ゾコーバ錠 125mg

第 2 部 (モジュール 2) : CTD の概要 (サマリー)

2.6 非臨床試験の概要文及び概要表

2.6.5 薬物動態試験概要表

塩野義製薬株式会社

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略号及び用語定義一覧表

略号	英語
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 to infinity
BA	bioavailability
BCRP	breast cancer resistance protein
BLD	below limit of detection
BLQ	below the lower limit of quantification
BSEP	bile-salt export pump
CL_{tot}	total clearance
C_{max}	maximum (plasma) concentration
CV	coefficient of variation
CYP	cytochrome P450
DMA	*N, N*-dimethyl acetamide
$E_2$17βG	estradiol 17β-D-glucuronide
EC_{50}	concentration causing half-maximal effect
E_{max}	maximum induction effect
ES	estrone sulfate
F	female
HPβCD	2-hydroxypropyl-β-cyclodextrin
IC_{50}	50% inhibitory concentration
K_I	half-maximal inactivation concentration
k_{inact}	maximal inactivation rate constant
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LC/MS^n	liquid chromatography with multistage mass spectrometry
LLOQ	lower limit of quantification
LSC	liquid scintillation counter
M	male
MATE	multidrug and toxin extrusion
MC	methylcellulose aqueous solution
M/P	ratio of the mean radioactivity concentration in milk to that in plasma
mRNA	messenger RNA
N/A	not applicable
NADPH	reduced form of β-nicotinamide adenine dinucleotide phosphate
NC	not calculated
ND	not detected
NS	no sample
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PAH	4-aminohippuric acid
P_{app}	apparent permeability
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QC	quality control
QWBA	quantitative whole-body autoradiography
Radio-HPLC	high performance liquid chromatography with radio-detector
RSD	relative standard deviation
SD	standard deviation
$t_{1/2,z}$	terminal elimination half-life

略号	英語
TK	Toxicokinetic(s)
T_{max}	time to maximum plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
Vd_{ss}	volume of distribution at steady state

2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験： 一覧表

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Analytical Methods and Validation					
Radiolabeled compounds	[^{14}C]-Ensitrelvir /[^{14}C]-Ensitrelvir fumaric acid	N/A	Shionogi & Co., Ltd.	S-217622-QB-003-N	4.2.2.1-01
Methods for determination of S-217622 in rat and monkey plasma by LC/MS/MS for TK analysis	Rat plasma, Monkey plasma	N/A	Shionogi & Co., Ltd.	S-217622-TB-002-N	4.2.2.1-02
Method for determination of S-217622 in rat plasma by LC/MS/MS for PK analysis	Rat plasma	N/A	[redacted]	S-217622-PF-015-N	4.2.2.1-03
Method for determination of S-217622 in monkey plasma by LC/MS/MS for PK analysis	Monkey plasma	N/A	[redacted]	S-217622-PF-014-N	4.2.2.1-04
Method for determination of S-217622 in rabbit plasma by LC/MS/MS for TK analysis	Rabbit plasma	N/A	[redacted]	S-217622-TF-047-N	4.2.2.1-05
Methods for determination of S-217622 in mouse plasma and lung homogenate by LC/MS/MS for PK analysis	Mouse plasma, Mouse lung homogenate	N/A	Shionogi & Co., Ltd.	S-217622-EB-004-N	4.2.2.1-06
Absorption					
Plasma concentrations of radioactivity and S-217622, oral bioavailability evaluation and excretion of radioactivity after a single oral administration of [^{14}C]-S-217622 fumaric acid in rats	Rat	Oral	[redacted]	S-217622-PF-020-N	4.2.2.2-01
Plasma concentrations of radioactivity and S-217622 and excretion of radioactivity after a single oral administration of [^{14}C]-S-217622 fumaric acid in monkeys	Monkey	Oral	[redacted]	S-217622-PF-026-N	4.2.2.2-02
Distribution					
Tissue distribution after a single oral administration of [^{14}C]-S-217622 fumaric acid	Pigmented rat, Pregnant rat	Oral	[redacted]	S-217622-PF-041-N	4.2.2.3-01
In vitro protein binding of [^{14}C]-S-217622	Rat serum, Monkey serum, Human serum	In vitro	Shionogi & Co., Ltd.	S-217622-PB-001-N	5.3.2.1-01

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
In vitro plasma/blood cell partitioning and protein binding of [^{14}C]-S-217622	Rat blood, Monkey blood, Human blood, Rabbit serum, Human serum protein solutions (albumin, α_1-acid glycoprotein, and γ-globulin)	In vitro	[redacted]	S-217622-PF-042-N	5.3.2.1-02
Excretion into milk after a single oral administration of [^{14}C]-S-217622 fumaric acid	Nursing rat	Oral	[redacted]	S-217622-PF-045-N	4.2.2.5-01
Metabolism					
Metabolite profiling of S-217622 after a single oral administration of [^{14}C]-S-217622 fumaric acid	Rat	Oral	[redacted]	S-217622-PF-043-N	4.2.2.4-01
Metabolite profiling of S-217622 after a single oral administration of [^{14}C]-S-217622 fumaric acid	Rabbit	Oral	Shionogi & Co., Ltd.	S-217622-PB-078-N	4.2.2.4-02
Metabolite profiling of S-217622 after a single oral administration of [^{14}C]-S-217622 fumaric acid	Monkey	Oral	[redacted]	S-217622-PF-044-N	4.2.2.4-03
In vitro metabolism of [^{14}C]-S-217622	Rat, Monkey, and Human hepatocytes	In vitro	Shionogi & Co., Ltd.	S-217622-PB-009-N	5.3.2.2-01
In vitro identification of responsible enzymes for S-217622 metabolism	Human liver microsomes, Recombinant human CYP enzymes	In vitro	[redacted]	S-217622-PF-048-N	5.3.2.2-02
CYP induction of S-217622 fumaric acid in human hepatocytes	Human hepatocytes	In vitro	[redacted]	S-217622-PF-013-N	5.3.2.2-03
CYP inhibition of S-217622 fumaric acid in human liver microsomes	Human liver microsomes	In vitro	[redacted]	S-217622-PF-016-N	5.3.2.2-04
UGT inhibition of S-217622 fumaric acid in human liver microsomes	Human liver microsomes	In vitro	[redacted]	S-217622-PF-030-N	5.3.2.2-05
Pharmacokinetic Drug Interactions					
Substrate and inhibitor assessment of S-217622 fumaric acid for human transporters	Caco-2 cell systems, OATP 1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K transfected HEK-293 cells	In vitro	[redacted]	S-217622-PF-006-N	5.3.2.2-06
Inhibitor assessment of S-217622 fumaric acid for BSEP	BSEP expressing vesicles	In vitro	[redacted]	S-217622-PF-107-N	5.3.2.2-07

BSEP = bile-salt export pump; CYP = cytochrome P450; LC/MS/MS = liquid chromatography combined with tandem mass spectrometry; MATE = multidrug and toxin extrusion; N/A = not applicable; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; PK = pharmacokinetic; TK = toxicokinetic; UGT = uridine diphosphate glucuronosyltransferase
S-217622 represents ensitrelvir.

2.6.5.2 分析方法及びバリデーション試験

2.6.5.2.1 [^{14}C]-エンシトレルビルのロット番号，比放射能，放射化学的純度，化学的純度及び性状

Lot Number	Specific Radioactivity	Radiochemical Purity	Chemical Purity	Description	Study Number	Location in CTD
202[redacted]-0083-001-01	2.06 MBq/mg (55.6 µCi/mg)	≥ 99.0%	≥ 98.5%	Pale yellow powder	S-217622-QB-003-N	4.2.2.1-01

2.6.5.2.2 [^{14}C]-エンシトレルビルフマル酸のロット番号，比放射能，放射化学的純度，化学的純度及び性状

Lot Number	Specific Radioactivity	Radiochemical Purity	Chemical Purity	Description	Study Number	Location in CTD
202[redacted]-0083-015-01	1.60 MBq/mg (43.2 µCi/mg)	99.7%	>99.9%	Yellowish white crystalline powder	S-217622-QB-003-N	4.2.2.1-01

2.6.5.2.3 LC/MS/MS によるラット血漿中エンシトレルビル濃度測定法

Testing Facility	Shionogi & Co., Ltd.			
Species (Strain) Matrix	Rat (Crl:CD [Sprague Dawley]) Plasma (Anticoagulant: heparin sodium)			
Study Number Supported	S-217622-TF-022-L，S-217622- TF-049-L，S-217622-TF-072-L			
Lower Limit of Quantification (μg/mL)	0.100			
Quantification Range (μg/mL)	0.100 to 1500			
Calibration Curve Range (μg/mL)	0.1 to 100			
	LLOQ	LLOQ [a]	Except for LLOQ	Except for LLOQ [a]
QC Levels (μg/mL) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	0.100 3.3 to 4.1 85.8 to 100.0 8.1 95.1	0.100 3.1 to 3.6 89.9 to 92.1 3.3 91.0	0.300，10.0，80.0 1.2 to 5.7 99.7 to 108.0 1.9 to 3.7 100.3 to 104.0	0.300，10.0，80.0 0.7 to 2.5 92.6 to 103.0 2.4 to 4.8 95.8 to 98.8
Dilution Factor Within-run Precision (RSD, %) Within-run Accuracy (%)	10 6.9 108.9		20 2.8 94.7	
Stability in Plasma	Stable after 5 freeze (−20°C) -thaw (room temperature) cycles in the concentration range of 0.1 to 100 μg/mL, at least for 54 days at −20°C in the concentration range of 0.1 to 100 μg/mL, 5 freeze (−80°C) -thaw (room temperature) cycles in the concentration range of 0.1 to 100 μg/mL, 1 freeze (−80°C) -thaw (room temperature) cycle in the concentration range of more than 100 to 1500 μg/mL, at least for 54 days at −80°C in the concentration range of 0.1 to 1500 μg/mL, at least for 24 hours at room temperature in the concentration range of 0.1 to 100 μg/mL, and for 6 hours at room temperature in the concentration range of more than 100 to 1500 μg/mL			
Processed Extract Stability	Stable at least for 88 hours at 15°C			
Study Number	S-217622-TB-002-N			
Location in CTD	4.2.2.1-02			

LLOQ = lower limit of quantification; QC = quality control; RSD = relative standard deviation

a data after changing preparation of assay solution

2.6.5.2.4 LC/MS/MS によるサル血漿中エンシトレルビル濃度測定法

Testing Facility	Shionogi & Co., Ltd.			
Species (Strain) Matrix	Monkey (Cynomolgus) Plasma (Anticoagulant: heparin sodium)			
Study Number Supported	S-217622-TF-023-L，S-217622-SF-033-L，S-217622-TF-073-L			
Lower Limit of Quantification (μg/mL)	0.100			
Quantification Range (μg/mL)	0.100 to 1500			
Calibration Curve Range (μg/mL)	0.1 to 100			
	LLOQ	LLOQ [a]	Except for LLOQ	Except for LLOQ [a]
QC Levels (μg/mL) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	0.100 3.5 to 7.4 95.8 to 97.9 4.9 96.7	0.100 4.2 to 5.9 94.4 to 95.6 4.6 95.1	0.300，10.0，80.0 0.9 to 4.8 98.0 to 109.0 1.9 to 4.3 101.0 to 107.0	0.300，10.0，80.0 0.9 to 8.9 93.1 to 105.0 3.3 to 5.9 97.8 to 101.0
Dilution Factor Within-run Precision (RSD, %) Within-run Accuracy (%)	10 9.7 104.8		20 3.4 97.3	
Stability inPlasma	Stable after 5 freeze (−20°C) -thaw (room temperature) cycles in the concentration range of 0.1 to 100 μg/mL, at least for 54 days at −20°C in the concentration range of 0.1 to 100 μg/mL, 5 freeze (−80°C) -thaw (room temperature) cycles in the concentration range of 0.1 to 100 μg/mL, 1 freeze (−80°C) -thaw (room temperature) cycle in the concentration range of more than 100 to 1500 μg/mL, at least for 54 days at −80°C in the concentration range of 0.1 to 1500 μg/mL, at least for 27 hours at room temperature in the concentration range of 0.1 to 100 μg/mL, and for 5.5 hours at room temperature in the concentration range of more than 100 to 1500 μg/mL			
Processed Extract Stability	Stable at least for 89 hours at 15°C			
Study Number	S-217622-TB-002-N			
Location in CTD	4.2.2.1-02			

a data after changing preparation of assay solution

2.6.5.2.5 LC/MS/MS によるラット血漿中エンシトレルビル濃度測定法 (2)

Testing Facility	[redacted]	
Species (Strain) Matrix	Rat (Crl:CD [Sprague Dawley]) Plasma (Anticoagulant: heparin sodium)	
Study Number Supported	S-217622-PF-020-N	
Lower Limit of Quantification (ng/mL)	1	
Quantification Range (ng/mL)	1 to 10000	
Calibration Curve Range (ng/mL)	1 to 1000	
QC Levels (ng/mL) Within-run Precision (CV, %) Within-run Accuracy (%) Between-run Precision (CV, %) Between-run Accuracy (%)	LLOQ 1 4.5 110.0 7.9 101.0	Except for LLOQ 3, 40, 800 1.4 to 3.6 99.5 to 104.8 2.3 to 3.0 101.4 to 104.8
Dilution Factor Within-run Precision (CV, %) Within-run Accuracy (%)	20 2.9 104.0	
Stability in Plasma	Stable after 3 freeze (−30.0 to −10.0°C) -thaw (room temperature) cycles, at least for 34 days at −30.0 to −10.0°C, at least for 24 hours at room temperature	
Processed Extract Stability	Stable at least for 48 hours at 15°C	
Study Number	S-217622-PF-015-N	
Location in CTD	4.2.2.1-03	

CV = coefficient of variation

2.6.5.2.6 LC/MS/MS によるサル血漿中エンシトレルビル濃度測定法 (2)

Testing Facility	[redacted]	
Species (Strain) Matrix	Monkey (Cynomolgus) Plasma (Anticoagulant: heparin sodium)	
Study Number Supported	S-217622-PF-026-N, S-217622-TF-191-N	
Lower Limit of Quantification (ng/mL)	10	
Quantification Range (ng/mL)	10 to 160000	
Calibration Curve Range (ng/mL)	10 to 10000	
	LLOQ	Except for LLOQ
QC Levels (ng/mL) Within-run Precision (CV, %) Within-run Accuracy (%) Between-run Precision (CV, %) Between-run Accuracy (%)	10 7.9 101.0 7.0 100.0	30, 400, 8000 2.6 to 2.9 87.4 to 102.7 3.5 to 8.2 98.0 to 103.7
Dilution Factor QC Levels (ng/mL) Within-run Precision (CV, %) Within-run Accuracy (%)	20 100000 4.0 100.0	20 160000 3.7 101.9
Stability in Plasma	Stable after 3 freeze (−30.0 to −10.0°C) -thaw (room temperature) cycles, at least for 34 days at −30.0 to −10.0°C, at least for 24 hours at room temperature	
Processed Extract Stability	Stable at least for 48 hours at 15°C	
Study Number	S-217622-PF-014-N, S-217622-TF-191-N	
Location in CTD	4.2.2.1-04, 4.2.3.7-18	

2.6.5.2.7 LC/MS/MS によるウサギ血漿中エンシトレルビル濃度測定法

Testing Facility	[redacted]	
Species (Strain) Matrix	Rabbit (Kbl:NZW) Plasma (Anticoagulant: heparin sodium)	
Study Number Supported	S-217622-TF-070-L, S-217622-TF-135-L	
Lower Limit of Quantification (µg/mL)	0.1	
Quantification Range (µg/mL)	0.1 to 800	
Calibration Curve Range (µg/mL)	0.1 to 100	
QC Levels (µg/mL) Within-run Precision (%CV) Within-run Accuracy (%Bias) Between-run Precision (%CV) Between-run Accuracy (%Bias)	LLOQ 0.1 3.1 10.0 10.4 −0.3	Except for LLOQ 0.3, 12, 80 1.8 to 2.6 5.4 to 5.8 3.1 to 4.2 1.5 to 3.3
Dilution Factor Within-run Precision (%CV) Within-run Accuracy (%Bias)	10 1.1 3.5	
Stability in Plasma	Stable after 5 freeze (−20°C) -thaw (room temperature) cycles, at least for 35 days at −20°C, 5 freeze (−80°C) -thaw (room temperature) cycle, at least for 35 days at −80°C, and at least for 24 hours at room temperature	
Processed Extract Stability	Stable at least for 49 hours at 15°C	
Study Number	S-217622-TF-047-N	
Location in CTD	4.2.2.1-05	

NZW = New Zealand White

2.6.5.2.8 LC/MS/MS によるマウス血漿中エンシトレルビル濃度測定法

Testing Facility	Shionogi & Co., Ltd.	
Species (Strain) Matrix	Mouse (BALB/cAJcl) Plasma (Anticoagulant: heparin sodium, inactivated with 4 fold acetonitrile)	
Study Number Supported	S-217622-EB-018-N	
Lower Limit of Quantification (ng/mL)	3.00	
Quantification Range (ng/mL)	3.00 to 200000	
Calibration Curve Range (ng/mL)	3 to 3000	
	LLOQ	Except for LLOQ
QC Levels (ng/mL) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	3.00 2.6 to 4.5 95.7 to 104.0 5.3 101.0	9.00, 300, 2400 1.0 to 3.6 93.1 to 104.0 2.4 to 3.8 94.8 to 102.1
Dilution Factor Within-run Precision (RSD, %) Within-run Accuracy (%)	100 2.2 114.0	
Stability in Plasma	Stable after 3 freeze (−80°C) -thaw (on ice) cycles in inactivated plasma, at least for 16 days at −80°C in inactivated plasma, and at least for 24 hours at room temperature in plasma	
Processed Extract Stability	Stable at least for 47 hours at 15°C	
Study Number	S-217622-EB-004-N	
Location in CTD	4.2.2.1-06	

2.6.5.2.9 LC/MS/MS によるマウス肺ホモジネート中エンシトレルビル濃度測定法

Testing Facility	Shionogi & Co., Ltd.	
Species (Strain) Matrix	Mouse (BALB/cAJcl) Lung homogenate (10% lung homogenate prepared with phosphate buffer saline, inactivated with 4 fold acetonitrile)	
Study Number Supported	S-217622-EB-018-N	
Lower Limit of Quantification (ng/g) [a]	0.500	
Quantification Range (ng/g) [a]	0.500 to 1000	
Calibration Curve Range (ng/g) [a]	0.5 to 1000	
	LLOQ	Except for LLOQ
QC Levels (ng/g) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	0.500 0.6 to 4.5 98.0 to 104.2 3.8 101.0	1.00，100，800 0.8 to 4.1 91.8 to 109.0 1.7 to 3.9 95.1 to 107.6
Stability in Lung Homogenate	Stable after 3 freeze (−80°C) -thaw (on ice) cycles in inactivated lung homogenate, at least for 14 days at −80°C in inactivated lung homogenate, and at least for 24 hours at room temperature in lung homogenate	
Processed Extract Stability	Stable at least for 49 hours at 15°C	
Study Number	S-217622-EB-004-N	
Location in CTD	4.2.2.1-06	

a as tissue concentration

2.6.5.3 薬物動態試験： 吸収：単回投与

2.6.5.3.1 ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の血液及び血漿中放射能濃度並びに血漿中エンシトレルビル濃度

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD(Sprague Dawley)		
Gender (M/F) Number of Animals	M/4 per group		
Feeding Condition	Non-fasting		
Vehicle/Formulation	0.5 (w/v) % MC/suspension		
Method of Administration	Single oral administration		
Dose [a] (mg/kg)	2		
Radionuclide	^{14}C		
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free		
Sample	Plasma and Blood (30 minutes, 1, 2, 4, 8, 24, and 48 hours post-dose)		
Analyte	Radioactivity (ensitrelvir equivalent), ensitrelvir		
Assay	LSC for radioactivity, LC/MS/MS for ensitrelvir		
Pharmacokinetic Parameters	Radioactivity in Plasma	Ensitrelvir in Plasma	Radioactivity in Blood
C_{max} (ng/mL)	2320 ± 450	2220 ± 590	1490 ± 240
T_{max} (hr)	2.00 ± 0.00	1.75 ± 0.50	2.00 ± 0.00
$t_{1/2,z}$ (hr)	5.24 ± 0.18	3.61 ± 0.56	4.31 ± 0.89
$AUC_{0\text{-}inf}$ (ng·hr/mL)	21100 ± 600	17800 ± 1500	14000 ± 1100
$AUC_{0\text{-}inf}$ Ratio to Radioactivity (%)		84.3 ± 7.7	
BA (%)		85.5 ± 7.1	
$AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 to infinity; BA = bioavailability; C_{max} = maximum plasma concentration; F = female; LSC = liquid scintillation counter; M = male; MC = methylcellulose aqueous solution; $t_{1/2,z}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration Data are expressed as the mean ± standard deviation (SD). a As a free form			
Study Number	S-217622-PF-020-N		
Location in CTD	4.2.2.2-01		

2.6.5.3.2 ラットにおけるエンシトレルビルフマル酸単回静脈内投与後のエンシトレルビルの血漿中濃度

Test Article: Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	M/4 per group
Feeding Condition	Non-fasting
Vehicle/Formulation	DMA/Ethanol/20 (w/v) % HPβCD = 2/3/5 (v/v/v)/solution
Method of Administration	Single intravenous administration
Dose [a] (mg/kg)	1
Sample	Plasma obtained 2, 5, 15, 30 minutes, 1, 2, 4, 6, 8, 24 hours post-dose
Analyte	Ensitrelvir
Assay	LC/MS/MS
Pharmacokinetic Parameters	1 mg/kg
$AUC_{0\text{-}inf}$ (ng·hr/mL)	10400 ± 2700
CL_{tot} (mL/hr/kg)	100 ± 22
$t_{1/2,z}$ (hr)	2.84 ± 0.27
Vd_{ss} (mL/kg)	291 ± 23
CL_{tot} = total clearance; DMA = *N*, *N*-dimethyl acetamide; HPβCD = 2-hydroxypropyl-β-cyclodextrin; Vd_{ss} = volume of distribution at steady state Data are expressed as the mean ± SD. a As a free form	
Study Number	S-217622-PF-020-N
Location in CTD	4.2.2.2-01

2.6.5.3.3 サルにおける[^{14}C]-エンシトレルビルフマル酸単回経口投与後の血液及び血漿中放射能濃度並びに血漿中エンシトレルビル濃度

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Monkey/Cynomolgus		
Gender (M/F)/Number of Animals	M/3		
Feeding Condition	Non-fasting		
Vehicle/Formulation	0.5% MC/suspension		
Method of Administration	Single oral administration		
Dose [a] (mg/kg)	2		
Radionuclide	^{14}C		
Specific Activity	1.60 MBq (43.2 μCi)/mg as fumaric acid 1.95 MBq (52.6 μCi)/mg as free		
Sample	Plasma and Blood obtained 15, 30 minutes, 1, 2, 4, 6, 8, 24, 48, and 72 hours post-dose		
Analyte	Radioactivity (ensitrelvir equivalent), ensitrelvir		
Assay	LSC for radioactivity, LC/MS/MS for ensitrelvir		
Pharmacokinetic Parameters	Radioactivity in Plasma	Ensitrelvir in Plasma	Radioactivity in Blood
C_{max} (ng/mL)	4120 ± 360	3680 ± 300	2410 ± 190
T_{max} (hr)	8.00 ± 0.00	8.00 ± 0.00	8.00 ± 0.00
$t_{1/2,z}$ (hr)	14.1 ± 1.5	11.6 ± 1.5	14.6 ± 1.2
$AUC_{0\text{-}inf}$ (ng·hr/mL)	119000 ± 17000	98400 ± 11500	72400 ± 10700
$AUC_{0\text{-}inf}$ Ratio to Radioactivity (%)		82.8 ± 2.1	
Data are expressed as the mean ± SD. a As a free form			
Study Number	S-217622-PF-026-N		
Location in CTD	4.2.2.2-02		

2.6.5.4 薬物動態試験： 吸収：反復投与

反復投与時の吸収は，2.6.7 項に TK として記載している．

2.6.5.5 薬物動態試験： 分布

2.6.5.5.1 有色ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の組織分布

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/ Long Evans
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasting
Vehicle/Formulation	0.5% MC/suspension
Method of Administration	Single oral administration
Dose [a](mg/kg)	2
Radionuclide	^{14}C
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free
Sample	Adrenal (cortex/medulla), Aorta (walls), Blood (cardiac), Bone (marrow/surface), Brain (cerebellum/cerebrum), Bulbo-urethral gland, Caecum (contents/mucosa), Choroid plexus, Epididymis, Ex-orbital lachrymal gland, Eye (Ciliary body/iris/lens/uveal tract/whole), Fat (brown/white), Forestomach mucosa, Glandular Stomach mucosa, Harderian gland, Intra-orbital lachrymal gland, Kidney (cortex/medulla/whole), Large intestine (contents/mucosa), Liver, Lung, Lymph node (mandibular), Lymph nodes, Meninges ,Muscle (skeletal), Myocardium, Nasal mucosa, Oesophagus, Pancreas, Periosteum, Pineal body, Pituitary gland, Plasma, Preputial gland, Prostate gland, Rectal mucosa, Salivary gland, Seminal vesicles, Skin (non-pigmented/pigmented), Small intestine (contents/mucosa), Spinal cord, Spleen, Stomach contents, Testis, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Urinary bladder (contents/wall), Vena cava (wall)
Analyte	Radioactivity (ensitrelvir equivalent)
Assay	LSC for plasma, QWBA for cardiac blood and other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)									$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr	840 hr	
Adrenal cortex	0.086	0.624	0.920	0.292	BLQ	ND	ND	ND	ND	-
Adrenal medulla	0.155	0.556	0.772	0.223	0.019	ND	ND	ND	ND	-
Aorta (walls)	0.029	0.393	0.693	0.251	ND	ND	ND	ND	ND	-
Blood (cardiac)	0.084	0.573	0.772	0.221	BLQ	ND	ND	ND	ND	-
Bone marrow	0.028	0.243	0.305	0.113	ND	ND	ND	ND	ND	-
Bone surface	BLQ	BLQ	BLQ	BLQ	ND	ND	ND	ND	ND	-
Brain cerebellum	ND	BLQ	BLQ	ND	ND	ND	ND	ND	ND	-
Brain cerebrum	ND	BLQ	BLQ	ND	ND	ND	ND	ND	ND	-
Bulbo-urethral gland	0.052	NS	0.639	0.146	BLQ	ND	ND	NS	ND	-
Caecum contents	ND	0.204	46.5[b]	25.5[b]	1.60	BLQ	ND	ND	ND	-
Caecum mucosa	0.052	0.500	1.49	0.583	0.096	ND	ND	ND	ND	-
Choroid plexus	0.051	0.339	0.260	0.072	ND	ND	ND	ND	ND	-
Epididymis	BLQ	0.084	0.406	0.182	BLQ	ND	ND	ND	ND	-
Ex-orbital lachrymal gland	0.027	0.317	0.509	0.163	BLQ	ND	ND	ND	ND	-

Tissues	Radioactivity Concentration in Tissue (μg/g)									$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr	840 hr	
Eye: Ciliary body/iris	0.019	0.318	1.15	0.701	0.281	0.072	ND	ND	ND	20.5
Eye: lens	ND	ND	ND	ND	ND	ND	ND	ND	ND	-
Eye: uveal tract	0.029	0.290	0.942	0.476	0.184	0.079	0.019	ND	ND	44.3
Eye: whole	BLQ	0.060	0.143	0.116	0.037	BLQ	BLQ	ND	ND	-
Fat: brown	0.030	0.363	0.476	0.113	ND	ND	ND	ND	ND	-
Fat: white	BLQ	0.025	0.032	BLQ	ND	ND	ND	ND	ND	-
Forestomach mucosa	1.55	1.25	1.18	0.465	0.076	BLQ	ND	ND	ND	5.49
Glandular Stomach mucosa	0.212	0.609	0.779	0.229	BLQ	ND	ND	ND	ND	-
Harderian gland	0.015	0.320	0.517	0.202	BLQ	ND	ND	ND	ND	-
Intra-orbital lachrymal gland	0.015	NS	0.599	0.132	NS	ND	ND	ND	ND	-
Kidney: Cortex	0.064	0.470	0.730	0.219	0.028	BLQ	BLQ	ND	ND	-
Kidney: Medulla	0.058	0.399	0.654	0.199	0.020	BLQ	BLQ	ND	ND	-
Kidney: Whole	0.050	0.435	0.684	0.215	0.024	BLQ	BLQ	ND	ND	-
Large intestine contents	ND	NS	12.6[b]	52.3[b]	2.64	0.022	ND	ND	ND	-
Large intestine mucosa	0.025	NS	3.69	0.663	0.108	ND	BLQ	ND	ND	-
Liver	0.356	1.78	3.33	1.19	0.322	0.173	0.031	BLQ	ND	42.0
Lung	0.092	0.538	0.736	0.230	BLQ	ND	ND	ND	ND	-
Lymph node: Mandibular	0.018	0.230	0.476	0.161	BLQ	ND	ND	ND	ND	-
Lymph nodes	0.021	0.266	0.369	0.101	ND	ND	ND	ND	ND	-
Meninges	ND	0.130	0.442	0.094	BLQ	ND	ND	ND	ND	-
Muscle (skeletal)	BLQ	0.166	0.270	0.071	ND	ND	ND	ND	ND	-
Myocardium	0.075	0.530	0.747	0.236	BLQ	ND	ND	ND	ND	-
Nasal mucosa	BLQ	0.110	0.343	0.108	0.030	0.035	0.032	BLQ	ND	-
Oesophagus	0.135	0.285	0.687	0.143	BLQ	ND	ND	ND	ND	-
Pancreas	0.058	0.373	0.528	0.169	ND	ND	ND	ND	ND	-
Periosteum	BLQ	0.140	0.219	0.086	ND	ND	ND	ND	ND	-
Pineal body	0.042	NS	NS	NS	ND	ND	ND	NS	NS	-
Pituitary gland	0.025	0.328	0.772	0.151	ND	ND	ND	ND	ND	-
Plasma[c]	0.106	1.19	1.92	0.570	0.038	BLD	BLD	BLD	BLD	NC
Preputial gland	BLQ	NS	0.365	0.140	ND	ND	ND	NS	ND	-
Prostate gland	0.019	0.133	0.403	0.043	ND	ND	ND	ND	ND	-
Rectal mucosa	0.025	NS	0.450	0.227	0.018	ND	ND	ND	ND	-
Salivary gland	0.054	0.391	0.601	0.155	BLQ	ND	ND	ND	ND	-
Seminal vesicles	BLQ	0.041	0.208	0.041	ND	ND	ND	ND	ND	-
Skin: Non-pigmented	BLQ	0.176	0.326	0.073	BLQ	BLQ	ND	ND	ND	-
Skin: Pigmented	BLQ	0.210	0.307	0.079	BLQ	BLQ	ND	ND	ND	-
Small intestine contents	15.6[b]	17.4[b]	43.6[b]	5.75	0.455	0.016	ND	ND	ND	7.98
Small intestine mucosa	0.345	3.33	2.51	0.654	0.032	BLQ	ND	ND	ND	3.31
Spinal cord	ND	BLQ	BLQ	ND	ND	ND	ND	ND	ND	-

Tissues	Radioactivity Concentration in Tissue (μg/g)									$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr	840 hr	
Spleen	0.051	0.339	0.436	0.145	BLQ	ND	ND	ND	ND	-
Stomach contents	40.6[b]	34.5[b]	9.18	3.35	0.551	BLQ	ND	BLQ	ND	5.22
Testis	ND	0.031	0.300	0.091	BLQ	ND	ND	ND	ND	-
Thymus	BLQ	0.140	0.275	0.059	ND	ND	ND	ND	ND	-
Thyroid gland	0.080	0.541	0.624	0.221	BLQ	ND	ND	ND	ND	-
Tongue	0.065	0.345	0.627	0.160	BLQ	ND	ND	ND	ND	-
Tooth pulp	0.029	0.446	0.989	0.262	NS	ND	ND	ND	ND	-
Trachea	0.047	0.229	0.307	0.105	ND	ND	ND	ND	ND	-
Urinary bladder contents	0.022	0.298	0.899	0.257	0.034	BLQ	ND	ND	ND	-
Urinary bladder wall	BLQ	0.178	0.457	0.157	BLQ	ND	ND	ND	ND	-
Vena cava (wall)	ND	ND	0.764	0.277	ND	ND	ND	ND	ND	-

– = tissue not detected; BLD = below limit of detection; BLQ = below the lower limit of quantification; NC = not calculated; ND = not detected; NS = no sample; QWBA = quantitative whole-body autoradiography
When quantitative data for one tissue were obtained from multiple sections, data are expressed as the mean value of each data. In the calculation of mean, BLQ was treated as zero.
When the data on all sections were BLQ, the mean is expressed as "BLQ".
a As a free form
b Above upper limit of accurate quantification – extrapolated value reported
c Determined by LSC

Study Number	S-217622-PF-041-N
Location in CTD	4.2.2.3-01

2.6.5.6 薬物動態試験： タンパク結合

2.6.5.6.1 [^{14}C]-エンシトレルビルの In Vitro タンパク結合

Test Article: [^{14}C]-Ensitrelvir

Test System	Serum under a fasting condition (Sprague Dawley rats [M], Cynomolgus monkeys [M], New Zealand White rabbits [F], and human volunteers [M]) or human serum protein solution (human serum albumin, α_1-acid glycoprotein and γ-globulin)		
Radionuclide	^{14}C		
Specific Activity	2.06 MBq/mg (55.6 μCi/mg)		
Concentration (μg/mL)	0.5, 5, 50		
Method	Ultrafiltration method for serum Equilibrium dialysis method (RED Device, at 37°C for 16 hours) for purified human serum protein		
Sample	Serum, Human serum protein solution, Filtrate		
Analyte	Radioactivity		
Assay	LSC		
Serum	Protein Binding Ratio (%)		
	0.5 μg/mL	5 μg/mL	50 μg/mL
Sprague Dawley rat	98.8 ± 0.2	98.7 ± 0.2	98.3 ± 0.3
Cynomolgus monkey	98.9 ± 0.1	98.7 ± 0.1	98.3 ± 0.1
New Zealand White rabbit	> 98.9 [a]	98.7 ± 0.1	97.4 ± 0.1
Human	98.7 ± 0.1	98.4 ± 0.1	97.7 ± 0.2
Data are expressed as the mean ± SD of 3 individuals. a The value is expressed as > Radiochemical purity.			
Purified Human Serum Protein	Protein Binding Ratio (%)		
	0.5 μg/mL	5 μg/mL	50 μg/mL
4% Albumin	94.8 ± 0.2	94.8 ± 0.2	94.7 ± 0.1
0.08% α_1-Acid glycoprotein	6.1 ± 2.9	3.7 ± 3.8	9.4 ± 1.5
1% γ-Globulin	14.7 ± 1.9	6.8 ± 3.1	10.4 ± 2.6
Data are expressed as the mean ± SD of triplicate assays.			
Study Number	S-217622-PB-001-N, S-217622-PF-042-N		
Location in CTD	5.3.2.1-01, 5.3.2.1-02		

2.6.5.6.2 [^{14}C]-エンシトレルビルの In Vitro 血球移行性

Test Article: [^{14}C]-Ensitrelvir

Test System	Blood under a fasting condition (Sprague Dawley rats [M], cynomolgus monkeys [M], and human volunteers [M])		
Radionuclide	^{14}C		
Specific Activity	2.06 MBq/mg (55.6 μCi/mg)		
Concentration (μg/mL)	0.5, 5, 50		
Incubation	At 37°C for 5 minutes		
Sample	Blood, Plasma		
Analyte	Radioactivity		
Assay	LSC		
Spicies	Distribution Ratio of Radioactivity in Blood Cells (%)		
	0.5 μg/mL	5 μg/mL	50 μg/mL
Sprague Dawley rat	12.9 ± 0.3	6.4 ± 0.6	5.6 ± 1.6
cynomolgus monkey	9.0 ± 0.8	9.4 ± 1.2	10.4 ± 2.1
Human	5.2 ± 1.2	6.1 ± 2.1	8.0 ± 1.8
Data are expressed as the mean ± SD of 3 individuals.			
Study Number	S-217622-PF-042-N		
Location in CTD	5.3.2.1-02		

2.6.5.6.3 ラット及びサルにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の血球移行性

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD(Sprague Dawley)	Monkey/Cynomolgus
Gender (M/F)/Number of Animals	M/4	M/3
Feeding Condition	Non-fasting	
Vehicle/Formulation	0.5% MC/suspension	
Method of Administration	Single oral administration	
Dose [a] (mg/kg)	2	
Radionuclide	^{14}C	
Specific Activity	1.60 MBq/mg (43.2 µCi/mg) as fumaric acid 1.95 MBq/mg (52.6 µCi/mg) as free	
Sample	Blood, Plasma	
Analyte	Radioactivity	
Assay	LSC	
Sampling time	Distribution of Radioactivity to Blood Cells (%)	
	Rat	Monkey
15 min	N/A	1.5 ± 2.6
30 min	13.5 ± 7.5	1.7 ± 2.9
1 hr	11.8 ± 2.2	1.1 ± 1.0
2 hr	11.9 ± 0.5	10.2 ± 3.5
4 hr	10.3 ± 2.7	9.5 ± 2.1
6 hr	N/A	9.2 ± 0.8
8 hr	15.8 ± 2.6	3.0 ± 1.6
24 hr	25.7 ± 0.8	6.4 ± 1.9
48 hr	17.8[b]	5.2 ± 1.7
72 hr	N/A	4.9 ± 6.4
Data are expressed as the mean ± SD. a As a free form b n = 1		
Study Number	S-217622-PF-020-N	S-217622-PF-026-N
Location in CTD	4.2.2.2-01	4.2.2.2-02

2.6.5.7 薬物動態試験： 妊娠又は授乳動物における試験

2.6.5.7.1 妊娠ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の組織分布

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD (Sprague Dawley)
Gender (M/F)/Number of Animals	F/1 per time point
Gestation Day	Day 17 of gestation
Feeding Condition	Non-fasting
Vehicle/Formulation	0.5% MC/suspension
Method of Administration	Single oral administration
Dose [a] (mg/kg)	2
Radionuclide	^{14}C
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free
Sample	Adrenal (cortex/medulla), Aorta (wall), Blood (cardiac), Bone (marrow/surface), Brain (fetal), Brain (Cerebrum/Cerebellum), Caecum (contents/mucosa), Cardiac blood (fetal), Choroid plexus, Clitoral gland, Ex-orbital lachrymal gland, Eye ball (fetal), Eye (ciliary body/iris/lens/uveal tract/whole), Fat (brown/white), Forestomach mucosa, Glandular Stomach mucosa, Harderian gland, Intra-orbital lachrymal gland, Kidney (cortex/medulla/whole), Large intestine (contents/mucosa), Liver, Liver (fetal), Lung, Lung (fetal), Lymph node (Mandibular), Lymph nodes, Mammary gland, Meninges, Muscle (skeletal), Myocardium, Nasal mucosa, Oesophagus, Ovary, Pancreas, Periosteum, Pineal body, Pituitary gland, Placenta, Plasma, Rectal mucosa, Salivary gland, Skin (non-pigmented/pigmented), Small intestine (contents/mucosa), Spinal cord, Spleen, Stomach contents, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Urinary bladder (contents/wall), Uterus, Vena cava (wall)
Analyte	Radioactivity (ensitrelvir equivalent)
Assay	LSC for plasma and whole blood, QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)						$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	48 hr	
Adrenal cortex	0.210	1.83	1.08	0.524	BLQ	BLQ	-
Adrenal medulla	0.347	1.98	1.49	0.389	0.017	0.019	7.29
Aorta (wall)	0.126	1.46	0.967	0.523	0.029	0.028	8.45
Blood (cardiac)	0.282	1.57	1.98	0.475	BLQ	BLQ	-
Bone marrow	0.076	0.639	0.694	0.233	BLQ	BLQ	-
Bone: Surface	ND	0.020	ND	ND	ND	ND	-
Brain (fetal)	ND	0.022	0.037	BLQ	ND	ND	-
Brain cerebellum	BLQ	0.025	0.031	BLQ	ND	ND	-
Brain: cerebrum	BLQ	0.025	0.031	BLQ	ND	ND	-
Caecum contents	BLQ	NS	37.6 [b]	NS	2.16	1.14	-
Caecum mucosa	0.162	NS	1.45	NS	0.073	0.093	-
Cardiac blood (fetal)	ND	0.098	0.145	0.033	ND	ND	-
Choroid plexus	0.152	0.856	1.27	0.360	ND	ND	-

Tissues	Radioactivity Concentration in Tissue (μg/g)						$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	48 hr	
Clitoral gland	0.103	NS	0.330	0.181	BLQ	NS	-
Ex-orbital lachrymal gland	0.044	0.805	0.832	0.273	BLQ	BLQ	-
Eye ball (fetal)	NS	NS	NS	BLQ	ND	ND	-
Eye: Ciliary body/iris	ND	0.029	0.267	NS	ND	ND	-
Eye: lens	ND	ND	0.028	ND	ND	ND	-
Eye: uveal tract	BLQ	0.318	0.330	0.039	ND	ND	-
Eye: whole	BLQ	0.060	0.084	BLQ	ND	ND	-
Fat: brown	0.044	0.692	0.816	0.315	BLQ	BLQ	-
Fat: white	BLQ	0.121	0.179	0.047	ND	ND	-
Forestomach mucosa	0.610	1.86	0.969	2.63	0.219	0.096	-
Glandular Stomach mucosa	0.317	1.54	1.03	0.515	BLQ	BLQ	-
Harderian gland	0.078	1.20	1.22	0.345	BLQ	BLQ	-
Intra-orbital lachrymal gland	0.048	0.748	1.04	0.290	NS	BLQ	-
Kidney: Cortex	0.189	1.34	1.57	0.477	0.021	0.017	-
Kidney: Medulla	0.195	1.19	1.26	0.433	0.016	BLQ	-
Kidney: Whole	0.206	1.31	1.26	0.427	0.018	0.015	7.01
Large intestine contents	NS	0.017	14.8 [b]	96.9 [b]	3.76	0.875	-
Large intestine mucosa	NS	2.19	1.20	1.70	0.095	0.085	9.91
Liver	0.872	5.09	5.11	2.73	0.418	0.146	9.78
Liver (fetal)	BLQ	0.111	0.175	0.052	ND	ND	-
Lung	0.244	1.51	1.90	0.458	0.015	BLQ	-
Lung (fetal)	ND	0.063	0.116	0.031	ND	ND	-
Lymph node: Mandibular	0.040	0.801	0.828	0.252	BLQ	BLQ	-
Lymph nodes	0.027	0.572	0.929	0.277	BLQ	ND	-
Mammary gland	0.047	0.690	0.761	0.252	BLQ	BLQ	-
Meninges	BLQ	0.187	0.217	0.019	ND	ND	-
Muscle (skeletal)	0.019	0.412	0.463	0.130	BLQ	BLQ	-
Myocardium	0.227	1.59	1.62	0.610	0.019	0.023	-
Nasal mucosa	0.074	0.669	0.637	0.121	0.039	0.079	-
Oesophagus	0.751	0.662	0.793	0.221	BLQ	0.026	-
Ovary	NS	NS	NS	0.109	NS	NS	-
Pancreas	0.132	1.22	1.16	0.338	BLQ	BLQ	-
Periosteum	0.029	0.227	0.565	0.164	ND	ND	-
Pineal body	NS	NS	1.16	0.301	NS	BLQ	-
Pituitary gland	0.148	0.982	1.22	0.359	BLQ	BLQ	-
Placenta	0.131	0.982	1.10	0.326	BLQ	BLQ	-
Plasma [c]	0.323	2.73	3.82	0.719	0.037	0.034	9.78 [d]
Rectal mucosa	0.079	NS	0.969	0.195	0.022	BLQ	-
Salivary gland	0.129	0.948	1.06	0.292	BLQ	BLQ	-

Tissues	Radioactivity Concentration in Tissue (μg/g)						$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	48 hr	
Skin: Non-pigmented	0.015	0.359	0.620	0.179	BLQ	BLQ	-
Small intestine contents	16.8 [a]	42.3 [b]	58.7 [b]	23.1 [b]	0.791	0.923	-
Small intestine mucosa	0.580	1.72	3.05	2.63	0.210	0.219	-
Spinal cord	ND	0.018	0.029	BLQ	ND	ND	-
Spleen	0.154	0.917	1.04	0.364	BLQ	0.015	-
Stomach contents	48.6[b]	49.0[b]	3.05	2.73	BLQ	0.075	8.01
Thymus	0.032	0.54	0.565	0.177	BLQ	BLQ	-
Thyroid gland	0.147	1.12	0.936	0.341	0.015	BLQ	3.41
Tongue	0.103	0.994	1.15	0.353	BLQ	0.015	-
Tooth pulp	0.187	1.26	1.98	0.380	BLQ	BLQ	-
Trachea	0.030	0.545	1.31	0.277	BLQ	ND	-
Urinary bladder contents	0.133	NS	NS	NS	BLQ	NS	-
Urinary bladder wall	0.029	NS	NS	NS	0.016	NS	-
Uterus	0.026	0.891	1.01	0.803	0.049	0.027	8.66
Vena cava (wall)	0.105	0.791	1.14	0.322	ND	ND	-

– = tissue not detected;
When quantitative data for one tissue were obtained from multiple sections, data are expressed as the mean value of each data. In the calculation of mean, BLQ was treated as zero. When the data on all sections were BLQ, the mean is expressed as "BLQ".
a As a free form
b Above upper limit of accurate quantification – extrapolated value reported
c Determined by LSC
d Square of correlation coefficient noted to be less than 0.7

Study Number	S-217622-PF-041-N
Location in CTD	4.2.2.3-01

2.6.5.7.2 授乳ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の乳汁移行性

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD(Sprague Dawley), Nursing rat						
Gender (M/F)/Number of Animals	F/5						
Feeding Condition	Non-fasting						
Vehicle/Formulation	0.5% MC/suspension						
Method of Administration	Single oral administration						
Dose [a] (mg/kg)	2						
Radionuclide	^{14}C						
Specific Activity	1.95 MBq/mg (52.6 μCi/mg)						
Sample	Milk, Plasma						
Analyte	Radioactivity (ensitrelvir equivalent)						
Assay	LSC						
Sample	Radioactivity Concentration in Tissue (ng eq./g)						$t_{1/2,z}$ (hr)
	0.25 hr	1 hr	4 hr	8 hr	24 hr	48 hr	
Milk	390 ± 64	1610 ± 500	1750 ± 250	1210 ± 360	80.7 ± 20.6	11.1 ± 5.1	5.95 ± 0.68
Plasma	2160 ± 440	2050 ± 400	1430 ± 310	640 ± 164	57.9 ± 11.1	5.00 ± 5.49	5.71 ± 0.84 [b]
M/P	0.18 ± 0.04	0.79 ± 0.28	1.25 ± 0.21	1.91 ± 0.37	1.45 ± 0.57	1.42 ± 0.10 [c]	N/A
M/P = ratio of the mean radioactivity concentration in milk to that in plasma; Data are expressed as the mean ± SD. a As a free form b Data are expressed as the mean ± SD of 4 animals. In 1 animal, $t_{1/2}$ was not calculated because the concentrations in the terminal elimination phase were not observed at last 3 time points or more. c Data are expressed as the mean ± SD of 3 animals. In 2 animals, M/P was not calculated because the concentration in the plasma was not detected.							
Study Number	S-217622-PF-045-N						
Location in CTD	4.2.2.5-01						

2.6.5.8 薬物動態試験： その他の分布試験

該当する試験なし.

2.6.5.9 薬物動態試験： 代謝：In Vivo

2.6.5.9.1 ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後のエンシトレルビルの代謝プロファイル

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain		Rat/Crl:CD (Sprague Dawley)					
Gender (M/F)/Number of Animals		M/2 per time point (plasma), M/4(urine, feces, and bile)					
Feeding condition		Non-fasting					
Vehicle/Formulation		0.5% MC/suspension					
Method of Administration		Single oral administration					
Dose [a] (mg/kg)		2					
Radionuclide		^{14}C					
Specific radio activity		1.95 MBq/mg (52.6 μCi/mg)					
Sample		Plasma obtained from intact rats, Urine and feces [b] obtained from intact rat, Bile [b] obtained from bile duct-cannulated rats					
Analyte		Ensitrelvir and its metabolites					
Assay		LSC, Radio-HPLC, LC/MS^n					
Metabolites ID	Name of metabolite	Composition (% of total radioactivity in sample)			Cumulative Excretion (% of dose)		
		2 hr plasma	8 hr plasma	24 hr plasma	0–24 hr urine	0–48 hr feces	0–48 hr bile
M8 [c]	Unknown	ND	ND	ND	0.3	2.7	2.9
M13 [d]	–	ND	ND	ND	0.0	ND	ND
M14 [d]	–	ND	ND	ND	0.1	ND	ND
M15	Glutathione conjugate of oxidized and dedifluorinated ensitrelvir (proposed)	ND	ND	ND	0.1	ND	2.7
M16 [d]	–	ND	ND	ND	ND	ND	2.6
M17 [d]	–	ND	ND	ND	0.1	ND	1.7
M18	Glutathione conjugate of oxidized and defluorinated ensitrelvir (proposed)	ND	ND	ND	ND	ND	5.7
M1	*N*- deindazolated form of ensitrelvir (proposed)	ND	ND	ND	0.1	2.1	1.4
M10 [d]	–	ND	ND	ND	0.1	ND	ND
M19 [d]	–	ND	ND	ND	ND	ND	1.3
M20	Oxidized ensitrelvir (proposed)	ND	ND	ND	ND	1.9	2.6
M2	Glucuronide of oxidized ensitrelvir (proposed)	ND	ND	ND	ND	ND	1.2
M4	Ensitrelvir triazole *N*-desmethyl	0.6	1.6	ND	0.6	6.4	6.0
Unchanged	Ensitrelvir	85.1	83.2	43.6	0.3	36.7	4.5
M6	Ensitrelvir indazole 4-Cl	0.7	2.3	3.7	ND	ND	ND

LC/MS^n = liquid chromatography with multistage mass spectrometry; Radio-HPLC = high performance liquid chromatography with radio-detector

a As a free form

b The samples were provided from excretion/pharmacokinetic/other study (Study No: S-217622 PF-020-N).

c The corresponding $[M+H]^+$ could not be found by MS.

d The metabolites were not be analyzed by MS.

Study Number	S-217622-PF-043-N
Location in CTD	4.2.2.4-01

2.6.5.9.2 ウサギにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後のエンシトレルビルの代謝プロファイル

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain		Rabbit/Kbl:NZW	
Gender (M/F)/Number of Animals		F/1 per time point	
Feeding Condition		Non-fasting	
Vehicle/Formulation		0.5% MC / suspension	
Method of Administration		Single oral administration	
Dose [a] (mg/kg)		2	
Radionuclide		^{14}C	
Specific Activity		1.95 MBq/mg (52.6 μCi/mg)	
Sample		Plasma [b] obtained at 4 and 24 hours after administration	
Analyte		Ensitrelvir and its metabolites	
Assay		LSC, Radio-HPLC, LC/MS^n	
Metabolites ID	Name of metabolite	Composition (% of total radioactivity in sample)	
		4 hr plasma	24 hr plasma
Unchanged	Ensitrelvir	86.0	74.2
M6	Ensitrelvir indazole 4-Cl	NC	1.5
a As a free form b Samples were provided from the dosing and plasma sample collection study (Study No.: S-217622-PF-063-N)			
Study Number	S-217622-PB-078-N		
Location in CTD	4.2.2.4-02		

2.6.5.9.3 サルにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後のエンシトレルビルの代謝プロファイル

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain		Monkey/Cynomolgus					
Gender (M/F)/Number of Animals		M/3 per time point (plasma), M/3 (urine and feces), and M/2 (bile)					
Feeding Condition		Non-fasting					
Vehicle/Formulation		0.5% MC/suspension					
Method of Administration		Single oral administration					
Dose [a] (mg/kg)		2					
Radionuclide		^{14}C					
Specific Activity		1.95 MBq/mg (52.6 μCi/mg)					
Sample		Plasma [b] obtained from intact monkeys, Urine, and feces [b] obtained from intact monkeys, Bile [b] obtained from bile duct-cannulated monkeys					
Analyte		Ensitrelvir and its metabolites					
Assay		Radio-HPLC, LC/MS^n					
Metabolites ID	Name of metabolite	Composition (% of total radioactivity in sample)			Cumulative Excretion (% of dose)		
		4 hr plasma	24 hr plasma	48 hr plasma	0–72 hr urine	0–96 hr feces	0–72 hr bile
M8 [c]	Unknown	ND	ND	ND	0.4	ND	ND
M9	Cysteine conjugate of oxidized and defluorinated ensitrelvir (proposed)	ND	ND	ND	ND	ND	3.3
M1	*N*-deindazolated form of ensitrelvir (proposed)	ND	ND	ND	0.4	4.7	ND [e]
M10 [d]	–	ND	ND	ND	0.2	ND	ND
M11	Glucuronide of oxidized ensitrelvir indazole *N*-desmethyl (proposed)	ND	ND	ND	ND	ND	4.0
M12	Glucuronide of oxidized ensitrelvir triazole *N*-desmethyl (proposed)	ND	ND	ND	ND	ND	1.6
M2	Glucuronide of oxidized ensitrelvir (proposed)	ND	ND	ND	ND [e]	ND	12.2
M3	Ensitrelvir 3-indazolinone	ND	ND	ND	ND [e]	4.7	1.4
M4	Ensitrelvir triazole *N*-desmethyl	1.0	1.4	1.7	5.3	6.8	3.5
M5	Ensitrelvir indazole *N*-desmethyl	ND	ND [e]	ND	0.4	ND [e]	ND [e]
Unchanged	Ensitrelvir	91.0	81.5	54.6	0.8	24.5	4.9
M6	Ensitrelvir indazole 4-Cl	0.7	4.0	8.0	ND	ND [e]	ND [e]
a As a free form b Samples were provided from excretion/pharmacokinetic/other study (Study No: S-217622-PF-026-N). c The corresponding $[M+H]^+$ could not be found by MS. d The metabolite was not be analyzed by MS. e Not detected on radiochromatogram, but detected on MS chromatogram							
Study Number	S-217622-PF-044-N						
Location in CTD	4.2.2.4-03						

2.6.5.10 薬物動態試験： 代謝：In Vitro

2.6.5.10.1 ラット，サル及びヒト肝細胞を用いた In Vitro 代謝

Test Article: [^{14}C]-Ensitrelvir

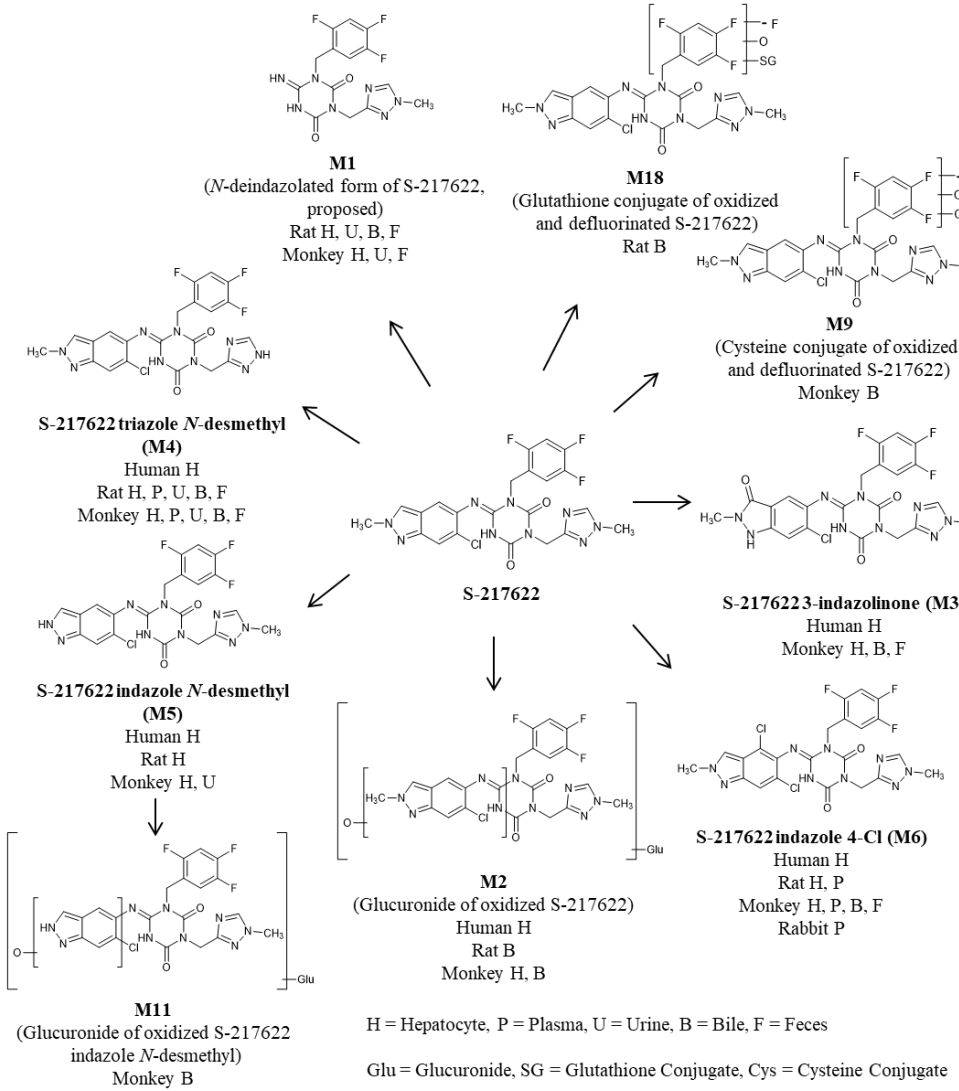
Test System		Cryopreserved rat (n = 8 pooled, [Lot No. 2010189, M]), monkey (n = 3 pooled, [Lot No. 1210031, F]), and human hepatocytes (2 Donors, individual [Lot No. HC4-5, and HC5-23])			
Incubation		At 37°C for 4 hours			
Concentration (μmol/L)		5			
Radionuclide		^{14}C			
Specific Activity		2.06 MBq/mg (55.6 μCi/mg)			
Sample		Reaction mixture after 4-hr incubation of [^{14}C]-ensitrelvir with cryopreserved rat, monkey, and human hepatocytes			
Analyte		Ensitrelvir and its metabolites			
Assay		LSC, Radio-HPLC, LC/MS^{n}			
Metabolites ID	Name of metabolite	Composition (% of total radioactivity in sample)			
		Rat	Monkey	Human (Lot No. HC4-5)	Human (Lot No. HC5-23)
M1	*N*-deindazolated form of ensitrelvir (proposed)	1.7	0.7	ND	ND
M2	Glucuronide of oxidized ensitrelvir (proposed)	ND	2.2	1.7	1.3
M3	Ensitrelvir 3-indazolinone	ND	ND [a]	ND [a]	ND [a]
M4	Ensitrelvir triazole *N*-desmethyl	3.5	1.7	0.9	ND [a]
M5	Ensitrelvir indazole *N*-desmethyl	0.4	0.7	0.7	0.5
Unchanged	Ensitrelvir	72.3	79.8	75.1	79.2
M6	Ensitrelvir indazole 4-Cl	ND [a]	ND [a]	ND [a]	ND [a]
Unknown	−	2.5	0.8	ND	ND
a The metabolite detected on LC/MS chromatogram without radioactive peak.					
Study Number		S-217622-PB-009-N			
Location in CTD		5.3.2.2-01			

2.6.5.10.2 エンシトレルビルの代謝に関わる酵素の同定

Test Article: [^{14}C]-Ensitrelvir

Test System	Human liver microsomes (a pool of 50 individual), Recombinant human CYP enzymes								
Incubation	At 37°C for 60 minutes (human liver microsomes), at 37°C for 90 minutes (recombinant human CYP enzymes)								
Concentration (μmol/L)	50								
Recombinant Enzymes	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5								
CYP Inhibitors	Furafylline (CYP1A2 inhibitor), Thio-TEPA (CYP2B6 inhibitor), Montelukast (CYP2C8 inhibitor), Sulfaphenazole (CYP2C9 inhibitor), S-(+)-*N*-3-Benzylnirvanol (CYP2C19 inhibitor), Quinidine (CYP2D6 inhibitor), Ketoconazole (CYP3A4/5 inhibitor)								
Radionuclide	^{14}C								
Specific Activity	2.06 MBq/mg (55.6 μCi/mg)								
Sample	Reaction mixture after incubation of [^{14}C]-ensitrelvir with recombinant enzymes or human liver microsomes								
Analyte	Ensitrelvir 3-indazolinone, Ensitrelvir indazole *N*-desmethyl, Ensitrelvir triazole *N*-desmethyl								
Assay	Radio-HPLC								
CYP enzyme		CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A5
Ensitrelvir metabolites formation with recombinant CYP (pmol/minutes/pmol P450)	Ensitrelvir 3-indazolinone	NC	NC	NC	NC	0.000372	0.00241	0.00296	NC
	Ensitrelvir triazole *N*-desmethyl	NC	NC	0.00352	0.00370	0.0139	0.0261	0.00296	0.00185
	Ensitrelvir indazole *N*-desmethyl	0.00148	0.000555	0.00556	0.00666	0.0589	0.00759	0.00352	0.00130
CYP enzyme		CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	
Effects of CYP inhibitors on ensitrelvir metabolite formation (% Inhibition from Control)	Ensitrelvir 3-indazolinone	−23.0	−8.4	−27.1	−20.9	−4.2	−27.1	6.3	
	Ensitrelvir triazole *N*-desmethyl	−3.2	−20.7	−4.7	−9.5	−6.3	0.0	38.1	
	Ensitrelvir indazole *N*-desmethyl	−3.9	10.2	14.1	7.7	−1.3	2.6	50.0	
Data are expressed as the mean of triplicate assays.									
Study Number	S-217622-PF-048-N								
Location in CTD	5.3.2.2-02								

2.6.5.11 薬物動態試験： 推定代謝経路



S-217622 in the figure represents ensitrelvir.

2.6.5.12 薬物動態試験： 薬物代謝酵素の誘導／阻害

2.6.5.12.1 ヒト CYP 酵素に対するエンシトレルビルの誘導作用

Test Article: Ensitrelvir fumaric acid

Test System	Primary cultures of cryopreserved human hepatocytes (3 Donors [Lot No. HC10-49, HC10-50, and HC7-33])
Exposure	At 37°C for 72 hours
Concentration (μmol/L)	0 (Control), 1, 3, 10, 25, 50, 75, 100
Positive controls (Concentration)	Omeprazole (50 μmol/L) for prototypical inducer of CYP1A2, Phenobarbital (1000 μmol/L) for prototypical inducer of CYP2B6, Rifampicin (20 μmol/L) for prototypical inducer of CYP2C8, CYP2C9, CYP2C19 and CYP3A
Substrates (Concentration)	Phenacetin (100 μmol/L) for CYP1A2, Bupropion (500 μmol/L) for CYP2B6, Midazolam (30 μmol/L) for CYP3A
Incubation	At 37°C for 45 min
Sample	CYP1A2, CYP2B6 and CYP3A activities after incubation of substrate with human hepatocytes which were exposed with ensitrelvir or positive control, RNA amount of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 from human hepatocytes which were exposed with ensitrelvir or positive control
Analyte	Acetaminophen (CYP1A2), hydroxybupropion (CYP2B6), 1'-hydroxymidazolam (CYP3A), mRNA
Assay	LC/MS/MS, Quantitative real-time polymerase chain reaction

CYP isoform	Test Article or Positive controls	Concentration (μmol/L)	mRNA level Fold induction to the corresponding control			Enzyme activity Fold induction to the corresponding control		
			HC10-49	HC10-50	HC7-33	HC10-49	HC10-50	HC7-33
CYP1A2	Ensitrelvir fumaric acid	1	0.927	0.911	0.766	1.15	0.993	1.17
		3	0.951	1.05	0.871	1.18	1.08	1.14
		10	0.935	1.05	0.877	1.77	1.41	1.34
		25	0.965	1.11	0.833	2.57	2.21	1.81
		50	1.04	1.22	0.597	4.39	3.00	2.67
		75	1.44	1.69	0.925	5.53	4.28	3.54
		100	1.37	1.88	0.773	6.72	4.87	4.11
	Omeprazole	50	28.5	35.3	23.1	26.2	37.2	17.8
CYP2B6	Ensitrelvir fumaric acid	1	0.829	0.967	1.02	1.32	0.936	1.29
		3	1.17	1.13	1.17	1.34	1.12	1.57
		10	1.33	1.57	2.08	2.93	1.72	2.35
		25	1.92	2.66	3.18	6.49	3.69	4.51
		50	2.84	5.98	4.10	15.4	6.06	8.38
		75	4.32	7.97	7.36	19.8	8.27	9.76
		100	4.24	11.2	6.29	25.4	8.79	12.7
	Phenobarbital	1000	11.1	20.4	8.70	27.1	7.63	20.7

CYP isoform	Test Article or Positive controls	Concentration (μmol/L)	mRNA level Fold induction to the corresponding control			Enzyme activity Fold induction to the corresponding control		
CYP2C8	Ensitrelvir fumaric acid	1	1.03	1.16	0.995	N/A	N/A	N/A
		3	1.19	1.04	1.13	N/A	N/A	N/A
		10	1.22	1.62	1.57	N/A	N/A	N/A
		25	1.60	2.28	2.42	N/A	N/A	N/A
		50	1.93	3.50	2.05	N/A	N/A	N/A
		75	2.35	4.26	3.49	N/A	N/A	N/A
		100	1.98	4.93	2.40	N/A	N/A	N/A
	Rifampicin	20	2.05	2.65	1.34	N/A	N/A	N/A
CYP2C9	Ensitrelvir fumaric acid	1	0.982	1.03	0.981	N/A	N/A	N/A
		3	1.10	1.18	1.16	N/A	N/A	N/A
		10	1.08	1.36	1.39	N/A	N/A	N/A
		25	1.30	1.93	1.88	N/A	N/A	N/A
		50	1.59	2.54	1.80	N/A	N/A	N/A
		75	2.00	2.92	2.63	N/A	N/A	N/A
		100	1.80	3.28	2.21	N/A	N/A	N/A
	Rifampicin	20	2.02	2.67	1.99	N/A	N/A	N/A
CYP2C19	Ensitrelvir fumaric acid	1	1.01	1.07	0.915	N/A	N/A	N/A
		3	0.956	1.14	1.10	N/A	N/A	N/A
		10	0.916	1.07	0.468	N/A	N/A	N/A
		25	0.878	1.16	0.490	N/A	N/A	N/A
		50	0.959	1.38	1.04	N/A	N/A	N/A
		75	1.08	1.41	1.80	N/A	N/A	N/A
		100	1.02	1.78	1.64	N/A	N/A	N/A
	Rifampicin	20	1.35	1.70	1.56	N/A	N/A	N/A
CYP3A	Ensitrelvir fumaric acid	1	1.02	1.31	1.16	1.09	0.886	0.996
		3	1.62	2.30	1.78	1.06	0.924	0.875
		10	2.78	7.36	6.50	1.73	1.48	0.734
		25	5.57	17.8	14.0	2.84	2.31	0.759
		50	6.87	30.3	14.9	3.63	2.79	0.771
		75	8.79	35.4	22.0	3.94	3.15	0.755
		100	7.92	44.1	22.1	4.45	3.04	0.849
	Rifampicin	20	8.66	27.5	16.4	19.9	15.5	2.83

CYP isoform	Induction Parameters	mRNA level			Enzyme activity		
		HC10-49	HC10-50	HC7-33	HC10-49	HC10-50	HC7-33
CYP1A2	EC_{50} (μmol/L)	N/A	N/A	N/A	40.7	41.2	44.1
	E_{max} (fold change)	N/A	N/A	N/A	7.23	5.50	4.95
CYP2B6	EC_{50} (μmol/L)	34.5	59.3	33.2	45.3	34.7	39.9
	E_{max} (fold change)	4.72	13.2	7.10	25.5	8.99	12.7
CYP2C8	EC_{50} (μmol/L)	N/A	32.1	N/A	N/A	N/A	N/A
	E_{max} (fold change)	N/A	5.17	N/A	N/A	N/A	N/A
CYP2C9	EC_{50} (μmol/L)	N/A	19.9	N/A	N/A	N/A	N/A
	E_{max} (fold change)	N/A	3.37	N/A	N/A	N/A	N/A
CYP2C19	EC_{50} (μmol/L)	NC	NC	NC	N/A	N/A	N/A
	E_{max} (fold change)	NC	NC	NC	N/A	N/A	N/A
CYP3A	EC_{50} (μmol/L)	17.7	33.8	20.2	16.4	11.7	N/A
	E_{max} (fold change)	8.05	41.3	20.4	4.20	3.05	N/A
EC_{50} = concentration causing half-maximal effect; E_{max} = maximum induction effect; mRNA = messenger RNA							
Study Number	S-217622-PF-013-N						
Location in CTD	5.3.2.2-03						

2.6.5.12.2 ヒト CYP 酵素に対するエンシトレルビルの阻害作用

Test Article: Ensitrelvir fumaric acid

Test System	Human liver microsomes (a pool of 200 donors)						
Concentration (μmol/L)	0 (control), 0.1, 0.3, 1, 3, 10, 30, 100						
Substrates (Concentration)	Phenacetin (90 μmol/L) for CYP1A2, Efavirenz (5 μmol/L) for CYP2B6, Amodiaquine (2 μmol/L) for CYP2C8, Diclofenac (12 μmol/L) for CYP2C9, S-Mephenytoin (60 μmol/L) for CYP2C19, Dextromethorphan (10 μmol/L) for CYP2D6, Testosterone (60 μmol/L) for CYP3A, Midazolam (3 μmol/L) for CYP3A						
Incubation	At 37°C for 5 min after 0 or 30 minutes preincubation						
Sample	Reaction mixture after incubation of substrate with human liver microsomes in the presence of ensitrelvir						
Analyte	Acetaminophen, 8-hydroxyefavirenz, *N*-desethylamodiaquine, 4'-hydroxydiclofenac, 4'-hydroxymephenytoin, dextrorphan, 6β-hydroxytestosterone, 1'-hydroxymidazolam						
Assay	LC/MS/MS						
CYP isoform	Direct inhibition (0 min)		Time-dependent inhibition (30 min)		Metabolism-dependent inhibition		Potential for time-dependent inhibition
	Zero-min preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH		
	IC_{50} (μmol/L)	Maximum inhibition (%)	IC_{50} (μmol/L)	Maximum inhibition (%)	IC_{50} (μmol/L)	Maximum inhibition (%)	
CYP1A2	> 100	0.8	> 100	N/A	> 100	N/A	No
CYP2B6	> 100	26.1	> 100	18.0	> 100	8.3	No
CYP2C8	35	68.9	34	68.3	34	68.3	No
CYP2C9	> 100	9.7	> 100	N/A	> 100	6.8	No
CYP2C19	> 100	34.6	> 100	38.4	> 100	37.9	No
CYP2D6	> 100	1.3	> 100	N/A	> 100	N/A	No
CYP3A (Midazolam)	> 100	42.9	> 100	28.5	39	47.8	Yes[a]
CYP3A (Testosterone)	> 100	24.5	> 100	9.9	81	42.5	Yes[b]
IC_{50} = 50% inhibitory concentration; K_I = half-maximal inactivation concentration; k_{inact} = maximal inactivation rate constant; NADPH = reduced form of β-nicotinamide adenine dinucleotide phosphate a The k_{inact} and K_I as enzyme inactivation parameters were 0.046 min^{-1} and 84 μmol/L, respectively. b The k_{inact} and K_I as enzyme inactivation parameters were 0.055 min^{-1} and 86 μmol/L, respectively.							
Study Number	S-217622-PF-016-N						
Location in CTD	5.3.2.2-04						

2.6.5.12.3 ヒト UGT 酵素に対するエンシトレルビルの阻害作用

Test Article: Ensitrelvir fumaric acid

Test System	Human liver microsomes (a pool of 200 donors)	
Concentration (μmol/L)	0 (control), 0.1, 0.3, 1, 3, 10, 30, 100	
Substrates (Concentration)	17β-Estradiol (12 μmol/L) for UGT1A1, chenodeoxycholic acid (160 μmol/L) for UGT1A3, trifluoperazine (20 μmol/L) for UGT1A4, 1-naphthol (2 μmol/L) for UGT1A6, propofol (16 μmol/L) for UGT1A9, morphine (400 μmol/L) for UGT2B7, oxazepam (100 μmol/L) for UGT2B15	
Incubation	At 37 ± 2°C for 10 minutes (UGT1A3 and UGT2B15) or 5 minutes (the other UGTs)	
Sample	Reaction mixture after incubation of substrate with human liver microsomes in the presence of ensitrelvir	
Analyte	17β-Estradiol 3-*O*-glucuronide, chenodeoxycholic acid 24-*O*-glucuronide, trifluoperazine *N*-glucuronide, 1-naphthol *O*-glucuronide, propofol *O*-glucuronide, morphine 3-*O*-glucuronide, *S*-oxazepam *O*-glucuronide	
Assay	LC/MS/MS	
UGT isoform	IC_{50} (μmol/L)	Maximum inhibition [a] (%)
UGT1A1	> 100	43.2
UGT1A3	> 100	8.7
UGT1A4	> 100	28.2
UGT1A6	> 100	14.5
UGT1A9	> 100	13.2
UGT2B7	> 100	9.5
UGT2B15	> 100	5.8
a Maximum inhibition observed (%) is calculated with the following formula: Maximum inhibition observed (%) = 100% − the minimum percent solvent control for any test article concentration.		
Study Number	S-217622-PF-030-N	
Location in CTD	5.3.2.2-05	

2.6.5.13 薬物動態試験： 排泄

2.6.5.13.1 ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の尿及び糞中排泄

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD (Sprague Dawley)			
Gender (M/F)/Number of Animals	M/4			
Feeding Condition	Non-fasting			
Vehicle/Formulation	0.5% MC/suspension			
Method of Administration	Single oral administration			
Dose [a] (mg/kg)	2			
Radionuclide	^{14}C			
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free			
Sample	Urine, Cage rinse, Feces			
Analyte	Radioactivity			
Assay	LSC			
Sampling time (hr)	Cumulative Excretion of Radioactivity (% of dose)			
	Urine	Cage rinse	Feces	Total
6	0.7 ± 0.3	0.4 ± 0.3	NS	NC
24	2.4 ± 0.6	0.5 ± 0.3	78.6 ± 6.3	81.5 ± 6.3
48	2.7 ± 0.6	0.5 ± 0.3	93.1 ± 1.3	96.2 ± 1.5
72	2.8 ± 0.6	0.5 ± 0.3	93.8 ± 1.0	97.0 ± 1.2
96	2.8 ± 0.6	0.5 ± 0.3	93.9 ± 0.9	97.2 ± 1.2
120	2.8 ± 0.6	0.5 ± 0.3	94.0 ± 0.9	97.3 ± 1.2
144	2.9 ± 0.6	0.5 ± 0.3	94.0 ± 0.9	97.4 ± 1.2
168	2.9 ± 0.6	0.5 ± 0.3	94.1 ± 0.9	97.4 ± 1.1
Data are expressed as the mean ± SD. a As a free form				
Study Number	S-217622-PF-020-N			
Location in CTD	4.2.2.2-01			

2.6.5.13.2 サルにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の尿及び糞中排泄

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Monkey/Cynomolgus			
Gender (M/F)/Number of Animals	M/3			
Feeding Condition	Non-fasting			
Vehicle/Formulation	0.5% MC/suspension			
Method of Administration	Single oral administration			
Dose [a] (mg/kg)	2			
Radionuclide	^{14}C			
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free			
Sample	Urine, Cage rinse, Feces			
Analyte	Radioactivity			
Assay	LSC			
Sampling time (hr)	Cumulative Excretion of Radioactivity (% of dose)			
	Urine	Cage rinse	Feces	Total
6	1.0 ± 0.2	0.3 ± 0.4	NS	NC
24	6.7 ± 0.8	0.8 ± 0.4	36.7 ± 13.5	44.2 ± 13.1
48	9.7 ± 0.5	1.1 ± 0.4	65.4 ± 3.8	76.2 ± 3.5
72	10.7 ± 0.3	1.3 ± 0.4	78.0 ± 4.6	90.0 ± 4.3
96	11.0 ± 0.3	1.5 ± 0.5	82.9 ± 1.8	95.4 ± 1.6
120	11.1 ± 0.3	1.5 ± 0.5	84.2 ± 1.5	96.8 ± 1.4
144	11.2 ± 0.3	1.5 ± 0.5	84.7 ± 1.4	97.5 ± 1.3
168	11.2 ± 0.3	1.5 ± 0.5	84.9 ± 1.4	97.6 ± 1.2
Data are expressed as the mean ± SD. a As a free form				
Study Number	S-217622-PF-026-N			
Location in CTD	4.2.2.2-02			

2.6.5.14 薬物動態試験： 排泄：胆汁中

2.6.5.14.1 ラットにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の尿，胆汁中及び糞排泄

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Rat/Crl:CD(Sprague Dawley)				
Gender (M/F)/Number of Animals	M/4				
Feeding Condition	Non-fasting				
Vehicle/Formulation	0.5% MC/suspension				
Method of Administration	Single oral administration				
Dose [a] (mg/kg)	2				
Radionuclide	^{14}C				
Specific Activity	1.60 MBq/mg (43.2 μCi/mg) as fumaric acid 1.95 MBq/mg (52.6 μCi/mg) as free				
Sample	Urine, Bile, Cage rinse, Feces, Gastro-intestinal contents				
Analyte	Radioactivity				
Assay	LSC				
Sampling time (hr)	Cumulative Excretion of Radioactivity (% of dose)				
	Urine	Bile	Cage rinse	Feces	Total
6	0.5 ± 0.3	20.5 ± 11.6	0.1 ± 0.2	NS	NC
24	3.2 ± 0.6	55.9 ± 10.0	0.3 ± 0.2	14.0 ± 3.8	73.4 ± 8.4
48	3.6 ± 0.8	59.7 ± 9.7	0.3 ± 0.2	32.5 ± 8.2	96.0 ± 0.8
72	3.8 ± 0.9	60.1 ± 9.6	0.3 ± 0.3	33.6 ± 8.4	97.9 ± 0.5 [b]
Data are expressed as the mean ± SD. a As a free form b Including the radioactivity in gastro-intestinal contents 72 hours post-dose (0.1 ± 0.1%).					
Study Number	S-217622-PF-020-N				
Location in CTD	4.2.2.2-01				

2.6.5.14.2 サルにおける [^{14}C]-エンシトレルビルフマル酸単回経口投与後の尿，胆汁及び糞中排泄

Test Article: [^{14}C]-Ensitrelvir fumaric acid

Species/Strain	Monkey/Cynomolgus				
Gender (M/F)/Number of Animals	M/2				
Feeding Condition	Non-fasting				
Vehicle/Formulation	0.5% MC/suspension				
Method of Administration	Single oral administration				
Dose [a] (mg/kg)	2				
Radionuclide	^{14}C				
Specific Activity	1.60 MBq (43.2 μCi)/mg as fumaric acid 1.95 MBq (52.7 μCi)/mg as free				
Sample	Urine, Bile, Cage rinse, Feces, Gastro-intestinal contents				
Analyte	Radioactivity				
Assay	LSC				
Sampling time (hr)	Cumulative Excretion of Radioactivity (% of dose)				
	Urine	Bile	Cage rinse	Feces	Total
6	3.4	14.9	0.7	NS	NC
24	10.9	41.8	1.0	16.0	69.7
48	13.7	54.7	1.4	26.1	95.7
72	14.4	57.5	1.6	27.2	101.0 [b]
Data are expressed as the mean ± SD. a As a free form b Including the radioactivity in gastro-intestinal contents 72 hours post-dose (0.3%).					
Study Number	S-217622-PF-026-N				
Location in CTD	4.2.2.2-02				

2.6.5.15 薬物動態試験： 薬物相互作用

2.6.5.15.1 ヒト排出トランスポーターに対するエンシトレルビルの基質評価

Test Article: [^{14}C]-Ensitrelvir

Test System	Caco-2 cells				
Concentration (µmol/L)	1, 10				
Typical Substrates (Concentration)	[^{3}H]-Digoxin (1 µmol/L for P-gp), [^{3}H]-ES (0.1 µmol/L for BCRP)				
Representative Inhibitors (Concentration)	Verapamil (30 µmol/L for P-gp), Ko143 (1 µmol/L for BCRP)				
Incubation	At 37°C for 0.5, 1 and 2 hours				
Sample	Apical side solution, Basal side solution				
Radionuclide	^{14}C				
Specific Activity	2.06 MBq/mg (55.6 µCi/mg)				
Analyte	Radioactivity				
Assay	LSC				
Test substance, typical substrate	Representative inhibitor (concentration)	Apparent Permeability (× 10^{-6} cm/sec)		P_{app} Ratio	% of control
		Apical to Basal	Basal to Apical		
[^{14}C]-Ensitrelvir (1 µmol/L)	None	4.24 ± 0.58	23.4 ± 0.5	5.5	100.0
	Verapamil (30 µmol/L)	8.44 ± 0.52	19.6 ± 0.4	2.3	28.9
	Ko143 (1 µmol/L)	6.48 ± 0.99	22.7 ± 0.6	3.5	55.6
[^{14}C]-Ensitrelvir (10 µmol/L)	None	4.79 ± 0.27	22.4 ± 0.7	4.7	100.0
	Verapamil (30 µmol/L)	9.67 ± 0.15	19.0 ± 0.7	2.0	27.0
	Ko143 (1 µmol/L)	6.69 ± 0.15	20.6 ± 0.8	3.1	56.8
[^{3}H]-Digoxin (1 µmol/L)	None	0.992 ± 0.079	11.6 ± 0.8	11.7	100.0
	Verapamil (30 µmol/L)	4.37 ± 0.23	5.53 ± 0.27	1.3	2.8
[^{3}H]-ES (0.1 µmol/L)	None	1.42 ± 0.00	27.3 ± 0.2	19.2	100.0
	Ko143 (1 µmol/L)	5.70 ± 0.44	5.71 ± 0.26	1.0	0.0
BCRP = breast cancer resistance protein; ES = estrone sulfate; P_{app} = apparent permeability; P-gp = P-glycoprotein Data are expressed as the mean ± SD of triplicate assays.					
Study Number	S-217622-PF-006-N				
Location in CTD	5.3.2.2-06				

2.6.5.15.2 ヒト取り込みトランスポーターに対するエンシトレルビルの基質評価

Test Article: [^{14}C]-Ensitrelvir

Test System	Human uptake transporter (OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K) transfected HEK-293 cells
Concentration (μmol/L)	1 or 10
Typical Substrates (Concentration)	[^{3}H]-E$_2$17βG (0.05 μmol/L for OATP1B1 and OATP1B3), [^{3}H]-PAH (1 μmol/L for OAT1), [^{3}H]-ES (0.05 μmol/L for OAT3), [^{14}C]-Metformin (10 μmol/L for OCT1, OCT2, MATE1 and MATE2-K)
Representative Inhibitors (Concentration)	Rifampicin (10 μmol/L for OATP1B1 and OATP1B3), probenecid (100 μmol/L for OAT1 and OAT3), quinidine (100 μmol/L for OCT1 and 300 μmol/L for OCT2), cimetidine (10 μmol/L for MATE1 and 100 μmol/L for MATE2-K)
Incubation	At 37°C for 2, 5, or 10 minutes
Radionuclide	^{14}C
Specific Activity	2.06 MBq/mg (55.6 μCi/mg)
Sample	Cell lysate
Analyte	Radioactivity
Assay	LSC

Uptake transporter	Test Substance (Concentration)	Representative inhibitor (Concentration)	Time (minutes)	Cleared volume ratio	% of control [a]
OATP1B1	[^{14}C]-Ensitrelvir (1 μmol/L)	None	2	1.0	NC
			5	0.9	NC
			10	1.0	NC
		Rifampicin (10 μmol/L)	2	0.9	NC
			5	1.0	NC
			10	1.0	NC
	[^{14}C]-Ensitrelvir (10 μmol/L)	None	2	1.3	NC
			5	1.0	NC
			10	0.9	NC
		Rifampicin (10 μmol/L)	2	1.3	NC
			5	0.9	NC
			10	0.9	NC
	[^{3}H]-E$_2$17βG (0.05 μmol/L)	None	2	153.6	100.0
		Rifampicin (10 μmol/L)	2	4.3	2.3

Uptake transporter	Test Substance (Concentration)	Representative inhibitor (Concentration)	Time (minutes)	Cleared volume ratio	% of control [a]
OATP1B3	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	0.9	NC
			5	0.9	NC
			10	0.9	NC
		Rifampicin (10 µmol/L)	2	0.9	NC
			5	1.0	NC
			10	1.0	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	1.0	NC
			5	1.1	NC
			10	1.1	NC
		Rifampicin (10 µmol/L)	2	0.9	NC
			5	1.0	NC
			10	1.0	NC
	[^{3}H]-E$_2$17βG (0.05 µmol/L)	None	2	52.3	100.0
		Rifampicin (10 µmol/L)	2	1.6	1.4
OAT1	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	1.0	NC
			5	1.0	NC
			10	1.1	NC
		Probenecid (100 µmol/L)	2	1.0	NC
			5	1.1	NC
			10	1.0	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	0.8	NC
			5	0.8	NC
			10	0.8	NC
		Probenecid (100 µmol/L)	2	0.7	NC
			5	0.9	NC
			10	0.8	NC
	[^{3}H]-PAH (1 µmol/L)	None	0.5	142.6	100.0
		Probenecid (100 µmol/L)	0.5	10.8	6.5

Uptake transporter	Test Substance (Concentration)	Representative inhibitor (Concentration)	Time (minutes)	Cleared volume ratio	% of control [a]
OAT3	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	1.0	NC
			5	0.9	NC
			10	0.9	NC
		Probenecid (100 µmol/L)	2	0.9	NC
			5	0.9	NC
			10	0.8	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	0.8	NC
			5	0.8	NC
			10	0.7	NC
		Probenecid (100 µmol/L)	2	0.9	NC
			5	0.8	NC
			10	0.7	NC
	[^{3}H]-ES (0.05 µmol/L)	None	2	37.3	100.0
		Probenecid (100 µmol/L)	2	3.7	8.5
OCT1	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	1.2	NC
			5	1.0	NC
			10	1.1	NC
		Quinidine (100 µmol/L)	2	1.2	NC
			5	1.0	NC
			10	1.3	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	1.0	NC
			5	1.0	NC
			10	0.9	NC
		Quinidine (100 µmol/L)	2	1.0	NC
			5	1.0	NC
			10	1.0	NC
	[^{14}C]-Metformin (10 µmol/L)	None	5	17.0	100.0
		Quinidine (100 µmol/L)	5	4.0	4.4

Uptake transporter	Test Substance (Concentration)	Representative inhibitor (Concentration)	Time (minutes)	Cleared volume ratio	% of control [a]
OCT2	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	1.0	NC
			5	1.4	NC
			10	1.2	NC
		Quinidine (300 µmol/L)	2	1.0	NC
			5	1.7	NC
			10	1.1	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	0.9	NC
			5	1.0	NC
			10	1.0	NC
		Quinidine (300 µmol/L)	2	1.0	NC
			5	1.0	NC
			10	1.0	NC
	[^{14}C]-Metformin (10 µmol/L)	None	2	63.6	100.0
		Quinidine (300 µmol/L)	2	2.9	0.8
MATE1	[^{14}C]-Ensitrelvir (1 µmol/L)	None	2	1.0	NC
			5	0.9	NC
			10	0.8	NC
		Cimetidine (10 µmol/L)	2	1.0	NC
			5	1.0	NC
			10	0.9	NC
	[^{14}C]-Ensitrelvir (10 µmol/L)	None	2	0.9	NC
			5	0.9	NC
			10	0.9	NC
		Cimetidine (10 µmol/L)	2	0.9	NC
			5	0.9	NC
			10	0.8	NC
	[^{14}C]-Metformin (10 µmol/L)	None	5	28.6	100.0
		Cimetidine (10 µmol/L)	5	4.6	7.9

Uptake transporter	Test Substance (Concentration)	Representative inhibitor (Concentration)	Time (minutes)	Cleared volume ratio	% of control [a]
MATE2-K	[^{14}C]-Ensitrelvir (1 μmol/L)	None	2	0.8	NC
			5	0.8	NC
			10	0.7	NC
		Cimetidine (100 μmol/L)	2	0.8	NC
			5	0.9	NC
			10	0.8	NC
	[^{14}C]-Ensitrelvir (10 μmol/L)	None	2	0.9	NC
			5	0.9	NC
			10	1.0	NC
		Cimetidine (100 μmol/L)	2	0.9	NC
			5	0.8	NC
			10	0.9	NC
	[^{14}C]-Metformin (10 μmol/L)	None	5	21.7	100.0
		Cimetidine (100 μmol/L)	5	5.2	14.7
$E_2$17βG = estradiol 17β-D-Glucuronide; PAH = 4-aminohippuric acid Data are expressed as the mean ± SD of triplicate assays. a The % of control was not calculated in the ensitrelvir group, since ensitrelvir was judged not a substrate for the transporter.					
Study Number	S-217622-PF-006-N				
Location in CTD	5.3.2.2-06				

2.6.5.15.3 ヒトトランスポーターに対するエンシトレルビルの阻害評価

Test Article: Ensitrelvir fumaric acid

Test System	Caco-2 cells, Human uptake transporter (OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K) transfected HEK-293 cells	
Concentration (μmol/L)	0.3, 1, 3, 10, 30, 100, and 250 (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K)	
Probe Substrates (Concentration)	[^{3}H]-Digoxin (1 μmol/L for P-gp), [^{3}H]-ES (0.1 μmol/L for BCRP, 0.05 μmol/L for OAT3), [^{3}H]-$E_2$17βG (0.05 μmol/L for OATP1B1 and OATP1B3), [^{3}H]-PAH (1 μmol/L for OAT1) and [^{14}C]-Metformin (10 μmol/L for OCT1, OCT2, MATE1, and MATE2-K)	
Representative Inhibitors (Concentration)	Verapamil (30 μmol/L for P-gp), Ko143 (1 μmol/L for BCRP), rifampicin (10 μmol/L for OATP1B1 and OATP1B3), probenecid (100 μmol/L for OAT1 and OAT3), quinidine (100 μmol/L for OCT1 and 300 μmol/L for OCT2) and cimetidine (10 μmol/L for MATE1 and 100 μmol/L for MATE2-K)	
Incubation	At 37°C for 2 hours (P-gp and BCRP), 2 minutes (OATP1B1, OATP1B3, OAT3 and OCT2), 0.5 minutes (OAT1) and 5 minutes (OCT1, MATE1 and MATE2-K)	
Sample	Apical side solution and basal side solution (P-gp and BCRP), cell lysate (OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K)	
Analyte	Radioactivity	
Assay	LSC	
Transporters	IC_{50} (μmol/L)	% of control at the maximum concentration
P-gp	11.5	0.0
BCRP	8.71	−2.7
OATP1B1	13.2	0.2
OATP1B3	3.51	0.2
OAT1	47.7	6.4
OAT3	8.37	1.2
OCT1	7.24	2.1
OCT2	202	40.0
MATE1	82.3	24.2
MATE2-K	> 250	63.5
Study Number	S-217622-PF-006-N	
Location in CTD	5.3.2.2-06	

2.6.5.15.4 ヒトトランスポーターに対するエンシトレルビルの阻害評価 (2)

Test Article: Ensitrelvir fumaric acid

Test System	BSEP expressing vesicles	
Concentration (μmol/L)	0.3, 1, 3, 10, 30, 100, and 150	
Probe Substrates (Concentration)	[^{3}H]-Taurocholic acid (2 μmol/L)	
Representative Inhibitors (Concentration)	Cyclosporin A (10 μmol/L)	
Incubation	At 37°C for 5 minutes	
Sample	Vesicle lysate	
Analyte	Radioactivity	
Assay	LSC	
Transporter	IC_{50} (μmol/L)	% of control at the maximum concentration
BSEP	> 150	63.8
Study Number	S-217622-PF-107-N	
Location in CTD	5.3.2.2-07	

2.6.5.16 薬物動態試験： その他

該当する試験なし