mg/dL 未満）が 0.4%（2/501 名）、血糖値（空腹時）（250 mg/dL 超）が 0.4%（2/501 名）、HbA1c（7.5%以上）が 1.7%（9/515 名）であった。プロラクチン（基準値上限の 5 倍以上）は 1.2%（6/514 名）であった。脂質関連では、トリグリセリド（300 mg/dL 超）が 10.6%（53/501 名）で、コレステロール（空腹時）（300 mg/dL 超）は 2.6%（13/501 名）であった。

いずれも二重盲検治療期の実薬群での割合と比較して著しく高くなったものはなかった。

表 2.7.4.3-5　臨床検査（血液生化学的検査）の顕著な異常値を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Alanine Aminotransferase	>=3 x ULN	4/127 (3.1)	9/194 (4.6)	4/193 (2.1)	13/387 (3.4)	17/514 (3.3)
Aspartate Aminotransferase	>=3 x ULN	2/127 (1.6)	5/194 (2.6)	2/192 (1.0)	7/386 (1.8)	9/513 (1.8)
Alkaline Phosphatase	>=1.5 x ULN	1/127 (0.8)	2/194 (1.0)	1/193 (0.5)	3/387 (0.8)	4/514 (0.8)
Sodium	<130 mEq/L	3/128 (2.3)	8/194 (4.1)	7/193 (3.6)	15/387 (3.9)	18/515 (3.5)
	>150 mEq/L	1/128 (0.8)	0/194	0/193	0/387	1/515 (0.2)
Potassium	<3 mEq/L	1/127 (0.8)	0/194	1/193 (0.5)	1/387 (0.3)	2/514 (0.4)
	>5.5 mEq/L	2/127 (1.6)	7/194 (3.6)	3/193 (1.6)	10/387 (2.6)	12/514 (2.3)
Chloride	<90 mEq/L	2/128 (1.6)	4/194 (2.1)	4/193 (2.1)	8/387 (2.1)	10/515 (1.9)
	>115 mEq/L	0/128	0/194	0/193	0/387	0/515
Glucose (fasting)	<50 mg/dL	0/125	0/188	2/188 (1.1)	2/376 (0.5)	2/501 (0.4)
	>250 mg/dL	0/125	0/188	2/188 (1.1)	2/376 (0.5)	2/501 (0.4)
Hemoglobin A1C	>=7.5 %	2/128 (1.6)	2/194 (1.0)	5/193 (2.6)	7/387 (1.8)	9/515 (1.7)
Bilirubin	>2 x ULN	0/128	1/194 (0.5)	1/193 (0.5)	2/387 (0.5)	2/515 (0.4)
Blood Urea Nitrogen	>30 mg/dL	0/128	0/194	1/193 (0.5)	1/387 (0.3)	1/515 (0.2)

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Creatinine	>2.0 mg/dL	0/128	1/194 (0.5)	0/193	1/387 (0.3)	1/515 (0.2)
Creatine Kinase	>3 x ULN	7/127 (5.5)	11/194 (5.7)	9/193 (4.7)	20/387 (5.2)	27/514 (5.3)
Prolactin	>=5 x ULN	1/128 (0.8)	5/193 (2.6)	0/193	5/386 (1.3)	6/514 (1.2)
Triglycerides (fasting)	>300 mg/dL	11/125 (8.8)	21/188 (11.2)	21/188 (11.2)	42/376 (11.2)	53/501 (10.6)
Cholesterol (fasting)	>300 mg/dL	3/125 (2.4)	6/188 (3.2)	4/188 (2.1)	10/376 (2.7)	13/501 (2.6)

ULN, upper limit of normal range. Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The final data at Open-Week 52 was used.

表 2.7.4.3-6　臨床検査（血液学的検査）の顕著な異常値を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Hemoglobin	Male: =<11.5 g/dL	2/82 (2.4)	6/114 (5.3)	6/113 (5.3)	12/227 (5.3)	14/309 (4.5)
	Female: =<9.5 g/dL	0/46	0/79	4/79 (5.1)	4/158 (2.5)	4/204 (2.0)
Hematocrit	Male: =<37 %	7/82 (8.5)	11/114 (9.6)	13/112 (11.6)	24/226 (10.6)	31/308 (10.1)
	Female: =<32 %	1/45 (2.2)	1/79 (1.3)	9/79 (11.4)	10/158 (6.3)	11/203 (5.4)
Leukocytes	=<2.8 x 10^3/uL	2/128 (1.6)	2/193 (1.0)	5/192 (2.6)	7/385 (1.8)	9/513 (1.8)
	>=16 x 10^3/uL	1/128 (0.8)	1/193 (0.5)	2/192 (1.0)	3/385 (0.8)	4/513 (0.8)
Platelets	=<75 x 10^3/uL	0/128	0/191	0/192	0/383	0/511
	>=700 x 10^3/uL	0/128	0/191	0/192	0/383	0/511

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The final data at Open-Week 52 was used.

(2) 40 試験

治験依頼者が臨床検査（血液生化学的検査、血液学的検査）ごとに設定した基準を超える値を顕著な異常値として、ロナセンテープ貼付期の顕著な異常値を示した被験者の割合を表 2.7.4.3-7 に示す。

血液生化学検査のうち、ナトリウムが 130 mEq/L 未満を示した被験者は 3.0%(6/200 名)であった。

糖関連では、グルコース（空腹時）の顕著な異常値（50 mg/dL 未満、又は 250 mg/dL 超）を示した被験者はいなかった。全体で HbA1c の顕著な異常値（7.5%以上）を示した被験者は 2.0%（4/200 名）で、このうち 3 名が糖尿病を合併していた。残りの 1 名はロナセンテープ貼付期ベースラインでは 5.5%であったが、Week 20 で 6.5%(中央測定の正常範囲:6.5%未満）と上昇したことから、有害事象「糖尿病」と報告された。糖尿病に対して処置なしで、その後 Week 36 に 7.6%、Week 52 に 6.7%と推移した。

プロラクチンの顕著な異常値（基準値上限の 5 倍以上）を示した被験者は 0.5%（1/200 名)であった。当該被験者のロナセン錠投与期のプロラクチン値は正常範囲内であったが、ロナセンテープ貼付開始前の検査で異常高値を示したことから、有害事象「高プロラクチン血症」と報告された。その後、Week 52 まで継続して異常高値を示した。

脂質関連では、トリグリセリド（空腹時）の顕著な異常値（300 mg/dL 超）を示した被験者は 3.4%（6/178 名）で、コレステロール（空腹時）の顕著な異常値（300 mg/dL 超）を示した被験者は 3.4%（6/178 名）であった。トリグリセリド（空腹時）の異常値を示した 6 名のうち 2 名が高脂血症あるいは脂質異常症を合併していた。また、コレステロール（空腹時）の異常値を示した被験者 6 名のうち、3 名が高脂血症あるいは脂質異常症を合併していた。いずれも脂質代謝系の有害事象と報告された被験者はいなかった。

表 2.7.4.3-7　臨床検査の顕著な異常値を示した被験者の割合（40 試験）

Safety population

Parameter	Criteria	Cohort 1 (N = 97) n/m (%)	Cohort 2 (N = 103) n/m (%)	Overall (N = 200) n/m (%)
Hemoglobin	Male: =<11.5 g/dL	1/43 (2.3)	1/48 (2.1)	2/91 (2.2)
	Female: =<9.5 g/dL	1/54 (1.9)	0/55	1/109 (0.9)
Hematocrit	Male: =<37 %	2/43 (4.7)	4/48 (8.3)	6/91 (6.6)
	Female: =<32 %	2/54 (3.7)	1/55 (1.8)	3/109 (2.8)
Leukocytes	=<2.8 x 10^3/uL	3/97 (3.1)	2/103 (1.9)	5/200 (2.5)
	>=16 x 10^3/uL	0/97	0/103	0/200
Platelets	=<75 x 10^3/uL	0/97	0/103	0/200
	>=700 x 10^3/uL	0/97	0/103	0/200
Alanine Aminotransferase	>=3 x ULN	6/97 (6.2)	3/103 (2.9)	9/200 (4.5)
Aspartate Aminotransferase	>=3 x ULN	3/97 (3.1)	1/103 (1.0)	4/200 (2.0)

Parameter	Criteria	Cohort 1 (N = 97) n/m (%)	Cohort 2 (N = 103) n/m (%)	Overall (N = 200) n/m (%)
Alkaline Phosphatase	>=1.5 x ULN	0/97	1/103 (1.0)	1/200 (0.5)
Sodium	<130 mEq/L	5/97 (5.2)	1/103 (1.0)	6/200 (3.0)
	>150 mEq/L	0/97	0/103	0/200
Potassium	<3 mEq/L	1/97 (1.0)	1/103 (1.0)	2/200 (1.0)
	>5.5 mEq/L	1/97 (1.0)	1/103 (1.0)	2/200 (1.0)
Chloride	<90 mEq/L	3/97 (3.1)	1/103 (1.0)	4/200 (2.0)
	>115 mEq/L	0/97	0/103	0/200
Glucose (fasting)	<50 mg/dL	0/85	0/93	0/178
	>250 mg/dL	0/85	0/93	0/178
Hemoglobin A1C	>=7.5 %	2/97 (2.1)	2/103 (1.9)	4/200 (2.0)
Bilirubin	>2 x ULN	1/97 (1.0)	0/103	1/200 (0.5)
Blood Urea Nitrogen	>30 mg/dL	0/97	0/103	0/200
Creatinine	>2.0 mg/dL	0/97	0/103	0/200
Creatine Kinase	>3 x ULN	1/97 (1.0)	4/103 (3.9)	5/200 (2.5)
Prolactin	>=5 x ULN	1/97 (1.0)	0/103	1/200 (0.5)
Triglycerides (fasting)	>300 mg/dL	3/85 (3.5)	3/93 (3.2)	6/178 (3.4)
Cholesterol (fasting)	>300 mg/dL	4/85 (4.7)	2/93 (2.2)	6/178 (3.4)

ULN, upper limit of normal range. Denominator of percentage (m) for each parameter is the number of subjects who has at least one post-baseline measurement.

2.7.4.4　バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1　バイタルサイン

20 試験の二重盲検治療期及びロナセンテープ貼付期、40 試験のいずれでもバイタルサイン各項目の平均値の推移に臨床的に問題となる変動は見られなかった(5.3.5.1.01、5.3.5.2.01 参照)。

2.7.4.4.2　体重

20 試験の二重盲検治療期及び 40 試験では、体重の平均値の推移に臨床的に問題となる変動は見られなかった（5.3.5.1.01、5.3.5.2.01 参照)。

20 試験のロナセンテープ貼付期（非盲検治療期 24 週時の解析）では、体重（mean±SD）は、プラセボ-FLEX 群ではベースラインで 65.85±17.155 kg、Week 24 に 70.01±19.726 kg、実薬-FLEX 群のベースラインで 62.89±14.585 kg、Week 30 に 64.80±14.748 kg と、長期間の

ロナセンテープ貼付によりいずれも増加する傾向を示した。

20 試験のロナセンテープ貼付期（非盲検治療期 52 週時の解析）では、体重（mean±SD）は、プラセボ-FLEX 群ではベースラインで 65.85±17.155 kg、Week 28 に 69.83±19.639 kg、実薬-FLEX 群のベースラインで 62.89±14.585 kg、Week 34 に 65.31±15.784 kg、DSP-5423P dosed population 合計ではベースラインで 63.64±15.308 kg、On-treatment（LOCF）に 65.29±15.989 kg であった。

2.7.4.4.2.1　体重の個々の臨床的に重要な異常

(1) 20 試験

二重盲検治療期

治験依頼者が設定した基準を超える値を顕著な異常として、体重の顕著な異常を示した被験者の割合を表 2.7.4.4-1 に示す。

7%以上の体重減少を示した割合はプラセボ群、40 mg 群、80 mg 群（以下、同順）でそれぞれ 2.7%（5/187 名）、5.6%（11/195 名）、4.1%（8/193 名）であり、7%以上の体重増加を示した割合は 5.9%（11/187 名）、7.7%（15/195 名）、8.3%（16/193 名）と、3 群間で大きな違いはなかった。

表 2.7.4.4-1　体重の顕著な異常を示した被験者の割合（20 試験・二重盲検治療期）

Safety population

Parameter	Criteria	PLCB (N = 190) n/Tested (%)	40MG (N = 196) n/Tested (%)	80MG (N = 194) n/Tested (%)	Active (N = 390) n/Tested (%)
Weight	>=7% decreased from baseline	5/187 (2.7)	11/195 (5.6)	8/193 (4.1)	19/388 (4.9)
	>=7% increased from baseline	11/187 (5.9)	15/195 (7.7)	16/193 (8.3)	31/388 (8.0)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup.

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

治験依頼者が設定した基準を超える値を顕著な異常として、体重の顕著な異常を示した被験者の割合を表 2.7.4.4-2 に示す。

20 試験のロナセンテープ貼付期（非盲検治療期 24 週時の解析）では、DSP-5423P dosed population 合計で 7%以上の体重減少を示した割合は 10.4%（54/518 名）、7%以上の体重増加を示した割合は 28.0%（145/518 名）であった。

表 2.7.4.4-2　顕著な体重の異常を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Weight	>=7% decreased from baseline	5/130 (3.8)	27/195 (13.8)	22/193 (11.4)	49/388 (12.6)	54/518 (10.4)
	>=7% increased from baseline	40/130 (30.8)	47/195 (24.1)	58/193 (30.1)	105/388 (27.1)	145/518 (28.0)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

治験依頼者が設定した基準を超える値を顕著な異常として、体重の顕著な異常を示した被験者の割合を表 2.7.4.4-3 に示す。

20 試験のロナセンテープ貼付期（非盲検治療期 52 週時の解析）では、DSP-5423P dosed population 合計で 7%以上の体重減少を示した割合は 11.8%（61/518 名）、7%以上の体重増加を示した割合は 30.1%（156/518 名）であった。

表 2.7.4.4-3　顕著な体重の異常を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
Weight	>=7% decreased from baseline	6/130 (4.6)	29/195 (14.9)	26/193 (13.5)	55/388 (14.2)	61/518 (11.8)
	>=7% increased from baseline	42/130 (32.3)	53/195 (27.2)	61/193 (31.6)	114/388 (29.4)	156/518 (30.1)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The final data at Open-Week 52 was used.

(2) 40 試験

治験依頼者が設定した基準を超える値を顕著な異常として、体重の顕著な異常を示した被験者の割合を表 2.7.4.4-4 に示す。

40 試験でロナセンテープ貼付開始から 7%以上の体重減少を示した被験者は、全体で 18.5%（37/200 名）で、7%以上の体重増加を示した被験者は 16.0%（32/200 名）であった。

表 2.7.4.4-4　体重の顕著な異常を示した被験者の割合（40 試験）

Safety population

Parameter	Criteria	Cohort 1 (N = 97) n/m (%)	Cohort 2 (N = 103) n/m (%)	Overall (N = 200) n/m (%)
Weight	>=7% decreased from baseline	16/97 (16.5)	21/103 (20.4)	37/200 (18.5)
	>=7% increased from baseline	16/97 (16.5)	16/103 (15.5)	32/200 (16.0)

Denominator of percentage (m) for each parameter is the number of subjects who has at least one post-baseline measurement.

2.7.4.4.3　12 誘導心電図検査

(1) 20 試験

二重盲検治療期

12 誘導心電図から QT 延長評価を中央判定した結果を表 2.7.4.4-5 に示す。

心電図パラメータ、心電図検査所見で異常と判断された被験者割合、心電図検査所見でベースライン時に正常から Week 6（LOCF）に異常となった被験者の割合、QTcB 及び QTcF であらかじめ設定した基準を超える異常値を示した被験者の割合に、3 群間で大きな違いはなかった。

本治験では心電図総括評価責任者による QTc 延長に対する影響の総合的な評価を行った。心電図総括評価責任者により、本治験の二重盲検治療期に対し「心電図パラメータ（QT interval / QTcB interval / QTcF interval）とそのベースラインからの変化量（要約統計量）及び顕著な異常値の発現被験者数とその発現割合から考えて、プラセボ群と実薬群で差はなく、ロナセンテープが QT 間隔を延長する作用を有しているとは言えないと考える。」と評価された。

表 2.7.4.4-5　QT 延長評価（20 試験・二重盲検治療期）

Safety population

Parameter	Criteria	PLCB (N = 190) n/Tested (%)	40MG (N = 196) n/Tested (%)	80MG (N = 194) n/Tested (%)	Active (N = 390) n/Tested (%)
QTcB, Bazett's Correction Formula	>450 msec	29/186 (15.6)	15/193 (7.8)	25/193 (13.0)	40/386 (10.4)
	>480 msec	3/186 (1.6)	0/193	1/193 (0.5)	1/386 (0.3)
	>500 msec	1/186 (0.5)	0/193	0/193	0/386
	Increased from baseline>30 msec	32/186 (17.2)	23/193 (11.9)	25/193 (13.0)	48/386 (12.4)
	Increased from baseline>60 msec	3/186 (1.6)	1/193 (0.5)	2/193 (1.0)	3/386 (0.8)
QTcF, Fridericia's Correction Formula	>450 msec	12/186 (6.5)	3/193 (1.6)	3/193 (1.6)	6/386 (1.6)
	>480 msec	1/186 (0.5)	0/193	1/193 (0.5)	1/386 (0.3)
	>500 msec	1/186 (0.5)	0/193	0/193	0/386
	Increased from baseline>30 msec	21/186 (11.3)	11/193 (5.7)	11/193 (5.7)	22/386 (5.7)
	Increased from baseline>60 msec	1/186 (0.5)	0/193	1/193 (0.5)	1/386 (0.3)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup.

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

12 誘導心電図から QT 延長評価を中央判定した結果を表 2.7.4.4-6 に示す。

DSP-5423P dosed population 合計で QT 間隔が 500 msec 超を示した被験者、ベースラインから 60 msec を超える上昇がみられた被験者は、QTcB ではそれぞれ 0.2%（1/514 名）及び 1.0%（5/514 名）、QTcF ではそれぞれ 0%及び 0.2%（1/514 名）であった。

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）に対し心電図総括評価責任者は、「心電図パラメータ（QT interval / QTcB interval / QTcF interval）とそのベースラインからの変化量（要約統計量）、顕著な異常値の発現被験者数とその発現割合及び異常を示した各被験者に対する評価結果から、ロナセンテープが QT 間隔を延長する作用を有しているとは言えないと考える。」と評価した。

表 2.7.4.4-6　QT 延長評価（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
QTcB, Bazett's Correction Formula	>450 msec	24/128 (18.8)	31/193 (16.1)	40/193 (20.7)	71/386 (18.4)	95/514 (18.5)
	>480 msec	0/128	1/193 (0.5)	2/193 (1.0)	3/386 (0.8)	3/514 (0.6)
	>500 msec	0/128	0/193	1/193 (0.5)	1/386 (0.3)	1/514 (0.2)
	Increased from baseline>30 msec	25/128 (19.5)	45/193 (23.3)	41/193 (21.2)	86/386 (22.3)	111/514 (21.6)
	Increased from baseline>60 msec	0/128	2/193 (1.0)	3/193 (1.6)	5/386 (1.3)	5/514 (1.0)
QTcF, Fridericia's Correction Formula	>450 msec	8/128 (6.3)	4/193 (2.1)	4/193 (2.1)	8/386 (2.1)	16/514 (3.1)
	>480 msec	0/128	0/193	1/193 (0.5)	1/386 (0.3)	1/514 (0.2)
	>500 msec	0/128	0/193	0/193	0/386	0/514
	Increased from baseline>30 msec	8/128 (6.3)	23/193 (11.9)	27/193 (14.0)	50/386 (13.0)	58/514 (11.3)
	Increased from baseline>60 msec	0/128	0/193	1/193 (0.5)	1/386 (0.3)	1/514 (0.2)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

12 誘導心電図から QT 延長評価を中央判定した結果を表 2.7.4.4-7 に示す。

DSP-5423P dosed population 合計で QT 間隔が 500 msec 超を示した被験者、ベースラインから 60 msec を超える上昇がみられた被験者は、QTcB ではそれぞれ 0.2%（1/514 名）及び 1.4%（7/514 名）、QTcF ではそれぞれ 0%及び 0.6%（3/514 名）であった。

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）に対し心電図総括評価責任者は、「心電図パラメータ（QT interval / QTcB interval / QTcF interval）とそのベースラインからの変化量（要約統計量）、顕著な異常値の発現被験者数とその発現割合及び異常を示した各被験者に対する評価結果から、DSP-5423P が QT 間隔を延長する作用を有しているとは言えないと考える。」と評価した。

表 2.7.4.4-7　QT 延長評価（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Parameter	Criteria	PLCB-to-FLEX DOSE (N = 131) n/Tested (%)	40MG-to-FLEX DOSE (N = 196) n/Tested (%)	80MG-to-FLEX DOSE (N = 194) n/Tested (%)	Active-to-FLEX DOSE (N = 390) n/Tested (%)	Overall-to-FLEX DOSE (N = 521) n/Tested (%)
QTcB, Bazett's Correction Formula	>450 msec	27/128 (21.1)	32/193 (16.6)	48/193 (24.9)	80/386 (20.7)	107/514 (20.8)
	>480 msec	1/128 (0.8)	1/193 (0.5)	2/193 (1.0)	3/386 (0.8)	4/514 (0.8)
	>500 msec	0/128	0/193	1/193 (0.5)	1/386 (0.3)	1/514 (0.2)
	Increased from baseline>30 msec	31/128 (24.2)	48/193 (24.9)	48/193 (24.9)	96/386 (24.9)	127/514 (24.7)
	Increased from baseline>60 msec	1/128 (0.8)	2/193 (1.0)	4/193 (2.1)	6/386 (1.6)	7/514 (1.4)
QTcF, Fridericia's Correction Formula	>450 msec	10/128 (7.8)	4/193 (2.1)	6/193 (3.1)	10/386 (2.6)	20/514 (3.9)
	>480 msec	0/128	0/193	1/193 (0.5)	1/386 (0.3)	1/514 (0.2)
	>500 msec	0/128	0/193	0/193	0/386	0/514
	Increased from baseline>30 msec	12/128 (9.4)	25/193 (13.0)	32/193 (16.6)	57/386 (14.8)	69/514 (13.4)
	Increased from baseline>60 msec	1/128 (0.8)	0/193	2/193 (1.0)	2/386 (0.5)	3/514 (0.6)

Denominator for percentage is defined as the total number of subjects tested for according parameter in each treatment group and subgroup. The final data at Open-Week 52 was used.

(2) 40 試験

12 誘導心電図から QT 延長評価を中央判定した結果を表 2.7.4.4-8 に示す。

QTcB、QTcF を含む心電図パラメータで、ロナセンテープ貼付後に臨床的に問題となる変動はなかった。

QTcB が 500 msec を超えた被験者はいなかった。QTcB が 480 msec を超えた被験者は全体で 1.5%（3/200 名）であった。QTcB がベースラインから 60 msec 超増加した被験者は 1.5%（3/200 名）であった。3 名のうち 1 名はコホート 1 で、QTcB が 480 msec を超えた被験者と同一であった。QTcB がベースラインから 30 msec 超増加した被験者は 25.5%（51/200 名）であった。QTcF が 500 msec を超えた被験者はいなかった。QTcF が 480 msec を超えた被験者は 0.5%（1/200 名）であった。QTcF がベースラインから 60 msec 超増加した被験者はいなかった。QTcF がベースラインから 30 msec 超増加した被験者は 11.5%（23/200 名）であった。該当する被験者の血漿中ブロナンセリン濃度に一定の傾向はみられなかった。

心電図総括評価責任者から、「顕著な異常値を示した被験者の個別の心電図については、波形を含めて別途考察することが望ましいが、心電図パラメータ（QT interval / QTcB interval / QTcF interval）とそのベースラインからの変化量（要約統計量）及び顕著な異常値の発現被験者数とその発現割合から考えて、ロナセンテープが普遍的に QT 間隔を延長する作用を有しているとは言えないと考える。」との見解を得た。

表 2.7.4.4-8　QT 延長評価（40 試験）

Safety population

Parameter	Criteria	Cohort 1 (N = 97) n/m (%)	Cohort 2 (N = 103) n/m (%)	Overall (N = 200) n/m (%)
QTCB	>450 msec	21/97 (21.6)	36/103 (35.0)	57/200 (28.5)
	>480 msec	1/97 (1.0)	2/103 (1.9)	3/200 (1.5)
	>500 msec	0/97	0/103	0/200
	Increased from baseline>30 msec	22/97 (22.7)	29/103 (28.2)	51/200 (25.5)
	Increased from baseline>60 msec	1/97 (1.0)	2/103 (1.9)	3/200 (1.5)
QTCF	>450 msec	5/97 (5.2)	15/103 (14.6)	20/200 (10.0)
	>480 msec	0/97	1/103 (1.0)	1/200 (0.5)
	>500 msec	0/97	0/103	0/200
	Increased from baseline>30 msec	7/97 (7.2)	16/103 (15.5)	23/200 (11.5)
	Increased from baseline>60 msec	0/97	0/103	0/200

QTCB, Bazett's Correction Formula; QTCF, Fridericia's Correction Formula. Denominator of percentage (m) for each parameter is the number of subjects who has at least one post-baseline measurement.

2.7.4.4.4　DIEPSS

(1) 20 試験

二重盲検治療期

Mixed Model for Repeated Measures（MMRM）での解析による、DIEPSS 合計スコア（概

括重症度を除く）変化量を表 2.7.4.4-9 に示す。

Week 6 の DIEPSS 合計スコア変化量のプラセボ群と 40 mg 群、80 mg 群の差［LS mean（95%信頼区間）］（以下、同順）は、それぞれ 0.2（−0.1、0.5）、0.3（0.0、0.6）と、40 mg 群及び 80 mg 群はプラセボ群と比べて大きな違いはなかった。

表 2.7.4.4-9　ベースラインから Week 6 の DIEPSS 合計スコア（概括重症度を除く）変化量（20 試験・二重盲検治療期）

Safety population

Visit	Statistics (Covariance matrix=UN)	PLCB (N = 190)	40MG (N = 196)	80MG (N = 194)
	Number of subjects analysed	189	196	192
Baseline	Mean (SD)	0.9 (2.23)	0.8 (2.25)	1.0 (2.42)
Week 1	Change from Baseline			
	Estimate (SE)	-0.1 (0.09)	0.1 (0.09)	0.2 (0.09)
	95% CI	(-0.3, 0.1)	(-0.1, 0.2)	(0.1, 0.4)
	Treatment Difference			
	Estimate (SE)		0.2 (0.12)	0.3 (0.12)
	95% CI		(-0.1, 0.4)	(0.1, 0.6)
	p-value		0.186	0.006
Week 2	Change from Baseline			
	Estimate (SE)	-0.1 (0.09)	0.0 (0.09)	0.3 (0.09)
	95% CI	(-0.3, 0.1)	(-0.2, 0.2)	(0.1, 0.5)
	Treatment Difference			
	Estimate (SE)		0.1 (0.13)	0.4 (0.13)
	95% CI		(-0.1, 0.4)	(0.2, 0.6)
	p-value		0.263	0.001
Week 4	Change from Baseline			
	Estimate (SE)	-0.1 (0.11)	0.0 (0.11)	0.2 (0.11)
	95% CI	(-0.4, 0.1)	(-0.3, 0.2)	(0.0, 0.4)
	Treatment Difference			
	Estimate (SE)		0.1 (0.15)	0.3 (0.15)
	95% CI		(-0.2, 0.4)	(0.0, 0.6)
	p-value		0.577	0.027
Week 6	Change from Baseline			
	Estimate (SE)	-0.2 (0.11)	0.0 (0.11)	0.1 (0.11)
	95% CI	(-0.4, 0.0)	(-0.2, 0.2)	(-0.1, 0.3)

Visit	Statistics (Covariance matrix=UN)	PLCB (N = 190)	40MG (N = 196)	80MG (N = 194)
	Treatment Difference			
	Estimate (SE)		0.2 (0.16)	0.3 (0.16)
	95% CI		(-0.1, 0.5)	(0.0, 0.6)
	p-value		0.259	0.032
	Effect size		0.126	0.238

Estimates, standard errors (SE), confidence intervals (CI) and p-values are based on a mixed model for repeated measures (MMRM) of the change from baseline score, with fixed effects for treatment group, visit as a categorical variable, baseline score, pooled center, and treatment by visit interaction. An unstructured matrix (UN) is used for within subject covariance matrix. For models that failed to converge under an unstructured matrix, a different covariance matrix was used instead: heterogeneous Toeplitz (TOEPH), heterogeneous first-order autoregressive (ARH(1)), and Toeplitz (TOEP). These alternative covariance structures use a robust sandwich estimator for the standard error of the fixed effect estimates. In case that all models were failed to converge, 'Non-calculable' is presented instead of model estimates.
DIEPSS total score is the sum of symptom scores excluding overall severity.

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

DIEPSS 合計スコア（概括重症度を除く）変化量を表 2.7.4.4-10 に示す。

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）では、ベースラインから最終評価時（LOCF）DIEPSS 合計スコア変化量（mean±SD）は、DSP-5423P dosed population 合計で −0.1±1.65 であった。

表 2.7.4.4-10　ベースラインから Week 24 の DIEPSS 合計スコア（概括重症度を除く）変化量（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

		PLCB-to-FLEX DOSE (N = 131)		40MG-to-FLEX DOSE (N = 196)		80MG-to-FLEX DOSE (N = 194)		Active-to-FLEX DOSE (N = 390)		Overall-to-FLEX DOSE (N = 521)	
Visit	Statistics	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
On-treatment Baseline	n	131		196		193		389		520	
	Mean (SD)	0.8 (2.10)		0.8 (2.25)		1.0 (2.42)		0.9 (2.34)		0.9 (2.28)	
	Median	0.0		0.0		0.0		0.0		0.0	
	Min, Max	0, 15		0, 14		0, 14		0, 14		0, 15	
On-treatment Week 1	n	129	129	196	196	192	192	388	388	517	517
	Mean (SD)	0.8 (2.11)	0.0 (0.52)	0.9 (2.41)	0.1 (1.48)	1.2 (2.60)	0.2 (1.13)	1.1 (2.50)	0.1 (1.32)	1.0 (2.41)	0.1 (1.17)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 16	-3, 2	0, 15	-10, 14	0, 13	-4, 7	0, 15	-10, 14	0, 16	-10, 14
On-treatment Week 2	n	129	129	179	179	183	183	362	362	491	491
	Mean (SD)	0.9 (2.31)	0.1 (0.93)	0.9 (2.33)	0.0 (1.26)	1.3 (2.70)	0.3 (1.38)	1.1 (2.53)	0.2 (1.33)	1.1 (2.47)	0.1 (1.23)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 16	-2, 5	0, 14	-10, 7	0, 13	-4, 10	0, 14	-10, 10	0, 16	-10, 10
On-treatment Week 4	n	125	125	167	167	174	174	341	341	466	466
	Mean (SD)	0.9 (2.24)	0.0 (0.97)	0.8 (2.13)	0.0 (1.24)	1.2 (2.43)	0.2 (2.04)	1.0 (2.29)	0.1 (1.70)	1.0 (2.28)	0.1 (1.53)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 17	-3, 7	0, 15	-10, 5	0, 12	-12, 9	0, 15	-12, 9	0, 17	-12, 9

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	PLCB-to-FLEX DOSE (N = 131) Change	40MG-to-FLEX DOSE (N = 196) Observed	40MG-to-FLEX DOSE (N = 196) Change	80MG-to-FLEX DOSE (N = 194) Observed	80MG-to-FLEX DOSE (N = 194) Change	Active-to-FLEX DOSE (N = 390) Observed	Active-to-FLEX DOSE (N = 390) Change	Overall-to-FLEX DOSE (N = 521) Observed	Overall-to-FLEX DOSE (N = 521) Change
On-treatment Week 6	n			156	156	166	166	322	322	322	322
	Mean (SD)			0.9 (2.17)	0.0 (1.68)	1.1 (2.36)	0.1 (1.88)	1.0 (2.27)	0.0 (1.78)	1.0 (2.27)	0.0 (1.78)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 13	-10, 11	0, 13	-12, 8	0, 13	-12, 11	0, 13	-12, 11
On-treatment Week 7	n			142	142	156	156	298	298	298	298
	Mean (SD)			0.8 (2.09)	-0.1 (1.61)	1.2 (2.43)	0.2 (1.96)	1.0 (2.28)	0.1 (1.81)	1.0 (2.28)	0.1 (1.81)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 8	0, 13	-12, 8	0, 13	-12, 8	0, 13	-12, 8
On-treatment Week 8	n	117	117	137	137	154	154	291	291	408	408
	Mean (SD)	0.9 (2.31)	0.1 (0.99)	0.9 (2.26)	-0.1 (1.59)	1.1 (2.16)	0.0 (1.87)	1.0 (2.21)	0.0 (1.74)	1.0 (2.23)	0.0 (1.56)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 15	-3, 6	0, 14	-10, 7	0, 11	-12, 8	0, 14	-12, 8	0, 15	-12, 8
On-treatment Week 10	n			134	134	146	146	280	280	280	280
	Mean (SD)			0.8 (2.21)	-0.1 (1.85)	1.0 (2.18)	-0.1 (1.75)	0.9 (2.19)	-0.1 (1.79)	0.9 (2.19)	-0.1 (1.79)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 14	-10, 8	0, 12	-12, 7	0, 14	-12, 8	0, 14	-12, 8
On-treatment Week 12	n	104	104							104	104
	Mean (SD)	0.9 (2.08)	0.0 (1.01)							0.9 (2.08)	0.0 (1.01)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 10	-5, 5							0, 10	-5, 5

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	PLCB-to-FLEX DOSE (N = 131) Change	40MG-to-FLEX DOSE (N = 196) Observed	40MG-to-FLEX DOSE (N = 196) Change	80MG-to-FLEX DOSE (N = 194) Observed	80MG-to-FLEX DOSE (N = 194) Change	Active-to-FLEX DOSE (N = 390) Observed	Active-to-FLEX DOSE (N = 390) Change	Overall-to-FLEX DOSE (N = 521) Observed	Overall-to-FLEX DOSE (N = 521) Change
On-treatment Week 14	n			127	127	142	142	269	269	269	269
	Mean (SD)			0.9 (2.12)	0.0 (1.71)	1.0 (2.14)	-0.1 (1.80)	0.9 (2.13)	0.0 (1.76)	0.9 (2.13)	0.0 (1.76)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 8	0, 11	-12, 7	0, 12	-12, 8	0, 12	-12, 8
On-treatment Week 16	n	99	99							99	99
	Mean (SD)	0.8 (1.94)	0.0 (1.32)							0.8 (1.94)	0.0 (1.32)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 9	-6, 6							0, 9	-6, 6
On-treatment Week 18	n			109	109	126	126	235	235	235	235
	Mean (SD)			0.8 (2.00)	-0.1 (1.80)	1.1 (2.29)	-0.1 (2.14)	0.9 (2.17)	-0.1 (1.98)	0.9 (2.17)	-0.1 (1.98)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 7	0, 11	-12, 8	0, 11	-12, 8	0, 11	-12, 8
On-treatment Week 20	n	90	90							90	90
	Mean (SD)	0.9 (2.09)	0.0 (1.22)							0.9 (2.09)	0.0 (1.22)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 12	-3, 5							0, 12	-3, 5
On-treatment Week 22	n			107	107	122	122	229	229	229	229
	Mean (SD)			0.7 (1.90)	-0.2 (1.70)	1.1 (2.25)	-0.1 (2.11)	0.9 (2.10)	-0.2 (1.93)	0.9 (2.10)	-0.2 (1.93)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 6	0, 11	-12, 9	0, 12	-12, 9	0, 12	-12, 9

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	PLCB-to-FLEX DOSE (N = 131) Change	40MG-to-FLEX DOSE (N = 196) Observed	40MG-to-FLEX DOSE (N = 196) Change	80MG-to-FLEX DOSE (N = 194) Observed	80MG-to-FLEX DOSE (N = 194) Change	Active-to-FLEX DOSE (N = 390) Observed	Active-to-FLEX DOSE (N = 390) Change	Overall-to-FLEX DOSE (N = 521) Observed	Overall-to-FLEX DOSE (N = 521) Change
On-treatment Week 24	n	89	89							89	89
	Mean (SD)	0.7 (1.73)	-0.2 (1.13)							0.7 (1.73)	-0.2 (1.13)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 9	-7, 4							0, 9	-7, 4
On-treatment Week 26	n			99	99	117	117	216	216	216	216
	Mean (SD)			0.6 (1.80)	-0.3 (1.57)	1.0 (2.18)	-0.2 (2.07)	0.9 (2.02)	-0.2 (1.85)	0.9 (2.02)	-0.2 (1.85)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 5	0, 11	-12, 9	0, 11	-12, 9	0, 11	-12, 9
On-treatment Week 30	n			92	92	113	113	205	205	205	205
	Mean (SD)			0.6 (1.79)	-0.3 (1.58)	1.1 (2.22)	-0.2 (2.25)	0.9 (2.04)	-0.2 (1.98)	0.9 (2.04)	-0.2 (1.98)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 2	0, 11	-12, 11	0, 11	-12, 11	0, 11	-12, 11
On-treatment (LOCF)	n	130	130	196	196	192	192	388	388	518	518
	Mean (SD)	0.7 (1.72)	-0.1 (1.07)	0.7 (1.83)	-0.1 (1.60)	0.9 (2.03)	-0.1 (2.00)	0.8 (1.93)	-0.1 (1.81)	0.8 (1.88)	-0.1 (1.65)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 9	-7, 4	0, 11	-10, 7	0, 11	-12, 11	0, 11	-12, 11	0, 11	-12, 11

On-treatment baseline is the last observation on or before the first dose date of DSP-5423P. On-treatment (LOCF) is the last post-baseline observation in the DSP-5423P treated period up to 7 days after final application of the study treatment. Summary statistics for the observed value and the change from baseline values are based on subjects with both a baseline and the target visit observation. DIEPSS total score is the sum of symptom scores excluding overall severity. The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

DIEPSS 合計スコア（概括重症度を除く）変化量を表 2.7.4.4-11 に示す。

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）では、ベースラインからの On-treatment (LOCF) DIEPSS 合計スコア変化量 (mean±SD) は、DSP-5423P dosed population 合計で−0.1±1.64 であった。

表 2.7.4.4-11　ベースラインからの DIEPSS 合計スコア（概括重症度を除く）変化量（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

		PLCB-to-FLEX DOSE (N = 131)		40MG-to-FLEX DOSE (N = 196)		80MG-to-FLEX DOSE (N = 194)		Active-to-FLEX DOSE (N = 390)		Overall-to-FLEX DOSE (N = 521)	
Visit	Statistics	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
On-treatment Baseline	n	131		196		193		389		520	
	Mean (SD)	0.8 (2.10)		0.8 (2.25)		1.0 (2.42)		0.9 (2.34)		0.9 (2.28)	
	Median	0.0		0.0		0.0		0.0		0.0	
	Min, Max	0, 15		0, 14		0, 14		0, 14		0, 15	
On-treatment Week 1	n	129	129	196	196	192	192	388	388	517	517
	Mean (SD)	0.8 (2.11)	0.0 (0.52)	0.9 (2.41)	0.1 (1.48)	1.2 (2.60)	0.2 (1.13)	1.1 (2.50)	0.1 (1.32)	1.0 (2.41)	0.1 (1.17)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 16	-3, 2	0, 15	-10, 14	0, 13	-4, 7	0, 15	-10, 14	0, 16	-10, 14
On-treatment Week 2	n	129	129	179	179	183	183	362	362	491	491
	Mean (SD)	0.9 (2.31)	0.1 (0.93)	0.9 (2.33)	0.0 (1.26)	1.3 (2.70)	0.3 (1.38)	1.1 (2.53)	0.2 (1.33)	1.1 (2.47)	0.1 (1.23)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 16	-2, 5	0, 14	-10, 7	0, 13	-4, 10	0, 14	-10, 10	0, 16	-10, 10
On-treatment Week 4	n	125	125	167	167	174	174	341	341	466	466
	Mean (SD)	0.9 (2.24)	0.0 (0.97)	0.8 (2.13)	0.0 (1.24)	1.2 (2.43)	0.2 (2.04)	1.0 (2.29)	0.1 (1.70)	1.0 (2.28)	0.1 (1.53)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 17	-3, 7	0, 15	-10, 5	0, 12	-12, 9	0, 15	-12, 9	0, 17	-12, 9

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	Change	40MG-to-FLEX DOSE (N = 196) Observed	Change	80MG-to-FLEX DOSE (N = 194) Observed	Change	Active-to-FLEX DOSE (N = 390) Observed	Change	Overall-to-FLEX DOSE (N = 521) Observed	Change
On-treatment Week 6	n			156	156	166	166	322	322	322	322
	Mean (SD)			0.9 (2.17)	0.0 (1.68)	1.1 (2.36)	0.1 (1.88)	1.0 (2.27)	0.0 (1.78)	1.0 (2.27)	0.0 (1.78)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 13	-10, 11	0, 13	-12, 8	0, 13	-12, 11	0, 13	-12, 11
On-treatment Week 7	n			142	142	156	156	298	298	298	298
	Mean (SD)			0.8 (2.09)	-0.1 (1.61)	1.2 (2.43)	0.2 (1.96)	1.0 (2.28)	0.1 (1.81)	1.0 (2.28)	0.1 (1.81)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 8	0, 13	-12, 8	0, 13	-12, 8	0, 13	-12, 8
On-treatment Week 8	n	117	117	137	137	154	154	291	291	408	408
	Mean (SD)	0.9 (2.31)	0.1 (0.99)	0.9 (2.26)	-0.1 (1.59)	1.1 (2.16)	0.0 (1.87)	1.0 (2.21)	0.0 (1.74)	1.0 (2.23)	0.0 (1.56)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 15	-3, 6	0, 14	-10, 7	0, 11	-12, 8	0, 14	-12, 8	0, 15	-12, 8
On-treatment Week 10	n			134	134	146	146	280	280	280	280
	Mean (SD)			0.8 (2.21)	-0.1 (1.85)	1.0 (2.18)	-0.1 (1.75)	0.9 (2.19)	-0.1 (1.79)	0.9 (2.19)	-0.1 (1.79)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 14	-10, 8	0, 12	-12, 7	0, 14	-12, 8	0, 14	-12, 8
On-treatment Week 12	n	104	104							104	104
	Mean (SD)	0.9 (2.08)	0.0 (1.01)							0.9 (2.08)	0.0 (1.01)
	Median	0.0	0.0							0.0	0.0

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	PLCB-to-FLEX DOSE (N = 131) Change	40MG-to-FLEX DOSE (N = 196) Observed	40MG-to-FLEX DOSE (N = 196) Change	80MG-to-FLEX DOSE (N = 194) Observed	80MG-to-FLEX DOSE (N = 194) Change	Active-to-FLEX DOSE (N = 390) Observed	Active-to-FLEX DOSE (N = 390) Change	Overall-to-FLEX DOSE (N = 521) Observed	Overall-to-FLEX DOSE (N = 521) Change
	Min, Max	0, 10	-5, 5							0, 10	-5, 5
On-treatment Week 14	n			127	127	142	142	269	269	269	269
	Mean (SD)			0.9 (2.12)	0.0 (1.71)	1.0 (2.14)	-0.1 (1.80)	0.9 (2.13)	0.0 (1.76)	0.9 (2.13)	0.0 (1.76)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 8	0, 11	-12, 7	0, 12	-12, 8	0, 12	-12, 8
On-treatment Week 16	n	99	99							99	99
	Mean (SD)	0.8 (1.94)	0.0 (1.32)							0.8 (1.94)	0.0 (1.32)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 9	-6, 6							0, 9	-6, 6
On-treatment Week 18	n			109	109	126	126	235	235	235	235
	Mean (SD)			0.8 (2.00)	-0.1 (1.80)	1.1 (2.29)	-0.1 (2.14)	0.9 (2.17)	-0.1 (1.98)	0.9 (2.17)	-0.1 (1.98)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 7	0, 11	-12, 8	0, 11	-12, 8	0, 11	-12, 8
On-treatment Week 20	n	90	90							90	90
	Mean (SD)	0.9 (2.09)	0.0 (1.22)							0.9 (2.09)	0.0 (1.22)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 12	-3, 5							0, 12	-3, 5
On-treatment Week 22	n			107	107	122	122	229	229	229	229

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	Change	40MG-to-FLEX DOSE (N = 196) Observed	Change	80MG-to-FLEX DOSE (N = 194) Observed	Change	Active-to-FLEX DOSE (N = 390) Observed	Change	Overall-to-FLEX DOSE (N = 521) Observed	Change
	Mean (SD)			0.7 (1.90)	-0.2 (1.70)	1.1 (2.25)	-0.1 (2.11)	0.9 (2.10)	-0.2 (1.93)	0.9 (2.10)	-0.2 (1.93)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 12	-10, 6	0, 11	-12, 9	0, 12	-12, 9	0, 12	-12, 9
On-treatment Week 24	n	89	89							89	89
	Mean (SD)	0.7 (1.73)	-0.2 (1.13)							0.7 (1.73)	-0.2 (1.13)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 9	-7, 4							0, 9	-7, 4
On-treatment Week 26	n			99	99	117	117	216	216	216	216
	Mean (SD)			0.6 (1.80)	-0.3 (1.57)	1.0 (2.18)	-0.2 (2.07)	0.9 (2.02)	-0.2 (1.85)	0.9 (2.02)	-0.2 (1.85)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 5	0, 11	-12, 9	0, 11	-12, 9	0, 11	-12, 9
On-treatment Week 28	n	83	83							83	83
	Mean (SD)	0.8 (1.88)	-0.1 (1.35)							0.8 (1.88)	-0.1 (1.35)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 9	-7, 5							0, 9	-7, 5
On-treatment Week 30	n			92	92	113	113	205	205	205	205
	Mean (SD)			0.6 (1.79)	-0.3 (1.58)	1.1 (2.22)	-0.2 (2.25)	0.9 (2.04)	-0.2 (1.98)	0.9 (2.04)	-0.2 (1.98)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 11	-10, 2	0, 11	-12, 11	0, 11	-12, 11	0, 11	-12, 11

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	PLCB-to-FLEX DOSE (N = 131) Change	40MG-to-FLEX DOSE (N = 196) Observed	40MG-to-FLEX DOSE (N = 196) Change	80MG-to-FLEX DOSE (N = 194) Observed	80MG-to-FLEX DOSE (N = 194) Change	Active-to-FLEX DOSE (N = 390) Observed	Active-to-FLEX DOSE (N = 390) Change	Overall-to-FLEX DOSE (N = 521) Observed	Overall-to-FLEX DOSE (N = 521) Change
On-treatment Week 34	n			91	91	114	114	205	205	205	205
	Mean (SD)			0.7 (1.82)	-0.3 (1.72)	0.9 (2.07)	-0.3 (2.15)	0.8 (1.96)	-0.3 (1.97)	0.8 (1.96)	-0.3 (1.97)
	Median			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max			0, 10	-10, 5	0, 11	-12, 10	0, 11	-12, 10	0, 11	-12, 10
On-treatment Week 36	n	17	17							17	17
	Mean (SD)	1.5 (2.24)	-0.4 (1.62)							1.5 (2.24)	-0.4 (1.62)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 7	-5, 3							0, 7	-5, 3
On-treatment Week 42	n			20	20	27	27	47	47	47	47
	Mean (SD)			2.1 (3.17)	-0.5 (1.57)	2.3 (3.27)	-0.6 (3.31)	2.2 (3.20)	-0.6 (2.68)	2.2 (3.20)	-0.6 (2.68)
	Median			0.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
	Min, Max			0, 11	-6, 1	0, 11	-12, 6	0, 11	-12, 6	0, 11	-12, 6
On-treatment Week 44	n	15	15							15	15
	Mean (SD)	1.5 (2.10)	-0.5 (1.51)							1.5 (2.10)	-0.5 (1.51)
	Median	1.0	0.0							1.0	0.0
	Min, Max	0, 7	-5, 1							0, 7	-5, 1
On-treatment Week 50	n			20	20	25	25	45	45	45	45
	Mean (SD)			2.1 (3.02)	-0.4 (1.73)	2.0 (3.10)	-0.9 (3.03)	2.0 (3.03)	-0.7 (2.52)	2.0 (3.03)	-0.7 (2.52)

Visit	Statistics	PLCB-to-FLEX DOSE (N = 131) Observed	Change	40MG-to-FLEX DOSE (N = 196) Observed	Change	80MG-to-FLEX DOSE (N = 194) Observed	Change	Active-to-FLEX DOSE (N = 390) Observed	Change	Overall-to-FLEX DOSE (N = 521) Observed	Change
	Median			0.5	0.0	1.0	0.0	1.0	0.0	1.0	0.0
	Min, Max			0, 10	-6, 1	0, 11	-12, 4	0, 11	-12, 4	0, 11	-12, 4
On-treatment Week 52	n	13	13							13	13
	Mean (SD)	1.6 (2.33)	-0.4 (1.39)							1.6 (2.33)	-0.4 (1.39)
	Median	0.0	0.0							0.0	0.0
	Min, Max	0, 7	-4, 1							0, 7	-4, 1
On-treatment Week 58	n			17	17	22	22	39	39	39	39
	Mean (SD)			2.6 (3.41)	0.0 (1.54)	2.3 (3.37)	-1.0 (3.02)	2.4 (3.35)	-0.6 (2.51)	2.4 (3.35)	-0.6 (2.51)
	Median			1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
	Min, Max			0, 11	-4, 3	0, 11	-12, 2	0, 11	-12, 3	0, 11	-12, 3
On-treatment (LOCF)	n	130	130	196	196	192	192	388	388	518	518
	Mean (SD)	0.7 (1.69)	-0.1 (1.11)	0.7 (1.86)	-0.1 (1.64)	0.9 (2.05)	-0.1 (1.92)	0.8 (1.96)	-0.1 (1.78)	0.8 (1.89)	-0.1 (1.64)
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 9	-7, 4	0, 11	-10, 7	0, 11	-12, 10	0, 11	-12, 10	0, 11	-12, 10

On-treatment baseline is the last observation on or before the first dose date of DSP-5423P. On-treatment (LOCF) is the last post-baseline observation in the DSP-5423P treated period up to 7 days after final application of the study treatment. Summary statistics for the observed value and the change from baseline values are based on subjects with both a baseline and the target visit observation. DIEPSS total score is the sum of symptom scores excluding overall severity. The final data at Open-Week 52 was used.

(2) 40 試験

評価時期ごとの DIEPSS 合計スコア（概括重症度を除く）及びロナセンテープ貼付期ベースライン（以下、ベースライン）からの変化量を表 2.7.4.4-12 に示す。

全体での DIEPSS 合計スコア（概括重症度を除く）はベースライン、Week 52（LOCF）、Week 52 の順に 0.9±1.68（mean±SD、以下、同様）、0.8±1.54、0.5±1.28、ベースラインからの変化量は Week 52（LOCF）、Week 52 の順に−0.1±1.55、−0.3±1.58 で、ロナセンテープ貼付後に臨床的に問題となる変動はなかった。

表 2.7.4.4-12　DIEPSS 合計スコア（概括重症度を除く）及びロナセンテープ貼付期ベースラインからの変化量（40 試験）

Safety population

		Cohort 1 (N = 97)		Cohort 2 (N = 103)		Overall (N = 200)	
Visit	Statistics	Observed	Change	Observed	Change	Observed	Change
Baseline	n	97		103		200	
	Mean (SD)	0.9 (1.81)		0.8 (1.56)		0.9 (1.68)	
	Median	0.0		0.0		0.0	
	Min, Max	0, 8		0, 6		0, 8	
Week 1	n	97	97	103	103	200	200
	Mean (SD)	0.8 (1.52)	-0.1 (1.13)	0.8 (1.80)	0.0 (0.84)	0.8 (1.67)	-0.1 (0.99)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 8	-5, 3	0, 9	-4, 4	0, 9	-5, 4
Week 2	n	89	89	100	100	189	189
	Mean (SD)	0.8 (1.52)	-0.1 (1.12)	0.7 (1.47)	-0.1 (0.82)	0.7 (1.49)	-0.1 (0.97)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 6	-5, 4	0, 8	-4, 3	0, 8	-5, 4
Week 4	n	87	87	99	99	186	186
	Mean (SD)	0.8 (1.45)	-0.2 (1.16)	0.8 (1.67)	0.0 (0.93)	0.8 (1.56)	-0.1 (1.05)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 7	-7, 2	0, 8	-4, 3	0, 8	-7, 3
Week 6	n	80	80	95	95	175	175
	Mean (SD)	0.7 (1.23)	-0.3 (1.51)	0.8 (1.65)	-0.1 (1.26)	0.7 (1.47)	-0.2 (1.38)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 7	-7, 3	0, 8	-4, 8	0, 8	-7, 8
Week 8	n	78	78	90	90	168	168
	Mean (SD)	0.8 (1.71)	-0.3 (1.50)	0.8 (1.59)	0.0 (1.14)	0.8 (1.64)	-0.1 (1.32)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 11	-8, 4	0, 6	-4, 6	0, 11	-8, 6
Week 12	n	75	75	88	88	163	163
	Mean (SD)	0.5 (1.07)	-0.4 (1.50)	0.8 (1.60)	-0.1 (1.19)	0.7 (1.38)	-0.2 (1.35)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 5	-8, 2	0, 7	-5, 4	0, 7	-8, 4

Visit	Statistics	Cohort 1 (N = 97) Observed	Change	Cohort 2 (N = 103) Observed	Change	Overall (N = 200) Observed	Change
Week 16	n	71	71	82	82	153	153
	Mean (SD)	0.7 (1.51)	-0.2 (1.51)	0.7 (1.57)	-0.2 (1.31)	0.7 (1.54)	-0.2 (1.40)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 7	-6, 4	0, 7	-6, 4	0, 7	-6, 4
Week 20	n	69	69	78	78	147	147
	Mean (SD)	0.6 (1.23)	-0.3 (1.45)	0.6 (1.42)	-0.2 (1.45)	0.6 (1.33)	-0.3 (1.44)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 7	-6, 3	0, 7	-6, 4	0, 7	-6, 4
Week 24	n	67	67	72	72	139	139
	Mean (SD)	0.6 (1.25)	-0.3 (1.47)	0.7 (1.53)	-0.3 (1.60)	0.6 (1.40)	-0.3 (1.54)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 6	-7, 4	0, 7	-6, 4	0, 7	-7, 4
Week 28	n	67	67	69	69	136	136
	Mean (SD)	0.8 (1.83)	-0.1 (1.78)	0.7 (1.72)	-0.3 (1.90)	0.7 (1.77)	-0.2 (1.84)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 9	-5, 9	0, 10	-6, 7	0, 10	-6, 9
Week 36	n	63	63	67	67	130	130
	Mean (SD)	0.9 (1.93)	0.1 (1.38)	0.5 (1.13)	-0.5 (1.68)	0.7 (1.57)	-0.2 (1.56)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 9	-4, 6	0, 6	-6, 3	0, 9	-6, 6
Week 44	n	60	60	61	61	121	121
	Mean (SD)	0.6 (1.51)	-0.1 (1.19)	0.6 (1.54)	-0.5 (1.88)	0.6 (1.52)	-0.3 (1.58)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 9	-6, 3	0, 9	-6, 6	0, 9	-6, 6
Week 52	n	57	57	60	60	117	117
	Mean (SD)	0.6 (1.23)	-0.1 (1.37)	0.5 (1.35)	-0.5 (1.74)	0.5 (1.28)	-0.3 (1.58)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 6	-7, 4	0, 8	-6, 5	0, 8	-7, 5
Week 52 (LOCF)	n	97	97	103	103	200	200
	Mean (SD)	0.9 (1.77)	0.0 (1.61)	0.6 (1.27)	-0.2 (1.49)	0.8 (1.54)	-0.1 (1.55)
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0, 7	-7, 6	0, 8	-6, 5	0, 8	-7, 6

Summary statistics for the observed value and change from baseline value (denoted by change) are based on subjects with both a baseline and the target visit observation. Week 52 (LOCF) endpoint is the last post-baseline observation in the DSP-5423P treatment phase up to 7 days after the final application of DSP-5423P. DIEPSS total score is the sum of symptom scores excluding overall severity.

2.7.4.4.5 C-SSRS

(1) 20 試験

二重盲検治療期

C-SSRS で自殺念慮及び自殺行動を示した被験者の割合を表 2.7.4.4-13 に、ベースライン

からの C-SSRS スコアの変化を表 2.7.4.4-14 に示す。

C-SSRS によりベースライン後に自殺念慮を示した被験者の割合はプラセボ群、40 mg 群、80 mg 群にそれぞれ 2.6%（5/190 名）、5.6%（11/196 名）、3.1%（6/194 名）で、自殺行動を示した被験者の割合は 80 mg 群 0.5%（1/194 名）であった。有害事象として 40 mg 群の 2 名で自殺念慮が、80 mg 群の 1 名で自殺企図が報告された。

実薬群合計で Any completed suicide（自殺既遂した被験者）はいなかった。Emergence of suicidal ideation（ベースライン時に C-SSRS の Suicidal ideation の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.3%（8/347 名）、Serious emergence of suicidal ideation（ベースライン時に C-SSRS の Suicidal ideation の項目 4[注 1)] と 5[注 2)] が共に No であったが、ロナセンテープ貼付開始後に Suicidal ideation の項目 4[注 1)] 又は 5[注 2)] で Yes が選択された被験者）が 0.3%（1/375 名）、Emergence of suicidal behavior（ベースライン時[注 1)] に C-SSRS の Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）はいなかった。Emergence of suicidality（ベースライン時に C-SSRS の Suicidal ideation の調査項目及び Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.3%（8/346 名）であった。

注 1）Active suicidal ideation with some intent to act, without specific plan
注 2）Active suicidal ideation with specific plan and intent

表 2.7.4.4-13　C-SSRS で自殺念慮及び自殺行動を示した被験者の割合（20 試験・二重盲検治療期）

Safety population

	PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)	Overall (N = 580) n (%)
Maximum suicidal ideation after baseline					
n	189	196	193	389	578
1: Wish to be dead	2 (1.1)	4 (2.0)	4 (2.1)	8 (2.1)	10 (1.7)
2: Non-specific active suicidal thoughts	3 (1.6)	6 (3.1)	0	6 (1.5)	9 (1.6)
3: Active suicidal ideation with any methods (not plan) without intent to act	0	0	1 (0.5)	1 (0.3)	1 (0.2)
4: Active suicidal ideation with some intent to act, without specific plan	0	1 (0.5)	0	1 (0.3)	1 (0.2)
5: Active suicidal ideation with specific plan and intent	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Any suicidal ideation after baseline	5 (2.6)	11 (5.6)	6 (3.1)	17 (4.4)	22 (3.8)
No suicidal ideation after baseline	184 (97.4)	185 (94.4)	187 (96.9)	372 (95.6)	556 (96.2)
Serious suicidal ideation Item 4 or 5 after baseline	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.3)
Suicidal Behavior after baseline					
n	189	196	193	389	578
1: Any actual attempts	0	0	0	0	0
2: Any interrupted attempts	0	0	0	0	0
3: Any aborted attempts	0	0	1 (0.5)	1 (0.3)	1 (0.2)
4: Any preparatory acts or behavior	0	0	0	0	0
Any suicidal behavior after baseline	0	0	1 (0.5)	1 (0.3)	1 (0.2)
No suicidal behavior after baseline	189 (100.0)	196 (100.0)	192 (99.5)	388 (99.7)	577 (99.8)
Suicidality after baseline					
n	189	196	193	389	578
Any suicidal ideation or behavior	5 (2.6)	11 (5.6)	6 (3.1)	17 (4.4)	22 (3.8)

表 2.7.4.4-14　ベースラインからの C-SSRS スコアの変化（20 試験・二重盲検治療期）

Safety population

	PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)	Overall (N = 580) n (%)
Emergence of any suicidal ideation after baseline					
n	168	172	175	347	515
Yes	1 (0.6)	6 (3.5)	2 (1.1)	8 (2.3)	9 (1.7)
No	167 (99.4)	166 (96.5)	173 (98.9)	339 (97.7)	506 (98.3)
Emergence of suicidal ideation Item 4 or 5 after baseline					
n	180	189	186	375	555
Yes	0	1 (0.5)	0	1 (0.3)	1 (0.2)

	PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)	Overall (N = 580) n (%)
No	180 (100.0)	188 (99.5)	186 (100.0)	374 (99.7)	554 (99.8)
Worsening of suicidal ideation after baseline					
n	189	196	192	388	577
Yes	2 (1.1)	6 (3.1)	3 (1.6)	9 (2.3)	11 (1.9)
No	187 (98.9)	190 (96.9)	189 (98.4)	379 (97.7)	566 (98.1)
Emergence of suicidal behavior after baseline					
n	178	189	183	372	550
Yes	0	0	0	0	0
No	178 (100.0)	189 (100.0)	183 (100.0)	372 (100.0)	550 (100.0)
Emergence of suicidality after baseline					
n	166	172	174	346	512
Yes	1 (0.6)	6 (3.5)	2 (1.1)	8 (2.3)	9 (1.8)
No	165 (99.4)	166 (96.5)	172 (98.9)	338 (97.7)	503 (98.2)
Any completed suicides after baseline					
n	189	196	193	389	578
Yes	0	0	0	0	0
No	189 (100.0)	196 (100.0)	193 (100.0)	389 (100.0)	578 (100.0)

Emergence of suicidal ideation or behavior is defined as subject has no suicidal ideation or behavior at baseline and developed any suicidal ideation or behavior in the double-blind treatment phase. Emergence of suicidal behavior after baseline is defined as subject has no suicidal behavior at baseline and subsequently has any type of suicidal behavior during the phase in the double-blind treatment phase. The denominator of percentages for emergence of suicidal ideation or suicidal behavior is the number of subjects who does not have any suicidal ideation or behavior at baseline. Suicidal ideation is defined as answered Yes for Item 4 or 5 of suicidal ideation. Completed suicide is any actual attempt of suicide results in death.

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

C-SSRS で自殺念慮及び自殺行動を示した被験者の割合を表 2.7.4.4-15 に、ベースラインからの C-SSRS スコアの変化を表 2.7.4.4-16 に示す。

DSP-5423P dosed population 合計で、C-SSRS によりベースライン後に自殺念慮を示した被験者の割合は 5.6%（29/519 名）で、自殺行動を示した被験者の割合は 0.6%（3/519 名）であった。自殺念慮の最大スコアがロナセンテープ貼付期間中にベースラインより悪化した割合は 3.3%（17/518 名）であった。有害事象として自殺既遂が 1 名、自殺企図が 2 名、自殺念慮が 9 名で報告された。

C-SSRS では Any completed suicide（自殺既遂した被験者）はいなかった。Emergence of suicidal ideation（ベースライン時[注1)] に C-SSRS の Suicidal ideation の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.8%（13/462 名）、emergence of suicidal ideation（ベースライン時[注1)] に C-SSRS の Suicidal ideation の項目 4[注2)] と 5[注3)] が共に No であったが、ロナセンテープ貼付開始後に Suicidal

ideation の項目 4[注2)] 又は 5[注3)] で Yes が選択された被験者）が 1.0%（5/498 名）、Emergence of suicidal behavior（ベースライン時[注1)] に C-SSRS の Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 0.4%(2/493 名)、Emergence of suicidality(ベースライン時[注1)]に C-SSRS の Suicidal ideation の調査項目及び Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.8%（13/459 名）であった。

注 1）すべての被験者で二重盲検治療期ベースライン
注 2）Active suicidal ideation with some intent to act, without specific plan
注 3）Active suicidal ideation with specific plan and intent

表 2.7.4.4-15　C-SSRS で自殺念慮及び自殺行動を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Maximum suicidal ideation after on-treatment baseline					
n	130	196	193	389	519
1: Wish to be dead	1 (0.8)	5 (2.6)	4 (2.1)	9 (2.3)	10 (1.9)
2: Non-specific active suicidal thoughts	3 (2.3)	7 (3.6)	0	7 (1.8)	10 (1.9)
3: Active suicidal ideation with any methods (not plan) without intent to act	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
4: Active suicidal ideation with some intent to act, without specific plan	1 (0.8)	3 (1.5)	0	3 (0.8)	4 (0.8)
5: Active suicidal ideation with specific plan and intent	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Any suicidal ideation after on-treatment baseline	6 (4.6)	16 (8.2)	7 (3.6)	23 (5.9)	29 (5.6)
No suicidal ideation after on-treatment baseline	124 (95.4)	180 (91.8)	186 (96.4)	366 (94.1)	490 (94.4)
Serious suicidal ideation Item 4 or 5 after on-treatment baseline	1 (0.8)	4 (2.0)	1 (0.5)	5 (1.3)	6 (1.2)
Suicidal Behavior after on-treatment baseline					
n	130	196	193	389	519
1: Any actual attempts	0	1 (0.5)	0	1 (0.3)	1 (0.2)
2: Any interrupted attempts	0	2 (1.0)	0	2 (0.5)	2 (0.4)
3: Any aborted attempts	0	0	1 (0.5)	1 (0.3)	1 (0.2)
4: Any preparatory acts or behavior	0	0	0	0	0
Any suicidal behavior after on-treatment baseline	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
No suicidal behavior after on-treatment baseline	130 (100.0)	194 (99.0)	192 (99.5)	386 (99.2)	516 (99.4)
Suicidality after on-treatment baseline					
n	130	196	193	389	519
Any suicidal ideation or behavior	6 (4.6)	16 (8.2)	7 (3.6)	23 (5.9)	29 (5.6)

The data cut-off at Open-Week 24 was used.

表 2.7.4.4-16　ベースラインからの C-SSRS スコアの変化（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Emergence of any suicidal ideation after on-treatment baseline					
n	115	172	175	347	462
Yes	2 (1.7)	9 (5.2)	2 (1.1)	11 (3.2)	13 (2.8)
No	113 (98.3)	163 (94.8)	173 (98.9)	336 (96.8)	449 (97.2)
Emergence of suicidal ideation Item 4 or 5 after on-treatment baseline					
n	123	189	186	375	498
Yes	1 (0.8)	4 (2.1)	0	4 (1.1)	5 (1.0)
No	122 (99.2)	185 (97.9)	186 (100.0)	371 (98.9)	493 (99.0)
Worsening of suicidal ideation after on-treatment baseline					
n	130	196	192	388	518
Yes	3 (2.3)	10 (5.1)	4 (2.1)	14 (3.6)	17 (3.3)
No	127 (97.7)	186 (94.9)	188 (97.9)	374 (96.4)	501 (96.7)
Emergence of suicidal behavior after on-treatment baseline					
n	121	189	183	372	493
Yes	0	2 (1.1)	0	2 (0.5)	2 (0.4)
No	121 (100.0)	187 (98.9)	183 (100.0)	370 (99.5)	491 (99.6)
Emergence of suicidality after on-treatment baseline					
n	113	172	174	346	459
Yes	2 (1.8)	9 (5.2)	2 (1.1)	11 (3.2)	13 (2.8)
No	111 (98.2)	163 (94.8)	172 (98.9)	335 (96.8)	446 (97.2)

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Any completed suicides after on-treatment baseline					
n	130	196	193	389	519
Yes	0	0	0	0	0
No	130 (100.0)	196 (100.0)	193 (100.0)	389 (100.0)	519 (100.0)

Emergence of suicidal ideation or behavior is defined as subject has no suicidal ideation or behavior at on-treatment baseline and developed any suicidal ideation or behavior in the DSP-5423P Treatment Period. The denominator of percentages for emergence of (serious) suicidal ideation or suicidal behavior is the number of subjects who does not have any suicidal ideation or behavior at on-treatment baseline. Serious ideation is defined as answered Yes for Item 4 or 5 of suicidal ideation. Completed suicide is any actual attempt of suicide results in death. The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

C-SSRS で自殺念慮及び自殺行動を示した被験者の割合を表 2.7.4.4-17 に、ベースラインからの C-SSRS スコアの変化を表 2.7.4.4-18 に示す。

DSP-5423P dosed population 合計で、C-SSRS によりベースライン後に自殺念慮を示した被験者の割合は 6.0%（31/519 名）で、自殺行動を示した被験者の割合は 0.6%（3/519 名）であった。自殺念慮の最大スコアがロナセンテープ貼付期間中にベースラインより悪化した割合は 3.5%（18/518 名）であった。有害事象として自殺既遂が 1 名、自殺企図が 2 名、自殺念慮が 9 名で報告された。

C-SSRS では Any completed suicide（自殺既遂した被験者）はいなかった。Emergence of suicidal ideation（ベースライン時[注 1)] に C-SSRS の Suicidal ideation の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.8%（13/462 名）、emergence of suicidal ideation（ベースライン時[注 1)] に C-SSRS の Suicidal ideation の項目 4[注 2)] と 5[注 3)] が共に No であったが、ロナセンテープ貼付開始後に Suicidal ideation の項目 4[注 2)] 又は 5[注 3)] で Yes が選択された被験者）が 1.0%（5/498 名）、Emergence of suicidal behavior（ベースライン時[注 1)] に C-SSRS の Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 0.4%(2/493 名)、Emergence of suicidality(ベースライン時[注 1)]に C-SSRS の Suicidal ideation の調査項目及び Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 2.8%（13/459 名）であった。

注 1）すべての被験者で二重盲検治療期ベースライン
注 2）Active suicidal ideation with some intent to act, without specific plan
注 3）Active suicidal ideation with specific plan and intent

表 2.7.4.4-17　C-SSRS で自殺念慮及び自殺行動を示した被験者の割合（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Maximum suicidal ideation after on-treatment baseline					
n	130	196	193	389	519
1: Wish to be dead	1 (0.8)	5 (2.6)	5 (2.6)	10 (2.6)	11 (2.1)
2: Non-specific active suicidal thoughts	3 (2.3)	8 (4.1)	0	8 (2.1)	11 (2.1)
3: Active suicidal ideation with any methods (not plan) without intent to act	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
4: Active suicidal ideation with some intent to act, without specific plan	1 (0.8)	3 (1.5)	0	3 (0.8)	4 (0.8)
5: Active suicidal ideation with specific plan and intent	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Any suicidal ideation after on-treatment baseline	6 (4.6)	17 (8.7)	8 (4.1)	25 (6.4)	31 (6.0)
No suicidal ideation after on-treatment baseline	124 (95.4)	179 (91.3)	185 (95.9)	364 (93.6)	488 (94.0)
Serious suicidal ideation Item 4 or 5 after on-treatment baseline	1 (0.8)	4 (2.0)	1 (0.5)	5 (1.3)	6 (1.2)
Suicidal Behavior after on-treatment baseline					
n	130	196	193	389	519
1: Any actual attempts	0	1 (0.5)	0	1 (0.3)	1 (0.2)
2: Any interrupted attempts	0	2 (1.0)	0	2 (0.5)	2 (0.4)
3: Any aborted attempts	0	0	1 (0.5)	1 (0.3)	1 (0.2)
4: Any preparatory acts or behavior	0	0	0	0	0
Any suicidal behavior after on-treatment baseline	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
No suicidal behavior after on-treatment baseline	130 (100.0)	194 (99.0)	192 (99.5)	386 (99.2)	516 (99.4)
Suicidality after on-treatment baseline					

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
n	130	196	193	389	519
Any suicidal ideation or behavior	6 (4.6)	17 (8.7)	8 (4.1)	25 (6.4)	31 (6.0)

The final data at Open-Week 52 was used.

表 2.7.4.4-18　ベースラインからの C-SSRS スコアの変化（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Emergence of any suicidal ideation after on-treatment baseline					
n	115	172	175	347	462
Yes	2 (1.7)	9 (5.2)	2 (1.1)	11 (3.2)	13 (2.8)
No	113 (98.3)	163 (94.8)	173 (98.9)	336 (96.8)	449 (97.2)
Emergence of suicidal ideation Item 4 or 5 after on-treatment baseline					
n	123	189	186	375	498
Yes	1 (0.8)	4 (2.1)	0	4 (1.1)	5 (1.0)
No	122 (99.2)	185 (97.9)	186 (100.0)	371 (98.9)	493 (99.0)
Worsening of suicidal ideation after on-treatment baseline					
n	130	196	192	388	518
Yes	3 (2.3)	11 (5.6)	4 (2.1)	15 (3.9)	18 (3.5)
No	127 (97.7)	185 (94.4)	188 (97.9)	373 (96.1)	500 (96.5)

	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Emergence of suicidal behavior after on-treatment baseline					
n	121	189	183	372	493
Yes	0	2 (1.1)	0	2 (0.5)	2 (0.4)
No	121 (100.0)	187 (98.9)	183 (100.0)	370 (99.5)	491 (99.6)
Emergence of suicidality after on-treatment baseline					
n	113	172	174	346	459
Yes	2 (1.8)	9 (5.2)	2 (1.1)	11 (3.2)	13 (2.8)
No	111 (98.2)	163 (94.8)	172 (98.9)	335 (96.8)	446 (97.2)
Any completed suicides after on-treatment baseline					
n	130	196	193	389	519
Yes	0	0	0	0	0
No	130 (100.0)	196 (100.0)	193 (100.0)	389 (100.0)	519 (100.0)

Emergence of suicidal ideation or behavior is defined as subject has no suicidal ideation or behavior at on-treatment baseline and developed any suicidal ideation or behavior in the DSP-5423P Treatment Period. The denominator of percentages for emergence of (serious) suicidal ideation or suicidal behavior is the number of subjects who does not have any suicidal ideation or behavior at on-treatment baseline. Serious ideation is defined as answered Yes for Item 4 or 5 of suicidal ideation. Completed suicide is any actual attempt of suicide results in death. The final data at Open-Week 52 was used.

(2) 40 試験

ベースラインからの C-SSRS スコアの変化を表 2.7.4.4-19 に示す。

全体で Any completed suicide（自殺既遂した被験者）はいなかった。Emergence of suicidal ideation（ベースライン時[注 1)] に C-SSRS の Suicidal ideation の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 10.1%（13/129 名）、Serious emergence of suicidal ideation（ベースライン時[注 1)] に C-SSRS の Suicidal ideation の項目 4[注 2)] と 5[注 3)] が共に No であったが、ロナセンテープ貼付開始後に Suicidal ideation の項目 4[注 2)] 又は 5[注 3)] で Yes が選択された被験者）が 0.6%（1/175 名）、Emergence of suicidal behavior（ベースライン時[注 1)] に C-SSRS の Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 0.6%（1/172 名）、Emergence of suicidality（ベースライン時[注 1)] に C-SSRS の Suicidal ideation の調査項目及び Suicidal behavior の調査項目がすべて No であったが、ロナセンテープ貼付開始後にいずれかの項目で Yes が選択された被験者）が 10.1%（13/129 名）であった。

注 1）コホート 1 はロナセン錠投与期ベースライン、コホート 2 はロナセンテープ貼付期ベースライン
注 2）Active suicidal ideation with some intent to act, without specific plan
注 3）Active suicidal ideation with specific plan and intent

表 2.7.4.4-19　ベースラインからの C-SSRS スコアの変化（40 試験）

Safety population

		Cohort 1 (N = 97) n (%)	Cohort 2 (N = 103) n (%)	Overall (N = 200) n (%)
Emergence of suicidal ideation	n	61	68	129
	Yes	4 (6.6)	9 (13.2)	13 (10.1)
	No	57 (93.4)	59 (86.8)	116 (89.9)
Serious emergence of suicidal ideation	n	85	90	175
	Yes	1 (1.2)	0	1 (0.6)
	No	84 (98.8)	90 (100.0)	174 (99.4)
Emergence of suicidal behavior	n	83	89	172
	Yes	1 (1.2)	0	1 (0.6)
	No	82 (98.8)	89 (100.0)	171 (99.4)
Emergence of suicidality	n	61	68	129
	Yes	4 (6.6)	9 (13.2)	13 (10.1)
	No	57 (93.4)	59 (86.8)	116 (89.9)
Any completed suicide	n	97	103	200
	Yes	0	0	0
	No	97 (100.0)	103 (100.0)	200 (100.0)

Emergence of suicidal ideation or behavior is defined as subject has no suicidal ideation or behavior at baseline (Tab-Baseline for Cohort 1, Baseline for Cohort 2) and developed any suicidal ideation or behavior in the DSP-5423P treatment phase. The denominator of percentages for emergence of (serious) suicidal ideation or suicidal behavior is the number of subjects who does not have any suicidal ideation or behavior at baseline. Serious ideation is defined as answered Yes for Item 4 or 5 of suicidal ideation. Completed suicide is any actual attempt of suicide results in death.

2.7.4.4.6　皮膚刺激性評価

(1)　20 試験

二重盲検治療期

皮膚刺激性評価スコアの推移を表 2.7.4.4-20 に示す。なお、二重盲検治療期にはブロナンセリン含量が 0 mg 又は 40 mg の 2 種類の治験薬を用い、プラセボ群は含量 0 mg の治験薬を 2 枚、40 mg 群は含量 0 mg 及び 40 mg の治験薬を各 1 枚、80 mg 群は含量 40 mg の治験薬を 2 枚貼付した。

二重盲検治療期中最も悪いスコアが反応なし（Negative）であった割合がいずれの群でも最も高く、プラセボ群、40 mg 群、80 mg 群（以下、同順）でそれぞれ 82.5%、77.6%、70.5%であった。次いで、軽度の紅斑（Faint erythema）、紅斑（Erythema）の割合が高く、最も悪いスコアが軽度の紅斑の割合は 12.2%、11.7%、13.0%、紅斑の割合は 4.2%、8.7%、14.5%であった。最も悪いスコアが軽度の紅斑であった割合は 3 群間で大きな違いはなく、紅斑であった割合は 2 枚の治験薬のうち DSP-5423P 40 mg を含むテープの枚数が多いほど高くなった。

二重盲検治療期中に大水疱（Coalescing vesicles）となった被験者はいなかった。プラセ

ボ群、40 mg 群、80 mg 群のいずれでも発現した最も悪いスコアは「紅斑 + 浮腫 + 丘疹、漿液性丘疹、小水疱」（Erythema + Edema + Papules, Serous papules, Vesicles）で、発現割合はいずれも 0.5%（各 1 名）であった。

表 2.7.4.4-20　皮膚刺激性評価スコアの推移（20 試験・二重盲検治療期）

Safety population

Visit		PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)	Overall (N = 580) n (%)
Baseline	n	189	196	193	389	578
	Negative	178 (94.2)	180 (91.8)	177 (91.7)	357 (91.8)	535 (92.6)
	Faint erythema	10 (5.3)	9 (4.6)	10 (5.2)	19 (4.9)	29 (5.0)
	Erythema	1 (0.5)	7 (3.6)	6 (3.1)	13 (3.3)	14 (2.4)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
Week 1	n	188	196	193	389	577
	Negative	176 (93.6)	168 (85.7)	160 (82.9)	328 (84.3)	504 (87.3)
	Faint erythema	8 (4.3)	19 (9.7)	19 (9.8)	38 (9.8)	46 (8.0)
	Erythema	4 (2.1)	7 (3.6)	11 (5.7)	18 (4.6)	22 (3.8)
	Erythema + Edema	0	2 (1.0)	2 (1.0)	4 (1.0)	4 (0.7)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
Week 2	n	172	179	184	363	535
	Negative	157 (91.3)	158 (88.3)	147 (79.9)	305 (84.0)	462 (86.4)
	Faint erythema	12 (7.0)	11 (6.1)	20 (10.9)	31 (8.5)	43 (8.0)
	Erythema	3 (1.7)	8 (4.5)	16 (8.7)	24 (6.6)	27 (5.0)
	Erythema + Edema	0	1 (0.6)	1 (0.5)	2 (0.6)	2 (0.4)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	1 (0.6)	0	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0

Visit		PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)	Overall (N = 580) n (%)
Week 4	n	154	167	174	341	495
	Negative	138 (89.6)	143 (85.6)	139 (79.9)	282 (82.7)	420 (84.8)
	Faint erythema	12 (7.8)	14 (8.4)	24 (13.8)	38 (11.1)	50 (10.1)
	Erythema	2 (1.3)	10 (6.0)	11 (6.3)	21 (6.2)	23 (4.6)
	Erythema + Edema	1 (0.6)	0	0	0	1 (0.2)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (0.6)	0	0	0	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
Week 6	n	143	156	166	322	465
	Negative	130 (90.9)	139 (89.1)	139 (83.7)	278 (86.3)	408 (87.7)
	Faint erythema	12 (8.4)	12 (7.7)	17 (10.2)	29 (9.0)	41 (8.8)
	Erythema	1 (0.7)	5 (3.2)	10 (6.0)	15 (4.7)	16 (3.4)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
Week 6 (LOCF)	n	189	196	193	389	578
	Negative	173 (91.5)	174 (88.8)	161 (83.4)	335 (86.1)	508 (87.9)
	Faint erythema	15 (7.9)	12 (6.1)	19 (9.8)	31 (8.0)	46 (8.0)
	Erythema	1 (0.5)	10 (5.1)	12 (6.2)	22 (5.7)	23 (4.0)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
Maximum severity during Double-blind treatment phase	n	189	196	193	389	578
	Negative	156 (82.5)	152 (77.6)	136 (70.5)	288 (74.0)	444 (76.8)
	Faint erythema	23 (12.2)	23 (11.7)	25 (13.0)	48 (12.3)	71 (12.3)
	Erythema	8 (4.2)	17 (8.7)	28 (14.5)	45 (11.6)	53 (9.2)
	Erythema + Edema	1 (0.5)	3 (1.5)	3 (1.6)	6 (1.5)	7 (1.2)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.5)
	Coalescing Vesicles	0	0	0	0	0

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）

皮膚刺激性評価スコアの推移を表 2.7.4.4-21 に示す。なお、非盲検治療期はロナセンテ

ープ 40 mg/日で開始し、40 mg/日で約 1 週間貼付した後、1 回あたり 20 mg/日の増減量で 40 mg/ 日、60 mg/日又は 80 mg/日に適宜増減することとした。ブロナンセリン含量が 20 mg 又は 40 mg の 2 種類の治験薬を用い、40 mg/日では含量 40 mg の治験薬を 1 枚、60 mg/日では含量 40 mg 及び 20 mg の治験薬を各 1 枚、80 mg/日では含量 40 mg の治験薬を 2 枚貼付することとした。

DSP-5423P dosed population 合計で、ロナセンテープ貼付期中に最も悪いスコアが反応なし（Negative）であった割合は 72.1%であった。軽度の紅斑（Faint erythema）は 13.7%、紅斑（Erythema）は 12.1%、「紅斑 + 浮腫」（Erythema + Edema）は 1.3%、「紅斑 + 浮腫 + 丘疹、漿液性丘疹、小水疱」（Erythema + Edema + Papules, Serous papules, Vesicles）は 0.8%で、大水疱（Coalescing Vesicles）となった被験者はいなかった。

表 2.7.4.4-21　皮膚刺激性評価スコアの推移（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Baseline	n	131	196	193	389	520
	Negative	120 (91.6)	180 (91.8)	177 (91.7)	357 (91.8)	477 (91.7)
	Faint erythema	10 (7.6)	9 (4.6)	10 (5.2)	19 (4.9)	29 (5.6)
	Erythema	1 (0.8)	7 (3.6)	6 (3.1)	13 (3.3)	14 (2.7)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 1	n	130	196	193	389	519
	Negative	122 (93.8)	168 (85.7)	160 (82.9)	328 (84.3)	450 (86.7)
	Faint erythema	6 (4.6)	19 (9.7)	19 (9.8)	38 (9.8)	44 (8.5)
	Erythema	2 (1.5)	7 (3.6)	11 (5.7)	18 (4.6)	20 (3.9)
	Erythema + Edema	0	2 (1.0)	2 (1.0)	4 (1.0)	4 (0.8)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 2	n	129	179	184	363	492
	Negative	117 (90.7)	158 (88.3)	147 (79.9)	305 (84.0)	422 (85.8)
	Faint erythema	8 (6.2)	11 (6.1)	20 (10.9)	31 (8.5)	39 (7.9)
	Erythema	2 (1.6)	8 (4.5)	16 (8.7)	24 (6.6)	26 (5.3)
	Erythema + Edema	1 (0.8)	1 (0.6)	1 (0.5)	2 (0.6)	3 (0.6)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (0.8)	1 (0.6)	0	1 (0.3)	2 (0.4)
	Coalescing Vesicles	0	0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Week 4	n	125	167	174	341	466
	Negative	115 (92.0)	143 (85.6)	139 (79.9)	282 (82.7)	397 (85.2)
	Faint erythema	8 (6.4)	14 (8.4)	24 (13.8)	38 (11.1)	46 (9.9)
	Erythema	2 (1.6)	10 (6.0)	11 (6.3)	21 (6.2)	23 (4.9)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 6	n		156	166	322	322
	Negative		139 (89.1)	139 (83.7)	278 (86.3)	278 (86.3)
	Faint erythema		12 (7.7)	17 (10.2)	29 (9.0)	29 (9.0)
	Erythema		5 (3.2)	10 (6.0)	15 (4.7)	15 (4.7)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 7	n		142	156	298	298
	Negative		132 (93.0)	129 (82.7)	261 (87.6)	261 (87.6)
	Faint erythema		4 (2.8)	19 (12.2)	23 (7.7)	23 (7.7)
	Erythema		6 (4.2)	7 (4.5)	13 (4.4)	13 (4.4)
	Erythema + Edema		0	1 (0.6)	1 (0.3)	1 (0.3)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Week 8	n	117	137	154	291	408
	Negative	102 (87.2)	131 (95.6)	127 (82.5)	258 (88.7)	360 (88.2)
	Faint erythema	10 (8.5)	4 (2.9)	19 (12.3)	23 (7.9)	33 (8.1)
	Erythema	5 (4.3)	2 (1.5)	8 (5.2)	10 (3.4)	15 (3.7)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 10	n		134	146	280	280
	Negative		128 (95.5)	123 (84.2)	251 (89.6)	251 (89.6)
	Faint erythema		3 (2.2)	18 (12.3)	21 (7.5)	21 (7.5)
	Erythema		3 (2.2)	5 (3.4)	8 (2.9)	8 (2.9)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 12	n	104				104
	Negative	95 (91.3)				95 (91.3)
	Faint erythema	6 (5.8)				6 (5.8)
	Erythema	3 (2.9)				3 (2.9)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Week 14	n		127	142	269	269
	Negative		118 (92.9)	121 (85.2)	239 (88.8)	239 (88.8)
	Faint erythema		7 (5.5)	17 (12.0)	24 (8.9)	24 (8.9)
	Erythema		2 (1.6)	4 (2.8)	6 (2.2)	6 (2.2)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 16	n	99				99
	Negative	90 (90.9)				90 (90.9)
	Faint erythema	6 (6.1)				6 (6.1)
	Erythema	2 (2.0)				2 (2.0)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (1.0)				1 (1.0)
	Coalescing Vesicles	0				0
On-treatment Week 18	n		109	126	235	235
	Negative		102 (93.6)	108 (85.7)	210 (89.4)	210 (89.4)
	Faint erythema		4 (3.7)	12 (9.5)	16 (6.8)	16 (6.8)
	Erythema		2 (1.8)	6 (4.8)	8 (3.4)	8 (3.4)
	Erythema + Edema		1 (0.9)	0	1 (0.4)	1 (0.4)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Week 20	n	90				90
	Negative	84 (93.3)				84 (93.3)
	Faint erythema	5 (5.6)				5 (5.6)
	Erythema	1 (1.1)				1 (1.1)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 22	n		107	123	230	230
	Negative		101 (94.4)	107 (87.0)	208 (90.4)	208 (90.4)
	Faint erythema		5 (4.7)	9 (7.3)	14 (6.1)	14 (6.1)
	Erythema		0	7 (5.7)	7 (3.0)	7 (3.0)
	Erythema + Edema		1 (0.9)	0	1 (0.4)	1 (0.4)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 24	n	89				89
	Negative	81 (91.0)				81 (91.0)
	Faint erythema	4 (4.5)				4 (4.5)
	Erythema	4 (4.5)				4 (4.5)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Week 26	n		99	117	216	216
	Negative		96 (97.0)	102 (87.2)	198 (91.7)	198 (91.7)
	Faint erythema		2 (2.0)	10 (8.5)	12 (5.6)	12 (5.6)
	Erythema		1 (1.0)	5 (4.3)	6 (2.8)	6 (2.8)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 30	n		92	113	205	205
	Negative		88 (95.7)	97 (85.8)	185 (90.2)	185 (90.2)
	Faint erythema		3 (3.3)	9 (8.0)	12 (5.9)	12 (5.9)
	Erythema		1 (1.1)	7 (6.2)	8 (3.9)	8 (3.9)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment (LOCF)	n	131	196	193	389	520
	Negative	122 (93.1)	179 (91.3)	159 (82.4)	338 (86.9)	460 (88.5)
	Faint erythema	5 (3.8)	10 (5.1)	20 (10.4)	30 (7.7)	35 (6.7)
	Erythema	4 (3.1)	7 (3.6)	13 (6.7)	20 (5.1)	24 (4.6)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Maximum severity during DSP-5423P Treatment Period	n	131	196	193	389	520
	Negative	105 (80.2)	144 (73.5)	126 (65.3)	270 (69.4)	375 (72.1)
	Faint erythema	15 (11.5)	30 (15.3)	26 (13.5)	56 (14.4)	71 (13.7)
	Erythema	9 (6.9)	18 (9.2)	36 (18.7)	54 (13.9)	63 (12.1)
	Erythema + Edema	0	3 (1.5)	4 (2.1)	7 (1.8)	7 (1.3)
	Erythema + Edema + Papules, Serous papules, Vesicles	2 (1.5)	1 (0.5)	1 (0.5)	2 (0.5)	4 (0.8)
	Coalescing Vesicles	0	0	0	0	0

The data cut-off at Open-Week 24 was used.

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）

皮膚刺激性評価スコアの推移を表 2.7.4.4-21 に示す。

DSP-5423P dosed population 合計で、ロナセンテープ貼付期中に最も悪いスコアが反応なし（Negative）であった割合は 71.5%であった。軽度の紅斑（Faint erythema）は 13.7%、紅斑（Erythema）は 12.7%、「紅斑 + 浮腫」（Erythema + Edema）は 1.3%、「紅斑 + 浮腫 + 丘疹、漿液性丘疹、小水疱」（Erythema + Edema + Papules, Serous papules, Vesicles）は 0.8%で、大水疱（Coalescing Vesicles）となった被験者はいなかった。

表 2.7.4.4-22　皮膚刺激性評価スコアの推移（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
On-treatment Baseline	n	131	196	193	389	520
	Negative	120 (91.6)	180 (91.8)	177 (91.7)	357 (91.8)	477 (91.7)
	Faint erythema	10 (7.6)	9 (4.6)	10 (5.2)	19 (4.9)	29 (5.6)
	Erythema	1 (0.8)	7 (3.6)	6 (3.1)	13 (3.3)	14 (2.7)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 1	n	130	196	193	389	519
	Negative	122 (93.8)	168 (85.7)	160 (82.9)	328 (84.3)	450 (86.7)
	Faint erythema	6 (4.6)	19 (9.7)	19 (9.8)	38 (9.8)	44 (8.5)
	Erythema	2 (1.5)	7 (3.6)	11 (5.7)	18 (4.6)	20 (3.9)
	Erythema + Edema	0	2 (1.0)	2 (1.0)	4 (1.0)	4 (0.8)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 2	n	129	179	184	363	492
	Negative	117 (90.7)	158 (88.3)	147 (79.9)	305 (84.0)	422 (85.8)
	Faint erythema	8 (6.2)	11 (6.1)	20 (10.9)	31 (8.5)	39 (7.9)
	Erythema	2 (1.6)	8 (4.5)	16 (8.7)	24 (6.6)	26 (5.3)
	Erythema + Edema	1 (0.8)	1 (0.6)	1 (0.5)	2 (0.6)	3 (0.6)

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (0.8)	1 (0.6)	0	1 (0.3)	2 (0.4)
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 4	n	125	167	174	341	466
	Negative	115 (92.0)	143 (85.6)	139 (79.9)	282 (82.7)	397 (85.2)
	Faint erythema	8 (6.4)	14 (8.4)	24 (13.8)	38 (11.1)	46 (9.9)
	Erythema	2 (1.6)	10 (6.0)	11 (6.3)	21 (6.2)	23 (4.9)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 6	n		156	166	322	322
	Negative		139 (89.1)	139 (83.7)	278 (86.3)	278 (86.3)
	Faint erythema		12 (7.7)	17 (10.2)	29 (9.0)	29 (9.0)
	Erythema		5 (3.2)	10 (6.0)	15 (4.7)	15 (4.7)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 7	n		142	156	298	298
	Negative		132 (93.0)	129 (82.7)	261 (87.6)	261 (87.6)
	Faint erythema		4 (2.8)	19 (12.2)	23 (7.7)	23 (7.7)
	Erythema		6 (4.2)	7 (4.5)	13 (4.4)	13 (4.4)
	Erythema + Edema		0	1 (0.6)	1 (0.3)	1 (0.3)

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 8	n	117	137	154	291	408
	Negative	102 (87.2)	131 (95.6)	127 (82.5)	258 (88.7)	360 (88.2)
	Faint erythema	10 (8.5)	4 (2.9)	19 (12.3)	23 (7.9)	33 (8.1)
	Erythema	5 (4.3)	2 (1.5)	8 (5.2)	10 (3.4)	15 (3.7)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0	0	0
	Coalescing Vesicles	0	0	0	0	0
On-treatment Week 10	n		134	146	280	280
	Negative		128 (95.5)	123 (84.2)	251 (89.6)	251 (89.6)
	Faint erythema		3 (2.2)	18 (12.3)	21 (7.5)	21 (7.5)
	Erythema		3 (2.2)	5 (3.4)	8 (2.9)	8 (2.9)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 12	n	104				104
	Negative	95 (91.3)				95 (91.3)
	Faint erythema	6 (5.8)				6 (5.8)
	Erythema	3 (2.9)				3 (2.9)
	Erythema + Edema	0				0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 14	n		127	142	269	269
	Negative		118 (92.9)	121 (85.2)	239 (88.8)	239 (88.8)
	Faint erythema		7 (5.5)	17 (12.0)	24 (8.9)	24 (8.9)
	Erythema		2 (1.6)	4 (2.8)	6 (2.2)	6 (2.2)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 16	n	99				99
	Negative	90 (90.9)				90 (90.9)
	Faint erythema	6 (6.1)				6 (6.1)
	Erythema	2 (2.0)				2 (2.0)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (1.0)				1 (1.0)
	Coalescing Vesicles	0				0
On-treatment Week 18	n		109	126	235	235
	Negative		102 (93.6)	108 (85.7)	210 (89.4)	210 (89.4)
	Faint erythema		4 (3.7)	12 (9.5)	16 (6.8)	16 (6.8)
	Erythema		2 (1.8)	6 (4.8)	8 (3.4)	8 (3.4)
	Erythema + Edema		1 (0.9)	0	1 (0.4)	1 (0.4)

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 20	n	90				90
	Negative	84 (93.3)				84 (93.3)
	Faint erythema	5 (5.6)				5 (5.6)
	Erythema	1 (1.1)				1 (1.1)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 22	n		107	123	230	230
	Negative		101 (94.4)	107 (87.0)	208 (90.4)	208 (90.4)
	Faint erythema		5 (4.7)	9 (7.3)	14 (6.1)	14 (6.1)
	Erythema		0	7 (5.7)	7 (3.0)	7 (3.0)
	Erythema + Edema		1 (0.9)	0	1 (0.4)	1 (0.4)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 24	n	89				89
	Negative	81 (91.0)				81 (91.0)
	Faint erythema	4 (4.5)				4 (4.5)
	Erythema	4 (4.5)				4 (4.5)
	Erythema + Edema	0				0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 26	n		99	117	216	216
	Negative		96 (97.0)	102 (87.2)	198 (91.7)	198 (91.7)
	Faint erythema		2 (2.0)	10 (8.5)	12 (5.6)	12 (5.6)
	Erythema		1 (1.0)	5 (4.3)	6 (2.8)	6 (2.8)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 28	n	83				83
	Negative	75 (90.4)				75 (90.4)
	Faint erythema	5 (6.0)				5 (6.0)
	Erythema	3 (3.6)				3 (3.6)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 30	n		92	113	205	205
	Negative		88 (95.7)	97 (85.8)	185 (90.2)	185 (90.2)
	Faint erythema		3 (3.3)	9 (8.0)	12 (5.9)	12 (5.9)
	Erythema		1 (1.1)	7 (6.2)	8 (3.9)	8 (3.9)
	Erythema + Edema		0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 34	n		91	114	205	205
	Negative		88 (96.7)	104 (91.2)	192 (93.7)	192 (93.7)
	Faint erythema		2 (2.2)	6 (5.3)	8 (3.9)	8 (3.9)
	Erythema		1 (1.1)	4 (3.5)	5 (2.4)	5 (2.4)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 36	n	17				17
	Negative	13 (76.5)				13 (76.5)
	Faint erythema	3 (17.6)				3 (17.6)
	Erythema	1 (5.9)				1 (5.9)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 42	n		20	27	47	47
	Negative		16 (80.0)	21 (77.8)	37 (78.7)	37 (78.7)
	Faint erythema		3 (15.0)	2 (7.4)	5 (10.6)	5 (10.6)
	Erythema		1 (5.0)	4 (14.8)	5 (10.6)	5 (10.6)
	Erythema + Edema		0	0	0	0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 44	n	15				15
	Negative	13 (86.7)				13 (86.7)
	Faint erythema	1 (6.7)				1 (6.7)
	Erythema	1 (6.7)				1 (6.7)
	Erythema + Edema	0				0
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 50	n		20	25	45	45
	Negative		17 (85.0)	19 (76.0)	36 (80.0)	36 (80.0)
	Faint erythema		2 (10.0)	5 (20.0)	7 (15.6)	7 (15.6)
	Erythema		1 (5.0)	1 (4.0)	2 (4.4)	2 (4.4)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment Week 52	n	13				13
	Negative	11 (84.6)				11 (84.6)
	Faint erythema	1 (7.7)				1 (7.7)
	Erythema	1 (7.7)				1 (7.7)
	Erythema + Edema	0				0

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema + Papules, Serous papules, Vesicles	0				0
	Coalescing Vesicles	0				0
On-treatment Week 58	n		17	22	39	39
	Negative		12 (70.6)	17 (77.3)	29 (74.4)	29 (74.4)
	Faint erythema		3 (17.6)	3 (13.6)	6 (15.4)	6 (15.4)
	Erythema		2 (11.8)	2 (9.1)	4 (10.3)	4 (10.3)
	Erythema + Edema		0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles		0	0	0	0
	Coalescing Vesicles		0	0	0	0
On-treatment (LOCF)	n	131	196	193	389	520
	Negative	122 (93.1)	178 (90.8)	165 (85.5)	343 (88.2)	465 (89.4)
	Faint erythema	6 (4.6)	10 (5.1)	16 (8.3)	26 (6.7)	32 (6.2)
	Erythema	3 (2.3)	8 (4.1)	11 (5.7)	19 (4.9)	22 (4.2)
	Erythema + Edema	0	0	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	1 (0.5)	1 (0.3)	1 (0.2)
	Coalescing Vesicles	0	0	0	0	0
Maximum severity during DSP-5423P Treatment Period	n	131	196	193	389	520
	Negative	103 (78.6)	143 (73.0)	126 (65.3)	269 (69.2)	372 (71.5)
	Faint erythema	16 (12.2)	30 (15.3)	25 (13.0)	55 (14.1)	71 (13.7)
	Erythema	10 (7.6)	19 (9.7)	37 (19.2)	56 (14.4)	66 (12.7)

Visit		PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
	Erythema + Edema	0	3 (1.5)	4 (2.1)	7 (1.8)	7 (1.3)
	Erythema + Edema + Papules, Serous papules, Vesicles	2 (1.5)	1 (0.5)	1 (0.5)	2 (0.5)	4 (0.8)
	Coalescing Vesicles	0	0	0	0	0

The final data at Open-Week 52 was used.

(2) 40 試験

皮膚刺激性評価スコアの推移を表 2.7.4.4-23 に示す。なお、いずれのコホートでもロナセンテープは、ブロナンセリン含量が 20 mg 又は 40 mg の 2 種類の治験薬を用い、40 mg/日では含量 40 mg の治験薬を 1 枚、60 mg/日では含量 40 mg 及び 20 mg の治験薬を各 1 枚、80 mg/日では含量 40 mg の治験薬を 2 枚貼付することとした。

全体で大水疱（Coalescing Vesicles）と判定された被験者はいなかった。最大スコアが「紅斑 + 浮腫 + 丘疹、漿液性丘疹、小水疱」（Erythema + Edema + Papules, Serous papules, Vesicles）であった被験者は 1.0%（2/200 名）、「紅斑 + 浮腫」（Erythema + Edema）であった被験者は 6.0%（12/200 名）、紅斑（Erythema）であった被験者は 24.0%（48/200 名）、軽度の紅斑（Faint erythema）であった被験者は 36.5%（73/200 名）であった。いずれのスコアも被験者の割合は貼付期間を通じて同じ程度であった。

表 2.7.4.4-23　皮膚刺激性評価スコアの推移（40 試験）

Safety population

Visit		Cohort 1 (N = 97) n (%)	Cohort 2 (N = 103) n (%)	Overall (N = 200) n (%)
Baseline	n	97	103	200
	Negative	96 (99.0)	103 (100.0)	199 (99.5)
	Faint erythema	1 (1.0)	0	1 (0.5)
	Erythema	0	0	0
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 1	n	97	103	200
	Negative	71 (73.2)	76 (73.8)	147 (73.5)
	Faint erythema	21 (21.6)	16 (15.5)	37 (18.5)
	Erythema	4 (4.1)	8 (7.8)	12 (6.0)
	Erythema + Edema	1 (1.0)	3 (2.9)	4 (2.0)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 2	n	89	100	189
	Negative	60 (67.4)	68 (68.0)	128 (67.7)
	Faint erythema	17 (19.1)	25 (25.0)	42 (22.2)
	Erythema	10 (11.2)	7 (7.0)	17 (9.0)
	Erythema + Edema	1 (1.1)	0	1 (0.5)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (1.1)	0	1 (0.5)
	Coalescing Vesicles	0	0	0

Visit		Cohort 1 (N = 97) n (%)	Cohort 2 (N = 103) n (%)	Overall (N = 200) n (%)
Week 4	n	87	99	186
	Negative	58 (66.7)	56 (56.6)	114 (61.3)
	Faint erythema	22 (25.3)	28 (28.3)	50 (26.9)
	Erythema	6 (6.9)	13 (13.1)	19 (10.2)
	Erythema + Edema	1 (1.1)	1 (1.0)	2 (1.1)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	1 (1.0)	1 (0.5)
	Coalescing Vesicles	0	0	0
Week 6	n	80	95	175
	Negative	52 (65.0)	62 (65.3)	114 (65.1)
	Faint erythema	23 (28.8)	24 (25.3)	47 (26.9)
	Erythema	5 (6.3)	9 (9.5)	14 (8.0)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 8	n	78	90	168
	Negative	51 (65.4)	54 (60.0)	105 (62.5)
	Faint erythema	19 (24.4)	28 (31.1)	47 (28.0)
	Erythema	6 (7.7)	8 (8.9)	14 (8.3)
	Erythema + Edema	2 (2.6)	0	2 (1.2)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 12	n	75	88	163
	Negative	53 (70.7)	54 (61.4)	107 (65.6)
	Faint erythema	14 (18.7)	26 (29.5)	40 (24.5)
	Erythema	8 (10.7)	8 (9.1)	16 (9.8)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 16	n	71	82	153
	Negative	43 (60.6)	55 (67.1)	98 (64.1)
	Faint erythema	20 (28.2)	18 (22.0)	38 (24.8)
	Erythema	7 (9.9)	8 (9.8)	15 (9.8)
	Erythema + Edema	1 (1.4)	1 (1.2)	2 (1.3)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0

Visit		Cohort 1 (N = 97) n (%)	Cohort 2 (N = 103) n (%)	Overall (N = 200) n (%)
Week 20	n	69	78	147
	Negative	49 (71.0)	57 (73.1)	106 (72.1)
	Faint erythema	15 (21.7)	14 (17.9)	29 (19.7)
	Erythema	5 (7.2)	7 (9.0)	12 (8.2)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 24	n	67	72	139
	Negative	47 (70.1)	53 (73.6)	100 (71.9)
	Faint erythema	13 (19.4)	11 (15.3)	24 (17.3)
	Erythema	7 (10.4)	8 (11.1)	15 (10.8)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 28	n	67	69	136
	Negative	50 (74.6)	50 (72.5)	100 (73.5)
	Faint erythema	8 (11.9)	14 (20.3)	22 (16.2)
	Erythema	9 (13.4)	5 (7.2)	14 (10.3)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 36	n	63	67	130
	Negative	44 (69.8)	48 (71.6)	92 (70.8)
	Faint erythema	15 (23.8)	13 (19.4)	28 (21.5)
	Erythema	4 (6.3)	6 (9.0)	10 (7.7)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 44	n	60	61	121
	Negative	44 (73.3)	41 (67.2)	85 (70.2)
	Faint erythema	12 (20.0)	13 (21.3)	25 (20.7)
	Erythema	4 (6.7)	6 (9.8)	10 (8.3)
	Erythema + Edema	0	1 (1.6)	1 (0.8)
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0

Visit		Cohort 1 (N = 97) n (%)	Cohort 2 (N = 103) n (%)	Overall (N = 200) n (%)
Week 52	n	57	60	117
	Negative	41 (71.9)	44 (73.3)	85 (72.6)
	Faint erythema	10 (17.5)	12 (20.0)	22 (18.8)
	Erythema	6 (10.5)	4 (6.7)	10 (8.5)
	Erythema + Edema	0	0	0
	Erythema + Edema + Papules, Serous papules, Vesicles	0	0	0
	Coalescing Vesicles	0	0	0
Week 52 (LOCF)	n	97	103	200
	Negative	65 (67.0)	73 (70.9)	138 (69.0)
	Faint erythema	20 (20.6)	23 (22.3)	43 (21.5)
	Erythema	9 (9.3)	6 (5.8)	15 (7.5)
	Erythema + Edema	2 (2.1)	0	2 (1.0)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (1.0)	1 (1.0)	2 (1.0)
	Coalescing Vesicles	0	0	0
Maximum severity during DSP-5423P treatment phase	n	97	103	200
	Negative	33 (34.0)	32 (31.1)	65 (32.5)
	Faint erythema	34 (35.1)	39 (37.9)	73 (36.5)
	Erythema	23 (23.7)	25 (24.3)	48 (24.0)
	Erythema + Edema	6 (6.2)	6 (5.8)	12 (6.0)
	Erythema + Edema + Papules, Serous papules, Vesicles	1 (1.0)	1 (1.0)	2 (1.0)
	Coalescing Vesicles	0	0	0

Week 52 (LOCF) endpoint is the last post-baseline observation in the DSP-5423P treatment phase up to 7 days after final application of the DSP-5423P treatment phase.

2.7.4.5　特別な患者集団及び状況下における安全性

2.7.4.5.1　内因性要因

ロナセンテープの安全性に影響する内因性要因として、人種、肝機能障害、腎機能障害、性別、年齢の影響を検討した。日本人集団、肝機能障害グレード別、腎機能障害グレード別、性別、年齢（65 歳未満及び 65 歳以上）別の部分集団解析を実施した。

2.7.4.5.1.1　日本人集団

20 試験は国際共同治験であり、日本を含む 8 つの国と地域で実施した。二重盲検治療期（6 週間）に継続する非盲検治療期は日本では 52 週間、日本以外では 28 週間とした。そのため、20 試験の二重盲検治療期及びロナセンテープ貼付期（非盲検治療期 24 週時の解

析）で、日本の実施医療機関で組み入れられた被験者を日本人とし、日本人集団の安全性プロファイルを検討した。

日本人205名から同意を取得し、観察期に入った174名のうち164名がランダム化され、プラセボ群、40 mg 群、80 mg 群にそれぞれ 52 名、55 名、57 名が割り当てられた。ランダム化された全164名（100%）が治験薬の貼付を開始し、110/164名（67.1%）が二重盲検治療期を完了した。プラセボ群、40 mg 群、80 mg 群（以下、同順）の貼付開始被験者は52名、55名、57名で、それぞれ29/52名（55.8%）、36/55名（65.5%）、45/57名（78.9%）が二重盲検治療期を完了した。二重盲検治療期中に中止した被験者はそれぞれ 23/52 名（44.2%）、19/55名（34.5%）、12/57名（21.1%）で、中止理由で多かったのは有害事象［計19名（10名、7名、2名）］、同意撤回［計19名（9名、6名、4名）］、効果不十分［計13名（4名、4名、5名）］であった。

全集団（2.7.4.1.2.1 項参照）、日本人集団のいずれでも二重盲検治療期を完了した被験者の割合がプラセボ、40 mg 群、80 mg 群の順に高くなる傾向は同様であったが、日本人集団では完了した被験者の割合はいずれの群でも全集団と比較して低く、特にプラセボ群、40 mg 群での差が大きかった。全集団と日本人集団で、中止理由に大きな違いはなかった。

日本人では、二重盲検治療期を完了したプラセボ群、40 mg 群、80 mg 群（以下、同順）はそれぞれ29名、36名、45名、計110名で、そのうち、27名、33名、42名、計102名が非盲検治療期の貼付を開始した。非盲検治療期 24 週時、68名が貼付継続中で、非盲検治療期中の中止は34名であった。非盲検治療期 52 週時に51名が貼付を完了し、非盲検治療期中の中止は51名であった。主な中止理由は同意の撤回（25名）、有害事象（16名）であった。全集団と日本人集団で、主な中止理由に大きな違いはなかった。非盲検治療期の貼付期間は、治験実施計画書で日本は52週、日本以外の28週と設定されており、日本と日本以外での貼付期間が異なった。そのため、非盲検治療期に移行した被験者での非盲検治療期の貼付期間（平均値）は日本では242.4日、全体では174.7日であった。実薬-FLEX群の二重盲検治療期の投与期間を含む DSP-5423P dosed population での貼付期間（中央値）は、日本（102名）では179.0日、全体では196.0日であった。

二重盲検治療期の日本人集団での人口統計学的特性及びその他の特性を表 2.7.4.5-1、疾患データを表 2.7.4.5-2 に、ロナセンテープ貼付期の日本人集団での人口統計学的特性及びその他の特性を2.7.4.7項付録表2.7.4.7-13、疾患データを2.7.4.7項付録表2.7.4.7-14に示す。

二重盲検治療期の日本人集団では、全群合計で男性の割合は49.4%、年齢（mean）は48.1歳、65歳以上の割合は20.1%、PANSS 合計スコア［mean（SD）］は103.0（16.09）、罹病期間（mean）は18.44年と、全集団（2.7.4.1.3 項参照）より年齢、65歳以上の割合が高く、罹病期間は長かった。

ロナセンテープ貼付期（非盲検治療期24週時の解析及び52週時の解析）の日本人集団では、DSP-5423P Dosed Population 合計で男性の割合は51.1%、年齢（mean）は48.5歳、65歳以上の割合は20.1%、PANSS 合計スコア［mean（SD）］は103.4（16.23）、罹病期間

（mean）は 19.40 年と、全集団（2.7.4.1.3 参照）より年齢、65 歳以上の割合が高く、罹病期間は長かった。

表 2.7.4.5-1　日本人集団での人口統計学的特性及びその他の特性
（20 試験・二重盲検治療期）

Safety population

Country: Japan	PLCB (N = 52)	40MG (N = 55)	80MG (N = 57)	Active (N = 112)	Overall (N = 164)
Sex, n (%)					
n	52	55	57	112	164
Male	26 (50.0)	26 (47.3)	29 (50.9)	55 (49.1)	81 (49.4)
Female	26 (50.0)	29 (52.7)	28 (49.1)	57 (50.9)	83 (50.6)
Age (years)					
n	52	55	57	112	164
Mean (SD)	49.0 (16.62)	47.5 (16.03)	48.0 (17.18)	47.8 (16.55)	48.1 (16.53)
Median	51.0	49.0	52.0	49.5	50.0
Min, Max	20, 80	20, 79	22, 81	20, 81	20, 81
Age (years), n (%)					
n	52	55	57	112	164
<65	40 (76.9)	45 (81.8)	46 (80.7)	91 (81.3)	131 (79.9)
>=65	12 (23.1)	10 (18.2)	11 (19.3)	21 (18.8)	33 (20.1)
Race, n (%)					
n	52	55	57	112	164
Asian	52 (100.0)	55 (100.0)	57 (100.0)	112 (100.0)	164 (100.0)
White	0	0	0	0	0
Ethnicity, n (%)					
n	52	55	57	112	164
Not Hispanic or Latino	52 (100.0)	55 (100.0)	57 (100.0)	112 (100.0)	164 (100.0)
Country, n (%)					
n	52	55	57	112	164
Japan	52 (100.0)	55 (100.0)	57 (100.0)	112 (100.0)	164 (100.0)
China	0	0	0	0	0
Korea	0	0	0	0	0
Malaysia	0	0	0	0	0
Philippines	0	0	0	0	0
Russia	0	0	0	0	0
Taiwan	0	0	0	0	0
Ukraine	0	0	0	0	0
Height (cm)					
n	52	55	57	112	164
Mean (SD)	161.61 (11.087)	161.02 (9.431)	160.78 (10.830)	160.90 (10.122)	161.13 (10.409)

Country: Japan	PLCB (N = 52)	40MG (N = 55)	80MG (N = 57)	Active (N = 112)	Overall (N = 164)
Median	161.05	162.10	160.00	160.55	160.80
Min, Max	132.0, 182.0	138.0, 184.2	130.5, 182.0	130.5, 184.2	130.5, 184.2
Weight (kg)					
n	52	55	57	112	164
Mean (SD)	60.42 (15.188)	58.47 (12.796)	56.54 (13.849)	57.49 (13.318)	58.42 (13.958)
Median	58.15	56.20	54.20	56.10	56.65
Min, Max	33.9, 109.9	35.8, 87.9	31.2, 93.6	31.2, 93.6	31.2, 109.9
BMI (kg/m^2)					
n	52	55	57	112	164
Mean (SD)	23.01 (4.786)	22.52 (4.446)	21.67 (3.924)	22.09 (4.191)	22.38 (4.395)
Median	22.36	21.69	20.47	20.92	21.33
Min, Max	15.4, 33.9	15.5, 36.1	13.9, 31.1	13.9, 36.1	13.9, 36.1
Any concomitant diseases, n (%)					
n	52	55	57	112	164
Yes	49 (94.2)	47 (85.5)	52 (91.2)	99 (88.4)	148 (90.2)
No	3 (5.8)	8 (14.5)	5 (8.8)	13 (11.6)	16 (9.8)
Hospitalization status at informed consent, n (%)					
n	52	55	57	112	164
Inpatient	47 (90.4)	48 (87.3)	55 (96.5)	103 (92.0)	150 (91.5)
Within 3 months (90 days)	40 (76.9)	33 (60.0)	43 (75.4)	76 (67.9)	116 (70.7)
Over 3 months	7 (13.5)	15 (27.3)	12 (21.1)	27 (24.1)	34 (20.7)
Unknown	0	0	0	0	0
Outpatient	5 (9.6)	7 (12.7)	2 (3.5)	9 (8.0)	14 (8.5)

表 2.7.4.5-2　日本人集団での疾患データ（20 試験・二重盲検治療期）

Safety population

Country: Japan	PLCB (N = 52)	40MG (N = 55)	80MG (N = 57)	Active (N = 112)	Overall (N = 164)
Number of episodes of schizophrenia					
n	46	40	48	88	134
Mean (SD)	3.5 (1.47)	3.3 (1.43)	3.9 (1.34)	3.6 (1.41)	3.6 (1.43)
Median	3.5	3.0	5.0	4.0	4.0
Min, Max	1, 5	1, 5	1, 5	1, 5	1, 5
Number of episodes of schizophrenia, n (%)					
n	52	55	57	112	164
1	4 (7.7)	4 (7.3)	3 (5.3)	7 (6.3)	11 (6.7)
2	11 (21.2)	11 (20.0)	6 (10.5)	17 (15.2)	28 (17.1)
3	8 (15.4)	9 (16.4)	9 (15.8)	18 (16.1)	26 (15.9)
4	3 (5.8)	3 (5.5)	5 (8.8)	8 (7.1)	11 (6.7)
5 or more	20 (38.5)	13 (23.6)	25 (43.9)	38 (33.9)	58 (35.4)
Unknown	6 (11.5)	15 (27.3)	9 (15.8)	24 (21.4)	30 (18.3)
Age at the first onset of schizophrenia (years)					
n	52	53	56	109	161

Country: Japan	PLCB (N = 52)	40MG (N = 55)	80MG (N = 57)	Active (N = 112)	Overall (N = 164)
Mean (SD)	31.3 (13.33)	29.5 (12.97)	28.3 (11.87)	28.9 (12.38)	29.7 (12.70)
Median	27.0	25.0	25.0	25.0	26.0
Min, Max	12, 73	12, 67	13, 60	12, 67	12, 73
Age at the first onset of schizophrenia (years), n (%)					
n	52	55	57	112	164
19 or less	11 (21.2)	12 (21.8)	16 (28.1)	28 (25.0)	39 (23.8)
20 to 29	18 (34.6)	22 (40.0)	18 (31.6)	40 (35.7)	58 (35.4)
30 to 39	10 (19.2)	7 (12.7)	11 (19.3)	18 (16.1)	28 (17.1)
40 to 49	8 (15.4)	7 (12.7)	8 (14.0)	15 (13.4)	23 (14.0)
50 or more	5 (9.6)	5 (9.1)	3 (5.3)	8 (7.1)	13 (7.9)
Unknown	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (1.8)
Duration of illness (years)					
n	52	53	56	109	161
Mean (SD)	17.71 (15.963)	17.97 (14.593)	19.58 (15.449)	18.79 (14.991)	18.44 (15.270)
Median	10.45	13.68	15.82	15.35	13.37
Min, Max	0.1, 47.8	0.3, 55.2	0.7, 50.6	0.3, 55.2	0.1, 55.2
Duration of illness (years), n (%)					
n	52	55	57	112	164
<1	4 (7.7)	4 (7.3)	1 (1.8)	5 (4.5)	9 (5.5)
>=1 to <5	11 (21.2)	9 (16.4)	8 (14.0)	17 (15.2)	28 (17.1)
>=5 to <10	9 (17.3)	5 (9.1)	13 (22.8)	18 (16.1)	27 (16.5)
>=10 to <20	7 (13.5)	15 (27.3)	11 (19.3)	26 (23.2)	33 (20.1)
>=20 to <30	8 (15.4)	9 (16.4)	10 (17.5)	19 (17.0)	27 (16.5)
>=30	13 (25.0)	11 (20.0)	13 (22.8)	24 (21.4)	37 (22.6)
Unknown	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (1.8)
Duration of current episode (months)					
n	52	55	57	112	164
Mean (SD)	7.17 (42.093)	8.38 (46.869)	9.27 (59.028)	8.84 (53.167)	8.31 (49.799)
Median	1.22	1.35	1.15	1.22	1.22
Min, Max	0.3, 304.8	0.0, 348.9	0.2, 447.0	0.0, 447.0	0.0, 447.0
Baseline PANSS total score					
n	52	55	57	112	164
Mean (SD)	101.6 (16.23)	102.8 (16.75)	104.5 (15.45)	103.7 (16.05)	103.0 (16.09)
Median	98.0	101.0	101.0	101.0	100.0
Min, Max	80, 147	80, 157	83, 155	80, 157	80, 157
PANSS composite subscale at baseline, n (%)					
n	52	55	57	112	164
Positive subscale score>Negative subscale score	20 (38.5)	24 (43.6)	21 (36.8)	45 (40.2)	65 (39.6)
Positive subscale score=Negative subscale score	3 (5.8)	2 (3.6)	5 (8.8)	7 (6.3)	10 (6.1)
Positive subscale score<Negative subscale score	29 (55.8)	29 (52.7)	31 (54.4)	60 (53.6)	89 (54.3)
Baseline PANSS total score, n (%)					

Country: Japan	PLCB (N = 52)	40MG (N = 55)	80MG (N = 57)	Active (N = 112)	Overall (N = 164)
n	52	55	57	112	164
<100	28 (53.8)	27 (49.1)	25 (43.9)	52 (46.4)	80 (48.8)
>=100 to <120	17 (32.7)	19 (34.5)	24 (42.1)	43 (38.4)	60 (36.6)
>=120	7 (13.5)	9 (16.4)	8 (14.0)	17 (15.2)	24 (14.6)
Baseline CGI-S score					
n	52	55	57	112	164
Mean (SD)	4.60 (0.748)	4.64 (0.825)	4.77 (0.887)	4.71 (0.856)	4.67 (0.822)
Median	4.00	4.00	5.00	5.00	4.00
Min, Max	4, 6	3, 7	3, 7	3, 7	3, 7
Baseline CGI-S score, n (%)					
n	52	55	57	112	164
1	0	0	0	0	0
2	0	0	0	0	0
3	0	1 (1.8)	1 (1.8)	2 (1.8)	2 (1.2)
4	29 (55.8)	28 (50.9)	25 (43.9)	53 (47.3)	82 (50.0)
5	15 (28.8)	17 (30.9)	19 (33.3)	36 (32.1)	51 (31.1)
6	8 (15.4)	8 (14.5)	10 (17.5)	18 (16.1)	26 (15.9)
7	0	1 (1.8)	2 (3.5)	3 (2.7)	3 (1.8)
Baseline DIEPSS total score (excluding overall severity)					
n	52	55	56	111	163
Mean (SD)	1.4 (2.23)	1.6 (3.00)	1.9 (3.54)	1.8 (3.27)	1.6 (2.97)
Median	0.5	0.0	0.0	0.0	0.0
Min, Max	0, 10	0, 14	0, 14	0, 14	0, 14

二重盲検治療期の日本人集団での有害事象及び副作用の発現状況を表 2.7.4.5-3 に、ロナセンテープ貼付期（非盲検治療期 24 週時の解析）の発現状況を表 2.7.4.5-4 に、ロナセンテープ貼付期（非盲検治療期 52 週時の解析）の発現状況を表 2.7.4.5-5 に示す。

二重盲検治療期の有害事象の発現割合は、日本人集団でプラセボ群、40 mg 群、80 mg 群の順に（以下、同順）69.2%（36/52 名）、65.5%（36/55 名）、78.9%（45/57 名）であった。副作用は、32.7%、43.6%、54.4%であった。全集団では有害事象の発現割合は 60.0%（114/190 名）、62.8%（123/196 名）、67.0%（130/194 名）、副作用は 30.5%、35.2%、42.3%であった（2.7.4.2.1 項参照）。日本人集団では死亡した被験者はいなかった。重篤な有害事象の発現被験者数（発現件数）発現割合は、日本人集団では 3 名（3 件）5.8%、3 名（3 件）5.5%、1 名（1 件）1.8%で、全集団では 9 名（9 件）4.7%、8 名（8 件）4.1%、10 名（10 件）5.2%であった。中止に至った有害事象の発現被験者数（発現件数）発現割合は、日本人集団で 10 名（10 件）19.2%、7 名（10 件）12.7%、1 名（1 件）1.8%で、全集団で 17 名（18 件）8.9%、16 名（19 件）8.2%、11 名（15 件）5.7%であった（2.7.4.2.1 項参照）。錐体外路系有害事象の発現割合は、日本人集団で 7.7%、12.7%、26.3%で、全集団では 7.9%、10.7%、20.6%であり、貼付部位の皮膚関連有害事象の発現割合は日本人集団で 9.6%、27.3%、33.3%で、全集団では 4.2%、13.3%、18.6%であった（2.7.4.2.1 項参照）。

日本人集団での貼付部位の皮膚関連有害事象の発現割合は、いずれの群でも全集団よりも高い傾向があったが、その他の有害事象の発現状況は、全集団と日本人集団で同様の傾向であった。

ロナセンテープ貼付期（非盲検治療期24週時の解析）では、日本人のDSP-5423P dosed population合計（139名）での有害事象の発現割合［発現被験者数、発現件数（以下、同様）］及び副作用の発現割合は、87.1%（121名、490件）及び65.5%（91名、245件）で、全集団（521名）では80.0%（417名、1583件）及び58.5%（305名、789件）であった。有害事象により死亡した被験者は日本人ではいなかったが、全集団では4名がロナセンテープ貼付期に有害事象により死亡した（2.7.4.2.1.2項参照）。日本人集団及び全集団（以下、同順）で、重篤な有害事象の発現割合は7.9%（11名、11件）及び11.7%（61名、67件）、中止に至った有害事象の発現割合は12.9%（18名、23件）及び12.1%（63名、72件）であった。また、錐体外路系有害事象の発現割合は26.6%及び22.6%、貼付部位の皮膚関連有害事象の発現割合は33.8%及び17.9%であった。日本人集団では全集団に比べ、貼付部位の皮膚関連の有害事象の発現割合が高いものの、その他の有害事象の発現状況に大きな違いはなかった。

ロナセンテープ貼付期（非盲検治療期52週時の解析）では、日本人のDSP-5423P dosed population合計（139名）での有害事象の発現割合［発現被験者数、発現件数（以下、同様）］及び副作用の発現割合は、87.8%（122名、629件）及び67.6%（94名、281件）で、全集団（521名）では80.8%（421名、1771件）及び59.5%（310名、855件）であった。有害事象により死亡した被験者は日本人で1名、全集団では4名がロナセンテープ貼付期に有害事象により死亡した（2.7.4.2.1.2項参照）。日本人集団及び全集団（以下、同順）で、重篤な有害事象の発現割合は15.1%（21名、22件）及び13.6%（71名、79件）、中止に至った有害事象の発現割合は17.3%（24名、29件）及び13.1%（68名、77件）であった。また、錐体外路系有害事象の発現割合は28.1%及び23.2%、貼付部位の皮膚関連有害事象の発現割合は36.7%及び18.6%であった。日本人集団では全集団に比べ、貼付部位の皮膚関連の有害事象の発現割合が高いものの、その他の有害事象の発現状況に大きな違いはなかった。

表 2.7.4.5-3　日本人集団での有害事象及び副作用発現状況（20 試験・二重盲検治療期）

Safety population

	PLCB (N = 52)		40MG (N = 55)		80MG (N = 57)		Active (N = 112)	
Country: Japan	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects with any TEAE	36 (69.2)	67	36 (65.5)	100	45 (78.9)	113	81 (72.3)	213
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	10 (19.2)	10	7 (12.7)	10	1 (1.8)	1	8 (7.1)	11
Serious	3 (5.8)	3	3 (5.5)	3	1 (1.8)	1	4 (3.6)	4
Extrapyramidal	4 (7.7)	4	7 (12.7)	8	15 (26.3)	22	22 (19.6)	30
Skin related	5 (9.6)	7	15 (27.3)	23	19 (33.3)	38	34 (30.4)	61
Subjects with any treatment-related TEAE	17 (32.7)	30	24 (43.6)	51	31 (54.4)	77	55 (49.1)	128
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	3 (5.8)	3	4 (7.3)	7	0	0	4 (3.6)	7
Serious	2 (3.8)	2	2 (3.6)	2	0	0	2 (1.8)	2
Extrapyramidal	2 (3.8)	2	6 (10.9)	7	15 (26.3)	22	21 (18.8)	29
Skin related	5 (9.6)	7	15 (27.3)	23	19 (33.3)	38	34 (30.4)	61

表 2.7.4.5-4　日本人集団での有害事象及び副作用発現状況（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

	PLCB-to-FLEX DOSE (N = 27)		40MG-to-FLEX DOSE (N = 55)		80MG-to-FLEX DOSE (N = 57)		Active-to-FLEX DOSE (N = 112)		Overall-to-FLEX DOSE (N = 139)	
Country: Japan	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects with any TEAE	19 (70.4)	59	49 (89.1)	205	53 (93.0)	226	102 (91.1)	431	121 (87.1)	490
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	1 (3.7)	1	11 (20.0)	14	6 (10.5)	8	17 (15.2)	22	18 (12.9)	23
Serious	2 (7.4)	2	5 (9.1)	5	4 (7.0)	4	9 (8.0)	9	11 (7.9)	11
Extrapyramidal	6 (22.2)	10	12 (21.8)	18	19 (33.3)	27	31 (27.7)	45	37 (26.6)	55
Skin related	4 (14.8)	5	17 (30.9)	30	26 (45.6)	49	43 (38.4)	79	47 (33.8)	84
Subjects with any treatment-related TEAE	15 (55.6)	29	35 (63.6)	97	41 (71.9)	119	76 (67.9)	216	91 (65.5)	245
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	0	0	7 (12.7)	10	2 (3.5)	4	9 (8.0)	14	9 (6.5)	14
Serious	0	0	4 (7.3)	4	0	0	4 (3.6)	4	4 (2.9)	4
Extrapyramidal	6 (22.2)	10	11 (20.0)	17	19 (33.3)	27	30 (26.8)	44	36 (25.9)	54
Skin related	4 (14.8)	5	17 (30.9)	30	26 (45.6)	49	43 (38.4)	79	47 (33.8)	84

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. Extrapyramidal TEAE are defined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the DSP-5423P dosed population of subgroup. Event is the number of episodes. The data cut-off at Open-Week 24 was used.

表 2.7.4.5-5　日本人集団での有害事象及び副作用発現状況（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Country: Japan	PLCB-to-FLEX DOSE (N = 27) n (%)	Event	40MG-to-FLEX DOSE (N = 55) n (%)	Event	80MG-to-FLEX DOSE (N = 57) n (%)	Event	Active-to-FLEX DOSE (N = 112) n (%)	Event	Overall-to-FLEX DOSE (N = 139) n (%)	Event
Subjects with any TEAE	20 (74.1)	91	49 (89.1)	255	53 (93.0)	283	102 (91.1)	538	122 (87.8)	629
Leading to death	1 (3.7)	1	0	0	0	0	0	0	1 (0.7)	1
Leading to treatment discontinuation	3 (11.1)	3	12 (21.8)	15	9 (15.8)	11	21 (18.8)	26	24 (17.3)	29
Serious	4 (14.8)	4	8 (14.5)	9	9 (15.8)	9	17 (15.2)	18	21 (15.1)	22
Extrapyramidal	7 (25.9)	12	13 (23.6)	23	19 (33.3)	27	32 (28.6)	50	39 (28.1)	62
Skin related	5 (18.5)	7	19 (34.5)	32	27 (47.4)	55	46 (41.1)	87	51 (36.7)	94
Subjects with any treatment-related TEAE	16 (59.3)	36	37 (67.3)	113	41 (71.9)	132	78 (69.6)	245	94 (67.6)	281
Leading to death	1 (3.7)	1	0	0	0	0	0	0	1 (0.7)	1
Leading to treatment discontinuation	1 (3.7)	1	7 (12.7)	10	2 (3.5)	4	9 (8.0)	14	10 (7.2)	15
Serious	1 (3.7)	1	4 (7.3)	4	0	0	4 (3.6)	4	5 (3.6)	5
Extrapyramidal	7 (25.9)	11	12 (21.8)	22	19 (33.3)	27	31 (27.7)	49	38 (27.3)	60
Skin related	5 (18.5)	7	19 (34.5)	32	27 (47.4)	55	46 (41.1)	87	51 (36.7)	94

日本人集団での主な有害事象（いずれかの群で発現割合が 2%以上の有害事象）の発現割合を二重盲検治療期について表 2.7.4.5-6 に、ロナセンテープ貼付期（非盲検治療期 24 週時の解析）について表 2.7.4.5-7 に、ロナセンテープ貼付期（非盲検治療期 52 週時の解析）について表 2.7.4.5-8 に示す。

二重盲検治療期に実薬群合計で 5%以上に発現した有害事象の発現割合は、適用部位そう痒感がプラセボ群、40 mg 群、80 mg 群（以下、同順）でそれぞれ 1.9%（1/52 名）、14.5%（8/55 名）、15.8%（9/57 名）、適用部位紅斑が 3.8%（2/52 名）、7.3%（4/55 名）、14.0%（8/57 名）、鼻咽頭炎が 11.5%（6/52 名）、7.3%（4/55 名）、12.3%（7/57 名）、アカシジアが 3.8%（2/52 名）、7.3%（4/55 名）、12.3%（7/57 名）、振戦が 3.8%（2/52 名）、1.8%（1/55 名）、10.5%（6/57 名）、便秘が 3.8%（2/52 名）、5.5%（3/55 名）、5.3%（3/57 名）、頭痛が 0%、5.5%（3/55 名）、5.3%（3/57 名）、統合失調症が 17.3%（9/52 名）、9.1%（5/55 名）、1.8%（1/57 名）であった。

ロナセンテープ貼付期（非盲検治療期 24 週時の解析）では、DSP-5423P dosed population 合計（139 名）で 5%以上に発現した有害事象の発現割合は、鼻咽頭炎 20.9%（29 名）、適用部位そう痒感 15.8%（22 名）、アカシジア 15.8%（22 名）、適用部位紅斑 10.8%（15 名）、統合失調症 10.8%（15 名）、頭痛 9.4%（13 名）、適用部位皮膚炎 7.2%（10 名）、振戦 7.2%（10 名）、便秘 6.5%（9 名）、下痢 5.8%（8 名）、血中プロラクチン増加 5.8%（8 名）、不眠症 5.0%（7 名）であった。

ロナセンテープ貼付期（非盲検治療期 52 週時の解析）では、DSP-5423P dosed population 合計（139 名）で 5%以上に発現した有害事象の発現割合は、鼻咽頭炎 25.2%（35 名）、適用部位そう痒感 17.3%（24 名）、アカシジア 15.8%（22 名）、統合失調症 12.2%（17 名）、適用部位紅斑 11.5%（16 名）、頭痛 9.4%（13 名）、適用部位皮膚炎 7.9%（11 名）、振戦 8.6%（12 名）、体重増加 7.2%（10 名）、便秘 6.5%（9 名）、下痢 6.5%（9 名）、嘔吐 6.5%（9 名）、血中プロラクチン増加 6.5%（9 名）、不眠症 6.5%（9 名）、湿疹 5.8%（8 名）、ジスキネジア 5.0%（7 名）であった。

二重盲検治療期及びロナセンテープ貼付期（非盲検治療期 24 週時の解析）のいずれでも、日本人集団では全集団と比べて適用部位そう痒感、適用部位紅斑などの貼付部位の皮膚関連有害事象の発現割合が高いものの、主な有害事象及びその発現割合は、全集団（2.7.4.2.1.1.1 項、表 2.7.4.2-5、表 2.7.4.2-6 参照）と日本人集団で同様の傾向であった。

表 2.7.4.5-6　日本人集団での主な有害事象（20 試験・二重盲検治療期）

Safety population

Country: Japan System Organ Class Preferred Term	PLCB (N = 52) n (%)	40MG (N = 55) n (%)	80MG (N = 57) n (%)	Active (N = 112) n (%)
Subjects with any TEAE	36 (69.2)	36 (65.5)	45 (78.9)	81 (72.3)
胃腸障害				
便秘	2 (3.8)	3 (5.5)	3 (5.3)	6 (5.4)
歯痛	0	1 (1.8)	1 (1.8)	2 (1.8)
下痢	1 (1.9)	1 (1.8)	3 (5.3)	4 (3.6)
流涎過多	0	0	1 (1.8)	1 (0.9)
一般・全身障害および投与部位の状態				
適用部位紅斑	2 (3.8)	4 (7.3)	8 (14.0)	12 (10.7)
適用部位そう痒感	1 (1.9)	8 (14.5)	9 (15.8)	17 (15.2)
適用部位皮膚炎	1 (1.9)	3 (5.5)	2 (3.5)	5 (4.5)
歩行障害	0	0	0	0
感染症および寄生虫症				
鼻咽頭炎	6 (11.5)	4 (7.3)	7 (12.3)	11 (9.8)
上気道感染	0	0	1 (1.8)	1 (0.9)
筋骨格系および結合組織障害				
筋固縮	0	1 (1.8)	2 (3.5)	3 (2.7)
神経系障害				
アカシジア	2 (3.8)	4 (7.3)	7 (12.3)	11 (9.8)
振戦	2 (3.8)	1 (1.8)	6 (10.5)	7 (6.3)
頭痛	0	3 (5.5)	3 (5.3)	6 (5.4)
運動緩慢	0	0	1 (1.8)	1 (0.9)

Country: Japan System Organ Class Preferred Term	PLCB (N = 52) n (%)	40MG (N = 55) n (%)	80MG (N = 57) n (%)	Active (N = 112) n (%)
ジスキネジア	0	1 (1.8)	2 (3.5)	3 (2.7)
精神障害				
不眠症	2 (3.8)	1 (1.8)	1 (1.8)	2 (1.8)
統合失調症	9 (17.3)	5 (9.1)	1 (1.8)	6 (5.4)
激越	0	0	0	0
精神病性障害	0	0	0	0
不安	1 (1.9)	0	0	0
呼吸器、胸郭および縦隔障害				
咳嗽	0	0	0	0
皮膚および皮下組織障害				
そう痒症	1 (1.9)	1 (1.8)	1 (1.8)	2 (1.8)

TEAE = Treatment-Emergent Adverse Event; A common TEAE refers to a PT experienced by equal or more than 2% of subjects in 40MG or 80MG group in the double-blind treatment phase. This table shows counts of subjects. If a subject experienced more than one episode of TEAE within a preferred term (PT), the subject is counted only once in the PT. The denominator of percentages is the number of subjects in the safety population of subgroup. TEAEs are coded by MedDRA version 19.1.

表 2.7.4.5-7　日本人集団での主な有害事象（20 試験・ロナセンテープ治療期、Open-24 週）

DSP-5423P dosed population

Country: Japan System Organ Class Preferred Term	器官別大分類 基本語	PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Subjects with any TEAE		19 (70.4)	49 (89.1)	53 (93.0)	102 (91.1)	121 (87.1)
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	1 (3.7)	1 (1.8)	0	1 (0.9)	2 (1.4)
Gastrointestinal disorders	胃腸障害					
Constipation	便秘	1 (3.7)	3 (5.5)	5 (8.8)	8 (7.1)	9 (6.5)
Salivary hypersecretion	流涎過多	0	2 (3.6)	2 (3.5)	4 (3.6)	4 (2.9)
Toothache	歯痛	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (2.2)
Diarrhoea	下痢	0	2 (3.6)	6 (10.5)	8 (7.1)	8 (5.8)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Application site erythema	適用部位紅斑	1 (3.7)	5 (9.1)	9 (15.8)	14 (12.5)	15 (10.8)
Application site pruritus	適用部位そう痒感	1 (3.7)	10 (18.2)	11 (19.3)	21 (18.8)	22 (15.8)
Application site dermatitis	適用部位皮膚炎	1 (3.7)	3 (5.5)	6 (10.5)	9 (8.0)	10 (7.2)
Infections and infestations	感染症および寄生虫症					
Nasopharyngitis	鼻咽頭炎	3 (11.1)	10 (18.2)	16 (28.1)	26 (23.2)	29 (20.9)
Upper respiratory tract infection	上気道感染	0	0	1 (1.8)	1 (0.9)	1 (0.7)
Investigations	臨床検査					
Weight increased	体重増加	4 (14.8)	1 (1.8)	1 (1.8)	2 (1.8)	6 (4.3)
Blood prolactin increased	血中プロラクチン増加	1 (3.7)	5 (9.1)	2 (3.5)	7 (6.3)	8 (5.8)
Alanine aminotransferase increased	アラニンアミノトランスフェラーゼ増加	1 (3.7)	0	3 (5.3)	3 (2.7)	4 (2.9)

Country: Japan System Organ Class Preferred Term	器官別大分類 基本語	PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (2.2)
Weight decreased	体重減少	0	3 (5.5)	1 (1.8)	4 (3.6)	4 (2.9)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Muscle rigidity	筋固縮	1 (3.7)	1 (1.8)	2 (3.5)	3 (2.7)	4 (2.9)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (22.2)	8 (14.5)	8 (14.0)	16 (14.3)	22 (15.8)
Tremor	振戦	0	1 (1.8)	9 (15.8)	10 (8.9)	10 (7.2)
Headache	頭痛	1 (3.7)	4 (7.3)	8 (14.0)	12 (10.7)	13 (9.4)
Bradykinesia	運動緩慢	0	1 (1.8)	1 (1.8)	2 (1.8)	2 (1.4)
Dyskinesia	ジスキネジア	0	2 (3.6)	3 (5.3)	5 (4.5)	5 (3.6)
Dizziness	浮動性めまい	0	3 (5.5)	1 (1.8)	4 (3.6)	4 (2.9)
Somnolence	傾眠	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (2.2)
Psychiatric disorders	精神障害					
Insomnia	不眠症	0	4 (7.3)	3 (5.3)	7 (6.3)	7 (5.0)
Schizophrenia	統合失調症	2 (7.4)	9 (16.4)	4 (7.0)	13 (11.6)	15 (10.8)
Psychotic disorder	精神病性障害	0	0	0	0	0
Agitation	激越	0	0	0	0	0
Anxiety	不安	0	2 (3.6)	0	2 (1.8)	2 (1.4)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害					
Cough	咳嗽	0	0	0	0	0

Country: Japan System Organ Class Preferred Term	器官別大分類 基本語	PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Vascular disorders	血管障害					
Hypertension	高血圧	1 (3.7)	0	1 (1.8)	1 (0.9)	2 (1.4)

TEAE = Treatment-Emergent Adverse Event; Treatment-related TEAE is TEAE with causality of definite, probably related, and possibly related. A common TEAE refers to a PT experienced by equal or more than 2% of subjects in Overall-to-FLEX DOSE group in the DSP-5423P treated period. This table shows counts of subjects. If a subject experienced more than one episode of TEAE within a preferred term (PT), the subject is counted only once in the PT. The denominator for percentages is the number of subjects in the DSP-5423P dosed population. TEAEs are coded by MedDRA version 19.1. The data cut-off at Open-Week 24 was used.

表 2.7.4.5-8　日本人集団での主な有害事象（20 試験・ロナセンテープ治療期、Open-52 週）

DSP-5423P dosed population

Country: Japan System Organ Class Preferred Term		PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Subjects with any TEAE		20 (74.1)	49 (89.1)	53 (93.0)	102 (91.1)	122 (87.8)
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	1 (3.7)	1 (1.8)	0	1 (0.9)	2 (1.4)
Gastrointestinal disorders	胃腸障害					
Constipation	便秘	1 (3.7)	3 (5.5)	5 (8.8)	8 (7.1)	9 (6.5)
Salivary hypersecretion	流涎過多	0	2 (3.6)	2 (3.5)	4 (3.6)	4 (2.9)
Toothache	歯痛	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (2.2)
Diarrhoea	下痢	1 (3.7)	2 (3.6)	6 (10.5)	8 (7.1)	9 (6.5)
Vomiting	嘔吐	0	4 (7.3)	5 (8.8)	9 (8.0)	9 (6.5)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Application site erythema	適用部位紅斑	1 (3.7)	5 (9.1)	10 (17.5)	15 (13.4)	16 (11.5)
Application site pruritus	適用部位そう痒感	1 (3.7)	12 (21.8)	11 (19.3)	23 (20.5)	24 (17.3)
Application site dermatitis	適用部位皮膚炎	2 (7.4)	3 (5.5)	6 (10.5)	9 (8.0)	11 (7.9)
Infections and infestations	感染症および寄生虫症					
Nasopharyngitis	鼻咽頭炎	5 (18.5)	11 (20.0)	19 (33.3)	30 (26.8)	35 (25.2)
Upper respiratory tract infection	上気道感染	0	0	1 (1.8)	1 (0.9)	1 (0.7)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症					

Country: Japan System Organ Class Preferred Term		PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Skin abrasion	皮膚擦過傷	0	1 (1.8)	1 (1.8)	2 (1.8)	2 (1.4)
Investigations	臨床検査					
Weight increased	体重増加	5 (18.5)	4 (7.3)	1 (1.8)	5 (4.5)	10 (7.2)
Blood prolactin increased	血中プロラクチン増加	2 (7.4)	5 (9.1)	2 (3.5)	7 (6.3)	9 (6.5)
Alanine aminotransferase increased	アラニンアミノトランスフェラーゼ増加	1 (3.7)	2 (3.6)	3 (5.3)	5 (4.5)	6 (4.3)
Weight decreased	体重減少	0	4 (7.3)	1 (1.8)	5 (4.5)	5 (3.6)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	2 (3.6)	1 (1.8)	3 (2.7)	3 (2.2)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Muscle rigidity	筋固縮	1 (3.7)	2 (3.6)	2 (3.5)	4 (3.6)	5 (3.6)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (22.2)	8 (14.5)	8 (14.0)	16 (14.3)	22 (15.8)
Tremor	振戦	1 (3.7)	2 (3.6)	9 (15.8)	11 (9.8)	12 (8.6)
Headache	頭痛	1 (3.7)	4 (7.3)	8 (14.0)	12 (10.7)	13 (9.4)
Bradykinesia	運動緩慢	0	1 (1.8)	1 (1.8)	2 (1.8)	2 (1.4)
Dyskinesia	ジスキネジア	1 (3.7)	3 (5.5)	3 (5.3)	6 (5.4)	7 (5.0)
Dizziness	浮動性めまい	0	3 (5.5)	2 (3.5)	5 (4.5)	5 (3.6)
Somnolence	傾眠	1 (3.7)	2 (3.6)	1 (1.8)	3 (2.7)	4 (2.9)
Psychiatric disorders	精神障害					
Schizophrenia	統合失調症	2 (7.4)	10 (18.2)	5 (8.8)	15 (13.4)	17 (12.2)
Insomnia	不眠症	1 (3.7)	4 (7.3)	4 (7.0)	8 (7.1)	9 (6.5)

Country: Japan System Organ Class Preferred Term		PLCB-to-FLEX DOSE (N = 27) n (%)	40MG-to-FLEX DOSE (N = 55) n (%)	80MG-to-FLEX DOSE (N = 57) n (%)	Active-to-FLEX DOSE (N = 112) n (%)	Overall-to-FLEX DOSE (N = 139) n (%)
Psychotic disorder	精神病性障害	0	0	0	0	0
Agitation	激越	0	0	0	0	0
Anxiety	不安	0	2 (3.6)	0	2 (1.8)	2 (1.4)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害					
Cough	咳嗽	0	0	0	0	0
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害					
Eczema	湿疹	0	6 (10.9)	2 (3.5)	8 (7.1)	8 (5.8)
Vascular disorders	血管障害					
Hypertension	高血圧	1 (3.7)	0	1 (1.8)	1 (0.9)	2 (1.4)

2.7.4.5.1.2　肝機能障害

20 試験及び 40 試験では、肝機能検査値に関する選択基準・除外基準を設定しなかった。20 試験のロナセンテープ貼付期（非盲検治療期 24 週時の解析及び 52 週時の解析）及び国内長期投与試験である 40 試験について、被験者のベースライン時の肝機能検査値を用い、表 2.7.4.5-9 に示すグレード別に有害事象の発現状況に対する部分集団解析を実施した結果を表 2.7.4.5-10 及び表 2.7.4.5-11 に示す。

20 試験の非盲検治療期 24 週時の解析の DSP-5423P dosed population で、肝機能正常、肝機能グレード 1 及び肝機能グレード 2 別の有害事象の発現割合［発現被験者数（以下、同様）］は 82.1%（326/397 名）、71.4%（75/105 名）及び 84.2%（16/19 名）、重篤な有害事象の発現割合は 11.6%（46/397 名）、11.4%（12/105 名）及び 15.8%（3/19 名）、錐体外路系有害事象の発現割合は 22.9%（91/397 名）、21.9%（23/105 名）及び 21.1%（4/19 名）であった。有害事象により死亡した被験者 4 名はいずれも肝機能正常の被験者であった。

20 試験の非盲検治療期 52 週時の解析の DSP-5423P dosed population で、肝機能正常、肝機能グレード 1 及び肝機能グレード 2 別の有害事象の発現割合［発現被験者数（以下、同様）］は 83.1%（330/397 名）、71.4%（75/105 名）及び 84.2%（16/19 名）、重篤な有害事象の発現割合は 13.9%（55/397 名）、12.4%（13/105 名）及び 15.8%（3/19 名）、錐体外路系有害事象の発現割合は 23.7%（94/397 名）、21.9%（23/105 名）及び 21.1%（4/19 名）であった。有害事象により死亡した被験者 5 名はいずれも肝機能正常の被験者であった。

40 試験では、肝機能正常、肝機能グレード 1 及び肝機能グレード 2 別の有害事象の発現割合は 85.5%（147/172 名）、95.2%（20/21 名）及び 100%（7/7 名）、重篤な有害事象の発現割合は 4.7%（8/172 名）、14.3%（3/21 名）及び 14.3%（1/7 名）、錐体外路系有害事象の発現割合は 23.8%（41/172 名）、33.3%（7/21 名）及び 42.9%（3/7 名）であった。

肝機能グレード別で有害事象の発現状況に大きな違いはなかった。

表 2.7.4.5-9　肝機能グレード分類

	Grade 1	Grade 2
総ビリルビン（mg/dL）	1.6≤ <3.0	3.0≤ <10
ALT、AST（U）	基準値上限の 1.25 倍≤ <2.5 倍 50≤ <100	基準値上限の 2.5 倍≤ <12 倍 100≤ <500
ALP	基準値上限の 1.25 倍≤ <2.5 倍	基準値上限の 2.5 倍≤ <5 倍
γ-GTP	基準値上限の 1.5 倍以上	–
LDH	基準値上限の 1.5 倍以上	–

薬安第 80 号「副作用の重症度分類基準」より引用

表 2.7.4.5-10　肝機能グレード別有害事象発現状況（20 試験、Open-24 週及び 40 試験）

	20 試験			40 試験			20 試験＋40 試験		
	No impairment N = 397 n (%)	Grade 1 N = 105 n (%)	Grade 2 N = 19 n (%)	No impairment N = 172 n (%)	Grade 1 N = 21 n (%)	Grade 2 N = 7 n (%)	No impairment N = 569 n (%)	Grade 1 N = 126 n (%)	Grade 2 N = 26 n (%)
有害事象	326 (82.1)	75 (71.4)	16 (84.2)	147 (85.5)	20 (95.2)	7 (100.0)	473 (83.1)	95 (75.4)	23 (88.5)
Leading to death	4 (1.0)	0	0	0	0	0	4 (0.7)	0	0
Leading to treatment discontinuation	47 (11.8)	12 (11.4)	4 (21.1)	21 (12.2)	5 (23.8)	2 (28.6)	68 (12.0)	17 (13.5)	6 (23.1)
Serious	46 (11.6)	12 (11.4)	3 (15.8)	8 (4.7)	3 (14.3)	1 (14.3)	54 (9.5)	15 (11.9)	4 (15.4)
錐体外路系	91 (22.9)	23 (21.9)	4 (21.1)	41 (23.8)	7 (33.3)	3 (42.9)	132 (23.2)	30 (23.8)	7 (26.9)
副作用	249 (62.7)	44 (41.9)	12 (63.2)	113 (65.7)	17 (81.0)	7 (100.0)	362 (63.6)	61 (48.4)	19 (73.1)
Leading to death	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	26 (6.5)	4 (3.8)	3 (15.8)	15 (8.7)	4 (19.0)	1 (14.3)	41 (7.2)	8 (6.3)	4 (15.4)
Serious	20 (5.0)	2 (1.9)	2 (10.5)	2 (1.2)	1 (4.8)	0	22 (3.9)	3 (2.4)	2 (7.7)
錐体外路系	84 (21.2)	19 (18.1)	4 (21.1)	34 (19.8)	5 (23.8)	3 (42.9)	118 (20.7)	24 (19.0)	7 (26.9)

N = 当該グレードの 20 試験、40 試験、又は 20 試験と 40 試験合計の DSP-5423P を貼付した被験者数

n (%) = 発現被験者数（発現割合）

Impairment of hepatic function グレード分類：薬安第 80 号を参考とした。

錐体外路系（Extrapyramidal）：MedDRA 基本語に基づいて錐体外路系と定義した有害事象を集計した。

副作用（Treatment-related TEAE）：治験薬との因果関係が、明らかに関連あり（definite）、多分関連あり（probable）又は関連あるかもしれない（possible）である有害事象とした。

The data cut-off at Open-Week 24 was used for 20 study.

表 2.7.4.5-11　肝機能グレード別有害事象発現状況（20 試験、Open-52 週及び 40 試験）

	20 試験			40 試験			20 試験＋40 試験		
	No impairment N = 397 n (%)	Grade 1 N = 105 n (%)	Grade 2 N = 19 n (%)	No impairment N = 172 n (%)	Grade 1 N = 21 n (%)	Grade 2 N = 7 n (%)	No impairment N = 569 n (%)	Grade 1 N = 126 n (%)	Grade 2 N = 26 n (%)
有害事象	330 (83.1)	75 (71.4)	16 (84.2)	147 (85.5)	20 (95.2)	7 (100.0)	477 (83.8)	95 (75.4)	23 (88.5)
Leading to death	5 (1.3)	0	0	0	0	0	5 (0.9)	0	0
Leading to treatment discontinuation	51 (12.8)	13 (12.4)	4 (21.1)	21 (12.2)	5 (23.8)	2 (28.6)	72 (12.7)	18 (14.3)	6 (23.1)
Serious	55 (13.9)	13 (12.4)	3 (15.8)	8 (4.7)	3 (14.3)	1 (14.3)	63 (11.1)	16 (12.7)	4 (15.4)
錐体外路系	94 (23.7)	23 (21.9)	4 (21.1)	41 (23.8)	7 (33.3)	3 (42.9)	135 (23.7)	30 (23.8)	7 (26.9)
副作用	253 (63.7)	45 (42.9)	12 (63.2)	113 (65.7)	17 (81.0)	7 (100.0)	366 (64.3)	62 (49.2)	19 (73.1)
Leading to death	1 (0.3)	0	0	0	0	0	1 (0.2)	0	0
Leading to treatment discontinuation	27 (6.8)	4 (3.8)	3 (15.8)	15 (8.7)	4 (19.0)	1 (14.3)	42 (7.4)	8 (6.3)	4 (15.4)
Serious	21 (5.3)	2 (1.9)	2 (10.5)	2 (1.2)	1 (4.8)	0	23 (4.0)	3 (2.4)	2 (7.7)
錐体外路系	86 (21.7)	19 (18.1)	4 (21.1)	34 (19.8)	5 (23.8)	3 (42.9)	120 (21.1)	24 (19.0)	7 (26.9)

N = 当該グレードの 20 試験（DSP-5423P dosed population）、40 試験（Safety population）、又は 20 試験（DSP-5423P dosed population）と 40 試験（Safety population）合計の被験者数

n (%) = 発現被験者数（発現割合）

Impairment of hepatic function グレード分類：薬安第 80 号を参考とした。

錐体外路系（Extrapyramidal）：MedDRA 基本語に基づいて錐体外路系と定義した有害事象を集計した。

副作用（Treatment-related TEAE）：治験薬との因果関係が、明らかに関連あり（definite）、多分関連あり（probable）又は関連あるかもしれない（possible）である有害事象とした。

The final data at Open-Week 52 was used for 20 study.

2.7.4.5.1.3　腎機能障害

20 試験及び 40 試験では、腎機能検査値に関する選択基準・除外基準を設定しなかった。20 試験のロナセンテープ貼付期（非盲検治療期 24 週時の解析及び 52 週時の解析）及び国内長期投与試験である 40 試験について、被験者のベースライン時の腎機能検査値を用い、表 2.7.4.5-12 に示すグレード別に有害事象の発現状況に対する部分集団解析を実施した結果を表 2.7.4.5-13 及び表 2.7.4.5-14 に示す。

20 試験の非盲検治療期 24 週時の解析 DSP-5423P dosed population で、腎機能グレード 1、グレード 2 及びグレード 3 別の有害事象の発現割合［発現被験者数（以下、同様）］は 85.7%（66/77 名）、78.8%（278/353 名）及び 80.2%（73/91 名）、重篤な有害事象の発現割合は 15.6%（12/77 名）、11.9%（42/353 名）及び 7.7%（7/91 名）、錐体外路系有害事象の発現割合は 31.2%（24/77 名）、20.7%（73/353 名）及び 23.1%（21/91 名）であった。有害事象により死亡した被験者はグレード 1 が 2 名、グレード 2 が 1 名、グレード 3 が 1 名であった。

20 試験の非盲検治療期 52 週時の解析 DSP-5423P dosed population で、腎機能グレード 1、グレード 2 及びグレード 3 別の有害事象の発現割合［発現被験者数（以下、同様）］は 87.0%（67/77 名）、79.3%（280/353 名）及び 81.3%（74/91 名）、重篤な有害事象の発現割合は 16.9%（13/77 名）、13.9%（49/353 名）及び 9.9%（9/91 名）、錐体外路系有害事象の発現割合は 31.2%（24/77 名）、21.5%（76/353 名）及び 23.1%（21/91 名）であった。有害事象により死亡した被験者はグレード 1 が 2 名、グレード 2 が 2 名、グレード 3 が 1 名であった。

40 試験では、腎機能グレード 1、グレード 2 及びグレード 3 別の有害事象の発現割合は 78.8%（26/33 名）、88.9%（120/135 名）及び 87.5%（28/32 名）、重篤な有害事象の発現割合は 9.1%（3/33 名）、6.7%（9/135 名）及び 0%（0/32 名）、錐体外路系有害事象の発現割合は 33.3%（11/33 名）、22.2%（30/135 名）及び 31.3%（10/32 名）であった。

腎機能グレード別で有害事象の発現状況に大きな違いはなかった。

表 2.7.4.5-12　腎機能グレード分類

	Grade 1	Grade 2	Grade 3
eGFR（mL/min/1.73m^2）	90≤	60 ≤ ＜90	30 ≤ ＜60

エビデンスに基づく CKD 診療ガイドライン 2018 [文献 1)] より作成

表 2.7.4.5-13　腎機能グレード別有害事象発現状況（20 試験、Open-24 週及び 40 試験）

	20 試験			40 試験			20 試験＋40 試験		
	Grade 1 N = 77 n (%)	Grade 2 N = 353 n (%)	Grade 3 N = 91 n (%)	Grade 1 N = 33 n (%)	Grade 2 N = 135 n (%)	Grade 3 N = 32 n (%)	Grade 1 N = 110 n (%)	Grade 2 N = 488 n (%)	Grade 3 N = 123 n (%)
有害事象	66 (85.7)	278 (78.8)	73 (80.2)	26 (78.8)	120 (88.9)	28 (87.5)	92 (83.6)	398 (81.6)	101 (82.1)
Leading to death	2 (2.6)	1 (0.3)	1 (1.1)	0	0	0	2 (1.8)	1 (0.2)	1 (0.8)
Leading to treatment discontinuation	9 (11.7)	41 (11.6)	13 (14.3)	5 (15.2)	18 (13.3)	5 (15.6)	14 (12.7)	59 (12.1)	18 (14.6)
Serious	12 (15.6)	42 (11.9)	7 (7.7)	3 (9.1)	9 (6.7)	0	15 (13.6)	51 (10.5)	7 (5.7)
錐体外路系	24 (31.2)	73 (20.7)	21 (23.1)	11 (33.3)	30 (22.2)	10 (31.3)	35 (31.8)	103 (21.1)	31 (25.2)
副作用	52 (67.5)	199 (56.4)	54 (59.3)	22 (66.7)	92 (68.1)	23 (71.9)	74 (67.3)	291 (59.6)	77 (62.6)
Leading to death	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	2 (2.6)	22 (6.2)	9 (9.9)	3 (9.1)	12 (8.9)	5 (15.6)	5 (4.5)	34 (7.0)	14 (11.4)
Serious	5 (6.5)	16 (4.5)	3 (3.3)	2 (6.1)	1 (0.7)	0	7 (6.4)	17 (3.5)	3 (2.4)
錐体外路系	21 (27.3)	67 (19.0)	19 (20.9)	8 (24.2)	26 (19.3)	8 (25.0)	29 (26.4)	93 (19.1)	27 (22.0)

N＝ 当該グレードの 20 試験、40 試験、又は 20 試験と 40 試験合計の DSP-5423P を貼付した被験者数

n (%)＝ 発現被験者数（発現割合）

Impairment of renal function グレード分類 : eGFR（mL/min/1.73 m^2）= 194*Age^-0.287*Cr^-1.094（女性は*0.739）に基づき、90 以上を Grade 1、60 以上 90 未満を Grade 2、30 以上 60 未満を Grade 3 とした。

錐体外路系（Extrapyramidal）：MedDRA 基本語に基づいて錐体外路系と定義した有害事象を集計した。

副作用（Treatment-related TEAE）：治験薬との因果関係が、明らかに関連あり（definite）、多分関連あり（probable）又は関連あるかもしれない（possible）である有害事象とした。

The data cut-off at Open-Week 24 was used for 20 study.

表 2.7.4.5-14　腎機能グレード別有害事象発現状況（20 試験、Open-52 週及び 40 試験）

	20 試験			40 試験			20 試験＋40 試験		
	Grade 1 N = 77 n (%)	Grade 2 N = 353 n (%)	Grade 3 N = 91 n (%)	Grade 1 N = 33 n (%)	Grade 2 N = 135 n (%)	Grade 3 N = 32 n (%)	Grade 1 N = 110 n (%)	Grade 2 N = 488 n (%)	Grade 3 N = 123 n (%)
有害事象	67 (87.0)	280 (79.3)	74 (81.3)	26 (78.8)	120 (88.9)	28 (87.5)	93 (84.5)	400 (82.0)	102 (82.9)
Leading to death	2 (2.6)	2 (0.6)	1 (1.1)	0	0	0	2 (1.8)	2 (0.4)	1 (0.8)
Leading to treatment discontinuation	10 (13.0)	44 (12.5)	14 (15.4)	5 (15.2)	18 (13.3)	5 (15.6)	15 (13.6)	62 (12.7)	19 (15.4)
Serious	13 (16.9)	49 (13.9)	9 (9.9)	3 (9.1)	9 (6.7)	0	16 (14.5)	58 (11.9)	9 (7.3)
錐体外路系	24 (31.2)	76 (21.5)	21 (23.1)	11 (33.3)	30 (22.2)	10 (31.3)	35 (31.8)	106 (21.7)	31 (25.2)
副作用	54 (70.1)	202 (57.2)	54 (59.3)	22 (66.7)	92 (68.1)	23 (71.9)	76 (69.1)	294 (60.2)	77 (62.6)
Leading to death	0	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Leading to treatment discontinuation	2 (2.6)	23 (6.5)	9 (9.9)	3 (9.1)	12 (8.9)	5 (15.6)	5 (4.5)	35 (7.2)	14 (11.4)
Serious	5 (6.5)	17 (4.8)	3 (3.3)	2 (6.1)	1 (0.7)	0	7 (6.4)	18 (3.7)	3 (2.4)
錐体外路系	21 (27.3)	69 (19.5)	19 (20.9)	8 (24.2)	26 (19.3)	8 (25.0)	29 (26.4)	95 (19.5)	27 (22.0)

N = 当該グレードの 20 試験（DSP-5423P dosed population）、40 試験（Safety population）、又は 20 試験（DSP-5423P dosed population）と 40 試験（Safety population）合計の被験者数

n (%) = 発現被験者数（発現割合）

Impairment of renal function グレード分類 : eGFR（mL/min/1.73 m^2）= 194*Age^-0.287*Cr^-1.094（女性は*0.739）に基づき、90 以上を Grade 1、60 以上 90 未満を Grade 2、30 以上 60 未満を Grade 3 とした。

錐体外路系（Extrapyramidal）: MedDRA 基本語に基づいて錐体外路系と定義した有害事象を集計した。

副作用（Treatment-related TEAE）: 治験薬との因果関係が、明らかに関連あり（definite）、多分関連あり（probable）又は関連あるかもしれない（possible）である有害事象とした。

The final data at Open-Week 52 was used for 20 study.

2.7.4.5.1.4　性別

20 試験の二重盲検治療期及びロナセンテープ貼付期、並びに 40 試験の有害事象発現状況に対する男女別の部分集団解析を実施した。性別での有害事象発現状況を 20 試験の二重盲検治療期について表 2.7.4.5-15 に、20 試験のロナセンテープ貼付期の非盲検治療期 24 週時の解析及び 52 週時の解析について表 2.7.4.5-16 及び表 2.7.4.5-17 に、40 試験について表 2.7.4.5-18 に示す。

20 試験の二重盲検治療期及びロナセンテープ貼付期の非盲検治療期 24 週時の解析及び 52 週時の解析、並びに 40 試験のいずれでも、有害事象の発現状況に性別で大きな違いはなかった。

表 2.7.4.5-15　性別での有害事象発現状況（20 試験・二重盲検治療期）

Safety population

Sex: Male	PLCB (N = 113) n (%)	Event	40MG (N = 116) n (%)	Event	80MG (N = 115) n (%)	Event	Active (N = 231) n (%)	Event
Subjects with any TEAE	61 (54.0)	125	72 (62.1)	167	78 (67.8)	203	150 (64.9)	370
Leading to death	0	0	0	0	1 (0.9)	1	1 (0.4)	1
Leading to treatment discontinuation	7 (6.2)	7	9 (7.8)	10	11 (9.6)	15	20 (8.7)	25
Serious	4 (3.5)	4	4 (3.4)	4	9 (7.8)	9	13 (5.6)	13
Extrapyramidal	9 (8.0)	13	12 (10.3)	17	22 (19.1)	36	34 (14.7)	53
Skin related	2 (1.8)	2	15 (12.9)	26	22 (19.1)	42	37 (16.0)	68
Subjects with any treatment-related TEAE	36 (31.9)	52	40 (34.5)	83	50 (43.5)	118	90 (39.0)	201
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	3 (2.7)	3	6 (5.2)	7	2 (1.7)	2	8 (3.5)	9
Serious	1 (0.9)	1	3 (2.6)	3	3 (2.6)	3	6 (2.6)	6
Extrapyramidal	7 (6.2)	11	10 (8.6)	15	19 (16.5)	31	29 (12.6)	46
Skin related	2 (1.8)	2	14 (12.1)	24	21 (18.3)	41	35 (15.2)	65

Sex: Female	PLCB (N = 77) n (%)	Event	40MG (N = 80) n (%)	Event	80MG (N = 79) n (%)	Event	Active (N = 159) n (%)	Event
Subjects with any TEAE	53 (68.8)	97	51 (63.8)	129	52 (65.8)	115	103 (64.8)	244
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	10 (13.0)	11	7 (8.8)	9	0	0	7 (4.4)	9
Serious	5 (6.5)	5	4 (5.0)	4	1 (1.3)	1	5 (3.1)	5
Extrapyramidal	6 (7.8)	6	9 (11.3)	15	18 (22.8)	34	27 (17.0)	49
Skin related	6 (7.8)	8	11 (13.8)	15	14 (17.7)	14	25 (15.7)	29

Sex: Female	PLCB (N = 77) n (%)	Event	40MG (N = 80) n (%)	Event	80MG (N = 79) n (%)	Event	Active (N = 159) n (%)	Event
Subjects with any treatment-related TEAE	22 (28.6)	36	29 (36.3)	51	32 (40.5)	63	61 (38.4)	114
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	4 (5.2)	5	4 (5.0)	6	0	0	4 (2.5)	6
Serious	1 (1.3)	1	2 (2.5)	2	0	0	2 (1.3)	2
Extrapyramidal	3 (3.9)	3	7 (8.8)	13	18 (22.8)	33	25 (15.7)	46
Skin related	5 (6.5)	7	10 (12.5)	13	14 (17.7)	14	24 (15.1)	27

Treatment emergent adverse events (TEAE) in the double-blind treatment phase are defined as events with start date on or after the initial application date of double-blind treatment phase, and up to 17 days after the date of final application of the double-blind treatment phase and before the first application of DSP-5423P in the open-label treatment phase. Extrapyramidal TEAE are determined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the safety population of subgroup. Event is the number of episodes.

表 2.7.4.5-16　性別での有害事象発現状況（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Sex: Male	PLCB-to-FLEX DOSE (N = 85)		40MG-to-FLEX DOSE (N = 116)		80MG-to-FLEX DOSE (N = 115)		Active-to-FLEX DOSE (N = 231)		Overall-to-FLEX DOSE (N = 316)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects with any TEAE	60 (70.6)	204	96 (82.8)	376	97 (84.3)	388	193 (83.5)	764	253 (80.1)	968
Leading to death	0	0	0	0	3 (2.6)	3	3 (1.3)	3	3 (0.9)	3
Leading to treatment discontinuation	7 (8.2)	7	14 (12.1)	15	16 (13.9)	20	30 (13.0)	35	37 (11.7)	42
Serious	10 (11.8)	10	16 (13.8)	18	17 (14.8)	21	33 (14.3)	39	43 (13.6)	49
Extrapyramidal	17 (20.0)	28	23 (19.8)	42	30 (26.1)	59	53 (22.9)	101	70 (22.2)	129
Skin related	5 (5.9)	7	17 (14.7)	34	31 (27.0)	57	48 (20.8)	91	53 (16.8)	98
Subjects with any treatment-related TEAE	44 (51.8)	86	63 (54.3)	183	74 (64.3)	218	137 (59.3)	401	181 (57.3)	487
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	4 (4.7)	4	9 (7.8)	10	5 (4.3)	5	14 (6.1)	15	18 (5.7)	19
Serious	4 (4.7)	4	10 (8.6)	11	5 (4.3)	6	15 (6.5)	17	19 (6.0)	21
Extrapyramidal	16 (18.8)	24	20 (17.2)	39	25 (21.7)	49	45 (19.5)	88	61 (19.3)	112
Skin related	5 (5.9)	7	16 (13.8)	32	30 (26.1)	56	46 (19.9)	88	51 (16.1)	95

Sex: Female	PLCB-to-FLEX DOSE (N = 46)		40MG-to-FLEX DOSE (N = 80)		80MG-to-FLEX DOSE (N = 79)		Active-to-FLEX DOSE (N = 159)		Overall-to-FLEX DOSE (N = 205)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects with any TEAE	34 (73.9)	97	64 (80.0)	250	66 (83.5)	268	130 (81.8)	518	164 (80.0)	615
Leading to death	0	0	0	0	1 (1.3)	1	1 (0.6)	1	1 (0.5)	1
Leading to treatment discontinuation	5 (10.9)	5	13 (16.3)	15	8 (10.1)	10	21 (13.2)	25	26 (12.7)	30
Serious	6 (13.0)	6	5 (6.3)	5	7 (8.9)	7	12 (7.5)	12	18 (8.8)	18
Extrapyramidal	7 (15.2)	12	16 (20.0)	31	25 (31.6)	58	41 (25.8)	89	48 (23.4)	101
Skin related	10 (21.7)	14	12 (15.0)	17	18 (22.8)	20	30 (18.9)	37	40 (19.5)	51
Subjects with any treatment-related TEAE	28 (60.9)	59	48 (60.0)	117	48 (60.8)	135	96 (60.4)	252	124 (60.5)	311
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	3 (6.5)	3	9 (11.3)	11	3 (3.8)	5	12 (7.5)	16	15 (7.3)	19
Serious	2 (4.3)	2	3 (3.8)	3	0	0	3 (1.9)	3	5 (2.4)	5

Sex: Female	PLCB-to-FLEX DOSE (N = 46) n (%)	Event	40MG-to-FLEX DOSE (N = 80) n (%)	Event	80MG-to-FLEX DOSE (N = 79) n (%)	Event	Active-to-FLEX DOSE (N = 159) n (%)	Event	Overall-to-FLEX DOSE (N = 205) n (%)	Event
Extrapyramidal	7 (15.2)	12	14 (17.5)	29	25 (31.6)	57	39 (24.5)	86	46 (22.4)	98
Skin related	10 (21.7)	14	11 (13.8)	15	18 (22.8)	20	29 (18.2)	35	39 (19.0)	49

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. Extrapyramidal TEAE are defined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the DSP-5423P dosed population of subgroup. Event is the number of episodes. The data cut-off at Open-Week 24 was used.

表 2.7.4.5-17　性別での有害事象発現状況（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Sex: Male	PLCB-to-FLEX DOSE (N = 85) n (%)	Event	40MG-to-FLEX DOSE (N = 116) n (%)	Event	80MG-to-FLEX DOSE (N = 115) n (%)	Event	Active-to-FLEX DOSE (N = 231) n (%)	Event	Overall-to-FLEX DOSE (N = 316) n (%)	Event
Subjects with any TEAE	60 (70.6)	237	96 (82.8)	399	98 (85.2)	427	194 (84.0)	826	254 (80.4)	1063
Leading to death	1 (1.2)	1	0	0	3 (2.6)	3	3 (1.3)	3	4 (1.3)	4
Leading to treatment discontinuation	9 (10.6)	9	14 (12.1)	15	16 (13.9)	20	30 (13.0)	35	39 (12.3)	44
Serious	12 (14.1)	12	16 (13.8)	18	19 (16.5)	24	35 (15.2)	42	47 (14.9)	54
Extrapyramidal	18 (21.2)	31	24 (20.7)	47	31 (27.0)	60	55 (23.8)	107	73 (23.1)	138
Skin related	6 (7.1)	8	18 (15.5)	35	31 (27.0)	61	49 (21.2)	96	55 (17.4)	104
Subjects with any treatment-related TEAE	45 (52.9)	95	65 (56.0)	192	75 (65.2)	230	140 (60.6)	422	185 (58.5)	517
Leading to death	1 (1.2)	1	0	0	0	0	0	0	1 (0.3)	1
Leading to treatment discontinuation	5 (5.9)	5	9 (7.8)	10	5 (4.3)	5	14 (6.1)	15	19 (6.0)	20
Serious	5 (5.9)	5	10 (8.6)	11	5 (4.3)	6	15 (6.5)	17	20 (6.3)	22
Extrapyramidal	17 (20.0)	26	21 (18.1)	44	25 (21.7)	49	46 (19.9)	93	63 (19.9)	119
Skin related	6 (7.1)	8	17 (14.7)	33	30 (26.1)	60	47 (20.3)	93	53 (16.8)	101

Sex: Female	PLCB-to-FLEX DOSE (N = 46) n (%)	Event	40MG-to-FLEX DOSE (N = 80) n (%)	Event	80MG-to-FLEX DOSE (N = 79) n (%)	Event	Active-to-FLEX DOSE (N = 159) n (%)	Event	Overall-to-FLEX DOSE (N = 205) n (%)	Event
Subjects with any TEAE	35 (76.1)	111	65 (81.3)	286	67 (84.8)	311	132 (83.0)	597	167 (81.5)	708
Leading to death	0	0	0	0	1 (1.3)	1	1 (0.6)	1	1 (0.5)	1
Leading to treatment discontinuation	5 (10.9)	5	14 (17.5)	16	10 (12.7)	12	24 (15.1)	28	29 (14.1)	33
Serious	6 (13.0)	6	8 (10.0)	9	10 (12.7)	10	18 (11.3)	19	24 (11.7)	25
Extrapyramidal	7 (15.2)	13	16 (20.0)	31	25 (31.6)	58	41 (25.8)	89	48 (23.4)	102
Skin related	10 (21.7)	15	13 (16.3)	18	19 (24.1)	22	32 (20.1)	40	42 (20.5)	55

Sex: Female	PLCB-to-FLEX DOSE (N = 46) n (%)	Event	40MG-to-FLEX DOSE (N = 80) n (%)	Event	80MG-to-FLEX DOSE (N = 79) n (%)	Event	Active-to-FLEX DOSE (N = 159) n (%)	Event	Overall-to-FLEX DOSE (N = 205) n (%)	Event
Subjects with any treatment-related TEAE	28 (60.9)	62	48 (60.0)	131	49 (62.0)	145	97 (61.0)	276	125 (61.0)	338
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	3 (6.5)	3	9 (11.3)	11	3 (3.8)	5	12 (7.5)	16	15 (7.3)	19
Serious	2 (4.3)	2	3 (3.8)	3	0	0	3 (1.9)	3	5 (2.4)	5
Extrapyramidal	7 (15.2)	13	14 (17.5)	29	25 (31.6)	57	39 (24.5)	86	46 (22.4)	99
Skin related	10 (21.7)	15	12 (15.0)	16	19 (24.1)	22	31 (19.5)	38	41 (20.0)	53

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. Extrapyramidal TEAE are defined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the DSP-5423P dosed population of subgroup. Event is the number of episodes. The final data at Open-Week 52 was used.

表 2.7.4.5-18　性別での有害事象発現状況（40 試験）

Safety population

Sex Male	Cohort 1 (N = 43) n (%)	Event	Cohort 2 (N = 48) n (%)	Event	Overall (N = 91) n (%)	Event
Subjects with any TEAE	33 (76.7)	113	44 (91.7)	177	77 (84.6)	290
Leading to death	0	0	0	0	0	0
Serious	3 (7.0)	3	4 (8.3)	4	7 (7.7)	7
Leading to treatment discontinuation	6 (14.0)	9	3 (6.3)	3	9 (9.9)	12
Severe	2 (4.7)	2	1 (2.1)	1	3 (3.3)	3
Extrapyramidal	9 (20.9)	12	12 (25.0)	15	21 (23.1)	27
Skin related	16 (37.2)	19	23 (47.9)	38	39 (42.9)	57
Subjects with any treatment-related TEAE	26 (60.5)	53	39 (81.3)	96	65 (71.4)	149
Leading to death	0	0	0	0	0	0
Serious	0	0	2 (4.2)	2	2 (2.2)	2
Leading to treatment discontinuation	4 (9.3)	7	3 (6.3)	3	7 (7.7)	10
Severe	1 (2.3)	1	0	0	1 (1.1)	1
Extrapyramidal	7 (16.3)	10	11 (22.9)	14	18 (19.8)	24
Skin related	16 (37.2)	19	21 (43.8)	36	37 (40.7)	55

Sex Female	Cohort 1 (N = 54) n (%)	Event	Cohort 2 (N = 55) n (%)	Event	Overall (N = 109) n (%)	Event
Subjects with any TEAE	49 (90.7)	193	48 (87.3)	265	97 (89.0)	458
Leading to death	0	0	0	0	0	0
Serious	3 (5.6)	3	2 (3.6)	3	5 (4.6)	6
Leading to treatment discontinuation	10 (18.5)	10	9 (16.4)	12	19 (17.4)	22
Severe	2 (3.7)	2	2 (3.6)	2	4 (3.7)	4
Extrapyramidal	12 (22.2)	15	18 (32.7)	36	30 (27.5)	51
Skin related	23 (42.6)	32	21 (38.2)	34	44 (40.4)	66
Subjects with any treatment-related TEAE	34 (63.0)	78	38 (69.1)	108	72 (66.1)	186

Sex Female	Cohort 1 (N = 54)		Cohort 2 (N = 55)		Overall (N = 109)	
	n (%)	Event	n (%)	Event	n (%)	Event
Leading to death	0	0	0	0	0	0
Serious	1 (1.9)	1	0	0	1 (0.9)	1
Leading to treatment discontinuation	7 (13.0)	7	6 (10.9)	9	13 (11.9)	16
Severe	1 (1.9)	1	1 (1.8)	1	2 (1.8)	2
Extrapyramidal	10 (18.5)	13	14 (25.5)	26	24 (22.0)	39
Skin related	21 (38.9)	28	20 (36.4)	33	41 (37.6)	61

TEAE, Treatment-Emergent Adverse Event. Treatment-related TEAE is defined as TEAE with causal relationship to DSP-5423P is definite, probable, or possible. n and % are number and percentage of subjects experienced at least one episode. Event is the number of episodes. Extrapyramidal TEAE are determined by preferred term prior to the database lock. Skin related TEAE are defined as the TEAE with the location of event of the application site.

2.7.4.5.1.5　高齢者

20 試験及び 40 試験では、選択基準で年齢を 18 歳以上とし、年齢の上限は設定しなかった。20 試験では、プラセボ群、40 mg 群、80 mg 群の順に 65 歳未満の被験者が 177 名 (93.2%)、185 名 (94.4%)、182 名 (93.8%)、65 歳以上の被験者が 13 名 (6.8%)、11 名 (5.6%)、12 名 (6.2%) 組み入れられた。65 歳以上の被験者数が少数であり、高齢者と非高齢者で安全性を比較することはできなかったが、20 試験の二重盲検治療期及びロナセンテープ貼付期の非盲検治療期 24 週時の解析及び 52 週時の解析、並びに 40 試験の有害事象発現状況に対する年齢 (65 歳未満及び 65 歳以上) 別の部分集団解析を実施した。高齢者と非高齢者別での有害事象発現状況を、20 試験の二重盲検治療期の非盲検治療期 24 週時の解析及び 52 週時の解析について表 2.7.4.5-19 及び表 2.7.4.5-21 に、20 試験のロナセンテープ貼付期について表 2.7.4.5-20 に、40 試験について表 2.7.4.5-22 に示す。

20 試験の二重盲検治療期及びロナセンテープ貼付期の非盲検治療期 24 週時の解析及び 52 週時の解析、並びに 40 試験のいずれでも、高齢者で有害事象の発現割合が特に高くなる傾向はみられなかった。

表 2.7.4.5-19　高齢者と非高齢者別での有害事象発現状況（20 試験・二重盲検治療期）

Safety population

Age: <65	PLCB (N = 177) n (%)	Event	40MG (N = 185) n (%)	Event	80MG (N = 182) n (%)	Event	Active (N = 367) n (%)	Event
Subjects with any TEAE	104 (58.8)	202	118 (63.8)	280	121 (66.5)	303	239 (65.1)	583
Leading to death	0	0	0	0	1 (0.5)	1	1 (0.3)	1
Leading to treatment discontinuation	14 (7.9)	15	15 (8.1)	16	11 (6.0)	15	26 (7.1)	31
Serious	7 (4.0)	7	8 (4.3)	8	9 (4.9)	9	17 (4.6)	17
Extrapyramidal	13 (7.3)	17	19 (10.3)	29	38 (20.9)	66	57 (15.5)	95
Skin related	6 (3.4)	6	25 (13.5)	40	34 (18.7)	54	59 (16.1)	94
Subjects with any treatment-related TEAE	52 (29.4)	76	65 (35.1)	128	77 (42.3)	174	142 (38.7)	302
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	5 (2.8)	6	9 (4.9)	10	2 (1.1)	2	11 (3.0)	12
Serious	1 (0.6)	1	5 (2.7)	5	3 (1.6)	3	8 (2.2)	8
Extrapyramidal	9 (5.1)	13	16 (8.6)	26	35 (19.2)	60	51 (13.9)	86
Skin related	5 (2.8)	5	23 (12.4)	36	33 (18.1)	53	56 (15.3)	89

Age: >=65	PLCB (N = 13) n (%)	Event	40MG (N = 11) n (%)	Event	80MG (N = 12) n (%)	Event	Active (N = 23) n (%)	Event
Subjects with any TEAE	10 (76.9)	20	5 (45.5)	16	9 (75.0)	15	14 (60.9)	31
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	3 (23.1)	3	1 (9.1)	3	0	0	1 (4.3)	3
Serious	2 (15.4)	2	0	0	1 (8.3)	1	1 (4.3)	1
Extrapyramidal	2 (15.4)	2	2 (18.2)	3	2 (16.7)	4	4 (17.4)	7
Skin related	2 (15.4)	4	1 (9.1)	1	2 (16.7)	2	3 (13.0)	3

Age: >=65	PLCB (N = 13) n (%)	Event	40MG (N = 11) n (%)	Event	80MG (N = 12) n (%)	Event	Active (N = 23) n (%)	Event
Subjects with any treatment-related TEAE	6 (46.2)	12	4 (36.4)	6	5 (41.7)	7	9 (39.1)	13
Leading to death	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	2 (15.4)	2	1 (9.1)	3	0	0	1 (4.3)	3
Serious	1 (7.7)	1	0	0	0	0	0	0
Extrapyramidal	1 (7.7)	1	1 (9.1)	2	2 (16.7)	4	3 (13.0)	6
Skin related	2 (15.4)	4	1 (9.1)	1	2 (16.7)	2	3 (13.0)	3

Treatment emergent adverse events (TEAE) in the double-blind treatment phase are defined as events with start date on or after the initial application date of double-blind treatment phase, and up to 17 days after the date of final application of the double-blind treatment phase and before the first application of DSP-5423P in the open-label treatment phase. Extrapyramidal TEAE are determined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the safety population of subgroup. Event is the number of episodes.

表 2.7.4.5-20　高齢者と非高齢者別での有害事象発現状況（20 試験・ロナセンテープ貼付期、Open-24 週）

DSP-5423P dosed population

Age: <65	PLCB-to-FLEX DOSE (N = 123) n (%)	Event	40MG-to-FLEX DOSE (N = 185) n (%)	Event	80MG-to-FLEX DOSE (N = 182) n (%)	Event	Active-to-FLEX DOSE (N = 367) n (%)	Event	Overall-to-FLEX DOSE (N = 490) n (%)	Event
Subjects with any TEAE	90 (73.2)	290	149 (80.5)	597	152 (83.5)	618	301 (82.0)	1215	391 (79.8)	1505
Leading to death	0	0	0	0	3 (1.6)	3	3 (0.8)	3	3 (0.6)	3
Leading to treatment discontinuation	11 (8.9)	11	26 (14.1)	27	22 (12.1)	26	48 (13.1)	53	59 (12.0)	64
Serious	14 (11.4)	14	21 (11.4)	23	23 (12.6)	25	44 (12.0)	48	58 (11.8)	62
Extrapyramidal	24 (19.5)	40	36 (19.5)	68	52 (28.6)	112	88 (24.0)	180	112 (22.9)	220
Skin related	15 (12.2)	21	27 (14.6)	49	46 (25.3)	74	73 (19.9)	123	88 (18.0)	144
Subjects with any treatment-related TEAE	68 (55.3)	139	105 (56.8)	290	114 (62.6)	340	219 (59.7)	630	287 (58.6)	769
Leading to death	0	0	0	0	0	0	0	0	0	0

Age: <65	PLCB-to-FLEX DOSE (N = 123) n (%)	Event	40MG-to-FLEX DOSE (N = 185) n (%)	Event	80MG-to-FLEX DOSE (N = 182) n (%)	Event	Active-to-FLEX DOSE (N = 367) n (%)	Event	Overall-to-FLEX DOSE (N = 490) n (%)	Event
Leading to treatment discontinuation	6 (4.9)	6	17 (9.2)	18	6 (3.3)	6	23 (6.3)	24	29 (5.9)	30
Serious	5 (4.1)	5	13 (7.0)	14	5 (2.7)	6	18 (4.9)	20	23 (4.7)	25
Extrapyramidal	23 (18.7)	36	32 (17.3)	64	47 (25.8)	101	79 (21.5)	165	102 (20.8)	201
Skin related	15 (12.2)	21	25 (13.5)	45	45 (24.7)	73	70 (19.1)	118	85 (17.3)	139

Age: >=65	PLCB-to-FLEX DOSE (N = 8) n (%)	Event	40MG-to-FLEX DOSE (N = 11) n (%)	Event	80MG-to-FLEX DOSE (N = 12) n (%)	Event	Active-to-FLEX DOSE (N = 23) n (%)	Event	Overall-to-FLEX DOSE (N = 31) n (%)	Event
Subjects with any TEAE	4 (50.0)	11	11 (100.0)	29	11 (91.7)	38	22 (95.7)	67	26 (83.9)	78
Leading to death	0	0	0	0	1 (8.3)	1	1 (4.3)	1	1 (3.2)	1
Leading to treatment discontinuation	1 (12.5)	1	1 (9.1)	3	2 (16.7)	4	3 (13.0)	7	4 (12.9)	8
Serious	2 (25.0)	2	0	0	1 (8.3)	3	1 (4.3)	3	3 (9.7)	5
Extrapyramidal	0	0	3 (27.3)	5	3 (25.0)	5	6 (26.1)	10	6 (19.4)	10
Skin related	0	0	2 (18.2)	2	3 (25.0)	3	5 (21.7)	5	5 (16.1)	5
Subjects with any treatment-related TEAE	4 (50.0)	6	6 (54.5)	10	8 (66.7)	13	14 (60.9)	23	18 (58.1)	29
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	1 (12.5)	1	1 (9.1)	3	2 (16.7)	4	3 (13.0)	7	4 (12.9)	8
Serious	1 (12.5)	1	0	0	0	0	0	0	1 (3.2)	1
Extrapyramidal	0	0	2 (18.2)	4	3 (25.0)	5	5 (21.7)	9	5 (16.1)	9
Skin related	0	0	2 (18.2)	2	3 (25.0)	3	5 (21.7)	5	5 (16.1)	5

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. Extrapyramidal TEAE are defined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the DSP-5423P dosed population of subgroup. Event is the number of episodes. The data cut-off at Open-Week 24 was used.

表 2.7.4.5-21　高齢者と非高齢者別での有害事象発現状況（20 試験・ロナセンテープ貼付期、Open-52 週）

DSP-5423P dosed population

Age: <65	PLCB-to-FLEX DOSE (N = 123) n (%)	Event	40MG-to-FLEX DOSE (N = 185) n (%)	Event	80MG-to-FLEX DOSE (N = 182) n (%)	Event	Active-to-FLEX DOSE (N = 367) n (%)	Event	Overall-to-FLEX DOSE (N = 490) n (%)	Event
Subjects with any TEAE	91 (74.0)	333	150 (81.1)	652	154 (84.6)	695	304 (82.8)	1347	395 (80.6)	1680
Leading to death	1 (0.8)	1	0	0	3 (1.6)	3	3 (0.8)	3	4 (0.8)	4
Leading to treatment discontinuation	13 (10.6)	13	27 (14.6)	28	24 (13.2)	28	51 (13.9)	56	64 (13.1)	69
Serious	16 (13.0)	16	23 (12.4)	26	28 (15.4)	31	51 (13.9)	57	67 (13.7)	73
Extrapyramidal	24 (19.5)	43	37 (20.0)	73	53 (29.1)	113	90 (24.5)	186	114 (23.3)	229
Skin related	16 (13.0)	23	29 (15.7)	51	46 (25.3)	76	75 (20.4)	127	91 (18.6)	150
Subjects with any treatment-related TEAE	69 (56.1)	148	107 (57.8)	313	116 (63.7)	358	223 (60.8)	671	292 (59.6)	819
Leading to death	1 (0.8)	1	0	0	0	0	0	0	1 (0.2)	1
Leading to treatment discontinuation	7 (5.7)	7	17 (9.2)	18	6 (3.3)	6	23 (6.3)	24	30 (6.1)	31
Serious	6 (4.9)	6	13 (7.0)	14	5 (2.7)	6	18 (4.9)	20	24 (4.9)	26
Extrapyramidal	23 (18.7)	38	33 (17.8)	69	47 (25.8)	101	80 (21.8)	170	103 (21.0)	208
Skin related	16 (13.0)	23	27 (14.6)	47	45 (24.7)	75	72 (19.6)	122	88 (18.0)	145

Age: >=65	PLCB-to-FLEX DOSE (N = 8) n (%)	Event	40MG-to-FLEX DOSE (N = 11) n (%)	Event	80MG-to-FLEX DOSE (N = 12) n (%)	Event	Active-to-FLEX DOSE (N = 23) n (%)	Event	Overall-to-FLEX DOSE (N = 31) n (%)	Event
Subjects with any TEAE	4 (50.0)	15	11 (100.0)	33	11 (91.7)	43	22 (95.7)	76	26 (83.9)	91
Leading to death	0	0	0	0	1 (8.3)	1	1 (4.3)	1	1 (3.2)	1
Leading to treatment discontinuation	1 (12.5)	1	1 (9.1)	3	2 (16.7)	4	3 (13.0)	7	4 (12.9)	8
Serious	2 (25.0)	2	1 (9.1)	1	1 (8.3)	3	2 (8.7)	4	4 (12.9)	6
Extrapyramidal	1 (12.5)	1	3 (27.3)	5	3 (25.0)	5	6 (26.1)	10	7 (22.6)	11
Skin related	0	0	2 (18.2)	2	4 (33.3)	7	6 (26.1)	9	6 (19.4)	9

Age: >=65	PLCB-to-FLEX DOSE (N = 8) n (%)	Event	40MG-to-FLEX DOSE (N = 11) n (%)	Event	80MG-to-FLEX DOSE (N = 12) n (%)	Event	Active-to-FLEX DOSE (N = 23) n (%)	Event	Overall-to-FLEX DOSE (N = 31) n (%)	Event
Subjects with any treatment-related TEAE	4 (50.0)	9	6 (54.5)	10	8 (66.7)	17	14 (60.9)	27	18 (58.1)	36
Leading to death	0	0	0	0	0	0	0	0	0	0
Leading to treatment discontinuation	1 (12.5)	1	1 (9.1)	3	2 (16.7)	4	3 (13.0)	7	4 (12.9)	8
Serious	1 (12.5)	1	0	0	0	0	0	0	1 (3.2)	1
Extrapyramidal	1 (12.5)	1	2 (18.2)	4	3 (25.0)	5	5 (21.7)	9	6 (19.4)	10
Skin related	0	0	2 (18.2)	2	4 (33.3)	7	6 (26.1)	9	6 (19.4)	9

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. Extrapyramidal TEAE are defined by preferred term prior to the data summary. Skin related TEAE are defined as the TEAE with the location of event of the application site. Treatment related TEAE are defined as the TEAE with causal relationship to the study treatment of definite, probable, or possible. If a subject experienced more than one episode of TEAE within the category, the subject is counted only once in the category. The denominator of percentages is the number of subjects in the DSP-5423P dosed population of subgroup. Event is the number of episodes. The final data at Open-Week 52 was used.

表 2.7.4.5-22　高齢者と非高齢者別での有害事象発現状況（40 試験）

Safety population

Age (years) <65	Cohort 1 (N = 87) n (%)	Event	Cohort 2 (N = 94) n (%)	Event	Overall (N = 181) n (%)	Event
Subjects with any TEAE	73 (83.9)	269	84 (89.4)	412	157 (86.7)	681
Leading to death	0	0	0	0	0	0
Serious	5 (5.7)	5	5 (5.3)	6	10 (5.5)	11
Leading to treatment discontinuation	14 (16.1)	17	10 (10.6)	13	24 (13.3)	30
Severe	3 (3.4)	3	2 (2.1)	2	5 (2.8)	5
Extrapyramidal	20 (23.0)	26	29 (30.9)	48	49 (27.1)	74
Skin related	32 (36.8)	41	39 (41.5)	66	71 (39.2)	107
Subjects with any treatment-related TEAE	55 (63.2)	121	73 (77.7)	198	128 (70.7)	319
Leading to death	0	0	0	0	0	0

Age (years) <65	Cohort 1 (N = 87)		Cohort 2 (N = 94)		Overall (N = 181)	
	n (%)	Event	n (%)	Event	n (%)	Event
Serious	1 (1.1)	1	2 (2.1)	2	3 (1.7)	3
Leading to treatment discontinuation	10 (11.5)	13	7 (7.4)	10	17 (9.4)	23
Severe	2 (2.3)	2	1 (1.1)	1	3 (1.7)	3
Extrapyramidal	17 (19.5)	23	25 (26.6)	40	42 (23.2)	63
Skin related	32 (36.8)	41	38 (40.4)	65	70 (38.7)	106

Age (years) >=65	Cohort 1 (N = 10)		Cohort 2 (N = 9)		Overall (N = 19)	
	n (%)	Event	n (%)	Event	n (%)	Event
Subjects with any TEAE	9 (90.0)	37	8 (88.9)	30	17 (89.5)	67
Leading to death	0	0	0	0	0	0
Serious	1 (10.0)	1	1 (11.1)	1	2 (10.5)	2
Leading to treatment discontinuation	2 (20.0)	2	2 (22.2)	2	4 (21.1)	4
Severe	1 (10.0)	1	1 (11.1)	1	2 (10.5)	2
Extrapyramidal	1 (10.0)	1	1 (11.1)	3	2 (10.5)	4
Skin related	7 (70.0)	10	5 (55.6)	6	12 (63.2)	16
Subjects with any treatment-related TEAE	5 (50.0)	10	4 (44.4)	6	9 (47.4)	16
Leading to death	0	0	0	0	0	0
Serious	0	0	0	0	0	0
Leading to treatment discontinuation	1 (10.0)	1	2 (22.2)	2	3 (15.8)	3
Severe	0	0	0	0	0	0
Extrapyramidal	0	0	0	0	0	0
Skin related	5 (50.0)	6	3 (33.3)	4	8 (42.1)	10

TEAE, Treatment-Emergent Adverse Event. Treatment-related TEAE is defined as TEAE with causal relationship to DSP-5423P is definite, probable, or possible. n and % are number and percentage of subjects experienced at least one episode. Event is the number of episodes. Extrapyramidal TEAE are determined by preferred term prior to the database lock. Skin related TEAE are defined as the TEAE with the location of event of the application site.

2.7.4.5.2　外因性要因

2.7.4.5.2.1　ロナセン錠からロナセンテープの切替え

40 試験のコホート 1 でロナセン錠投与からロナセンテープ貼付への切替えの安全性を評価した。

2.7.4.5.2.1.1　切替えによる有害事象発現への影響

ロナセン錠投与期の有害事象の発現割合を表 2.7.4.5-23 に示す。

ロナセン錠投与期の有害事象の発現割合は 51.9%（56/108 名）、ロナセン錠との因果関係が否定されなかった有害事象の発現割合は 35.2%（38/108 名）であった。発現割合が 5%以上であったロナセン錠投与期の有害事象は、アカシジア（14.8%）、鼻咽頭炎（10.2%）、傾眠（8.3%）であった。ロナセンテープ貼付部位に発現した有害事象を除き、ロナセン錠投与期とロナセンテープ貼付期（Week 6 まで）（表 2.7.4.2-14 参照）を比較して、発現割合に大きな差がある事象はなかった。

表 2.7.4.5-23　ロナセン錠投与期の有害事象の発現割合（40 試験）

Subjects treated with DSP-5423 (tablet)

System Organ Class Preferred Term	器官別大分類 基本語	Adverse event (N = 108) n (%)	Treatment-related adverse event (N = 108) n (%)
Subjects with any adverse event in DSP-5423 (tablet) treatment phase		56 (51.9)	38 (35.2)
Endocrine disorders	内分泌障害	3 (2.8)	3 (2.8)
Hyperprolactinaemia	高プロラクチン血症	3 (2.8)	3 (2.8)
Eye disorders	眼障害	2 (1.9)	1 (0.9)
Eye irritation	眼刺激	1 (0.9)	0
Oculogyric crisis	眼球回転発作	1 (0.9)	1 (0.9)
Gastrointestinal disorders	胃腸障害	8 (7.4)	4 (3.7)
Dental caries	齲歯	2 (1.9)	0
Diarrhoea	下痢	2 (1.9)	0
Nausea	悪心	2 (1.9)	2 (1.9)
Salivary hypersecretion	流涎過多	2 (1.9)	2 (1.9)
Vomiting	嘔吐	2 (1.9)	0
Toothache	歯痛	1 (0.9)	0
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (0.9)	1 (0.9)
Gait disturbance	歩行障害	1 (0.9)	1 (0.9)

System Organ Class Preferred Term	器官別大分類 基本語	Adverse event (N = 108) n (%)	Treatment-related adverse event (N = 108) n (%)
Hepatobiliary disorders	肝胆道系障害	1 (0.9)	1 (0.9)
Hepatic function abnormal	肝機能異常	1 (0.9)	1 (0.9)
Infections and infestations	感染症および寄生虫症	13 (12.0)	0
Nasopharyngitis	鼻咽頭炎	11 (10.2)	0
Bronchitis	気管支炎	1 (0.9)	0
Dermatophytosis of nail	爪の皮膚糸状菌症	1 (0.9)	0
Upper respiratory tract infection	上気道感染	1 (0.9)	0
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	2 (1.9)	0
Contusion	挫傷	1 (0.9)	0
Stab wound	刺創	1 (0.9)	0
Investigations	臨床検査	5 (4.6)	3 (2.8)
Blood prolactin increased	血中プロラクチン増加	3 (2.8)	3 (2.8)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	1 (0.9)	0
Blood glucose increased	血中ブドウ糖増加	1 (0.9)	1 (0.9)
Liver function test increased	肝機能検査値上昇	1 (0.9)	0
Weight decreased	体重減少	1 (0.9)	0
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	3 (2.8)	2 (1.9)
Muscle rigidity	筋固縮	2 (1.9)	2 (1.9)
Musculoskeletal chest pain	筋骨格系胸痛	1 (0.9)	0
Nervous system disorders	神経系障害	33 (30.6)	30 (27.8)
Akathisia	アカシジア	16 (14.8)	16 (14.8)
Somnolence	傾眠	9 (8.3)	7 (6.5)
Parkinsonism	パーキンソニズム	5 (4.6)	5 (4.6)
Dystonia	ジストニア	4 (3.7)	4 (3.7)
Tremor	振戦	4 (3.7)	4 (3.7)
Dyskinesia	ジスキネジア	3 (2.8)	3 (2.8)
Dizziness postural	体位性めまい	1 (0.9)	1 (0.9)
Headache	頭痛	1 (0.9)	0
Hypoaesthesia	感覚鈍麻	1 (0.9)	1 (0.9)
Psychiatric disorders	精神障害	6 (5.6)	4 (3.7)
Insomnia	不眠症	3 (2.8)	3 (2.8)
Abulia	無為	1 (0.9)	1 (0.9)

System Organ Class Preferred Term	器官別大分類 基本語	Adverse event (N = 108) n (%)	Treatment-related adverse event (N = 108) n (%)
Schizophrenia	統合失調症	1 (0.9)	0
Suicidal ideation	自殺念慮	1 (0.9)	0
Renal and urinary disorders	腎および尿路障害	2 (1.9)	2 (1.9)
Pollakiuria	頻尿	1 (0.9)	1 (0.9)
Urinary incontinence	尿失禁	1 (0.9)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	2 (1.9)	1 (0.9)
Choking sensation	息詰まり感	1 (0.9)	1 (0.9)
Cough	咳嗽	1 (0.9)	0
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害	3 (2.8)	0
Dermatitis	皮膚炎	1 (0.9)	0
Eczema	湿疹	1 (0.9)	0
Pruritus	そう痒症	1 (0.9)	0

Adverse events in the DSP-5423 (tablet) treatment phase, of which onset date is between initial dose date of DSP-5423 (tablet) and a day before the initial application date of DSP-5423P are summarized. Adverse events are coded by MedDRA version 19.1. Treatment-related adverse event is defined as TEAE with causal relationship to the study treatment is definite, probable, or possible. If a subject experienced more than one episode of adverse event within a preferred term (PT) or a system organ class (SOC), the subject is counted only once in the PT or the SOC.

ロナセン錠投与期の錐体外路系有害事象の発現割合を表 2.7.4.5-24 に示す。

錐体外路系有害事象の発現割合は 23.1%（25/108 名）で、そのうち 5%以上発現した事象はアカシジア 14.8%（16/108 名）であった。コホート 1 のロナセンテープ貼付期（Week 6 まで）の錐体外路系有害事象の発現割合は 8.2%（8/97 名）で、そのうちアカシジアは 4.1%（4/97 名）であった（表 2.7.4.2-43 参照）。コホート 1 のロナセンテープ貼付期（52 週間）の錐体外路系有害事象の発現割合は 21.6%（21/97 名）で、アカシジアは 6.2%（6/97 名）、振戦は 4.1%（4/97 名）に発現した（表 2.7.4.2-40 参照）。錐体外路系有害事象に重篤な事象はなく、重度と判断された事象はアカシジア 1 名（0.5%）であった（表 2.7.4.2-10 参照）。ロナセンテープへの切り替え後に錐体外路系有害事象の発現割合が高くなることはなく、重症化することもなかった。

表 2.7.4.5-24　ロナセン錠投与期の錐体外路系有害事象の発現割合（40 試験）

Subjects treated with DSP-5423 (tablet)

System Organ Class Preferred Term	器官別大分類 基本語	Adverse event (N = 108) n (%)	Treatment-related adverse event (N = 108) n (%)
Subjects with any adverse event in DSP-5423 (tablet) treatment phase		25 (23.1)	25 (23.1)
Eye disorders	眼障害	1 (0.9)	1 (0.9)
Oculogyric crisis	眼球回転発作	1 (0.9)	1 (0.9)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (0.9)	1 (0.9)
Gait disturbance	歩行障害	1 (0.9)	1 (0.9)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	2 (1.9)	2 (1.9)
Muscle rigidity	筋固縮	2 (1.9)	2 (1.9)
Nervous system disorders	神経系障害	24 (22.2)	24 (22.2)
Akathisia	アカシジア	16 (14.8)	16 (14.8)
Parkinsonism	パーキンソニズム	5 (4.6)	5 (4.6)
Dystonia	ジストニア	4 (3.7)	4 (3.7)
Tremor	振戦	4 (3.7)	4 (3.7)
Dyskinesia	ジスキネジア	3 (2.8)	3 (2.8)

Adverse events in the DSP-5423 (tablet) treatment phase, of which onset date is between initial dose date of DSP-5423 (tablet) and a day before the initial application date of DSP-5423P are summarized. Adverse events are coded by MedDRA version 19.1. Treatment-related adverse event is defined as TEAE with causal relationship to the study treatment is definite, probable, or possible. If a subject experienced more than one episode of adverse event within a preferred term (PT) or a system organ class (SOC), the subject is counted only once in the PT or the SOC. Extrapyramidal TEAE are determined by preferred term prior to the database lock.

2.7.4.5.2.1.2　切替えによる DIEPSS への影響

ロナセン錠投与期の DIEPSS 合計スコア（概括重症度を除く）変化量を表 2.7.4.5-25 に示す。ロナセン錠投与開始前からロナセン錠投与後 6 週の DIEPSS 合計スコア（概括重症度を除く）の変化量（mean±SD、以下、同様）は 0.3±1.56 で、コホート 1 のロナセンテープ貼付期のベースラインから Week 6 で−0.3±1.51、Week 52（LOCF）で 0.0±1.61 であった（表 2.7.4.4-12 参照）。DIEPSS 合計スコア（概括重症度を除く）でロナセン錠投与からロナセンテープ貼付への切替えによる臨床的に問題となる変動はなかった。

表 2.7.4.5-25　ロナセン錠投与期の DIEPSS 合計スコア（概括重症度を除く）変化量（40 試験）

Subjects treated with DSP-5423 (tablet)

		Cohort 1 (N = 108)	
Visit	Statistics	Observed	Change
Tab-Baseline	n	108	
	Mean (SD)	0.6 (1.48)	
	Median	0.0	
	Min, Max	0, 8	
Tab-Week 1	n	108	108
	Mean (SD)	0.9 (2.14)	0.3 (1.38)
	Median	0.0	0.0
	Min, Max	0, 17	-3, 11
Tab-Week 2	n	104	104
	Mean (SD)	0.9 (2.09)	0.3 (1.38)
	Median	0.0	0.0
	Min, Max	0, 15	-3, 9
Tab-Week 4	n	101	101
	Mean (SD)	0.9 (1.86)	0.3 (1.57)
	Median	0.0	0.0
	Min, Max	0, 10	-3, 10
Tab-Week 6	n	99	99
	Mean (SD)	0.9 (1.80)	0.3 (1.56)
	Median	0.0	0.0
	Min, Max	0, 8	-4, 8

DIEPSS total score is the sum of symptom scores excluding overall severity. Summary statistics for the observed value and change from Tab-baseline value (denoted by change) are based on subjects with both a baseline of the DSP-5423 (tablet) treatment phase and the target visit observation.

2.7.4.5.3　薬物相互作用

本申請にあたり、薬物相互作用試験は実施しなかった。なお、ロナセンテープの薬物動態に与える各種 CYP 阻害剤の影響は、ロナセン錠での結果及び SimCYP®を用いた CYP3A4 阻害剤及び誘導剤による肝 CYP3A4 活性変化のシミュレーション結果に基づいて

考察した（2.7.2.1.2 項、2.7.2.3.3 項参照）。

20 試験及び 40 試験のいずれでも、ブロナンセリンは主として CYP3A4 によって代謝されることから、ブロナンセリン血漿中濃度を増加させると考えられる CYP3A4 阻害作用を有する薬剤及び食品を併用禁止薬として設定した。20 試験の二重盲検治療期の実薬群で 1 名、20 試験の非盲検治療期に 3 名、40 試験に 4 名が CYP3A4 阻害作用を有する薬剤を使

用したが、薬物相互作用によると考えられる有害事象の報告はなかった。

2.7.4.5.4　妊娠及び授乳時の使用

20 試験及び 40 試験では妊婦、妊娠している可能性のある患者、適切な避妊手段を講じず本人又は女性パートナーが妊娠する可能性のある患者、及び授乳中の患者を除外した。20 試験では二重盲検治療期中に台湾の女性被験者（40 mg 群）が妊娠し、治験を中止した。出産を希望せず、人工妊娠中絶を行った。ロナセンテープ貼付期（非盲検治療期 24 週時の解析）では、妊娠の報告はされていない。40 試験では 1 名の被験者が妊娠した。本被験者はコホート 1 にてロナセンテープ貼付開始から 14 日目に妊娠が判明し、治験中止となった。治験中止から 12 日後（ロナセンテープ貼付開始から 26 日目）に人工妊娠中絶術が行われた。これらのことから、妊娠・授乳時に対する本剤の安全性に関する新たな情報は得られていない。

2.7.4.5.5　過量投与

20 試験及び 40 試験で、十数名が剥がし忘れなどにより 1～3 日間、160 mg/日まで規定貼付量を超えて貼付したが、規定貼付量を大きく超えて貼付した被験者はいなかった。また、過量に貼付したことによると考えられた有害事象は発現しなかった。

2.7.4.5.6　薬物乱用

薬物依存性を評価した臨床試験は実施していない。20 試験と 40 試験では薬物依存性を示唆する有害事象は発現していない。

2.7.4.5.7　離脱症状及び反跳現象

離脱症状及び反跳現象を評価した臨床試験は実施していない。

2.7.4.5.8　自動車運転及び機械操作に対する影響又は精神機能の障害

ブロナンセリンは中枢抑制作用がある。注目すべき有害事象として、鎮静関係の有害事象を評価した。20 試験の二重盲検治療期で、鎮静関連有害事象に該当したのは過眠症及び傾眠で、発現割合はプラセボ群、40 mg 群、80 mg 群で過眠症が 0%、0%、0.5%、傾眠が 2.6%、1.5%、1.0%であった。40 試験で、鎮静関連有害事象に該当したのは疲労及び傾眠で、発現割合は疲労が 0.5%、傾眠が 2.5%であった。

また、易興奮性や脱抑制は 20 試験及び 40 試験のいずれでも発現しなかった。

2.7.4.6　市販後データ

本剤の市販後データはない。

【参考文献】

1) 日本腎臓学会編. CQ1-2. CKD の重症度はどのように評価するか. In:エビデンスに基づく CKD 診療ガイドライン 2018. 東京: 東京医学社; 2018. P.2-5. 【5.4.44】

2.7.4.7 付録

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表2.7.4.7-1　注目すべき有害事象とした基本語一覧

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
錐体外路	10076668	早期発症原発性ジストニア	10010331	先天性、家族性および遺伝性障害
	10005159	眼瞼痙攣	10015919	眼障害
	10030071	眼球回転発作		
	10006532	頬舌症候群	10017947	胃腸障害
	10013924	食道ジスキネジア		
	10030184	食道痙攣		
	10037076	舌突出		
	10043981	舌痙攣		
	10017577	歩行障害	10018065	一般・全身障害および投与部位の状態
	10049460	歩行不能		
	10075002	異常不随意運動評価尺度	10022891	臨床検査
	10028330	筋固縮	10028395	筋骨格系および結合組織障害
	10028334	筋痙縮		
	10028347	筋攣縮		
	10036436	姿勢異常		
	10044074	斜頚		
	10044684	開口障害		
	10048334	運動性低下		
	10048615	新生児筋緊張亢進		
	10049816	筋緊張		
	10052904	筋骨格硬直		
	10001540	アカシジア	10029205	神経系障害
	10001541	無動		
	10003620	アテトーゼ		
	10006100	運動緩慢		
	10008748	舞踏病		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC
	10008754	舞踏病アテトーゼ	
	10009848	歯車様固縮	
	10013642	よだれ	
	10013916	ジスキネジア	
	10013922	新生児ジスキネジア	
	10013983	ジストニア	
	10014566	前弯痙攣	
	10015832	錐体外路障害	
	10020651	運動過多	
	10020652	新生児運動過多	
	10020852	筋緊張亢進	
	10021021	運動低下	
	10021022	新生児運動減退	
	10027138	メージ症候群	
	10028035	運動障害	
	10028293	不随意性筋収縮	
	10028335	筋痙直	
	10030312	オンオフ現象	
	10030899	弓なり緊張	
	10034010	パーキンソニズム	
	10035628	側反弓	
	10037211	精神運動亢進	
	10039198	痙笑	
	10043118	遅発性ジスキネジア	
	10044565	振戦	
	10044575	新生児振戦	
	10048868	パーキンソン発症	
	10050908	口蓋垂痙攣	

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10056242	パーキンソン歩行		
	10056437	パーキンソン病安静時振戦		
	10057333	小字症		
	10057570	呼吸器ジスキネジア		
	10058504	バリズム		
	10060904	すくみ現象		
	10061296	運動機能障害		
	10061536	パーキンソン病		
	10061991	しかめ面		
	10063006	顔面痙攣		
	10067206	姿勢反射障害		
	10067672	痙攣性発声障害		
	10067954	口下顎ジストニア		
	10068395	兎の口症候群		
	10071243	パーキンソニズム・異常高熱症候群		
	10071390	安静時振戦		
	10072249	書痙		
	10072413	動作時振戦		
	10072889	筋緊張性障害		
	10073210	ジストニア振戦		
	10073211	姿勢時振戦		
	10076288	微細運動機能障害		
	10078576	表情減少		
	10036437	不自然な姿勢	10037175	精神障害
	10038743	落ち着きのなさ		
	10043833	チック		
	10044076	心因性斜頚		
	10050012	精神緩慢		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10067468	ドーパミン調節障害症候群		
	10074835	パーキンソン病精神病		
	10076661	慢性チック障害		
	10076663	複雑チック		
	10076694	暫定的チック障害		
	10076702	二次チック		
	10013952	発声障害	10038738	呼吸器、胸郭および縦隔障害
	10023891	喉頭痙攣		
	10031111	口腔咽頭痙攣		
	10070912	咽頭ジスキネジア		
	10053204	歩行障害者	10041244	社会環境
鎮静関連	10016256	疲労	10018065	一般・全身障害および投与部位の状態
	10010071	昏睡	10029205	神経系障害
	10012373	意識レベルの低下		
	10020765	過眠症		
	10039897	鎮静		
	10041349	傾眠		
	10042264	昏迷		
耐糖能異常関連	10078338	ウォルフラム症候群	10010331	先天性、家族性および遺伝性障害
	10020466	空腹	10018065	一般・全身障害および投与部位の状態
	10043458	口渇		
	10071265	糖尿病性肝障害	10019805	肝胆道系障害
	10022472	インスリン自己免疫症候群	10021428	免疫系障害
	10005425	血中コレステロール増加	10022891	臨床検査
	10005554	血中ブドウ糖異常		
	10005557	血中ブドウ糖増加		
	10005606	血中インスリン異常		
	10005613	血中インスリン減少		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10005635	血中乳酸増加		
	10005697	血液浸透圧上昇		
	10005839	血中トリグリセリド増加		
	10005895	ボディ・マス・インデックス減少		
	10005897	ボディ・マス・インデックス増加		
	10017395	フルクトサミン増加		
	10018428	耐糖能低下		
	10018433	ブドウ糖負荷試験異常		
	10018478	尿中ブドウ糖陽性		
	10018484	グリコヘモグロビン増加		
	10022494	インスリン耐性試験異常		
	10024592	脂質増加		
	10047895	体重減少		
	10047899	体重増加		
	10049439	抗膵島細胞抗体陽性		
	10049803	血中ブドウ糖変動		
	10053814	抗インスリン抗体陽性		
	10053815	抗インスリン抗体増加		
	10057597	尿中ケトン体陽性		
	10059728	抗ＧＡＤ抗体陽性		
	10065367	血中１，５－アンヒドログルシトール減少		
	10068225	抗インスリン受容体抗体陽性		
	10068226	抗インスリン受容体抗体増加		
	10072498	抗ＩＡ２抗体陽性		
	10072530	抗亜鉛輸送体８抗体陽性		
	10078582	耐糖能境界型		
	10000159	異常体重減少	10027433	代謝および栄養障害

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC
	10000188	異常体重増加	
	10000486	アシドーシス	
	10012174	脱水	
	10012596	糖尿病を合併する妊娠	
	10012601	糖尿病	
	10012607	コントロール不良の糖尿病	
	10012631	高浸透圧をともなう糖尿病	
	10012671	糖尿病性ケトアシドーシス	
	10018429	耐糖能障害	
	10018430	妊娠時の耐糖能障害	
	10020603	高コレステロール血症	
	10020635	高血糖	
	10020660	高乳酸血症	
	10020697	高浸透圧状態	
	10020710	過食	
	10020869	高トリグリセリド血症	
	10020993	低血糖	
	10021654	食欲亢進	
	10021664	インスリン必要量の増加	
	10022489	インスリン抵抗性	
	10022490	インスリン抵抗性症候群	
	10022491	インスリン抵抗性糖尿病	
	10023379	ケトアシドーシス	
	10023391	ケトーシス	
	10023676	乳酸アシドーシス	
	10027417	代謝性アシドーシス	
	10028933	新生児糖尿病	
	10029883	肥満	

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10033307	過体重		
	10033660	膵性糖尿病		
	10036067	多飲症		
	10048828	過少体重		
	10052066	代謝症候群		
	10052341	インスリン分泌障害		
	10053247	インスリン必要２型糖尿病		
	10056997	空腹時血中ブドウ糖不良		
	10062060	高脂血症		
	10065941	中心性肥満		
	10066389	成人潜在性自己免疫性糖尿病		
	10067584	１型糖尿病		
	10067585	２型糖尿病		
	10070070	低インスリン血症		
	10072628	劇症１型糖尿病		
	10072659	３型糖尿病		
	10073667	後天性脂肪萎縮性糖尿病		
	10074309	糖尿病性代謝代償不全		
	10075980	単一遺伝子性糖尿病		
	10076413	高浸透圧性高血糖状態		
	10001854	意識変容状態	10029205	神経系障害
	10010071	昏睡		
	10012373	意識レベルの低下		
	10012650	糖尿病性昏睡		
	10012668	糖尿病性高血糖昏睡		
	10012669	糖尿病性高浸透圧性昏睡		
	10012672	糖尿病性ケトアシドーシス性高血糖昏睡		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10024855	意識消失		
	10041045	刺激反応遅滞		
	10045555	刺激無反応		
	10071286	高血糖性意識消失		
	10071394	高血糖性痙攣		
	10018209	妊娠糖尿病	10036585	妊娠、産褥および周産期の状態
	10018473	糖尿	10038359	腎および尿路障害
	10018475	妊娠糖尿		
	10023388	ケトン尿		
	10036142	多尿		
	10077357	糖尿病性動脈炎	10047065	血管障害
体重増加関連	10016251	脂肪組織増加	10018065	一般・全身障害および投与部位の状態
	10020466	空腹		
	10005897	ボディ・マス・インデックス増加	10022891	臨床検査
	10047899	体重増加		
	10064863	ウエスト周囲径増加		
	10020710	過食	10027433	代謝および栄養障害
	10021654	食欲亢進		
	10029883	肥満		
	10033307	過体重		
	10049040	体重変動		
	10049084	体重減少不良		
	10052066	代謝症候群		
	10055164	体脂肪異常		
	10056465	食物渇望		
	10058097	代謝障害		
	10060961	食欲障害		
	10061832	摂食障害症状		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10065941	中心性肥満		
	10004716	気晴らし食い	10037175	精神障害
	10014062	摂食障害		
	10068007	強迫的ためこみ		
	10050300	体重管理	10042613	外科および内科処置
血中プロラクチン値増加関連	10020737	高プロラクチン血症	10014698	内分泌障害
	10005777	血中プロラクチン	10022891	臨床検査
	10005778	血中プロラクチン異常		
	10005780	血中プロラクチン増加		
	10036831	プロラクチン産生性下垂体腫瘍	10029104	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）
	10002652	無オルガズム症	10037175	精神障害
	10024419	リビドー減退		
	10024870	リビドー消失		
	10031085	オルガズム異常		
	10052449	オルガズム感減少		
	10061221	リビドー障害		
	10001928	無月経	10038604	生殖系および乳房障害
	10006223	乳房分泌		
	10006242	乳房腫大		
	10006298	乳房痛		
	10006313	乳房圧痛		
	10014326	射精障害		
	10017600	乳汁漏出症		
	10018800	女性化乳房		
	10027339	不規則月経		
	10027514	不正子宮出血		
	10030295	希発月経		

注目すべき有害事象	MedDRA/J PT		MedDRA/J SOC	
	10040477	性機能不全		
	10057671	女性性機能不全		
	10057672	男性性機能不全		
	10061461	勃起不全		
	10063928	乳汁漏出無月経症候群		
QTc間隔延長及び催不整脈作用関連	10007515	心停止	10007541	心臓障害
	10007617	心肺停止		
	10024803	ＱＴ延長症候群		
	10044066	トルサード　ド　ポアント		
	10047281	心室性不整脈		
	10047290	心室細動		
	10047294	心室粗動		
	10047302	心室性頻脈		
	10061592	心細動		
	10065341	心室性頻脈性不整脈		
	10057926	先天性ＱＴ延長症候群	10010331	先天性、家族性および遺伝性障害
	10042434	突然死	10018065	一般・全身障害および投与部位の状態
	10049418	心突然死		
	10049993	心臓死		
	10014387	心電図ＱＴ延長	10022891	臨床検査
	10052464	心電図再分極異常		
	10055032	心電図Ｕ波異常		
	10063748	心電図ＱＴ間隔異常		
	10024855	意識消失	10029205	神経系障害
	10039906	痙攣発作		
	10042772	失神		

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表2.7.4.7-2　治験薬の貼付期間（20試験・二重盲検治療期）
Safety Population

	PLCB (N = 190)	40MG (N = 196)	80MG (N = 194)	Active (N = 390)	Overall (N = 580)
Duration of exposure (days)					
n	190	196	194	390	580
Mean (SD)	34.1 (13.29)	35.0 (12.56)	37.4 (10.37)	36.2 (11.58)	35.5 (12.19)
Median	41.0	41.0	42.0	42.0	42.0
Min, Max	1, 43	1, 46	1, 44	1, 46	1, 46
Duration of exposure (days), n (%)					
1 to 7	17 (8.9)	17 (8.7)	11 (5.7)	28 (7.2)	45 (7.8)
8 to 14	18 (9.5)	11 (5.6)	8 (4.1)	19 (4.9)	37 (6.4)
15 to 21	6 (3.2)	7 (3.6)	2 (1.0)	9 (2.3)	15 (2.6)
22 to 28	5 (2.6)	6 (3.1)	4 (2.1)	10 (2.6)	15 (2.6)
29 to 35	4 (2.1)	5 (2.6)	4 (2.1)	9 (2.3)	13 (2.2)
36 or more	140 (73.7)	150 (76.5)	165 (85.1)	315 (80.8)	455 (78.4)

Duration of exposure = last dose date – first dose date + 1, during the double-blind treatment phase. Duration will not be calculated if either date is missing.
Control No:<<t14-01-10-02-ex.sas, 2018-02-05T10:56:46>>

表2.7.4.7-3　ロナセンテープ貼付期間（20試験・ロナセンテープ貼付期、Open-24週）
DSP-5423P Dosed Population

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
Duration of exposure (days)					
n	131	196	194	390	521
Mean (SD)	133.0 (55.42)	130.0 (84.64)	149.3 (78.96)	139.6 (82.33)	137.9 (76.46)
Median	167.0	170.0	205.0	203.0	168.0
Min, Max	2, 175	1, 217	1, 219	1, 219	1, 219
Duration of exposure (weeks), n (%)					
1 to 6	16 (12.2)	53 (27.0)	37 (19.1)	90 (23.1)	106 (20.3)
7 to 12	13 (9.9)	25 (12.8)	19 (9.8)	44 (11.3)	57 (10.9)
13 to 24	71 (54.2)	20 (10.2)	20 (10.3)	40 (10.3)	111 (21.3)
25 to 36	31 (23.7)	98 (50.0)	118 (60.8)	216 (55.4)	247 (47.4)
37 to 48	0	0	0	0	0
49 or more	0	0	0	0	0
Mean daily dose (mg/day)					
n	131	196	194	390	521
Mean (SD)	61.9 (14.35)	51.1 (12.22)	69.9 (10.99)	60.4 (14.95)	60.8 (14.80)
Median	65.2	45.3	75.2	63.3	63.5
Min, Max	40, 78	40, 71	47, 80	40, 80	40, 80
Maximum daily dose, n (%)					
n	131	196	194	390	521
40 mg	24 (18.3)	87 (44.4)	0	87 (22.3)	111 (21.3)
60 mg	26 (19.8)	32 (16.3)	0	32 (8.2)	58 (11.1)
80 mg	81 (61.8)	77 (39.3)	194 (100.0)	271 (69.5)	352 (67.6)
Modal daily dose, n (%)					

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
n	131	196	194	390	521
40 mg	37 (28.2)	120 (61.2)	36 (18.6)	156 (40.0)	193 (37.0)
60 mg	27 (20.6)	20 (10.2)	21 (10.8)	41 (10.5)	68 (13.1)
80 mg	67 (51.1)	56 (28.6)	137 (70.6)	193 (49.5)	260 (49.9)
Last daily dose (mg/day)					
n	131	196	194	390	521
Mean (SD)	67.0 (16.44)	58.3 (18.31)	68.6 (16.13)	63.4 (17.99)	64.3 (17.67)
Median	80.0	60.0	80.0	80.0	80.0
Min, Max	40, 80	40, 80	40, 80	40, 80	40, 80
Last daily dose, n (%)					
40 mg	29 (22.1)	91 (46.4)	39 (20.1)	130 (33.3)	159 (30.5)
60 mg	27 (20.6)	31 (15.8)	33 (17.0)	64 (16.4)	91 (17.5)
80 mg	75 (57.3)	74 (37.8)	122 (62.9)	196 (50.3)	271 (52.0)
Cumulative dose (mg)					
n	131	196	194	390	521
Mean (SD)	8308.2 (4037.38)	7278.1 (5390.48)	10051.8 (5486.69)	8657.8 (5606.25)	8569.9 (5254.55)
Median	8540.0	8340.0	10750.0	9590.0	9280.0
Min, Max	80, 13620	40, 15120	80, 16820	40, 16820	40, 16820

Duration of exposure = last dose date – first dose date + 1, during the DSP-5423P treatment period. Duration will not be calculated if either date is missing. Modal daily dose is the most frequently prescribed daily dose during the DSP-5423P treatment period. In the case that two or more dose are the most frequent dose, the maximum of them will be the modal daily dose. Note that for the DSP-5423P treatment period, and subjects who take placebo in the double-blind treatment phase, initial application date will be a one that DSP-5423P is initially applied. The data cut-off at Open-Week 24 was used.

Control No:<<t14-01-10-04-ex.sas, 2018-06-07T13:06:56>>

表2.7.4.7-4　人口統計学的特性及びその他の特性（20試験・ロナセンテープ貼付期、Open-24週）
DSP-5423P Dosed Population

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
Sex, n (%)					
n	131	196	194	390	521
Male	85 (64.9)	116 (59.2)	115 (59.3)	231 (59.2)	316 (60.7)
Female	46 (35.1)	80 (40.8)	79 (40.7)	159 (40.8)	205 (39.3)
Age (years)					
n	131	196	194	390	521
Mean (SD)	41.7 (13.10)	40.7 (13.34)	40.6 (14.31)	40.6 (13.81)	40.9 (13.63)
Median	41.0	40.0	38.0	39.0	39.0
Min, Max	18, 73	18, 79	18, 81	18, 81	18, 81
Age (years), n (%)					
n	131	196	194	390	521
<65	123 (93.9)	185 (94.4)	182 (93.8)	367 (94.1)	490 (94.0)
>=65	8 (6.1)	11 (5.6)	12 (6.2)	23 (5.9)	31 (6.0)
Race, n (%)					
n	131	196	194	390	521
Asian	108 (82.4)	167 (85.2)	167 (86.1)	334 (85.6)	442 (84.8)
White	23 (17.6)	29 (14.8)	27 (13.9)	56 (14.4)	79 (15.2)
Ethnicity, n (%)					
n	131	196	194	390	521
Not Hispanic or Latino	131 (100.0)	196 (100.0)	194 (100.0)	390 (100.0)	521 (100.0)
Country, n (%)					
n	131	196	194	390	521

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
Japan	27 (20.6)	55 (28.1)	57 (29.4)	112 (28.7)	139 (26.7)
China	8 (6.1)	9 (4.6)	10 (5.2)	19 (4.9)	27 (5.2)
Korea	3 (2.3)	7 (3.6)	7 (3.6)	14 (3.6)	17 (3.3)
Malaysia	43 (32.8)	58 (29.6)	54 (27.8)	112 (28.7)	155 (29.8)
Philippines	22 (16.8)	22 (11.2)	22 (11.3)	44 (11.3)	66 (12.7)
Russia	10 (7.6)	13 (6.6)	12 (6.2)	25 (6.4)	35 (6.7)
Taiwan	5 (3.8)	15 (7.7)	17 (8.8)	32 (8.2)	37 (7.1)
Ukraine	13 (9.9)	17 (8.7)	15 (7.7)	32 (8.2)	45 (8.6)
Height (cm)					
n	131	196	194	390	521
Mean (SD)	164.35 (10.312)	163.55 (9.455)	163.43 (9.555)	163.49 (9.492)	163.70 (9.702)
Median	164.00	164.00	164.15	164.00	164.00
Min, Max	137.0, 200.0	125.0, 185.0	130.5, 183.0	125.0, 185.0	125.0, 200.0
Weight (kg)					
n	131	196	194	390	521
Mean (SD)	66.06 (17.065)	63.09 (14.656)	62.69 (14.547)	62.89 (14.585)	63.69 (15.291)
Median	62.70	59.85	60.65	60.00	60.80
Min, Max	39.6, 149.8	35.8, 118.0	27.9, 118.7	27.9, 118.7	27.9, 149.8
BMI (kg/m^2)					
n	131	196	194	390	521
Mean (SD)	24.36 (5.248)	23.56 (5.036)	23.39 (4.792)	23.48 (4.911)	23.70 (5.007)
Median	23.18	22.60	22.51	22.54	22.77
Min, Max	16.9, 44.2	14.5, 46.8	13.6, 45.8	13.6, 46.8	13.6, 46.8
Any concomitant diseases, n (%)					
n	131	196	194	390	521
Yes	66 (50.4)	112 (57.1)	112 (57.7)	224 (57.4)	290 (55.7)

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
No	65 (49.6)	84 (42.9)	82 (42.3)	166 (42.6)	231 (44.3)
Hospitalization status at informed consent, n (%)					
n	131	196	194	390	521
Inpatient	127 (96.9)	188 (95.9)	189 (97.4)	377 (96.7)	504 (96.7)
Within 3 months (90 days)	118 (90.1)	168 (85.7)	174 (89.7)	342 (87.7)	460 (88.3)
Over 3 months	8 (6.1)	20 (10.2)	15 (7.7)	35 (9.0)	43 (8.3)
Unknown	1 (0.8)	0	0	0	1 (0.2)
Outpatient	4 (3.1)	8 (4.1)	5 (2.6)	13 (3.3)	17 (3.3)

The denominator of percentages is the number of subjects in analysis population. The data cut-off at Open-Week 24 was used.
Control No:<<t14-01-04-06-dm.sas, 2018-06-07T13:05:15>>

表2.7.4.7-5　疾患データ（20試験・ロナセンテープ貼付期、Open-24週）
DSP-5423P Dosed Population

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
Number of episodes of schizophrenia					
n	128	178	184	362	490
Mean (SD)	3.7 (1.36)	3.7 (1.33)	3.8 (1.37)	3.7 (1.35)	3.7 (1.35)
Median	4.0	4.0	4.0	4.0	4.0
Min, Max	1, 5	1, 5	1, 5	1, 5	1, 5
Number of episodes of schizophrenia, n (%)					
n	131	196	194	390	521
1	6 (4.6)	8 (4.1)	10 (5.2)	18 (4.6)	24 (4.6)
2	27 (20.6)	38 (19.4)	37 (19.1)	75 (19.2)	102 (19.6)
3	23 (17.6)	35 (17.9)	24 (12.4)	59 (15.1)	82 (15.7)
4	12 (9.2)	23 (11.7)	22 (11.3)	45 (11.5)	57 (10.9)
5 or more	60 (45.8)	74 (37.8)	91 (46.9)	165 (42.3)	225 (43.2)
Unknown	3 (2.3)	18 (9.2)	10 (5.2)	28 (7.2)	31 (6.0)
Age at the first onset of schizophrenia (years)					
n	129	192	191	383	512
Mean (SD)	26.9 (9.02)	26.8 (9.49)	26.5 (9.60)	26.7 (9.53)	26.7 (9.40)
Median	26.0	24.0	24.0	24.0	25.0
Min, Max	6, 58	8, 67	8, 60	8, 67	6, 67
Age at the first onset of schizophrenia (years), n (%)					
n	131	196	194	390	521
19 or less	25 (19.1)	38 (19.4)	40 (20.6)	78 (20.0)	103 (19.8)
20 to 29	58 (44.3)	94 (48.0)	97 (50.0)	191 (49.0)	249 (47.8)
30 to 39	35 (26.7)	41 (20.9)	34 (17.5)	75 (19.2)	110 (21.1)
40 to 49	10 (7.6)	13 (6.6)	13 (6.7)	26 (6.7)	36 (6.9)

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
50 or more	1 (0.8)	6 (3.1)	7 (3.6)	13 (3.3)	14 (2.7)
Unknown	2 (1.5)	4 (2.0)	3 (1.5)	7 (1.8)	9 (1.7)
Duration of illness (years)					
n	129	192	191	383	512
Mean (SD)	14.76 (12.287)	13.79 (11.196)	13.78 (12.197)	13.78 (11.691)	14.03 (11.839)
Median	11.35	11.05	9.71	10.66	10.80
Min, Max	0.1, 47.8	0.0, 55.2	0.0, 50.6	0.0, 55.2	0.0, 55.2
Duration of illness (years), n (%)					
n	131	196	194	390	521
<1	11 (8.4)	11 (5.6)	11 (5.7)	22 (5.6)	33 (6.3)
>=1 to <5	20 (15.3)	38 (19.4)	44 (22.7)	82 (21.0)	102 (19.6)
>=5 to <10	25 (19.1)	38 (19.4)	42 (21.6)	80 (20.5)	105 (20.2)
>=10 to <20	37 (28.2)	57 (29.1)	45 (23.2)	102 (26.2)	139 (26.7)
>=20 to <30	20 (15.3)	31 (15.8)	30 (15.5)	61 (15.6)	81 (15.5)
>=30	16 (12.2)	17 (8.7)	19 (9.8)	36 (9.2)	52 (10.0)
Unknown	2 (1.5)	4 (2.0)	3 (1.5)	7 (1.8)	9 (1.7)
Duration of current episode (months)					
n	131	196	194	390	521
Mean (SD)	3.69 (26.544)	3.71 (25.866)	3.84 (32.103)	3.77 (29.098)	3.75 (28.453)
Median	1.22	1.10	1.17	1.13	1.15
Min, Max	0.1, 304.8	0.0, 348.9	0.2, 447.0	0.0, 447.0	0.0, 447.0
Baseline PANSS total score					
n	131	196	194	390	521
Mean (SD)	99.6 (13.67)	101.6 (15.55)	101.5 (14.69)	101.6 (15.11)	101.1 (14.77)
Median	96.0	99.0	99.0	99.0	99.0
Min, Max	80, 141	80, 157	80, 168	80, 168	80, 168

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
PANSS composite subscale at baseline, n (%)					
n	131	196	194	390	521
Positive subscale score>Negative subscale score	64 (48.9)	104 (53.1)	85 (43.8)	189 (48.5)	253 (48.6)
Positive subscale score=Negative subscale score	8 (6.1)	11 (5.6)	11 (5.7)	22 (5.6)	30 (5.8)
Positive subscale score<Negative subscale score	59 (45.0)	81 (41.3)	98 (50.5)	179 (45.9)	238 (45.7)
Baseline PANSS total score, n (%)					
n	131	196	194	390	521
<100	73 (55.7)	105 (53.6)	99 (51.0)	204 (52.3)	277 (53.2)
>=100 to <120	48 (36.6)	63 (32.1)	75 (38.7)	138 (35.4)	186 (35.7)
>=120	10 (7.6)	28 (14.3)	20 (10.3)	48 (12.3)	58 (11.1)
Baseline CGI-S score					
n	131	196	194	390	521
Mean (SD)	4.79 (0.713)	4.84 (0.780)	4.92 (0.734)	4.88 (0.758)	4.86 (0.747)
Median	5.00	5.00	5.00	5.00	5.00
Min, Max	4, 7	3, 7	3, 7	3, 7	3, 7
Baseline CGI-S score, n (%)					
n	131	196	194	390	521
1	0	0	0	0	0
2	0	0	0	0	0
3	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
4	49 (37.4)	70 (35.7)	54 (27.8)	124 (31.8)	173 (33.2)
5	62 (47.3)	84 (42.9)	101 (52.1)	185 (47.4)	247 (47.4)
6	19 (14.5)	38 (19.4)	35 (18.0)	73 (18.7)	92 (17.7)
7	1 (0.8)	2 (1.0)	3 (1.5)	5 (1.3)	6 (1.2)
Baseline DIEPSS total score (excluding overall severity)					

	PLCB-to-FLEX DOSE (N = 131)	40MG-to-FLEX DOSE (N = 196)	80MG-to-FLEX DOSE (N = 194)	Active-to-FLEX DOSE (N = 390)	Overall-to-FLEX DOSE (N = 521)
n	131	196	193	389	520
Mean (SD)	1.0 (2.60)	0.8 (2.25)	1.0 (2.42)	0.9 (2.34)	0.9 (2.40)
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 16	0, 14	0, 14	0, 14	0, 16

The denominator of percentages is the number of subjects in analysis population. Duration of illness is years from the initial episode of schizophrenia to the informed consent. Duration of current episode is months from the onset of current episode to the informed consent. In regard to 'Number of episodes of schizophrenia', a category '5 or more' is set to 5 for descriptive purpose. The data cut-off at Open-Week 24 was used.

Control No:<<t14-01-05-06-ph.sas, 2018-06-07T13:05:30>>

表2.7.4.7-6　主な有害事象の副作用発現割合（20試験・二重盲検治療期）
Safety Population

System Organ Class Preferred Term	PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)
Subjects with any treatment-related TEAE	58 (30.5)	69 (35.2)	82 (42.3)	151 (38.7)
胃腸障害				
便秘	1 (0.5)	3 (1.5)	4 (2.1)	7 (1.8)
流涎過多	1 (0.5)	0	4 (2.1)	4 (1.0)
下痢	0	0	1 (0.5)	1 (0.3)
歯痛	0	1 (0.5)	0	1 (0.3)
一般・全身障害および投与部位の状態				
適用部位紅斑	2 (1.1)	9 (4.6)	17 (8.8)	26 (6.7)
適用部位そう痒感	1 (0.5)	10 (5.1)	14 (7.2)	24 (6.2)
適用部位皮膚炎	1 (0.5)	4 (2.0)	2 (1.0)	6 (1.5)
歩行障害	1 (0.5)	1 (0.5)	4 (2.1)	5 (1.3)
感染症および寄生虫症				
鼻咽頭炎	1 (0.5)	0	0	0
上気道感染	0	0	0	0
筋骨格系および結合組織障害				
筋固縮	0	3 (1.5)	6 (3.1)	9 (2.3)
神経系障害				
アカシジア	2 (1.1)	11 (5.6)	18 (9.3)	29 (7.4)
振戦	3 (1.6)	6 (3.1)	15 (7.7)	21 (5.4)
運動緩慢	0	1 (0.5)	6 (3.1)	7 (1.8)

System Organ Class Preferred Term	PLCB (N = 190) n (%)	40MG (N = 196) n (%)	80MG (N = 194) n (%)	Active (N = 390) n (%)
頭痛	1 (0.5)	5 (2.6)	1 (0.5)	6 (1.5)
ジスキネジア	2 (1.1)	1 (0.5)	4 (2.1)	5 (1.3)
精神障害				
統合失調症	2 (1.1)	5 (2.6)	2 (1.0)	7 (1.8)
不眠症	3 (1.6)	2 (1.0)	3 (1.5)	5 (1.3)
精神病性障害	3 (1.6)	5 (2.6)	0	5 (1.3)
激越	2 (1.1)	1 (0.5)	3 (1.5)	4 (1.0)
不安	1 (0.5)	0	3 (1.5)	3 (0.8)
呼吸器、胸郭および縦隔障害				
咳嗽	0	0	0	0
皮膚および皮下組織障害				
そう痒症	0	0	1 (0.5)	1 (0.3)

Treatment emergent adverse events (TEAE) in the double-blind treatment phase are defined as events with start date on or after the initial application date of double-blind treatment phase, and up to 17 days after the date of final application of the double-blind treatment phase and before the first application of DSP-5423P in the open-label treatment phase. TEAEs are coded by MedDRA version 19.1. If a subject experienced more than one episode of TEAE within a preferred term (PT) or a system organ class (SOC), the subject is counted only once in the PT or the SOC. The denominator of percentages is the number of subjects in the safety population. Treatment-related TEAE is TEAE with causality of definite, probably related, and possibly related.

Control No:<<t50-aesocpt-related-d20s.sas, 2018-06-07T16:28:19>>

表2.7.4.7-7　主な有害事象の副作用発現割合（20試験・ロナセンテープ貼付期、Open-24週）

20試験 DSP-5423P Dosed Population

System Organ Class Preferred Term	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Subjects with any treatment-related TEAE	72 (55.0)	111 (56.6)	122 (62.9)	233 (59.7)	305 (58.5)
内分泌障害	3 (2.3)	5 (2.6)	4 (2.1)	9 (2.3)	12 (2.3)
高プロラクチン血症	3 (2.3)	5 (2.6)	4 (2.1)	9 (2.3)	12 (2.3)
胃腸障害	9 (6.9)	13 (6.6)	28 (14.4)	41 (10.5)	50 (9.6)
流涎過多	3 (2.3)	5 (2.6)	10 (5.2)	15 (3.8)	18 (3.5)
便秘	3 (2.3)	3 (1.5)	9 (4.6)	12 (3.1)	15 (2.9)
下痢	0	0	3 (1.5)	3 (0.8)	3 (0.6)
歯痛	0	1 (0.5)	0	1 (0.3)	1 (0.2)
一般・全身障害および投与部位の状態	17 (13.0)	35 (17.9)	58 (29.9)	93 (23.8)	110 (21.1)
適用部位紅斑	8 (6.1)	10 (5.1)	21 (10.8)	31 (7.9)	39 (7.5)
適用部位そう痒感	4 (3.1)	12 (6.1)	19 (9.8)	31 (7.9)	35 (6.7)
適用部位皮膚炎	1 (0.8)	4 (2.0)	6 (3.1)	10 (2.6)	11 (2.1)
感染症および寄生虫症	1 (0.8)	4 (2.0)	2 (1.0)	6 (1.5)	7 (1.3)
上気道感染	0	2 (1.0)	0	2 (0.5)	2 (0.4)
鼻咽頭炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
臨床検査	22 (16.8)	26 (13.3)	27 (13.9)	53 (13.6)	75 (14.4)
体重増加	13 (9.9)	10 (5.1)	10 (5.2)	20 (5.1)	33 (6.3)
血中プロラクチン増加	3 (2.3)	5 (2.6)	7 (3.6)	12 (3.1)	15 (2.9)
アラニンアミノトランスフェラーゼ増加	2 (1.5)	3 (1.5)	6 (3.1)	9 (2.3)	11 (2.1)

System Organ Class Preferred Term	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
体重減少	2 (1.5)	3 (1.5)	2 (1.0)	5 (1.3)	7 (1.3)
血中クレアチンホスホキナーゼ増加	1 (0.8)	4 (2.0)	1 (0.5)	5 (1.3)	6 (1.2)
筋骨格系および結合組織障害	4 (3.1)	8 (4.1)	11 (5.7)	19 (4.9)	23 (4.4)
筋固縮	4 (3.1)	4 (2.0)	10 (5.2)	14 (3.6)	18 (3.5)
神経系障害	27 (20.6)	44 (22.4)	57 (29.4)	101 (25.9)	128 (24.6)
アカシジア	11 (8.4)	22 (11.2)	24 (12.4)	46 (11.8)	57 (10.9)
振戦	7 (5.3)	11 (5.6)	24 (12.4)	35 (9.0)	42 (8.1)
運動緩慢	1 (0.8)	6 (3.1)	11 (5.7)	17 (4.4)	18 (3.5)
頭痛	4 (3.1)	6 (3.1)	5 (2.6)	11 (2.8)	15 (2.9)
ジスキネジア	2 (1.5)	4 (2.0)	7 (3.6)	11 (2.8)	13 (2.5)
傾眠	2 (1.5)	5 (2.6)	3 (1.5)	8 (2.1)	10 (1.9)
浮動性めまい	2 (1.5)	5 (2.6)	2 (1.0)	7 (1.8)	9 (1.7)
精神障害	13 (9.9)	30 (15.3)	27 (13.9)	57 (14.6)	70 (13.4)
不眠症	1 (0.8)	8 (4.1)	8 (4.1)	16 (4.1)	17 (3.3)
統合失調症	3 (2.3)	9 (4.6)	4 (2.1)	13 (3.3)	16 (3.1)
精神病性障害	3 (2.3)	6 (3.1)	0	6 (1.5)	9 (1.7)
激越	0	2 (1.0)	5 (2.6)	7 (1.8)	7 (1.3)
不安	0	2 (1.0)	3 (1.5)	5 (1.3)	5 (1.0)
呼吸器、胸郭および縦隔障害					
咳嗽	0	0	0	0	0
血管障害	5 (3.8)	2 (1.0)	3 (1.5)	5 (1.3)	10 (1.9)

System Organ Class Preferred Term	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
高血圧	4 (3.1)	1 (0.5)	3 (1.5)	4 (1.0)	8 (1.5)

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. TEAEs are coded by MedDRA version 19.1. If a subject experienced more than one episode of TEAE within a preferred term (PT) or a system organ class (SOC), the subject is counted only once in the PT or the SOC. The denominator of percentages is the number of subjects in the DSP-5423P dosed population. Treatment-related TEAE is TEAE with causality of definite, probably related, and possibly related. The data cut-off at Open-Week 24 was used.

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表2.7.4.7-8　重症度別有害事象の発現割合（20試験・ロナセンテープ貼付期、Open-24週）
DSP-5423P Dosed Population

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Subjects with any TEAE	94 (71.8)	160 (81.6)	163 (84.0)	323 (82.8)	417 (80.0)
Mild	48 (36.6)	87 (44.4)	89 (45.9)	176 (45.1)	224 (43.0)
Moderate	39 (29.8)	61 (31.1)	58 (29.9)	119 (30.5)	158 (30.3)
Severe	7 (5.3)	12 (6.1)	16 (8.2)	28 (7.2)	35 (6.7)
血液およびリンパ系障害	0	4 (2.0)	1 (0.5)	5 (1.3)	5 (1.0)
貧血	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
欠乏性貧血	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
好酸球増加症	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
鉄欠乏性貧血	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
白血球増加症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
白血球減少症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心臓障害	4 (3.1)	6 (3.1)	5 (2.6)	11 (2.8)	15 (2.9)
徐脈	2 (1.5)	1 (0.5)	1 (0.5)	2 (0.5)	4 (0.8)
Mild	2 (1.5)	1 (0.5)	1 (0.5)	2 (0.5)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
洞性徐脈	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
動悸	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
頻脈	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
急性心筋梗塞	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
第二度房室ブロック	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
右脚ブロック	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心室内伝導障害	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心筋虚血	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
耳および迷路障害	0	2 (1.0)	0	2 (0.5)	2 (0.4)
耳垢栓塞	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
乗物酔い	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
内分泌障害	3 (2.3)	6 (3.1)	4 (2.1)	10 (2.6)	13 (2.5)
高プロラクチン血症	3 (2.3)	6 (3.1)	4 (2.1)	10 (2.6)	13 (2.5)
Mild	3 (2.3)	6 (3.1)	3 (1.5)	9 (2.3)	12 (2.3)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
眼障害	4 (3.1)	8 (4.1)	8 (4.1)	16 (4.1)	20 (3.8)
眼乾燥	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Mild	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
白内障	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
眼球回転発作	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
眼瞼炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
結膜出血	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
結膜充血	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
アレルギー性結膜炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
複視	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
眼脂	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
眼部腫脹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
眼瞼浮腫	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
遠視	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
涙液分泌低下	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
流涙増加	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
近視	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
眼充血	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
霧視	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
胃腸障害	20 (15.3)	37 (18.9)	52 (26.8)	89 (22.8)	109 (20.9)
便秘	6 (4.6)	8 (4.1)	13 (6.7)	21 (5.4)	27 (5.2)
Mild	6 (4.6)	8 (4.1)	13 (6.7)	21 (5.4)	27 (5.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
流涎過多	3 (2.3)	5 (2.6)	10 (5.2)	15 (3.8)	18 (3.5)
Mild	3 (2.3)	4 (2.0)	9 (4.6)	13 (3.3)	16 (3.1)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
歯痛	3 (2.3)	6 (3.1)	5 (2.6)	11 (2.8)	14 (2.7)
Mild	3 (2.3)	6 (3.1)	5 (2.6)	11 (2.8)	14 (2.7)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
下痢	1 (0.8)	2 (1.0)	9 (4.6)	11 (2.8)	12 (2.3)
Mild	1 (0.8)	1 (0.5)	9 (4.6)	10 (2.6)	11 (2.1)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
悪心	1 (0.8)	5 (2.6)	4 (2.1)	9 (2.3)	10 (1.9)
Mild	1 (0.8)	5 (2.6)	3 (1.5)	8 (2.1)	9 (1.7)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
齲歯	4 (3.1)	3 (1.5)	1 (0.5)	4 (1.0)	8 (1.5)
Mild	4 (3.1)	2 (1.0)	1 (0.5)	3 (0.8)	7 (1.3)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
嘔吐	0	4 (2.0)	4 (2.1)	8 (2.1)	8 (1.5)
Mild	0	3 (1.5)	4 (2.1)	7 (1.8)	7 (1.3)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
胃炎	3 (2.3)	1 (0.5)	3 (1.5)	4 (1.0)	7 (1.3)
Mild	3 (2.3)	1 (0.5)	3 (1.5)	4 (1.0)	7 (1.3)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
腹痛	1 (0.8)	1 (0.5)	3 (1.5)	4 (1.0)	5 (1.0)
Mild	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
上腹部痛	2 (1.5)	2 (1.0)	1 (0.5)	3 (0.8)	5 (1.0)
Mild	2 (1.5)	2 (1.0)	1 (0.5)	3 (0.8)	5 (1.0)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
腹部不快感	1 (0.8)	2 (1.0)	0	2 (0.5)	3 (0.6)
Mild	1 (0.8)	2 (1.0)	0	2 (0.5)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
消化不良	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
腹部膨満	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
裂肛	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
慢性胃炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
大腸炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
口内乾燥	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
嚥下障害	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
胃食道逆流性疾患	0	0	1 (0.5)	1 (0.3)	1 (0.2)

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Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血便排泄	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
痔核	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口唇出血	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口腔内潰瘍形成	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口腔内不快感	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
舌突出	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口内炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
舌障害	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
上部消化管出血	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
一般・全身障害および投与部位の状態	19 (14.5)	44 (22.4)	64 (33.0)	108 (27.7)	127 (24.4)
適用部位紅斑	8 (6.1)	12 (6.1)	22 (11.3)	34 (8.7)	42 (8.1)
Mild	8 (6.1)	10 (5.1)	19 (9.8)	29 (7.4)	37 (7.1)
Moderate	0	2 (1.0)	3 (1.5)	5 (1.3)	5 (1.0)
Severe	0	0	0	0	0
適用部位そう痒感	4 (3.1)	12 (6.1)	19 (9.8)	31 (7.9)	35 (6.7)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	3 (2.3)	12 (6.1)	17 (8.8)	29 (7.4)	32 (6.1)
Moderate	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Severe	0	0	0	0	0
適用部位皮膚炎	1 (0.8)	4 (2.0)	6 (3.1)	10 (2.6)	11 (2.1)
Mild	0	4 (2.0)	5 (2.6)	9 (2.3)	9 (1.7)
Moderate	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Severe	0	0	0	0	0
無力症	0	6 (3.1)	3 (1.5)	9 (2.3)	9 (1.7)
Mild	0	6 (3.1)	2 (1.0)	8 (2.1)	8 (1.5)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
歩行障害	1 (0.8)	2 (1.0)	6 (3.1)	8 (2.1)	9 (1.7)
Mild	1 (0.8)	1 (0.5)	3 (1.5)	4 (1.0)	5 (1.0)
Moderate	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Severe	0	0	0	0	0
発熱	2 (1.5)	3 (1.5)	4 (2.1)	7 (1.8)	9 (1.7)
Mild	2 (1.5)	2 (1.0)	4 (2.1)	6 (1.5)	8 (1.5)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
適用部位刺激感	1 (0.8)	2 (1.0)	2 (1.0)	4 (1.0)	5 (1.0)
Mild	1 (0.8)	2 (1.0)	2 (1.0)	4 (1.0)	5 (1.0)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

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倦怠感	0	2 (1.0)	3 (1.5)	5 (1.3)	5 (1.0)
Mild	0	2 (1.0)	2 (1.0)	4 (1.0)	4 (0.8)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
適用部位湿疹	1 (0.8)	1 (0.5)	2 (1.0)	3 (0.8)	4 (0.8)
Mild	1 (0.8)	1 (0.5)	2 (1.0)	3 (0.8)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
胸部不快感	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位びらん	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位発疹	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位小水疱	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)

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Moderate	0	0	0	0	0
Severe	0	0	0	0	0
非心臓性胸痛	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
末梢性浮腫	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位ざ瘡	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位変色	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位乾燥	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

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適用部位丘疹	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位反応	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
死亡	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
疲労	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
熱感	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
浮腫	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
疼痛	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
末梢腫脹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
肝胆道系障害	4 (3.1)	5 (2.6)	0	5 (1.3)	9 (1.7)
肝機能異常	2 (1.5)	2 (1.0)	0	2 (0.5)	4 (0.8)
Mild	2 (1.5)	1 (0.5)	0	1 (0.3)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	1 (0.5)	0	1 (0.3)	1 (0.2)
慢性胆嚢炎	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
肝障害	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	1 (0.5)	0	1 (0.3)	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
脂肪肝	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
免疫系障害	0	0	2 (1.0)	2 (0.5)	2 (0.4)
食物アレルギー	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
季節性アレルギー	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
感染症および寄生虫症	28 (21.4)	47 (24.0)	47 (24.2)	94 (24.1)	122 (23.4)
鼻咽頭炎	8 (6.1)	13 (6.6)	22 (11.3)	35 (9.0)	43 (8.3)
Mild	6 (4.6)	11 (5.6)	18 (9.3)	29 (7.4)	35 (6.7)
Moderate	2 (1.5)	2 (1.0)	4 (2.1)	6 (1.5)	8 (1.5)
Severe	0	0	0	0	0
上気道感染	6 (4.6)	11 (5.6)	5 (2.6)	16 (4.1)	22 (4.2)
Mild	6 (4.6)	11 (5.6)	4 (2.1)	15 (3.8)	21 (4.0)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
結膜炎	1 (0.8)	3 (1.5)	2 (1.0)	5 (1.3)	6 (1.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	1 (0.8)	3 (1.5)	1 (0.5)	4 (1.0)	5 (1.0)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
インフルエンザ	0	3 (1.5)	3 (1.5)	6 (1.5)	6 (1.2)
Mild	0	3 (1.5)	3 (1.5)	6 (1.5)	6 (1.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
ウイルス性気道感染	2 (1.5)	2 (1.0)	0	2 (0.5)	4 (0.8)
Mild	2 (1.5)	2 (1.0)	0	2 (0.5)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
蜂巣炎	2 (1.5)	0	1 (0.5)	1 (0.3)	3 (0.6)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Severe	0	0	0	0	0
皮膚真菌感染	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
胃腸炎	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
咽頭炎	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Mild	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
肺炎	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
白癬感染	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
体部白癬	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
爪の皮膚糸状菌症	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
感染性湿疹	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)

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Moderate	0	0	0	0	0
Severe	0	0	0	0	0
せつ	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
感染性皮膚潰瘍	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
外耳炎	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
爪囲炎	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
鼻炎	2 (1.5)	0	0	0	2 (0.4)
Mild	2 (1.5)	0	0	0	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

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尿路感染	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
四肢膿瘍	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口腔膿瘍	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
適用部位膿瘍	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
適用部位感染	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
細菌感染	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)

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Severe	0	0	0	0	0
真菌感染	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
歯肉炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
B型肝炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
ヘルペス性皮膚炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
シラミ寄生	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口唇感染	0	0	1 (0.5)	1 (0.3)	1 (0.2)

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Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
中耳炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
耳下腺炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
歯周炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
咽頭扁桃炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
肺結核	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0

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膿疱性皮疹	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
卵管卵巣炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
副鼻腔炎	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
足部白癬	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
癜風	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
気管炎	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0

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Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
膣感染	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
水痘	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
外陰部膣カンジダ症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
ブドウ球菌性創感染	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
傷害、中毒および処置合併症	12 (9.2)	19 (9.7)	18 (9.3)	37 (9.5)	49 (9.4)
裂傷	3 (2.3)	5 (2.6)	2 (1.0)	7 (1.8)	10 (1.9)
Mild	3 (2.3)	3 (1.5)	2 (1.0)	5 (1.3)	8 (1.5)
Moderate	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0

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皮膚擦過傷	2 (1.5)	4 (2.0)	4 (2.1)	8 (2.1)	10 (1.9)
Mild	1 (0.8)	4 (2.0)	4 (2.1)	8 (2.1)	9 (1.7)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
挫傷	2 (1.5)	1 (0.5)	3 (1.5)	4 (1.0)	6 (1.2)
Mild	2 (1.5)	1 (0.5)	3 (1.5)	4 (1.0)	6 (1.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
擦過傷	2 (1.5)	0	2 (1.0)	2 (0.5)	4 (0.8)
Mild	2 (1.5)	0	2 (1.0)	2 (0.5)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
転倒	2 (1.5)	0	1 (0.5)	1 (0.3)	3 (0.6)
Mild	2 (1.5)	0	1 (0.5)	1 (0.3)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
軟部組織損傷	2 (1.5)	1 (0.5)	0	1 (0.3)	3 (0.6)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
各種物質毒性	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Mild	0	0	0	0	0

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Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	1 (0.8)	0	0	0	1 (0.2)
外傷性血腫	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
Mild	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
節足動物咬傷	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
靭帯捻挫	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
熱傷	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
足関節部骨折	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
節足動物刺傷	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
鎖骨骨折	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
粉砕骨折	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
耳擦過傷	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
経口曝露	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
顔面骨骨折	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
手骨折	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
頭部損傷	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
上腕骨骨折	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
四肢損傷	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口唇損傷	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
外傷後頚部症候群	0	1 (0.5)	0	1 (0.3)	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
肺挫傷	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
臨床検査	23 (17.6)	31 (15.8)	35 (18.0)	66 (16.9)	89 (17.1)
体重増加	15 (11.5)	10 (5.1)	12 (6.2)	22 (5.6)	37 (7.1)
Mild	10 (7.6)	8 (4.1)	9 (4.6)	17 (4.4)	27 (5.2)
Moderate	5 (3.8)	2 (1.0)	3 (1.5)	5 (1.3)	10 (1.9)
Severe	0	0	0	0	0
血中プロラクチン増加	3 (2.3)	5 (2.6)	7 (3.6)	12 (3.1)	15 (2.9)
Mild	3 (2.3)	5 (2.6)	7 (3.6)	12 (3.1)	15 (2.9)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
アラニンアミノトランスフェラーゼ増加	3 (2.3)	3 (1.5)	6 (3.1)	9 (2.3)	12 (2.3)
Mild	3 (2.3)	3 (1.5)	5 (2.6)	8 (2.1)	11 (2.1)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
血中クレアチンホスホキナーゼ増加	1 (0.8)	8 (4.1)	2 (1.0)	10 (2.6)	11 (2.1)
Mild	1 (0.8)	8 (4.1)	0	8 (2.1)	9 (1.7)
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
体重減少	2 (1.5)	7 (3.6)	2 (1.0)	9 (2.3)	11 (2.1)
Mild	1 (0.8)	7 (3.6)	2 (1.0)	9 (2.3)	10 (1.9)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
血中ブドウ糖増加	2 (1.5)	2 (1.0)	3 (1.5)	5 (1.3)	7 (1.3)
Mild	1 (0.8)	2 (1.0)	1 (0.5)	3 (0.8)	4 (0.8)
Moderate	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Severe	0	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	2 (1.5)	2 (1.0)	2 (1.0)	4 (1.0)	6 (1.2)
Mild	2 (1.5)	2 (1.0)	2 (1.0)	4 (1.0)	6 (1.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
γ－グルタミルトランスフェラーゼ増加	1 (0.8)	1 (0.5)	3 (1.5)	4 (1.0)	5 (1.0)
Mild	1 (0.8)	1 (0.5)	3 (1.5)	4 (1.0)	5 (1.0)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中コレステロール増加	1 (0.8)	3 (1.5)	0	3 (0.8)	4 (0.8)
Mild	1 (0.8)	3 (1.5)	0	3 (0.8)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中アルカリホスファターゼ増加	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中乳酸脱水素酵素増加	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血圧上昇	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中トリグリセリド増加	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
肝酵素上昇	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
尿中蛋白陽性	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
白血球数増加	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中ビリルビン増加	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中クレアチニン増加	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血中ブドウ糖異常	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
血中カリウム増加	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
拡張期血圧上昇	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
体温上昇	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心電図ＳＴ部分下降	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心電図Ｔ波振幅減少	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心電図Ｔ波増高	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
好酸球数増加	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
心拍数減少	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
リンパ球数増加	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
好中球数減少	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
好中球数増加	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血小板数減少	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
尿中ウロビリノーゲン増加	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
白血球数減少	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
代謝および栄養障害	6 (4.6)	13 (6.6)	12 (6.2)	25 (6.4)	31 (6.0)
食欲減退	1 (0.8)	5 (2.6)	2 (1.0)	7 (1.8)	8 (1.5)
Mild	1 (0.8)	5 (2.6)	2 (1.0)	7 (1.8)	8 (1.5)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
低カリウム血症	0	1 (0.5)	4 (2.1)	5 (1.3)	5 (1.0)
Mild	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
低ナトリウム血症	1 (0.8)	3 (1.5)	1 (0.5)	4 (1.0)	5 (1.0)
Mild	1 (0.8)	2 (1.0)	0	2 (0.5)	3 (0.6)
Moderate	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
高脂血症	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Mild	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
糖尿病	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
高コレステロール血症	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
食欲亢進	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
脱水	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
拒食	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
脂質異常症	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
高トリグリセリド血症	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
空腹時血中ブドウ糖不良	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
多飲症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
２型糖尿病	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
筋骨格系および結合組織障害	8 (6.1)	15 (7.7)	20 (10.3)	35 (9.0)	43 (8.3)
筋固縮	4 (3.1)	4 (2.0)	11 (5.7)	15 (3.8)	19 (3.6)
Mild	3 (2.3)	1 (0.5)	6 (3.1)	7 (1.8)	10 (1.9)
Moderate	1 (0.8)	3 (1.5)	5 (2.6)	8 (2.1)	9 (1.7)
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
筋肉痛	2 (1.5)	1 (0.5)	2 (1.0)	3 (0.8)	5 (1.0)
Mild	2 (1.5)	0	2 (1.0)	2 (0.5)	4 (0.8)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
背部痛	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Mild	0	1 (0.5)	3 (1.5)	4 (1.0)	4 (0.8)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
四肢痛	1 (0.8)	2 (1.0)	1 (0.5)	3 (0.8)	4 (0.8)
Mild	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
関節痛	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
筋骨格硬直	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
関節腫脹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
四肢不快感	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
筋痙縮	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
筋力低下	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
筋骨格系胸痛	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
頚部痛	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
骨減少症	1 (0.8)	0	0	0	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
骨膜炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
滑液嚢腫	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	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	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
脂肪腫	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
子宮平滑筋腫	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
神経系障害	29 (22.1)	50 (25.5)	70 (36.1)	120 (30.8)	149 (28.6)
アカシジア	11 (8.4)	22 (11.2)	27 (13.9)	49 (12.6)	60 (11.5)
Mild	7 (5.3)	18 (9.2)	20 (10.3)	38 (9.7)	45 (8.6)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	4 (3.1)	3 (1.5)	6 (3.1)	9 (2.3)	13 (2.5)
Severe	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
振戦	7 (5.3)	13 (6.6)	26 (13.4)	39 (10.0)	46 (8.8)
Mild	6 (4.6)	12 (6.1)	22 (11.3)	34 (8.7)	40 (7.7)
Moderate	1 (0.8)	1 (0.5)	4 (2.1)	5 (1.3)	6 (1.2)
Severe	0	0	0	0	0
頭痛	5 (3.8)	12 (6.1)	17 (8.8)	29 (7.4)	34 (6.5)
Mild	5 (3.8)	12 (6.1)	15 (7.7)	27 (6.9)	32 (6.1)
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
運動緩慢	1 (0.8)	6 (3.1)	11 (5.7)	17 (4.4)	18 (3.5)
Mild	1 (0.8)	5 (2.6)	7 (3.6)	12 (3.1)	13 (2.5)
Moderate	0	1 (0.5)	4 (2.1)	5 (1.3)	5 (1.0)
Severe	0	0	0	0	0
ジスキネジア	2 (1.5)	4 (2.0)	8 (4.1)	12 (3.1)	14 (2.7)
Mild	1 (0.8)	4 (2.0)	7 (3.6)	11 (2.8)	12 (2.3)
Moderate	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Severe	0	0	0	0	0
浮動性めまい	2 (1.5)	6 (3.1)	3 (1.5)	9 (2.3)	11 (2.1)
Mild	2 (1.5)	6 (3.1)	3 (1.5)	9 (2.3)	11 (2.1)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
傾眠	2 (1.5)	5 (2.6)	4 (2.1)	9 (2.3)	11 (2.1)
Mild	2 (1.5)	4 (2.0)	3 (1.5)	7 (1.8)	9 (1.7)
Moderate	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
ジストニア	2 (1.5)	2 (1.0)	4 (2.1)	6 (1.5)	8 (1.5)
Mild	1 (0.8)	2 (1.0)	2 (1.0)	4 (1.0)	5 (1.0)
Moderate	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Severe	0	0	0	0	0
睡眠の質低下	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
全身性強直性間代性発作	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	1 (0.5)	0	1 (0.3)	1 (0.2)
パーキンソン歩行	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	0	0	0
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
無動	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

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Severe	0	0	0	0	0
体位性めまい	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
よだれ	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
構語障害	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
顔面不全麻痺	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
ギラン・バレー症候群	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
過眠症	0	0	1 (0.5)	1 (0.3)	1 (0.2)

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Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
筋緊張亢進	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
感覚鈍麻	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
運動障害	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
精神運動亢進	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
表情減少	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0

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安静時振戦	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
鎮静	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
失神	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
精神障害	26 (19.8)	71 (36.2)	53 (27.3)	124 (31.8)	150 (28.8)
不眠症	4 (3.1)	22 (11.2)	19 (9.8)	41 (10.5)	45 (8.6)
Mild	2 (1.5)	17 (8.7)	12 (6.2)	29 (7.4)	31 (6.0)
Moderate	2 (1.5)	5 (2.6)	7 (3.6)	12 (3.1)	14 (2.7)
Severe	0	0	0	0	0
統合失調症	11 (8.4)	21 (10.7)	12 (6.2)	33 (8.5)	44 (8.4)
Mild	3 (2.3)	2 (1.0)	1 (0.5)	3 (0.8)	6 (1.2)
Moderate	7 (5.3)	14 (7.1)	3 (1.5)	17 (4.4)	24 (4.6)
Severe	1 (0.8)	5 (2.6)	8 (4.1)	13 (3.3)	14 (2.7)
精神病性障害	7 (5.3)	11 (5.6)	5 (2.6)	16 (4.1)	23 (4.4)

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Mild	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Moderate	4 (3.1)	8 (4.1)	4 (2.1)	12 (3.1)	16 (3.1)
Severe	2 (1.5)	2 (1.0)	0	2 (0.5)	4 (0.8)
激越	2 (1.5)	9 (4.6)	8 (4.1)	17 (4.4)	19 (3.6)
Mild	0	6 (3.1)	6 (3.1)	12 (3.1)	12 (2.3)
Moderate	2 (1.5)	3 (1.5)	2 (1.0)	5 (1.3)	7 (1.3)
Severe	0	0	0	0	0
不安	0	7 (3.6)	6 (3.1)	13 (3.3)	13 (2.5)
Mild	0	4 (2.0)	2 (1.0)	6 (1.5)	6 (1.2)
Moderate	0	3 (1.5)	4 (2.1)	7 (1.8)	7 (1.3)
Severe	0	0	0	0	0
易刺激性	3 (2.3)	2 (1.0)	5 (2.6)	7 (1.8)	10 (1.9)
Mild	3 (2.3)	2 (1.0)	3 (1.5)	5 (1.3)	8 (1.5)
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
自殺念慮	1 (0.8)	7 (3.6)	1 (0.5)	8 (2.1)	9 (1.7)
Mild	0	5 (2.6)	1 (0.5)	6 (1.5)	6 (1.2)
Moderate	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Severe	1 (0.8)	0	0	0	1 (0.2)
攻撃性	1 (0.8)	4 (2.0)	3 (1.5)	7 (1.8)	8 (1.5)
Mild	0	3 (1.5)	2 (1.0)	5 (1.3)	5 (1.0)
Moderate	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.6)
Severe	0	0	0	0	0

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落ち着きのなさ	3 (2.3)	4 (2.0)	1 (0.5)	5 (1.3)	8 (1.5)
Mild	2 (1.5)	4 (2.0)	1 (0.5)	5 (1.3)	7 (1.3)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
精神症状	2 (1.5)	2 (1.0)	2 (1.0)	4 (1.0)	6 (1.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	1 (0.8)	0	2 (1.0)	2 (0.5)	3 (0.6)
Severe	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
衝動行為	1 (0.8)	2 (1.0)	1 (0.5)	3 (0.8)	4 (0.8)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Severe	0	0	0	0	0
異常行動	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
睡眠障害	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
自殺企図	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)

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Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
異常な夢	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
カタトニー	1 (0.8)	0	0	0	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	1 (0.8)	0	0	0	1 (0.2)
自殺既遂	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
妄想	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
抑うつ気分	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

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幻視	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
敵意	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
初期不眠症	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
悪夢	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
心因性呼吸窮迫	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
精神病的行動	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

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Severe	0	0	0	0	0
不適切な性的行動	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	1 (0.5)	0	1 (0.3)	1 (0.2)
腎および尿路障害	2 (1.5)	5 (2.6)	4 (2.1)	9 (2.3)	11 (2.1)
排尿困難	0	2 (1.0)	2 (1.0)	4 (1.0)	4 (0.8)
Mild	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
頻尿	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
蛋白尿	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
糖尿	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
血尿	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
失禁	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
腹圧性尿失禁	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
生殖系および乳房障害	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
月経困難症	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
不規則月経	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
陰部そう痒症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
呼吸器、胸郭および縦隔障害	5 (3.8)	10 (5.1)	16 (8.2)	26 (6.7)	31 (6.0)
咳嗽	3 (2.3)	3 (1.5)	6 (3.1)	9 (2.3)	12 (2.3)
Mild	2 (1.5)	3 (1.5)	6 (3.1)	9 (2.3)	11 (2.1)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
鼻出血	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
Mild	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
口腔咽頭痛	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Mild	0	1 (0.5)	2 (1.0)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
鼻漏	1 (0.8)	2 (1.0)	0	2 (0.5)	3 (0.6)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
慢性気管支炎	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Mild	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
呼吸障害	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
アレルギー性鼻炎	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
喘息	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
気管支痙攣	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
息詰まり	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
肺塞栓症	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	0	0	0
Severe	0	0	1 (0.5)	1 (0.3)	1 (0.2)
上気道の炎症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚および皮下組織障害	8 (6.1)	28 (14.3)	27 (13.9)	55 (14.1)	63 (12.1)
湿疹	1 (0.8)	6 (3.1)	2 (1.0)	8 (2.1)	9 (1.7)
Mild	0	6 (3.1)	2 (1.0)	8 (2.1)	8 (1.5)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
そう痒症	0	3 (1.5)	6 (3.1)	9 (2.3)	9 (1.7)
Mild	0	3 (1.5)	6 (3.1)	9 (2.3)	9 (1.7)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚炎	1 (0.8)	4 (2.0)	2 (1.0)	6 (1.5)	7 (1.3)
Mild	1 (0.8)	4 (2.0)	2 (1.0)	6 (1.5)	7 (1.3)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚乾燥	1 (0.8)	1 (0.5)	5 (2.6)	6 (1.5)	7 (1.3)
Mild	1 (0.8)	1 (0.5)	5 (2.6)	6 (1.5)	7 (1.3)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
発疹	0	4 (2.0)	2 (1.0)	6 (1.5)	6 (1.2)
Mild	0	4 (2.0)	1 (0.5)	5 (1.3)	5 (1.0)
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
過角化	0	0	3 (1.5)	3 (0.8)	3 (0.6)
Mild	0	0	3 (1.5)	3 (0.8)	3 (0.6)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮脂欠乏性湿疹	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
汗疹	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚潰瘍	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
顔面腫脹	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)
Mild	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.4)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
ざ瘡	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚嚢腫	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
アレルギー性皮膚炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
接触皮膚炎	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮下出血	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
多汗症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
嵌入爪	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
間擦疹	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
爪肥厚	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
光線過敏性反応	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
全身性そう痒症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Severe	0	0	0	0	0
乾癬	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
全身性皮疹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
斑状丘疹状皮疹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
そう痒性皮疹	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	0	0	0	0
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
脂漏性皮膚炎	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚亀裂	0	1 (0.5)	0	1 (0.3)	1 (0.2)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
皮膚刺激	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
蕁麻疹	1 (0.8)	0	0	0	1 (0.2)
Mild	1 (0.8)	0	0	0	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
社会環境	0	0	1 (0.5)	1 (0.3)	1 (0.2)
社会的入院	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Mild	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
血管障害	7 (5.3)	8 (4.1)	7 (3.6)	15 (3.8)	22 (4.2)
高血圧	5 (3.8)	3 (1.5)	5 (2.6)	8 (2.1)	13 (2.5)
Mild	4 (3.1)	0	4 (2.1)	4 (1.0)	8 (1.5)
Moderate	1 (0.8)	3 (1.5)	1 (0.5)	4 (1.0)	5 (1.0)
Severe	0	0	0	0	0
低血圧	1 (0.8)	1 (0.5)	2 (1.0)	3 (0.8)	4 (0.8)
Mild	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)

System Organ Class Preferred Term Maximum Severity	PLCB-to-FLEX DOSE (N = 131) n (%)	40MG-to-FLEX DOSE (N = 196) n (%)	80MG-to-FLEX DOSE (N = 194) n (%)	Active-to-FLEX DOSE (N = 390) n (%)	Overall-to-FLEX DOSE (N = 521) n (%)
Moderate	0	0	2 (1.0)	2 (0.5)	2 (0.4)
Severe	0	0	0	0	0
本態性高血圧症	1 (0.8)	1 (0.5)	0	1 (0.3)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	1 (0.8)	0	0	0	1 (0.2)
Severe	0	0	0	0	0
血腫	0	2 (1.0)	0	2 (0.5)	2 (0.4)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Severe	0	0	0	0	0
動脈硬化症	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
高血圧クリーゼ	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Mild	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

Treatment emergent adverse events (TEAE) in the DSP-5423P treatment period are defined as events with start date on or after the initial application date of DSP-5423P and up to 17 days after the final application date of DSP-5423P over the DSP-5423P treatment period. TEAEs are coded by MedDRA version 19.1. If a subject experienced more than one episode of TEAE within a preferred term (PT), the subject is counted only once in the PT for the maximum severity. The denominator of percentages is the number of subjects in the DSP-5423P dosed population. The data cut-off at Open-Week 24 was used.

Control No:<<t55-aesocpt-sev-d20d.sas, 2018-06-07T16:29:35>>

表2.7.4.7-9　重篤な有害事象の一覧（20試験・ロナセンテープ貼付期、Open-24週）
DSP-5423P Dosed Population

二重盲検治療期の群：DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]01/ 5[redacted]/ F/ JPN	3	Nervous system disorders/神経系障害 Generalised tonic-clonic seizure/全身性強直性間代性発作 Tonic-clonic convulsions	[redacted](20) [redacted](21) 2 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ Y (Other medically important event)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 4[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Aggravation of schizophrenia	[redacted](14) ONGOING - Double-blind treatment phase 40 mg/day *	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
	1[redacted]10/ 4[redacted]/ M/ JPN	501	Nervous system disorders/神経系障害 Akathisia/アカシジア akathisia	[redacted](81) [redacted](93) 13 Open-label treatment phase 80 mg/day	SEVERE/ DEFINITE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	1[redacted]03/ 2[redacted]/ F/ JPN	506	Psychiatric disorders/精神障害 Suicidal ideation/自殺念慮 suicidal idea	[redacted](179) ONGOING - Open-label treatment phase 80 mg/day	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]07/ 6[redacted]/ F/ JPN	3	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Humerus fracture/上腕骨骨折 fracture of humerus	[redacted](16) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DOSE NOT CHANGED

二重盲検治療期の群：DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	2[redacted]07/ 3[redacted]/ M/ KOR	6	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](26) [redacted](32) 7 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]02/ 2[redacted]/ F/ KOR	5	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	[redacted](24) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DOSE NOT CHANGED
[redacted]	3[redacted]01/ 3[redacted]/ M/ TWN	503	Nervous system disorders/神経系障害 Akathisia/アカシジア Akathisia	[redacted](75) [redacted](89) 15 Open-label treatment phase 80 mg/day	MODERATE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
	3[redacted]11/ 3[redacted]/ M/ TWN	505	Psychiatric disorders/精神障害 Suicide attempt/自殺企図 Sucide attempt	[redacted](146) ONGOING - Open-label treatment phase 80 mg/day *	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
	3[redacted]16/ 4[redacted]/ M/ TWN	502	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Comminuted fracture/粉砕骨折 LEFT CLAVICULAR COMMINUTED FRACTURE	[redacted](78) [redacted](82) 5 Open-label treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	3[redacted]01/ 3[redacted]/ M/ TWN	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenic disorder	[redacted](51) [redacted](83) 33 Open-label treatment phase 60 mg/day *	MODERATE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ NOT APPLICABLE

二重盲検治療期の群：DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]19/ 2[redacted]/ M/ MYS	504	Psychiatric disorders/精神障害 Suicidal ideation/自殺念慮 Suicidal Ideations	[redacted](146) [redacted](148) 3 Follow-up phase 60 mg/day *	MILD/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ NOT APPLICABLE
[redacted]	4[redacted]24/ 3[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of psychosis	[redacted](31) ONGOING - Double-blind treatment phase 40 mg/day	SEVERE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	4[redacted]02/ 4[redacted]/ M/ MYS	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Relapse of Schizophrenia	[redacted](135) [redacted](157) 23 Open-label treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE INCREASED
	4[redacted]13/ 2[redacted]/ M/ MYS	501	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia (Worsening of symptoms)	[redacted](49) [redacted](85) 37 Open-label treatment phase 60 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
		505	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](167) ONGOING - Open-label treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERING/RESOLVING/ DOSE NOT CHANGED
[redacted]	4[redacted]20/ 2[redacted]/ F/ MYS	1	Psychiatric disorders/精神障害 Psychiatric symptom/精神症状 Exacerbation of Psychiatric Symptom.	[redacted](15) [redacted](20) 6 Double-blind treatment phase 40 mg/day	MILD/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED

二重盲検治療期の群：DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
	4[redacted]28/ 3[redacted]/ M/ MYS	501	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Relapse Schizophrenia	[redacted](165) [redacted](205) 41 Open-label treatment phase 80 mg/day	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization, Results in persistent or significant disability/incapacity)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]01/ 2[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](30) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DOSE NOT CHANGED
[redacted]	4[redacted]02/ 2[redacted]/ M/ MYS	501	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of the psychotic symptoms	[redacted](46) [redacted](64) 19 Open-label treatment phase 40 mg/day	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
[redacted]	5[redacted]06/ 4[redacted]/ M/ PHL	513	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia, in relapse	[redacted](185) [redacted](198) 14 Open-label treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED WITH SEQUELAE/ DOSE NOT CHANGED
[redacted]	7[redacted]06/ 3[redacted]/ M/ RUS	503	Psychiatric disorders/精神障害 Psychiatric symptom/精神症状 Worsening of psychic state	[redacted](48) [redacted](73) 26 Open-label treatment phase 40 mg/day	MODERATE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
		512	Psychiatric disorders/精神障害 Psychiatric symptom/精神症状 Worsening of psychic state	[redacted](175) [redacted](215) 41 Open-label treatment phase 80 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN

二重盲検治療期の群：DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]03/ 3[redacted]/ M/ JPN	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	[redacted](156) ONGOING - Open-label treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]02/ 5[redacted]/ F/ JPN	1	Respiratory, thoracic and mediastinal disorders/呼吸器、胸郭および縦隔障害 Choking/息詰まり Choked on food	[redacted](9) [redacted](9) 1 Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Life threatening)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	1[redacted]04/ 2[redacted]/ F/ JPN	501	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](74) [redacted](92) 19 Open-label treatment phase 60 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]04/ 2[redacted]/ F/ JPN	505	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggrevated	[redacted](47) ONGOING - Open-label treatment phase 40 mg/day *	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	2[redacted]01/ 3[redacted]/ M/ KOR	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	[redacted](7) [redacted](40) 34 Double-blind treatment phase 80 mg/day	SEVERE/ DEFINITE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]04/ 5[redacted]/ F/ KOR	512	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizoprenia	[redacted](87) ONGOING - Follow-up phase 80 mg/day *	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

二重盲検治療期の群：DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]08/ 2[redacted] M/ MYS	1	Psychiatric disorders/精神障害 Suicide attempt/自殺企図 Suicidal attempt	[redacted](22) [redacted](31) 10 Double-blind treatment phase 80 mg/day *	SEVERE/ PROBABLE/ Y (Life threatening, Requires or prolongs hospitalization)	RECOVERED/RESOLVED WITH SEQUELAE/ DRUG WITHDRAWN
[redacted]	4[redacted]12/ 6[redacted] M/ MYS	503	Vascular disorders/血管障害 Hypotension/低血圧 HYPOTENSION	[redacted](67) [redacted](68) 2 Open-label treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]12/ 6[redacted] M/ MYS	1	Infections and infestations/感染症および寄生虫症 Pneumonia/肺炎 Pneumonia	[redacted](5) [redacted](12) 8 Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Other medically important event)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]18/ 4[redacted] M/ MYS	1	Cardiac disorders/心臓障害 Acute myocardial infarction/急性心筋梗塞 Cardiogenic shock secondary to NSTEMI	[redacted](35) [redacted](36) 2 Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Results in death, Requires or prolongs hospitalization)	FATAL/ DRUG WITHDRAWN
	4[redacted]25/ 4[redacted] M/ MYS	501	Gastrointestinal disorders/胃腸障害 Colitis/大腸炎 Colitis	[redacted](71) [redacted](71) 1 Open-label treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Results in death)	FATAL/ DRUG WITHDRAWN
[redacted]	4[redacted]08/ 3[redacted] M/ MYS	1	Nervous system disorders/神経系障害 Guillain-Barre syndrome/ギラン・バレー症候群 GUILLAIN BARRE SYNDROME	[redacted](3) ONGOING - Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Results in persistent or significant disability/incapacity)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

二重盲検治療期の群：DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]01/ 3[redacted]/ M/ MYS	501	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia - Relapse	[redacted](70) [redacted](106) 37 Open-label treatment phase 40 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
	4[redacted]06/ 4[redacted]/ M/ MYS	501	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Toxicity to various agents/各種物質毒性 Drug Intoxication	[redacted](149) [redacted](168) 20 Open-label treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]13/ 1[redacted]/ M/ MYS	503	Psychiatric disorders/精神障害 Abnormal behaviour/異常行動 Worsening of behavioral problem.	[redacted](107) [redacted](109) 3 Open-label treatment phase 80 mg/day	MILD/ PROBABLE/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
	4[redacted]27/ 3[redacted]/ M/ MYS	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Relapse due to probable non compliance	[redacted](83) [redacted](90) 8 Open-label treatment phase 80 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
		503	Psychiatric disorders/精神障害 Aggression/攻撃性 Aggressive Behavior (Relapse) due to Probable Non Compliance	[redacted](160) [redacted](177) 18 Open-label treatment phase 80 mg/day	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]04/ 2[redacted]/ M/ MYS	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	[redacted](39) ONGOING - Double-blind treatment phase 80 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERING/RESOLVING/ DOSE NOT CHANGED

二重盲検治療期の群：DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
		501 (2)	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	[redacted] (39) [redacted] (98) 60 Double-blind treatment phase 80 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
		502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia symptoms	[redacted] (134) ONGOING - Open-label treatment phase 80 mg/day	MODERATE/ PROBABLE/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	4[redacted]01/ 3[redacted]/ M/ MYS	511	Respiratory, thoracic and mediastinal disorders/呼吸器、胸郭および縦隔障害 Asthma/喘息 Acute exacerbation of bronchial asthma	[redacted] (150) [redacted] (154) 5 Open-label treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]07/ 2[redacted]/ F/ MYS	501	Social circumstances/社会環境 Social stay hospitalisation/社会的入院 HOSPITALIZATION DUE TO SISTER REQUEST	[redacted] (68) [redacted] (73) 6 Open-label treatment phase 60 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
	4[redacted]08/ 6[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of psychotic symptoms with aggression	[redacted] (23) [redacted] (40) 18 Double-blind treatment phase 80 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
		501	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 exacerbation of psychotic symptoms	[redacted] (71) [redacted] (81) 11 Open-label treatment phase 40 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED

二重盲検治療期の群：DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
		503	General disorders and administration site conditions/一般・全身障害および投与部位の状態 Death/死亡 Natural cause of death due to old age	[redacted](123) [redacted](123) 1 Open-label treatment phase 60 mg/day *	SEVERE/ NOT RELATED/ Y (Results in death)	FATAL/ NOT APPLICABLE
[redacted]	5[redacted]10/ 3[redacted]/ M/ PHL	1	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Traumatic haematoma/外傷性血腫 Contusion Hematomas, left zygoma and left supraorbital area	[redacted](19) [redacted](26) 8 Double-blind treatment phase 80 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
[redacted]	5[redacted]09/ 4[redacted]/ F/ PHL	501	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 relapse of symptoms/Schizophrenia	[redacted](119) ONGOING - Open-label treatment phase 40 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
	5[redacted]11/ 3[redacted]/ M/ PHL	2	Infections and infestations/感染症および寄生虫症 Pulmonary tuberculosis/肺結核 Pulmonary Tuberculosis	[redacted](41) ONGOING - Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	5[redacted]01/ 2[redacted]/ F/ PHL	506	Psychiatric disorders/精神障害 Completed suicide/自殺既遂 Suicide attempt completed	[redacted](142) [redacted](142) 1 Open-label treatment phase 40 mg/day	SEVERE/ NOT RELATED/ Y (Results in death)	FATAL/ DRUG WITHDRAWN

二重盲検治療期の群：Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]04/ 7[redacted]/ M/ JPN	503	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	[redacted](142) [redacted](177) 36 Open-label treatment phase 60 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
[redacted]	1[redacted]01/ 2[redacted]/ F/ JPN	507	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsoring of schizophrenia	[redacted](89) [redacted](103) 15 Open-label treatment phase 80 mg/day *	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]05/ 5[redacted]/ M/ KOR	524	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](129) ONGOING - Open-label treatment phase 80 mg/day *	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ NOT APPLICABLE
[redacted]	2[redacted]02/ 5[redacted]/ F/ KOR	513	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	[redacted](58) ONGOING - Open-label treatment phase 80 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DOSE NOT CHANGED
[redacted]	4[redacted]20/ 3[redacted]/ M/ MYS	502	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening psychosis	[redacted](87) [redacted](98) 12 Open-label treatment phase 80 mg/day	MODERATE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]27/ 5[redacted]/ F/ MYS	501	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening of psychosis	[redacted](23) [redacted](36) 14 Open-label treatment phase 80 mg/day *	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ NOT APPLICABLE

二重盲検治療期の群：Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]04/ 5[redacted]/ F/ MYS	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening Of Schizophrenia	[redacted](21) [redacted](50) 30 Open-label treatment phase 40 mg/day	SEVERE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]04/ 3[redacted]/ M/ MYS	508	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Toxicity to various agents/各種物質毒性 Methamphetamine Intoxication	[redacted](86) ONGOING - Open-label treatment phase 60 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
	4[redacted]11/ 3[redacted]/ F/ MYS	502	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	[redacted](24) ONGOING - Open-label treatment phase 60 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DOSE NOT CHANGED
[redacted]	4[redacted]19/ 4[redacted]/ M/ MYS	510	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Relapse Due to Probable non compliance	[redacted](89) [redacted](95) 7 Open-label treatment phase 80 mg/day	MILD/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	RECOVERED/RESOLVED/ DOSE NOT CHANGED
	4[redacted]22/ 3[redacted]/ M/ MYS	505	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Relapse due to poor compliance	[redacted](155) ONGOING - Open-label treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
	4[redacted]29/ 4[redacted]/ M/ MYS	502	Psychiatric disorders/精神障害 Suicidal ideation/自殺念慮 Suicide Risk due to Psychosis	[redacted](15) [redacted](16) 2 Open-label treatment phase 80 mg/day	SEVERE/ POSSIBLE/ Y (Life threatening)	RECOVERED/RESOLVED/ DOSE INCREASED

二重盲検治療期の群：Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]03/ 3[redacted]/ F/ MYS	511	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 schizophrenia	[redacted](84) [redacted](104) 21 Open-label treatment phase 40 mg/day	MILD/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
[redacted]	4[redacted]05/ 3[redacted]/ M/ MYS	501	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of psychotic symptoms and very irritability	[redacted](11) [redacted](21) 11 Open-label treatment phase 60 mg/day	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DOSE INCREASED
[redacted]	5[redacted]04/ 2[redacted]/ M/ PHL	502	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of Psychosis Symptoms	[redacted](122) [redacted](167) 46 Open-label treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	6[redacted]04/ 6[redacted]/ M/ CHN	501	Gastrointestinal disorders/胃腸障害 Upper gastrointestinal haemorrhage/上部消化管出血 Upper gastrointestinal bleeding	[redacted](9) [redacted](25) 17 Open-label treatment phase 60 mg/day *	MODERATE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN

JPN = JAPAN, CHN = CHINA, KOR = KOREA, REPUBLIC OF, MYS = MALAYSIA, PHL = PHILIPPINES, RUS = RUSSIAN FEDERATION, TWN = TAIWAN, UKR = UKRAINE

Adverse events are coded by MedDRA version 19.1. In case that subjects didn't recieve an active treatment, study day (Day) is relative to the initial application in the double-blind treatment phase, but if subjects recieved an active treatment, study day (Day) is relative to the first day of receiving an active treatment regardless of treatment phase.

(#): No. in DB treatment (only in case of the ongoing AE from DB treatment) or No. in the Open-label phase (only in the case of worsened during the Open-label phase)

*, in the case that the dose at onset date is zero or missing, the most recent non-zero dose is displayed.

The data cut-off at Open-Week 24 was used.

表2.7.4.7-10　治験薬の貼付中止に至った有害事象の一覧（20試験・二重盲検治療期）
All Patients

DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]01/ 5[redacted]/ F/ JPN	3	Nervous system disorders/神経系障害 Generalised tonic-clonic seizure/全身性強直性間代性発作 Tonic-clonic convulsions	(20) (21) 2 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ Y (Other medically important event)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]03/ 4[redacted]/ F/ JPN	3	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(3) ONGOING - Double-blind treatment phase 40 mg/day *	MODERATE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 7[redacted]/ F/ JPN	1	Nervous system disorders/神経系障害 Dyskinesia/ジスキネジア tongue dyskinesia	(4) ONGOING - Double-blind treatment phase 40 mg/day	MILD/ DEFINITE/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
		2	Metabolism and nutrition disorders/代謝および栄養障害 Decreased appetite/食欲減退 anorexia aggravated	(10) ONGOING - Double-blind treatment phase 40 mg/day	MILD/ DEFINITE/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
		3	Nervous system disorders/神経系障害 Akinesia/無動 akinesia	(10) ONGOING - Double-blind treatment phase 40 mg/day	MILD/ DEFINITE/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]03/ 6[redacted]/ F/ JPN	1	Psychiatric disorders/精神障害 Suicidal ideation/自殺念慮 suicidal ideation	(6) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 4[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Aggravation of schizophrenia	(14) ONGOING - Double-blind treatment phase 40 mg/day *	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]08/ 6[redacted]/ M/ JPN	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 worsening of shizophrenia	(4) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 5[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(9) (14) 6 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
		2	Psychiatric disorders/精神障害 Sexually inappropriate behaviour/不適切な性的行動 Sexually inappropriate behaviour	(9) (14) 6 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]07/ 3[redacted]/ M/ KOR	6	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	(26) (32) 7 Double-blind treatment phase 40 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN

DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	2[redacted]01/ 3[redacted]/ F/ KOR	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	(-2) ONGOING - Washout phase 0 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]02/ 4[redacted]/ M/ MYS	3	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of psychosis	(17) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ POSSIBLE/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]03/ 3[redacted]/ F/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening of psychosis	(10) ONGOING - Double-blind treatment phase 40 mg/day	MODERATE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	4[redacted]08/ 3[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Worsening of psychosis	(12) (20) 9 Double-blind treatment phase 40 mg/day	MODERATE/ PROBABLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]15/ 4[redacted]/ F/ MYS	2	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening of psychotic symptom	(9) (10) 2 Double-blind treatment phase 40 mg/day *	SEVERE/ PROBABLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]24/ 3[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Exacerbation of psychosis	(31) ONGOING - Double-blind treatment phase 40 mg/day	SEVERE/ PROBABLE/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN

DSP-5423P 40 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
	4[redacted]28/ 5[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Worsening of psychosis	(3) (6) 4 Double-blind treatment phase 40 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]37/ 1[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Worsening psychosis	(7) (13) 7 Double-blind treatment phase 40 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]10/ 2[redacted]/ F/ MYS	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 WORSENING SCHIZOPHRENIA	(21) ONGOING - Double-blind treatment phase 40 mg/day	SEVERE/ PROBABLE/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]03/ 5[redacted]/ F/ JPN	3	General disorders and administration site conditions/一般・全身障害および投与部位の状態 Application site pruritus/適用部位そう痒感 itching(application site)	(-5) (24) 29 Washout phase 0 mg/day	MILD/ DEFINITE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 5[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(11) ONGOING - Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]04/ 2[redacted]/ M/ KOR	1	Psychiatric disorders/精神障害 Agitation/激越 psychotic agitation	(25) ONGOING - Double-blind treatment phase 80 mg/day	MILD/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]01/ 3[redacted]/ M/ KOR	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	(7) (40) 34 Double-blind treatment phase 80 mg/day	SEVERE/ DEFINITE/ Y (Requires or prolongs hospitalization)	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]08/ 2[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Suicide attempt/自殺企図 Suicidal attempt	(22) (31) 10 Double-blind treatment phase 80 mg/day *	SEVERE/ PROBABLE/ Y (Life threatening, Requires or prolongs hospitalization)	RECOVERED/RESOLVED WITH SEQUELAE/ DRUG WITHDRAWN
		2	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Pulmonary contusion/肺挫傷 BILATERAL LUNGS CONTUSSION	(22) (31) 10 Double-blind treatment phase 80 mg/day *	SEVERE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN

DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
		3	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Ankle fracture/足関節部骨折 LEFT CALCANEUM FRACTURE	(22) ONGOING - Double-blind treatment phase 80 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
		4	Injury, poisoning and procedural complications/傷害、中毒および処置合併症 Clavicle fracture/鎖骨骨折 RIGHT CLAVICLE FRACTURE	(22) ONGOING - Double-blind treatment phase 80 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
		5	Respiratory, thoracic and mediastinal disorders/呼吸器、胸郭および縦隔障害 Pulmonary embolism/肺塞栓症 TRO PULMONARY EMBOLISM	(26) (30) 5 Follow-up phase 80 mg/day *	SEVERE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]06/ 3[redacted]/ M/ MYS	1	Investigations/臨床検査 Blood creatine phosphokinase increased/血中クレアチンホスホキナーゼ増加 WORSENING OF CK ELEVATION	(4) (15) 12 Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]16/ 2[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 WORSENING OF PSYCHOTIC SYMPTOMS	(11) (19) 9 Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]12/ 6[redacted]/ M/ MYS	1	Infections and infestations/感染症および寄生虫症 Pneumonia/肺炎 Pneumonia	(5) (12) 8 Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Other medically important event)	RECOVERED/RESOLVED/ DRUG WITHDRAWN

DSP-5423P 80 mg

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
	4[redacted]18/ 4[redacted]/ M/ MYS	1	Cardiac disorders/心臓障害 Acute myocardial infarction/急性心筋梗塞 Cardiogenic shock secondary to NSTEMI	(35) (36) 2 Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Results in death, Requires or prolongs hospitalization)	FATAL/ DRUG WITHDRAWN
	4[redacted]29/ 2[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening of psychosis	(8) (16) 9 Double-blind treatment phase 80 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]08/ 3[redacted]/ M/ MYS	1	Nervous system disorders/神経系障害 Guillain-Barre syndrome/ギラン・バレー症候群 GUILLAIN BARRE SYNDROME	(3) ONGOING - Double-blind treatment phase 80 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Results in persistent or significant disability/incapacity)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	5[redacted]11/ 3[redacted]/ M/ PHL	2	Infections and infestations/感染症および寄生虫症 Pulmonary tuberculosis/肺結核 Pulmonary Tuberculosis	(41) ONGOING - Double-blind treatment phase 80 mg/day	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization, Other medically important event)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]02/ 4[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Catatonia/カタトニー Catatonia	(19) ONGOING - Double-blind treatment phase 0 mg/day	SEVERE/ POSSIBLE/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]02/ 6[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(41) ONGOING - Double-blind treatment phase 0 mg/day	MODERATE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]02/ 7[redacted]/ F/ JPN	1	General disorders and administration site conditions/一般・全身障害および投与部位の状態 Application site eczema/適用部位湿疹 eczema(application site)	(8) (21) 14 Double-blind treatment phase 0 mg/day	MILD/ PROBABLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]02/ 3[redacted]/ F/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 exacerbation of schizophrenic symptoms	(6) ONGOING - Double-blind treatment phase 0 mg/day *	MODERATE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]02/ 3[redacted]/ F/ JPN	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(10) ONGOING - Double-blind treatment phase 0 mg/day *	SEVERE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	1[redacted]06/ 5[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of Schizophrenia	(9) ONGOING - Double-blind treatment phase 0 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN

Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]02/ 5[redacted] F/ JPN	5	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(32) ONGOING - Double-blind treatment phase 0 mg/day	SEVERE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]03/ 3[redacted] M/ JPN	3	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	(20) ONGOING - Double-blind treatment phase 0 mg/day	MILD/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]09/ 2[redacted] F/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 worsening of shizophrenia	(5) ONGOING - Double-blind treatment phase 0 mg/day *	MODERATE/ NOT RELATED/ N	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 6[redacted] F/ JPN	4	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 aggravation of Schizophrenia	(30) (32) 3 Double-blind treatment phase 0 mg/day	MODERATE/ PROBABLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]10/ 2[redacted] F/ KOR	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 worsening of schizophrenia	(1) ONGOING - Double-blind treatment phase 0 mg/day	SEVERE/ NOT RELATED/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	2[redacted]03/ 4[redacted] F/ KOR	2	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	(8) ONGOING - Double-blind treatment phase 0 mg/day *	MODERATE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN

Placebo

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	4[redacted]11/ 3[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening of psychosis	(10) (18) 9 Double-blind treatment phase 0 mg/day	MODERATE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
	4[redacted]36/ 4[redacted]/ F/ MYS	1	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 worsening psychosis	(1) ONGOING - Double-blind treatment phase 0 mg/day	MODERATE/ POSSIBLE/ N	NOT RECOVERED/NOT RESOLVED/ DRUG WITHDRAWN
[redacted]	4[redacted]07/ 3[redacted]/ M/ MYS	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 worsening of schizophrenia	(10) (35) 26 Double-blind treatment phase 0 mg/day	SEVERE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	5[redacted]04/ 3[redacted]/ M/ PHL	3	Psychiatric disorders/精神障害 Psychotic disorder/精神病性障害 Worsening of psychotic symptoms related to Schizophrenia	(18) ONGOING - Double-blind treatment phase 0 mg/day	SEVERE/ NOT RELATED/ Y (Requires or prolongs hospitalization)	RECOVERING/RESOLVING/ DRUG WITHDRAWN
[redacted]	7[redacted]02/ 3[redacted]/ F/ RUS	2	Nervous system disorders/神経系障害 Psychomotor hyperactivity/精神運動亢進 Psychomotor agitation	(7) (22) 16 Double-blind treatment phase 0 mg/day	SEVERE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
		3	Psychiatric disorders/精神障害 Negativism/拒絶症 Negativism	(7) (22) 16 Double-blind treatment phase 0 mg/day	SEVERE/ POSSIBLE/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN

Untreated

Site	Subject ID/ Age/ Sex/ Country	# (#)	MedDRA System Organ Class/ MedDRA Preferred Term/ Reported Term for the Adverse Event	Start Date (Day) End Date (Day) Duration (days) Epoch of Onset Dose at Onset Date	Severity/ Causality/ Serious Event (Details)	Outcome/ Action Taken with Study Treatment
[redacted]	1[redacted]03/ 7[redacted]/ F/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Schizophrenia aggravated	(-) (-) - Washout phase -	MODERATE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN
[redacted]	1[redacted]01/ 5[redacted]/ M/ JPN	1	Psychiatric disorders/精神障害 Schizophrenia/統合失調症 Worsening of schizophrenia	(-) (-) - Washout phase -	SEVERE/ NOT RELATED/ N	RECOVERED/RESOLVED/ DRUG WITHDRAWN

JPN = JAPAN, CHN = CHINA, KOR = KOREA, REPUBLIC OF, MYS = MALAYSIA, PHL = PHILIPPINES, RUS = RUSSIAN FEDERATION, TWN = TAIWAN, UKR = UKRAINE

Adverse events are coded by MedDRA version 19.1. In case of double-blind treatment phase, study day (Day) is relative to the initial application in the double-blind treatment phase, but open-label treatment phase, study day (Day) is relative to the first day of receiving an active treatment in the open-label treatment phase. A day before Day 1 is Day -1. Duration of adverse event is end date - start date + 1.

(#): No. in DB treatment (only in case of the ongoing AE from DB treatment) or No. in the Open-label phase (only in the case of worsened during the Open-label phase)

*, in the case that the dose at onset date is zero or missing, the most recent non-zero dose is displayed.

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