ゾフルーザ錠 10mg，同 20mg

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

目次

略号及び用語定義一覧表 4
2.6.7 毒性試験概要表 6
2.6.7.1 毒性試験： 一覧表 6
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 10
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 [a] 11
2.6.7.4 毒性試験： 被験物質 (ロット毎) 一覧 13
2.6.7.5 単回投与毒性試験 15
2.6.7.6 反復投与毒性試験： 重要な試験以外の試験 16
2.6.7.7 反復投与毒性試験：重要な試験 18
2.6.7.7.1 Two-Week Repeat-Dose Toxicity Study in Rats 18
2.6.7.7.2 Four-Week Repeat-Dose Toxicity Study in Rats 21
2.6.7.7.3 Two-Week Repeat-Dose Toxicity Study in Monkeys 23
2.6.7.7.4 Two-Week Repeat-Dose Toxicity Study in Monkeys (Supplement) 30
2.6.7.7.5 Four-Week Repeat-Dose Toxicity Study in Monkeys 32
2.6.7.8 In Vitro 遺伝毒性試験 38
2.6.7.8.1 Reverse Mutation Test with Bacteria 38
2.6.7.8.2 Reverse Mutation Test with Bacteria 41
2.6.7.8.3 In Vitro Micronucleus Test in Culture Mammalian Cells 45
2.6.7.8.4 In Vitro Micronucleus Test in Culture Mammalian Cells 46
2.6.7.9 *In Vivo* 遺伝毒性試験 47
2.6.7.9.1 Micronucleus Test in Rats 47
2.6.7.10 がん原性試験 47
2.6.7.11 生殖発生毒性試験： 重要な試験以外の試験 48
2.6.7.12 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 49
2.6.7.12.1 Fertility and Early Embryonic Development to Implantation in Rats 49
2.6.7.13 生殖発生毒性試験： 胚・胎児発生に関する試験 51
2.6.7.13.1 Embryo-Fetal Development in Rats 51
2.6.7.13.2 Embryo-Fetal Development in Rabbits 53
2.6.7.14 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 56
2.6.7.14.1 Prenatal and Postnatal Development, Including Maternal Function in Rats 56
2.6.7.15 新生児を用いた試験 61
2.6.7.15.1 新生児を用いた試験：重要な試験以外の試験 61
2.6.7.15.2 新生児を用いた試験：重要な試験 63
2.6.7.15.2.1 Forty-Day Repeat-Dose Toxicity Study in Juvenile Rats 63
2.6.7.16 局所刺激性試験 66
2.6.7.17 その他の毒性試験 67
2.6.7.17.1 Effect of Vitamin K on S-033188-induced PT and APTT Prolongation in Rats 67

2.6.7.17.2 Photosafety Study: In Vivo 68

略号及び用語定義一覧表

略号	用語定義
A/G ratio	albumin/globulin ratio
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMY	amylase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0\text{-}24hr}$	area under the concentration-time curve from 0 to 24 hours
B	for behavioral evaluations
BLQ	below the lower limit of quantification
BW	body weight
$C_{0.5\ (1)\ hr}$	plasma concentration at 0.5 (1) hr after dosing
C_{max}	maximum plasma concentration
Day 1	the first day of dosing
Day 1 of recovery	the first day of recovery
D.Bil	direct bilirubin
DMSO	dimethyl sulfoxide
Eos	eosinophil
F	female
Fbg	fibrinogen concentration
G	gestation day
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
HCT	hematocrit
HGB	hemoglobin concentration
IE	immature erythrocytes
L	lactation day
LAP	leucyl aminopeptidase
LLOQ	lower limit of quantification
M	male
MC	methylcellulose aqueous solution
MCHC	mean cell hemoglobin concentration
MCV	mean corpuscular volume
MNBN	micronucleated binucleate cells
MNIE	micronucleated immature erythrocytes
N/A	not applicable
N.C.	not calculated
N.E.	not examined
NF/ND	number of fetuses examined/number of dams examined
PLT	platelet count
PND	postnatal day
PT	prothrombin time
R	for reproductive function observations
RBC	red blood cell count
RDW	red blood cell volume distribution width
S9	supernatant at 9000×g
S9 mix	metabolic activation system
T.Bil	total bilirubin
TG	triglyceride
TK	toxicokinetics

T_{max}	time to maximum plasma concentration
T.Cho	total cholesterol
T.Pro	total protein

2.6.7 毒性試験概要表

2.6.7.1 毒性試験： 一覧表

Test Article: S-033188, S-033447

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
DRF Repeat-Dose Toxicity	Rat/Sprague Dawley	Oral gavage	1 or 2 weeks	0, 200, 600, 2000	No	Shionogi	TOX-20[redacted]-MTS-0576188A-02	4.2.3.2-06
	Monkey/ Cynomolgus	Oral gavage	2 weeks	0, 6, 20, 60, 200	No	[redacted]	OSC20[redacted]-0027	4.2.3.2-07
Repeat-Dose Toxicity	Rat/Sprague Dawley	Oral gavage	2 weeks	0, 20, 200, 2000	Yes	Shionogi	R-033188-TB-032-L	4.2.3.2-01
	Rat/Sprague Dawley	Oral gavage	4 weeks	0, 20, 200, 2000	Yes	Shionogi	S-033188-TB-131-L	4.2.3.2-02
	Monkey/ Cynomolgus	Oral gavage	2 weeks	0, 20, 60, 200	Yes	[redacted]	R-033188-TF-043-L	4.2.3.2-03
	Monkey/ Cynomolgus	Oral gavage	2 weeks	0, 3, 10	Yes	[redacted]	R-033188-TF-083-L	4.2.3.2-04
	Monkey/ Cynomolgus	Oral gavage	4 weeks	0, 1, 10, 100	Yes	[redacted]	S-033188-TF-132-L	4.2.3.2-05
	Electron Microscopic Examination of Liver of Monkey/ Cynomolgus[b]	Oral gavage	4 weeks	0, 100	No	[redacted]	S-033188-TF-189-N	4.2.3.2-08
Genotoxicity	*Salmonella typhimurium* and *Escherichia coli*	In vitro	N/A	−S9: 156, 313, 625, 1250, 2500, 5000 µg/plate +S9: 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA98), 2.44, 4.88, 9.77, 19.5, 39.1,78.1 µg/plate (TA100, TA1535, TA1537, WP2*uvrA*)	Yes	Shionogi	R-033188-TB-064-L	4.2.3.3-01

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
	Salmonella typhimurium and *Escherichia coli* [c]	In vitro	N/A	−S9: 0.610, 1.22, 2.44, 4.88, 9.77, 19.5 µg/plate (TA100, TA1535, TA1537), 2.44, 4.88, 9.77, 19.5, 39.1, 78.1 µg/plate (TA98, WP2*uvrA*) +S9: 0.61, 1.22, 2.44, 4.88, 9.77, 19.5 µg/plate (TA1535, TA1537), 2.44, 4.88, 9.77, 19.5, 39.1, 78.1 µg/plate (TA100, WP2*uvrA*), 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA98)	Yes	Shionogi	R-033188-TB-065-L	4.2.3.3-02
	Human lymphoblast cell line (TK6)	In vitro	N/A	−S9, 3 hour treatment: 43.2, 72.0, 120 µg/mL +S9, 3 hour treatment: 25.9, 43.2, 72.0 µg/mL −S9, 24 hour treatment: 2.02, 5.62, 15.6 µg/mL	Yes	[redacted]	R-033188-TF-060-L	4.2.3.3-03
	Human lymphoblast cell line (TK6) [c]	In vitro	N/A	−S9, 3 hour treatment: 50.0, 80.0, 160 µg/mL +S9, 3 hour treatment: 50.0, 80.0, 160 µg/mL -S9, 24 hour treatment: 1.56, 3.13, 6.25 µg/mL	Yes	[redacted]	R-033188-TF-059-L	4.2.3.3-04
	Rat/Sprague Dawley	Oral gavage	2 days	0, 500, 1000, 2000	Yes	[redacted]	R-033188-TF-085-L	4.2.3.3-05
DRF Reproductive and Developmental Toxicity	Rabbit/NZW (Non-pregnant)	Oral gavage	2 weeks	0, 100, 300, 1000	Yes	[redacted]	R-033188-TF-066-L	4.2.3.5-06
	Rabbit/NZW	Oral gavage	G7–19	0, 100, 300, 1000	Yes	[redacted]	R-033188-TF-087-L	4.2.3.5-07

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
	Juvenile Rat/Sprague Dawley	Oral gavage	3 weeks	0, 100, 300, 1000	No	[redacted]	S-033188-TF-091-R	4.2.3.5-08
Reproductive and Developmental Toxicity	Rat/Sprague Dawley	Oral gavage	M: Approximately 4 weeks premating until necropsy F: 2 weeks premating until G7	0, 20, 200, 1000	Yes	Shionogi	S-033188-TB-130-L	4.2.3.5-01
	Rat/Sprague Dawley	Oral gavage	G6–17	0, 20, 200, 1000	Yes	Shionogi	R-033188-TB-070-L	4.2.3.5-02
	Rabbit/NZW	Oral gavage	G7–19	0, 30, 100, 1000	Yes	[redacted]	S-033188-TF-135-L	4.2.3.5-03
	Rat/Sprague Dawley	Oral gavage	G6–L20	0, 20, 200, 1000	Yes	[redacted]	S-033188-TF-159-L	4.2.3.5-04
	Juvenile Rat/Sprague Dawley	Oral gavage	40 days	0, 20, 200, 1000	Yes	[redacted]	S-033188-TF-128-L	4.2.3.5-05
Other Toxicity								
Effect of Sterilized Food on PT and APTT Prolongation	Rat/Sprague Dawley	Oral gavage	1 week	0, 600	No	Shionogi	R-033188-TB-007-R	4.2.3.7-03
Effect of Vitamin K on PT and APTT Prolongation	Rat/Sprague Dawley	Oral gavage	2 weeks	S-033188/Vitamin K: 0/0, 2000/0, 2000/0.3	Yes	Shionogi	R-033188-TB-047-L	4.2.3.7-01
Preliminary Skin Phototoxicity	Mouse/HR-1	Oral gavage	Single	0, 200, 1000 mg/kg	No	Shionogi	TOX-20[redacted]-MTS-0576188A-03	4.2.3.7-04
	Mouse/HR-1	Intraperitoneal	Single	100 mg/kg	No	Shionogi	S-033188-TB-144-R	4.2.3.7-05
Skin Phototoxicity	Mouse/HR-1	Oral gavage, Intraperitoneal	Single	Oral gavage: 0, 1000 mg/kg Intraperitoneal: 10, 30, 100 mg/kg	Yes	Shionogi	S-033188-TB-149-L	4.2.3.7-02

Abbreviations: APTT, activated partial thromboplastin time; [redacted] DRF, dose range-finding; [redacted] G, gestation day; GLP, Good Laboratory Practice; L, lactation day; N/A, not applicable; PT, prothrombin time; [redacted].

a For Repeat-Dose Toxicity, Reproductive and Developmental Toxicity (reproductive functions, maternal reproductive function, and embryo-fetal development), and Skin Phototoxicity, the highest NOAEL (No Observed Adverse Effect Level) is underlined.

b Liver samples from one-month oral toxicity study in monkeys (S-033188-TF-132-L) were examined.

c Test article: S-033447, an active form of S-033188.

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: 033188

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Study Number	Location in CTD
Repeat-Dose Toxicity (2-Week)	Rat	Oral gavage	0, 20, 200, 2000	Yes	R-033188-TB-032-L	4.2.3.2-01
Repeat-Dose Toxicity (4-Week)	Rat	Oral gavage	0, 20, 200, 2000	Yes	S-033188-TB-131-L	4.2.3.2-02
Repeat-Dose Toxicity (2-Week)	Monkey	Oral gavage	0, 20, 60, 200	Yes	R-033188-TF-043-L	4.2.3.2-03
Repeat-Dose Toxicity (2-Week)	Monkey	Oral gavage	0, 3, 10	Yes	R-033188-TF-083-L	4.2.3.2-04
Repeat-Dose Toxicity (4-Week)	Monkey	Oral gavage	0, 1, 10, 100	Yes	S-033188-TF-132-L	4.2.3.2-05
Embryo-Fetal Development	Rat	Oral gavage	0, 20, 200, 1000	Yes	R-033188-TB-070-L	4.2.3.5-02
Embryo-Fetal Development	Rabbit	Oral gavage	0, 30, 100, 1000	Yes	S-033188-TF-135-L	4.2.3.5-03
Juvenile Toxicity (40 days)	Rat	Oral gavage	0, 20, 200, 1000	Yes	S-033188-TF-128-L	4.2.3.5-05

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[a]

Test Article: S-033188

Daily Dose (mg/kg)	Steady State C_{max} of S-033447 (μg/mL)					
	Rats		Rabbits	Monkeys		Humans[c]
	M	F	F	M	F	M & F
0.8[b]						0.123
1				0.0515[h]	0.0527[h]	
3				0.129[g]	0.148[g]	
10				0.314[g], 0.242[h]	0.368[g], 0.229[h]	
20	0.162[d], 0.124[e], 0.109[k]	0.144[d], 0.123[e], 0.324[i], 0.104[k]		0.559[f]	0.563[f]	
30			0.485[j]			
60				1.37[f]	0.736[f]	
100			0.883[j]	0.714[h]	0.642[h]	
200	0.243[d], 0.198[e], 0.295[k]	0.291[d], 0.204[e], 0.622[i], 0.382[k]		1.29[f]	2.12[f]	
1000	0.248[k]	0.621[i], 0.282[k]	1.35[j]			
2000	0.274[d], 0.275[e]	0.497[d], 0.460[e]				
Daily Dose (mg/kg)	Steady State $AUC_{0\text{-}24hr}$ of S-033447 (μg·hr/mL)					
	Rats		Rabbits	Monkeys		Humans[l]
	M	F	F	M	F	M & F
0.8[b]						1.71
1				0.527[q]	0.456[q]	
3				1.56[p]	1.89[p]	
10				4.53[p], 3.05[q]	4.28[p], 3.14[q]	
20	0.872[m], 0.817[n], 0.667[t]	0.853[m], 0.722[n], 1.88[r], 0.554[t]		9.46[o]	7.79[o]	
30			4.60[s]			
60				19.8[o]	10.5[o]	
100			9.26[s]	11.6[q]	9.06[q]	
200	2.00[m], 1.66[n], 2.570[t]	3.40[m], 1.72[n], 6.18[r], 2.760[t]		22.4[o]	37.2[o]	
1000	2.950[t]	7.17[r], 3.050[t]	20.9[s]			
2000	3.34[m], 3.40[n]	5.47[m], 4.76[n]				

Abbreviations: $AUC_{0\text{-}24hr}$, area under the plasma concentration-time curve from time 0 to 24 hours post-dose; C_{max}, maximum plasma concentration.

a As plasma concentrations of S-033188 were below the lower limit of quantification (BLQ, < 0.00500 μg/mL) in almost all samples examined, plasma concentrations of S-033447, an active form of S-033188, were shown in this table.

b Calculated from the clinical dose (40 mg tablet) and human body weight (assumed to be 50 kg).

c The C_{max} at the intended clinical dose (40 mg/day).

d The C_{max} on Day 14 of a repeat-dose toxicity study (2-week) in rats (Study No.: R-033188-TB-032-L).

e The C_{max} on Day 28 of a repeat-dose toxicity study (4-week) in rats (Study No.:S-033188-TB-131-L).

f The C_{max} on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Study No.: R-033188-TF-043-L).

g The C_{max} on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Supplement) (Study No.: R-033188-TF-083-L).

h The C_{max} on Day 28 of a repeat-dose toxicity study (4-week) in monkeys (Study No.: S-033188-TF-132-L).

i The C_{max} on Gestation Day 17 of a study on embryo-fetal development in rats (Study No.: R-033188-TB-070-L).

j The C_{max} on Gestation Day 19 of a study on embryo-fetal development in rabbits (Study No.: S-033188-TF-135-L).

k The C_{max} on Day 49 of age (the last dosing day) of a juvenile toxicity study (40-day) in rats (Study No.: S-033188-TF-128-L).

l The $AUC_{0\text{-}\tau}$ at the intended clinical dose (40 mg/day).

m The $AUC_{0\text{-}24hr}$ on Day 14 of a repeat-dose toxicity study (2-week) in rats (Study No.: R-033188-TB-032-L).

n The $AUC_{0\text{-}24hr}$ on Day 28 of a repeat-dose toxicity study (4-week) in rats (Study No.:S-033188-TB-131-L).

o The $AUC_{0\text{-}24hr}$ on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Study No.: R-033188-TF-043-L).

p The $AUC_{0\text{-}24hr}$ on Day 14 of a repeat-dose toxicity study (2-week) in monkeys (Supplement) (Study No.: R-033188-TF-083-L).

q The $AUC_{0\text{-}24hr}$ on Day 28 of a repeat-dose toxicity study (4-week) in monkeys (Study No.: S-033188-TF-132-L).

r The $AUC_{0\text{-}24hr}$ on Gestation Day 17 of a study on embryo-fetal development in rats (Study No.: R-033188-TB-070-L).

s The $AUC_{0\text{-}24h}$ on Gestation Day 19 of a study on embryo-fetal development in rabbits (Study No.: S-033188-TF-135-L).

t The $AUC_{0\text{-}24h}$ on Day 49 of age (the last dosing day) of a juvenile toxicity study (40-day) in rats (Study No.: S-033188-TF-128-L).

2.6.7.4 毒性試験： 被験物質 (ロット毎) 一覧

Test Article: S-033188

S-033188

Batch No.	Purity (%)	Study Number	Type of Study
A47001	97.5	R-033188-TB-032-L	Repeat-dose toxicity (2-week) in rats
		R-033188-TF-043-L	Repeat-dose toxicity (2-week) in monkeys
		R-033188-TF-083-L	Repeat-dose toxicity (2-week) in monkeys (supplement)
		R-033188-TB-064-L	Reverse mutation in bacteria
		R-033188-TF-060-L	Micronucleus in cultured mammalian cells
		R-033188-TF-085-L	Micronucleus in rats
		R-033188-TF-066-L	DRF repeat-dose toxicity (2-week) in non-pregnant rabbits
		R-033188-TB-047-L	Effect of vitamin K on PT and APTT prolongation in rats
A48005	97.4	R-033188-TB-070-L	Embryo-fetal development in rats
		R-033188-TF-087-L	DRF embryo-fetal development in rabbits
A4X006	98.8	S-033188-TF-091-R	DRF repeat-dose toxicity (3-week) in juvenile rats
A580012	98.2	S-033188-TB-131-L	Repeat-dose toxicity (4-week) in rats
		S-033188-TB-130-L	Fertility and early embryonic development to implantation in rats
		S-033188-TF-159-L	Pre- and postnatal development including maternal function in rats
		S-033188-TF-128-L	Repeat-dose toxicity (40-day) in juvenile rats
		S-033188-TB-149-L	Skin phototoxicity in hairless mice
		S-033188-TB-144 R	Preliminary skin phototoxicity in hairless mice
A580013	98.0	S-033188-TF-132-L	Repeat-dose toxicity (4-week) in monkeys
		S-033188-TF-135-L	Effects on embryo-fetal development in rabbits

Test article: S-033447

S-033447

Batch No.	Purity (%)	Study Number	Type of Study
A46001	99.4	R-033188-TB-065-L	Reverse mutation in bacteria
		R-033188-TB-059-L	Micronucleus in cultured mammalian cells

Impurities	Batch No.	Specified Impurities (%)					
		S-033188					S-033447
		A47001	A48005	A580012	A580013	A4X006	A46001
Related Substances							
Total		2.21	2.22	1.19	1.63	0.44	0.47
S-033447		0.59	0.61	–	–	0.09	–
S199YH		–	–	0.34	0.43	–	–
S199BE		–	–	0.44	0.45	–	–
S199ZR		–	–	–	–	0.09	–
S199ZP		–	–	–	–	0.01	–
S199ZQ		–	–	–	–	0.15	–
S199AT		–	–	–	–	0.06	–
Stereoisomers							
S199ZN ((12a*S*, 11*R*)-S-033188)		< 0.10	< 0.10	< 0.10	< 0.10	< 0.05	–
S199BD ((12a*R*, 11*R*)-S-033188)		< 0.10	< 0.10	< 0.10	< 0.10	< 0.05	–
S199ZM ((12a*S*, 11*S*)-S-033188)		< 0.10	< 0.10	< 0.10	< 0.10	< 0.05	–
S199ZL ((12a*S*, 11*R*)-S-033447)		–	–	–	–	–	< 0.10
S199AW ((12a*R*, 11*R*)-S-033447)		–	–	–	–	–	< 0.10
S199ZK ((12a*S*, 11*S*)-S-033447)		–	–	–	–	–	< 0.10

2.6.7.5 単回投与毒性試験

該当する試験なし.

2.6.7.6 反復投与毒性試験： 重要な試験以外の試験

Test Article: S-033188

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses (mg/kg/day)</th><th>Gender and No. per Group</th><th>NOAEL (mg/kg /day)</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Rat/
Crl:CD(SD)</td><td>Oral gavage
(0.5 w/v% MC/
Suspension)</td><td>1 week or 2 weeks</td><td>0, 200, 600, 2000</td><td>4M, 4F</td><td>2000</td><td>2000:
Prolongation of APTT (female, Day 15), increase of GGT AMY, and Fbg (male, Day 15), increase of T.Cho (female, Day 15), decreases of RBC, HGB, and HCT (female, Day 8), decrease of A/G (male and female, Day8 and/or 15), fatty change of periportal hepatocytes (male, Day 15).
≥ 600:
Prolongation of PT (female, Day 15), prolongation of APTT (male, Day 8; female, Day 8), hyperplasia of follicular epithelium in thyroid (female, Day 8 and 15).
≥ 200:
Prolongation of PT (male, Day 8 and 15; female, Day 8), prolongation of APTT (male, Day 15), increase of GGT (female, Day 8 and 15), increase of liver weight (female, Day 8 and 15), fatty change of periportal hepatocytes (female, Day 8 and 15)

Toxicokinetics of S-033447 (n=3, mean value)
<table>
<tr><th rowspan="2">Daily dose (mg/kg)</th><th rowspan="2">Day</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 rowspan="3">200</td><td>1</td><td>0.836</td><td>0.900</td><td>7.22</td><td>6.49</td></tr>
<tr><td>7</td><td>0.285</td><td>0.290</td><td>2.24</td><td>2.36</td></tr>
<tr><td>14</td><td>0.234</td><td>0.234</td><td>2.04</td><td>1.81</td></tr>
<tr><td rowspan="3">600</td><td>1</td><td>0.962</td><td>1.32</td><td>8.61</td><td>12.6</td></tr>
<tr><td>7</td><td>0.361</td><td>0.304</td><td>3.13</td><td>2.70</td></tr>
<tr><td>14</td><td>0.208</td><td>0.337</td><td>2.30</td><td>3.94</td></tr>
<tr><td rowspan="3">2000</td><td>1</td><td>1.37</td><td>1.46</td><td>12.5</td><td>17.2</td></tr>
<tr><td>7</td><td>0.296</td><td>0.677</td><td>3.62</td><td>6.34</td></tr>
<tr><td>14</td><td>0.272</td><td>0.341</td><td>3.08</td><td>4.01</td></tr>
<tr><td colspan="6">The LLOQ of S-033447 was 0.00500 μg/mL</td></tr>
</table></td><td>TOX-20[redacted]-MTS-05761 88A-02/ 4.2.3.2-06</td></tr>
</table>

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses (mg/kg/day)</th><th>Gender and No. per Group</th><th>NOAEL (mg/kg /day)</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Monkey/ Cynomolgus</td><td>Oral gavage (0.5 w/v% MC/ Suspension)</td><td>2 weeks</td><td>0, 6, 20, 60, 200</td><td>1M, 1F</td><td>60</td><td>200:
Increase of AST, ALT and GLDH (male and female, Day 7 and 14), increase of LAP, GGT, and 5'-nucleotidase (male, Day 7 and 14), increase of total bile acids (male and female, Day 7)

Toxicokinetics of S-033447 (n=1)
<table>
<tr><th rowspan="2">Daily dose (mg/kg)</th><th rowspan="2">Day</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 rowspan="3">6</td><td>1</td><td>0.128</td><td>0.201</td><td>2.34</td><td>1.76</td></tr>
<tr><td>7</td><td>0.240</td><td>0.249</td><td>3.05</td><td>2.66</td></tr>
<tr><td>14</td><td>0.196</td><td>0.261</td><td>3.20</td><td>3.46</td></tr>
<tr><td rowspan="3">20</td><td>1</td><td>0.302</td><td>0.325</td><td>5.23</td><td>4.36</td></tr>
<tr><td>7</td><td>0.563</td><td>0.222</td><td>7.89</td><td>3.27</td></tr>
<tr><td>14</td><td>0.485</td><td>0.381</td><td>8.12</td><td>5.60</td></tr>
<tr><td rowspan="3">60</td><td>1</td><td>0.361</td><td>0.284</td><td>6.69</td><td>4.85</td></tr>
<tr><td>7</td><td>0.634</td><td>0.383</td><td>10.1</td><td>6.88</td></tr>
<tr><td>14</td><td>0.573</td><td>0.292</td><td>10.2</td><td>5.39</td></tr>
<tr><td rowspan="3">200</td><td>1</td><td>0.566</td><td>0.504</td><td>10.2</td><td>7.85</td></tr>
<tr><td>7</td><td>1.43</td><td>1.03</td><td>25.7</td><td>16.1</td></tr>
<tr><td>14</td><td>0.979</td><td>1.46</td><td>20.6</td><td>23.7</td></tr>
<tr><td colspan="6">The LLOQ of S-033447 was 0.00500 μg/mL</td></tr>
</table>
</td><td>OSC20[redacted]-0027/ 4.2.3.2-07</td></tr>
<tr><td>Monkey[a]/ Cynomolgus</td><td>Oral gavage (0.5 w/v% MC/ Suspension)</td><td>4 weeks</td><td>0, 100</td><td>3M, 3F</td><td>NA</td><td>Electron microscopic examination of the liver:
No remarkable changes.</td><td>S-033188-TF-189-N/ 4.2.3.2-08</td></tr>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Day 1, the first day of dosing; F, female; GLDH, glutamate dehydrogenase; GGT, γ-glutamyltransferase; LAP, leucyl aminopeptidase; LLOQ, lower limit of quantification; M, male; MC, methylcellulose aqueous solution.

a Liver samples from one-month oral toxicity study (S-033188-TF-132-L) were used.

2.6.7.7 反復投与毒性試験：重要な試験

2.6.7.7.1 Two-Week Repeat-Dose Toxicity Study in Rats

Test Article: S-033188

Report Title: Two-Week Oral Toxicity Study of RSC-033188 in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** R-033188-TB-032-L
Initial Age: 8 weeks	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-01
Date of First Dose: Male: [redacted], 20[redacted] Female: [redacted], 20[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 2000 mg/kg/day			

Daily Dose (mg/kg)			**0 (Control)**		**20**		**200**		**2000**	
Toxicokinetics[a]										
No. Evaluated			M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
S-033447[b]	**C_{max} (µg/mL)**	**Day 1**	N.C.	N.C.	0.254	0.156	0.621	0.744	0.713	1.19
		Day 7	N.C.	N.C.	0.163	0.121	0.224	0.248	0.340	0.515
		Day 14	N.C.	N.C.	0.162	0.144	0.243	0.291	0.274	0.497
	$AUC_{0\text{-}24hr}$ (µg·hr/mL)	**Day 1**	N.C.	N.C.	1.40	1.03	5.68	6.48	7.99	15.2
		Day 7	N.C.	N.C.	0.868	0.640	1.77	2.14	3.54	5.06
		Day 14	N.C.	N.C.	0.872	0.853	2.00	3.40	3.34	5.47
Noteworthy Findings										
No. Evaluated			**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation[c]	**Partially white-colored feces**		0	0	0	0	1	0	15	15
Body Weight			–	–	–	–	–	–	–	–
Food Consumption (%)[d]	**Day 1-2**		27.0 g/day	16.5 g/day	−3	+5	−3	−5	−19**	−15**
Ophthalmoscopy			–	–	–	–	–	–	–	–
Urinalysis	**No. Examined**		10	10	10	10	10	10	10	10
	Volume		–	–	–	–	–	–	–	–
	Specific gravity[a]		–	1.018	–	1.021	–	1.029	–	1.038*
	Protein[c]		–		–		–		–	††
		Negative		7		7		6		1
		±		3		2		1		3
		30 mg/dL		0		1		1		4
		100 mg/dL		0		0		1		1

Daily Dose (mg/kg)				0 (Control)		20		200		2000	
Urinalysis	Ketone body[c]				–		–	†	–	††	–
			Negative	6	–	4	–	1	–	0	–
			5 mg/dL	4	–	4	–	6	–	7	–
			15 mg/dL	0	–	2	–	3	–	3	–
Hematology[a]	RBC (x 10^6/μL)			7.75	–	7.43	–	7.42	–	7.33*	–
	HGB (g/dL)			15.5	14.3	15.2	14.3	15.3	14.3	14.7**	13.6*
	HCT (%)			47.0	42.1	45.7	42.4	45.6	41.9	44.3**	40.0*
	PLT (x 10^3/μL)			–	952	–	928	–	1132**	–	1190**
	PT (sec)			22.8	13.4	25.3	13.7	39.4*	16.8**	55.3**	18.9**
	APTT (sec)			22.4	15.8	23.8	15.9	28.7**	19.0**	36.5**	21.2**
	Fbg (mg/dL)			–	217	–	223	–	250*	–	275**
Blood Chemistry[a]	T.Pro (g/dL)			5.65	5.59	5.58	5.78	5.71	5.65	5.96**	5.94**
	Alb (g/dL)			–	4.07	–	4.09	–	3.79**	–	3.76**
	ALT (U/L)			27	21	25	23	29	24	31*	32**
	AMY (U/L)			–	661	–	781	–	927**	–	935**
	T.Bil (mg/dL)			0.04	0.05	0.03**	0.03**	0.02**	0.02**	0.02**	0.02**
	A/G ratio			2.31	2.68	2.15	2.42*	2.16	2.06**	1.90**	1.72**
Organ Weight (%)[c]	Liver	Absolute		11.0682 g	6.6238 g	+3	0	+11	+9	+25**	+26**
		Relative		2.9086 g/ 100 g BW	2.9868 g/ 100 g BW	+4	+1	+12*	+10**	+23**	+28**
Gross Pathology[c]	Liver	Accentuated lobular pattern		0	0	1	2	2	3	4	3
Histopathology[c]											
Liver	Hypertrophy		minimal	0	0	0	0	0	1	1	1
			mild	0	0	0	0	0	0	0	2
	Fatty change of periportal hepatocytes		minimal	0	1	1	4	2	5	5	7
			mild	0	0	0	3	0	0	1	0
Pituitary	Hypertrophy of basophilic cell in the pars distalis		minimal	0	0	0	N.E.	1	N.E.	4	0
Thyroid	Hyperplasia of follicular epithelium		minimal	0	0	0	0	1	0	4	2
	Decrease of colloid		minimal	1	0	5	3	7	5	7	5
			mild	0	0	0	0	1	0	3	2

Daily Dose (mg/kg)			0 (Control)		20		200		2000	
Postdose Evaluation-Noteworthy Findings										
No. Evaluated			M: 5	F: 5	M: 0	F: 0	M: 0	F: 0	M: 5	F: 5
No. Died or Sacrificed Moribund			0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation [c]			–	–	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	–	–
Ophthalmoscopy			–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis			–	–	N/A	N/A	N/A	N/A	–	–
Hematology [a]	PLT (x 10^3/μL)		–	881	NA	NA	NA	NA	–	1036§
Blood Chemistry			–	–	N/A	N/A	N/A	N/A	–	–
Organ Weight			–	–	N/A	N/A	N/A	N/A	–	–
Gross Pathology			–	–	N/A	N/A	N/A	N/A	–	–
Histopathology [c]										
Liver	Fatty change of periportal hepatocytes	minimal	0	1	N/A	N/A	N/A	N/A	1	0
Pituitary	Hypertrophy of basophilic cell in the pars distalis	minimal	0	0	N/A	N/A	N/A	N/A	2	0
Thyroid	Decrease of colloid	minimal	2	0	N/A	N/A	N/A	N/A	3	1

Abbreviations: A/G ratio, albumin/globulin ratio; Alb, albumin; AMY, amylase; BW, body weight; Fbg, fibrinogen concentration; HCT, hematocrit; HGB, hemoglobin concentration; N.C., not calculated; N.E., not examined; PLT, platelet count; RBC, red blood cell count; T.Bil, total bilirubin; T.Pro, total protein.

–, No noteworthy findings.

* P < 0.05, ** P < 0.01 vs. control (Dunnett's test).

† p < 0.05, †† p < 0.01 vs. control (Steel test).

§ p < 0.05 vs. control (Welch's t-test).

a Group means are shown.

b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 μg/mL. All the plasma concentrations of S-033188 in the control, 20, 200, and 2000 mg/kg/day groups were BLQ (< 0.00500 μg/mL).

c Number of animals with findings

d For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percentage differences).

e For controls, group means (absolute weights or relative weights to 100 g body weights) are shown. For treated groups, percent differences from absolute or relative control are shown. Statistical significance based on actual absolute or relative data (not on the percentage differences from absolute or relative control).

2.6.7.7.2 Four-Week Repeat-Dose Toxicity Study in Rats

Test Article: S-033188

Report Title: One-Month Oral Toxicity Study of S-033188 in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-033188-TB-131-L
Initial Age: 6 weeks	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-02
Date of First Dose: Male: [redacted], 20[redacted] Female: [redacted], 20[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 2000 mg/kg/day			

Daily Dose (mg/kg)			**0 (Control)**		**20**		**200**		**2000**	
Toxicokinetics[a]										
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
S-033447[b]	C_{max} (µg/mL)	**Day 1**	N.C.	N.C.	0.240	0.189	0.713	0.730	1.03	1.24
		Day 14	N.C.	N.C.	0.137	0.0848	0.195	0.229	0.307	0.305
		Day 28	N.C.	N.C.	0.124	0.123	0.198	0.204	0.275	0.460
	$AUC_{0\text{-}24hr}$ (µg·hr/mL)	**Day 1**	N.C.	N.C.	1.34	0.990	5.90	6.18	11.1	17.3
		Day 14	N.C.	N.C.	0.807	0.576	1.74	1.83	3.75	3.30
		Day 28	N.C.	N.C.	0.817	0.722	1.66	1.72	3.40	4.76
Noteworthy Findings										
No. Evaluated			**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation[c]	**Partially white-colored feces**		0	0	0	0	0	0	7	5
Body Weight[d]			–	–	–	–	–	–	–	–
Food Consumption (%)[d]	**Day 1 to 4**		24.4 g	–	–2	–	–3	–	–11**	–
	Day 12 to 16		–	17.2 g	–	+2	–	–1	–	–12*
	Day 16 to 20		–	17.5 g	–	+3	–	+1	–	+10*
Ophthalmoscopy			–	–	–	–	–	–	–	–
Urinalysis			–	–	–	–	–	–	–	–
Hematology[a]	**PLT (x 10^3/µL)**		1012	–	1049	–	1044	–	1153**	–
	PT (sec)		27.2	14.0	28.7	14.4	35.0	15.2	48.8**	16.7**
	APTT (sec)		24.2	15.5	25.4	17.2	27.5	19.2**	32.5**	20.5**
	Fbg (mg/dL)		–	231	–	232	–	245	–	274**
Blood Chemistry[a]	**T.Pro (g/dL)**		5.80	–	5.82	–	5.89	–	6.08*	–
	A/G		–	2.60	–	2.53	–	2.25*	–	1.99**
	T.Bil (mg/dL)		0.04	0.04	0.03*	0.03**	0.02**	0.02**	0.02**	0.02**
	T.Cho (mg/dL)		–	59	–	55	–	67	–	80**
	AMY (U/L)		–	707	–	827	–	891*	–	969**

Daily Dose (mg/kg)				0 (Control)		20		200		2000	
Organ Weight (%)[d]	Liver	Absolute		12.1871 g	6.5273 g	−1	+5	+7	+15*	+13*	+36**
		Relative		3.0310 g/ 100 g BW	2.9519 g/ 100 g BW	+3	+3	+9*	+15**	+17**	+32**
Gross Pathology[c]	Liver	Accentuated lobular pattern		0	0	0	0	0	0	3	3
		Enlargement		0	–	0	–	0	–	2	–
Histopathology[c]											
Liver	Centrilobular hypertrophy of hepatocytes		minimal	0	0	0	0	0	0	3	3
	Fatty change of periportal hepatocytes		minimal	0	1	1	4	1	2	1	3
			mild	0	0	0	0	0	1	1	1
Pituitary	Hypertrophy of basophilic cells in the pars distalis		minimal	0	–	0	N/A	1	N/A	2	–
Thyroid	Diffuse hyperplasia of follicular epithelium		minimal	0	0	0	0	1	0	2	2
	Decrease of colloid		minimal	2	0	2	0	4	3	4	4
			mild	0	0	0	0	0	0	1	2
Postdose Evaluation-Noteworthy Findings											
No. Evaluated				M: 5	F: 5	M: 0	F: 0	M: 0	F: 0	M:5	F: 5
No. Died or Sacrificed Moribund				0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation				–	–	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	–	–
Ophthalmoscopy				–	–	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	–	–
Organ Weight				–	–	N/A	N/A	N/A	N/A	–	–
Gross Pathology				–	–	N/A	N/A	N/A	N/A	–	–
Histopathology[c]											
Liver	Fatty change of periportal hepatocytes		minimal	0	–	N/A	N/A	N/A	N/A	2	–

Abbreviation: T.Cho, total cholesterol.
–, No noteworthy findings.
* P < 0.05, ** P < 0.01 vs. control (Dunnett's test).
a Group means are shown. b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 µg/mL. Almost all the plasma concentrations of S-033188 in the control, 20, 200, and 2000 mg/kg/day groups were BLQ (< 0.00500 µg/mL). S-033188 was occasionally detected at a concentration less than or equal to 0.0369 µg/mL in rats (8 time points out of 432 time points in total) c Number of animals with findings. d For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percentage differences).

2.6.7.7.3 Two-Week Repeat-Dose Toxicity Study in Monkeys

Test Article: S-033188

Report Title: Two-Week Oral Toxicity Study of RSC-033188 in Monkeys			
Species/Strain: Monkey/Cynomolgus	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** R-033188-TF-043-L
Initial Age: 4 to 5 years	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-03
Date of First Dose: Male: [redacted], 20 Female: [redacted], 20	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: below 20 mg/kg/day			

Daily Dose (mg/kg)			**0 (Control)**		**20**		**60**		**200**	
Toxicokinetics[a]										
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
S-033447[b]	C_{max} (µg/mL)	**Day 1**	N.C.	N.C.	0.440	0.444	0.659	0.484	0.820	1.34
		Day 7	N.C.	N.C.	0.656	0.525	1.14	0.487	1.27	1.62
		Day 14	N.C.	N.C.	0.559	0.563	1.37	0.736	1.29	2.12
	$AUC_{0\text{-}24hr}$ (µg·hr/mL)	**Day 1**	N.C.	N.C.	6.73	6.57	10.4	8.00	13.4	21.4
		Day 7	N.C.	N.C.	9.74	8.07	14.5	7.99	19.3	27.1
		Day 14	N.C.	N.C.	9.46	7.79	19.8	10.5	22.4	37.2
Noteworthy Findings										
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation[c]	**Vomiting**		0	0	0	0	0	0	4 (# 23, 25 to 27)	3 (# 28, 30, 31)
Body Weight			–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–
Ophthalmoscopy			–	–	–	–	–	–	–	–
Urinalysis			–	–	–	–	–	–	–	–
Electrocardiography			–	–	–	–	–	–	–	–
Hematology			–	–	–	–	–	–	–	–
Blood Chemistry[a]	**Day −20**	**AST (IU/L)**	30.8	36.8	33.0	35.7	37.0 41 (# 17)	40.0	34.2 30 (# 23) 30 (# 25) 49 (# 27)	43.2 36 (# 28) 49 (# 29) 44 (# 30) 29 (# 31) 58 (# 32)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	(Day −20)	ALT (IU/L)	35.2	44.8	35.0 40 (# 11)	39.3 44 (# 16)	45.0 32 (# 17) 50 (# 18) 53 (# 19)	36.7 35 (# 21) 33 (# 22)	44.4 28 (# 23) 46 (# 24) 42 (# 25) 32 (# 26) 74 (# 27)	65.8** 54 (# 28) 75 (# 29) 61 (# 30) 67 (# 31) 72 (# 32)
		ALP (IU/L)	1357.6	567.0	1450.0	457.3	1480.0	477.3	1877.4 2657 (# 23)	433.2 305 (# 29) 332 (# 30)
		LAP (IU/L)	54.0	51.4	55.7	60.0 77 (# 16)	74.7 63 (# 17) 64 (# 18) 97 (# 19)	41.7	59.6 59 (# 23) 46 (# 24) 64 (# 25) 63 (# 26) 66 (# 27)	56.2 58 (# 28) 43 (# 29) 45 (# 30) 68 (# 31) 67 (# 32)
		GGT (IU/L)	60.2	57.8	72.0	63.3 74 (# 16)	77.3 81 (# 19)	49.3	83.4 86 (# 23) 111 (# 25)	57.6 53 (# 28) 52 (# 29) 83 (# 30) 58 (# 31)
		T.Bil (mg/dL)	–	0.182	–	0.187	–	0.193	–	0.198 0.21 (# 29)
		D.Bil (mg/dL)	0.042	0.068	0.037	0.070	0.047	0.067	0.056 0.06 (# 23)	0.078 0.09 (# 29) 0.06 (# 30)
		Phospholipids (mg/dL)	–	210.2	–	198.0	–	212.7	–	192.0 160 (# 29)
		TG (mg/dL)	43.4	–	34.3	–	23.3	–	25.6 18 (# 27)	–
		T.Cho (mg/dL)	–	137.4	–	128.0	–	148.0	–	127.8 110 (# 29)
		GLDH (U/L)	15.66	21.18	12.20 18.2 (# 11)	13.37 16.1 (# 15) 17.7 (# 16)	16.73 14.2 (# 17) 12.5 (# 18) 23.5 (# 19)	12.77 12.5 (# 21) 14.0 (# 22)	21.08 13.8 (# 23) 27.2 (# 24) 15.7 (# 25) 20.8 (# 26) 27.9 (# 27)	26.92 14.6 (# 28) 18.0 (# 29) 57.3 (# 30) 21.4 (# 31) 23.3 (# 32)
		Total bile acids (μmol/L)	6.44	4.60	2.57	1.87	2.43	2.63 0.7 (# 21)	4.40 7.9 (# 27)	4.26 2.5 (# 29)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	Day −7	AST (IU/L)	37.4	33.2	32.3	37.3	33.0 34 (# 17)	26.7	32.6 40 (# 23) 27 (# 25) 39 (# 27)	39.0 31 (# 28) 37 (# 29) 56 (# 30) 29 (# 31) 42 (# 32)
		ALT (IU/L)	49.4	57.4	38.0 52 (# 11)	45.3 47 (# 16)	53.0 34 (# 17) 51 (# 18) 74 (# 19)	34.7 41 (# 21) 30 (# 22)	46.2 35 (# 23) 49 (# 24) 33 (# 25) 36 (# 26) 78 (# 27)	71.0 54 (# 28) 82 (# 29) 83 (# 30) 70 (# 31) 66 (# 32)
		ALP (IU/L)	1320.0	569.8	1329.3	398.3	1346.3	506.7	1813.2 2872 (# 23)	434.0 301 (# 29) 313 (# 30)
		LAP (IU/L)	54.4	50.6	52.7	54.0 63 (# 16)	76.7 63 (# 17) 64 (# 18) 103 (# 19)	39.0	57.0 59 (# 23) 47 (# 24) 60 (# 25) 60 (# 26) 59 (# 27)	53.8 55 (# 28) 40 (# 29) 44 (# 30) 62 (# 31) 68 (# 32)
		GGT (IU/L)	62.8	56.0	66.3	60.0 71 (# 16)	72.0 72 (# 19)	44.0	82.6 86 (# 23) 101 (# 25)	54.0 50 (# 28) 51 (# 29) 75 (# 30) 53 (# 31)
		T.Bil (mg/dL)	–	0.122	–	0.140	–	0.113	–	0.152 0.13 (# 29)
		D.Bil (mg/dL)	0.038	0.048	0.043	0.050	0.037	0.040	0.048 0.04 (# 23)	0.060 0.06 (# 29) 0.05 (# 30)
		Phospholipids (mg/dL)	–	205.0	–	196.7	–	199.0	–	191.4 156 (# 29)
		TG (mg/dL)	39.8	–	32.7	–	40.7	–	28.2 36 (# 27)	–
		T.Cho (mg/dL)	–	135.2	–	124.0	–	133.7	–	121.0 102 (# 29)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	(Day −7)	GLDH (U/L)	14.78	17.26	13.07 19.5 (# 11)	14.93 18.5 (# 15) 19.7 (# 16)	19.27 10.0 (# 17) 14.1 (# 18) 33.7 (# 19)	16.37 22.8 (# 21) 15.4 (# 22)	28.30 16.1 (# 23) 30.5 (# 24) 13.5 (# 25) 31.7 (# 26) 49.7 (# 27)	30.98 19.0 (# 28) 15.3 (# 29) 67.0 (# 30) 27.2 (# 31) 26.4 (# 32)
		Total bile acids (μmol/L)	10.46	3.36	2.30	6.63	4.40	4.03 2.7 (# 21)	4.92 8.0 (# 27)	5.72 10.6 (# 29)
	Day 7	AST (IU/L)	33.6	29.4	40.3	40.0	70.0* ↑97 (# 17)	46.3	60.4 ↑93 (# 27)	115.4†† ↑209 (# 29) ↑144 (# 31) ↑88 (# 32)
		ALT (IU/L)	41.2	38.8	69.0	106.7 ↑204 (# 16)	320.3† ↑415 (# 17) ↑185 (# 18) ↑361 (# 19)	118.3 ↑177 (# 21) ↑117 (# 22)	338.2†† ↑370 (# 23) ↑320 (# 24) ↑233 (# 25) ↑289 (# 26) ↑479 (# 27)	666.2†† ↑473 (# 28) ↑588 (# 29) ↑374 (# 30) ↑1468 (# 31) ↑428 (# 32)
		ALP (IU/L)	–	595.6	–	439.0	–	542.7	–	1229.2** ↑1765 (# 30)
		LAP (IU/L)	53.6	46.6	54.7	109.3 ↑210 (# 16)	204.0 ↑181 (# 17) ↑321 (# 19)	54.3	236.6† ↑319 (# 23) ↑197 (# 24) ↑176 (# 25) ↑258 (# 26) ↑233 (# 27)	406.6†† ↑295 (# 28) ↑746 (# 29) ↑327 (# 30) ↑531 (# 31) ↑134 (# 32)
		GGT (IU/L)	60.2	54.8	68.0	72.3 ↑106 (# 16)	105.7 ↑134 (# 19)	47.0	121.4** ↑159 (# 23)	256.0* ↑154 (# 28) ↑377 (# 29) ↑362 (# 30) ↑312 (# 31)
		D.Bil (mg/dL)	–	0.052	–	0.050	–	0.037	–	0.118 ↑0.21 (# 30)
		GLDH (U/L)	18.88	13.86	31.93 ↑63.8 (# 11)	86.43 ↑80.7 (# 15) ↑171.2 (# 16)	471.53† ↑448.1 (# 17) ↑193.2 (# 18) ↑773.3 (# 19)	126.70 ↑213.3 (# 21) ↑139.9 (# 22)	507.10† ↑563.2 (# 23) ↑399.2 (# 24) ↑438.5 (# 25) ↑532.1 (# 26) ↑602.5 (# 27)	1028.74†† ↑560.7 (# 28) ↑1332.3 (# 29) ↑674.3 (# 30) ↑1963.3 (# 31) ↑613.1 (# 32)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	(Day 7)	Total bile acids (μmol/L)	–	4.14	–	8.43	–	30.93 ↑75.4 (# 21)	–	81.68 ↑361.1 (# 29)
	Day 14	AST (IU/L)	33.6	28.8	48.0	32.3	61.3	51.0	88.4† ↑98 (# 23) ↑87 (# 25) ↑157 (# 27)	209.2†† ↑132 (# 28) ↑252 (# 29) ↑446 (# 30) ↑119 (# 31) ↑97 (# 32)
		ALT (IU/L)	38.8	34.4	88.3 ↑159 (# 11)	73.7	257.3 ↑272 (# 17) ↑180 (# 18) ↑320 (# 19)	162.7 ↑134 (# 21) ↑294 (# 22)	324.6†† ↑432 (# 23) ↑245 (# 24) ↑290 (# 25) ↑238 (# 26) ↑418 (# 27)	555.8†† ↑513 (# 28) ↑582 (# 29) ↑706 (# 30) ↑626 (# 31) ↑352 (# 32)
		ALP (IU/L)	1317.8	586.0	1469.3	452.3	1610.3	562.7	2272.4† ↑4255 (# 23)	2382.0 ↑7280 (# 29) ↑1445 (# 30)
		LAP (IU/L)	49.6	49.0	56.3	108.3 ↑198 (# 16)	223.3 ↑164 (# 17) ↑140 (# 18) ↑366 (# 19)	64.7	277.0†† ↑467 (# 23) ↑198 (# 24) ↑227 (# 25) ↑288 (# 26) ↑205 (# 27)	589.8†† ↑359 (# 28) ↑1528 (# 29) ↑293 (# 30) ↑625 (# 31) ↑144 (# 32)
		GGT (IU/L)	55.8	56.8	64.0	73.3 ↑102 (# 16)	113.7 ↑153 (# 19)	55.3	136.0* ↑224 (# 23) ↑153 (# 25)	435.0† ↑207 (# 28) ↑1066 (# 29) ↑417 (# 30) ↑400 (# 31)
		T.Bil (mg/dL)	–	0.160	–	0.183	–	0.143	–	0.370 ↑0.87 (# 29)
		D.Bil (mg/dL)	0.044	0.064	0.043	0.070	0.050	0.053	0.070 ↑0.11 (# 23)	0.224 ↑0.66 (# 29) ↑0.16 (# 30)
		Phospholipids (mg/dL)	–	196.6	–	178.0	–	206.0	–	239.4 ↑431 (# 29)
		TG (mg/dL)	31.2	–	27.7	–	53.7	–	57.6 ↑115 (# 27)	–
		T.Cho (mg/dL)	–	136.6	–	119.0	–	141.0	–	149.8 ↑246 (# 29)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	(Day 14)	GLDH (U/L)	19.50	13.56	71.97 ↑186.5 (# 11)	44.27	362.20 ↑140.0 (# 17) ↑170.8 (# 18) ↑775.8 (# 19)	197.93 ↑140.9 (# 21) ↑431.3 (# 22)	456.94† ↑641.8 (# 23) ↑264.8 (# 24) ↑539.0 (# 25) ↑393.1 (# 26) ↑446.0 (# 27)	1098.34†† ↑814.7 (# 28) ↑1432.6 (# 29) ↑2140.1 (# 30) ↑468.3 (# 31) ↑636.0 (# 32)
		Total bile acids (μmol/L)	14.56	1.34	2.33	4.10	31.97	13.83	73.18 ↑333.8 (# 27)	86.80†† ↑406.3 (# 29)
Organ Weight			–	–	–	–	–	–	–	–
Gross Pathology			–	–	–	–	–	–	–	–
Histopathology			–	–	–	–	–	–	–	–
Postdose Evaluation-Noteworthy Findings										
No. Evaluated			M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
No. Died or Sacrificed Moribund			0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation			–	–	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	–	–
Electrocardiography			–	–	N/A	N/A	N/A	N/A	–	–
Ophthalmoscopy			–	–	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[a]	Day 7 of recovery	ALP (IU/L)	–	652.5	N/A	N/A	N/A	N/A	–	1918.5 ↑3127 (# 29)
		LAP (IU/L)	45.5	48.5	N/A	N/A	N/A	N/A	170.5 ↑240 (# 23)	439.5 ↑208 (# 28) ↑671 (# 29)
		GGT (IU/L)	55.5	49.5	N/A	N/A	N/A	N/A	135.0 ↑162 (# 23)	351.0 ↑152 (# 28) ↑550 (# 29)
		D.Bil (mg/dL)	–	0.035	N/A	N/A	N/A	N/A	–	0.135 ↑0.24 (# 29)
		GLDH (U/L)	–	17.05	N/A	N/A	N/A	N/A	–	80.30 ↑92.4 (# 29)
	Day 14 of recovery	ALP (IU/L)	–	649.0	NA	NA	NA	NA	–	1099.0 ↑1601 (# 29)
		LAP (IU/L)	49.5	49.5	NA	NA	NA	NA	101.0 ↑137 (# 23)	235.5 ↑119 (# 28) ↑352 (# 29)

Daily Dose (mg/kg)			0 (Control)		20		60		200	
Blood Chemistry[a]	(Day 14 of recovery)	GGT (IU/L)	–	50.0	NA	NA	NA	NA	–	227.0 ↑107 (# 28) ↑347 (# 29)
		D.Bil (mg/dL)	–	0.040	NA	NA	NA	NA	–	0.095 ↑0.16 (# 29)
Organ Weight			–	–	N/A	N/A	N/A	N/A	–	–
Gross Pathology			–	–	N/A	N/A	N/A	N/A	–	–
Histopathology			–	–	N/A	N/A	N/A	N/A	–	–

Abbreviations: ALP, alkaline phosphatase; Day 1 of recovery, the first day of recovery; D.Bil, direct bilirubin; TG, triglyceride.
–, No noteworthy findings; ↑, increase; ( ), animal number.
* $P < 0.05$, ** $P < 0.01$ vs. control (Dunnett's test).
† $P < 0.05$, †† $P < 0.01$ vs. control (Dunnett-type test).
a Group means are shown.
b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 µg/mL. Almost all the plasma concentrations of S-033188 in the control, 20, 60, and 200 mg/kg/day groups were BLQ (< 0.00500 µg/mL). S-033188 was occasionally detected at a concentration less than or equal to 0.133 µg/mL in monkeys (14 time points out of 440 time points in total).
c Number of animals with findings.

2.6.7.7.4 Two-Week Repeat-Dose Toxicity Study in Monkeys (Supplement)

Test Article: S-033188

Report Title: Two-Week Oral Toxicity Study of RSC-033188 in Monkeys (Supplement)			
Species/Strain: Monkey/Cynomolgus	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** None	**Study No.** R-033188-TF-083-L
Initial Age: 4 to 5 years	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-04
Date of First Dose: [redacted], 20[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: This study focused on blood chemistry evaluation.			
NOAEL: 10 mg/kg/day (Based on the results in the present study and the previous 2-week study)			

Daily Dose (mg/kg)			**0 (Control)**		**3**		**10**	
Toxicokinetics[a]								
No. Evaluated			**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
S-033447[b]	**C_{max} (μg/mL)**	**Day 1**	N.C.	N.C.	0.102	0.113	0.199	0.220
		Day 7	N.C.	N.C.	0.143	0.153	0.281	0.293
		Day 14	N.C.	N.C.	0.129	0.148	0.314	0.368
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**Day 1**	N.C.	N.C.	1.28	1.43	3.24	3.31
		Day 7	N.C.	N.C.	1.57	2.21	4.44	4.24
		Day 14	N.C.	N.C.	1.56	1.89	4.53	4.28
Noteworthy Findings								
No. Evaluated			**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
No. Died or Sacrificed Moribund			0	0	0	0	0	0
Clinical Observation			–	–	–	–	–	–
Body Weight			–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–
Blood Chemistry[a]	**Day −13**	**AST (IU/L)**	–	34.7	–	43.3 31 (# 10)	–	32.0
		ALT (IU/L)	–	34.7	–	39.7 23 (# 10)	–	48.7
		GLDH (U/L)	–	16.13	–	18.67 10.9 (# 10)	–	16.30
	Day −3	**AST (IU/L)**	–	26.3	–	28.0 25 (# 10)	–	21.7
		ALT (IU/L)	–	32.3	–	34.3 24 (# 10)	–	32.7
		GLDH (U/L)	–	17.67	–	20.00 15.5 (# 10)	–	10.27
	Day 7	**AST (IU/L)**	–	26.3	–	49.3 ↑72 (# 10)	–	30.3
		ALT (IU/L)	–	44.3	–	90.7 ↑167 (# 10)	–	49.0

Daily Dose (mg/kg)			0 (Control)		3		10	
Blood Chemistry[a]	(Day 7)	GLDH (U/L)	–	27.00	–	76.30 ↑184.8 (# 10)	–	13.60
	Day 14	AST (IU/L)	–	26.0	–	71.0 ↑140 (# 10)	–	22.7
		ALT (IU/L)	–	40.7	–	141.7 ↑343 (# 10)	–	40.0
		GLDH (U/L)	–	21.87	–	215.33 ↑616.5 (# 10)	–	11.53

–, No noteworthy findings; ↑, increase; ( ), animal number.

a Group means are shown.

b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 μg/mL. All the plasma concentrations of S-033188 in the control, 3, and 10 mg/kg/day groups were BLQ (< 0.00500 μg/mL).

2.6.7.7.5 Four-Week Repeat-Dose Toxicity Study in Monkeys

Test Article: S-033188

Report Title: One-Month Oral Toxicity Study of S-033188 in Monkeys			
Species/Strain: Monkey/Cynomolgus	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-033188-TF-132-L
Initial Age: 4 to 6 years	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.2-05
Date of First Dose: Male: [redacted], 20[redacted] Female: [redacted], 20[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 10 mg/kg/day			

Daily Dose (mg/kg)			**0 (Control)**		**1**		**10**		**100**	
Toxicokinetics[a]										
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
S-033447[b]	**C_{max} (μg/mL)**	**Day 1**	N.C.	N.C.	0.0507	0.0523	0.236	0.189	0.496	0.449
		Day 14	N.C.	N.C.	0.0667	0.0694	0.277	0.285	0.876	0.627
		Day 28	N.C.	N.C.	0.0515	0.0527	0.242	0.229	0.714	0.642
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**Day 1**	N.C.	N.C.	0.555	0.589	3.43	2.66	8.96	7.68
		Day 14	N.C.	N.C.	0.632	0.740	4.14	3.69	14.8	10.2
		Day 28	N.C.	N.C.	0.527	0.456	3.05	3.14	11.6	9.06
Noteworthy Findings										
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation			–	–	–	–	–	–	–	–
Body Weight			–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–
Ophthalmoscopy			–	–	–	–	–	–	–	–
Urinalysis			–	–	–	–	–	–	–	–
Electrocardiography			–	–	–	–	–	–	–	–
Hematology			–	–	–	–	–	–	–	–
Blood Chemistry[a]	**Day −16**	**AST (IU/L)**	30.0	33.8	30.3	22.0	27.3	51.0	44.6 26 (# 23) 72 (# 26)	42.8 91 (# 28) 28 (# 31)
		ALT (IU/L)	32.8	41.4	32.3	31.7	27.0 34.0 (# 17)	68.3	53.0 32 (# 23) 49 (# 24) 35 (# 25) 67 (# 26) 82 (# 27)	49.0 105 (# 28) 40 (# 31)

Daily Dose (mg/kg)			0 (Control)		1		10		100	
Blood Chemistry[a]	(Day −16)	LAP (IU/L)	54.6	43.2	56.7	44.0	49.7	50.0	44.2 47 (# 23) 57 (# 26)	45.4 51 (# 28) 53 (# 31)
		GGT (IU/L)	59.8	65.4	76.3	38.7	61.0	56.0	60.8 50 (# 23) 63 (# 26)	45.2 35 (# 31)
		GLDH (U/L)	15.00	23.12	13.83	13.63	13.47 19.8 (#17)	43.07	21.58 23.1 (# 23) 26.7 (# 24) 12.6 (# 25) 24.4 (# 26) 21.1 (# 27)	30.66 100.1 (# 28) 17.0 (# 29) 12.4 (# 31)
	Day −8	AST (IU/L)	25.4	45.4	29.7	24.0	27.7	39.7	45.0 46 (# 23) 62 (# 26)	45.6 47 (# 28) 31 (# 31)
		ALT (IU/L)	40.2	83.6	33.7	33.3	28.3 34.0 (# 17)	75.0	70.2† 48 (# 23) 37 (# 24) 90 (# 25) 88 (# 26) 88 (# 27)	68.0 89 (# 28) 86 (# 31)
		LAP (IU/L)	55.2	42.8	56.0	41.0	45.7	49.7	46.2 46 (# 23) 72 (# 26)	43.8 47 (# 28) 55 (# 31)
		GGT (IU/L)	58.2	65.8	74.0	37.3	58.3	54.7	58.4 47 (# 23) 67 (# 26)	43.8 35 (# 31)
		GLDH (U/L)	14.90	45.14	13.43	10.00	12.03 17.1 (#17)	33.63	21.00 22.2 (# 23) 15.9 (# 24) 11.6 (# 25) 35.7 (# 26) 19.6 (# 27)	29.06 50.9 (# 28) 13.6 (# 29) 29.8 (# 31)
	Day 7	AST (IU/L)	30.2	–	41.7	–	30.7	–	83.8† ↑183 (# 26)	–
		ALT (IU/L)	41.8	54.6	46.3	32.3	40.7	63.0	263.4† ↑403 (# 23) ↑135 (# 24) ↑235 (# 25) ↑427 (# 26) ↑117 (# 27)	117.2 ↑275 (# 31)

Daily Dose (mg/kg)			0 (Control)		1		10		100	
Blood Chemistry[a]	(Day 7)	LAP (IU/L)	54.0	–	57.7	–	46.3	–	113.2 ↑180 (# 23) ↑171 (# 26)	–
		GLDH (U/L)	15.44	30.12	18.03	10.87	18.00	22.40	356.14†† ↑615.0 (# 23) ↑140.9 (# 24) ↑310.3 (# 25) ↑657.4 (# 26) ↑57.1 (# 27)	90.88 ↑226.5 (# 31)
	Day 14	AST (IU/L)	53.6	–	26.0	–	29.0	–	80.4 ↑209 (# 26)	–
		ALT (IU/L)	42.0	41.2	39.3	30.7	41.3	53.3	257.0† ↑465 (# 23) ↑157 (# 24) ↑158 (# 25) ↑413 (# 26)	144.2† ↑247 (# 28) ↑208 (# 31)
		LAP (IU/L)	52.0	–	54.0	–	49.0	–	118.4 ↑198 (# 23) ↑186 (# 26)	–
		GGT (IU/L)	51.4	–	68.0	–	57.7	–	101.2** ↑120 (# 23) ↑126 (# 26)	–
		GLDH (U/L)	14.04	16.44	14.70	13.80	17.27	16.23	276.54† ↑558.2 (# 23) ↑147.7 (# 24) ↑130.3 (# 25) ↑515.1 (# 26)	116.60† ↑205.4 (# 28) ↑129.0 (# 29) ↑138.1 (# 31)

Daily Dose (mg/kg)			0 (Control)		1		10		100	
Blood Chemistry[a]	Day 21	AST (IU/L)	37.6	25.2	28.3	22.7	24.7	29.0	62.0 ↑140 (# 26)	61.0† ↑125 (# 28)
		ALT (IU/L)	42.2	44.2	39.7	30.3	50.7 ↑101 (# 17)	53.0	214.2 ↑404 (# 23) ↑98 (# 24) ↑168 (# 25) ↑319 (# 26)	242.8† ↑566 (# 28) ↑418 (# 31)
		LAP (IU/L)	54.2	41.2	57.0	41.0	66.0	45.3	114.0 ↑216 (# 23) ↑154 (# 26)	84.0 ↑125 (# 28) ↑114 (# 31)
		GGT (IU/L)	53.4	–	66.7	–	63.0	–	102.0* ↑144 (# 23) ↑120 (#26)	–
		GLDH (U/L)	15.64	19.00	12.17	13.37	62.67 ↑164.1 (# 17)	18.73	177.18† ↑346.4 (# 23) ↑58.1 (# 24) ↑156.9 (# 25) ↑287.9 (# 26) ↑36.6 (# 27)	236.96† ↑554.0 (# 28) ↑473.9 (# 31)
	Day 27	AST (IU/L)	30.6	29.2	25.7	24.7	20.3	31.0	85.2 ↑122 (# 23) ↑192 (# 26)	68.4 ↑110 (# 28) ↑122 (# 31)
		ALT (IU/L)	46.2	55.0	40.3	37.0	32.0	55.7	258.6 ↑503 (# 23) ↑136 (# 24) ↑170 (# 25) ↑394 (# 26)	223.2 ↑350 (# 28) ↑540 (# 31)
		LAP (IU/L)	53.8	41.4	54.7	42.0	58.0	45.3	121.8 ↑221 (# 23) ↑169 (# 26)	88.4 ↑143 (# 31)
		GGT (IU/L)	52.6	69.6	65.0	38.7	61.7	56.7	112.8† ↑168 (# 23) ↑146 (# 26)	83.6 ↑116 (# 31)

Daily Dose (mg/kg)			0 (Control)		1		10		100	
Blood Chemistry[a]	(Day 27)	GLDH (U/L)	19.80	22.50	16.13	14.97	15.73	18.63	255.28↑ ↑615.6 (# 23) ↑112.1 (# 24) ↑138.9 (# 25) ↑371.6 (# 26) ↑38.2 (# 27)	219.82 ↑222.7 (# 28) ↑748.3 (# 31)
Organ Weight			–	–	–	–	–	–	–	–
Gross Pathology			–	–	–	–	–	–	–	–
Histopathology			–	–	–	–	–	–	–	–
Postdose Evaluation-Noteworthy Findings										
No. Evaluated			M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
No. Died or Sacrificed Moribund			0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation			–	–	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	–	–
Ophthalmoscopy			–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis			–	–	N/A	N/A	N/A	N/A	–	–
Electrocardiography			–	–	N/A	N/A	N/A	N/A	–	–
Hematology			–	–	N/A	N/A	N/A	N/A	–	–
Blood Chemistry[a]	Day 7 of recovery	ALT (IU/L)	33.0	–	N/A	N/A	N/A	N/A	113.0 ↑161 (# 23)	–
		LAP (IU/L)	60.5	–	N/A	N/A	N/A	N/A	110.0 ↑150 (# 23)	–
		GGT (IU/L)	55.5	–	N/A	N/A	N/A	N/A	100.5 ↑136 (# 23)	–
		GLDH (U/L)	14.00	–	N/A	N/A	N/A	N/A	46.70 ↑64.8 (# 23)	–
	Day 14 of recovery	ALT (IU/L)	30.0	–	NA	NA	NA	NA	70.0 ↑98 (# 23)	–
		GLDH (U/L)	11.30	–	NA	NA	NA	NA	44.00 ↑71.7 (# 23)	–

Daily Dose (mg/kg)	0 (Control)		1		10		100	
Organ Weight	–	–	N/A	N/A	N/A	N/A	–	–
Gross Pathology	–	–	N/A	N/A	N/A	N/A	–	–
Histopathology	–	–	N/A	N/A	N/A	N/A	–	–

–, No noteworthy findings; ↑, increase; ( ), animal number.
* P < 0.05, ** P < 0.01 vs. control (Dunnett's test).
† P < 0.05, †† P < 0.01 vs. control (Dunnett-type test).
§ P < 0.05 vs. control (Cumulative Chi-squares test with Dunn-Sidak adjustment).
a Group means are shown.
b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 μg/mL. All the plasma concentrations of S-033188 in the control, 1, 10, and 100 mg/kg/day groups were BLQ (< 0.00500 μg/mL).

2.6.7.8 In Vitro 遺伝毒性試験

2.6.7.8.1 Reverse Mutation Test with Bacteria

Test Article: S-033188

Report Title: Bacterial Reverse Mutation Test of RSC-033188		
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Assays:** 2	**Study No.** R-033188-TB-064-L
Strains: *Salmonella typhimurium* and *Escherichia coli*	**No. of Replicate Cultures:** 3 (Negative control and test article), 2 (Positive controls)	**Location in CTD:** 4.2.3.3-01
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 10% in the S9 mix	**No. of Cells Analyzed/Cultured:** −	**GLP Compliance:** Yes
Vehicles: **For Test Article:** Dimethyl sulfoxide (DMSO) **For Positive Controls :** DMSO		**Date of Treatment:** [redacted], 20[redacted]
Treatment: Plate incorporation method and plate incubation for 48 hr (37°C)		
Cytotoxic Effects: The cytotoxicity (reduction of the bacterial background lawn) was observed at doses of 78.1 µg/plate with the S9 mix in TA100, TA1535, TA1537, and WP2*uvrA*, at doses of 313 µg/plate with the S9 mix in TA98, and at dose of 2500 µg/plate and above without the S9 mix in TA1537.		
Genotoxic Effects: None		

Metabolic Activation	Test Article	Dose Level (µg/plate)	First mutagenicity test				
			Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without Activation	DMSO	100 µL/plate	120	7	35	25	6
	S-033188	156	132	7	32	25	9
		313	143	11	36	24	6
		625	137	12	29	19	9
		1250[a]	125	11	30	26	7
		2500[a]	122	12	26	16	8[b]
		5000[a]	130	12	22	18	5[b]
	2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide[c]	0.01	573	N/A	219	N/A	N/A
		0.1	N/A	N/A	N/A	484	N/A
	Sodium azide[c]	0.5	N/A	242	N/A	N/A	N/A
	9-Aminoacridine hydrochloride[c]	80	N/A	N/A	N/A	N/A	807

Metabolic Activation	Test Article	Dose Level (μg/plate)	First mutagenicity test Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2*uvrA*	TA98	TA1537
With Activation	DMSO	100 μL/plate	152	11	33	29	14
	S-033188	2.44	154	13	32	N/A	10
		4.88	131	14	33	N/A	13
		9.77	150	16	45	33	10
		19.5	144	19	34	29	14
		39.1	154	18	45	31	13
		78.1	66[b]	18[b]	49[b]	24	15[b]
		156	N/A	N/A	N/A	17	N/A
		313	N/A	N/A	N/A	16[b]	N/A
	2-Aminoanthracene[c]	0.5	N/A	N/A	N/A	439	N/A
		1	1368	N/A	N/A	N/A	N/A
		2	N/A	446	N/A	N/A	294
		10	N/A	N/A	806	N/A	N/A

Metabolic Activation	Test Article	Dose Level (μg/plate)	Second mutagenicity test				
			Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2uvrA	TA98	TA1537
Without Activation	DMSO	100 μL/plate	123	8	29	20	10
	S-033188	156	109	12	38	18	11
		313	119	12	35	19	14
		625[a]	132	7	34	15	11
		1250[a]	123	6	30	20	10
		2500[a]	120	8	35	19	10
		5000[a]	114	9	35	15	11
	2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide[c]	0.01	581	N/A	214	N/A	N/A
		0.1	N/A	N/A	N/A	517	N/A
	Sodium azide[c]	0.5	N/A	370	N/A	N/A	N/A
	9-Aminoacridine hydrochloride[c]	80	N/A	N/A	N/A	N/A	725
With Activation	DMSO	100 μL/plate	122	10	32	24	19
	S-033188	2.44	133	13	38	N/A	24
		4.88	134	9	39	N/A	20
		9.77	135	13	40	28	16
		19.5	140	16	45	27	19
		39.1	121	17	44	27	18
		78.1	36[b]	17[b]	49[b]	26	21[b]
		156	N/A	N/A	N/A	15	N/A
		313	N/A	N/A	N/A	13[b]	N/A
	2-Aminoanthracene[c]	0.5	N/A	N/A	N/A	520	N/A
		1	1345	N/A	N/A	N/A	N/A
		2	N/A	479	N/A	N/A	302
		10	N/A	N/A	626	N/A	N/A

Abbreviations: DMSO, dimethyl sulfoxide; N/A, not applicable; S9, supernatant at 9000 × g.

a Precipitation derived from the test article.

b Reduction of the bacterial background lawn.

c Positive control.

2.6.7.8.2 Reverse Mutation Test with Bacteria

Test Article: S-033447

Report Title: Bacterial Reverse Mutation Test of RSC-033447		
Test for Induction of: Reverse mutation in bacterial cells	**No. of Independent Assays:** 3	**Study No.** R-033188-TB-065-L
Strains: *Salmonella typhimurium* and *Escherichia coli*	**No. of Replicate Cultures:** 3 (Negative control and test article), 2 (Positive controls)	**Location in CTD:** 4.2.3.3-02
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 10% in the S9 mix	**No. of Cells Analyzed/Cultured:** −	**GLP Compliance:** Yes
Vehicles: **For Test Article:** DMSO **For Positive Controls :** DMSO		**Date of Treatment:** [redacted], 20[redacted]
Treatment: Plate incorporation method and plate incubation for 48 hr (37°C)		
Cytotoxic Effects: Cytotoxicity (the growth inhibition of bacteria) by the test article was observed at doses of 78.1 µg/plate without the S9 mix and 156 and 313 µg/plate with the S9 mix in TA98, at doses of 19.5 µg/plate without the S9 mix and 39.1 and 78.1 µg/plate with the S9 mix in TA100, at dose of 19.5 µg/plate with and without the S9 mix in TA1535 and TA1537, and at doses of 78.1 µg/plate without the S9 mix and 39.1 and 78.1 µg/plate with the S9 mix in WP2*uvrA*.		
Genotoxic Effects: None		

Metabolic Activation	Test Article	Dose Level (µg/plate)	First mutagenicity test				
			Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without Activation	DMSO	100 µL/plate	107	12	29	17	8
	S-033447	0.610	104	12	N/A	N/A	8
		1.22	105	11	N/A	N/A	8
		2.44	127	8	34	15	10
		4.88	121	10	37	15	8
		9.77	115	13	35	17	8
		19.5	138[a]	19[a]	32	13	9[a]
		39.1	N/A	N/A	44	10	N/A
		78.1	N/A	N/A	46[a]	15[a]	N/A
	2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide[b]	0.01	627	N/A	185	N/A	N/A
		0.1	N/A	N/A	N/A	481	N/A
	Sodium azide[b]	0.5	N/A	420	N/A	N/A	N/A
	9-Aminoacridine hydrochloride[b]	80	N/A	N/A	N/A	N/A	735

Metabolic Activation	Test Article	Dose Level (μg/plate)	First mutagenicity test Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2*uvrA*	TA98	TA1537
With Activation	DMSO	100 μL/plate	124	14	39	23	18
	S-033447	0.61	N/A	10	N/A	N/A	13
		1.22	N/A	13	N/A	N/A	16
		2.44	138	9	45	N/A	16
		4.88	123	11	43	N/A	12
		9.77	127	16	47	23	15
		19.5	129	20[a]	43	27	17[a]
		39.1	121[a]	N/A	58	26	N/A
		78.1	31[a]	N/A	53[a]	15	N/A
		156	N/A	N/A	N/A	17[a]	N/A
		313	N/A	N/A	N/A	30[a]	N/A
	2-Aminoanthracene[b]	0.5	N/A	N/A	N/A	497	N/A
		1	1430	N/A	N/A	N/A	N/A
		2	N/A	492	N/A	N/A	258
		10	N/A	N/A	836	N/A	N/A

Metabolic Activation	Test Article	Dose Level (μg/plate)	Second mutagenicity test Revertant Colony Counts (Mean)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2uvrA	TA98	TA1537
Without Activation	DMSO	100 μL/plate	130	14	36	16	6
	S-033447	0.610	139	10	N/A	N/A	7
		1.22	132	9	N/A	N/A	7
		2.44	126	11	29	23	7
		4.88	119	12	32	20	9
		9.77	127	17	31	15	8
		19.5	114 a	19[a]	43	16	12[a]
		39.1	N/A	N/A	42	14	N/A
		78.1	N/A	N/A	53[a]	15[a]	N/A
	2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide[b]	0.01	514	N/A	152	N/A	N/A
		0.1	N/A	N/A	N/A	372	N/A
	Sodium azide[b]	0.5	N/A	295	N/A	N/A	N/A
	9-Aminoacridine hydrochloride[b]	80	N/A	N/A	N/A	N/A	313
With Activation	DMSO	100 μL/plate	119	12	31	22	11
	S-033447	0.61	N/A	9	N/A	N/A	9
		1.22	N/A	8	N/A	N/A	8
		2.44	120	9	36	N/A	10
		4.88	122	14	36	N/A	9
		9.77	128	13	36	26	10
		19.5	126	17[a]	41	26	13[a]
		39.1	100[a]	N/A	43[a]	19	N/A
		78.1	20[a]	N/A	77[a]	26	N/A
		156	N/A	N/A	N/A	17[a]	N/A
		313	N/A	N/A	N/A	7[a]	N/A
	2-Aminoanthracene[b]	0.5	N/A	N/A	N/A	357	N/A
		1	1021	N/A	N/A	N/A	N/A
		2	N/A	374	N/A	N/A	251
		10	N/A	N/A	734	N/A	N/A

Metabolic Activation	Test Article	Dose Level (μg/plate)	Third mutagenicity test Revertant Colony Counts (Mean) WP2*uvrA*
With Activation	DMSO	100 μL/plate	27
	S-033447	2.44	40
		4.88	37
		9.77	44
		19.5	53
		39.1	44 [a]
		78.1	44 [a]
	2-Aminoanthracene [b]	10	943

Abbreviation: S9 mix, metabolic activation system.
S-033447 is an active form of S-033188.
a Reduction of the bacterial background lawn.
b Positive control.

2.6.7.8.3 In Vitro Micronucleus Test in Culture Mammalian Cells

Test Article: S-033188

Report Title: Micronucleus Test of RSC-033188 with Cultured Mammalian Cells		
Test for Induction of: Micronuclei	**No. of Independent Assays:** 1	**Study No.** R-033188-TF-060-L
Strains: TK6 Cell	**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 vol%	**No. of Cells Analyzed/Cultured:** 1000	**GLP Compliance:** Yes
Vehicles: **For Test Article:** DMSO **For Positive Controls:** Isotonic sodium chloride solution		**Date of Treatment:** [redacted], 20[redacted]
Treatment: Short-term treatment for 3 hr and recovery time for 24 hr with and without S9 mix, continuous treatment for 24 hr without S9 mix		
Cytotoxic Effects: The percentages of cytostasis were 46.3 at 120 µg/mL in the short-term treatment for 3 hr without S9 mix, 57.1 at 72.0 µg/mL in the short-term treatment for 3 hr with S9 mix, and 46.5 at 15.6 µg/mL in the continuous treatment for 24 hr without S9 mix.		
Genotoxic Effects: None		

Metabolic Activation	Treatment – Recovery (hour)	Test Article	Dose (µg/mL)	Cytostasis (%)	Frequency of MNBN[a] (%)
Without Activation	**3–24**	**DMSO**	1 vol %	N/A	0.5
		S-033188	43.2	18.4	0.7
			72.0	30.6	0.3
			120	46.3	0.9
		Colchicine[b]	0.03	20.7	1.6 *
With Activation	**3–24**	**DMSO**	1 vol %	N/A	0.5
		S-033188	25.9	18.6	0.4
			43.2	40.6	0.4
			72.0	57.1	0.9
		Cyclophosphamide[b]	8	61.4	1.8*
Without Activation	**24–0**	**DMSO**	1 vol %	N/A	0.7
		S-033188	2.02	26.3	0.8
			5.62	37.4	0.8
			15.6	46.5	0.9
		Mitomycin C[b]	0.2	58.9	2.4*

Abbreviation: MNBN, micronucleated binucleate cells.
* $P \leq 0.05$ vs. control (Fisher's exact test).
a Number of micronucleated binucleate cells / 2000 binucleate cells.
b Positive control.

2.6.7.8.4 In Vitro Micronucleus Test in Culture Mammalian Cells

Test Article: S-033447

Report Title: Micronucleus Test of RSC-033447 with Cultured Mammalian Cells		
Test for Induction of: Micronuclei	**No. of Independent Assays:** 1	**Study No.** R-033188-TF-059-L
Strains: TK6 Cell	**No. of Replicate Cultures:** 2	**Location in CTD:** 4.2.3.3-04
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 2 vol%	**No. of Cells Analyzed/Cultured:** 1000	**GLP Compliance:** Yes
Vehicles: **For Test Article:** DMSO **For Positive Controls:** Isotonic sodium chloride solution		**Date of Treatment:** [redacted], 20[redacted]
Treatment: Short-term treatment for 3 hrs and recovery time for 24 hrs with and without S9 mix, continuous treatment for 24 hrs without S9 mix		
Cytotoxic Effects: The percentages of cytostasis were 47.7 at 160 µg/mL in the short-term treatment for 3 hrs without S9 mix, 49.8 at 160 µg/mL in the short-term treatment for 3 hrs with S9 mix, and 44.5 at 6.25 µg/mL in the continuous treatment for 24 hrs without S9 mix.		
Genotoxic Effects: None		

Metabolic Activation	Treatment – Recovery (hour)	Test Article	Dose (µg/mL)	Cytostasis (%)	Frequency of MNBN[a] (%)
Without Activation	**3–24**	**DMSO**	1 vol%	N/A	0.8
		S-033447	50.0	32.2	0.9
			80.0	36.6	0.7
			160	47.7	1.0
		Colchicine[b]	0.03	21.0	1.8*
With Activation	**3–24**	**DMSO**	1 vol%	N/A	0.6
		S-033447	50.0	35.7	0.9
			80.0	42.7	0.9
			160	49.8	1.2
		Cyclophosphamide[b]	8	62.0	2.3*
Without Activation	**24–0**	**DMSO**	1 vol%	N/A	0.5
		S-033447	1.56	28.9	1.1
			3.13	39.0	0.8
			6.25	44.5	1.0
		Mitomycin C[b]	0.2	58.1	2.4*

* $P \leq 0.05$ vs. control (Fisher's exact test).

a Number of micronucleated binucleate cells / 2000 binucleate cells.

b Positive control.

2.6.7.9 *In Vivo* 遺伝毒性試験

2.6.7.9.1 Micronucleus Test in Rats

Test Article: S-033188

Report Title: Micronucleus Test of RSC-033188 in Rats		
Test for Induction of: Bone marrow micronuclei	**Treatment Schedule:** 2 days (Once daily)	**Study No.** R-033188-TF-085-L
Species/Strain: Rat/Crl:CD(SD)	**Sampling Time:** 24 hours after 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	
No. of Cells Evaluated/Animal: 2000		
Special Features: None		
Toxic/Cytotoxic Effects: None		
Genotoxic Effects: None		
Evidence of Exposure: Toxicokinetics of two-week oral toxicity study of S-033188 in rats (Study No. R-033188-TB-032-L)		

Test Article	Dose (mg/kg/day)	Gender and No. per Group	Ratio of IE (%)[a] (Mean ± SD)	Frequency of MNIE (%)[b] (Mean ± SD)
Vehicle	0	5 males	50.0 ± 6.2	0.11 ± 0.07
S-033188	500	5 males	54.4 ± 3.2	0.12 ± 0.06
	1000	5 males	52.8 ± 2.2	0.14 ± 0.05
	2000	5 males	48.4 ± 2.6	0.18 ± 0.08
Mitomycin C[c]	2	5 males	45.9 ± 4.1	4.30 ± 1.20*

Abbreviations: IE, immature erythrocytes; MNIE, micronucleated immature erythrocytes.
* $P \leq 0.025$ vs. control (Kastenbaum and Bowman method).
a Number of immature erythrocytes / 500 erythrocytes per animal.
b Number of micronucleated immature erythrocytes / 2000 immature erythrocytes per animal.
c Positive control, single intravenous injection.

2.6.7.10 がん原性試験

該当する試験なし.

2.6.7.11 生殖発生毒性試験： 重要な試験以外の試験

<table>
<tr><th>Species/
Strain</th><th>Method of
Administration
(Vehicle/
Formulation)</th><th>Duration of
Dosing</th><th>Doses
(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 w/v% MC /
Suspension)</td><td>2 weeks</td><td>0, 100, 300,
1000</td><td>3F (Non-
pregnant)</td><td>1000:
Abnormal stool color (greyish brown), Decrease of body weight or body weight gain (Days 4 to 6), Decrease of food consumption (Day 6)

Toxicokinetics of S-033447 (n=3, mean value)
<table>
<tr><th>Dose
(mg/kg)</th><th>Day</th><th>Cmax
(μg/mL)</th><th>$AUC_{0\text{-}24hr}$
(μg·hr/mL)</th></tr>
<tr><td>0
(Control)</td><td>1</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td></td><td>14</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td>100</td><td>1</td><td>1.36</td><td>13.7</td></tr>
<tr><td></td><td>14</td><td>1.53</td><td>14.3</td></tr>
<tr><td>300</td><td>1</td><td>1.61</td><td>27.1</td></tr>
<tr><td></td><td>14</td><td>1.80</td><td>20.5</td></tr>
<tr><td>1000</td><td>1</td><td>1.65</td><td>36.6</td></tr>
<tr><td></td><td>14</td><td>1.69</td><td>28.1</td></tr>
</table>
The LLOQ of S-033447 was 0.00500 μg/mL</td><td>R-033188-
TF-066-L/
4.2.3.5-06</td></tr>
<tr><td>Rabbit/
Kbl:NZW</td><td>Oral gavage
(0.5 w/v% MC /
Suspension)</td><td>G7–19</td><td>0, 100, 300,
1000</td><td>7 or 8F
(Pregnant)</td><td><u>Dams:</u>
1000:
Abnormal stool color (greyish brown)
≥300:
Suppression of body weight gain, Decrease in food consumption
<u>Embryos and Fetuses:</u>
1000:
High frequency of cervical rib in fetuses
≥300:
Increase of post implantation loss</td><td>R-033188-
TF-087-L/
4.2.3.5-07</td></tr>
</table>

2.6.7.12 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

2.6.7.12.1 Fertility and Early Embryonic Development to Implantation in Rats

Test Article: S-033188

Report Title: Oral Study for Effects of S-033188 on Fertility and Early Embryonic Development to Implantation in Rats		
Design similar to ICH 4.1.1.: Yes	**Duration of Dosing:** M: Approximately 4 weeks prior to mating and continuing until the day before necropsy F: Approximately 2 weeks prior to mating, through G7	**Study No.** S-033188-TB-130-L
Species/Strain: Rat/Crl:CD(SD)		
Initial Age: M: 7 weeks, F: 9 weeks		**Location in CTD:** 4.2.3.5-01
Day of Mating: G0	**Day of Caesarean section:** G13	**GLP Compliance :** Yes
Date of First Dose: M: [redacted], 20[redacted] F: [redacted], 20[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension	
NOAEL: F0 Males: 1000 mg/kg/day F0 Females: 1000 mg/kg/day F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg)		**0 (Control)**	**20**	**200**	**1000**
F0 Males					
No. Males Evaluated		**20**	**20**	**20**	**20**
Noteworthy Findings					
Died or Sacrificed Moribund		0	0	1[a]	0
Clinical Observation[b]	**Partially white-colored feces**	0	0	0	19
Body Weight		–	–	–	–
Body Weight Gain		–	–	–	–
Food Consumption		–	–	–	–
Reproductive Organ Weight[c]		–	–	–	–
Gross Pathology		–	–	–	–
Number of Sperms per Testis		–	–	–	–
Mean No. Days Prior to Copulation		2.4	2.5	2.3	2.2
No. of Males Copulated (%, Copulation)		20/20 (100)	20/20 (100)	20/20 (100)	20/20 (100)
No. of Fertile Males (%, Fertility)		19/20 (95)	19/20 (95)	19/20 (95)	20/20 (100)
F0 Females					
No. Females Evaluated		**20**	**20**	**20**	**20**
No. Died or Sacrificed Moribund		0	0	0	0

Daily Dose (mg/kg)		0 (Control)	20	200	1000
Clinical Observation [b]	Pre-Copulating Periods				
	Partially white-colored feces	0	0	0	7
	Pregnancy Periods				
	Partially white-colored feces	0	0	0	2
Body Weight		–	–	–	–
Body Weight Gain		–	–	–	–
Food Consumption (%) [d]	Days 1-4 (Before Pairing)	17.6 g/day	+2	−6*	−6*
Reproductive organ weight [e]		–	–	–	–
Gross Pathology		–	–	–	–
Mean Days per Estrus Cycle		4.0	4.2	4.2	4.2
Mean Incidence of Estrus/15 days (%)		24.2	24.6	23.9	24.8
Mean No. Days Prior to Copulation		2.4	2.5	2.3	2.2
No. of Females Sperm-Positive (%, Copulation)		20/20 (100)	20/20 (100)	20/20 (100)	20/20 (100)
No. of Pregnant Females (%, Fertility)		19/20 (95)	19/20 (95)	19/20 (95)	20/20 (100)
Mean No. Corpora Lutea		16.1	16.8	15.2	15.9
Mean No. Implantations		14.7	15.5	14.2	14.2
Mean % Pre-implantation Loss		8.3	7.2	5.3	10.5
Embryos					
No. Litters Evaluated		19	19	19	20
Mean No. Live Embryos		13.9	14.7	13.4	13.1
Mean % Post-implantation Loss		6.4	4.4	5.8	7.1

−, No noteworthy findings.
* $P < 0.05$ vs. control (Dunnett's test).
a One male in the 200 mg/kg/day group died accidentally on Day 39.
b Numerals represent the number of animals with the finding.
c Testes, epididymides, seminal vesicles, and ventral prostate.
d For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percentage differences).
e Ovaries.

2.6.7.13 生殖発生毒性試験： 胚・胎児発生に関する試験

2.6.7.13.1 Embryo-Fetal Development in Rats

Test Article: S-033188

Report Title: Oral Study for Effects of RSC-033188 on Embryo-Fetal Development in Rats		
Design similar to ICH 4.1.3.: Yes	**Duration of Dosing:** G6–17	**Study No.** R-033188-TB-070-L
Species/Strain: Rat/Crl:CD(SD)	**Day of Mating:** G0	**Location in CTD:** 4.2.3.5-02
Initial Age: 11 to 13 weeks of age	**Day of Caesarean section:** G21	**GLP Compliance:** Yes
Date of First Dose: [redacted], 20[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension	
NOAEL: F0 dam: 1000 mg/kg/day F1 litter: 1000 mg/kg/day		

Daily Dose (mg/kg)			**0 (Control)**	**20**	**200**	**1000**
Dams						
Toxicokinetics[a]						
No. Evaluated			**5**	**4**	**5**	**4**
S-033447[b]	**C_{max} (μg/mL)**	**G6**	N.C.	0.214	0.739	1.25
		G17	N.C.	0.324	0.622	0.621
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**G6**	N.C.	1.26	6.49	15.3
		G17	N.C.	1.88	6.18	7.17
Noteworthy Findings						
No. Pregnant			**20**	**20**	**20**	**20**
No. Died or Sacrificed Moribund			0	0	0	0
No. Aborted or with Total Resorption Loss			0	0	0	0
Clinical Observation[c]	**White colored feces**		0	0	0	15
Body Weight			–	–	–	–
Body Weight Gain (g)[a]	**G6–7**		4.0	4.4	1.4	1.1*
	G6–8		9.5	9.5	5.9*	7.7
	G6–9		14.5	14.5	10.5**	13.8
Food Consumption (%)[d]	**G7**		23.7 g/day	−4	−12**	−19**
	G8		23.6 g/day	−3	−8*	−11**
	G9		24.5 g/day	−6	−13**	−14**
	G10		23.8 g/day	−3	−11**	−11**
Gross Pathology			–	–	–	–
Mean No. Corpora Lutea			15.7	15.8	15.4	15.7

Daily Dose (mg/kg)		0 (Control)	20	200	1000
Mean No. Implantations		14.1	13.6	14.2	15.1
Mean % Pre-implantation Loss		8.9	11.9	7.1	3.7
F1 Litters					
No. Litters Evaluated		20	20	20	20
Mean No. Live Fetuses		12.9	13.0	13.7	14.0
Mean % Early Resorptions		9.1	5.1	3.7	6.8
Mean % Late Resorptions		0	0	0	0
Mean % Dead Fetuses		0	0	0	0
Mean % Post-implantation Loss		9.1	5.1	3.7	6.8
Fetal Sex Ratio (Male/Male + Female)[a]		0.53	0.50	0.52	0.51
Mean Fetal Body Weight (g)	Male	5.69	5.78	5.83	5.85
	Female	5.39	5.48	5.51	5.46
Mean Placental Weight (g)	Male	0.478	0.475	0.496	0.519
	Female	0.462	0.459	0.472	0.513
Placental Malformations		–	–	–	–
External Malformations		–	–	–	–
Visceral Malformations		–	N.E.	N.E.	–
Visceral Variations		–	N.E.	N.E.	–
Skeletal Malformations		–	N.E.	N.E.	–
Skeletal Variations		–	N.E.	N.E.	–
Degree of Ossification		–	N.E.	N.E.	–

–, No noteworthy findings.
* $P < 0.05$, ** $P < 0.01$ vs. control (Dunnett's test).
a Group means are shown.
b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 μg/mL. All plasma concentrations of S-033188 in the control, 20, 200 and 1000 mg/kg groups were BLQ (< 0.00500μg/mL).
c Numerals represent number of animals with the finding.
d For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

2.6.7.13.2 Embryo-Fetal Development in Rabbits

Test Article: S-033188

Report Title: Oral Study for Effects of S-033188 on Embryo-Fetal Development in Rabbits		
Design similar to ICH 4.1.3.: Yes	**Duration of Dosing:** G7–19	**Study No.** S-033188-TF-135-L
Species/Strain: Rabbits/Kbl:NZW	**Day of Mating:** G0	**Location in CTD:** 4.2.3.5-03
Initial Age: 18 to 20 weeks	**Day of Caesarean section:** G28	**GLP Compliance:** Yes
Date of First Dose: [redacted], 20[redacted]	**Method of Administration:** Oral gavage	
Special Features: None	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension	
NOAEL: F0 dams: 100 mg/kg/day F1 litter: 100 mg/kg/day		

Daily Dose (mg/kg)			**0 (Control)**	**30**	**100**	**1000**
Dams						
Toxicokinetics[a]						
No. Evaluated			**5**	**5**	**4**	**5**
S-033447[b]	**C_{max} (μg/mL)**	**G7**	N.C.	0.586	1.24	1.83
		G19	N.C.	0.485	0.883	1.35
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**G7**	N.C.	6.29	14.4	35.6
		G19	N.C.	4.60	9.26	20.9
Noteworthy Findings						
No. Pregnant			**20**	**18**	**19**	**19**
No. Died or Sacrificed Moribund			0	0	0	0
No. Aborted			1[c]	0	0	2[c]
No. with Total Resorption of Litter			0	0	0	0
No. Delivered Prematurely						
Clinical Observation[d]	**Decrease in stool volume**		0	0	0	1
	No stool		0	0	0	1
	Abnormal stool color (greyish brown)		0	0	0	2
Body Weight			–	–	–	–
Body Weight Gain (kg)[a]	**G7–8**		0.007	–0.004	–0.008	–0.031**
	G7–9		0.007	0.008	0.006	–0.028*
	G7–10		0.023	0.016	0.010	–0.019**
	G7–11		0.031	0.030	0.025	–0.015**
Food Consumption (%)[e]	**G8**		149.4 g/day	–4	0	–29**
	G9		149.0 g/day	–3	–1	–15*
Gross Pathology			–	–	–	–

Daily Dose (mg/kg)		0 (Control)	30	100	1000
Mean No. Corpora Lutea		8.2	7.8	8.4	7.1
Mean No. Implantations		7.6	7.6	7.9	6.5
Mean % Implantation		93.9	95.5	93.4	91.5
F1 Litters					
No. Litters Evaluated		19	18	19	17
Total No. Live Fetuses		133	124	143	107
Mean No. Live Fetuses		7.0	6.9	7.5	6.3
Mean % Fetal Viability		91.7	92.4	95.9	96.8
Mean No. Dead Embryos/Fetuses[f]		0.6	0.7	0.4	0.2
Mean % Post-implantation Loss		8.4	7.6	4.1	3.4
Fetal Sex Ratio (Male/Male + Female)[a]		0.545	0.543	0.492	0.386*
Mean Fetal Body Weight (g)	Male	33.80	34.93	35.25	36.42
	Female	32.78	33.98	33.08	35.42
Mean Placental Weight (g)	Male	5.20	5.67	5.04	5.60
	Female	4.97	5.41	4.67	5.24
Placental Malformations		–	–	–	–
External Malformations		–	–	–	–
Visceral Malformations		–	–	–	–
Visceral Variations		–	–	–	–
Skeletal Malformations		–	–	–	–
Skeletal Variations	NF/ND	133/19	124/18	143/19	107/17
Short supernumerary cervical rib	No. Fetuses (%)	0	0	1 (0.75)	34 (33.70)††
	No. Litters (%)	0	0	1 (5.3)	13 (76.5) §§
Full supernumerary rib	No. Fetuses (%)	66 (51.86)	60 (48.53)	45 (31.49)	13 (11.42)††
	No. Litters (%)	16 (84.2)	16 (88.9)	16 (84.2)	8 (47.1)§
Degree of Ossification[g]		–	–	–	–

−, No noteworthy findings.
* P < 0.05, ** P < 0.01 vs. control (Dunnett's test).
†† P < 0.01 vs. control (Dunnet-type test).
§ P<0.05, §§ P<0.01 vs. control (Fisher's exact test).
a Group means are shown.
b S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 µg/mL. TK parameters for S-033188 were not calculated because all values from the test substance and the control groups were BLQ (<0.00500 µg/mL).
c Abortion on G25 or G26.
d Numerals represent number of animals with the finding.
e For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).
f Total of early resorption, late resorption, and dead fetuses.
g Number of sternebrae, sacro-caudal vertebrae.

2.6.7.14 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

2.6.7.14.1 Prenatal and Postnatal Development, Including Maternal Function in Rats

Test Article: S-033188

Report Title: Oral Study for Effects of S-033188 on Pre- and Postnatal Development, Including Maternal Function, in Rats		
Design similar to ICH 4.1.2.: Yes	**Duration of Dosing:** G6–L20 **Day of Mating:** G0	**Study No.** S-033188-TF-159-L
Species/Strain: Rat/Crl:CD(SD)	**Method of Administration:** Oral gavage	**Location in CTD:** 4.2.3.5-04
Initial Age: 12 to 13 weeks	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension	
Date of First Dose: [redacted], 20[redacted]	**Litters Culled/Not Culled:** Culled to 4/sex/litter	**GLP Compliance:** Yes
Special Features: None		
NOAEL: F0 dam: 1000 mg/kg/day F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg)	**0 (Control)**	**20**	**200**	**1000**
F0 Females				
No. Pregnant	**22**	**20**	**22**	**22**
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	0
Clinical Observation	–	–	–	–
Body Weight	–	–	–	–
Body Weight Gain	–	–	–	–
Food Consumption	–	–	–	–
Gross Pathology	–	–	–	–
Mean Duration of Gestation (days)	21.86	21.83	21.82	22.00
No. Delivery (%, Gestation Index)[a]	22 (100.0)	20 (100.0)	22 (100.0)	22 (100.0)
Abnormal Delivery	–	–	–	–
F1 Litters (Pre-weaning)				
No. Litters Evaluated	**22**	**20**	**22**	**22**
Mean No. Pups/Litter	12.4	13.2	13.3	12.3
Mean No. Live Born Pups/Litter	12.3	13.1	13.2	12.3
Mean No. Stillborn Pups/Litter	0.1	0.1	0.1	0.0
Birth Index (Liveborns/Implantations, %)	92.21	87.67	93.25	90.98
Mean Pup Body Weight	–	–	–	–
Mean Pup Sex Ratio (Male/Male + Female)	0.50	0.52	0.48	0.50

Daily Dose (mg/kg)			0 (Control)	20	200	1000
Mean % Postnatal Survival to Day 4 of age			99.05	98.62	99.68	99.03
Mean % Postnatal Survival to Weaning			100.00	98.75	99.43	97.95
Pup External Malformation			–	–	–	–
Pup Clinical Observation [b]	Eyeball: Dark red discoloration		0	0	2	4
	Eyeball: Enlargement		0	0	2	4
Physical Development [c]			–	–	–	–
Functional Development [d]			–	–	–	–
Pup Gross Pathology [b]	Eyeball: Dark red discoloration		0	0	0	1
	Eyeball: Enlargement		0	0	0	1
Histopathology of Eyeball [b]						
No. Examined F1 Pups			3	N.E.	N.E.	1
Adhesion, cornea-iris		Moderate	0	N/A	N/A	1
Blood pool, intraocular		Slight	0	N/A	N/A	1
Hemorrhage, iris		Moderate	0	N/A	N/A	1
Vacuolation, lens		Slight	0	N/A	N/A	1
F1 Males (Post-weaning)						
No. Males Evaluated (R, B)			44 (22, 22)	39 (20, 19)	44 (22, 22)	44 (22, 22)
No. Died or Sacrificed Moribund			0	0	0	0
Clinical Observation [b]	Eyeball: Dark red discoloration		0	0	1	1
	Eyeball: Enlargement		0	0	1	1
	Eyeball: Opacity		0	0	1	1
Body Weight			–	–	–	–
Open Field Test			–	–	–	–
Water Maze Test			–	–	–	–
Sexual Maturation (Cleavage of the Balano-Preputial Gland)			–	–	–	–
Mean No. of Days Prior to Copulation			2.8	3.0	2.2	4.2
No. Males Copulated (%, Copulation)			19/22 (86.4)	20/20 (100.0)	21/22 (95.5)	20/22 (90.9)
No. Fertile Males (%, Fertility)			16/19 (84.2)	20/20 (100.0)	19/21 (90.5)	20/20 (100.0)
Ophthalmology [b]						
No. Examined Animals			20	19	22	22
Days 21 to 24 of age	Slit-Lamp Examination	Anterior chamber hyphema	0	0	1	1
	Funduscopic Examination		–	–	–	–
Days 71 to 74 of age	Slit-Lamp Examination	Anterior chamber hyphema	0	0	1	0
		Corneal opacity	0	0	1	1
		Corneal vascularization	0	0	0	1
		Iris mass	0	0	0	1

Daily Dose (mg/kg)			0 (Control)	20	200	1000
		Abnormal iris blood flow	0	0	0	1
	Funduscopic Examination		–	–	–	–
Gross Pathology[b]	Eyeball: Dark red discoloration		0	0	1	0
	Eyeball: Enlargement		0	0	1	0
	Eyeball: Opacity		0	0	1	1
Histopahology of Eyeball[b]						
No. Examined Animals			3	N.E.	1	1
Adhesion, cornea-iris		Moderate	0	N/A	1	0
Adhesion, lens-iris		Marked	0	N/A	0	1
Erythrocyte/ pigmented macrophage/ fibrin, intraocular		Moderate	0	N/A	1	1
Inflammation, chronic, cornea		Slight	0	N/A	1	1
Inflammation, chronic, iris		Moderate	0	N/A	1	0
		Marked	0	N/A	0	1
Necrosis, lens		Slight	0	N/A	1	1
F1 Females (Post-weaning)						
No. Females Evaluated (R, B)			44 (22, 22)	39 (20, 19)	44 (22, 22)	43 (22, 21)
No. Died or Sacrificed Moribund			0	0	0	0
Clinical Observation[b]	Eyeball: Bulge		0	0	1	1
	Eyeball: Dark red discoloration		0	0	1	2
	Eyeball: Enlargement		0	0	1	2
	Eyeball: Opacity		0	0	1	2
	Eyeball: Rough		0	0	1	0
Body Weight			–	–	–	–
Open Field Test			–	–	–	–
Water Maze Test			–	–	–	–
Sexual Maturation (Vaginal Opening)			–	–	–	–
Mean No. Estrus/14 days			3.4	3.2	3.4	3.4
Mean Days of Estrous Cycle			4.17	4.05	4.02	4.12
No. Females Copulated (%, Copulation)			19/22 (86.4)	20/20 (100.0)	21/22 (95.5)	20/22 (90.9)
No. Pregnant Females (%, Fertility)			16/19 (84.2)	20/20 (100.0)	19/21 (90.5)	20/20 (100.0)
Mean No. Corpora Lutea			13.4	13.5	12.4	14.3
Mean No. Implantations			12.6	12.5	11.8	13.3
Mean % Pre-implantation Loss			8.4	7.5	5.3	7.4
Ophthalmology[b]						
No. Examined Animals			20	19	22	21

Daily Dose (mg/kg)			0 (Control)	20	200	1000
Days 21 to 24 of age	Slit-Lamp Examination	Anterior chamber hyphema	0	0	1	2
		Anterior chamber opacity	0	0	0	1
		Enlargement of anterior chamber	0	0	0	1
		Proterior synechia	0	0	0	1
	Funduscopic Examination		–	–	–	–
Days 71 to 74 of age	Slit-Lamp Examination	Abnormal sclera color	0	0	0	1
		Anterior chamber hyphema	0	0	0	1
		Anterior chamber opacity	0	0	0	1
		Corneal mass	0	0	1	0
		Corneal opacity	0	0	0	2
		Corneal vascularization	0	0	0	1
		Enlargement of eyeball	0	0	0	1
		Iris hyphema	0	0	0	1
		Iris protrude	0	0	0	1
	Funduscopic Examination		–	–	–	–
Gross Pathology [b]	Eyeball: Bulge		0	0	1	0
	Eyeball: Enlargement		0	0	0	1
	Eyeball: Opacity		0	0	1	2
Histopahology of Eyeball [b]						
No. Examined Animals			3	N.E.	1	2
Adhesion, cornea-iris		Moderate	0	N/A	0	1
		Marked	0	N/A	1	1
Adhesion, lens-iris		Moderate	0	N/A	1	2
Atrophy, retina		Slight	0	N/A	0	1
Erythrocyte/ pigmented macrophage/ fibrin, intraocular		Moderate	0	N/A	0	1
		Marked	0	N/A	1	1
Inflammation, chronic, cornea		Slight	0	N/A	0	1
		Marked	0	N/A	1	1
Inflammation, chronic, iris		Moderate	0	N/A	0	1
		Marked	0	N/A	1	1
Necrosis, lens		Slight	0	N/A	1	2
F2 Litters						
No. Litters Evaluated			16	20	19	20
Mean No. Live Embryos			11.6	11.0	10.9	12.1
Mean No. Dead Embryos			1.0	1.6	0.9	1.2

Daily Dose (mg/kg)	0 (Control)	20	200	1000
Mean % Post-implantation Loss	6.6	12.3	6.2	8.7

Abbreviations: B, For behavioral evaluations; R, For reproductive function observations.
−, No noteworthy findings.
* $P < 0.05$, ** $P < 0.01$ vs. control (Dunnett's test).
a (Number of dams with live newborns/number of pregnant dams) × 100.
b Number of animals with findings.
c Pinna detachment, incisor eruption, and eyelid opening.
d Righting reflex, negative geotaxis, pupillary reflex, Preyer reflex, and pain response.

2.6.7.15 新生児を用いた試験

2.6.7.15.1 新生児を用いた試験：重要な試験以外の試験

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses (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>Rat/
Crl:CD(SD)</td><td>Oral gavage
(0.5 w/v% MC /
Suspension)</td><td>3 weeks</td><td>0, 100, 300,
1000</td><td>10M, 10F</td><td>1000:
Swollen abdomen (Days 11 to 15 of age), Slight decrease of body weight gain (Days 10 to 13 of age), Slight increase of MCV, Decrease in Eos (females), Slight increase of T.Pro (males), Slight decrease of A/G ratio (females), Hepatocyte hypertrophy and prominent mitotic activity in liver
≥300:
Slight decrease of MCHC (females), Decrease of concentration and percentage of Eos (males), Slight decrease of A/G ratio (males), Increase of liver and spleen weights
≥100:
Slight decrease of MCHC (males), Slight increase of T.Pro (females), Increase of spleen weight (females), Extramedullary hematopoiesis in liver

Toxicokinetics (n=3, mean value)
S-033188
<table>
<tr><th rowspan="2">Dose (mg/kg)</th><th rowspan="2">Day</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 rowspan="3">100</td><td>1</td><td>0.018</td><td>0.0201</td><td>0.0294</td><td>0.0275</td></tr>
<tr><td>10</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td>20</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td rowspan="3">300</td><td>1</td><td>0.0437</td><td>0.04</td><td>0.114</td><td>0.157</td></tr>
<tr><td>10</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td>20</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td rowspan="3">1000</td><td>1</td><td>0.196</td><td>0.0922</td><td>0.478</td><td>0.275</td></tr>
<tr><td>10</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td>20</td><td>N.C.</td><td>N.C.</td><td>N.C.</td><td>N.C.</td></tr>
<tr><td colspan="6">The LLOQ of S-033188 was 0.00500 μg/mL.</td></tr>
</table></td><td>S-033188-
TF-091-R/
4.2.3.5-08</td></tr>
</table>

					S-033447						
					Dose (mg/kg)	Day	C_{max} (μg/mL)		$AUC_{0\text{-}24hr}$ (μg·hr/mL)		
							M	F	M	F	
					100	1	6.75	7.06	79.3	84.9	
						10	1.3	1.03	7.56	7.17	
						20	0.367	0.282	1.71	2.13	
					300	1	6.22	6.83	84.9	96.7	
						10	1.67	1.68	14.3	11.4	
						20	0.456	0.497	3.40	3.67	
					1000	1	8.28	7.05	91.1	76.4	
						10	1.17	1.27	17	17.6	
						20	0.475	0.705	4.13	7.05	
					The LLOQ of S-033447 was 0.00500 μg/mL.						

Abbreviations: Eos, eosinophil; MCHC, mean cell hemoglobin concentration; MCV, mean corpuscular volume.

2.6.7.15.2 新生児を用いた試験：重要な試験

2.6.7.15.2.1 Forty-Day Repeat-Dose Toxicity Study in Juvenile Rats

Test Article: S-033188

Report Title: Oral Toxicity Study of S-033188 in Juvenile Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 40 days	**Duration of Postdose:** 4 weeks	**Study No.** S-033188-TF-128-L
Initial Age: Day 10 of age	**Method of Administration:** Oral gavage		**Location in CTD:** 4.2.3.5-05
Date of First Dose: [redacted], 20[redacted]	**Vehicle/Formulation:** 0.5 w/v% MC / Suspension		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 1000 mg/kg/day			

Daily Dose (mg/kg)			**0 (Control)**		**20**		**200**		**1000**	
Toxicokinetics [a]										
No. Evaluated			**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
S-033188 [b]	**C_{max} (μg/mL)**	**Day 10 of age**	N.C.	N.C.	0.00774	0.00983	0.0284	0.0756	0.999	5.40
		Day 30 of age	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
		Day 49 of age	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**Day 10 of age**	N.C.	N.C.	N.C.	N.C.	0.154	0.450	2.08	5.65
		Day 30 of age	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
		Day 49 of age	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
S-033447 [c]	**C_{max} (μg/mL)**	**Day 10 of age**	N.C.	N.C.	2.14	2.29	7.02	7.09	8.24	9.69
		Day 30 of age	N.C.	N.C.	0.218	0.194	0.295	0.300	0.331	0.512
		Day 49 of age	N.C.	N.C.	0.109	0.104	0.295	0.382	0.248	0.282
	$AUC_{0\text{-}24hr}$ (μg·hr/mL)	**Day 10 of age**	N.C.	N.C.	26.1	27.8	87.1	103	133	147
		Day 30 of age	N.C.	N.C.	1.23	0.844	2.42	2.74	3.59	5.98
		Day 49 of age	N.C.	N.C.	0.667	0.554	2.57	2.76	2.95	3.05
Noteworthy Findings										
No. Evaluated			**M: 22**	**F: 22**	**M: 22**	**F: 22**	**M: 22**	**F: 22**	**M: 22**	**F: 22**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation [d]	**Swollen abdomen**		0	0	0	0	0	0	11	12
Body Weight (%) [e]	**Day 12 of age**		29.5 g	–	−3	–	−3†	–	−6††	–
	Day 13 of age		32.0 g	30.7 g	−3	−3	−3	0	−8††	−6†
	Day 14 of age		35.1 g	33.8 g	−3†	−4	−3†	0	−9††	−7†
	Day 15 of age		37.8 g	36.6 g	−4	−4	−2	0	−7††	−6†
	Day 16 of age		40.4 g	39.2 g	−3	−3	0	+2	−7**	−6†
	Day 17 of age		43.0 g	–	−2	–	0	–	−6**	–
	Day 18 of age		45.5 g	–	−2	–	0	–	−6**	–

Daily Dose (mg/kg)			0 (Control)		20		200		1000	
	Day 19 of age		48.5 g	–	−2	–	+1	–	−6**	–
	Day 20 of age		52.7 g	–	−2	–	+3	–	−8**	–
	Day 21 of age		57.0 g	54.3 g	−1	0	+3	+6*	−8**	−4
	Day 24 of age		71.2 g	66.9 g	0	0	+4	+6*	−5§	−3
	Day 28 of age		–	87.7 g	–	+2	–	+7**	–	0
	Day 31 of age		–	105.1 g	–	+1	–	+8*	–	+3*
	Day 35 of age		–	130.2 g	–	+2	–	+7*	–	+4*
	Day 38 of age		–	146.3 g	–	+2	–	+8**	–	+5**
	Day 42 of age		–	167.0 g	–	+2	–	+7**	–	+6**
	Day 45 of age		–	180.2 g	–	+2	–	+8**	–	+6**
	Day 49 of age		–	195.5 g	–	+3	–	+9**	–	+7**
Body Weight Gain (g/day)[a]	Day 10-14 of age		10.7	10.5	9.8	10.0	10.4	10.7	7.4**	7.8††
	Day 14-49 of age		–	161.8	–	168.8	–	178.4**	–	177.4**
Food Consumption (%)[e]	Day 24-27		–	11 g/day	–	+9	–	+9	–	+9
	Day 28-30		–	13 g/day	–	0	–	+8*	–	+8*
	Day 31-34		–	15 g/day	–	0	–	+7*	–	+7**
	Day 35-37		–	16 g/day	–	+6	–	+6*	–	+6*
	Day 38-41		–	18 g/day	–	+6	–	+6*	–	+11**
	Day 42-44		–	18 g/day	–	+6	–	+6*	–	+6*
	Day 45-48		–	18 g/day	–	0	–	+6	–	+6*
Ulna Length			–	–	–	–	–	–	–	–
Total Activity Scores (Beam Breaks)		High beam level	–	–	–	–	–	–	–	–
		Low beam level	–	–	–	–	–	–	–	–
Pre-pulse Inhibition (Auditory Startle Response)			–	–	–	–	–	–	–	–
Morris Maze			–	–	–	–	–	–	–	–
Sexual Maturation			–	–	–	–	–	–	–	–
No. Evaluated			M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Hematology[a]	RDW (%)		11.9	10.9	12.0	11.2	12.4*	11.6**	12.4*	12.3**
	PLT ($x10^9$/L)		–	1089	–	1125	–	1118	–	1212*
	APTT (sec)		15.0	–	15.5	–	16.9**	–	18.3**	–
Blood Chemistry[a]	A/G ratio		1.43	–	1.40	–	1.35	–	1.31*	–
Organ Weight (%)[f]	Thyroid + Parathyroid	Relative	0.016 g	–	−6	–	0	–	+19	–
		Adjusted	0.016 g	–	−6	–	−6	–	+19*	–
Gross Pathology			–	–	–	–	–	–	–	–

Daily Dose (mg/kg)			0 (Control)		20		200		1000	
Histopathology[d]										
Thyroid	Follicular cell hypertrophy	minimal	0	0	0	0	4	3	6	8
Postdose Evaluation-Noteworthy Findings										
No. Evaluated			M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
No. Died or Sacrificed Moribund			0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation			–	–	N/A	N/A	N/A	N/A	–	–
Body Weight (%)[c]	Day 52 of age		–	199.1 g	–	+5	–	+12**	–	+9**
	Day 56 of age		–	212.4 g	–	+4	–	+11**	–	+9**
	Day 59 of age		–	224.2 g	–	+3	–	+10**	–	+9**
	Day 63 of age		–	229.3 g	–	+4	–	+10**	–	+11**
	Day 66 of age		–	237.5 g	–	+5	–	+10**	–	+12**
	Day 70 of age		–	247.1 g	–	+5	–	+11**	–	+10**
	Day 73 of age		–	254.8 g	–	+5	–	+9*	–	+8*
	Day 77 of age		–	263.4 g	–	+5	–	+8*	–	+8*
	Day 78 of age		–	244.8 g	–	+6	–	+9**	–	+10**
Body Weight Gain (g)[a]	Day 49-78 of age		–	53.4	–	59.9	–	60.1	–	66.0*
Food Consumption (%)[c]	Day 49-51 of age		–	18 g/day	–	+6	–	+11	–	+17*
	Day 52-55 of age		–	19 g/day	–	0	–	0	–	+11*
Ulna Length			–	–	–	–	–	–	–	–
Total Activity Scores (Beam Breaks)		High beam level	–	–	–	–	–	–	–	–
		Low beam level	–	–	–	–	–	–	–	–
Pre-pulse Inhibition (Auditory Startle Response)			–	–	–	–	–	–	–	–
Hematology[a]	RDW (%)		10.9	–	11.1	–	11.0	–	11.6*	–
	APTT (sec)		–	16.4	–	15.6	–	15.8	–	14.2**
Blood Chemistry[a]	A/G ratio		1.28	1.41	1.22	1.38	1.29	1.31	1.17**	1.30*
Organ Weight			–	–	–	–	–	–	–	–
Gross Pathology			–	–	–	–	–	–	–	–
Histopathology			–	–	–	–	–	–	–	–

Abbreviation: RDW, red blood cell volume distribution width.
–, No noteworthy findings.
* $P < 0.05$, ** $P < 0.01$ vs. control (Williams' test).
† $P < 0.05$, †† $P < 0.01$ vs. control (Shirley's test).
§ $P < 0.05$ vs. control (Dunnett's test).
a Group means are shown.
b Almost all the plasma concentrations of S-033188 in the 20, 200, and 2000 mg/kg/day groups at Days 30 and 49 of age were BLQ (< 0.00500 µg/mL). S-033188 was

occasionally detected at a concentration less than or equal to 0.0192 μg/mL in juvenile rats (5 time points out of 212 time points in total).
c S-033447 is an active form of S-033188. The LLOQ of S-033447 was 0.00500 μg/mL.
d Number of animals with findings.
e For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percentage differences).
f For controls, group means (relative weights to 100 g body weights or adjusted from covariance analyses using terminal body weights) are shown. For treated groups, percent differences from relative or adjusted control are shown. Statistical significance based on actual relative or adjusted data (not on the percentage differences from absolute or relative control).

2.6.7.16 局所刺激性試験

該当する試験なし.

2.6.7.17 その他の毒性試験

2.6.7.17.1 Effect of Vitamin K on S-033188-induced PT and APTT Prolongation in Rats

Test Article: S-033188

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Rat [a]/ Crl:CD(SD)	Oral gavage (0.5 w/v% MC/ Suspension)	1 week	0 (fast/non-fast)[b], 600 (fast/non-fast)	4M	No	S-033188 has the potential to decrease the activities of vitamin K dependent coagulation factors (II, VII, IX and X) resulting in prolongation of PT and APTT. The magnitudes of the changes by S-033188 treatment were much smaller than those by fasting, and the changes disappear completely when the animals were fed with non-sterilized food and not fasted.	R-033188-TB-007-R/ 4.2.3.7-03
Rat/ Crl:CD(SD)	Oral gavage (0.5 w/v% MC/ Suspension)	2 weeks	S-033188/ Vitamin K_1: 0/0 (fast/non-fast)[c], 2000/0 (fast/non-fast), 2000/0.3 (fast)	5M	Yes	Prolongations of PT and/or APTT were observed in the 2000/0 (fast and non-fast) groups when compared to 0/0 (fast and non-fast) groups, respectively. The degree of the prolongations observed between 0/0 (non-fast) and 2000/0 (non-fast) groups were apparently slight as compared to that observed between 0/0 (fast) and 2000/0 (fast) groups. The prolongations were completely recovered by the concomitant dosing of vitamin K_1. Toxicokinetics of S-033447 (n=3, mean value):	R-033188-TB-047-L/ 4.2.3.7-01

Daily dose [d] (mg/kg)	Day	C_{max} (μg/mL)	$AUC_{0\text{-}24hr}$ (μg·hr/mL)
0/0 (Control)	1	N.C.	N.C.
	14	N.C.	N.C.
2000/0	1	0.897	10.4
	14	0.295	3.59
2000/0.3	1	0.878	10.4
	14	0.263	3.77
The LLOQ of S-033447 was 0.00500 μg/mL			

a Rats were fed with non-sterilized, autoclaved or radiation-sterilized food.
b "fast" means fasting for at least 17 hours prior to necropsy on Day 8. "non-fast" means feeding was maintained before necropsy.
c "fast" means fasting for at least 16 hours prior to necropsy on Day 15. "non-fast" means feeding was maintained before necropsy.
d S-033188/vitamin K_1.

2.6.7.17.2 Photosafety Study: In Vivo

Test Article: S-033188

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Mouse/ Hos:HR-1	Oral gavage (0.5 w/v% MC/ Suspension)	Single	0, 200, 1000	3F	No	No skin phototoxicity in the S-033188-treated groups. Toxicokinetics of S-033447 (n=3, mean value): Dose (mg/kg) / Day / C_{max} (μg/mL) / $AUC_{0\text{-}24hr}$ (μg·hr/mL) 200 / 1 / 1.21 / 8.28 1000 / 1 / 1.91 / 18.8	TOX-20[redacted]-MTS-0576188A-03/ 4.2.3.7-04
Mouse/ Hos:HR-1	Intraperitoneal (0.5 w/v% MC/ Suspension)	Single	100 (TK: 0, 1, 10, 100)	3F	No	Hairless mice well tolerated up to 100 mg/kg of a single intraperitoneal dose of S-033188. Toxicokinetics (n=3, mean value): Dose (mg/kg) / Day / C_{max} (μg/mL) S-033188 / S-033447 0 (Control) / 1 / N.C. / N.C. 1 / 1 / 0.000708 / 0.0538 10 / 1 / 0.0373 / 0.363 100 / 1 / 0.362 / 0.981 The LLOQ of S-033447 was 0.000500 μg/mL	S-033188-TB-144-R/ 4.2.3.7-05
Mouse/ Hos:HR-1	Oral gavage/ Intraperitoneal (0.5 w/v% MC/ Suspension)	Single	Oral gavage: 0, 1000 Intraperitoneal: 10, 30, 100	5F, 10F[a]	Yes	No skin phototoxicity. Toxicokinetics (n=4, mean value): Dose (mg/kg) / Route / Day / Plasma concentration[b] (μg/mL) S-033188 / S-033447 0 (Control) / Oral gavage / 1 / N.C. / N.C. 1000 / Oral gavage / 1 / N.C. / 1.29 10 / Intra-peritoneal / 1 / 0.0478 / 0.406 30 / Intra-peritoneal / 1 / 0.152 / 0.741 100 / Intra-peritoneal / 1 / 0.250 / 0.696 The LLOQ of S-033447 was 0.00500 μg/mL	S-033188-TB-149-L/ 4.2.3.7-02

Abbreviation: TK, toxicokinetics.

a 5F: The 0 mg/kg (control) groups with or without UV irradiation and the S-033188-treated groups without UV irradiation; 10F: The S-033188-treated groups with UV irradiation.

b C_{1hr} for the groups dosed by oral gavage and $C_{0.5hr}$ for the groups dosed intraperitoneally.