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

2.6.7 毒性試験概要表

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
2AA	2-aminoanthracene
4NQO	4-nitroquinoline 1-oxide
9AA	9-aminoacridine hydrochloride monohydrate
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from time 0 to 24 hours postdose
CLC	colchicine
CM	chylomicron
C_{max}	maximum plasma concentration
CP	cyclophosphamide monohydrate
DMSO	dimethyl sulfoxide
F	female
GD	gestation day
GLP	Good Laboratory Practice
HDL	high density lipoprotein
IC_{50}	50% inhibition concentration
IEs	immature erythrocytes
L	lactation day
LCAT	lecithin cholesterol acyltransferase
LDL	low density lipoprotein
M	male
MC	methylcellulose aqueous solution
MEC	molar extinction coefficient
MMC	mitomycin C
MNIEs	micronucleated immature erythrocytes
MPE	mean photo effect
N/A	not applicable
NaN_3	sodium azide
NC	not calculated
ND	no data
NE	not examined
NF/NL	number of fetuses evaluated/number of litterss evaluated
NOAEL	no observed adverse effect level
NZW	New Zealand White
PIF	photo irritation factor
S9 mix	metabolic activation system
SD	standard deviation
T_{max}	time to maximum plasma concentration
VLDL	very low density lipoprotein

2.6.7 毒性試験概要表

2.6.7.1 毒性試験： 一覧表

Test Article: Ensitrelvir fumaric acid

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses [a] (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-dose Toxicity [b]	Rat/Sprague Dawley	Oral gavage	Single	100, 300, 1000 mg/kg	No	Shionogi & Co., Ltd.	TOX-20[redacted]-S-217622-01	4.2.3.1-01
	Monkey/ Cynomolgus	Oral gavage	Single	100, 300, 1000 mg/kg	No	Shionogi & Co., Ltd.	TOX-20[redacted]-S-217622-02	4.2.3.1-02
Repeat-dose Toxicity	Rat/Sprague Dawley	Oral gavage	2 weeks	0, 20, 100, 1000	Yes	[redacted]	S-217622-TF-022-L	4.2.3.2-01
	Rat/Sprague Dawley	Oral gavage	4 weeks	0, 20, 50, 1000	Yes		S-217622-TF-072-L	4.2.3.2-02
	Monkey/ Cynomolgus	Oral gavage	2 weeks	M: 0, 10, 50, 1000/300/100 F: 0, 10, 50, 300/100	Yes		S-217622-TF-023-L	4.2.3.2-03
	Monkey/ Cynomolgus	Oral gavage	4 weeks	0, 3, 10, 30	Yes		S-217622-TF-073-L	4.2.3.2-04
Genotoxicity	*Salmonella typhimurium* and *Escherichia coli*	In vitro	N/A	20.6 to 5000 µg/plate	No		Ames-[redacted]-003	4.2.3.3-02
	S. typhimurium and *E. coli*	In vitro	N/A	0, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate	Yes		S-217622-TF-027-L	4.2.3.3-01
	Human lymphoblastoid derived TK6 cells	In vitro	N/A	−S9 or +S9 mix, 3 hour treatment: 62.5 125, 250 µg/mL −S9 mix, 24-hour treatment: 31.3, 62.5, 125 µg/mL	No		Mvit-[redacted]-003	4.2.3.3-04

＊新薬承認情報提供時に置換

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses [a] (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Genotoxicity	Human lymphoblastoid derived TK6 cells	In vitro	N/A	−S9 or +S9 mix, 3 hour treatment: 0, 150, 200, 250 µg/mL −S9 mix, 24-hour treatment: 75, 100, 125 µg/mL	Yes	[redacted]	S-217622-TF-028-L	4.2.3.3-03
	Rat/Sprague Dawley	Oral gavage	3 times	0, 250, 500, 1000, 2000	Yes	[redacted]	S-217622-TF-029-L	4.2.3.3-05
Reproductive and Developmental Toxicity	Rat/Sprague Dawley	Oral gavage	M: 4 weeks premating until necropsy F: 2 weeks premating until GD7	0, 20, 60, 1000	Yes	[redacted]	S-217622-TF-071-L	4.2.3.5-01
	Rat/Sprague Dawley	Oral gavage	GD6– GD17	0, 20, 60, 1000	Yes	[redacted]	S-217622-TF-049-L	4.2.3.5-02
	Rabbit/ Kbl:NZW	Oral gavage	GD6–GD19	0, 30, 300, 1000	No	[redacted]	S-217622-TF-052-R	4.2.3.5-04
	Rabbit/ Kbl:NZW	Oral gavage	GD6–GD19	0, 30, 100, 300	Yes	[redacted]	S-217622-TF-070-L	4.2.3.5-03
	Rabbit/ Kbl:NZW	Oral gavage	GD6-GD9	0, 300, 500, 750, 1000	No	[redacted]	S-217622-TF-119-R	4.2.3.5-06
	Rabbit/ Kbl:NZW	Oral gavage	GD6–GD19	0, 100, 300	Yes	[redacted]	S-217622-TF-137-L	4.2.3.5-07
	Rabbit/ Kbl:NZW	Oral gavage	GD9-GD19 (control) GD6-GD9, GD10-GD12 GD13-GD15 GD16-GD19	0, 300	Yes	[redacted]	S-217622-TF-135-L	4.2.3.5-08
	Rat/Sprague Dawley	Oral gavage	GD6–L20	0, 20, 60, 1000	Yes	[redacted]	S-217622-TF-050-L	4.2.3.5-05

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Other Toxicity								
Phototoxicity	–	–	N/A	0.1200 mmol/L (wavelength range: 290 to 700 nm and 400 to 700 nm)	No [c]	[redacted]	S-217622-TF-019-N	4.2.3.7-01
	BALB/c 3T3 cells	In vitro	N/A	0.781 to 100 µg/mL	Yes	[redacted]	S-217622-TF-040-L	4.2.3.7-02
Mechanism for HDL reduction	Rat plasma	In vitro	N/A	0.00824, 0.0247, 0.0740, 0.222, 0.668, 2.00, 6.00, 18.0 µg/mL	No [c]	Shionogi & Co., Ltd.	S-217622-TB-123-N	4.2.3.7-03
	THP-1 cell (human leukemic monocyte)	In vitro	N/A	6.25, 12.5, 25.0, 50.0, 100, and 200 µg/mL	No [c]	Shionogi & Co., Ltd.	S-217622-TB-124-N	5.3.2.3-01
	Human plasma	Oral	5 days	750 mg on Day 1 [the first day of dosing] and 250 mg on Days 2 to 5	No [c]	Shionogi & Co., Ltd.	S-217622-CB-114-N	5.3.2.3-02
	Monkey/ Cynomologus	Oral	10 days	10	No [c]	[redacted] (main study)	S-217622-TF-191-N	4.2.3.7-18
					No [c]	[redacted] (blood examination)	S-217622-TF-192-N	4.2.3.7-19

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Impurities								
Reverse Mutation Test of 不純物G* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 1250 µg/plate	Yes	[redacted]	S-217622-TF-053-L	4.2.3.7-04
Reverse Mutation Test of 不純物A* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	39.1 to 1250 µg/plate	Yes		S-217622-TF-055-L	4.2.3.7-05
Reverse Mutation Test of 不純物D* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	39.1 to 1250 µg/plate	Yes		S-217622-TF-057-L	4.2.3.7-06
Reverse Mutation Test of 不純物C* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	313 to 5000 µg/plate	Yes		S-217622-TF-058-L	4.2.3.7-07
Reverse Mutation Test of 不純物B* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	156 to 5000 µg/plate	Yes		S-217622-TF-059-L	4.2.3.7-08
Reverse Mutation Test of 不純物E* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	313 to 5000 µg/plate	Yes		S-217622-TF-066-L	4.2.3.7-09
Reverse Mutation Test of 不純物H* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	156 to 5000 µg/plate	Yes		S-217622-TF-067-L	4.2.3.7-10
Reverse Mutation Test of 不純物F* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	39.1 to 1250 µg/plate	Yes		S-217622-TF-083-L	4.2.3.7-11
Reverse Mutation Test of 不純物L* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	−S9 mix 0.61 to 313 µg/plate +S9 mix: 4.88 to 313 µg/plate	Yes		[redacted]	4.2.3.7-12
Reverse Mutation Test of 不純物K* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	39.1 to 1250 µg/plate	Yes			4.2.3.7-13
Reverse Mutation Test of 不純物J* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	1.22 to 5000 µg/plate	Yes			4.2.3.7-14

＊新薬承認情報提供時に置換

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Reverse Mutation Test of 不純物I* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	−S9 mix 156 to 5000 µg/plate +S9 mix: 78.1 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-15
Reverse Mutation Test of 不純物M* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	313 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-16
Reverse Mutation Test of 不純物Z* with Bacteria	*S. typhimurium* and *E. coli*	In vitro	N/A	61.7 to 5000 µg/plate	No	[redacted]	[redacted]	4.2.3.7-17

F = female; GD = gestation day; GLP = Good Laboratory Practice; HDL = high density lipoprotein; L = lactation day; M = male; N/A = not applicable; NZW = New Zealand White;
S9 mix = metabolic activation system

a Unless otherwise specified. For Repeat-Dose Toxicity, and Reproductive and Developmental Toxicity (reproductive functions, maternal reproductive function, and embryo-fetal development), the highest NOAEL (No Observed Adverse Effect Level) is underlined. As free form.

b The studies were conducted as exploratory toxicokinetics study.

c The studies were conducted in compliance with the Reliability Criteria of Application Data in Japan.

＊新薬承認情報提供時に置換

2.6.7.2 トキシコキネティクス： トキシコキネティクス試験の一覧表

Test Article: Ensitrelvir fumaric acid

Type of Study	Test System	Method of Administration	Doses [a] (mg/kg/day)	GLP Compliance	Study Number	Location in CTD
Repeat-dose Toxicity (2-Week)	Rat	Oral gavage	0, 20, 100, 1000	Yes	S-217622-TF-022-L	4.2.3.2-01
Repeat-dose Toxicity (2-Week)	Monkey	Oral gavage	M: 0, 10, 50, 1000/300/100 F: 0, 10, 50, 300/100	Yes	S-217622-TF-023-L	4.2.3.2-03
Repeat-dose Toxicity (4-Week)	Rat	Oral gavage	0, 20, 50, 1000	Yes	S-217622-TF-072-L	4.2.3.2-02
Repeat-dose Toxicity (4-Week)	Monkey	Oral gavage	0, 3, 10, 30	Yes	S-217622-TF-073-L	4.2.3.2-04
Embryo-fetal development	Rat	Oral gavage	0, 20, 60, 1000	Yes	S-217622-TF-049-L	4.2.3.5-02
Embryo-fetal development	Rabbit	Oral gavage	0, 30, 100, 300	Yes	S-217622-TF-070-L	4.2.3.5-03
Embryo-fetal development (additional study)	Rabbit	Oral gavage	0, 300	Yes	S-217622-TF-135-L	4.2.3.5-08

a As free form.

2.6.7.3 トキシコキネティクス： トキシコキネティクス試験成績の一覧

Test Article: Ensitrelvir fumaric acid

Daily Dose [a] (mg/kg)	Steady State C_{max} (µg/mL)					
	Rats		Rabbits	Monkeys		Humans
	M	F	F	M	F	M & F
3				16.4 [b]	19.9 [b]	
10				77.6 [c], 76.8 [b]	75.2 [c], 95.9 [b]	
20	37.9 [d], 39.6 [e]	38.8 [d], 51.6 [e], 46.1 [f]				
30			68.8 [g]	241 [b]	211 [b]	
50	114 [e]	142 [e]		404 [c]	378 [c]	
60		134 [f]				
100	178 [d]	206 [d]	167 [g]			
300/100 [h]					430 [c]	
300			220 [g], 196-427 [p]			
1000/300/100 [i]				409 [c]		
1000	269 [d], 263 [e]	319 [d], 359 [e], 240 [f]				
Daily Dose [a] (mg/kg)	Steady State $AUC_{0\text{-}24hr}$ (µg·hr/mL)					
	Rats		Rabbits	Monkeys		Humans
	M	F	F	M	F	M & F
3				242 [j]	333 [j]	
10				1220 [k], 1170 [j]	1170 [k], 1850 [j]	
20	370 [l] 388 [m]	344 [l], 500 [m], 618 [n]				
30			1260 [o]	4170 [j]	4490 [j]	
50	1700 [m]	1780 [m]		7810 [k]	7390 [k]	
60		1990 [n]				
100	2510 [l]	2890 [l]	2580 [o]			
300/100 [h]					8170 [k]	
300			3840 [o], 3200-7890 [q]			
1000/300/100 [i]				7840 [k]		
1000	3850 [l], 4270 [m]	3940 [l], 5380 [m], 3400 [n]				

$AUC_{0\text{-}24hr}$ = area under the plasma concentration-time curve from time 0 to 24 hours postdose; C_{max} = maximum plasma concentration

a As free form.
b The C_{max} on Day 28 of a repeat-dose toxicity study (4-week) in monkeys (Study No.: S-217622-TF-073-L).
c The C_{max} on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Study No.: S-217622-TF-023-L).
d The C_{max} on Day 14 of a repeat-dose toxicity study (2-week) in rats (Study No.: S-217622-TF-022-L).
e The C_{max} on Day 28 a repeat-dose toxicity study (4-week) in rats (Study No.: S-217622-TF-072-L).
f The C_{max} on GD17 of a embryo-fetal development study in rats (Study No.: S-217622-TF-049-L).
g The C_{max} on GD19 of a embryo-fetal development study in rabbits (Study No.: S-217622-TF-070-L).
h The dose level was reduced from 300 mg/kg/day to 100 mg/kg/day on Day 9 of dosing.

i The dose level was reduced from 1000 mg/kg/day to 300 mg/kg/day from Day 3 of dosing, and from 300 mg/kg/day to 100 mg/kg/day from Day 8 of dosing.
j The $AUC_{0\text{-}24hr}$ on Day 28 of a repeat-dose toxicity study (4-week) in monkeys (Study No.: S-217622-TF-073-L).
k The $AUC_{0\text{-}24hr}$ on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Study No.: S-217622-TF-023-L).
l The $AUC_{0\text{-}24hr}$ on Day 14 of a repeat-dose toxicity study (2-week) in rats (Study No.: S-217622-TF-022-L).
m The $AUC_{0\text{-}24hr}$ on Day 28 of a repeat-dose toxicity study (4-week) in rats (Study No.: S-217622-TF-072-L).
n The $AUC_{0\text{-}24hr}$ on GD17 of a embryo-fetal development study in rats (Study No.: S-217622-TF-049-L).
o The $AUC_{0\text{-}24hr}$ on GD19 of a embryo-fetal development study in rabbits (Study No.: S-217622-TF-070-L).
p The range of C_{max} on GD9, GD12, GD15, or GD19 in each group of a embryo-fetal development study in rabbits (Study No.: S-217622-TF-135-L).
q The range of $AUC_{0\text{-}24h}$ on GD9, GD12, GD15, or GD19 in each group of a embryo-fetal development study in rabbits (Study No.: S-217622-TF-135-L).

2.6.7.4 毒性試験： 被験物質（ロット毎）一覧

Test Article: Ensitrelvir fumaric acid

Batch No.	Content (on the anhydrous basis) (%)	Specified Impurities (%)	Study Number	Type of Study
		Related substance		
A15001	98.4 [a]	0.11	S-217622-TF-022-L	Repeat-dose toxicity (2-week) in rats
			S-217622-TF-023-L	Repeat-dose toxicity (2-week) in monkeys
			S-217622-TF-027-L	Bacterial reverse mutation test
			S-217622-TF-028-L	Micronuleus test with cultured mammalian cells
			S-217622-TF-029-L	Micronucleus test in rats
			S-217622-TF-040-L	3T3 assay
			S-217622-TF-019-N	Molar extinction coefficient
B170021	81.0 [b]	0.11	S-217622-TF-072-L	Repeat-dose toxicity (4-week) in rats
			S-217622-TF-073-L	Repeat-dose toxicity (4-week) in monkeys
			S-217622-TF-071-L	Fertility and early embryonic development in rats
			S-217622-TF-070-L	Embryo-fetal development in rabbits
			S-217622-TF-135-L	Embryo-fetal development in rabbits (additional study)
202[redacted]-7425-068-01	98.3 [a]	0.22	S-217622-TF-072-L	Repeat-dose toxicity (4-week) in rats
			S-217622-TF-049-L	Embryo-fetal development in rats
			S-217622-TF-050-L	Pre- and postnatal development in rats
C1X0032	100.1 [a]	0.07	S-217622-TF-137-L	Repeat-dose toxicity (2-week) in rabbits
			S-217622-TF-191-N	Effect on cholesterol excretion in monkeys

a as ensitrelvir fumaric acid basis
b as ensitrelvir free basis

2.6.7.5 単回投与毒性試験：重要な試験以外の試験

Test Article: Ensitrelvir fumaric acid

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Doses [a] (mg/kg)</th><th>Gender and No. per Group</th><th>Observed Maximum Non-lethal Dose (mg/kg)</th><th>Approxi-mate Lethal Dose (mg/kg)</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Rat/
Crl:CD
(Sprague Dawley)</td><td>Oral gavage
(0.5% MC/
Suspension)</td><td>100, 300, 1000</td><td>3M, 3F</td><td>≥ 1000</td><td>> 1000</td><td>No noteworthy findings at any dosage levels.

Toxicokinetics (n = 3, mean value)
<table>
<tr><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">$AUC_{0\text{-}24hr}$ (µg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>100</td><td>192</td><td>250</td><td>2220</td><td>2870</td></tr>
<tr><td>300</td><td>346</td><td>387</td><td>5330</td><td>6250</td></tr>
<tr><td>1000</td><td>338</td><td>417</td><td>6040</td><td>7170</td></tr>
</table></td><td>TOX-20[redacted]-S-217622-01/ 4.2.3.1-01</td></tr>
<tr><td>Monkey/
Cynomolgus</td><td>Oral gavage
(0.5% MC/
Suspension)</td><td>100, 300, 1000</td><td>1F</td><td>≥ 1000</td><td>> 1000</td><td>1000:
Vomitus, a decrease in food consumption, relatively high creatinine and urea nitrogen
≥ 100:
High total bilirubin and direct bilirubin

Toxicokinetics (n = 1)
<table>
<tr><th rowspan="2">Dose (mg/kg)</th><th>C_{max} (µg/mL)</th><th>$AUC_{0\text{-}24hr}$ (µg·hr/mL)</th></tr>
<tr><th>F</th><th>F</th></tr>
<tr><td>100</td><td>257</td><td>5590</td></tr>
<tr><td>300</td><td>333</td><td>6810</td></tr>
<tr><td>1000</td><td>546</td><td>11900</td></tr>
</table></td><td>TOX-20[redacted]-S-217622-02/ 4.2.3.1-02</td></tr>
</table>

MC = methylcellulose aqueous solution
a As free form.
These studies were conducted as exploratory toxicokinetics study.

2.6.7.6 反復投与毒性試験： 重要な試験

2.6.7.6.1 ラット 2 週間反復経口投与毒性試験

Test Article: Ensitrelvir fumaric acid

Report Title: 2-Week Oral Toxicity Study of S-217622 fumaric acid in Rats			
Species/Strain: Rat/Crl:CD(Sprague Dawley)	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** S-217622-TF-022-L
Initial Age: 8 weeks	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-01
Date of First Dose: Male: [redacted]202[redacted] Female: [redacted]202[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC/suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 1000 mg/kg/day			

Dose (mg/kg/day, as free form)	0 (control)[a]		20		100		1000	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Toxicokinetics								
C_{max} (µg/mL)								
Day 1	NC	NC	22.1	38.0	133	214	294	375
Day 14	NC	NC	37.9	38.8	178	206	269	319
T_{max} (hr)								
Day 1	NC	NC	1.8	1.8	4.0	2.0	3.8	1.8
Day 14	NC	NC	1.3	1.3	2.5	1.8	1.8	1.5
$AUC_{0\text{-}24hr}$ (µg·hr/mL)								
Day 1	NC	NC	227	330	1930	2750	5400	6720
Day 14	NC	NC	370	344	2510	2890	3850	3940

Dose (mg/kg/day, as free form)	0 (control)[a]		20		100		1000	
Number of Animals	M: 15	F: 15	M: 10	F: 10	M: 10	F: 10	M: 15	F: 15
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	0	0	0	0	0	0
Clinical Signs	–	–	–	–	–	–	–	–
Body Weight (g)[c]		–		–		–		–
Day −1	257.2		258.7		258.8		256.9	
Day 1	271.9		270.6		275.7		266.3	
Day 3	284.3		283.4		287.7		278.5	
Day 5	297.7		294.8		302.1		288.9	
Day 8	316.3		311.1		318.4		304.2*	
Day 11	333.4		324.7		334.5		318.5*	
Day 14	345.2		334.5		339.6		326.4**	
Body Weight Gain (g)[c]		–		–		–		–
Day −1 to 1	14.7		11.9		16.9		9.3*	
Day 1 to 3	12.5		12.8		12.0		12.2	
Day 3 to 5	13.3		11.4		14.4		10.4*	
Day 5 to 8	18.7		16.3		16.3		15.3	
Day 8 to 11	17.1		13.6		16.1		14.3	
Day 11 to 14	11.8		9.8		5.1**		7.9	
Food Consumption (g/animal/day)[d]								
Day 1 to 3	24.9	18.4	24.2	18.4	25.0	18.0	22.1*	16.6*
Day 3 to 5	25.9	18.9	24.6	19.0	25.4	17.6	24.0	17.4
Day 5 to 8	25.3	19.7	24.6	19.6	25.0	18.8	23.7	19.3
Day 8 to 11	25.7	18.9	24.2	19.2	25.0	16.0	24.1	18.9
Day 11 to 14	25.6	20.6	24.2	19.4	25.0	20.4	23.6	20.0

Dose (mg/kg/day, as free form)	0 (control)[a]		20		100		1000	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Noteworthy Findings								
Ophthalmology	–	–	–	–	–	–	–	–
Urinalysis	–	–	–	–	–	–	–	–
Hematology	–	–	–	–	–	–	–	–
Blood Chemistry		–		–		–		–
Glucose (mg/dL)	114.0		112.1		102.7		93.0**	
Necropsy	–	–	–	–	–	–	–	–
Organ Weight	–	–	–	–	–	–	–	–
Histopathology	–	–	NE	NE	NE	NE	–	–

Dose (mg/kg/day, as free form)	0 (control)[a]		20		100		1000	
Postdose Evaluation								
Number of Animals	M: 5	F: 5	M: 0	F: 0	M: 0	F: 0	M: 5	F: 5
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Signs	−	−	N/A	N/A	N/A	N/A	−	−
Body Weight	−	−	N/A	N/A	N/A	N/A	−	−
Food Consumption	−	−	N/A	N/A	N/A	N/A	−	−
Ophthalmology	−	−	N/A	N/A	N/A	N/A	−	−
Urinalysis	−	−	N/A	N/A	N/A	N/A	−	−
Hematology	−	−	N/A	N/A	N/A	N/A	−	−
Blood Chemistry	−	−	N/A	N/A	N/A	N/A	−	−
Necropsy	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dose (mg/kg/day, as free form)	0 (control)[a]		20		100		1000	
Postdose Evaluation								
Number of Animals	M: 5	F: 5	M: 0	F: 0	M: 0	F: 0	M: 5	F: 5
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Signs	−	−	N/A	N/A	N/A	N/A	−	−
Body Weight	−	−	N/A	N/A	N/A	N/A	−	−
Food Consumption	−	−	N/A	N/A	N/A	N/A	−	−
Ophthalmology	−	−	N/A	N/A	N/A	N/A	−	−
Urinalysis	−	−	N/A	N/A	N/A	N/A	−	−
Hematology	−	−	N/A	N/A	N/A	N/A	−	−
Blood Chemistry	−	−	N/A	N/A	N/A	N/A	−	−
Necropsy	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

− = no noteworthy findings; NC = Not calculated. All individual values in the control group were below the lower limit of quantification (< 0.100 μg/mL).
NE = not examined; T_{max} = time to maximum plasma concentration
The first day of dosing was designated as Day 1.
a 0.5% MC
b Numerals represent the number of animals.
c Mean values of all animals are shown.
d Mean values of 7 cages (control and 1000 mg/kg/day groups) and 5 cages (20 and 100 mg/kg/day groups)
* P < 0.05 , ** P < 0.01 : Significantly different from control (Dunnett's test).
S-217622 represents ensitrelvir

2.6.7.6.2 ラット 4 週間反復経口投与毒性試験

Test Article: Ensitrelvir fumaric acid

Report Title: 4-Week Oral Toxicity Study of S-217622 fumaric acid in Rats			
Species/Strain: Rat/Crl:CD(Sprague Dawley)	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-217622-TF-072-L
Initial Age: 8 weeks	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-02
Date of First Dose: Male: [redacted]202[redacted] Female: [redacted]202[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC/suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 1000 mg/kg/day			

Dose (mg/kg/day, as free form)	0 (control) [a]		20		50		1000	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Toxicokinetics								
C_{max} (µg/mL)								
Day 1	NC	NC	26.0	44.1	68.4	114	272	381
Day 28	NC	NC	39.6	51.6	114	142	263	359
T_{max} (hr)								
Day 1	NC	NC	1.3	1.3	2.0	1.8	4.8	5.3
Day 28	NC	NC	2.0	1.5	4.0	1.3	5.3	3.7
$AUC_{0\text{-}24hr}$ (µg·hr/mL)								
Day 1	NC	NC	214	327	758	1110	4420	6060
Day 28	NC	NC	388	500	1700	1780	4270	5380

Dose (mg/kg/day, as free form)	0 (control)[a]		20		50		1000	
Number of Animals	M: 18	F: 18	M: 12	F: 12	M: 12	F: 12	M: 18	F: 18
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	0	0	0	0	0	0
Clinical Signs	–	–	–	–	–	–	–	–
Body Weight	–	–	–	–	–	–	–	–
Body Weight Gain	–	–	–	–	–	–	–	–
Food consumption	–	–	–	–	–	–	–	–
Ophthalmology	–	–	–	–	–	–	–	–
Urinalysis	–	–	–	–	–	–	–	–
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Hematology								
Lymphocyte count (10^3/μL)	9.321	–	8.432	–	8.920	–	11.428*	–
Blood Chemistry								
Total bilirubin (mg/dL)	0.035	0.069	0.047	0.074	0.031	0.061	0.013**	0.033**
Direct bilirubin (mg/dL)	0.033	0.041	0.034	0.038	0.028	0.036	0.020**	0.023**
Necropsy	–	–	–	–	–	–	–	–
Organ Weight	–	–	–	–	–	–	–	–
Histopathology	–	–	–	–	–	–	–	–

Dose (mg/kg/day, as free form)	0 (control)[a]		20		50		1000	
Postdose Evaluation								
Number of Animals	M: 6	F: 6	M: 0	F: 0	M: 0	F: 0	M: 6	F: 6
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Signs	−	−	N/A	N/A	N/A	N/A	−	−
Body Weight	−	−	N/A	N/A	N/A	N/A	−	−
Food Consumption	−	−	N/A	N/A	N/A	N/A	−	−
Ophthalmology	−	−	N/A	N/A	N/A	N/A	−	−
Urinalysis	−	−	N/A	N/A	N/A	N/A	−	−
Hematology	−	−	N/A	N/A	N/A	N/A	−	−
Blood Chemistry	−	−	N/A	N/A	N/A	N/A	−	−
Necropsy	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology	−	−	N/A	N/A	N/A	N/A	−	−

− = No noteworthy findings

The first day of dosing was designated as Day 1 of dosing.

a 0.5% MC

b Numerals represent the number of animals.

* P < 0.05, ** P < 0.01: Significantly different from control (Dunnett's test).

S-217622 represents ensitrelvir

2.6.7.6.3 サル 2 週間反復経口投与毒性試験

Test Article: Ensitrelvir fumaric acid

Report Title: 2-Week Oral Toxicity Study of S-217622 fumaric acid in Monkeys			
Species/Strain: Monkey/Cynomolgus	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** S-217622-TF-023-L
Initial Age: 2 to 5 years	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-03
Date of First Dose: Males: [redacted]202[redacted] Females: [redacted]202[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC/suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 10 mg/kg/day			

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Toxicokinetics								
C_{max} (µg/mL)								
Day 1	NC	NC	37.1	36.1	142	174	520	433
Day 14	NC	NC	77.6	75.2	404	378	409 [c]	430 [d]
T_{max} (hr)								
Day 1	NC	NC	1.7	1.0	6.7	4.0	11.2	6.4
Day 14	NC	NC	4.0	1.0	4.0	2.0	3.0 [c]	2.3 [d]
$AUC_{0\text{-}24hr}$ (µg·hr/mL)								
Day 1	NC	NC	550	503	2940	2980	10700	8920
Day 14	NC	NC	1220	1170	7810	7390	7840 [c]	8170 [d]

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Died or Euthanized Moribund [c]	0	0	0	0	0	0	2 (#25, 26)	1 (#30)
Clinical Signs [c]								
Decrease in spontaneous activity (slight)	0	0	0	0	0	0	1 (#25)	
Lateral position	–	–	–	–	–	–	1 (#26)	–
Sitting position	–	–	–	–	–	–	–	1 (#30)
Hypothermia	–	–	–	–	–	–	1 (#26)	–
Suppression of touch response	–	–	–	–	–	–	1 (#26)	–
Dehydration signs	–	–	–	–	–	–	2 (#24, 27)	2 (#30, 31)
Vomiting	–	–	–	–	–	–	5 (#23 to 27)	2 (#29, 31)
Diarrhea	–	–	–	–	–	–	1 (#27)	–
Soft stool	–	–	–	–	–	–	1 (#24)	–
Body Weight (kg) [d]								
Day −1	3.064	–	3.020	–	3.710	–	3.356	–
Day 14	2.998	–	2.933	–	3.423 ↓2.27 (#19)	–	2.930 [e]	–
Food Consumption (g) [d]								
Acclimation period	64.8 to 108.0	76.8 to 108.0	86.0 to 108.0	108.0	80.0 to 108.0	72.0 to 108.0	87.6 to 108.0	76.8 to 108.0
Day 1	108.0	93.6	100.0	108.0	90.0	104.0	84.0 ↓30 (#26)	72.0
Day 2	108.0	98.4	94.0	108.0	98.0	92.0	55.2 ↓24 (#24) ↓24 (#26) ↓12 (#27)	70.8 ↓36 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Food Consumption (g) [c]								
Day 2	108.0	98.4	94.0	108.0	98.0	92.0	55.2 ↓ 24 (#24) ↓ 24 (#26) ↓ 12 (#27)	70.8 ↓ 36 (#30)
Day 3	108.0	108.0	108.0	108.0	80.0	108.0	46.5* [d] ↓ 18 (#24) ↓ 12 (#25) ↓ 48 (#27)	78.0* ↓ 48 (#30)
Day 4	108.0	106.8	108.0	108.0	84.0 ↓ 36 (#18)	98.0	64.5* [d] ↓ 12 (#24) ↓ 42 (#25)	66.0* ↓ 18 (#30) ↓ 24 (#31)
Day 5	108.0	108.0	108.0	108.0	96.0	90.0	60.0* [d] ↓ 24 (#24) ↓ 36 (#27)	70.8 ↓ 24 (#30) ↓ 30 (#31)
Day 6	108.0	105.6	108.0	108.0	84.0	98.0	28.5** [d] ↓ 24 (#24) ↓ 0 (#25) ↓ 6 (#27)	56.4* ↓ 0 (#30) ↓ 36 (#31)
Day 7	108.0	108.0	108.0	108.0	62.0 ↓ 24 (#19)	94.0	34.5* [d] ↓ 6 (#24) ↓ 0 (#25) ↓ 24 (#27)	55.2** ↓ 6 (#30) ↓ 6 (#31)
Day 9	108.0	106.8	106.0	108.0	56.0 ↓ 24 (#18) ↓ 36 (#19)	86.0	52.0 [e] ↓ 42 (#24) ↓ 6 (#27)	72.0* [d] ↓ 36 (#31)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Food Consumption (g) [c]								
Day 10	108.0	108.0	108.0	108.0	68.0* ↓36 (#19)	100.0	54.0* [d] ↓6 (#27)	79.5 [e] ↓36 (#31)
Day 11	106.8	108.0	108.0	108.0	68.0 ↓12 (#19)	100.0	72.0 [d] ↓24 (#27)	90.0 [e]
Day 12	108.0	106.8	108.0	108.0	94.0	86.0	64.0* [d] ↓12 (#27)	93.0 [e]
Day 13	108.0	97.2	108.0	104.0	72.0 ↓36 (#19)	64.0	76.0 [d] ↓36 (#27)	73.5 [e] ↓24 (#31)
Day 14	108.0	108.0	108.0	108.0	84.0 ↓36 (#19)	94.0	82.0 [d] ↓30 (#27)	84.0 [d]
Ophthalmology	–	–	–	–	–	–	–	–
Electrocardiography	–	–	–	–	–	–	–	–
Urinalysis [c]								
pH								
Day −8	7.5 to 8.5	–	8 to 8.5	–	8.5	–	8.5	–
Day 13	8.5	–	8.5	–	↓7 (#19)	–	↓7 (#27)	–
Urobilinogen								
Day −8	Grade 0	–	Grade 0	–	Grade 0	–	Grade 0	–
Day 13	Grade 0	–	Grade 0	–	↑Grade 1 (#19)	–	↑Grade 1 (#23)	–
Protein (mg/dL)								
Day −8	1.50	–	1.07	–	1.77 0.5 (#19)	–	1.14 1.4 (#27)	–
Day 13	2.02	–	0.40	–	13.00 ↑33.8 (#19)	–	19.63 ↑43.8 (#27)	–

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Urinalysis [c]								
Sodium excretion (mEq)								
Day −8	2.316	−	2.827	−	4.683 2.32 (#19)	−	3.062 1.34 (#27)	−
Day 13	2.088	−	1.660	−	1.223 ↓0.36 (#19)	−	2.387 [d] ↓0.56 (#27)	−
Potassium excretion (mEq)								
Day −8	8.132	−	8.717	−	8.780	−	7.802 6.38 (#27)	−
Day 13	7.956	−	9.407	−	5.673	−	4.113 [d] ↓2.34 (#27)	−
Chloride excretion (mEq)								
Day −8	6.006	−	5.260	−	8.603 5.31 (#19)	−	5.290 2.50 (#27)	−
Day 13	5.136	−	4.760	−	2.650 ↓0.75 (#19)	−	3.610 [d] ↓0.85 (#27)	−
Hematology [c]								
Erythrocyte count (× 10^6/μL)								
Day −7	5.458	5.014	5.920	5.127	5.527 5.83 (#18)	5.153	5.352 5.61 (#24) 5.42 (#27)	5.324 4.52 (#29) 5.30 (#30) 5.17 (#32)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓3.88 (#30)
Day 14	5.042	4.992	5.250	5.100	4.127 ↓3.65 (#18)	4.593	3.360** [d] ↓3.55 (#24) ↓2.28 (#27)	4.148 [e] ↓3.88 (#29) ↓2.99 (#32)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Hematology [c]								
Hemoglobin concentration (g/dL)								
Day −7	13.18	12.26	13.37	12.80	13.17 13.2 (#18)	12.50	13.00 13.6 (#24) 12.9 (#27)	12.72 11.1 (#29) 13.0 (#30) 13.1 (#32)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓9.4 (#30)
Day 14	12.14	12.00	11.80	12.40	9.83 ↓8.8 (#18)	10.90	8.67* [d] ↓8.5 (#24) ↓6.5 (#27)	9.58** [e] ↓9.0 (#29) ↓8.0 (#32)
Hematocrit value (%)								
Day −7	42.72	39.72	45.23	41.07	43.10 44.6 (#18)	40.53	41.84 43.9 (#24) 40.5 (#27)	41.46 37.4 (#29) 41.1 (#30) 41.6 (#32)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓32.2 (#30)
Day 14	39.44	38.80	39.30	40.30	32.93 ↓28.8 (#18)	35.90	27.50 [d] ↓28.9 (#24) ↓18.2 (#27)	32.70* [e] ↓31.8 (#29) ↓26.2 (#32)
Platelet count (× 10^3/μL)								
Day −7	484.2	442.6	441.3	394.0	505.0	369.3 352 (#21)	430.8 562 (#27)	414.4 444 (#32)
Day 14	603.6	452.8	503.0	398.3	506.3	323.0 ↓62 (#21)	374.3 [d] ↓12 (#27)	626.3 [e] ↑794 (#32)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Hematology [c]								
Reticulocyte ratio (%)								
Day −7	0.990	0.766	0.533	0.547	0.757	1.083	0.688 0.55 (#24) 0.50 (#27)	0.722 0.65 (#32)
Day 14	1.462	0.962	1.330	1.377	0.997	1.203	3.117 [d] ↑ 4.74 (#24) ↑ 3.26 (#27)	2.503 [e] ↑ 6.61 (#32)
Reticulocyte count (10^9/L)								
Day −7	53.46	37.80	31.70	28.07	40.97	56.40	36.60 30.9 (#24) 27.1 (#27)	38.68 33.6 (#32)
Day 14	72.74	47.90	69.87	70.97	40.97	54.30	100.00 [d] ↑ 168.3 (#24) ↑ 74.3 (#27)	86.83 [e] ↑ 197.6 (#32)
Neutrophil count (× 10^3/μL)								
Day −7	−	6.082	−	4.647	−	4.720	−	5.624 6.51 (#31)
Day 14	−	4.630	−	3.423	−	3.493	−	6.223 [e] ↑ 12.81 (#31)
Lymphocyte count (× 10^3/μL)								
Day −7	7.690	3.660	4.617	3.900	6.800	6.733	4.598 3.55 (#26)	4.764 4.63 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓ 0.61 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓ 1.03 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Hematology [c]								
Monocyte count (× 10^3/μL)								
Day −7	0.832	0.524	0.533	0.597	0.560 0.42 (#18)	0.613	0.448 0.45 (#24)	0.530 0.57 (#31)
Day 14	0.912	0.432	0.850	0.730	1.057 ↑ 1.80 (#18)	0.733	1.043 [d] ↑ 1.68 (#24)	0.888* [e] ↑ 1.40 (#31)
Prothrombin time (s)								
Day −7	10.08	10.32	10.33	10.07	10.07	10.00	10.04 10.3 (#26)	10.10 10.5 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑ 13.2 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 12.2 (#30)
Activated partial thromboplastin time (s)								
Day −7	−	19.60	−	22.40	−	19.60	−	20.42 18.5 (#30)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 31.4 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Hematology [c]								
Fibrinogen (mg/dL)								
Day −7	204.68	195.38	192.77	179.90	208.10 233.6 (#17) 188.4 (#18) 202.3 (#19)	196.07	197.92 199.8 (#23) 243.9 (#24) 159.0 (#26) 182.1 (#27)	190.40 188.4 (#30) 170.7 (#31) 221.2 (#32)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑636.8 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑798.2 (#30)
Day 14	242.66	175.30	238.70	171.93	609.23* ↑312.5 (#17) ↑675.8 (#18) ↑839.4 (#19)	250.33	487.17 [d] ↑354.9 (#23) ↑430.8 (#24) ↑675.8 (#27)	343.05** [e] ↑467.3 (#31) ↑347.1 (#32)
Blood Chemistry [c]								
Lactate dehydrogenase (IU/L)								
Day −7	−	340.0	−	325.0	−	490.3	−	350.0 464 (#30)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑1504 (#30)
Creatine kinase (IU/L)								
Day −7	−	247.6	−	303.3	−	309.0	−	643.4 556 (#30)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑4517 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Total bilirubin (mg/dL)								
Day −7	0.082	0.102	0.147	0.103	0.077	0.127	0.102	0.102
					0.11 (#17)	0.13 (#20)	0.10 (#23)	0.08 (#28)
					0.07 (#18)	0.15 (#21)	0.11 (#24)	0.11 (#29)
					0.05 (#19)	0.10 (#22)	0.14 (#26)	0.11 (#30)
							0.09 (#27)	0.10 (#31)
								0.11 (#32)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑1.30 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑1.77 (#30)
Day 14	0.084	0.102	0.150	0.147	0.737*	0.540*	0.720 [d]	0.625** [e]
					↑0.78 (#17)	↑0.39 (#20)	↑0.95 (#23)	↑0.43 (#28)
					↑0.50 (#18)	↑0.79 (#21)	↑0.46 (#24)	↑0.63 (#29)
					↑0.93 (#19)	↑0.44 (#22)	↑0.75 (#27)	↑0.89 (#31)
								↑0.55 (#32)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Direct bilirubin								
Day −7	0.034	0.046	0.067	0.043	0.037 0.05 (#17) 0.03 (#18) 0.03 (#19)	0.053 0.06 (#20) 0.05 (#21) 0.05 (#22)	0.054 0.07 (#23) 0.06 (#24) 0.14 (#26) 0.03 (#27)	0.042 0.03 (#28) 0.04 (#29) 0.05 (#30) 0.04 (#31) 0.05 (#32)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑0.63 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑0.82 (#30)
Day 14	0.028	0.036	0.070	0.070	0.253* ↑0.32 (#17) ↑0.17 (#18) ↑0.27 (#19)	0.153** ↑0.14 (#20) ↑0.20 (#21) ↑0.12 (#22)	0.283 [d] ↑0.41 (#23) ↑0.23 (#24) ↑0.21 (#27)	0.168** [e] ↑0.12 (#28) ↑0.19 (#29) ↑0.22 (#31) ↑0.14 (#32)
Total protein (g/dL)								
Day −7	6.90	7.62	7.70	7.37	7.20	7.40	7.08 7.3 (#26) 6.5 (#27)	7.12 7.7 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓5.6 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓6.3 (#30)
Day 14	6.78	−	7.33	−	7.53	−	6.53 [d] ↓5.5 (#27)	−

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Albumin (g/dL)								
Day −7	3.80	4.20	4.23	4.03	4.07	3.90	3.90 4.2 (#26) 3.7 (#27)	4.02 4.4 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓ 2.8 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓ 3.0 (#30)
Day 14	3.40	−	3.83	−	3.17	−	2.97 [d] ↓ 2.2 (#27)	−
Triglyceride (mg/dL)								
Day −7	56.6	45.8	52.0	48.0	51.7 78 (#19)	31.0	40.2 81 (#27)	34.4 47 (#30) 43 (#31)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 156 (#30)
Day 14	51.2	49.6	51.0	43.0	300.3 ↑ 709 (#19)	40.7	339.3 [d] ↑ 967 (#27)	134.0 [e] ↑ 288 (#31)
Total cholesterol (mg/dL)								
Day −7	−	122.0	−	113.0	−	117.3 170 (#21)	−	142.2 124 (#31) 175 (#32)
Day 14	−	121.2	−	69.7	−	187.7 ↑ 265 (#21)	−	231.5 [e] ↑ 248 (#31) ↑ 252 (#32)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Glucose (mg/dL)								
Day −7	89.8	85.4	84.3	76.7	91.0	67.7	81.2 80 (#24) 75 (#26)	83.6 104 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓ 7 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 203 (#30)
Day 14	75.6	−	91.0	−	107.3	−	71.7 [d] ↓ 42 (#24)	−
Urea nitrogen (mg/dL)								
Day −7	23.60	18.20	25.03	23.93	20.97	18.77	24.38 22.4 (#26)	22.50 20.2 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑ 63.6 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 33.0 (#30)
Creatinine (mg/dL)								
Day −7	0.628	0.756	0.770	0.890	0.700	0.893	0.716 0.58 (#26)	0.768 0.89 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↑ 1.14 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 1.51 (#30)
Inorganic phosphorus (mg/dL)								
Day −7	4.932	−	5.103	−	4.613	−	4.116 2.99 (#27)	−
Day 14	5.408	−	5.503	−	4.183	−	3.910 [d] ↓ 2.52 (#27)	−

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Calcium (mg/dL)								
Day −7	9.86	9.98	9.97	9.97	10.07 10.0 (#17) 9.3 (#18) 10.9 (#19)	9.73	10.02 9.8 (#23) 10.5 (#24) 9.9 (#26) 9.9 (#27)	10.02 9.1 (#29) 10.3 (#30) 10.4 (#31) 10.2 (#32)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓ 7.4 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓ 7.6 (#30)
Day 14	9.78	9.54	9.57	9.77	8.57** ↓ 8.8 (#17) ↓ 8.3 (#18) ↓ 8.6 (#19)	9.17	8.47** [d] ↓ 8.6 (#23) ↓ 9.0 (#24) ↓ 7.8 (#27)	8.70* [e] ↓ 8.5 (#29) ↓ 8.6 (#31) ↓ 8.7 (#32)
Sodium (mEq/L)								
Day −7	148.6	149.4	151.7	147.3	149.3 149 (#19)	146.0	147.6 147 (#26) 147 (#27)	148.0 148 (#30)
Day 3 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	↓ 142 (#26)	N/A
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓ 132 (#30)
Day 14	147.6	–	148.0	–	144.0 ↓ 142 (#19)	–	142.7* [d] ↓ 140 (#27)	–
Potassium (mEq/L)								
Day −7	–	5.06	–	4.57	–	4.33	–	4.46 5.0 (#30)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↑ 5.9 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Blood Chemistry [c]								
Chloride (mEq/L)								
Day −7	−	109.8	−	108.3	−	108.0	−	108.8
								110 (#30)
Day 8 (at moribundity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	↓93 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Necropsy [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Abdominal cavity								
Ascites, pale red, turbid	0	0	0	0	0	0	1 (#27)	0
Adrenals								
Dark discoloration, bilateral	0	0	0	0	1 (#18)	0	1 (#27)	0
Heart								
Red focus	0	0	0	0	0	0	1 (#27)	0
Large intestine, colon								
Red focus, mucosa, multiple	0	0	0	0	0	0	1 (#27)	0
Large intestine, rectum								
Red focus, mucosa, multiple	0	0	0	0	0	0	1 (#27)	0
Lungs								
Pale discoloration	0	0	0	0	0	0	1 (#27)	1 (#32)
Spleen								
Black discoloration	0	0	0	0	0	0	1 (#27)	0
Enlargement	0	0	0	0	1 (#17)	1 (#21)	0	0
Stomach								
Red focus, mucosa, multiple	0	0	0	0	0	0	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Necropsy [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Adrenals								
Enlargement, bilateral	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Bronchus								
Foamy fluid	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Heart								
Red focus	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	1 (#30)
Large intestine, cecum								
Dilatation	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Large intestine, colon								
Dilatation	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Lungs								
Edema	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Lymph nodes, submandibular								
Induration, surrounding tissue, bilateral	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Submandibular glands								
White focus, bilateral	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Trachea								
Foamy fluid	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Organ Weight [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Pancreas (absolute, g)	4.17	–	5.53	–	4.93	–	7.35 ↑ 9.6 (#27)	–
Pancreas (relative, g/kg)	1.387	–	1.860	–	1.473	–	2.325 ↑ 3.18 (#27)	–
Thymus (absolute, g)	5.13	–	2.43	–	0.97	–	0.65* ↓ 0.6 (#23) ↓ 0.7 (#27)	–
Thymus (relative, g/kg)	1.813	–	0.877	–	0.303	–	0.200* ↓ 0.17 (#23) ↓ 0.23 (#27)	–
Submandibular gland (left, absolute, g)	1.23	–	1.30	–	1.90 ↑ 2.5 (#18)	–	1.00	–
Submandibular gland (left, relative, g/kg)	0.383	–	0.450	–	0.577 ↑ 0.66 (#18)	–	0.310	–
Submandibular gland (bilateral, absolute, g)	2.50	–	2.63	–	3.70 ↑ 4.7 (#18)	–	2.10	–
Submandibular gland (bilateral, relative, g/kg)	0.780	–	0.917	–	1.123 ↑ 1.30 (#18)	–	0.645	–
Spleen (absolute, g)	3.60	2.73	3.23	4.00	7.37 ↑ 11.6 (#17)	5.27 ↑ 7.3 (#21)	4.85	5.45 ↑ 5.2 (#31) ↑ 5.7 (#32)
Spleen (relative, g/kg)	1.203	0.967	1.127	1.367	2.123 ↑ 2.57 (#17)	1.760* ↑ 2.07 (#21)	1.520	2.420** ↑ 2.48 (#31) ↑ 2.36 (#32)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Organ Weight [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Lung (absolute, g)	15.57	−	16.00	−	19.63 ↑ 30.7 (#17)	−	16.70	−
Lung (relative, g/kg)	5.190	−	5.423	−	5.477 ↑ 6.81 (#17)	−	5.140	−
Liver (absolute, g)	58.37	−	61.37	−	89.50 ↑ 105.9 (#17)	−	86.20 ↑ 98.1 (#27)	−
Liver (relative, g/kg)	19.393	−	21.140	−	26.523 ↑ 23.48 (#17)	−	26.915 ↑ 32.48 (#27)	−
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Adrenal gland (right, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	−	↑ 0.30 (#30)
Adrenal gland (right, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	−	↑ 0.107 (#30)
Adrenal gland (left, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	0.525 ↑ 0.43 (#26)	↑ 0.43 (#30)
Adrenal gland (left, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	0.1565 ↑ 0.189 (#26)	↑ 0.154 (#30)
Adrenal gland (bilateral, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	−	↑ 0.73 (#30)
Adrenal gland (bilateral, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	−	↑ 0.261 (#30)
Lung (absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	42.35 ↑ 70.3 (#25)	−
Lung (relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	10.215 ↑ 14.09 (#25)	−

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Organ Weight [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Liver (absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	126.20 ↑ 190.7 (#25)	↑ 83.3 (#30)
Liver (relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	32.700 ↑ 38.22 (#25)	↑ 29.75 (#30)
Kidney (right, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	10.20 ↑ 13.1 (#25)	↑ 8.6 (#30)
Kidney (right, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	2.925 ↑ 2.63 (#25)	↑ 3.07 (#30)
Kidney (left, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	9.95 ↑ 12.7 (#25)	↑ 8.3 (#30)
Kidney (left, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	2.860 ↑ 2.55 (#25)	↑ 2.96 (#30)
Kidney (bilateral, absolute, g)	N/A	N/A	N/A	N/A	N/A	N/A	20.15 ↑ 25.8 (#25)	↑ 16.9 (#30)
Kidney (bilateral, relative, g/kg)	N/A	N/A	N/A	N/A	N/A	N/A	5.780 ↑ 5.17 (#25)	↑ 6.04 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Adrenals								
Hypertrophy, cortical, diffuse								
Very slight	0	0	0	0	0	0	1 (#23)	1 (#32)
Slight	0	0	0	0	0	0	1 (#27)	1 (#31)
Decreased lipid, zona fasciculata cell								
Very slight	0	0	0	0	2 (#17, 19)	0	0	0
Slight	0	0	0	0	0	1 (# 22)	0	0
Moderate	0	0	0	0	1 (#18)	0	0	0
Aorta								
Hemorrhage, adipose tissue (suspected agonal hemorrhage)								
Slight	0	0	0	NE	0	NE	1 (#27)	0
Bone marrow, femur								
Increased hematopoiesis								
Slight	0	0	0	0	2 (#18, 19)	0	1 (#27)	1 (#31)
Moderate	0	0	0	0	0	0	0	1 (#32)
Serous atrophy of fat								
Very slight	0	0	0	0	1 (#19)	0	1 (#23)	0
Slight	0	0	0	0	0	0	1 (#27)	0
Bone marrow, sternum								
Increased cellularity, megakaryocyte								
Slight	0	0	0	0	0	0	1 (#27)	0
Increased hematopoiesis								
Very slight	0	0	0	0	0	0	0	2 (#31, 32)
Slight	0	0	0	0	2 (#18, 19)	0	0	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Epididymides								
Infiltrate, mononuclear cell, perivascular, multifocal								
Very slight	0	N/A	0	N/A	1 (#17)	N/A	1 (#27)	N/A
Slight	0	N/A	0	N/A	1 (#18)	N/A	0	N/A
Moderate	0	N/A	0	N/A	1 (#19)	N/A	0	N/A
Esophagus								
Atrophy, mucosal epithelium								
Slight	0	0	0	NE	0	NE	1 (#27)	0
Infiltrate, mononuclear cell, mucosa, focal/multifocal								
Very slight	0	0	0	NE	3 (#17 to 19)	NE	2 (#23, 27)	0
Eyeballs								
Infiltrate, mononuclear cell, conjunctiva, bulbar								
Moderate	0	0	0	NE	0	NE	1 (#27)	0
Gallbladder								
Hemorrhage, lamina propria, focal (suspected agonal hemorrhage)								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Infiltrate, mononuclear cell, lamina propria, diffuse								
Very slight	0	0	0	NE	0	NE	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Heart								
Atrophy, adipose tissue								
Very slight	0	0	0	0	2 (#18, 19)	0	0	1 (#31)
Moderate	0	0	0	0	0	0	1 (#27)	0
Hemorrhage, adipose tissue (suspected agonal hemorrhage)								
Slight	0	0	0	0	0	0	1 (#27)	0
Hemorrhage, endocardial/epicardial, mural (suspected agonal hemorrhage)								
Slight	0	0	0	0	0	0	1 (#27)	0
Infiltrate, mixed inflammatory cell, adipose tissue								
Very slight	0	0	0	0	0	0	0	1 (#31)
Kidneys								
Hemorrhage, adipose tissue, pelvis (suspected agonal hemorrhage)								
Very slight	0	0	0	0	0	0	1 (#27)	0
Hemorrhage, submucosa, pelvis (suspected agonal hemorrhage)								
Slight	0	0	0	0	0	0	1 (#27)	0
Lacrimal glands								
Infiltrate, mononuclear cell, diffuse								
Very slight	0	0	0	NE	2 (#17, 18)	NE	0	0
Moderate	0	0	0	NE	0	NE	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Large intestine, colon								
Abscess, crypt, multifocal								
Slight	0	0	0	NE	0	NE	1 (#27)	0
Erosion, focal								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Hemorrhage, lamina propria, multifocal (suspected agonal hemorrhage)								
Slight	0	0	0	NE	0	NE	1 (#27)	0
Large intestine, rectum								
Hemorrhage, lamina propria, focal (suspected agonal hemorrhage)								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Liver								
Degeneration, mural, artery, focal								
Slight	0	0	0	0	0	0	1 (#27)	0
Hypertrophy, hepatocyte, periportal								
Very slight	0	0	0	0	1 (#19)	0	1 (#23)	1 (#31)
Slight	0	0	0	0	0	0	1 (#27)	1 (#32)
Infiltrate, mixed inflammatory cell, portal								
Slight	0	0	0	0	0	0	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Lungs/Bronchi								
Hemorrhage, perivascular, focal (suspected agonal hemorrhage)								
Very slight	0	0	0	0	0	0	1 (#27)	0
Infiltrate, mononuclear cell, perivascular, multifocal								
Very slight	0	0	0	0	2 (#18, 19)	0	0	1 (#32)
Slight	0	0	0	0	1 (#17)	2 (#21, 22)	2 (#23, 27)	0
Moderate	0	0	0	0	0	1 (#20)	0	1 (#31)
Lymph node, mesenteric								
Decreased cellularity, lymphocyte								
Slight	0	0	0	0	0	0	2 (#23, 27)	0
Increased cellularity, histiocyte								
Slight	0	0	0	0	0	0	0	1 (#31)
Increased cellularity, plasma cell								
Very slight	0	0	0	0	0	0	0	1 (#31)
Slight	0	0	0	0	1 (#18)	0	0	0
Lymph node, submandibular								
Decreased cellularity, lymphocyte								
Very slight	0	0	0	0	2 (#17, 18)	0	2 (#23, 27)	0
Slight	0	0	0	0	1 (#19)	1 (#22)	0	0
Increased cellularity, histiocyte								
Slight	0	0	0	0	1 (#18)	2 (#20, 21)	1 (#23)	0
Moderate	0	0	0	0	1 (#17)	1 (#22)	0	2 (#31, 32)
Marked	0	0	0	0	1 (#19)	0	0	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Lymph node, submandibular								
Increased cellularity, plasma cell								
Very slight	0	0	0	0	0	1 (#22)	0	0
Slight	0	0	0	0	1 (#17)	0	0	1 (#32)
Moderate	0	0	0	0	2 (#18, 19)	0	1 (#27)	1 (#31)
Infiltrate, neutrophil, sinus								
Very slight	0	0	0	0	0	0	1 (#27)	1 (#32)
Pancreas								
Secretory depletion, acinar cell								
Very slight	0	0	0	0	3 (#17 to 19)	0	0	0
Slight	0	0	0	0	0	0	1 (#27)	0
Moderate	0	0	0	0	0	0	0	1 (#32)
Peyer's patches								
Decreased cellularity, lymphocyte								
Very slight	0	0	0	0	1 (#19)	0	0	1 (#32)
Slight	0	0	0	0	0	0	2 (#23, 27)	0
Pituitary								
Infiltrate, plasma cell, pars nervosa								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Skeletal muscle, gastrocnemius								
Atrophy, muscle fiber								
Slight	0	0	0	0	0	0	1 (#27)	0
Skin/Subcutis								
Infiltrate, mononuclear cell, dermis, multifocal								
Very slight	0	0	0	NE	0	NE	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Skin/Subcutis								
Atrophy, adipose tissue, subcutis								
Slight	0	0	0	NE	1 (#18)	NE	0	0
Small intestine, duodenum								
Atrophy, Brunner's gland								
Very slight	0	0	0	0	2 (#17, 19)	0	0	0
Moderate	0	0	0	0	0	0	1 (#27)	0
Small intestine, ileum								
Hemorrhage, lamina propria, multifocal (suspected agonal hemorrhage)								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Small intestine, jejunum								
Hemorrhage, lamina propria, multifocal (suspected agonal hemorrhage)								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Spleen								
Congestion								
Very slight	0	0	0	0	1 (#19)	1 (#21)	0	0
Slight	0	0	0	0	0	0	0	2 (#31, 32)
Moderate	0	0	0	0	0	0	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Spleen								
Decreased cellularity, lymphocyte, white pulp								
Very slight	0	0	0	0	3 (#17 to 19)	1 (#22)	0	0
Slight	0	0	0	0	0	0	2 (#23, 27)	0
Extramedullary hematopoiesis								
Slight	0	0	0	0	0	0	1 (#27)	0
Increased cellularity, histiocyte, white pulp								
Very slight	0	0	0	0	1 (#18)	1 (#22)	0	1 (#32)
Slight	0	0	0	0	0	0	0	1 (#31)
Moderate	0	0	0	0	2 (#17, 19)	0	0	0
Increased cellularity, plasma cell								
Very slight	0	0	0	0	1 (#18)	0	0	2 (#31, 32)
Moderate	0	0	0	0	2 (#17, 19)	0	0	0
Stomach								
Hemorrhage, lamina propria, multifocal (suspected agonal hemorrhage)								
Very slight	0	0	0	0	0	0	1 (#27)	1 (#32)
Sublingual glands								
Hypertrophy, mucous cell								
Slight	0	0	0	NE	0	NE	1 (#23)	0
Infiltrate, mononuclear cell, oral mucosa								
Very slight	0	0	0	NE	0	NE	1 (#27)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Scheduled Necropsy								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 2
Submandibular glands								
Infiltrate, mononuclear cell, focal								
Moderate	0	0	0	NE	0	NE	1 (#27)	0
Testes								
Hemorrhage (suspected agonal hemorrhage)								
Very slight	0	N/A	0	N/A	0	N/A	1 (#27)	N/A
Thymus								
Atrophy								
Moderate	0	0	0	0	2 (#18, 19)	0	1 (#23)	2 (#31, 32)
Tongue								
Atrophy, mucosal epithelium, dorsal								
Very slight	0	0	0	NE	0	NE	2 (#23, 27)	0
Atrophy, mucosal epithelium, ventral								
Very slight	0	0	0	NE	0	NE	1 (#27)	0
Uterus								
Hemorrhage, submucosa, focal (suspected agonal hemorrhage)								
Very slight	N/A	0	N/A	0	N/A	1 (#21)	N/A	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Adrenals								
Hemorrhage, cortical (suspected agonal hemorrhage)								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Hypertrophy, cortical, diffuse								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	1 (#30)
Aorta								
Atrophy, adipose tissue								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Bone marrow, femur								
Bacteria-like particle, macrophage/neutrophil								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Inflammation, neutrophil, multifocal								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Bone marrow, sternum								
Decreased cellularity, hematopoietic cell								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	1 (#30)
Increased cellularity, megakaryocyte								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Eyeballs								
Atrophy, corneal epithelium								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Gallbladder								
Degeneration, mural, artery								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Hemorrhage, mural, artery								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Heart								
Accumulation, mixed inflammatory cell, intravascular								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Atrophy, adipose tissue								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Degeneration, mural, artery								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Hemorrhage, adipose tissue (suspected agonal hemorrhage)								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Hemorrhage, endocardial/epicardial, mural (suspected agonal hemorrhage)								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Kidneys								
Dilatation, distal tubule								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Large intestine, colon								
Necrosis, mural, artery, focal								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Liver								
Degeneration, mural, artery,								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Hypertrophy, hepatocyte, periportal								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Increased number, mixed inflammatory cell, sinusoid								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Necrosis, focal								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Lungs/Bronchi								
Accumulation, mixed inflammatory cell, intravascular								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	0
Bacteria-like particle, macrophage/neutrophil								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	0
Edema, pulmonary								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Exudate, fibrinous, alveolus, multifocal								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Hemorrhage, alveolus, multifocal								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Lymph node, mesenteric								
Decreased cellularity, lymphocyte								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Lymph node, submandibular								
Accumulation, mixed inflammatory cell, intravascular								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Bacteria-like particle, macrophage/neutrophil								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Decreased cellularity, lymphocyte								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	1 (#30)
Edema, capsule								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Hemorrhage (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Increased cellularity, histiocyte								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Infiltrate, neutrophil, capsule								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Inflammation, neutrophil								
Marked	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Pancreas								
Hemorrhage, islet, focal (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Secretory depletion, acinar cell								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Peyer's patches								
Decreased cellularity, lymphocyte								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Pituitary								
Hemorrhage, pars nervosa, focal (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Infiltrate, mixed inflammatory cell, pars nervosa, focal								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Skeletal muscle, gastrocnemius								
Atrophy, muscle fiber								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Skin/Subcutis								
Atrophy, adipose tissue, subcutis								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Small intestine, duodenum								
Atrophy, Brunner's gland								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	1 (#30)
Hemorrhage, subserosa (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Spleen								
Congestion								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Decreased cellularity, lymphocyte, white pulp								
Slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	2 (#25, 26)	0
Hemorrhage, white pulp (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	0	1 (#30)
Submandibular glands								
Accumulation, mixed inflammatory cell, interstitium								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Accumulation, mixed inflammatory cell, intravascular								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Edema, interstitium								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Noteworthy Findings								
Histopathology [c]								
Died or Euthanized Moribund Animals								
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 1
Thymus								
Atrophy								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	1 (#30)
Hemorrhage (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#25)	0
Increased number, tingible body macrophage								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Increased single cell, necrosis, cortex								
Moderate	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Tongue								
Atrophy, mucosal epithelium, ventral								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	1 (#26)	0
Uterus								
Hemorrhage, submucosa, focal (suspected agonal hemorrhage)								
Very slight	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (#30)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Postdose Evaluation								
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 1	F: 2
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Signs [c]								
Dehydration signs	0	0	N/A	N/A	N/A	N/A	1 (#24)	0
Body Weight	−	−	N/A	N/A	N/A	N/A	−	−
Food Consumption	−	−	N/A	N/A	N/A	N/A	−	−
Ophthalmology	−	−	N/A	N/A	N/A	N/A	−	−
Electrocardiography	−	−	N/A	N/A	N/A	N/A	−	−
Urinalysis	−	−	N/A	N/A	N/A	N/A	−	−
Hematology	−	−	N/A	N/A	N/A	N/A	−	−
Blood Chemistry	−	−	N/A	N/A	N/A	N/A	−	−
Necropsy	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology [c]								
Adrenals								
Hypertrophy, cortical, diffuse								
Very slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)
Bone marrow, femur								
Increased hematopoiesis								
Very slight	0	0	N/A	N/A	N/A	N/A	1 (#24)	1 (#29)
Slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)
Bone marrow, sternum								
Increased hematopoiesis								
Very slight	0	0	N/A	N/A	N/A	N/A	0	1 (#29)
Slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)

Dose (mg/kg/day, as free form)	0 (control) [a]		10		50		1000→300→100 [b]	300→100 [b]
Postdose Evaluation								
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 1	F: 2
Noteworthy Findings								
Histopathology[c]								
Lymph node, mesenteric								
Extramedullary hematopoiesis								
Very slight	0	0	N/A	N/A	N/A	N/A	0	1 (#29)
Slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)
Lymph node, submandibular								
Extramedullary hematopoiesis								
Slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)
Increased cellularity, lymphocyte								
Slight	0	0	N/A	N/A	N/A	N/A	0	1 (#28)
Thymus								
Increased ratio, corticomedullary								
Moderate	0	0	N/A	N/A	N/A	N/A	1 (#24)	0

↑ Increase; ↓ Decrease
The first day of dosing was designated as Day 1.
Numeral in parenthesis represents animal number with the finding.
a 0.5% MC
b Reduced from 1000 mg/kg/day to 300 mg/kg/day from Day 3 (males) and from 300 mg/kg/day to 100 mg/kg/day from Days 8 (males) and 9 (females) of dosing.
c Mean values of all animals are shown. Values with animal Nos. are individual values.
d Mean values of 3 animals are shown.
e Mean values of 4 animals are shown.
*: $P < 0.05$, **: $P < 0.01$, Significantly different from control
S-217622 represents ensitrelvir

2.6.7.6.4 サル 4 週間反復経口投与毒性試験

Test Article: Ensitrelvir fumaric acid

Report Title: 4-Week Oral Toxicity Study of S-217622 fumaric acid in Monkeys			
Species/Strain: Monkey/Cynomolgus	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-217622-TF-073-L
Initial Age: 2 to 7 years	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-04
Date of First Dose: Male: [redacted] 202[redacted] Female: [redacted] 202[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC/suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 10 mg/kg/day			

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Toxicokinetics								
C_{max} (µg/mL)								
Day 1	NC	NC	8.92	9.67	34.9	40.0	83.0	89.8
Day 28	NC	NC	16.4	19.9	76.8	95.9	241	211
T_{max} (hr)								
Day 1	NC	NC	3.0	1.8	2.8	2.8	4.7	3.7
Day 28	NC	NC	1.5	2.8	3.0	3.0	2.7	5.8
$AUC_{0\text{-}24hr}$ (µg·hr/mL)								
Day 1	NC	NC	118	139	508	656	1540	1710
Day 28	NC	NC	242	333	1170	1850	4170	4490

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Died or Euthanized Moribund [b]	0	0	0	0	0	0	0	0
Clinical Signs	−	−	−	−	−	−	−	−
Body Weight (kg) [c]								
Day −1	−	3.643	−	4.600	−	5.633	−	4.222 6.45 (#39) 5.70 (#40)
Day 28	−	3.532	−	4.418	−	5.468*	−	4.000 ↓ 5.65 (#39) ↓ 4.84 (#40)
Food Consumption (g) [c]								
Acclimation period	−	14.0 to 103.0	−	21.0 to 108.0	−	10.5 to 108.0	−	26.0 to 108.0
Day 10	−	83.0	−	88.5	−	94.5	−	84.0 ↓ 48 (#39) ↓ 24 (#40)
Day 11	−	94.0	−	106.5	−	102.0	−	85.0 ↓ 48 (#40)
Day 12	−	93.0	−	100.5	−	106.5	−	82.0 ↓ 12 (#40)
Day 13	−	95.0	−	103.5	−	105.0	−	81.0 ↓ 0 (#40)
Day 14	−	94.0	−	105.0	−	108.0	−	79.0 ↓ 0 (#40)
Day 15	−	96.0	−	99.0	−	108.0	−	69.0 ↓ 12 (#40)
Day 16	−	102.0	−	102.0	−	108.0	−	68.0 ↓ 36 (#39) ↓ 0 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Food Consumption (g) [b]								
Day 17	–	92.0	–	105.0	–	105.0	–	66.0 ↓ 6 (#39) ↓ 6 (#40)
Day 18	–	90.0	–	105.0	–	108.0	–	65.0 ↓ 24 (#39) ↓ 6 (#40)
Day 19	–	102.0	–	108.0	–	105.0	–	69.0 ↓ 24 (#39) ↓ 6 (#40)
Day 20	–	82.0	–	108.0	–	108.0	–	70.0 ↓ 12 (#39) ↓ 12 (#40)
Day 21	–	92.0	–	108.0	–	100.5	–	73.0 ↓ 6 (#39) ↓ 0 (#40)
Day 23	–	96.0	–	93.0	–	108.0	–	70.0 ↓ 12 (#39) ↓ 0 (#40)
Day 24	–	103.0	–	96.0	–	108.0	–	65.0 ↓ 12 (#39) ↓ 0 (#40)
Day 25	–	101.0	–	108.0	–	108.0	–	76.0 ↓ 18 (#39) ↓ 6 (#40)
Day 26	–	100.0	–	97.5	–	108.0	–	72.0 ↓ 0 (#39) ↓ 0 (#40)
Day 27	–	108.0	–	108.0	–	106.5	–	84.0 ↓ 24 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Food Consumption (g) [b]								
Day 28	−	96.0	−	103.5	−	105.0	−	76.0 ↓ 30 (#39) ↓ 6 (#40)
Ophthalmology	−	−	−	−	−	−	−	−
Electrocardiography [b]								
QT interval (ms)								
Day −11/−8	−	175.7	−	179.5	−	181.3	−	175.7 169 (#40)
Day 23	−	171.8	−	175.0	−	186.8	−	196.5 ↑ 242 (#40)
QTc interval								
Day −11/−8	−	345.8	−	343.8	−	344.3	−	333.8 324 (#40)
Day 23	−	338.8	−	337.5	−	347.8	−	354.5 ↑ 408 (#40)
Urinalysis [b]								
pH								
Day −6/−9	−	8.5	−	8.5	−	8.5	−	8.5
Day 26	−	8.5	−	8.5	−	8.5	−	↓ 6.5 (#36) ↓ 6.5 (#40)
Ketone body								
Day −6/−9	−	Grade 0	−	Grade 0	−	Grade 0	−	Grade 0
Day 26	−	Grade 0	−	Grade 0	−	Grade 0	−	↑ Grade 2 (#39, 40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Urinalysis [b]								
Bilirubin								
Day −6/−9	−	Grade 0	−	Grade 0	−	Grade 0	−	Grade 0
Day 26	−	Grade 0	−	Grade 0	−	Grade 0	−	↑ Grade 3 (#40)
Urobilinogen								
Day −6/−9	−	Grade 0	−	Grade 0	−	Grade 0	−	Grade 0
Day 26	−	Grade 0	−	Grade 0	−	Grade 0	−	↑ Grade 2 (#40)
Protein (mg/dL)								
Day −6/−9	−	4.68	−	4.13	−	3.78	−	2.80 0.9 (#40)
Day 26	−	3.67	−	3.93	−	3.05	−	69.35* ↑ 142.4 (#40)
Glucose (mg/dL)								
Day −6/−9	−	2.3	−	2.0	−	3.5	−	3.2 7 (#39) 2 (#40)
Day 26	−	2.2	−	2.8	−	2.3	−	6.2 ↑ 9 (#39) ↑ 15 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Urinalysis [b]								
Leukocytes in sediment								
Day −6/−9	−	Grade 0 to 2	−	Grade 0 to 2	−	Grade 0 to 1	−	Grade 0
Day 26	−	Grade 0	−	Grade 0	−	Grade 0	−	↑ Grade 3 (#40)
Hematology [b]								
Erythrocyte count (10^6/μL)								
Day −5/−8	−	5.595	−	5.423	−	5.850	−	5.095 5.54 (#36) 5.63 (#39) 5.21 (#40)
Day 27	−	5.493	−	5.108	−	5.373	−	3.912** ↓ 3.42 (#36) ↓ 4.35 (#39) ↓ 1.84 (#40)
Hemoglobin concentration (g/dL)								
Day −5/−8	−	13.33	−	13.00	−	13.55	−	12.80 12.6 (#36) 13.2 (#39) 14.6 (#40)
Day 27	−	13.20	−	12.53	−	12.30	−	9.73** ↓ 8.5 (#36) ↓ 9.5 (#39) ↓ 5.7 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Hematology [b]								
Hematocrit value (%)								
Day −5/−8	−	42.92	−	41.63	−	44.23	−	40.92 42.1 (#36) 42.8 (#39) 45.0 (#40)
Day 27	−	42.60	−	40.55	−	40.63	−	31.40** ↓ 27.8 (#36) ↓ 33.5 (#39) ↓ 18.0 (#40)
Reticulocyte ratio (%)								
Day −5/−8	−	0.807	−	0.875	−	0.910	−	1.010 1.25 (#40)
Day 27	−	0.823	−	1.123	−	1.425	−	3.377* ↑ 12.85 (#40)
Reticulocyte count (10^9/L)								
Day −5/−8	−	44.65	−	47.55	−	52.25	−	50.60 65.1 (#40)
Day 27	−	45.25	−	57.10	−	75.15	−	91.47 ↑ 236.4 (#40)
Leukocyte count (10^3/L)								
Day −5/−8	−	10.748	−	10.733	−	8.920	−	10.450 15.08 (#39) 10.50 (#40)
Day 27	−	12.278	−	11.903	−	11.943	−	21.558 ↑ 28.93 (#39) ↑ 65.81 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Hematology [b]								
Neutrophil count (10^3/L)								
Day −5/−8	−	5.430	−	6.193	−	4.818	−	5.537 10.64 (#39) 4.94 (#40)
Day 27	−	6.012	−	6.305	−	5.800	−	14.215 ↑ 23.92 (#39) ↑ 43.55 (#40)
Lymphocyte count (10^3/L)								
Day −5/−8	−	4.617	−	3.788	−	3.500	−	4.302 4.80 (#40)
Day 27	−	5.368	−	4.650	−	5.080	−	4.852 ↑ 12.73 (#40)
Monocyte count (10^3/L)								
Day −5/−8	−	0.517	−	0.523	−	0.498	−	0.477 0.63 (#40)
Day 27	−	0.640	−	0.588	−	0.740	−	1.855 ↑ 7.54 (#40)
Basophil count (10^3/L)								
Day −5/−8	−	0.023	−	0.023	−	0.020	−	0.017 0.02 (#40)
Day 27	−	0.030	−	0.035	−	0.073	−	0.298 ↑ 1.24 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Hematology [b]								
Fibrinogen (mg/dL)								
Day −5/−8	−	157.30	−	205.63	−	154.75	−	182.67 227.7 (#39) 249.0 (#40)
Day 10	−	180.92	−	189.35	−	172.15	−	275.70 ↑ 346.9 (#39) ↑ 622.0 (#40)
Day 27	−	173.95	−	187.35	−	189.88	−	347.60 ↑ 380.7 (#39) ↑ 483.4 (#40)
Immunophenotyping in Peripheral Blood [b]								
$CD3^+$ cell ratio (%)								
Day −5/−8	−	61.577	−	63.245	−	60.775	−	69.415 53.59 (#40)
Day 27	−	64.745	−	65.055	−	69.438	−	66.202 ↓ 15.61 (#40)
$CD3^+CD4^+$ cell ratio (%)								
Day −5/−8	−	35.395	−	43.488	−	34.005	−	42.418 36.33 (#40)
Day 27	−	37.292	−	43.483	−	36.108	−	42.698 ↓ 9.22 (#40)
$CD3^+CD8^+$ cell count ($10^3/\mu L$)								
Day −5/−8	1.547	−	1.483	−	1.273	−	1.443 1.52 (#31)	−
Day 27	1.093	−	1.228	−	2.885	−	1.003 ↓ 0.03 (#31)	−

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Immunophenotyping in Peripheral Blood [b]								
$CD3^+CD8^+$ cell ratio (%)								
Day −5/−8	24.665	23.837	22.085	20.873	22.715	26.248	26.895 20.93 (#31)	25.742 16.07 (#40)
Day 27	21.628	26.127	20.195	24.130	21.828	34.163	22.017 ↓ 0.82 (#31)	21.922 ↓ 4.44 (#40)
$CD3^-CD20^+$ cell ratio (%)								
Day −5/−8	−	20.423	−	18.805	−	19.135	−	16.018 16.26 (#39) 16.81 (#40)
Day 27	−	15.647	−	13.953	−	11.055	−	6.233* ↓ 1.30 (#39) ↓ 1.03 (#40)
Blood chemistry [b]								
Alkaline phosphatase (IL/L)								
Day −5/−8	−	786.2	−	469.5	−	300.8	−	530.2 284 (#40)
Day 27	−	792.2	−	429.5	−	383.3	−	1256.3 ↑ 2176 (#40)
Lactate dehydrogenase (IL/L)								
Day −5/−8	−	383.7	−	258.8	−	285.0	−	237.7 252 (#40)
Day 27	−	377.0	−	547.5	−	364.8	−	555.0 ↑ 1180 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
Total bilirubin (mg/dL)								
Day −5/−8	0.075	0.195	0.108	0.163	0.100	0.183	0.093 0.11 (#30) 0.09 (#34)	0.110 0.11 (#36) 0.13 (#39) 0.09 (#40)
Day 10	0.123	0.152	0.140	0.165	0.140	0.255	0.312** ↑ 0.45 (#30) ↑ 0.34 (#34)	0.340* ↑ 0.56 (#39) ↑ 0.72 (#40)
Day 27	0.122	0.143	0.120	0.160	0.105	0.228	0.295* ↑ 0.56 (#30) ↑ 0.35 (#34)	0.400* ↑ 0.47 (#36) ↑ 0.51 (#39) ↑ 0.76 (#40)
Direct bilirubin (mg/dL)								
Day −5/−8	0.035	0.063	0.038	0.068	0.038	0.075	0.037 0.05 (#30)	0.050 0.07 (#39) 0.03 (#40)
Day 10	0.048	0.052	0.055	0.070	0.063	0.118	0.107** ↑ 0.19 (#30)	0.112 ↑ 0.19 (#39) ↑ 0.21 (#40)
Day 27	0.050	0.050	0.040	0.065	0.053	0.108	0.085 ↑ 0.18 (#30)	0.162* ↑ 0.24 (#39) ↑ 0.38 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
Albumin (g/dL)								
Day −5/−8	−	4.15	−	4.05	−	4.15	−	4.03 4.2 (#36) 4.1 (#39) 4.0 (#40)
Day 10	−	4.08	−	3.93	−	3.93	−	3.82 ↓ 3.3 (#40)
Day 27	−	4.02	−	4.00	−	3.95	−	2.90* ↓ 3.4 (#36) ↓ 3.0 (#39) ↓ 2.2 (#40)
Albumin/Globulin								
Day −5/−8	−	1.213	−	1.085	−	1.153	−	1.188 1.17 (#36) 1.05 (#40)
Day 10	−	1.188	−	1.058	−	1.083	−	1.083 ↓ 0.79 (#40)
Day 27	−	1.148	−	1.140	−	1.085	−	0.800* ↓ 0.79 (#36) ↓ 0.50 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
Triglyceride (mg/dL)								
Day −5/−8	−	28.8	−	28.5	−	36.0	−	33.2 36 (#38) 57 (#40)
Day 10	−	31.5	−	32.5	−	61.5	−	80.5 ↑ 246 (#40)
Day 27	−	36.3	−	36.8	−	46.0	−	152.8 ↑ 575 (#38) ↑ 200 (#40)
Glucose (mg/dL)								
Day −5/−8	−	64.5	−	74.3	−	83.3	−	76.2 88 (#40)
Day 27	−	66.0	−	72.5	−	84.3*	−	65.8 ↓ 34 (#40)
Total cholesterol (mg/dL)								
Day −5/−8	140.3	163.3	139.8	122.0	150.0	137.5	136.3 149 (#34)	129.5 124 (#38)
Day 10	146.0	161.0	124.3	118.5	↓ 97.5	↓ 92.0*	174.3 ↑ 244 (#34)	163.0
Day 27	140.3	166.5	123.0	115.0	↓ 87.3*	↓ 82.3**	187.2 ↑ 318 (#34)	175.5 ↑ 354 (#38)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
HDL-cholesterol (mg/dL)								
Day −5/−8	63.7	74.8	65.8	62.0	69.0	69.8	70.3	53.5
					52 (#23)	47 (#25)	61 (#29)	48 (#35)
						81 (#26)	69 (#30)	42 (#37)
						76 (#27)	69 (#31)	52 (#38)
						75 (#28)	81 (#32)	44 (#39)
							73 (#33)	78 (#40)
Day 10	65.0	72.8	56.3	57.0	38.5*	27.8*	24.7**	25.7**
					↓ 29 (#23)	↓ 23 (#25)	↓ 22 (#29)	↓ 22 (#35)
						↓ 32 (#26)	↓ 18 (#30)	↓ 26 (#37)
						↓ 28 (#27)	↓ 21 (#31)	↓ 18 (#38)
						↓ 28 (#28)	↓ 23 (#32)	↓ 29 (#39)
							↓ 28 (#33)	↓ 27 (#40)
Day 27	65.8	72.5	58.8	58.3	36.8**	28.5**	27.5**	24.2**
					↓ 30 (#23)	↓ 24 (#25)	↓ 23 (#29)	↓ 19 (#35)
						↓ 31 (#26)	↓ 18 (#30)	↓ 24 (#37)
						↓ 31 (#27)	↓ 19 (#31)	↓ 27 (#38)
						↓ 28 (#28)	↓ 23 (#32)	↓ 27 (#39)
							↓ 30 (#33)	↓ 14 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
LDL-cholesterol (mg/dL)								
Day −5/−8	71.0	76.8	64.0	53.0	72.5 47 (#24)	57.0 79 (#25) 52 (#26) 40 (#27)	58.0 47 (#29) 66 (#30) 50 (#31) 48 (#32) 66 (#33) 71 (#34)	73.3 79 (#37) 71 (#38) 37 (#39) 73 (#40)
Day 10	73.3	75.2	62.0	53.3*	48.8 ↓ 26 (#24)	29.3** ↓ 30 (#25) ↓ 26 (#26) ↓ 20 (#27)	25.3** ↓ 27 (#29) ↓ 27 (#30) ↓ 23 (#31) ↓ 26 (#32) ↓ 27 (#33) ↓ 22 (#34)	29.0** ↓ 32 (#37) ↓ 24 (#38) ↓ 14 (#39) ↓ 10 (#40)
Day 27	69.8	80.8	56.8	51.0	43.3 ↓ 29 (#24)	31.8** ↓ 36 (#25) ↓ 29 (#26) ↓ 23 (#27)	24.8** ↓ 28 (#29) ↓ 31 (#30) ↓ 19 (#31) ↓ 23 (#32) ↓ 27 (#33) ↓ 21 (#34)	30.8** ↓ 34 (#37) ↓ 7 (#39) ↓ 7 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
Calcium (mg/dL)								
Day −5/−8	10.92	10.07	10.33	10.40	10.23	10.45	10.18	10.07 10.1 (#39) 10.4 (#40)
Day 27	–	10.00	–	10.28	–	10.18	–	8.82* ↓ 8.8 (#39) ↓ 7.8 (#40)
Sodium (mEq/L)								
Day −5/−8	–	148.7	–	149.5	–	151.0	–	148.7 150 (#40)
Day 27	–	145.8	–	146.5	–	147.3	–	141.3* ↓ 141 (#40)
Chloride (mEq/L)								
Day −5/−8	–	111.3	–	111.0	–	111.8	–	112.8 116 (#40)
Day 27	–	107.3	–	106.3	–	108.8	–	103.7 ↓ 98 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Blood chemistry [b]								
Ferritin (ng/dL)								
Day −5/−8	−	11.43	−	8.00	−	10.78	−	5.87 5.5 (#40)
Day 27	−	11.05	−	11.30	−	16.60	−	71.05 ↑ 324.5 (#40)
C-reactive protein (mg/dL)								
Day −5/−8	−	0.20	−	0.25	−	0.23	−	0.23 0.3 (#36) 0.3 (#39) 0.1 (#40)
Day 10	−	0.20	−	0.18	−	0.65	−	2.52* 4.5 (#39) 8.3 (#40)
Day 27	−	0.20	−	0.18	−	0.68	−	3.52** ↑ 3.8 (#36) ↑ 4.7 (#39) ↑ 9.9 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Serum Cytokine Analysis	–	–	–	–	–	–	–	–
Necropsy [b]								
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Pericardial cavity								
Accumulation, pericardial fluid	0	0	0	0	0	0	0	1 (#40)
Organ Weight [c]								
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Spleen (absolute, g)	–	2.80	–	3.55	–	4.55*	–	7.38* ↑ 12.5 (#39) ↑ 9.6 (#40)
Spleen (relative, g/kg)	–	0.728	–	0.818	–	0.885	–	1.610* ↑ 2.24 (#39) ↑ 1.98 (#40)
Liver (absolute, g)	–	66.50	–	72.38	–	92.20	–	96.05 ↑ 94.3 (#38) ↑ 134.4 (#40)
Liver (relative, g/kg)	18.898	17.653	17.868	16.928	19.890	17.118	21.233* ↑ 22.28 (#31)	22.758 ↑ 26.56 (#38) ↑ 27.65 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Histopathology [b]								
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Adrenals								
Decreased lipid, zona fasciculata cell								
Very slight	0	0	0	0	0	0	2 (#32, 34)	1 (#39)
Slight	0	0	0	0	0	0	0	1 (#37)
Moderate	0	0	0	0	0	0	1 (#31)	2 (#38, 40)
Bone marrow, femur								
Increased cellularity, hematopoietic cell								
Very slight	0	0	0	0	0	0	0	1 (#40)
Bone marrow, sternum								
Increased cellularity, hematopoietic cell								
Slight	0	0	0	0	0	0	0	1 (#40)
Gallbladder								
Infiltrate, mixed inflammatory cell, muscle layer/fibrous membrane								
Very slight	0	0	0	0	0	0	0	1 (#40)
Heart								
Fat necrosis/inflammation, granulomatous, pericardial fat								
Slight	0	0	0	0	0	0	0	1 (#39)
Moderate	0	0	0	0	0	0	0	1 (#40)
Large intestine, colon								
Fat necrosis/inflammation, granulomatous, submucosa								
Very slight	0	0	0	0	0	0	0	1 (#39)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Histopathology [b]								
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Liver								
Erythrophagia, Kupffer cell								
Very slight	0	0	0	0	0	0	0	1 (#40)
Extramedullary hematopoiesis								
Slight	0	0	0	0	0	0	0	1 (#40)
Hypertrophy, hepatocyte								
Very slight	0	0	0	0	0	0	0	1 (#38)
Slight	0	0	0	0	0	0	0	1 (#40)
Infiltrate, mononuclear cell, portal								
Very slight	0	0	0	0	0	0	0	2 (#38, 40)
Vacuolation, hepatocyte, periportal								
Very slight	0	0	0	0	0	0	0	1 (#39)
Slight	0	0	0	0	0	0	0	1 (#40)
Lymph node, submandibular								
Decreased cellularity, lymphocyte								
Slight	0	0	0	0	0	0	0	1 (#40)
Pancreas								
Dilatation, acinar cell, multifocal								
Slight	0	0	0	0	0	0	0	1 (#40)
Secretory depletion, acinar cell								
Slight	0	0	0	0	0	0	0	1 (#39)
Parotid glands								
Secretory depletion, acinar cell								
Slight	0	0	0	0	0	0	0	1 (#40)
Skin/Subcutis								
Fat necrosis/inflammation, granulomatous, subcutis								
Very slight	0	0	0	0	0	0	0	2 (#39, 40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings								
Histopathology [b]								
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Spleen								
Congestion								
Slight	0	0	0	0	0	0	0	1 (#39)
Moderate	0	0	0	0	0	0	0	1 (#40)
Extramedullary hematopoiesis								
Very slight	0	0	0	0	0	0	0	1 (#39)
Slight	0	0	0	0	0	0	0	1 (#40)
Urinary bladder								
Fat necrosis/inflammation, granulomatous, adipose tissue, serosa								
Very slight	0	0	0	0	0	0	0	1 (#40)
Uterus								
Infiltrate, mononuclear cell, perivascular, muscle layer, multifocal								
Slight	N/A	0	N/A	0	N/A	0	N/A	1 (#40)

Dose (mg/kg/day, as free form)	0 (control) [a]		3		10		30	
Postdose Evaluation								
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Noteworthy Findings								
Died or Sacrificed Moribund[b]	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Signs	−	−	N/A	N/A	N/A	N/A	−	−
Body Weight	−	−	N/A	N/A	N/A	N/A	−	−
Food Consumption	−	−	N/A	N/A	N/A	N/A	−	−
Ophthalmology	−	−	N/A	N/A	N/A	N/A	−	−
Electrocardiography	−	−	N/A	N/A	N/A	N/A	−	−
Urinalysis	−	−	N/A	N/A	N/A	N/A	−	−
Hematology	−	−	N/A	N/A	N/A	N/A	−	−
Immunophenotyping in Peripheral Blood	−	−	N/A	N/A	N/A	N/A	−	−
Blood Chemistry	−	−	N/A	N/A	N/A	N/A	−	−
Serum Cytokine Analysis	−	−	N/A	N/A	N/A	N/A	−	−
Necropsy	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology	−	−	N/A	N/A	N/A	N/A	−	−

−: No noteworthy findings; ↑ Increase; ↓ Decrease
The first day of dosing was designated as Day 1.
Numeral in parenthesis represents animal number with the finding.
a 0.5% MC
b Numerals represent the number of animals.
c Mean values of all animals are shown. Values with animal Nos. are individual values.
*: $P < 0.05$, **: $P < 0.01$, Significantly different from control
S-217622 represents ensitrelvir

2.6.7.7 In Vitro 遺伝毒性試験

2.6.7.7.1 In vitro 遺伝毒性毒性試験： 重要な試験以外の試験

Test system	Treatment	Doses	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
S. typhimurium and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	20.6 to 5000 µg/plate	No	Negative	Ames-[redacted]-003/ 4.2.3.3-02
Human lymphoblastoid derived TK6 cells	3 hours with and without metabolic activation and 24 hours without metabolic activation	−S9 or +S9 mix, 3-hour treatment: 62.5 125, 250 µg/mL −S9 mix, 24-hour treatment: 31.3, 62.5, 125 µg/mL	No	Negative	Mvit-[redacted]-003/ 4.2.3.3-04

2.6.7.7.2 細菌を用いる復帰突然変異試験

Test Article: Ensitrelvir fumaric acid

Report Title: Bacterial Reverse Mutation Test of S-217622 fumaric acid		
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Assays:** 1	**Study No.** S-217622-TF-027-L
Strains: *S. typhimurium* and *E. coli*	**No. of Replicate Cultures:** 3	**Location in CTD:** 4.2.3.3-01
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 10% in metabolic activation system (S9 mix)	**No. of Cells Analyzed/Cultured:** −	**GLP Compliance:** Yes
Vehicles: For Test Article: Dimethyl sulfoxide (DMSO)	**For Positive Controls:** Water for injection and DMSO	**Date of Treatment:** [redacted]202[redacted]
Treatment: Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)		
Cytotoxic Effects: Growth inhibition was observed at 1250 µg/plate and greater in TA1537 with and without metabolic activation.		
Genotoxic Effects: None		

Metabolic Activation	Test Substance	Dose Level [a] (µg/plate)	Main Test Revertant Colony Counts (Mean) TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without Activation	Negative control (DMSO)	100 µL/plate	124	11	26	17	5
	Ensitrelvir fumaric acid	39.1	N/A	N/A	N/A	N/A	4
		78.1	N/A	N/A	N/A	N/A	5
		156	118	7	22	21	5
		313	134	7	22	15	4
		625	114	6	23	19	5
		1250	122	6	20	21	3 [b]
		2500 [c]	108	4	21	18	3 [b]
		5000 [c]	108	3	16	13	2 [b]
	4NQO [d]	0.1	710	N/A	N/A	N/A	N/A
		0.2	N/A	N/A	336	178	N/A
	NaN_3 [d]	0.5	N/A	383	N/A	N/A	N/A
	9AA [d]	80	N/A	N/A	N/A	N/A	169

Metabolic Activation	Test Substance	Dose Level [a] (µg/plate)	Main Test Revertant Colony Counts (Mean) TA100	TA1535	WP2*uvrA*	TA98	TA1537
With Activation	Negative control (DMSO)	100 µL/plate	149	8	32	35	11
	Ensitrelvir fumaric acid	39.1	N/A	N/A	N/A	N/A	10
		78.1	N/A	N/A	N/A	N/A	13
		156	144	8	26	32	9
		313	140	9	29	38	11
		625	154	7	29	41	7
		1250	146	8	36	36	7 [b]
		2500 [c]	138	6	30	38	3 [b]
		5000 [c]	150	8	18	34	4 [b]
	2AA [d]	0.5	N/A	N/A	N/A	444	N/A
		1	812	N/A	N/A	N/A	N/A
		2	N/A	179	N/A	N/A	160
		10	N/A	N/A	395	N/A	N/A

2AA = 2-aminoanthracene; 4NQO = 4-nitroquinoline 1-oxide; 9AA = 9-aminoacridine hydrochloride monohydrate; DMSO = dimethyl sulfoxide; NaN_3 = sodium azide
a: As free form
b: Growth inhibition was observed.
c: Precipitation of the test substance was observed.
d: Positive control
S-217622 represents ensitrelvir

2.6.7.7.3 ほ乳類の培養細胞を用いる小核試験

Test Article: Ensitrelvir fumaric acid

Report Title: Micronucleus Test of S-217622 fumaric acid with Cultured Mammalian Cells		
Test for Induction of: Chromosomal aberrations	**No. of Independent Assays:** 1	**Study No.** S-217622-TF-028-L
Strains: Human lymphoblastoid derived TK6 cells	**No. of Replicate Cultures:** 2	**Location in CTD:** 4.2.3.3-03
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 2%	**No. of Cells Analyzed/Cultured:** 1000	**GLP Compliance:** Yes
Vehicles: For Test Article: DMSO **For Positive Controls:** Physiological saline		**Date of Treatment:** [redacted] 202[redacted]
Treatment: 3 hours with and without metabolic activation and 24 hours without metabolic activation		
Cytotoxic Effects: The cell proliferation ratios determined by population doubling showed dose-dependent decreases under all treatment conditions.		
Genotoxic Effects: None		

Metabolic Activation	Treatment-Recovery (hours)	Test Substance	Dose Level [a] (μg/mL)	Cell Proliferation Ratio[b] (% of Negative Control)	Number of Micronucleated Cells per 2000 Cells	Incidence of Micronucleated Cells (%)
Without Activation	3-21	Negative control (DMSO)	0	100	20	1.0
		Ensitrelvir fumaric acid	50	94.9	NE	NE
			100	78.1	NE	NE
			150	91.2	22	1.1
			200	62.9	18	0.9
			250	54.0	21	1.1
			300	18.0	NE	NE
			350	No net growth	NE	NE
			400	No net growth	NE	NE
		MMC [b]	0.1	44.8	91*	4.6
With Activation	3-21	Negative control (DMSO)	0	100	21	1.1
		Ensitrelvir fumaric acid	50	80.2	NE	NE
			100	104.0	NE	NE
			150	88.1	16	0.8
			200	76.9	15	0.8
			250	54.3	22	1.1
			300	4.7	NE	NE
			350	No net growth	NE	NE
			400	No net growth	NE	NE
		CP [c]	2	45.5	47*	2.4

Metabolic Activation	Treatment-Recovery (hours)	Test Substance	Dose Level [a] (µg/mL)	Cell Proliferation Ratio [b] (% of Negative Control)	Number of Micronucleated Cells per 2000 Cells	Incidence of Micronucleated Cells (%)
Without Activation	24-0	Negative control (DMSO)	0	100	22	1.1
		Ensitrelvir fumaric acid	50	85.7	NE	NE
			75	78.2	24	1.2
			100	67.8	24	1.2
			125	50.5	22	1.1
			150	26.1	NE	NE
			175	13.3	NE	NE
			200	No net growth	NE	NE
		CLC [c]	0.0075	44.5	109*	5.5

CLC = colchicine; CP = cyclophosphamide monohydrate; MMC = mitomycin C
a As free form
b Based on relative population doubling
c Positive control
* Significant increase from the concurrent negative control (Fisher's exact test, $P < 0.05$, one-tailed)
S-217622 represents ensitrelvir

2.6.7.8 In Vivo 遺伝毒性試験

2.6.7.8.1 げっ歯類を用いる小核試験

Test Article: Ensitrelvir fumaric acid

Report Title: Micronucleus Test of S-217622 fumaric acid in Rats		
Test for Induction of: Bone marrow micronuclei	**Treatment Schedule:** 3 times (0, 24, and 45 hours after the first dosing)	**Study No.** S-217622-TF-029-L
Species/Strain: Rat/Crl:CD(Sprague Dawley)	**Sampling Time:** Approximately 3 hours after the final dosing	**Location in CTD:** 4.2.3.3-05
Age at dosing: 8 weeks	**Method of Administration:** Oral gavage	**GLP Compliance:** Yes
Cell Evaluated: Immature erythrocytes	**Vehicle/Formulation:** 0.5 w/v% MC /suspension	**Date of Dosing:** [redacted]202[redacted]
No. of Cells Evaluated/Animal: 4000		
Special Features: None		
Toxic/Cytotoxic Effects: None		
Genotoxic Effects: None		
Evidence of Exposure: None		

Test Substance	Dose Level [a] (mg/kg/day)	No. of Animals	Mean % IEs ± SD	No. of MNIEs [b] (/20000 IEs)	Mean % MNIEs ± SD
Vehicle (negative control)	0	5M	50.1 ± 5.7	35	0.18 ± 0.03
Ensitrelvir fumaric acid	250	5M	NE	NE	NE
	500	5M	52.0 ± 5.0	33	0.17 ± 0.07
	1000	5M	50.0 ± 4.8	31	0.16 ± 0.06
	2000	5M	50.3 ± 3.4	25	0.13 ± 0.05
Ethyl methanesulfonate [c]	200	5M	40.3 ± 4.5	262*	1.31 ± 0.19

IEs = immature erythrocytes; MNIEs = micronucleated immature erythrocytes; SD = standard diviation
* Significant increase from the negative control (Kastenbaum and Bowman's method, $P < 0.05$, one-tailed)
a As free form
b Total number of MNIEs per group
c Positive control (orally administered 2 times [0 and 21 hours after the first dosing])
S-217622 represents ensitrelvir

2.6.7.9 がん原性試験

該当する試験なし

2.6.7.10 生殖発生毒性試験： 重要な試験以外の試験

Test Article: Ensitrelvir fumaric acid

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Rabbit/ Kbl:NZW</td><td>Oral gavage (0.5% MC aqueous solution /Suspension)</td><td>GD6-19</td><td>0, 30, 300, 1000</td><td>3 or 4F (Pregnant)</td><td>Dams:
1000:
Abortion, abnormal stool color (test substance-like color)
≥ 300:
Decrease in stool volume
Decrease in body weight
Decrease in food consumption

Embryos and Fetuses:
1000:
High postimplantation loss rate, low fetal viability rate, low fetal body weight (female)
≥ 300:
Low fetal body weight (male)

Toxicokinetics (n = 3 or 4, mean value)
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>C_{max} (μg/mL)</th><th>$AUC_{0\text{-}24hr}$ (μg·hr/mL)</th></tr>
<tr><td>0</td><td>GD6</td><td>N/A</td><td>N/A</td></tr>
<tr><td></td><td>GD19</td><td>N/A</td><td>N/A</td></tr>
<tr><td>30</td><td>GD6</td><td>34.3</td><td>391</td></tr>
<tr><td></td><td>GD19</td><td>46.6</td><td>604</td></tr>
<tr><td>300</td><td>GD6</td><td>349</td><td>7230</td></tr>
<tr><td></td><td>GD19</td><td>289</td><td>4510</td></tr>
<tr><td>1000</td><td>GD6</td><td>539</td><td>11500</td></tr>
<tr><td></td><td>GD19</td><td>296</td><td>4700</td></tr>
</table></td><td>S-217622-TF-052-R /4.2.3.5-04</td></tr>
<tr><td>Rabbit/ Kbl:NZW</td><td>Oral gavage (0.5% MC aqueous solution /Suspension)</td><td>GD6-9</td><td>0, 300, 500, 750, 1000</td><td>3 or 4F (Pregnant)</td><td>Dams:
1000:
Abnormal stool color (test substance-like color)
≥300:
Decrease in stool volume, Decrease in body weight, Suppression body weight gain, Decrease in food consumption, Decrease in RET, Reduction in PT and APTT, Increase in Fibrin., Decrease in TP and Albumin, Increase in TG</td><td>S-217622-TF-119-R /4.2.3.5-06</td></tr>
</table>

					Toxicokinetics (n = 3 or 4, mean value) Dose (mg/kg/day) / Day / C_{max} (µg/mL) / $AUC_{0\text{-}24hr}$ (µg·hr/mL) 0 / GD9 / N/A / N/A 300 / GD9 / 362 / 5600 500 / GD9 / 265 / 3840 750 / GD9 / 365 / 5680 1000 / GD9 / 338 / 5010	

GD = Gestation day
a As free form.

2.6.7.11 生殖発生毒性試験： 受胎能及び着床までの初期胚発生に関する試験

2.6.7.11.1 ラット受胎能及び着床までの初期胚発生に関する試験

Test Article: Ensitrelvir fumaric acid

Report Title: Study on Fertility and Early Embryonic Development to Implantation following Oral Administration of S-217622 fumaric acid in Rats		
Design similar to ICH 4.1: Yes	**Duration of Dosing:** M: 4 weeks prior to mating and continuing until the day before necropsy F: 2 weeks prior to mating, through GD7	**Study No.** S-217622-TF-071-L
Species/Strain: Rat/Crl:CD(Sprague Dawley)		
Initial Age: M: 11 weeks, F: 12 weeks		**Location in CTD:** 4.2.3.5-01
Day of Mating: GD0	**Day of Caesarean section:** GD15	**GLP Compliance :** Yes
Date of First Dose: M: [redacted]202[redacted] F: [redacted]202[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5 w/v% MC/suspension	
NOAEL: F0 Males: 1000 mg/kg/day for general toxicity and reproductive function F0 Females: 1000 mg/kg/day for general toxicity and reproductive function F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	20	60	1000
Males:				
No. Animals	20	20	20	20
No. Died or Sacrificed Moribund	0	0	0	0
Clinical Signs	–	–	–	–
Body Weight	–	–	–	–
Body Weight Gain	–	–	–	–
Food Consumption (%) [a]				
Day 1 of dosing	27.4 g/day	0	−5	−14**
Reproductive Organ Weight [b]	–	–	–	–
Gross Pathology	–	–	–	–
Mean No. Days Prior to Copulation	2.4	2.7	2.6	2.6
No. Males that Copulated (Copulation Rate, %)	19 (95.0)	19 (95.0) [c]	20 (100.0)	19 (95.0)
No. Fertile Males (Fertility Rate, %)	19 (100.0)	19 (100.0)[c]	19 (95.0)	19 (100.0)

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	20	60	1000
Male:				
No. Animals	20	20	20	20
Sperm Examination				
Weight of caudal epididymis (mg)	323.76	303.12	302.43	287.47**
Sperm activity (%)	83.75	82.97	80.66	75.09##
Motile sperm (%)	81.36	81.48	78.19	76.73##
Total sperm count in caudal epididymis (×10^6)	198.05	192.90	184.58	168.60##
Histopathology [b]	–	NE	NE	–
Females:				
No. Animals	20	20	20	20
No. Died or Sacrificed Moribund	0	0	0	0
Clinical Signs	–	–	–	–
Body Weight, Pre-Pairing Period	–	–	–	–
Body Weight, Pregnancy Period	–	–	–	–
Body Weight Gain, Pre-Pairing Period	–	–	–	–
Body Weight Gain, Pregnancy Period	–	–	–	–
Food Consumption (%) [a]				
Day 1 of dosing	19.0 g/day	2	−2	−14**
Day 4 of dosing	18.3 g/day	−4	−14**	−11*
Gross Pathology	–	–	–	–
Frequency of Estrus (times/2 weeks)	3.2	3.2	3.6	3.5
Mean Days of Estrous Cycle	4.10	4.05	4.03	4.02
Mean No. Days Prior to Copulation	2.4	2.7	2.6	2.6
No. Females that Mated (Copulation Rate, %)	19 (95.0)	19 (95.0) [c]	20 (100.0)	19 (95.0)
No. Pregnant Females (Fertility Rate, %)	19 (100.0)	19 (100.0) [c]	19 (95.0)	19 (100.0)
No. Litters Evaluated	19	18 [d]	19	19
Mean No. Corpora Lutea	14.9	15.3	14.6	15.4
Mean No. Implantations	14.7	15.1	14.2	14.9
Mean % Implantation	97.6	98.9	97.2	96.9
Mean % Preimplantation Loss	2.4	1.1	2.8	3.1

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	20	60	1000
Embryos:				
No. Litters Evaluated	19	18 [d]	19	19
Mean No. Postimplantation Loss	0.9	0.8	0.4	0.9
Mean % Postimplantation Loss	8.2	5.7	2.6	6.5
Mean No. Live Embryos	13.8	14.3	13.8	13.9
Mean % Embryonic Viability Rate	91.8	94.3	97.4	93.6

－ = No noteworthy findings

a For controls, group means are shown. For treated group, percentage differences from controls are also shown. Statistical significance is based on actual data (not on percentage differences).

b Testes, epididymides, and ventral prostate

c Including 1 animal in which copulation was overlooked

d Excluding 1 animal in which copulation was overlooked

* P < 0.05, ** P < 0.01: Dunnett's test, ## P < 0.01: Dunnett-type test (Miller's test)

2.6.7.12 生殖発生毒性試験： 胚・胎児発生に関する試験

2.6.7.12.1 ラット胚・胎児発生に関する試験

Test Article: Ensitrelvir fumaric acid

Report Title: Study on Embryo-Fetal Development following Oral Administration of S-217622 fumaric acid in Rats		
Design similar to ICH 4.2.: Yes	**Duration of Dosing:** GD6–17	**Study No.** S-217622-TF-049-L
Species/Strain: Rat/Crl:CD(Sprague Dawley)	**Day of Mating:** GD0	**Location in CTD:** 4.2.3.5-02
Initial Age: 12 to 13 weeks	**Day of Caesarean section:** GD20	**GLP Compliance:** Yes
Date of First Dose: [redacted] 202[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5 w/v% MC/suspension	
NOAEL: F0 dams: 60 mg/kg/day for general toxicity and 1000 mg/kg/day for maternal reproductive function F1 litters: 60 mg/kg/day		

Dose (mg/kg/day, as free form)	0 (Vehicle)[a]	20	60	1000
Dams:				
Toxicokinetics for ensitrelvir				
No. of Dams	5	5	5	5
C_{max} (µg/mL)				
GD 6	NC	36.9	125	266
GD 17	NC	46.1	134	240
$AUC_{0\text{-}24hr}$ (µg·hr/mL)				
GD 6	NC	368	1590	4070
GD 17	NC	618	1990	3400
T_{max} (hr)				
GD 6	NC	1.2	1.4	1.8
GD 17	NC	1.0	1.0	1.4

Dose (mg/kg/day, as free form)	0 (Vehicle)[a]	20	60	1000
Dams:				
No. Pregnant	17	18	19	20
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted	0	0	0	0
No. with Total Resorption of Litter	0	0	0	0
Clinical Signs	–	–	–	–
Body Weight (%)[b]				
GD 6	289.9 g	0	–1	–1
GD 7	293.3 g	1	–1	–2
GD 8	297.1 g	0	–1	–2
GD 9	301.1 g	1	–1	–2
GD 10	305.6 g	1	0	–2
GD 11	313.1 g	0	–1	–2
GD 12	316.5 g	1	0	–2
GD 13	321.8 g	0	0	–2
GD 14	327.6 g	0	0	–2
GD 15	334.5 g	0	0	–2
GD 16	344.4 g	0	0	–2
GD 17	356.5 g	0	0	–3
GD 18	372.8 g	0	0	–3
Body Weight Gain (g)[c]				
GD 7	3.4	5.8	2.5	1.3
GD 8	7.2	8.1	5.1	2.3**
GD 9	11.2	13.9	10.1	8.3
GD 10	15.8	17.9	16.2	12.4
GD 11	23.2	24.2	21.3	19.4
GD 12	26.6	29.4	27.6	23.8
GD 13	31.9	33.7	32.2	29.2
GD 14	37.7	39.2	38.9	35.2
GD 15	44.6	46.3	45.4	41.2
GD 16	54.5	55.7	54.7	48.8
GD 17	66.6	68.0	67.5	59.7*
GD 18	82.9	84.9	83.5	75.7*

Dose (mg/kg/day, as free form)	0 (Vehicle)[a]	20	60	1000
Dams:				
No. Pregnant	17	18	19	20
Food Consumption (%)[b]				
GD 7	21.6 g/day	4	–9	–25**
GD 8	22.3 g/day	–4	–6	–18**
Necropsy Findings	–	–	–	–
Mean No. Corpora Lutea	14.7	14.5	15.6	14.4
Mean No. Implantations	14.1	14.1	13.8	14.1
Mean % Implantation	95.9	97.7	94.7	97.9
Mean % Preimplantation Loss	4.1	2.3	5.3	2.1
Litters:				
No. Litters Evaluated	17	18	19	20
No. Live Fetuses	229	245	256	269
Mean No. Live Fetuses	13.5	13.6	13.5	13.5
Mean % Fetal Viability	95.5	96.5	97.5	95.4
Mean No. Dead Fetuses	0.0	0.0	0.0	0.0
Mean No. Resorotions (Total) [d]	0.6	0.5	0.4	0.7
Mean % Postimplantation Loss	4.5	3.5	2.5	4.6
Fetal Sex Ratio (Males/Total)	0.499	0.568	0.466	0.540

Dose (mg/kg/day, as free form)	0 (Vehicle)[a]	20	60	1000
Litters:				
No. Litters Evaluated	17	18	19	20
No. Live Fetuses	229	245	256	269
Mean Fetal Body Weight (g)				
Male	3.86	3.84	3.85	3.71
Female	3.68	3.69	3.62	3.44*
Mean Placental Weight (g)				
Male	0.54	0.53	0.55	0.56
Female	0.53	0.52	0.54	0.55
Placental Abnormalities	–	–	–	–
Fetal Anomalies				
External Abnormalities	–	–	–	–
Visceral Abnormalities	–	–	–	–
Visceral Variations	–	–	–	–
Skeletal Abnormalities	–	–	–	–
Skeletal Variations NF/NL[c]	118/17	127/18	133/19	138/20
Mean frequencies				
No. Fetuses (%)	28 (22.38)	16 (12.66)	18 (13.82)	80 (58.88) ##
No. Litters (%)	10 (58.8)	12 (66.7)	12 (63.2)	19 (95.0) $
Short supernumerary rib				
No. Fetuses (%)	24 (19.02)	8 (6.71)	16 (12.29)	80 (58.88) ##
No. Litters (%)	8 (47.1)	8 (44.4)	12 (63.2)	19 (95.0) $$
Degree of Skeletal Ossification				
No. Sternebrae	5.18	5.36	5.16	4.72*
No. Sacral and Caudal Vertebrae	7.78	7.61	7.54	7.57

– = No noteworthy findings

a 0.5%MC

b For control, group means are shown. For treated groups, percentage differences from control are also shown. Statistical significance is based on actual data (not on percentage differences).

c Based on body weight on GD6

d Mean number of implantation site and placental remnant

e Number of fetuses evaluated (NF)/number of litters evaluated (NL)

* P < 0.05, ** P < 0.01: Dunnett's test, ## P < 0.01: Dunnett-type test (Miller's test), $ P < 0.05, $$ P < 0.01: Fisher's exact test

S-217622 represents ensitrelvir

2.6.7.12.2 ウサギ胚・胎児発生に関する試験

Test Article: Ensitrelvir fumaric acid

Report Title: Study on Embryo-Fetal Development following Oral Administration of S-217622 fumaric acid in Rabbits		
Design similar to ICH 4.2: Yes	**Duration of Dosing:** GD6–19	**Study No.** S-217622-TF-070-L
Species/Strain: Rabbit/Kbl:NZW	**Day of Mating:** GD0	**Location in CTD:** 4.2.3.5-03
Initial Age: 17 to 20 weeks	**Day of Caesarean section:** GD28	**GLP Compliance:** Yes
Date of First Dose: [redacted]202[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5% MC/Suspension	
NOAEL: F0 dam: 30 mg/kg/day for general toxicity and 30 mg/kg/day for maternal reproductive function F1 litter: 30 mg/kg/day		

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	30	100	300
Dams:				
Toxicokinetics for ensitrelvir				
No. of Dams	3	5	4	3
C_{max} (µg/mL)				
GD 6	NC	36.6	123	307
GD 19	NC	68.8	167	220
$AUC_{0\text{-}24hr}$ (µg·hr/mL)				
GD 6	NC	450	2010	6010
GD 19	NC	1260	2580	3840
T_{max} (hr)				
GD 6	NC	2.4	4.5	9.0
GD 19	NC	7.0	4.3	5.3
No. Pregnant	18	18	17	17
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted	0	0	1	0
No. with Total Resorption of Litter	0	0	0	2
Clinical Signs[a]				
Decrease in stool volume	0	0	13	14
No stool	0	0	4	0

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	30	100	300
Dams:				
No. Pregnant	18	18	17	17
Body Weight (%)[b]				
GD 8	3.322 kg	0	–2	–2
GD 9	3.342 kg	0	–4	–5
GD 10	3.357 kg	0	–4	–5
GD 11	3.367 kg	0	–5	–5
GD 12	3.378 kg	0	–5	–5
GD 13	3.396 kg	0	–5	–5
GD 14	3.423 kg	0	–5	–6*
GD 15	3.456 kg	–1	–6*	–7*
GD 16	3.465 kg	0	–6	–7*
GD 17	3.478 kg	0	–5	–6*
GD 18	3.493 kg	0	–5	–8**
GD 19	3.502 kg	0	–5	–7*
GD 20	3.511 kg	–1	–4	–8**
GD 21	3.518 kg	–1	–4	–7*
Body Weight Gain (kg)[c]				
GD 7	–0.021	–0.027	–0.046	–0.077**
GD 8	–0.012	–0.017	–0.092**	–0.153**
GD 9	0.008	–0.018	–0.119**	–0.217**
GD 10	0.022	0.004	–0.133**	–0.213**
GD 11	0.032	0.018	–0.144**	–0.203**
GD 12	0.044	0.029	–0.139##	–0.191##
GD 13	0.061	0.044	–0.106##	–0.177##
GD 14	0.088	0.063	–0.105##	–0.179##
GD 15	0.121	0.071	–0.098##	–0.168##
GD 16	0.131	0.098	–0.075##	–0.167##
GD 17	0.143	0.107	–0.038##	–0.146##
GD 18	0.158	0.121	–0.031##	–0.172##
GD 19	0.168	0.132	–0.003##	–0.139##
GD 20	0.176	0.127	0.012**	–0.162**
GD 21	0.184	0.137	0.043*	–0.111**
GD 22	0.206	0.157	0.091*	–0.057**
GD 23	0.219	0.180	0.114	–0.024**

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	30	100	300
Dams:				
No. Pregnant	18	18	17	17
Body Weight Gain (kg)[c]				
GD 24	0.238	0.207	0.123	0.003##
GD 25	0.256	0.251	0.133*	0.022**
GD 26	0.279	0.264	0.170	0.049**
GD 27	0.308	0.284	0.203	0.056**
GD 28	0.330	0.311	0.221	0.086**
Food Consumption (%)[b]				
GD 7	141.2 g/day	–7	–29**	–66**
GD 8	148.1 g/day	–12	–60##	–94##
GD 9	147.1 g/day	–17	–66##	–88##
GD 10	148.9 g/day	–11	–63##	–50##
GD 11	144.6 g/day	–4	–62##	–41##
GD 12	139.2 g/day	–6	–55##	–39##
GD 13	133.4 g/day	–13	–47##	–42##
GD 14	130.4 g/day	–20	–55##	–50##
GD 15	138.9 g/day	–24	–51##	–58##
GD 16	146.2 g/day	–23	–44##	–61##
GD 17	144.5 g/day	–12	–28	–48##
GD 18	148.1 g/day	–7	–29	–46##
GD 19	142.7 g/day	–9	–16	–36##
GD 20	145.1 g/day	–19	–13	–41##
GD 23	126.7 g/day	10	21*	29**
GD 24	120.6 g/day	15	17	30**
GD 25	118.8 g/day	20*	18	28**
GD 27	121.8 g/day	8	21*	14
Necropsy Findings	–	–	–	–
Mean No. Corpora Lutea	8.1	8.1	8.2	8.0
Mean No. Implantations	6.9	7.0	7.3	7.3
Mean % Implantation	85.3	84.1	88.3	91.1
Mean % Preimplantation Loss	14.7	16.2	11.8	9.2

Daily Dose (mg/kg/day, as free form)		0 (Vehicle)	30	100	300
Litters:					
No. Litters Evaluated		18	18	16	15
No. Live Fetuses		114	122	105	75
Mean No. Live Fetuses		6.3	6.8	6.6	4.4
Mean % Fetal Viability		90.2	96.4	90.3	66.3
Mean No. Dead Fetuses		0.3	0.0	0.3	0.3
Mean No. Resorotions (Total) [d]		0.3	0.2	0.5	2.6
Mean % Postimplantation Loss		9.9	3.7	9.8	33.7
Fetal Sex Ratio (Males/Total)		0.533	0.504	0.561	0.514
Mean Fetal Body Weight (g)[b]					
Male		34.63 g	–1	0	–8
Female		33.67 g	3	–1	–8
Mean Placental Weight (g)[b]					
Male		5.04 g	5	21**	17**
Female		4.98 g	4	22**	6
Placental Abnormalities		–	–	–	–
Fetal Anomalies					
External Abnormalities	**NF/NL**[e]	114/18	122/18	105/16	75/15
Mean frequencies					
No. Fetuses (%)		1 (0.56)	0 (0.00)	1 (0.89)	4 (4.57)
No. Litters (%)		1 (5.6)	0 (0.0)	1 (6.3)	2 (13.3)
Short tail					
No. Fetuses (%)		0 (0.00)	0 (0.00)	1 (0.89)	4 (4.57)
No. Litters (%)		0 (0.0)	0 (0.0)	1 (6.3)	2 (13.3)
Visceral Abnormalities		–	–	–	–
Visceral Variations		–	–	–	–
Skeletal Abnormalities	**NF/NL**[e]	114/18	122/18	105/16	75/15
Mean frequencies					
No. Fetuses (%)		0 (0.00)	2 (1.01)	5 (4.00)	22 (31.73) ##
No. Litters (%)		0 (0.0)	1 (5.6)	4 (25.0) $	10 (66.7) $$
Fused sternebra					
No. Fetuses (%)		0 (0.00)	1 (0.51)	3 (2.48)	3 (3.73)
No. Litters (%)		0 (0.0)	1 (5.6)	2 (12.5)	3 (20.0)
Branched rib					
No. Fetuses (%)		0 (0.00)	0 (0.00)	1 (0.63)	2 (2.62)
No. Litters (%)		0 (0.0)	0 (0.0)	1 (6.3)	2 (13.3)

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	30	100	300
Litters:				
No. Litters Evaluated	18	18	16	15
Skeletal Abnormalities NF/NL[e]	114/18	122/18	105/16	75/15
Fused rib				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	4 (3.97)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Absent rib				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (6.67)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Fused cervical centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.11)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Supernumerary thoracic vertebra				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (6.67)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Small thoracic arch				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.95)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Fused thoracic arch				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.00)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Fused thoracic centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.00)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Misaligned thoracic centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	4 (4.19)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Misaligned lumbar vertebra				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (7.62)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Fused caudal centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	1 (0.89)	3 (2.74)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (6.3)	2 (13.3)
Misaligned caudal centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	3 (4.33)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)

Daily Dose (mg/kg/day, as free form)	0 (Vehicle)	30	100	300
Litters:				
No. Litters Evaluated	18	18	16	15
Skeletal Abnormalities NF/NL[e]	114/18	122/18	105/16	75/15
Misaligned sacral and caudal vertebrae				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	3 (2.86)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Skeletal Variations NF/NL[e]	114/18	122/18	105/16	75/15
Mean frequencies				
No. Fetuses (%)	76 (70.77)	97 (81.76)	94 (91.29) **	69 (93.21) **
No. Litters (%)	18 (100.0)	18 (100.0)	16 (100.0)	15 (100.0)
Full supernumerary rib				
No. Fetuses (%)	51 (51.11)	74 (59.55)	83 (83.56) **	64 (82.97) **
No. Litters (%)	17 (94.4)	18 (100.0)	16 (100.0)	14 (93.3)
Splitting of thoracic centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (8.00)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Dumbbell ossification of thoracic centrum				
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.78)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Supernumerary lumbar vertebra				
No. Fetuses (%)	9 (5.41)	32 (23.32)	14 (15.49)	26 (32.93) #
No. Litters (%)	4 (22.2)	10 (55.6)	5 (31.3)	10 (66.7) $
Degree of Skeletal Ossification[f]	–	–	–	–

– = No noteworthy findings
a Numerals represent numbers of animals with the finding
b For controls, group means are shown. For treated group, percentage differences from controls are also shown.
Statistical significance is based on actual data (not on percentage differences).
c Based on body weight on GD 6
d Mean number of implantation site and placental remnant
e Number of fetuses evaluated/number of litters evaluated
f Number of ossified sternebrae and sacral and caudal vertebrae
* P < 0.05, ** P < 0.01: Dunnett's test, # < P 0.05, ## P < 0.01: Dunnett-type test,
$ P < 0.05, $$ P < 0.01: Fisher's exact test
S-217622 represents ensitrelvir

2.6.7.12.3 妊娠ウサギ２週間反復経口投与毒性試験

Test Article: Ensitrelvir fumaric acid

Report Title: Oral Toxicity Study of S-217622 fumaric acid in Pregnant Rabbits During Organogenesis Period		
Design similar to ICH 4.2: No	**Duration of Dosing:** GD6–19	**Study No.** S-217622-TF-137-L
Species/Strain: Rabbit/Kbl:NZW	**Day of Mating:** GD0	**Location in CTD:** 4.2.3.5-07
Initial Age: 23 weeks	**Day of Caesarean section:** GD20	**GLP Compliance:** Yes
Date of First Dose: [redacted] 202[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5% MC/Suspension	

Daily Dose (mg/kg/day)	0 (Vehicle)	100	300
Dams:			
No. Pregnant	5	5	5
No. Died or Sacrificed Moribund	0	0	0
No. Aborted	0	0	0
Clinical Signs[a]			
Decrease in stool volume	0	5	5
Body Weight (%)[b]			
GD 7	3.606 kg	–3	–4
GD 8	3.600 kg	–5	–7*
GD 9	3.614 kg	–6	–8*
GD 10	3.632 kg	–8*	–7
GD 11	3.622 kg	–9**	–7*
GD 12	3.642 kg	–8*	–7*
GD 13	3.638 kg	–8*	–8*
GD 14	3.648 kg	–7	–8
GD 15	3.662 kg	–7	–7
GD 16	3.652 kg	–7	–7
GD 17	3.654 kg	–7	–7
GD 18	3.674 kg	–7	–8
GD 19	3.690 kg	–6	–8*
GD 20	3.702 kg	–6	–8*

Daily Dose (mg/kg/day)	0 (Vehicle)	100	300
Dams:			
No. Pregnant	5	5	5
Body Weight Gain (kg)[c]			
GD 7	–0.016	–0.072#	–0.062#
GD 8	–0.022	–0.128**	–0.170**
GD 9	–0.008	–0.174**	–0.198**
GD 10	0.010	–0.224##	–0.144#
GD 11	0.000	–0.250**	–0.140**
GD 12	0.020	–0.216**	–0.144**
GD 13	0.016	–0.196**	–0.154**
GD 14	0.026	–0.162**	–0.150*
GD 15	0.040	–0.168**	–0.122*
GD 16	0.030	–0.158*	–0.118
GD 17	0.032	–0.158	–0.106
GD 18	0.052	–0.128*	–0.124*
GD 19	0.068	–0.102**	–0.120**
GD 20	0.080	–0.084*	–0.098**
Food Consumption (%)[b]			
GD 7	138.0 g/day	–56**	–81**
GD 8	138.0 g/day	–89**	–95**
GD 9	139.2 g/day	–96##	–74
GD 10	141.8 g/day	–96##	–33
GD 11	124.0 g/day	–83**	–20
GD 12	135.4 g/day	–68**	–46**
GD 13	117.2 g/day	–48*	–58**
GD 14	93.4 g/day	–36	–49*
GD 15	100.2 g/day	–67	–35
GD 16	104.0 g/day	–75*	–54
GD 17	114.4 g/day	–68*	–46
GD 18	129.0 g/day	–50	–44
GD 19	116.2 g/day	–37	–27
GD 20	123.6 g/day	–18	–28

Daily Dose (mg/kg/day)	0 (Vehicle)	100	300
Dams:			
No. Pregnant	5	5	5
Hematology			
GD 12			
Reticulocyte ratio (%)	5.062	1.658**	1.780**
Activated partial thromboplastin time (s)	18.28	14.74*	14.80*
GD 19			
Erythrocyte count (10^6/μL)	6.266	5.454**	5.460**
Hemoglobin concentration (g/dL)	13.20	11.34**	11.14**
Hematocrit value (%)	41.62	37.52**	36.22**
Blood Chemistry			
GD 12			
Triglyceride (mg/dL)	66.4	126.6	172.2#
Creatinine (mg/dL)	1.032	1.448##	1.286#
Necropsy Findings	–	–	–

–: No noteworthy findings
* $p < 0.05$, ** $p < 0.01$: Student's t-test, # < p 0.05, ## $p < 0.01$: The Aspin-Welch test
a: Numerals represent numbers of animals with the finding
b: For controls, group means are shown. For treated group, percentage differences from controls are shown.
Statistical significance is based on actual data (not on percentage differences).
c: Based on body weight on GD 6
S-217622 represents ensitrelvir

2.6.7.12.4 ウサギ胚・胎児発生に関する試験（短期間投与の胚・胎児発生への影響）

Test Article: Ensitrelvir fumaric acid

Report Title: Study on Embryo-Fetal Development following Oral Administration of S-217622 fumaric acid During the Divided Organogenesis Period in Rabbits		
Design similar to ICH 4.2: No	**Duration of Dosing:** GD 6 to GD 19 (Group 1), GD 6 to GD 9 (Group 2), GD 10 to GD 12 (Group 3), GD 13 to GD 15 (Group 4), and GD 16 to GD 19 (Group 5)	**Study No.** S-217622-TF-135-L
Species/Strain: Rabbit/Kbl:NZW	**Day of Mating:** GD0	**Location in CTD:** 4.2.3.5-08
Initial Age: 20 to 22 weeks	**Day of Caesarean section:** GD28	**GLP Compliance:** Yes
Date of First Dose: [redacted] 202[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5% MC/Suspension	

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Dams:					
Toxicokinetics for ensitrelvir					
No. of Dams	5	5	5	4	5
C_{max} (µg/mL)					
First day of dosing	NC	311	323	254	226
Final day of dosing	NC	332	427	376	196
$AUC_{0\text{-}24hr}$ (µg·hr/mL)					
First day of dosing	NC	6710	6980	5280	4860
Final day of dosing	NC	4620	7890	7600	3200
T_{max} (hr)					
First day of dosing	NC	13.6	6.8	14.3	17.6
Final day of dosing	NC	2.2	3.8	5.3	2.8

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Dams:					
No. Pregnant	17	18	19	18	20
No. Died or Sacrificed Moribund	0	0	0	0	0
No. Aborted	0	0	0	1	1
No. with Total Resorption of Litter	0	1	0	0	0
Clinical Signs[a]					
Decrease in stool volume	0	14	17	17	20
No stool	0	2	2	0	3
Body Weight (%)[b]					
GD 7	3.520 kg	–2	1	1	1
GD 8	3.519 kg	–4*	2	1	1
GD 9	3.525 kg	–5**	2	1	2
GD 10	3.542 kg	–5*	1	1	2
GD 11	3.552 kg	–3	–1	1	2
GD 12	3.565 kg	–2	–3	1	2
GD 13	3.575 kg	–2	–4*	1	2
GD 14	3.600 kg	–1	–5*	–1	2
GD 15	3.621 kg	–1	–3	–3	2
GD 16	3.641 kg	–2	–2	–5*	2
GD 17	3.646 kg	–1	–1	–4	0
GD 18	3.661 kg	–1	–1	–3	–2
GD 19	3.673 kg	–1	–1	–1	–4
GD 20	3.674 kg	–1	–1	–1	–3
GD 21	3.678 kg	–1	0	–1	–3
GD 22	3.694 kg	–1	0	–1	–2
GD 23	3.702 kg	–1	0	–2	–3
GD 24	3.707 kg	–1	0	–1	–3
GD 25	3.728 kg	–2	0	–1	–3
GD 26	3.739 kg	–1	0	–1	–2
GD 27	3.754 kg	–1	0	–1	–2
GD 28	3.778 kg	–1	0	–1	–2

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Dams:					
No. Pregnant	17	18	19	18	20
Body Weight Gain (kg)[c]					
GD 7	–0.004	–0.087**	0.005	0.014	0.012
GD 8	–0.004	–0.171**	0.019*	0.017	0.010
GD 9	0.001	–0.203**	0.027*	0.026	0.039**
GD 10	0.019	–0.178**	0.039	0.043	0.058*
GD 11	0.028	–0.100**	–0.033**	0.051	0.065*
GD 12	0.041	–0.058**	–0.096**	0.066	0.076*
GD 13	0.051	–0.026**	–0.139**	0.078	0.095*
GD 14	0.076	0.009**	–0.117**	0.012*	0.115
GD 15	0.098	0.023**	–0.032**	–0.052**	0.138
GD 16	0.118	0.038**	0.031**	–0.094**	0.160
GD 17	0.123	0.068*	0.057*	–0.051**	0.099
GD 18	0.137	0.083*	0.067*	0.003**	0.031**
GD 19	0.149	0.097*	0.086*	0.076*	–0.006**
GD 20	0.150	0.103	0.098	0.106	0.002**
GD 21	0.155	0.108	0.105*	0.106	0.041**
GD 22	0.171	0.111*	0.128	0.108	0.061**
GD 23	0.179	0.112*	0.133	0.097#	0.063**
GD 24	0.184	0.108	0.156	0.103*	0.059**
GD 25	0.204	0.119*	0.167	0.127	0.088**
GD 26	0.216	0.142*	0.177	0.175	0.114**
GD 27	0.230	0.158*	0.199	0.172	0.136**
GD 28	0.255	0.185	0.219	0.208	0.154**

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Dams:					
No. Pregnant	17	18	19	18	20
Food Consumption (%)[b]					
GD 7	137.8 g/day	–85##	10	7	9
GD 8	139.8 g/day	–98##	5	4	2
GD 9	136.8 g/day	–76**	8	4	6
GD 10	141.6 g/day	–37**	10	1	5
GD 11	135.5 g/day	2	–78**	1	5
GD 12	139.6 g/day	8	–92**	–7	–1
GD 13	128.9 g/day	13	–90**	–9	–3
GD 14	123.6 g/day	8	–42##	–88##	–9
GD 15	121.4 g/day	5	9	–97##	–7
GD 16	122.5 g/day	4	27**	–88**	–3
GD 17	129.7 g/day	6	16	–41**	–85##
GD 18	138.3 g/day	6	11	–17	–92##
GD 19	137.2 g/day	11*	18**	3	–85**
GD 20	135.4 g/day	2	17*	6	–54**
GD 21	133.8 g/day	1	10	0	–21#
GD 22	136.4 g/day	–12	9	–8	–13
GD 23	116.5 g/day	0	19*	–1	–3
Hematology[d]					
Final dosing day					
Reticulocyte ratio (%)	6.668$	2.060	4.074	5.758$$	3.522$$
Leukocyte count (10^3/μL)	8.475$	8.000	4.034$$	4.323$$	5.738$
Neutrophil count (10^3/μL)	1.835	1.584	1.122$	1.235	1.266
Lymphocyte count (10^3/μL)	5.375$	5.676	2.494$$	2.255$$	3.862$$
Monocyte count (10^3/μL)	0.575	0.374$	0.192$	0.418	0.358$
Basophil count (10^3/μL)	0.560	0.262	0.172$$	0.353	0.162$$
Activated partial thromboplastin time (s)	20.98	14.98	14.04$	15.00	15.24$

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Dams:					
No. Pregnant	17	18	19	18	20
Blood Chemistry[d]					
Final dosing day					
Triglyceride (mg/dL)	84.8	174.2$$	95.6	56.0	177.4$$
Creatinine (mg/dL)	1.043$	1.282$	1.428$$	1.498$$	1.308$
GD 19					
Triglyceride (mg/dL)	84.8	120.6$	221.4$$	124.5$	177.4$$
Necropsy Findings	–	–	–	–	–
Mean No. Corpora Lutea	8.4	8.0	8.5	8.8	8.4
Mean No. Implantations	7.4	7.7	8.2	8.4	7.9
Mean % Implantation	86.1	96.6	96.4	94.9	94.1
Mean % Preimplantation Loss	13.9	3.4	3.6	5.1	5.9
Litters:					
No. Litters Evaluated	17	18	19	17	19
No. Live Fetuses	114	110	149	129	140
Mean No. Live Fetuses	6.7	6.1	7.8	7.6	7.4
Mean % Fetal Viability	93.4	78.7#	96.7	90.9	93.8
Mean No. Dead Fetuses	0.2	0.2	0.1	0.1	0.3
Mean No. Resorptions (Total)[e]	0.5	1.4	0.3	0.6	0.3
Mean % Postimplantation Loss	6.7	21.3	3.4	9.2	6.2
Fetal Sex Ratio (Males/Total)	0.453	0.580	0.445	0.505	0.454
Mean Fetal Body Weight (%)[b]					
Male	35.67 g	–10*	–3	–9	–15**
Female	34.48 g	–12**	–2	–7	–13**
Mean Placental Weight (%)[b]					
Male	5.31 g	–6	–9	–3	–8
Female	4.98 g	–8	–2	2	–4
Placental Abnormalities	–	–	–	–	–

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Litters:					
No. Litters Evaluated	17	17	19	17	19
Fetal Abnomalies					
External Abnormalities NF/NL[f]	114/17	110/17	149/19	129/17	140/19
Mean frequencies					
No. Fetuses (%)	0 (0.00)	3 (2.89)	0 (0.00)	1 (0.59)	0 (0.00)
No. Litters (%)	0 (0.0)	3 (17.6)	0 (0.0)	1 (5.9)	0 (0.0)
Short tail					
No. Fetuses (%)	0 (0.00)	3 (2.89)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Spina bifida					
No. Fetuses (%)	0 (0.00)	1 (1.18)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Skeletal Abnormalities NF/NL[f]	114/17	110/17	149/19	129/17	140/19
Mean frequencies					
No. Fetuses (%)	1 (1.47)	15 (13.65)##	7 (4.57)	6 (5.13)	1 (0.58)
No. Litters (%)	1 (5.9)	8 (47.1)@	3 (15.8)	6 (35.3)	1 (5.3)
Fused sternebra					
No. Fetuses (%)	0 (0.00)	0 (0.00)	4 (2.41)	4 (3.74)#	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	2 (10.5)	4 (23.5)	0 (0.0)
Misaligned sternebra					
No. Fetuses (%)	0 (0.00)	1 (1.18)	1 (0.75)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	1 (5.3)	0 (0.0)	0 (0.0)
Absent rib					
No. Fetuses (%)	0 (0.00)	3 (2.78)	1 (0.66)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	1 (5.3)	0 (0.0)	0 (0.0)
Branched rib					
No. Fetuses (%)	0 (0.00)	2 (1.49)	0 (0.00)	1 (0.74)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	0 (0.0)	1 (5.9)	0 (0.0)

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Litters:					
No. Litters Evaluated	17	17	19	17	19
Skeletal Abnormalities NF/NL[r]	114/17	110/17	149/19	129/17	140/19
Fused rib					
No. Fetuses (%)	0 (0.00)	5 (4.27)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Misaligned cervical vertebra					
No. Fetuses (%)	0 (0.00)	1 (0.74)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fused thoracic arch					
No. Fetuses (%)	0 (0.00)	3 (2.78)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Absent thoracic centrum					
No. Fetuses (%)	0 (0.00)	1 (0.65)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fused thoracic centrum					
No. Fetuses (%)	0 (0.00)	3 (2.61)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hemicentric thoracic centrum					
No. Fetuses (%)	0 (0.00)	3 (2.78)	0 (0.00)	1 (0.74)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	0 (0.0)	1 (5.9)	0 (0.0)
Thoracic hemivertebra					
No. Fetuses (%)	0 (0.00)	2 (2.31)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Supernumerary thoracic vertebra					
No. Fetuses (%)	0 (0.00)	1 (1.18)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fused sacral centrum					
No. Fetuses (%)	0 (0.00)	1 (1.18)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hemicentric sacral centrum					
No. Fetuses (%)	0 (0.00)	1 (1.18)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)

Daily Dose (mg/kg/day)	0 (Vehicle)	300	300	300	300
Dosing Period	GD 6 to GD 19	GD 6 to GD 9	GD 10 to GD 12	GD 13 to GD 15	GD 16 to GD 19
Litters:					
No. Litters Evaluated	17	17	19	17	19
Skeletal Abnormalities NF/NL[f]	114/17	110/17	149/19	129/17	140/19
Absent sacral and caudal arch					
No. Fetuses (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.65)	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Fused caudal centrum					
No. Fetuses (%)	0 (0.00)	1 (0.74)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Misaligned sacral and caudal vertebrae					
No. Fetuses (%)	1 (1.47)	4 (3.41)	2 (1.34)	1 (0.65)	0 (0.00)
No. Litters (%)	1 (5.9)	4 (23.5)	2 (10.5)	1 (5.9)	0 (0.0)
Skeletal Variations NF/NL[f]					
Mean frequencies					
No. Fetuses (%)	89 (74.94)	94 (87.54)	108 (72.34)	90 (71.09)	105 (74.19)
No. Litters (%)	15 (88.2)	16 (94.1)	18 (94.7)	17 (100.0)	19 (100.0)
Dumbbell ossification of thoracic centrum					
No. Fetuses (%)	0 (0.00)	2 (1.96)	0 (0.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Degree of Skeletal Ossification[g]					
No. Sternebrae	5.57	5.55	5.61	5.64	5.27*

–: No noteworthy findings
* p < 0.05, ** p < 0.01: Student's t-test, # < p 0.05, ## p < 0.01: The Aspin-Welch test, $ p < 0.05, $$ p < 0.01: Paired t-test, @ p < 0.05: Fisher's exact test
NC: TK parameters for the control group were not calculated because all values were BLQ (< 0.1 μg/mL).
a: Numerals represent numbers of animals with the finding
b: For controls, group means are shown. For treated group, percentage differences from controls are also shown.
Statistical significance is based on actual data (not on percentage differences).
c: Based on body weight on GD 6
d: Paired t-test was performed for comparisons between the Baseline (defined as the determined on GD 6 for Groups 1 and 2, on GD 10 for Group 3, on GD 13 for Group 4, and on GD 16 for Group 5) and values at each measurement point.
e: Mean number of implantation site and placental remnant
f: Number of fetuses evaluated/number of litters evaluated
g: Number of ossified sternebrae and sacral and caudal vertebrae
S-217622 represents ensitrelvir

2.6.7.13 生殖発生毒性試験： 出生前及び出生後の発生並びに母体の機能に関する試験

2.6.7.13.1 ラット出生前及び出生後の発生並びに母体の機能に関する試験

Test Article: Ensitrelvir fumaric acid

Report Title: Study on Pre- and Postnatal Development, Including Maternal Function, following Oral Administration of S-217622 fumaric acid in Rats		
Design similar to ICH 4.3.: Yes	**Duration of Dosing:** GD6–L20 **Day of Mating:** GD0	**Study No.** S-217622-TF-050-L
Species/Strain: Rat/Crl:CD(Sprague Dawley)	**Method of Administration:** Oral gavage	**Location in CTD:** 4.2.3.5-05
Initial Age: 12 to 13 weeks	**Vehicle/Formulation:** 0.5% MC/Suspension	
Date of First Dose: [redacted] 202[redacted]	**Litters Culled/Not Culled:** Culled to 4/sex/litter	**GLP Compliance:** Yes
Special Features: None		
NOAEL: F0 dam: 60 mg/kg/day F1 litters: 60 mg/kg/day		

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F0 Females:				
No. Pregnant	20	18	19	20[a]
No. Died or Sacrificed Moribund	0	0	0	0
No. Dams with No Delivery	0	0	0	0
No. Total Litter Loss	0	0	0	5[b]
Clinical Signs	–	–	–	–
Body Weight (%)[c]				
Gestation Period				
GD 7	306.5 g	0	0	–2
GD 8	310.3 g	0	0	–2
GD 9	314.9 g	0	–1	–1
GD 10	320.9 g	0	0	–1
GD 11	327.1 g	0	0	–2
GD 12	332.0 g	0	0	–2
GD 13	337.6 g	0	0	–2
GD 14	342.8 g	0	–1	–2
GD 15	348.8 g	0	–1	–2
GD 16	358.8 g	0	–1	–2
GD 17	371.4 g	0	–1	–3

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F0 Females:				
No. Pregnant	20	18	19	20[a]
Body Weight (%)[c]				
Gestation Period				
GD 18	388.6 g	0	–1	–3
GD 19	403.9 g	0	–1	–2
GD 20	421.6 g	0	–1	–2
Lactation Period				
L 0	315.4 g	1	0	1
L 4	332.7 g	0	–2	–2
L 7	343.1 g	–2	0	–3
L 11	358.0 g	0	0	–3
L 14	370.3 g	–1	–1	–4
L 18	363.0 g	1	0	–1
L 21	353.2 g	0	–1	–3
Day of total litter loss (g)	ND	ND	ND	297 to 315
Body Weight Gain (g)				
Gestation Period[d]				
GD 7	4.8	4.3	3.5	0.2##
GD 8	8.6	8.7	7.8	3.6**
GD 9	13.2	13.4	10.0	9.8
GD 10	19.2	18.5	16.5	14.8*
GD 11	25.4	24.2	23.8	18.9**
GD 12	30.3	29.7	29.7	23.0**
GD 13	35.9	35.7	34.2	28.4**
GD 14	41.1	40.2	38.0	34.0*
GD 15	47.1	46.6	43.8	39.7*
GD 16	57.1	57.0	52.7	48.7*
GD 17	69.7	70.1	64.6	59.8*
GD 18	86.9	84.9	81.0	76.7#
GD 19	102.2	99.8	97.2	93.4
GD 20	119.9	119.3	113.6	110.5

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F0 Females:				
No. Pregnant	20	18	19	20[a]
Body Weight Gain (g)				
Lactation Period[e]				
L 4	17.3	13.3	11.5	7.9
L 7	27.7	18.1	25.7	17.7
L 11	42.6	38.0	41.6	28.8*
L 14	54.9	47.4	51.0	40.5*
L 18	47.6	46.6	49.2	42.4
L 21	37.9	34.1	34.8	25.8
Day of total litter loss (g)	ND	ND	ND	–36 to –10
Food Consumption (%)[c]				
Gestation Period				
GD 7	23.2 g/day	0	–5	–29**
GD 8	22.6 g/day	4	0	–10**
GD 9	23.5 g/day	2	–6	–6
GD 10	24.3 g/day	0	–2	–9*
Lactation Period				
L 5	46.2 g/day	–7	–5	–24**
L 8	49.9 g/day	0	0	–16**
L 12	65.4 g/day	–8	–5	–18**
L 15	69.6 g/day	–4	–5	–19##
L 19	73.2 g/day	–3	–4	–15##
L 21	80.4 g/day	–3	–2	–19**
Gross Pathology	–	–	–	–
Mean Duration of Gestation (days)	21.90	22.06	21.89	21.90
No. Delivery (%, Gestation Index)[f]	20 (100.0)	18 (100.0)	19 (100.0)	20 (95.0)[g]
Abnormal Delivery	–	–	–	–

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F1 Litters (Pre-weaning):				
No. Litters Evaluated	20	18	19	20[a]
Mean No. Pups/Litter	14.3	13.4	13.3	12.2#
Mean No. Live Born Pups/Litter	14.1	12.6	12.8	11.5##
Mean Pup Sex Ratio (Male/Male + Female)	0.49	0.56	0.47	0.51
Mean No. Stillborn Pups/Litter	0.3	0.8	0.5	0.7
Birth Index (Liveborns/Implantations, %)	93.70	86.42	85.98	80.90#
Pup External Malformation	–	–	–	–
Mean % Postnatal Survival to Day 4 after Birth	92.70	94.92	92.82	69.27#
Mean % Postnatal Survival to Weaning	98.75	99.31	99.34	98.21
Pup Body Weight (g)				
Male				
Day 0 after birth	6.68	7.03	6.55	6.22*
Day 4 after birth	9.86	9.84	9.56	8.55*
Day 4 after birth (After culling)	9.85	9.81	9.58	8.57*
Day 7 after birth	16.52	15.69	15.67	13.17**
Day 11 after birth	26.77	24.33	25.19	20.78##
Day 14 after birth	35.09	32.23	33.25	27.27##
Day 18 after birth	46.20	43.05	44.49	36.11##
Day 21 after birth	59.43	55.50	57.04	44.95##
Female				
Day 0 after birth	6.27	6.70	6.25	5.83
Day 4 after birth	9.44	9.39	9.09	8.19
Day 4 after birth (After culling)	9.52	9.39	9.11	8.19*
Day 7 after birth	15.72	15.25	14.88	12.54**
Day 11 after birth	25.56	24.36	24.02	19.74**
Day 14 after birth	33.59	32.11	32.01	25.69**
Day 18 after birth	44.47	42.98	42.93	33.75**
Day 21 after birth	56.91	55.20	55.08	42.44**
Functional Development[h]	–	–	–	–
Physical Development[i]				
Male				
Eyelid opening (%, Day 14 after birth)	62.9	62.9	45.9	23.1**
Eyelid opening (%, Day 16 after birth)	–	–	–	–

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F1 Litters (Pre-weaning):				
No. Litters Evaluated	20	18	19	20[a]
Physical Development[i]				
Female				
Eyelid opening (%, Day 14 after birth)	67.5	73.5	50.8	20.2**
Eyelid opening (%, Day 16 after birth)	–	–	–	–
Pup Clinical Signs	–	–	–	–
Pup Gross Pathology	–	–	–	–
F1 Males (Post-weaning):				
No. Evaluated Post-weaning (R, B)	40 (20, 20)	35 (18, 17)	36 (18, 18)	30 (15, 15)
No. Died or Sacrificed Moribund	0	1[j]	0	0
Clinical Signs	–	–	–	–
Body Weight (g)				
Day 28 after birth	100.7	99.9	97.8	83.1##
Day 35 after birth	161.2	160.5	158.4	139.9**
Day 42 after birth	229.3	229.4	227.3	208.3**
Day 49 after birth	293.8	295.3	294.8	271.6**
Day 56 after birth	354.3	354.0	353.9	336.7
Day 63 after birth	401.9	402.4	403.0	387.5
Day 70 after birth	441.2	440.6	442.3	431.9
Day of necropsy	607.1	611.1	604.4	603.5
Open Field Test	–	–	–	–
Water Maze Test	–	–	–	–
Cleavage of the Balano-Preputial Gland (%)[k]				
Day 45 after birth	55.0	58.8	44.4	33.3
Day 46 after birth	70.0	76.5	77.8	60.0
Day 47 after birth	75.0	88.2	77.8	66.7
Day 48 after birth	80.0	88.2	88.9	66.7
Day 49 after birth	85.0	94.1	94.4	66.7
Day 50 after birth	90.0	94.1	94.4	80.0
Day 51 after birth	–	–	–	–
Mean No. Days Prior to Copulation	2.3	2.6	2.6	2.7
No. Males Copulated (%, Copulation Index)	19/20 (95.0)	17/17 (100.0)[l]	19/19 (100.0)	15/15 (100.0)
No. Fertile Males (%, Fertility Index)	19/19 (100.0)	16/17 (94.1)[l]	18/19 (94.7)	13/15 (86.7)
Gross Pathology	–	–	–	–

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F1 Females (Post-weaning):				
No. Evaluated Post-weaning (R, B)	39 (20, 19)	34 (17, 17)	37 (19, 18)	28 (14, 14)
No. Died or Sacrificed Moribund	0	0	0	0
Clinical Signs	–	–	–	–
Body Weight (g)				
Pre-Pairing Period				
Day 28 after birth	93.8	90.9	90.6	74.1**
Day 35 after birth	139.4	135.0	137.0	116.5**
Day 42 after birth	176.5	172.8	175.4	157.2**
Day 49 after birth	206.8	201.2	204.5	187.0**
Day 56 after birth	232.1	227.5	232.2	213.6**
Day 63 after birth	252.3	248.3	253.2	234.8**
Day 70 after birth	267.5	264.9	269.4	251.7*
Day of necropsy	337.1	326.8	326.1	314.1
Pregnancy Period				
GD 0	296.4	296.3	304.1	279.9
GD 7	335.6	328.3	340.9	316.7
GD 15	376.5	366.5	384.2	363.2
Open Field Test	–	–	–	–
Water Maze Test	–	–	–	–
Vaginal Opening (%)[k]				
Day 35 after birth	90.0	94.1	100.0	50.0@
Day 40 after birth	–	–	–	–
Frequency of Estrus (times/2 weeks)	3.5	3.6	3.4	3.4
Mean Days of Estrous Cycle	4.03	4.03	4.04	4.06
Mean No. Days Prior to Copulation	2.3	2.6	2.6	2.7
No. Females Copulated (%, Copulation Index)	19/20 (95.0)	17/17 (100.0)[l]	19/19 (100.0)	15/15 (100.0)
No. Pregnant Females (%, Fertility Index)	19/19 (100.0)	16/17 (94.1)[l]	18/19 (94.7)	13/15 (86.7)
Mean No. Corpora Lutea	15.6	14.4	15.8	16.0
Mean No. Implantations	13.4	13.3	15.1	15.3
Mean % Pre-implantation Loss	13.6	7.9	4.0	3.8
Gross Pathology	–	–	–	–

Daily Dose (mg/kg, as free form)	0 (Vehicle)	20	60	1000
F2 Litters:				
No. Litters Evaluated	19	15[m]	18	13
Mean No. Postimplantation Loss	0.4	0.9	0.8	0.5
Mean % Postimplantation Loss	2.5	10.4	5.2	3.4
Mean No. Live Embryos	13.1	12.4	14.3	14.8
Mean % Embryonic Viability Rate	97.5	89.6	94.8	96.6

− = No noteworthy findings; ND = no data
*P < 0.05, **P < 0.01: Dunnett's test, #P < 0.05, ## P < 0.01: Dunnett-type test, @ P <0.05: Fisher's exact test
R: For reproductive function observations, B: For behavioral evaluations
a Total litter loss occurred in 5 dams/litters on Ls 0 to 3.
b Total litter loss on Ls 0 to 3
c For control, group means are shown. For treated groups, percentage differences from control are shown. Statistical significance is based on actual data (not on percentage differences).
d Based on body weight on GD6
e Based on body weight on L0
f (number of pregnant animals that delivered live pups/number of pregnant animals) × 100
g Including 1 litter had total litter loss on L0
h Righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, and pain response
i Pinna detachment, incisor eruption, and eyelid opening
j Animal No. 10038-M1 died on Day 23 after birth
k (number of animals completed/number of animals for examination) × 100
l Including 1 animal in which copulation was overlooked.
m Excluding 1 animal in which copulation was overlooked
S-217622 represents ensitrelvir

2.6.7.14 新生児を用いた試験

該当する試験なし

2.6.7.15 局所刺激性試験

該当する試験なし

2.6.7.16 その他の毒性試験

2.6.7.16.1 光毒性試験

Test Article: Ensitrelvir fumaric acid

Test system	Treatment	Doses [a]	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
–	–	0.1200 mmol/L	No	Wavelength range: 290 to 700 nm and 400 to 700 nm The MEC exceeds 1000 L/mol/cm in the wavelength range of 290 to 400 nm and there was no potential for the MEC to exceed 1000 L/mol/cm in the wavelength range of 400 to 700 nm.	S-217622-TF-019-N/ 4.2.3.7-01
BALB/c 3T3 cells	1 hour followed by UV-A (5 J/cm^2) and UV-B (68.7 mJ/cm^2) irradiation	0.781 to 100 µg/mL	Yes	No phototoxicity [PIF: Not determined, MPE: 0.022, IC_{50} (−UV): Not determined, IC_{50} (+UV): Not determined]	S-217622-TF-040-L/ 4.2.3.7-02

IC_{50} = 50% inhibition concentration; MEC = molar extinction coefficient; MPE = mean photo effect; PIF = photo irritation factor
a As free form

2.6.7.16.2 血漿中レシチンコレステロールアシルトランスフェラーゼ活性に対する作用

Test Article: Ensitrelvir fumaric acid

Species/Biological material	Rat plasma		
Concentration as Free Form (μg/mL)	0.00824, 0.0247, 0.0740, 0.222, 0.668, 2.00, 6.00, 18.0		
Positive Control (concentration)	Sodium iodoacetate (3.2 mmol/L)	**Vehicle**	DMSO
Evaluation Item	LCAT activity, inhibitory rate of LCAT activity (%)		
Evaluation Method	The plasma samples (4 μL) and assay buffer containing substrate reagent (96 μL) were mixed to make a total volume 100 μL. The assay plate was incubated for 2.5 hours at 37°C. The LCAT activity of the measurement samples was assessed by measuring the fluorescence intensity using the Roar LCAT Activity Assay Kit (Roar Biomedical, Inc.). The fluorescence intensity was measured with a multilabel plate reader. Ratio of the fluorescence intensity of intact substrate/hydrolysis product (460 nm/400 nm) was calculated. The LCAT activity was calculated by the following formula: LCAT activity = the ratio of the fluorescence intensity of the non-incubated samples – that of the incubated samples. Inhibitory rate was calculated from the LCAT activity of each sample, negative control samples (A), and positive control samples (B). Inhibitory rate = (the mean of A – LCAT activity of each sample)/(the mean of A – the mean of B) × 100.		
Noteworthy Findings	Ensitrelvir fumaric acid had no effects on the LCAT activity up to 18.0 μg/mL.		
Study Number [Location in CTD]	S-217622-TB-123-N [4.2.3.7-03]		

Substance	**Concentrations as free form (μg/mL)[c]**	**LCAT activity[d] (Change in the ratio of the fluorescence intensity)**		**Inhibitory rate[e] (%)**	
		Mean	**SD**	**Mean**	**SD**
Vehicle[a]	0.06 v/v%	0.383	0.014	0.00	4.34
Ensitrelvir fumaric acid	0.00824	0.355	0.039	8.48	11.97
	0.0247	0.383	0.010	–0.22	3.12
	0.0740	0.401	0.018	–5.63	5.64
	0.222	0.384	0.005	–0.48	1.56
	0.668	0.399	0.023	–5.06	7.04
	2.00	0.393	0.017	–3.05	5.41
	6.00	0.390	0.009	–2.16	2.94
	18.0	0.324	0.018	18.22	5.50
Sodium iodoacetate[b]	3.2 mmol/L	0.060	0.027	100.00	8.43

LCAT = lecithin cholesterol acyltransferase

a DMSO, negative control

b positive control

c Concentrations in the reaction mixures where plasma samples (ensitrelvir concentration as free form: 0.206 to 450 μg/mL; sodium iodoacetate concentration: 80 mmol/L; vehicle concentration: 1.5 v/v%) were added at a rate of 4%

d LCAT activity = A – B
A: the ratio of the fluorescence intensity of the non-incubated samples; B: the ratio of the fluorescence intensity of the incubated samples

e Inhibitory rate = (C – LCAT activity of each sample)/(C − D) × 100
C: the mean of the LCAT activity of the negative control samples; D: the mean of the LCAT activity of the positive control samples

2.6.7.16.3 THP-1 細胞からのコレステロール流出に対する作用

Test Article: Ensitrelvir fumaric acid

Species/Biological material	THP-1 cells (human leukemic monocyte), human serum
Concentration as free form (µg/mL)	6.25, 12.5, 25.0, 50.0, 100, 200
Vehicle	DMSO
Evaluation item	Percent of vehicle control (ratio of net cholesterol efflux compared with the vehicle control, 0.2% DMSO)
Evaluation Method	The cholesterol efflux activity of the measurement samples was assessed by Cholesterol Efflux Assay Kit (Cell-based) (abcam) Analytical method: each fluorescence intensity of the labeled-cholesterol analogue (Ex/Em = 485/535 nm) of the supernatant and cell lysate was measured with a multilabel plate reader. Data were expressed as relative fluorescence unit.
Noteworthy Findings	No effects of ensitrelvir fumaric acid on cholesterol efflux activity from THP-1 cells were noted up to 200 µg/mL.
Results	
Concentrations as free form (µg/mL)	**Percent of vehicle control**
6.25	73.3%
12.5	82.3%
25.0	76.3%
50.0	79.3%
100	75.5%
200	63.9%
Study Number [Location in CTD]	S-217622-TB-124-N [5.3.2.3-01]

2.6.7.16.4 ヒト血漿における脂質解析

Species/Biological material	Human plasma (Phase 1 study [multiple dose study] of S-217622, “A Phase 1 study of S-217622 in healthy adult participants, Clinical Study Number: 2102T1211”)
Dosing Regimen	750 mg on Day 1 (the first day of dosing) and 250 mg on Days 2 to 5, once daily for 5 days
Subjects	Six subjects (2 received placebo and 4 received ensitrelvir)
Sampling Points	Days 1 (pre-dosing, 2, 4, and 8 hours after dosing), 2 (pre-dosing [24 hours after the first dosing]), and 6 (24 hours after the fifth dosing) (total 6 points)
Evaluation Item	Contents of cholesterol, triglyceride, and free glycerol in lipoprotein, and particle number and size of lipoprotein
Evaluation Method	Lipoproteins of the subjects were classified into 4 major classes and 20 subclasses using LipoSEARCH program (patented method for analyzing lipoproteins; lipoproteins in plasma were separated and analyzed with proprietary gel-filtration HPLC and analyzing algorithm), and the changes in each evaluation item over time of those who received ensitrelvir were compared with those who received placebo.
Noteworthy Findings	The most noticeable change was a decrease of cholesterol in medium HDL accompanied by a decrease of particle number from 4 hours after dosing.

Results

	Total Cholesterol (mg/dL) [a]		Total Triglyceride (mg/dL) [a]	
	Placebo	**Ensitrelvir**	**Placebo**	**Ensitrelvir**
Pre	152.08	147.84	127.39	129.86
2 hr	149.96	147.21	115.76	135.63
4 hr	152.58	143.50	121.02	133.00
8 hr	137.80	133.45	140.63	161.33
24 hr	148.60	110.81	95.21	155.25
Day 6	152.38	110.16	93.55	161.51

Four Major Classes

	Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]		Particle Size Calculated by Cholesterol Waveform Peak Top (nm) [a]		Particle Size Calculated by Triglyceride Waveform Peak Top (nm) [a]	
	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
CM										
Pre	2.17	2.78	10.64	13.78	1.14	1.47	N/A	N/A	N/A	N/A
2 hr	2.58	3.31	11.42	14.36	1.26	1.59	N/A	N/A	N/A	N/A
4 hr	2.61	3.64	10.90	14.69	1.22	1.66	N/A	N/A	N/A	N/A
8 hr	2.34	5.05	15.82	25.68	1.58	2.72	N/A	N/A	N/A	N/A
24 hr	1.28	4.53	7.67	19.67	0.78	2.17	N/A	N/A	N/A	N/A
Day 6	0.94	4.33	5.27	19.77	0.55	2.15	N/A	N/A	N/A	N/A
VLDL										
Pre	29.40	27.22	91.87	89.20	122.15	113.41	43.43	43.92	49.71	51.34
2 hr	28.64	30.48	79.77	93.29	115.82	121.68	43.08	44.90	48.82	51.50
4 hr	31.96	33.71	85.66	89.58	120.01	129.19	43.26	45.68	50.27	51.93
8 hr	26.95	36.99	96.62	99.62	127.08	153.93	43.08	48.32	48.10	51.89
24 hr	24.86	34.97	64.53	87.00	102.78	161.22	42.74	N/A	48.39	49.38
Day 6	24.00	32.07	64.73	81.21	102.58	154.58	N/A	N/A	47.90	49.86
LDL										
Pre	82.03	77.78	15.17	15.95	993.06	959.82	26.28	26.33	N/A	N/A
2 hr	80.38	75.64	14.52	15.34	962.20	905.39	26.38	26.76	N/A	N/A
4 hr	79.44	71.81	14.42	15.13	960.05	832.37	26.28	27.30	N/A	29.45
8 hr	73.93	63.84	16.54	18.06	921.91	741.68	26.23	28.02	N/A	N/A
24 hr	82.61	53.21	15.12	31.28	991.34	708.89	26.38	28.47	N/A	29.05
Day 6	86.16	62.02	15.86	49.80	1056.01	899.97	26.12	28.10	N/A	28.53
HDL										
Pre	38.48	40.06	9.73	10.93	11666.52	11725.61	10.60	10.74	10.74	10.85
2 hr	38.36	37.79	10.05	12.64	11476.57	11323.85	10.61	10.75	10.77	10.83
4 hr	38.57	34.34	10.04	13.59	11821.40	10559.18	10.55	10.74	10.70	10.79
8 hr	34.59	27.58	11.66	17.97	11212.92	9635.28	10.51	10.64	10.68	10.69
24 hr	39.86	18.10	7.90	17.30	11766.06	8388.94	10.61	10.11	10.72	10.20
Day 6	41.30	11.75	7.69	10.74	12330.48	5467.26	10.59	10.07	10.72	10.15

20 Subclasses

		Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]	
		Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
G01							
	Pre	1.11	1.59	5.00	7.57	1.14 [b]	1.47 [b]
	2 hr	1.45	1.92	6.19	8.09	1.26 [b]	1.59 [b]
	4 hr	1.40	2.10	5.52	8.29	1.22 [b]	1.66 [b]
	8 hr	1.43	3.17	10.23	16.80	1.58 [b]	2.72 [b]
	24 hr	0.70	2.87	3.94	12.38	0.78 [b]	2.17 [b]
	Day 6	0.49	2.79	2.47	12.54	0.55 [b]	2.15 [b]
G02							
	Pre	1.06	1.19	5.64	6.21	–	–
	2 hr	1.13	1.39	5.23	6.27	–	–
	4 hr	1.21	1.54	5.38	6.40	–	–
	8 hr	0.91	1.88	5.59	8.88	–	–
	24 hr	0.58	1.67	3.72	7.28	–	–
	Day 6	0.45	1.54	2.80	7.23	–	–
G03							
	Pre	2.87	3.00	15.11	16.04	4.25	4.50
	2 hr	2.76	3.35	12.45	16.51	3.64	4.72
	4 hr	3.21	3.64	14.18	16.27	4.17	4.77
	8 hr	2.44	3.93	14.28	18.55	3.92	5.36
	24 hr	1.77	3.23	9.84	14.25	2.73	4.19
	Day 6	1.58	2.99	8.63	13.53	2.41	3.95
G04							
	Pre	5.14	5.25	28.15	28.56	14.11	14.34
	2 hr	4.64	5.96	22.93	30.78	11.78	15.65
	4 hr	5.48	6.35	26.71	30.03	13.77	15.60
	8 hr	4.75	6.65	27.04	32.53	13.44	16.75
	24 hr	3.07	5.11	18.15	23.47	8.95	12.29
	Day 6	2.97	4.43	18.02	21.23	8.83	10.99

		Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]	
		Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
G05							
	Pre	10.95	9.33	31.00	28.84	35.40	31.92
	2 hr	10.71	10.49	27.17	30.64	32.33	34.60
	4 hr	12.34	11.00	28.63	28.74	35.31	33.81
	8 hr	9.65	9.83	33.81	30.91	35.90	34.01
	24 hr	9.76	8.80	21.60	25.43	27.16	28.82
	Day 6	9.34	8.06	22.36	22.60	27.23	25.90
G06							
	Pre	4.96	4.45	13.64	11.98	34.46	30.50
	2 hr	5.00	4.23	13.29	11.67	34.01	29.45
	4 hr	5.68	3.85	12.34	10.69	34.25	26.90
	8 hr	5.00	3.93	16.82	12.35	39.60	29.75
	24 hr	4.49	4.69	11.16	14.56	29.33	35.23
	Day 6	4.81	4.50	11.83	11.91	31.18	30.54
G07							
	Pre	5.49	5.19	3.97	3.78	33.93	32.14
	2 hr	5.54	6.44	3.93	3.69	34.06	37.27
	4 hr	5.25	8.87	3.81	3.86	32.51	48.11
	8 hr	5.11	12.66	4.68	5.29	34.22	68.06
	24 hr	5.76	13.14	3.78	9.29	34.61	80.70
	Day 6	5.30	12.09	3.89	11.94	32.94	83.20
G08							
	Pre	23.54	21.81	5.56	5.43	181.49	169.34
	2 hr	23.98	24.88	5.47	5.50	184.08	190.25
	4 hr	22.46	28.24	5.36	5.85	173.39	214.27
	8 hr	20.46	29.79	6.35	7.69	164.08	232.39
	24 hr	24.45	26.49	5.55	14.18	187.55	237.23
	Day 6	23.17	30.04	5.48	23.13	178.62	298.43

		Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]	
		Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
G09							
	Pre	36.38	34.45	5.28	5.40	448.00	427.02
	2 hr	36.19	32.76	5.02	5.21	444.09	406.68
	4 hr	35.87	29.31	5.05	5.10	440.61	366.89
	8 hr	32.32	23.47	5.50	5.72	403.74	305.23
	24 hr	36.78	18.46	5.45	10.22	453.79	280.12
	Day 6	37.94	22.73	5.64	17.81	468.26	381.51
G10							
	Pre	15.83	15.30	2.82	3.19	235.32	231.29
	2 hr	14.48	12.86	2.58	2.86	215.16	195.87
	4 hr	15.23	10.10	2.61	2.56	225.46	156.39
	8 hr	15.08	7.46	2.90	2.67	225.88	122.01
	24 hr	15.35	5.74	2.77	4.19	228.34	111.61
	Day 6	17.81	6.53	3.20	6.02	264.82	137.30
G11							
	Pre	4.95	4.88	0.94	1.15	84.78	85.82
	2 hr	4.46	3.98	0.84	1.01	76.35	70.65
	4 hr	4.63	3.12	0.86	0.89	79.17	56.26
	8 hr	4.76	2.17	0.97	0.92	82.30	42.01
	24 hr	4.75	1.61	0.88	1.39	81.27	37.87
	Day 6	5.72	1.93	1.06	1.79	97.77	46.69
G12							
	Pre	0.50	0.52	0.31	0.44	13.79	15.89
	2 hr	0.47	0.43	0.33	0.42	13.38	13.73
	4 hr	0.46	0.40	0.30	0.41	12.85	13.02
	8 hr	0.52	0.43	0.47	0.63	16.22	16.15
	24 hr	0.50	0.48	0.26	0.77	13.06	19.00
	Day 6	0.64	0.36	0.26	0.56	15.81	14.07

		Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]	
		Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
G13							
	Pre	0.83	0.80	0.25	0.33	29.69	30.46
	2 hr	0.79	0.73	0.27	0.33	29.14	28.21
	4 hr	0.80	0.65	0.24	0.32	28.58	25.53
	8 hr	0.77	0.52	0.34	0.44	29.69	23.89
	24 hr	0.78	0.44	0.21	0.53	27.32	23.07
	Day 6	0.88	0.44	0.22	0.47	30.72	21.99
G14							
	Pre	0.50	0.48	0.20	0.27	28.99	30.15
	2 hr	0.49	0.46	0.23	0.28	29.55	29.72
	4 hr	0.45	0.47	0.20	0.30	26.79	30.60
	8 hr	0.43	0.47	0.32	0.47	29.18	35.51
	24 hr	0.56	0.43	0.18	0.50	31.26	34.44
	Day 6	0.59	0.29	0.17	0.33	32.50	23.07
G15							
	Pre	1.44	1.59	0.44	0.51	119.57	133.28
	2 hr	1.52	1.80	0.52	0.64	128.86	153.87
	4 hr	1.44	1.82	0.45	0.70	120.21	157.65
	8 hr	1.14	1.49	0.54	0.95	103.01	145.08
	24 hr	1.07	0.67	0.27	0.63	86.30	74.46
	Day 6	1.11	0.48	0.27	0.42	89.05	52.24
G16							
	Pre	6.49	8.22	1.87	2.33	884.24	1116.78
	2 hr	6.32	8.04	1.96	2.64	870.60	1117.77
	4 hr	6.09	7.45	1.84	2.73	835.33	1055.86
	8 hr	4.94	5.85	2.03	3.46	716.48	923.18
	24 hr	5.88	1.95	1.35	1.71	775.90	347.32
	Day 6	6.23	0.71	1.30	0.75	813.09	135.84

		Cholesterol (mg/dL) [a]		Triglyceride (mg/dL) [a]		Particle Number (nmol/L) [a]	
		Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid	Placebo	Ensitrelvir fumaric acid
G17							
	Pre	13.72	14.47	3.28	3.61	3024.96	3209.31
	2 hr	14.15	13.01	3.43	4.02	3126.17	2975.88
	4 hr	13.74	11.44	3.39	4.25	3040.98	2702.72
	8 hr	12.24	8.47	3.88	5.35	2811.67	2262.49
	24 hr	15.84	4.53	2.92	4.51	3389.51	1406.00
	Day 6	15.89	2.79	2.74	2.76	3376.61	863.62
G18							
	Pre	11.72	10.91	2.53	2.58	4392.35	4138.46
	2 hr	11.63	10.31	2.53	3.17	4365.69	4058.23
	4 hr	12.30	9.29	2.71	3.55	4621.84	3800.77
	8 hr	11.37	7.76	3.19	4.91	4413.25	3570.01
	24 hr	12.05	7.04	2.02	6.45	4400.04	3645.19
	Day 6	12.46	5.03	2.04	4.10	4539.47	2501.69
G19							
	Pre	3.42	3.17	0.59	0.71	2227.01	2122.31
	2 hr	3.04	3.00	0.53	0.89	1980.48	2086.76
	4 hr	3.32	2.76	0.58	1.03	2163.43	1998.85
	8 hr	3.32	2.52	0.80	1.58	2246.07	2060.40
	24 hr	3.28	2.52	0.42	2.26	2081.49	2304.85
	Day 6	3.75	1.65	0.45	1.29	2369.61	1438.11
G20							
	Pre	1.20	1.22	0.81	0.91	989.40	975.31
	2 hr	1.20	1.18	0.85	1.00	975.21	901.62
	4 hr	1.24	1.11	0.86	1.03	1012.82	812.74
	8 hr	1.14	1.01	0.90	1.25	893.27	638.61
	24 hr	1.19	0.95	0.74	1.24	1001.56	576.69
	Day 6	1.28	0.79	0.71	1.09	1110.15	452.69

CM = chylomicron; HDL = high density lipoprotein; LDL = low density lipoprotein, VLDL = very low density lipoprotein
− = The data are shown in the G01 column as the mean value of G01 and G02;
Pre = pre-dosing on the first day of dosing; 2 hr = 2 hours after the first dosing; 4 hr = 4 hours after the first dosing; 8 hr = 8 hours after the first dosing;
24 hr = 24 hours after the first dosing (pre-dosing on the second day of dosing); Day 6 = 24 hours after the fifth dosing;
G01, G02 = chylomicron fraction; G03, G04, G05 = large very low density lipoprotein fraction;
G06 = medium very low density lipoprotein fraction; G07 = small very low density lipoprotein fraction; G08 = large low density lipoprotein fraction;
G09 = medium low density lipoprotein fraction; G10 = small low density lipoprotein fraction;
G11, G12, G13 = very small low density lipoprotein fraction; G14, G15 = very large high density lipoprotein fraction;
G16 = large high density lipoprotein fraction; G17 = medium high density lipoprotein fraction; G18 = small high density lipoprotein fraction;
G19, G20 = very small high density lipoprotein fraction
a Group means are shown.
b Group means of G01 and G02 are shown.

Study Number [Location in CTD]	S-217622-CB-114-N [5.3.2.3-02]

S-217622 represents ensitrelvir.

2.6.7.16.5 サルにおけるコレステロール排泄への作用

Test Article: Ensitrelvir fumaric acid

Report Title: Effect of S-217622 fumaric acid on Cholesterol Excretion in Monkeys			
Study No.: S-217622-TF-191-N			
Species/Strain: Monkey/Cynomolgus	**Age:** 3 years	**Gender:** Male	
Method of Administration: Oral gavage	**Vehicle/Formulation:** 0.5 w/v% MC/suspension	**Duration of Dosing:** 10 days	
Dose level: 10 mg/kg/day as free form	**Location in CTD:** 4.2.3.7-18	**GLP Compliance:** No	
Group Composition:			
Study group	Bile-duct cannulation	Specimen	Number of animals used (animal number)
Group 1	With cannulation	Plasma, serum, feces, and bile	Three animals/group (No. 1 to No. 3)
Group 2	Without cannulation	Plasma, serum, and feces	Four animals/group (No. 5 to No. 8)
Evaluation Item: Total cholesterol and total bile acid in feces and bile, blood chemistry examination (total cholesterol, total bile acid, HDL and LDL cholesterol), toxicokinetics			
Sampling, determination of total cholesterol and total bile acid in feces and bile, determination of plasma ensitrelvir by LC/MS/MS were conducted in the non-GLP separate study (Study No.: S-217622-TF-191-N). Blood chemistry was investigated in the separate non-GLP study (Study No.: S-217622-TF-192-N [**Location in CTD:** 4.2.3.7-19]). The profiles of total cholesterol and total bile acid in the feces and bile were investigated before and during a repeated oral administration of ensitrelvir fumaric acid at a dose of 10 mg/kg/day to eight male cynomolgus monkeys to examine the effects of ensitrelvir fumaric acid on excretion of total cholesterol and total bile acid. Four out of the eight animals received the bile-duct cannulation seven days or twelve days before administration. The samples (bile-duct cannulated group: feces and bile, and non-cannulated group: feces) were collected from two days before administration to ten days after administration. In addition, serum samples were collected from one day before administration to ten days after administration for blood chemistry examination, and plasma samples were collected serially on one day and ten days after administration to assess systemic exposure to ensitrelvir. One cannulated animal (No. 4) was excluded from this study because of the stop of bile excresion before the completion of administration period, the reason for which was considered to be some kind of defect in the inserted cannula. The plasma concentration profile in the non-cannulated group was similar to that in the bile-duct cannulated group. The administration of ensitrelvir fumaric acid decreased total cholesterol, HDL cholesterol, and LDL cholesterol in plasma from Day 2, but did not affect the excretion of total cholesterol and total bile acid into the feces and bile. S-217622 represents ensitrelvir			

2.6.7.16.6 不純物に関する試験：In Vitro

Test Article	Test system	Treatment	Doses (µg/plate)	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Genotoxicity						
不純物G*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 1250	Yes	Positive	S-217622-TF-053-L/ 4.2.3.7-04
不純物A*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	39.1 to 1250	Yes	Negative	S-217622-TF-055-L/ 4.2.3.7-05
不純物D*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	39.1 to 1250	Yes	Negative	S-217622-TF-057-L/ 4.2.3.7-06
不純物C*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	313 to 5000	Yes	Negative	S-217622-TF-058-L/ 4.2.3.7-07
不純物B*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	156 to 5000	Yes	Negative	S-217622-TF-059-L/ 4.2.3.7-08
不純物E*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	313 to 5000	Yes	Negative	S-217622-TF-066-L/ 4.2.3.7-09
不純物H*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	156 to 5000	Yes	Positive	S-217622-TF-067-L/ 4.2.3.7-10
不純物F*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	39.1 to 1250	Yes	Negative	S-217622-TF-083-L/ 4.2.3.7-11
不純物L*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	−S9 mix 0.61 to 313 +S9 mix: 4.88 to 313	Yes	Positive	[redacted]/ 4.2.3.7-12
不純物K*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	39.1 to 1250	Yes	Positive	[redacted]/ 4.2.3.7-13
不純物J*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	1.22 to 5000	Yes	Positive	[redacted]/ 4.2.3.7-14

＊新薬承認情報提供時に置換

Test Article	Test system	Treatment	Doses (µg/plate)	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
不純物I*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	−S9 mix 156 to 5000 +S9 mix: 78.1 to 5000	Yes	Positive	[redacted]/ 4.2.3.7-15
不純物M*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	313 to 5000	Yes	Negative	[redacted]/4.2.3.7-16
不純物Z*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	61.7 to 5000	No	Positive	[redacted]/4.2.3.7-17

＊新薬承認情報提供時に置換