フェトロージャ点滴静注用 1g

第 2 部 (モジュール 2) : CTD の概要 (サマリー)

2.6 非臨床試験の概要文及び概要表

2.6.7 毒性試験概要表

塩野義製薬株式会社

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略号及び用語定義一覧表

略号	英語
2AA	2-aminoanthracene
9AA	9-aminoacridine hydrochloride
AF-2	2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide
A/G ratio	albumin/globulin ratio
Alb	albumin
AMY	amylase
APTT	activated partial thromboplastin time
ASA	active systemic anaphylaxis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}6hr}$	area under the concentration-time curve from time 0 to 6 hours postdose
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing
AUC_{all}	area under the concentration-time curve from the start of dosing to infinity after the completion of dosing
AUC_{total}	area under the concentration-time curve from the start of dosing to the last sampling time after dosing
B	for behavioral evaluations
b.i.d.	twice daily (bis in die)
BLQ	below the lower limit of quantification
BW	body weight
C_0	concentration at the completion of dosing
CK	creatine kinase
Cl	chloride
C_{max}	maximum concentration
DMSO	dimethylsulfoxide
DRF	dose range-finding
ELISA	enzyme-linked immunosorbent assay
F	female
FA	Freund’s adjuvant
Fbg	fibrinogen concentration
G	gestation day
Glob	globulin
GLP	Good Laboratory Practice
GSA	guinea pig serum albumin
HCT	hematocrit
HGB	hemoglobin concentration
IC_{50}	50% inhibitory concentration

略号	英語
K	potassium
L	lactation day
LD	lactate dehydrogenase
Lymph	lymphocyte
M	male
MF	mutant frequency
N/A	not applicable
Na	sodium
NaN_3	sodium azide
N.C.	not calculated
Neut	neutrophil
NOAEL	no observed adverse effect level
PCA	passive cutaneous anaphylaxis
PND	postnatal day
q.d.	once daily (quaque die)
QTc	corrected QT interval
R	for reproductive function observations
RBC	red blood cell count
Retic	reticulocyte
RS0	relative survival on day 0
RSG	relative suspension growth
RTG	relative total growth
S9	supernatant at 9000 g
SD	Sprague Dawley
T.Bil	total bilirubin
TG	triglyceride
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: Cefiderocol sodium drug product

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses [a] (mg/kg/day)	GLP Compliance	Testing Facility	Study Number	Location in CTD
Single-Dose Toxicity	Rat/ Sprague Dawley	Intravenous	Single day	2000 q.d., 2000 (1000 b.i.d.)	No	Shionogi & Co., Ltd.	R-649266-TB-053-R	4.2.3.1-01
DRF Repeat-Dose Toxicity	Rat/ Sprague Dawley	Intravenous	2 weeks	0, 200, 600, 2000	No	Shionogi & Co., Ltd.	[redacted]	4.2.3.2-08
	Rat/ Sprague Dawley	Intravenous	2 weeks	0, 1500 q.d., 2000 (1000 b.i.d.), 3000 (1500 b.i.d.)	No	[redacted]	S-649266-TF-124-R	4.2.3.2-09
	Monkey/ Cynomolgus	Intravenous	2 weeks	0, 100, 300, 1000	No	Shionogi & Co., Ltd.	[redacted]	4.2.3.2-10
Repeat-Dose Toxicity	Rat/ Sprague Dawley	Intravenous	2 weeks	0, 250, 500, 1000	Yes	[redacted]	R-649266-TF-021-L	4.2.3.2-01
	Rat/ Sprague Dawley	Intravenous	1 month	0, 300, 1000, 1500	Yes	[redacted]	S-649266-TF-130-L	4.2.3.2-02
	Rat/ Sprague Dawley	Intravenous	3 months	0, 300, 1000, 1500	Yes	[redacted]	S-649266-TF-182-L	4.2.3.2-03
	Rat/ Sprague Dawley	Intravenous	3 months	0, 500, 750	Yes	[redacted]	S-649266-TF-224-L	4.2.3.2-04
	Monkey/ Cynomolgus	Intravenous	2 weeks	0, 100, 300, 1000	Yes	[redacted]	R-649266-TF-022-L	4.2.3.2-05
	Monkey/ Cynomolgus	Intravenous	1 month	0, 100, 300, 600, 1000	Yes	[redacted]	S-649266-TF-121-L	4.2.3.2-06
	Monkey/ Cynomolgus	Intravenous	3 months	0, 100, 300, 1000	Yes	[redacted]	S-649266-TF-183-L	4.2.3.2-07

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
Genotoxicity	Bacteria/ *Salmonella typhimurium* and *Escherichia coli*	In vitro	N/A	0, 0.153, 0.305, 0.610, 1.22, 2.44, 4.88, 9.77, 19.5 µg/plate	Yes	Shionogi & Co., Ltd.	R-649266-TB-011-L	4.2.3.3-01
	Human lymphoblast cell	In vitro	N/A	−S9 or +S9, 4-hour treatment: 0, 1800, 3000, 5000 µg/mL, −S9, 24-hour treatment: 0, 84.0, 140, 233, 389 µg/mL	Yes	[redacted]	R-649266-TF-012-L	4.2.3.3-02
	Mouse lymphoma cell	In vitro	N/A	−S9, 3-hour treatment: 0, 156, 313, 625, 1250, 2500, 5000 µg/mL, +S9, 3-hour treatment: 0, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/mL, −S9, 24-hour treatment: 0, 100, 200, 300, 400, 500, 600, 700, 800 µg/mL	Yes	[redacted]	R-649266-TF-014-L	4.2.3.3-03
	Chinese hamster lung cell	In vitro	N/A	0, 63, 125, 250, 500 µg/mL	Yes	[redacted]	S-649266-TF-071-L	4.2.3.3-04
	Rat/ Sprague Dawley	Intravenous	2 days	0, 500, 1000, 2000	Yes	[redacted]	R-649266-TF-013-L	4.2.3.3-05
	Rat/ Sprague Dawley	Intravenous	2 days	0, 500, 1000, 1500	Yes	[redacted]	R-649266-TF-052-L	4.2.3.3-06

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 Reproductive and Developmental Toxicity	Rat/ Sprague Dawley (Pregnant)	Intravenous	G6–G17	0, 500, 1000	No	Shionogi & Co., Ltd.	R-649266-TB-006-R	4.2.3.5-06
	Mouse/CD-1 (Pregnant)	Subcutaneous	G6–G15	0, 500, 1000, 2000 (0, 250, 500, 1000 b.i.d.)	No	GlaxoSmithKline	[redacted]	4.2.3.5-08
	Juvenile Rat/ Sprague Dawley	Subcutaneous	PND7–PND13	0, 200, 600, 2000	No	[redacted]	S-649266-TF-258-R	4.2.3.5-09
		Intravenous	PND28–PND34	0, 100, 300, 600				
Reproductive and Developmental Toxicity	Rat/ Sprague Dawley	Intravenous	M: 4 weeks premating until necropsy F: 2 weeks premating until G7	0, 100, 300, 1000	Yes	[redacted]	S-649266-TF-159-L	4.2.3.5-01
	Rat/ Sprague Dawley	Intravenous	G6–G17	0, 100, 300, 1000	Yes	[redacted]	S-649266-TF-132-L	4.2.3.5-02
	Rabbit/ New Zealand White	Intravenous	G7–G19	0, 10, 50, 100, 300, 1000	No	[redacted]	[redacted]	4.2.3.5-07
	Mouse/CD-1	Subcutaneous	G6–G15	0, 500, 1000, 2000 (0, 250, 500, 1000 b.i.d.)	Yes	[redacted]	S-649266-TF-131-L	4.2.3.5-03
	Rat/ Sprague Dawley	Intravenous	G6–L20	0, 100, 300, 1000	Yes	[redacted]	S-649266-TF-190-L	4.2.3.5-04
	Juvenile Rat/ Sprague Dawley	Subcutaneous	PND7–PND27	0, 100, 300, 1000	Yes	[redacted]	S-649266-TF-274-L	4.2.3.5-05
		Intravenous	PND28–PND48	0, 100, 300, 600				

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
Antigenicity	Guinea pig/ Hartley	Immunization: Subcutaneous Challenge in ASA test: Intravenous Elicitation in PCA test: Intravenous	Five times a week for 3 weeks (without FA); challenge 31 days later, Twice a week for 3 weeks (with FA); challenge 31 days later	Immunization: 10 mg/animal (without FA), 1 mg/animal (with FA) Challenge in ASA test: 4 or 10 mg/animal Elicitation in PCA test: 1 or 10 mg/animal	Yes	Shionogi & Co., Ltd.	R-649266-TB-025-L	4.2.3.7-01
Assay for Effects of Various Factors on Solution Color	N/A	N/A	N/A	N/A	No	Shionogi & Co., Ltd.	[redacted]	4.2.3.7-03
Assays for effects on urinary test paper	N/A	N/A	N/A	N/A	No	Shionogi & Co., Ltd.	R-649266-TB-044-R	4.2.3.7-04
Bacterial Reverse Mutation Test for ICH M7	Bacteria/ *Salmonella typhimurium* and *E. coli*	In vitro	N/A	7.71 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-153-L	4.2.3.7-05
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	6.86 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-154-L	4.2.3.7-06
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	6.86 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-155-L	4.2.3.7-07
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	7.63 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-156-L	4.2.3.7-08

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
Bacterial Reverse Mutation Test for ICH M7	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-168-L	4.2.3.7-09
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-169-L	4.2.3.7-10
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-170-L	4.2.3.7-11
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-171-L	4.2.3.7-12
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-212-L	4.2.3.7-13
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-217-L	4.2.3.7-14
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-218-L	4.2.3.7-15
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-219-L	4.2.3.7-16
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	6.86 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-241-L	4.2.3.7-17
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	6.86 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-18
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	3.91 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-19

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
Bacterial Reverse Mutation Test for ICH M7	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	1.2 to 5000 µg/plate	No	[redacted]	[redacted]	4.2.3.7-20
	Bacteria/ *S. typhimurium*	In vitro	N/A	16.7 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-28
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	50 to 5000 µg/plate	No	GlaxoSmithKline	Ames-295 and Ames-332	4.2.3.7-29
	Bacteria/ *S. typhimurium*	In vitro	N/A	50 to 5000 µg/plate	Yes	[redacted]	[redacted]	4.2.3.7-30
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	150 to 5000 µg/plate (*S. typhimurium*) 15 to 5000 µg/plate (*E. coli*)	No	GlaxoSmithKline	Ames-2064	4.2.3.7-31
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	150 to 5000 µg/plate (*S. typhimurium*) 15 to 5000 µg/plate (*E. coli*)	No	GlaxoSmithKline	Ames-2065	4.2.3.7-32
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-280-L	4.2.3.7-21
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-281-L	4.2.3.7-22
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-282-L	4.2.3.7-23
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-283-L	4.2.3.7-24

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
Bacterial Reverse Mutation Test for ICH M7	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-284-L	4.2.3.7-25
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	4.88 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-285-L	4.2.3.7-26
	Bacteria/ *S. typhimurium* and *E. coli*	In vitro	N/A	78.1 to 5000 µg/plate	Yes	[redacted]	S-649266-TF-335-L	4.2.3.7-27
Phototoxicity	Rat/Long-Evans	Intravenous	3 days	0, 600, 1000	Yes	Shionogi & Co., Ltd.	S-649266-TB-214-L	4.2.3.7-02
In vitro hemolysis	Rat blood, Monkey blood	In vitro	N/A	0, 15, 25, 50 mg/mL	No	GlaxoSmithKline	[redacted]	4.2.3.7-33
	Rabbit blood	In vitro	N/A	0, 6, 30, 50 mg/mL	No	GlaxoSmithKline	[redacted]	4.2.3.7-35
	Human blood	In vitro	N/A	0, 10, 20, 40, 50 mg/mL	No	GlaxoSmithKline	[redacted]	4.2.3.7-34

ASA = active systemic anaphylaxis; b.i.d. = twice daily; DRF = dose range-finding; F = female; FA = Freund's adjuvant; G = gestation day; GLP = Good Laboratory Practice; L = lactation day; M = male; N/A = not applicable; PCA = passive cutaneous anaphylaxis; PND = postnatal day; q.d. = once daily; S9 = supernatant at 9000 g [redacted]

a As free form, unless otherwise specified, for repeat-dose toxicity, and reproductive and developmental toxicity (reproductive functions, maternal reproductive function, and embryo-fetal development), the highest NOAEL (No Observed Adverse Effect Level) is underlined.

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

Type of Study	Test System	Method of Administration	Doses [a] (mg/kg/day)	GLP Compliance	Study Number	Location in CTD
Repeat-Dose Toxicity (2-Week)	Rat	Intravenous	0, 250, 500, 1000	Yes	R-649266-TF-021-L	4.2.3.2-01
Repeat-Dose Toxicity (1-Month)	Rat	Intravenous	0, 300, 1000, 1500	Yes	S-649266-TF-130-L	4.2.3.2-02
Repeat-Dose Toxicity (3-Month)	Rat	Intravenous	0, 300, 1000, 1500	Yes	S-649266-TF-182-L	4.2.3.2-03
Repeat-Dose Toxicity (3-Month, Supplemental)	Rat	Intravenous	0, 500, 750	Yes	S-649266-TF-224-L	4.2.3.2-04
Repeat-Dose Toxicity (2-Week)	Monkey	Intravenous	0, 100, 300, 1000	Yes	R-649266-TF-022-L	4.2.3.2-05
Repeat-Dose Toxicity (1-Month)	Monkey	Intravenous	0, 100, 300, 600, 1000	Yes	S-649266-TF-121-L	4.2.3.2-06
Repeat-Dose Toxicity (3-Month)	Monkey	Intravenous	0, 100, 300, 1000	Yes	S-649266-TF-183-L	4.2.3.2-07
Embryo-Fetal Development	Rat	Intravenous	0, 100, 300, 1000	Yes	S-649266-TF-132-L	4.2.3.5-02
Embryo-Fetal Development	Mouse	Subcutaneous	0, 500, 1000, 2000 (0, 250, 500, 1000 b.i.d.)	Yes	S-649266-TF-131-L	4.2.3.5-03
Embryo-Fetal Development (Preliminary)	Rabbit	Intravenous	0, 10, 50, 100, 300, 1000	No	[redacted]	4.2.3.5-07
Repeat-Dose Toxicity (3-Week)	Juvenile Rat	Subcutaneous	0, 100, 300, 1000	Yes	S-649266-TF-274-L	4.2.3.5-05

a As free form

2.6.7.3 トキシコキネティクス：トキシコキネティクス試験成績の一覧

Test Article: Cefiderocol sodium drug product

Daily Dose [a] (mg/kg)	Steady State C_0 or C_{max} (µg/mL)						
	Mice [b]	Rats		Monkeys		Rabbits	Humans [c]
	F	M	F	M	F	F	M & F
10						27.2 [n]	
50						145 [n]	
100		149 [o], 389 [p]	249 [f], 188 [o], 321 [p]	300 [k], 295 [l],297 [m]	291 [k], 313 [l], 308 [m]	197 [n]	
120 [d]							89.7
250	366 [e]	503 [g]	450 [g]				
300		649 [h], 725 [i], 409 [o], 1150 [p]	748 [f], 669 [h], 615 [i], 468 [o], 1060 [p]	770 [k], 845 [l], 876 [m]	775 [k], 810 [l], 850 [m]	580 [n]	
500	609 [e]	972 [g], 1040 [j]	765 [g], 1030 [j]				
600		2170 [p]	2220 [p]	1610 [l]	1530 [l]		
750		1610 [j]	1500 [j]				
1000	1340 [e]	1980 [g], 2110 [h], 2220 [i], 606 [o]	2010 [f], 1700 [g], 2050 [h], 2170 [i], 605 [o]	2300 [k], 2450 [l], 2600 [m]	2360 [k], 2560 [l], 2540 [m]	1410 [n]	
1500		3110 [h], 3490 [i]	2920 [h], 3250 [i]				

Daily Dose [a] (mg/kg)	Steady State AUC (μg·hr/mL)						
	Mice	Rats		Monkeys		Rabbits	Humans [q]
	F	M	F	M	F	F	M & F
10						49.9 [A]	
50						274 [A]	
100		179 [B], 172 [C]	195 [s], 192 [B], 132 [C]	516 [x], 500 [y], 503 [z]	470 [x], 535 [y], 496 [z]	435 [A]	
120 [d]							1158.3
250		387 [t]	327 [t]				
300		505 [u], 534 [v], 552 [B], 465 [C]	601 [s], 498 [u], 490 [v], 561 [B], 375 [C]	1400 [x], 1420 [y], 1520 [z]	1310 [x], 1350 [y], 1470 [z]	1010 [A]	
500	654 [r]	705 [t], 760 [w]	534 [t], 667 [w]				
600		904 [C]	760 [C]	2850 [y]	2680 [y]		
750		998 [w]	946 [w]				
1000	1330 [r]	1360 [t], 1470 [u], 1600 [v], 839 [B]	1600 [s], 1080 [t], 1440 [u], 1380 [v], 828 [B]	4370 [x], 4630 [y], 4150 [z]	4120 [x], 4250 [y], 4110 [z]	3415 [A]	
1500		2120 [u], 2480 [v]	1920 [u], 2020 [v]				
2000	2320 [r]						

AUC = area under the concentration-time curve; C_0 = concentration at the completion of dosing; C_{max} = maximum concentration

a As free form

b Doses were divided into 2 equal daily doses of 250, 500, or 1000 mg/kg/dose, given subcutaneously approximately 6 hours apart.

c The C_{max} at the intended clinical dose regimen (2 g, infused over 3 hours, three times daily), the C_{max} value of cefiderocol in the clinical study (2 g infused over 3 hours, q.d.) [refer to CTD Section 2.7.2.3.8.1]

d Calculated from the clinical dose (6 g/man) and human body weight (assumed to be 50 kg).

e The C_{max} on Gestation Day 15 of an embryo-fetal development study in mice [Study No.: S-649266-TF-131-L]

f The C_0 on Gestation Day 17 of an embryo-fetal development study in rats [Study No.: S-649266-TF-132-L]

g The C_0 on Day 14 of a repeat-dose toxicity study (2-week) in rats [Study No.: R-649266-TF-021-L]

h The C_0 on Day 28 of a repeat-dose toxicity study (1-month) in rats [Study No.: S-649266-TF-130-L]

i The C_0 on Day 91 of a repeat-dose toxicity study (3-month) in rats [Study No.: S-649266-TF-182-L]

j The C_0 on Day 91 of a repeat-dose toxicity study (3-month, supplemental) in rats [Study No.: S-649266-TF-224-L]

k The C_0 on Day 14 of a repeat-dose toxicity study (2-week) in monkeys [Study No.: R-649266-TF-022-L]

l The C_0 on Day 28 of a repeat-dose toxicity study (1-month) in monkeys [Study No.: S-649266-TF-121-L]

m The C_0 on Day 91 of a repeat-dose toxicity study (3-month) in monkeys [Study No.: S-649266-TF-183-L]

n The C_{max} on Gestation Day 11 of a preliminary embryo-fetal development study in rabbits [Study No.: [redacted]]

o The C_{max} on PND27 of a repeat-dose toxicity study (3-week) in juvenile rats [Study No.: S-649266-TF-274-L]

p The C_0 on PND48 of a repeat-dose toxicity study (3-week) in juvenile rats [Study No.: S-649266-TF-274-L]

q The AUC from time 0 to infinity ($AUC_{0\text{-}inf}$) at the intended clinical dose regimen (2 g, infused over 3 hours, three times daily), 3-fold of the $AUC_{0\text{-}inf}$ value of cefiderocol in the clinical study (2 g infused over 3 hours, q.d.) [refer to CTD Section 2.7.2.3.8.1]

r Doubled the $AUC_{0\text{-}5hr}$ after the first dosing on Gestation Day 15 of an embryo-fetal development study in mice [Study No.: S-649266-TF-131-L].

s The AUC from the start of dosing to the last sampling time after dosing (AUC_{total}) on Gestation Day 17 of an embryo-fetal development study in rats [Study No.: S-649266-TF-132-L]

t The AUC_{total} on Day 14 of a repeat-dose toxicity study (2-week) in rats [Study No.: R-649266-TF-021-L]

u The AUC_{total} on Day 28 of a repeat-dose toxicity study (1-month) in rats [Study No.: S-649266-TF-130-L]

v The AUC_{total} on Day 91 of a repeat-dose toxicity study (3-month) in rats [Study No.: S-649266-TF-182-L]

w The AUC_{total} on Day 91 of a repeat-dose toxicity study (3-month, supplemental) in rats [Study No.: S-649266-TF-224-L]

x The AUC_{total} on Day 14 of a repeat-dose toxicity study (2-week) in monkeys [Study No.: R-649266-TF-022-L]

y The AUC_{total} on Day 28 of a repeat-dose toxicity study (1-month) in monkeys [Study No.: S-649266-TF-121-L]

z The $AUCt_{total}$ on Day 91 of a repeat-dose toxicity study (3-month) in monkeys [Study No.: S-649266-TF-183-L]

A The AUC from time 0 to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-}t}$) on Gestation Day 11 in a preliminary embryo-fetal development study in rabbits [Study No.: [redacted]]

B The AUC from time 0 to 6 hours postdose ($AUC_{0\text{-}6hr}$) on PND27 of a repeat-dose toxicity study (3-week) in juvenile rats [Study No.: S-649266-TF-274-L]

C The $AUC_{0\text{-}6hr}$ on PND48 of a repeat-dose toxicity study (3-week) in juvenile rats [Study No.: S-649266-TF-274-L]

2.6.7.4 毒性試験： 被験物質（ロット毎）一覧

Test Article: Cefiderocol sodium drug product

Lot No.	Amount/Vial	Purity (%)	Study Number	Type of Study
[redacted]	500 mg	97.4	[redacted]	Embryo-fetal development in rabbits (preliminary)
[redacted]	500 mg	96.8	R-649266-TF-022-L	Repeat-dose toxicity (2-week) in monkeys
[redacted]	50 mg	97.1	R-649266-TF-021-L	Repeat-dose toxicity (2-week) in rats
			R-649266-TF-022-L	Repeat-dose toxicity (2-week) in monkeys
[redacted]	500 mg	96.8	R-649266-TF-021-L	Repeat-dose toxicity (2-week) in rats
			R-649266-TF-022-L	Repeat-dose toxicity (2-week) in monkeys
			R-649266-TB-011-L	Gene mutation test with bacteria
			R-649266-TF-012-L	Chromosomal aberration test in cultured cells
			R-649266-TF-014-L	Gene mutation and chromosomal aberration test in cultured cells
			S-649266-TF-071-L	Gene mutation test in cultured cells
			R-649266-TF-013-L	Micronucleus test in rats
			R-649266-TF-052-L	Comet assay in rats
			R-649266-TB-025-L	Antigenicity test in guinea pigs
[redacted]	1 g [a]	97.5	S-649266-TF-121-L	Repeat-dose toxicity (1-month) in monkeys
			S-649266-TF-131-L	Embryo-fetal development in mice
			S-649266-TF-132-L	Embryo-fetal development in rats
			S-649266-TF-190-L	Pre- and postnatal development in rats
			S-649266-TB-214-L	Phototoxicity study in rats
[redacted]	1 g	97.4	S-649266-TF-130-L	Repeat-dose toxicity (1-month) in rats
			S-649266-TF-159-L	Fertility and early embryonic development in rats
[redacted]	1 g	96.1	S-649266-TF-182-L	Repeat-dose toxicity (3-month) in rats
			S-649266-TF-183-L	Repeat-dose toxicity (3-month) in monkeys
			S-649266-TF-274-L	Repeat-dose toxicity (3-week) in juvenile rats
[redacted]	1 g	96.0	S-649266-TF-183-L	Repeat-dose toxicity (3-month) in monkeys
[redacted]	1 g	96.4	S-649266-TF-224-L	Repeat-dose toxicity (3-month) in rats (supplemental)

a As S-649266 sodium drug product

Specified Impurities (%)	Lot No. [redacted]								
Related Substances									
Total	2.63	3.18	2.93	3.23	2.52	2.58	3.89	4.04	3.63
化合物A*	0.46	0.47	0.43	0.47	0.58	0.58	0.63	0.65	0.57
化合物B*	0.25	0.27	0.26	0.29	0.12	0.12	0.32	0.32	0.32
化合物C*	0.16	0.17	0.17	0.16	0.03	0.03	0.05	0.05	0.03
化合物D*	0.19	0.19	0.19	0.18	0.03	0.04	< 0.03	< 0.03	< 0.03
化合物E*	0.09	0.11	0.12	0.11	0.11	0.12	0.12	0.12	0.10

＊新薬承認情報提供時に置換

2.6.7.5 単回投与毒性試験

Test Article: Cefiderocol sodium drug product

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Doses [a] (mg/kg/day)	Gender and No. per Group	Observed Maximum Nonlethal Dose (mg/kg/day)	Approximate Lethal Dose (mg/kg/day)	Noteworthy Findings			Study Number/ Location in CTD
Rat/ Crl:CD(SD)	Intravenous administration for 30 minutes/animal (Physiological saline/Solution)	2000 q.d., 2000 (1000 b.i.d.)	8M (q.d.), 4M (b.i.d.)	2000 (1000 b.i.d.)	2000 q.d.	2000 q.d.: Death, Acute symptoms including convulsions and abnormal respiration, Chromaturia. 2000 (1000 b.i.d.): Chromaturia. Toxicokinetics [b] (Mean value of 3 surviving rats in the 2000 mg/kg q.d. group and 4 rats in the 2000 [1000 b.i.d.] mg/kg group)			R-649266-TB-053-R/ 4.2.3.1-01
						Dose (mg/kg/day)	C_0 (µg/mL) M	AUC_{total} (µg·hr/mL) M	
						2000 q.d.	3620	2720	
						2000 (1000 b.i.d.)	1660	2770	

AUC_{total} = area under the concentration-time curve from the start of dosing to the last sampling time after dosing; SD = Sprague Dawley

a As free form
b Non-validated data

2.6.7.6 反復投与毒性試験： 重要な試験以外の試験

Test Article: Cefiderocol sodium drug product or cefiderocol sodium

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>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>Intravenous administration for 2.5 or 10 minutes/animal (Physiological saline/Solution)</td><td>2 weeks</td><td>0, 200, 600, 2000</td><td>4M, 4F</td><td>600</td><td>2000:
Death, Convulsions, Abnormal respiration, Low values of RBC, HGB and HCT, High Lymph count, Low Neut count, Cecum dilatation.
≥ 600:
Spleen enlargement.
≥ 200:
Transiently low food consumption, Chromaturia (reddish brown), High urinary specific gravity, Positive reactions of occult blood, ketone body, and protein in urinary reagent strips, Development of germinal center of the spleen, High value of spleen weight.
Toxicokinetics [b] (Mean value of 3 rats)
<table>
<tr><th rowspan="2">Daily dose (mg/kg)</th><th rowspan="2">Day</th><th colspan="2">C_0 (μg/mL)</th><th colspan="2">$AUC_{0\text{-}6hr}$ (μg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">200</td><td>1</td><td>960</td><td>1070</td><td>431</td><td>382</td></tr>
<tr><td>14</td><td>1089</td><td>1064</td><td>434</td><td>309</td></tr>
<tr><td rowspan="2">600</td><td>1</td><td>2841</td><td>2842</td><td>1388</td><td>1110</td></tr>
<tr><td>14</td><td>3268</td><td>3393</td><td>1453</td><td>1169</td></tr>
<tr><td rowspan="2">2000</td><td>1</td><td>9036 [c]</td><td>7796</td><td>4282 [c]</td><td>3724</td></tr>
<tr><td>14</td><td>9414 [c]</td><td>8060</td><td>3354 [c]</td><td>3035</td></tr>
</table>
</td><td>[redacted]/ 4.2.3.2-08</td></tr>
</table>

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>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>Intravenous administration for 30 minutes/animal (Physiological saline/Solution)</td><td>2 weeks</td><td>0, 1500 (q.d.), 2000 (1000 b.i.d.) [d], 3000 (1500 b.i.d.) [d]</td><td>3M</td><td>3000 (1500 b.i.d.) [e]</td><td>3000:
Two males were euthanized because of difficulty in continuing dosing due to severe local irritation at injection site (Day 10 and Day 11).
≥ 2000:
Dark red discoloration of injection site.
2000:
One male was euthanized because of difficulty in continuing dosing due to severe local irritation at injection site (Day 10), Decreased food consumption (Day 4), High Retic ratio, Low alkaline phosphatase.
≥ 1500:
Pale red urine, Decreased food consumption (Day 1), Low total Na excretion in urine (at 1500 and 2000), Granulated substance in urinary sediment, Low Fbg (at 1500 and 2000), Cecum dilatation with hypertrophy of mucosal epithelium, Development of germinal center in the spleen, Hyaline droplet in the proximal renal tubule, Macroscopic and microscopic findings suggesting local irritation at injection site.
1500:
Low total Cl excretion in urine, Low Neut count.
Toxicokinetics [b] (Mean value of 3 rats)
<table>
<tr><th>Daily dose (mg/kg)</th><th>Day</th><th>C_0 (μg/mL)</th><th>AUC_{all} (μg·hr/mL)</th></tr>
<tr><th></th><th></th><th>M</th><th>M</th></tr>
<tr><td>1500 (q.d.)</td><td>1</td><td>N/A</td><td>N/A</td></tr>
<tr><td></td><td>7</td><td>2590</td><td>1760</td></tr>
<tr><td>2000 (1000 b.i.d.)</td><td>1</td><td>1670 [c]</td><td>2490 [c]</td></tr>
<tr><td></td><td>7</td><td>1860</td><td>2450</td></tr>
<tr><td>3000 (1500 b.i.d.)</td><td>1</td><td>2410</td><td>3510</td></tr>
<tr><td></td><td>7</td><td>2560 [c]</td><td>3300 [c]</td></tr>
</table>
</td><td>S-649266-TF-124-R/ 4.2.3.2-09</td></tr>
</table>

<table>
<tr><th>Species/ Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>NOAEL (mg/kg/ day)</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Monkey/ Cynomolgus Monkey</td><td>Intravenous administration for 20 minutes/animal (Physiological saline/Solution)</td><td>2 weeks</td><td>0, 100, 300, 1000</td><td>1M,1F</td><td>300</td><td>1000:
Prolongation of QTc, Vomiting or retching, Regeneration of the renal tubule with mononuclear cell infiltration, High value of kidney weight, High urinary ketone body and protein, Urinary occult blood, High values of serum T.Bil, CK, and TG.
≥ 100:
Hyaline droplet in the proximal renal tubule, Chromaturia.
Toxicokinetics [b] (Value of 1 monkey)
<table>
<tr><th rowspan="2">Daily dose (mg/kg)</th><th rowspan="2">Day</th><th colspan="2">C_0 (μg/mL)</th><th colspan="2">AUC_{total} (μg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">100</td><td>1</td><td>875</td><td>879</td><td>1540</td><td>846</td></tr>
<tr><td>14</td><td>775</td><td>639</td><td>1430</td><td>736</td></tr>
<tr><td rowspan="2">300</td><td>1</td><td>2260</td><td>2060</td><td>4290</td><td>3000</td></tr>
<tr><td>14</td><td>1730</td><td>1720</td><td>3630</td><td>1960</td></tr>
<tr><td rowspan="2">1000</td><td>1</td><td>7750</td><td>6260</td><td>14100</td><td>7620</td></tr>
<tr><td>14</td><td>6980</td><td>6030</td><td>9840</td><td>6550</td></tr>
</table></td><td>[redacted]/ 4.2.3.2-10</td></tr>
</table>

$AUC_{0\text{-}6hr}$ = area under the concentration-time curve from time 0 to 6 hours postdose; AUC_{all} = area under the concentration-time curve from the start of dosing to infinity after the completion of dosing; CK = creatine kinase; Cl = chloride; Fbg = fibrinogen concentration; HCT = hematocrit; HGB = hemoglobin concentration; Lymph = lymphocyte; Na = sodium; NOAEL = no observed adverse effect level; Neut = neutrophil; QTc = corrected QT interval; RBC = red blood cell count; Retic = reticulocyte; T.Bil = total bilirubin; TG = triglyceride

a As free form
b Non-validated data
c Mean value of 2 rats
d b.i.d. at 6-hour intervals
e Excluding injection site changes

2.6.7.7 反復投与毒性試験： 重要な試験

2.6.7.7.1 ラット２週間反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: Two-Week Intravenous Toxicity Study of RSC-649266 (GSK2696266) sodium Drug Product in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** R-649266-TF-021-L
Initial Age: 6 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes		**Location in CTD:** 4.2.3.2-01
Date of First Dose: Male: 23 Aug 20[redacted] Female: 24 Aug 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: Hepatic enzyme induction evaluated at termination.			
NOAEL: 1000 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**0 (Reference)**		**250**		**500**		**1000**	
Toxicokinetics [a]												
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_0 (µg/mL)**	**Day 1**	N.C.	N.C.	N.C.	N.C.	464	440	952	806	1830	1610
		Day 14	N.C.	N.C.	N.C.	N.C.	503	450	972	765	1980	1700
	AUC_{total} (µg·hr/mL)	**Day 1**	N.C.	N.C.	N.C.	N.C.	369	330	747	580	1370	1140
		Day 14	N.C.	N.C.	N.C.	N.C.	387	327	705	534	1360	1080
Noteworthy Findings												
No. Evaluated			**M: 15**	**F: 15**	**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	0	0
Clinical Observation [b]	**Chromaturia (reddish-brown)**		0	0	0	0	10	10	10	10	15	15
Body Weight			–	–	–	–	–	–	–	–	–	–
Food Consumption (%) [c]	**Day 1**		24.8 g/rat	18.4 g/rat	+2	+3	−14**	−10	−19**	−20**	−20**	−20**

Daily Dose (mg/kg, as free form)			0 (Control)		0 (Reference)		250		500		1000	
No. Evaluated			**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Ophthalmology			–	–	–	–	–	–	–	–	–	–
Urinalysis	**Day 12** [d]											
	Total Na excretion [a] **(mEq)**		1.869	1.384	1.876	1.194	1.651	1.225	1.215**	0.833**	0.720**	0.611**
	Day 14 [e]											
	No. Examined		0	5	0	5	0	5	0	5	0	5
	Granulated substance in sediment [b]		N/A	0	N/A	0	N/A	5	N/A	5	N/A	5
Hematology [a]	**Neut count (10^3/mm^3)**		1.241	0.910	1.274	0.999	0.517**	0.353*	0.441**	0.400**	0.495**	0.379**
	Neut ratio (%)		15.14	12.57	15.18	15.38	6.48**	5.37**	4.90**	5.74**	6.25**	5.94**
	Lymph ratio (%)		81.14	83.23	80.87	80.76	89.87**	90.26**	91.78**	90.69**	90.23**	90.40**
Blood Chemistry			–	–	–	–	–	–	–	–	–	–
Organ Weight			–	–	–	–	–	–	–	–	–	–
Macropathology [b]	**Cecum**	**Dilatation**	0	0	0	0	0	0	0	0	3	2
Histopathology [b]												
Cecum	**Atrophy, mucosa**	**Very slight**	0	0	0	0	0	0	5	0	9	8
Kidney	**Increase, hyaline droplet, proximal tubule**	**Very slight**	0	0	0	0	0	0	0	4	0	3
		Slight	0	0	0	0	0	0	0	0	10	7
Hepatic Drug-Metabolizing Enzyme Analysis			–	–	–	–	–	–	–	–	–	–
Postdose Evaluation- Noteworthy Findings												
No. Evaluated			**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 0**	**F: 0**	**M: 0**	**F: 0**	**M: 5**	**F: 5**
No. Died or Sacrificed Moribund			0	0	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 (%) [d]	**Day 3**		26.4 g/rat	–	0	–	N/A	N/A	N/A	N/A	+17††	–
	Day 5		27.4 g/rat	–	+1	–	N/A	N/A	N/A	N/A	+17†	–
	Day 7		28.0 g/rat	–	+4	–	N/A	N/A	N/A	N/A	+14†	–
	Day 9		27.6 g/rat	–	−3	–	N/A	N/A	N/A	N/A	+11†	–
Ophthalmology			–	–	–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis			–	–	–	–	N/A	N/A	N/A	N/A	–	–
Hematology [a]	**Neut count (10^3/mm^3)**		1.272	–	1.174	–	N/A	N/A	N/A	N/A	0.842††	–

Daily Dose (mg/kg, as free form)	0 (Control)		0 (Reference)		250		500		1000	
Blood Chemistry	−	−	−	−	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	−	−	N/A	N/A	N/A	N/A	−	−
Macropathology	−	−	−	−	N/A	N/A	N/A	N/A	−	−
Histopathology	−	−	−	−	N/A	N/A	N/A	N/A	−	−
Hepatic Drug-Metabolizing Enzyme Analysis	−	−	−	−	N/A	N/A	N/A	N/A	−	−

Day 1 = the first day of dosing; N.C. = not calculated because it was below the lower limit of quantification (BLQ < 2.00 μg/mL)
−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test or Dunnett-type test [Miller's test])
† $p < 0.05$, †† $p < 0.01$ vs control (Student's t-test or Aspin-Welch test)

a Group means are shown
b Number of animals with findings
c For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
d Data on fresh urine collected before dosing or preserved urine
e Data on fresh urine collected after the end of dosing. Only urinary sediment was examined.

2.6.7.7.2 ラット 1 ヵ月反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: One-Month Intravenous Toxicity Study of S-649266 sodium Drug Product in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-649266-TF-130-L
Initial Age: 7 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes		**Location in CTD:** 4.2.3.2-02
Date of First Dose: Male: 25 Nov 20[redacted] Female: 26 Nov 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 1500 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**300**		**1000**		**1500**	
Toxicokinetics [a]										
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_0 (μg/mL)**	**Day 1**	N.C.	N.C.	657	569	1810	1670	2740	2540
		Day 28	N.C.	N.C.	649	669	2110	2050	3110	2920
	AUC_{total} (μg·hr/mL)	**Day 1**	N.C.	N.C.	488	419	1310	1220	1950	1760
		Day 28	N.C.	N.C.	505	498	1470	1440	2120	1920
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 [b, c]	**Chromaturia (pale red)**		0	0	10	10	10	10	15	15
	Abnormalities (blackening, trauma, crust, and/or loss) at the injection site (tail)		0	0	0	0	1	1	2	4
Body Weight			–	–	–	–	–	–	–	–
Food Consumption (%) [d]	**Day 1**		25.7 g/rat	15.5 g/rat	−25**	−16**	−26**	−17**	−24**	−22**
	Day 3		24.8 g/rat	–	−11*	–	−13*	–	−14**	–
No. Evaluated			**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Ophthalmology			–	–	–	–	–	–	–	–
Urinalysis	**Day 25** [e]									
	Total Na excretion (mEq) [a]		1.727	0.917	1.613	0.803	0.956**	0.575**	0.827**	0.644*
	Total Cl excretion (mEq) [a]		2.159	–	2.193	–	2.016	–	1.662††	–
	Day 26 [f]									
	Pale red urine [b]		0	0	10‡‡	10‡‡	10‡‡	10‡‡	10‡‡	10‡‡
	Granulated substance in sediment [b]		0	0	10§§	10§§	10§§	10§§	10§§	10§§

Daily Dose (mg/kg, as free form)			0 (Control)		300		1000		1500	
Hematology [a]	HGB (g/dL)		–	14.65	–	14.02*	–	14.02*	–	13.94**
	HCT (%)		–	42.31	–	40.71*	–	40.71*	–	40.61**
	Retic ratio (%)		–	2.42	–	2.96	–	3.20	–	3.40*
	Neut count (10^3/µL)		1.591	0.967	0.777††	1.051	0.988†	0.929†	0.886†	0.482††
	Neut ratio (%)		19.48	15.09	10.95††	12.84	12.08††	12.75††	12.25†	7.77††
	Lymph ratio (%)		76.32	79.95	84.61**	81.77	84.14**	83.72††	83.80**	88.96††
Blood Chemistry [a]	T.Pro (g/dL)		5.43	5.88	5.31	5.80	5.20*	5.45††	5.25	5.45†
	Glob (g/dL)		2.53	2.36	2.37	2.28	2.34*	2.13**	2.34*	2.07**
	A/G ratio		–	1.479	–	1.529	–	1.552	–	1.629*
Organ Weight (%) [g]	Spleen	Absolute	760.4 mg	507.8 mg	−1	+8	+5	±0	+23*	+22*
		Relative	200.3 mg/ 100 g BW	226.4 mg/ 100 g BW	−1	+9	+7	+5	+22*	+20**
Macropathology [b]	Cecum	Dilatation	0	0	5	5	10	10	10	10
	Injection site (tail)	Crust, blackening, and/or loss	0	0	0	0	1	1	1	1
Histopathology [b]										
Cecum	Hypertrophy, mucosal epithelium	Very slight	0	0	3	1	9	8	9	9
Spleen	Development, germinal center	Very slight	0	0	3	4	7	7	5	6
		Slight	0	0	0	0	0	2	4	4
Kidney	Increase, hyaline droplet, proximal tubule	Very slight	0	0	9	10	7	8	1	5
		Slight	0	0	1	0	3	2	9	5
Injection site (tail) [h]	Inflammation, chronic	Very slight	0	0	0	0	1	0	0	0
		Slight	0	0	0	0	0	1	1	1
	Scab formation	Very slight	0	0	0	0	1	0	0	0
		Slight	0	0	0	0	0	1	1	1
	Thrombus		0	0	0	0	1	0	0	1
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	Individual body weight gain from Day 28 to Day R4		7 to 22 g	8 to 11 g	N/A	N/A	N/A	N/A	−8 to 21 g	−5 to 2 g
Food Consumption			–	–	N/A	N/A	N/A	N/A	–	–

Daily Dose (mg/kg, as free form)				0 (Control)		300		1000		1500	
Ophthalmology				–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis				–	–	N/A	N/A	N/A	N/A	–	–
Hematology				–	–	N/A	N/A	N/A	N/A	–	–
Blood Chemistry [a]	**T.Pro (g/dL)**			–	6.12	N/A	N/A	N/A	N/A	–	5.58[$]
	Glob (g/dL)			2.72	2.54	N/A	N/A	N/A	N/A	2.48[@]	2.26[@@]
	A/G ratio			1.056	–	N/A	N/A	N/A	N/A	1.244[@]	–
Organ Weight				–	–	N/A	N/A	N/A	N/A	–	–
Macropathology [b]	**Injection site (tail)**	**Blackening and loss**		0	−	N/A	N/A	N/A	N/A	1	−
Histopathology [b]	**Injection site (tail)**	**Inflammation, chronic**	**Slight**	0	−	N/A	N/A	N/A	N/A	1	−
		Scab formation	**Slight**	0	−	N/A	N/A	N/A	N/A	1	−

A/G ratio = albumin/globulin ratio; BW = body weight; Day R1 = the first day of recovery period; Glob = globulin; 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 (Dunnett-type test [Miller's test])
‡‡ $p < 0.01$ vs control (Fisher's exact test)
§§ $p < 0.01$vs control (Wilcoxon's rank sum test)
$ $p < 0.05$ vs control (Aspin-Welch test)
@ $p < 0.05$, @@ $p < 0.01$ vs control (Student's t-test)

a Group means are shown.
b Number of animals with findings
c In satellite animals for toxicokinetic analysis, 1 male of the 1500 mg/kg/day group showed convulsions during restraint for toxicokinetics sampling 8 minutes post-dose on Day 1 of dosing.
d For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
e Data on fresh urine collected before dosing or preserved urine
f Data on fresh urine collected after the end of dosing. Only urinary color and sediment were examined.
g 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 is calculated based on actual absolute or relative data (not on the percentage differences from absolute or relative control).
h Data of macroscopic lesions. No test article-related changes were observed at the examination site without macroscopic lesions.

2.6.7.7.3 ラット 3 ヵ月反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: Three-Month Intravenous Toxicity Study of S-649266 sodium Drug Product in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 13 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-649266-TF-182-L
Initial Age: 7 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes		**Location in CTD:** 4.2.3.2-03
Date of First Dose: Male: 01 Mar 20[redacted] Female: 02 Mar 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 300 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**300**		**1000**		**1500**	
Toxicokinetics [a]										
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_0 (μg/mL)**	**Day 1**	N.C.	N.C.	592	527	1850 [b]	1540	2730 [b]	2340 [b]
		Day 91	N.C.	N.C.	725	615	2220	2170	3490	3250
	AUC_{total} (μg·hr/mL)	**Day 1**	N.C.	N.C.	448	379	1250 [b]	1010	1920 [b]	1540 [b]
		Day 91	N.C.	N.C.	534	490	1600	1380	2480	2020
Noteworthy Findings										
No. Evaluated			**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 14**	**F: 14**	**M: 21**	**F: 21**
No. Died or Sacrificed Moribund [c]			0	0	0	0	0	1 (Day 31)	1 (Day 2)	3 (Days 49, 69, 84)
No. Animals for Which Dosing Could not be Continued due to Local Irritation at the Injection Sites			0	0	0	0	1 (Day 86)	0	2 (Days 85, 88)	2 (Days 58, 73)
Clinical Observation [c, d]	**Chromaturia (pale red)**		0	0	10	10	14	14	21	21
	Clonic convulsion		0	0	0	0	1 (Day 91)	1 (Day 31)	2 (Days 2, 53)	2 (Days 49, 69)
	Lateral position		0	0	0	0	0	1	1	2
	Abnormalities (blackening, loss, trauma, crust, and/or scar) at the injection site (tail)		0	1	0	0	9	11	19	20

Daily Dose (mg/kg, as free form)			0 (Control)		300		1000		1500	
Body Weight (%) [e]	**Week 8**		463.9 g	–	−4	–	−6	–	−6*	–
	Week 9		478.4 g	–	−4	–	−7	–	−7*	–
	Week 10		491.0 g	–	−4	–	−8*	–	−8*	–
	Week 11		501.9 g	–	−4	–	−8*	–	−8**	–
	Week 12		512.5 g	–	−4	–	−7*	–	−8*	–
	Week 13		522.7 g	–	−4	–	−8*	–	−10**	–
Food Consumption			–	–	–	–	–	–	–	–
No. Evaluated			**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Ophthalmology			–	–	–	–	–	–	–	–
Urinalysis	**Days 45, 87** [f]									
	Volume (mL) [a]	**Day 45**	–	9.40	–	6.90	–	5.50†	–	5.85
	Specific gravity [a]	**Day 45**	–	1.0548	–	1.0626	–	1.0740**	–	1.0736**
		Day 87	–	1.0489	–	1.0496	–	1.0607	–	1.0669*
	Total Na excretion (mEq)[a]	**Day 45**	–	1.396	–	1.083*	–	0.998**	–	0.978**
		Day 87	2.051	–	1.989	–	1.818	–	1.689	–
	Total K excretion (mEq)[a]	**Day 45**	–	2.164	–	1.981	–	1.573**	–	1.682*
		Day 87	2.553	–	2.351	–	2.076*	–	1.997**	–
	Total Cl excretion (mEq)[a]	**Day 45**	–	1.748	–	1.599	–	1.160**	–	1.211**
		Day 87	2.389	–	2.349	–	1.978	–	1.891*	–
	Days 46, 88 [g]									
	Pale red or red urine [d]	**Day 46**	0	0	10‡‡	10‡‡	10‡‡	10‡‡	10‡‡	10‡‡
		Day 88	0	0	10‡‡	10‡‡	10‡‡	10‡‡	9‡‡ [h]	10‡‡
	Granulated substance in sediment [d]	**Day 46**	0	0	10§§	10§§	10§§	10§§	10§§	10§§
		Day 88	0	0	10§§	10§§	10§§	10§§	9§§ [h]	10§§
Hematology [a]	**RBC (10^6/μL)**		8.311	7.378	8.506	7.109	8.071	6.894	7.565**	6.208††
	HGB (g/dL)		15.17	13.88	15.23	13.79	14.08**	13.39 [12.4, 11.8]	13.79**	12.13††
	HCT (%)		43.66	40.07	43.90	39.56	41.08**	38.73 [36.2, 34.1]	40.54**	35.48**
	Retic count (10^9/L)		161.35	183.31	165.47	189.47	200.44†	238.39†	251.72††	314.46††
	Retic ratio (%)		1.93	2.50	1.95	2.70	2.50†	3.51†	3.41††	5.29††
	Neut count (10^3/μL)		0.965	–	0.847	–	0.840	–	0.906 [3.22]	–
	Fbg (mg/dL)		204.91	159.31	208.51	152.83	206.81	158.97	196.56 [298.2]	226.49

Daily Dose (mg/kg, as free form)			0 (Control)		300		1000		1500	
Blood Chemistry [a]	**AMY (IU/L)**		1498.4	–	1361.5	–	1269.5*	–	1242.5*	–
	T.Pro (g/dL)		5.96	6.23	5.66*	6.08	5.63*	5.82*	5.35**	5.85*
	Alb (g/dL)		–	3.46	–	3.52	–	3.33	–	3.04**
	Glob (g/dL)		3.03	2.77	2.85	2.56	2.80*	2.49††	2.56**	2.81
	A/G ratio		0.967	1.250	0.993	1.377	1.013	1.339	1.097**	1.096
Organ Weight (%) [i]	**Adrenal**	**Absolute**	59.54 mg	–	+15	–	+12	–	+17	–
		Relative	11.89 mg/ 100 g BW	–	+21*	–	+21*	–	+28**	–
	Spleen	**Absolute**	768.1 mg	568.5 mg	+10	−5	+17	+20	+53††	+30†
		Relative	154.0 mg/ 100 g BW	202.6 mg/ 100 g BW	+15	+2	+25†	+27**	+65††	+41**
	Liver	**Relative**	–	2.447 g/ 100 g BW	–	+3	–	+8*	–	+16**
	Kidney	**Relative**	659.8 mg/ 100 g BW	685.1 mg/ 100 g BW	+12**	+9	+11*	+10*	+16**	+17**
	Brain	**Relative**	427.9 mg/ 100 g BW	–	+5	–	+6	–	+9*	–
Macropathology [j]	**Cecum**	**Dilatation**	0	0	8	5	9	6 (0)	10 (0)	8 (3)
	Injection site (tail)	**Black discoloration, loss, trauma, crust, and/or red focus**	0	1	0	0	4	6 (0)	9 (0)	10 (2)
	Urinary bladder	**Retention, red urine**	0	0	0	0	0	0 (0)	0 (1)	0 (0)
Histopathology [j]										
Cecum	**Hypertrophy, mucosal epithelium**	**Very slight**	0	0	3	3	3	3 (0)	1 (0)	2 (0)
Spleen	**Development, germinal center**	**Very slight**	0	0	2	5	2	4 (0)	5 (0)	5 (0)
		Slight	0	0	1	1	4	1 (1)	3 (0)	2 (0)
	Increase, extramedullary hematopoiesis	**Very slight**	2	3	2	4	5	7 (0)	4 (0)	4 (2)
		Slight	0	0	0	0	1	0 (0)	2 (1)	2 (0)
Kidney	**Increase, hyaline droplet, proximal tubule**	**Very slight**	0	0	6	10	5	10 (1)	3 (0)	6 (0)
		Slight	0	0	4	0	5	0 (0)	7 (1)	4 (3)

Daily Dose (mg/kg, as free form)			0 (Control)		300		1000		1500	
Injection site (tail)	Inflammation, chronic	Very slight	1	1	0	0	1	3 (0)	1 (0)	1 (0)
		Slight	0	1	0	0	3	4 (0)	7 (0)	8 (2)
	Necrosis	Very slight	0	1	0	0	0	0 (0)	0 (0)	0 (0)
		Slight	0	0	0	0	0	2 (0)	3 (0)	8 (0)
	Scab formation	Very slight	0	0	0	0	1	1 (0)	1 (0)	0 (2)
		Slight	0	0	0	0	3	3 (0)	6 (0)	6 (1)
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]										
Abnormalities (blackening, loss, crust, and/or scar) at the injection site (tail)		Day R1	0	0	N/A	N/A	N/A	N/A	5	5
		Day R29	0	0	N/A	N/A	N/A	N/A	3	4
Body Weight			–	–	N/A	N/A	N/A	N/A	–	–
Food Consumption			–	–	N/A	N/A	N/A	N/A	–	–
Ophthalmology			–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis			–	–	N/A	N/A	N/A	N/A	–	–
Hematology			–	–	N/A	N/A	N/A	N/A	–	–
Blood Chemistry			–	–	N/A	N/A	N/A	N/A	–	–
Organ Weight (%) [i]	Spleen	Absolute	846.4 mg	579.0 mg	N/A	N/A	N/A	N/A	+14	+26
		Relative	153.0 mg/ 100 g BW	189.0 mg/ 100 g BW	N/A	N/A	N/A	N/A	+26[@]	+33
	Kidney	Absolute	3264.2 mg	–	N/A	N/A	N/A	N/A	+12	–
		Relative	589.6 mg/ 100 g BW	681.4 mg/ 100 g BW	N/A	N/A	N/A	N/A	+25[$$]	+11
Macropathology [d]	Cecum	Dilatation	0	0	N/A	N/A	N/A	N/A	0	2
	Injection site (tail)	Black discoloration, loss, and/or red focus	0	0	N/A	N/A	N/A	N/A	3	4

Daily Dose (mg/kg, as free form)			0 (Control)		300		1000		1500	
Histopathology [d]										
Cecum	**Hypertrophy, mucosal epithelium**	**Very slight**	0	0	N/A	N/A	N/A	N/A	1	1
Kidney	**Increase, hyaline droplet, proximal tubule**	**Very slight**	0	0	N/A	N/A	N/A	N/A	3	5
Injection site (tail)	**Inflammation, chronic**	**Very slight**	0	0	N/A	N/A	N/A	N/A	1	0
		Slight	0	0	N/A	N/A	N/A	N/A	3	4
	Necrosis	**Very slight**	0	0	N/A	N/A	N/A	N/A	0	1
		Slight	0	0	N/A	N/A	N/A	N/A	2	2
	Scab formation	**Very slight**	0	0	N/A	N/A	N/A	N/A	0	1
		Slight	0	0	N/A	N/A	N/A	N/A	1	2

Alb = albumin; AMY = amylase; K = potassium
−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)
† $p < 0.05$, †† $p < 0.01$ vs control (Dunnett-type test [Miller's test])
‡‡ $p < 0.01$ vs control (Fisher's exact test)
§§ $p < 0.01$ vs control (Wilcoxon's rank sum test)
@ $p < 0.05$ vs control (Student's t-test)
$$ $p < 0.01$ vs control (Aspin-Welch test)

a Group means are shown (bracket shows individual data).
b 3 animals/group/time point at 30 minutes after the completion of dosing
c In satellite animals for toxicokinetic analysis, clonic convulsions and subsequent death or moribundity were observed in males and females of the 1000 and 1500 mg/kg/day groups.
d Number of animals with findings
e For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
f Data on fresh urine collected before dosing or preserved urine
g Data on fresh urine collected after the end of dosing. Only urinary color and sediment were examined.
h N = 9
i 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 is calculated based on actual absolute or relative data (not on the percentage differences from absolute or relative control).
j Number of animals with findings. Parenthesis shows data of animals that died.

2.6.7.7.4 ラット 3 ヵ月反復静脈内投与毒性試験 (補遺)

Test Article: Cefiderocol sodium drug product

Report Title: Supplemental Three-Month Intravenous Toxicity Study of S-649266 sodium Drug Product in Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 13 weeks	**Duration of Postdose:** None	**Study No.** S-649266-TF-224-L
Initial Age: 7 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes		**Location in CTD:** 4.2.3.2-04
Date of First Dose: Male: 21 Jul 20[redacted] Female: 22 Jul 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
No Observed Effect Level for Convulsion: 750 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**500**		**750**	
Toxicokinetics [a]								
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_0 (μg/mL)**	**Day 1**	N.C.	N.C.	974	860	1280	1380
		Day 91	N.C.	N.C.	1040	1030	1610	1500
	AUC_{total} (μg·hr/mL)	**Day 1**	N.C.	N.C.	708	540	868	864
		Day 91	N.C.	N.C.	760	667	998	946
Noteworthy Findings								
No. Evaluated			**M: 10**	**F: 10**	**M: 14**	**F: 14**	**M: 14**	**F: 14**
No. Died or Sacrificed Moribund			0	0	0	0	0	0
Clinical Observation [b]	**Chromaturia (pale red)**		0	0	14	14	14	14
	Abnormalities (blackening, loss, trauma, crust, and/or scar) at the injection site (tail)		0	0	1	0	1	3
Body Weight			–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–

–, No noteworthy findings

a Group means are shown.
b Number of animals with findings

2.6.7.7.5 サル２週間反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: Two-Week Intravenous Toxicity Study of RSC-649266 (GSK2696266) Sodium Drug Product in Monkeys			
Species/Strain: Monkey/Cynomolgus monkey	**Duration of Dosing:** 2 weeks	**Duration of Postdose:** 2 weeks	**Study No.** R-649266-TF-022-L
Initial Age: 3 to 5 Years	**Method of Administration/Dosing Duration:** Intravenous/1 hour		**Location in CTD:** 4.2.3.2-05
Date of First Dose: Male: 23 Aug 20[redacted] Female: 30 Aug 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: Hepatic enzyme induction evaluated at termination.			
NOAEL: 300 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**0 (Reference)**		**100**		**300**		**1000**	
Toxicokinetics [a]												
No. Evaluated			**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Cefiderocol	**C_0 (µg/mL)**	**Day 1**	N.C.	N.C.	N.C.	N.C.	303	263	914	786	2810	2630
		Day 14	N.C.	N.C.	N.C.	N.C.	300	291	770	775	2300	2360
	AUC_{total} (µg·hr/mL)	**Day 1**	N.C.	N.C.	N.C.	N.C.	548	483	1700	1380	5980	4780
		Day 14	N.C.	N.C.	N.C.	N.C.	516	470	1400	1310	4370	4120
Noteworthy Findings												
No. Evaluated			**M: 5**	**F: 5**	**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	0	0
Clinical Observation [b]	**Chromaturia (pale red)**		0	0	0	0	2	3	3	3	5	5
	Vomiting		0	0	0	0	0	0	0	0	3	1
Body Weight			–	–	–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–	–	–
Ophthalmology			–	–	–	–	–	–	–	–	–	–
Urinalysis [b]	**Day 13** [c]											
	Occult blood		0	0	0	0	0	0	0	0	0	1
	Day 14 [d]		–	–	–	–	–	–	–	–	–	–
Electrocardiography [a]	**QTc**	**Day −18**	337.4	336.6							341.6 327 (34)	331.8 348 (39)
		Day −5	341.6	336.8							330.4 334 (34)	326.2 338 (39)
		Day 11	342.8	332.0	–	–	–	–	–	–	359.4 376 (34)	352.0 388 (39)

Daily Dose (mg/kg, as free form)			0 (Control)		0 (Reference)		100		300		1000	
Hematology [a]	**RBC (10^6/μL)**	**Day −18**	5.316	5.094							5.832 5.58 (33) 5.49 (35)	5.438 5.41 (39) 5.54 (42)
		Day −6	4.904	4.950							5.310 5.03 (33) 4.96 (35)	5.202 4.96 (39) 5.38 (42)
		Day 7	4.752	4.800	–	–	–	–	–	–	4.890 4.60 (33) 4.38 (35)	4.682 4.43 (39) 4.50 (42)
		Day 14	4.840	4.772	–	–	–	–	–	–	4.664 4.32 (33) 4.29 (35)	4.682 4.21 (39) 4.48 (42)
	HCT (%)	**Day −18**	42.34	41.32							45.72 43.6 (33) 41.5 (35)	43.82 43.9 (39) 42.4 (42)
		Day −6	38.78	40.68							41.36 39.5 (33) 38.4 (35)	41.98 39.5 (39) 41.5 (42)
		Day 7	38.60	39.82	–	–	–	–	–	–	38.62 36.8 (33) 34.3 (35)	37.82 35.8 (39) 34.5 (42)
		Day 14	39.30	39.48	–	–	–	–	–	–	36.86 35.2 (33) 33.8 (35)	38.10 34.8 (39) 34.7 (42)
	HGB (g/dL)	**Day −18**	13.38	13.08							14.34 14.0 (33) 13.6 (35)	13.50 12.9 (39) 13.5 (42)
		Day −6	12.50	12.62							13.16 12.9 (33) 12.4 (35)	12.94 12.0 (39) 13.0 (42)
		Day 7	11.82	11.96	–	–	–	–	–	–	11.72 11.3 (33) 10.6 (35)	11.18 10.2 (39) 10.2 (42)
		Day 14	11.96	12.02	–	–	–	–	–	–	11.10 10.5 (33) 10.4 (35)	11.28 10.0 (39) 10.4 (42)

Daily Dose (mg/kg, as free form)			0 (Control)		0 (Reference)		100		300		1000	
Blood Chemistry [a]	**AST (IU/L)**	**Day −18**	37.6						34.7 31 (28)		31.2 32 (33) 37 (36) 28 (37)	
		Day −6	40.8						41.7 50 (28)		59.2 60 (33) 88 (36) 49 (37)	
		Day 7	35.4	–	47.8	–	40.0	–	65.0 111 (28)	–	103.8** 156 (33) 137 (36) 82 (37)	–
		Day 14	34.4	–	43.2	–	37.7	–	73.3 119 (28)	–	91.6** 105 (33) 106 (36) 111 (37)	–
	TG (mg/dL)	**Day −18**		29.6								37.4 54 (40) 65 (41)
		Day −6		28.0								36.6 40 (40) 52 (41)
		Day 7	–	40.2	–	–	–	–	–	–	–	56.4 75 (40) 102 (41)
		Day 14	–	36.6	–	50.2	–	52.7	–	44.3	–	76.8* 99 (40) 110 (41)
No. Evaluated			**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
Organ Weight (%) [c]	**Kidney**	**Absolute, total**	11.93 g	–	+9	–	+13*	–	+23**	–	+29**	–
Macropathology			–	–	–	–	–	–	–	–	–	–
Histopathology [b]												
Injection site	**Thrombus**		0	0	0	0	0	0	0	0	2	1
Kidney	**Hyaline droplet, proximal tubule**	**Very slight**	0	0	0	0	1	3	3	3	0	0
		Slight	0	0	0	0	0	0	0	0	3	3
Hepatic Drug-Metabolizing Enzyme Analysis			–	–	–	–	–	–	–	–	–	–

Daily Dose (mg/kg, as free form)	0 (Control)		0 (Reference)		100		300		1000	
Postdose Evaluation- Noteworthy Findings										
No. Evaluated	**M: 2**	**F: 2**	**M: 2**	**F: 2**	**M: 0**	**F: 0**	**M: 0**	**F: 0**	**M: 2**	**F: 2**
No. Died or Sacrificed Moribund	0	0	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	–	–
Ophthalmology	–	–	–	–	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	−	−	–	–	N/A	N/A	N/A	N/A	−	−
Organ Weight	−	−	–	–	N/A	N/A	N/A	N/A	−	−
Macropathology	−	−	–	–	N/A	N/A	N/A	N/A	−	−
Histopathology	−	−	–	–	N/A	N/A	N/A	N/A	−	−

AST = aspartate aminotransferase
−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test or Dunnett-type test [Miller's test])

a Group means are shown. Numeral in parenthesis represents animal number with the finding, and values with animal numbers are individual values.
b Number of animals with findings
c Data on fresh urine before dosing or preserved urine
d Data on fresh urine after the end of dosing. Only urinary sediment was examined.
e For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).

2.6.7.7.6 サル１ヵ月反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: One-Month Intravenous Toxicity Study of S-649266 sodium Drug Product in Monkeys			
Species/Strain: Monkey/Cynomolgus Monkey	**Duration of Dosing:** 4 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-649266-TF-121-L
Initial Age: 3 to 5 Years	**Method of Administration/Dosing Duration:** Intravenous/1 hour		**Location in CTD:** 4.2.3.2-06
Date of First Dose: Male: 19 Nov 20[redacted] Female: 26 Nov 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 300 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**600**		**1000**	
Toxicokinetics [a]												
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Cefiderocol	**C_0 (μg/mL)**	**Day 1**	N.C.	N.C.	337	374	867	962	1800	1720	2810	2940
		Day 14	N.C.	N.C.	297	323	895	769	1710	1670	2550	2610
		Day 28	N.C.	N.C.	295	313	845	810	1610	1530	2450	2560
	AUC_{total} (μg·hr/mL)	**Day 1**	N.C.	N.C.	580	593	1750	1750	3750	3210	6130	5410
		Day 14	N.C.	N.C.	502	526	1580	1280	3150	2620	4730	4080
		Day 28	N.C.	N.C.	500	535	1420	1350	2850	2680	4630	4250
Noteworthy Findings												
No. Evaluated			**M: 5**	**F: 5**	**M: 3**	**F: 3**	**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	0	0
Clinical Observation [b]	**Chromaturia (pale red)**		0	0	3	3	3	3	3	3	5	5
	Vomiting		0	0	0	0	0	0	0	1	4	2
	Diarrhea		0	0	0	0	0	0	0	0	1	0
	Soft stool		0	0	0	0	0	0	2	1	3	2
Body Weight			–	–	–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–	–	–
Ophthalmology			–	–	–	–	–	–	–	–	–	–

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		600		1000	
Urinalysis	**Day 26** [c]											
	Pale red urine [b]		0	0	0	0	0	0	1	0	1	0
	Protein (mg/dL) [a]	**Day −7**	0.92	4.62					3.07 4.7 (23) 3.7 (24)		2.40 1.3 (31)	5.30 0.3 (34)
		Day 26	1.34	2.04	–	–	–	–	17.00 28.8 (23) 21.5 (24)	–	7.96 22.8 (31)	16.28 65.7 (34)
Urinalysis	**Day 27** [d]											
	Pale red or red urine [b]		0	0	1	3	3	3	3	3	5	5
Electrocardiography [a]	**QTc**	**Day −12**	333.2	350.8					328.0 328 (25)	343.0 340 (26)		338.0 330 (35) 340 (36) 346 (37)
		Day –4	337.2	363.0					318.3 319 (25)	355.7 366 (26)		353.6 358 (35) 358 (36) 348 (37)
		Day 24	346.8	365.8	–	–	–	–	351.3 361 (25)	374.3 397 (26)	–	371.8 382 (35) 384 (36) 380 (37)
Hematology [a]	**RBC (10^6/μL)**	**Day −14**		5.512								5.784 5.99 (34) 5.84 (35) 6.09 (37)
		Day −6		5.278								5.552 5.85 (34) 5.71 (35) 5.73 (37)
		Day 14	–	5.078	–	–	–	–	–	–	–	4.894 4.60 (35) 4.80 (37)
		Day 28	–	5.150	–	–	–	–	–	–	–	4.482 2.72 (34) 4.89 (35) 4.83 (37)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		600		1000	
Hematology [a]	**HGB (g/dL)**	**Day −14**		13.04								13.70 13.0 (34) 14.6 (35) 14.4 (37)
		Day −6		12.46								13.16 12.6 (34) 14.4 (35) 13.5 (37)
		Day 14	–	11.92	–	–	–	–	–	–	–	11.28 11.1 (35) 11.0 (37)
		Day 28	–	12.06	–	–	–	–	–	–	–	10.54 5.5 (34) 11.7 (35) 11.4 (37)
	HCT (%)	**Day −14**		42.52								44.74 42.7 (34) 47.6 (35) 47.5 (37)
		Day −6		40.28								42.20 41.7 (34) 46.1 (35) 42.4 (37)
		Day 14	–	38.76	–	–	–	–	–	–	–	37.24 37.4 (35) 36.0 (37)
		Day 28	–	40.06	–	–	–	–	–	–	–	35.02 18.1 (34) 39.2 (35) 37.7 (37)
	Retic ratio (%)	**Day −14**		0.86								1.18 1.2 (34)
		Day −6		1.02								1.14 1.6 (34)
		Day 14	–	1.54	–	1.63	–	2.17	–	2.40	–	3.74[†]
		Day 28	–	1.64	–	–	–	–	–	–	–	2.12 0.4 (34)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		600		1000	
Hematology [a]	**Platelet count (10^3/μL)**	**Day −14**		398.2								446.6 538 (34)
		Day −6		450.0								455.8 496 (34)
		Day 14	–	485.8	–	–	–	–	–	–	–	–
		Day 28	–	454.2	–	–	–	–	–	–	–	395.4 103 (34)
Blood Chemistry			–	–	–	–	–	–	–	–	–	–
No. Evaluated			**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
Organ Weight (%) [c]	**Kidney**	**Absolute**	–	13.93 g	–	−9	–	+8	–	+4	–	+25**
		Relative	–	4.517 g/ 1 kg BW	–	−10	–	+6	–	+6	–	+20**
Macropathology			–	–	–	–	–	–	–	–	–	–
Histopathology[b]												
Kidney	**Hyaline droplet, proximal tubule**	**Very slight**	0	0	3	3	3	3	2	1	0	0
		Slight	0	0	0	0	0	0	1	2	3	3
Postdose Evaluation - Noteworthy Findings												
No. Evaluated			**M: 2**	**F: 2**	**M: 0**	**F: 0**	**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	N/A	N/A	0	0
Clinical Observation[f]	**Pale oral mucosa**		0	0	NA	NA	NA	NA	NA	NA	0	1 (34)
Body Weight			–	–	N/A	N/A	N/A	N/A	N/A	N/A	–	–
Food Consumption			–	–	N/A	N/A	N/A	N/A	N/A	N/A	–	–
Ophthalmology			–	–	N/A	N/A	N/A	N/A	N/A	N/A	–	–
Electrocardiography			–	–	N/A	N/A	N/A	N/A	N/A	N/A	–	–
Urinalysis			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−
Hematology			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−
Blood Chemistry			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−
Organ Weight			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−
Macropathology			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−
Histopathology			−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−

−, No noteworthy findings

† $p < 0.05$ vs control (Dunnett type test [Miller's test])

** $p < 0.01$ vs control (Dunnett's test)

a Group means are shown. Numeral in parenthesis represents animal number with the finding, and values with animal numbers are individual values.

b Number of animals with findings

c Data on fresh urine collected before dosing or preserved urine

d Data on fresh urine collected after the end of dosing. Only urinary color and sediment were examined.
e For controls, group means (absolute weights or relative weights to 1 kg body weights) are shown. For treated groups, percent differences from absolute or relative control are shown. Statistical significance is calculated based on actual absolute or relative data (not on the percentage differences from absolute or relative control).
f Number of animals with findings. Numeral in parenthesis represents animal number with the finding.

2.6.7.7.7 サル３ヵ月反復静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: Three-Month Intravenous Toxicity Study of S-649266 sodium Drug Product in Monkeys			
Species/Strain: Monkey/Cynomolgus Monkey	**Duration of Dosing:** 13 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-649266-TF-183-L
Initial Age: 3 to 5 Years	**Method of Administration/Dosing Duration:** Intravenous/1 hour		**Location in CTD:** 4.2.3.2-07
Date of First Dose: Male: 31 Mar 20[redacted] Female: 07 Apr 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
NOAEL: 100 mg/kg/day			

Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**1000**	
Toxicokinetics [a]										
No. Evaluated			**M: 7**	**F: 7**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 7**	**F: 7**
Cefiderocol	**C_0 (μg/mL)**	**Day 1**	N.C.	N.C.	299	300	947	943	2830	2760
		Day 42	N.C.	N.C.	310	323	882	812	2510	2530
		Day 91	N.C.	N.C.	297	308	876	850	2600	2540 [b]
	AUC_{total} (μg·hr/mL)	**Day 1**	N.C.	N.C.	519	522	1940	1790	5560	5650
		Day 42	N.C.	N.C.	527	499	1680	1460	4180	4290
		Day 91	N.C.	N.C.	503	496	1520	1470	4150	4110 [b]
Noteworthy Findings										
No. Evaluated			**M: 7**	**F: 7**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 7**	**F: 7** [c]
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation [d]	**Vomiting**		0	0	0	0	0	0	5	4
	Chromaturia (pale red or dark red)		0	0	4	4	4	4	7	7
	Excoriation on the tail (one of the injection sites)		0	0	0	0	0	0	0	1 (42)
Body Weight (kg) [a]	**Day −1**		3.407						3.513 5.25 (32)	
	Day 56		3.681	–	–	–	–	–	3.607 4.60 (32)	–
	Day 63		3.739	–	–	–	–	–	3.666 4.53 (32)	–
	Day 70		3.777	–	–	–	–	–	3.636 4.44 (32)	–
	Day 77 [b]		3.810	–	–	–	–	–	3.736 4.57 (32)	–

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Food Consumption			–	–	–	–	–	–	–	–
Ophthalmology			–	–	–	–	–	–	–	–
Urinalysis	**Days 40, 89[e]**									
	Protein (mg/dL) [a]	**Day −9**	1.06						0.91 2.7 (32)	
		Day 40	0.43	–	0.80	–	1.15	–	3.56† 14.8 (32)	–
	Total Na excretion (mEq) [a]	**Day −9**	2.981	3.104	2.960		3.150		3.821 6.60 (37)	2.931 5.21 (39)
		Day 89	6.886	7.091	9.153		11.750		13.261* 24.00 (37)	11.495 [b] 20.42 (39)
	Total K excretion (mEq) [a]	**Day −9**	7.806						8.157 9.59 (31) 5.76 (36)	
		Day 40	9.784	–	10.558	–	4.633	–	2.191** 0.85 (31) 0.66 (36)	–
	Total Cl excretion (mEq) [a]	**Day −9**	5.954	4.799					6.584 9.65 (37)	4.539 5.83 (39)
		Day 89	11.379	10.064	–	–	–	–	13.551 24.60 (37)	12.397 [b] 19.43 (39)
	Days 39, 88[f]									
	Abnormal urine color (red, pale red, or pale blackish red, orange, or pale orange)[d]	**Day −9**	0	0	0	0	0	0	0	0
		Day 39	0	0	0	0	3‡	4‡	7‡‡	7‡‡
		Day 88	0	0	0	0	4‡‡	4‡‡	7‡‡	6‡‡ [b]
	Granulated substance in sediment [d]	**Day 88**	0	0	0	0	0	0	1	0 [b]
Electrocardiography [a]	**QT (msec)**	**Day −16**	176.7	173.9	163.5	180.3	174.5	176.0	181.4	173.4
		Day −8	191.0	190.4	168.8	180.3	187.5	185.3	185.1	180.6
		Day 49	–	191.9	–	185.5	–	212.0	–	220.6†
		Day 85	191.4	–	181.0	–	193.5	–	231.6†	–

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Electrocardiography [a]	**QT_c**	**Day −16**	329.4	332.3	324.8	338.8	334.0	339.3	341.9 338 (32) 323 (33) 341 (34) 368 (35) 342 (36) 341 (37)	338.7 342 (39) 321 (40) 333 (43) 335 (44)
		Day −8	331.4	339.0	328.5	339.3	339.5	336.3	343.9 316 (32) 329 (33) 346 (34) 377 (35) 358 (36) 338 (37)	334.1 323 (39) 329 (40) 329 (43) 331 (44)
		Day 49	337.3	344.4	336.3	339.0	344.0	350.5	376.6** 387 (33) 429 (35) 388 (36) 375 (37)	371.7* 369 (39) 377 (40) 371 (43) 410 (44)
		Day 85	331.4	347.7	337.0	340.8	348.8	351.8	372.9** 383 (32) 383 (33) 384 (34)	374.5* [b] 368 (40) 423 (44)
Hematology [a]	**RBC (10^6/μL)**	**Day −16**	5.503	5.351	5.398	5.228	5.615 5.11 (25)	5.200 4.97 (28)	5.419 5.47 (33) 5.90 (34) 5.33 (35) 5.31 (37)	5.477 5.27 (40) 5.33 (42) 5.76 (43) 5.61 (44)
		Day −8	5.271	5.143	5.225	5.045	5.423 5.02 (25)	4.993 5.01 (28)	5.273 5.49 (33) 5.59 (34) 5.15 (35) 5.21 (37)	5.301 5.33 (40) 5.33 (42) 5.64 (43) 5.29 (44)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Hematology [a]	**RBC (10^6/µL)**	**Day 41**	5.490	5.367	5.238	–	5.225	4.665 3.52 (28)	4.710** 4.64 (33) 4.43 (35) 3.97 (37)	5.017 4.42 (43)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4.64 (42)
		Day 90	5.466	5.431	5.180	5.070	5.138 4.46 (25)	4.810 3.60 (28)	4.841* 4.12 (34)	4.830†[b] 4.49 (40) 4.56 (43) 4.71 (44)
	HGB (g/dL)	**Day −16**	13.31	12.63	13.70	12.68	13.40 12.5 (25)	12.80 12.2 (28)	13.39 13.8 (33) 12.9 (34) 13.3 (35) 13.6 (37)	12.84 12.8 (40) 12.9 (42) 13.2 (43) 13.7 (44)
		Day −8	12.66	12.13	12.95	12.28	12.88 12.5 (25)	12.38 12.5 (28)	12.73 13.4 (33) 12.0 (34) 12.6 (35) 13.2 (37)	12.41 12.9 (40) 12.9 (42) 12.9 (43) 12.8 (44)
		Day 41	13.10	12.79	13.05	–	12.55	11.60 9.3 (28)	11.30** 11.4 (33) 10.5 (35) 10.3 (37)	11.60 10.2 (43)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	11.1 (42)
		Day 90	13.19	12.99	13.35	12.65	12.50 11.1 (25)	12.00 9.8 (28)	11.83* 9.6 (34)	11.33†[b] 10.7 (40) 11.0 (43) 11.6 (44)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Hematology [a]	**HCT (%)**	**Day −16**	42.80	39.99	44.10	40.78	42.08 39.3 (25) 40.9 (26)	41.45 38.5 (28)	41.79 41.4 (32) 41.6 (33) 40.7 (34) 40.8 (35) 43.9 (37)	42.14 41.0 (39) 41.0 (40) 41.2 (42) 43.6 (43) 44.9 (44)
		Day −8	39.86	38.54	41.28	39.63	40.10 39.2 (25) 40.2 (26)	39.68 39.4 (28)	39.83 40.0 (32) 40.9 (33) 38.2 (34) 39.3 (35) 42.3 (37)	40.57 38.6 (39) 41.0 (40) 41.7 (42) 42.9 (43) 40.9 (44)
		Day 41	40.69	39.99	40.50		37.63 35.2 (26)	35.83 26.5 (28)	34.37** 35.6 (32) 35.2 (33) 32.2 (35) 29.9 (37)	37.74 34.5 (40) 33.1 (43)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	36.2 (42)
		Day 90	40.57	39.83	40.55	38.75	37.20 32.6 (25) 35.6 (26)	36.63 29.4 (28)	35.73* 29.9 (34) 33.4 (35) 35.7 (37)	35.70†[b] 34.4 (39) 32.6 (40) 33.4 (43) 36.5 (44)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Hematology [a]	**Retic ratio (%)**	**Day −16**	1.37	1.17	1.08	1.00	1.38 1.2 (25) 1.8 (26)	1.05 1.0 (28)	1.64 2.2 (33) 0.8 (34) 2.1 (35) 1.7 (37)	1.26 1.4 (40) 1.6 (43) 1.3 (44)
		Day −8	1.44	1.64	1.28	1.75	1.13 1.1 (25) 1.4 (26)	1.88 1.3 (28)	1.50 1.7 (33) 1.1 (34) 1.9 (35) 1.6 (37)	1.97 1.2 (40) 2.1 (43) 2.6 (44)
		Day 41	0.99	1.31	1.33	1.15	1.55	4.15 11.0 (28)	2.99† 3.4 (33) 3.9 (35) 8.2 (37)	2.77† 6.6 (43)
		Day 90	0.89	0.64	1.10	0.90	1.90 2.6 (25) 3.1 (26)	2.45 6.7 (28)	3.33†† 10.4 (34) 3.7 (35)	2.73†† [b] 3.3 (40) 3.2 (43) 5.7 (44)
	Retic count (10^9/L)	**Day −16**	74.97	62.83	56.83	52.28	78.98 63.6 (25) 104.6 (26)	54.98 47.8 (28)	88.04 118.8 (33) 46.8 (34) 110.9 (35) 90.3 (37)	69.56 74.9 (40) 94.5 (43) 73.0 (44)
		Day −8	77.01	84.59	65.93	87.08	62.13 56.0 (25) 81.1 (26)	92.88 63.9 (28)	79.06 93.2 (33) 62.3 (34) 96.1 (35) 83.4 (37)	104.43 64.1 (40) 120.8 (43) 135.2 (44)
		Day 41	54.27	69.74	–	60.38	–	167.88 385.6 (28)	131.59 158.0 (33) 170.7 (35) 324.5 (37)	134.73† 290.1 (43)
		Day 90	47.04	34.99	57.35	45.78	94.55 117.7 (25) 161.4 (26)	100.83 242.7 (28)	151.81†† 427.9 (34) 177.6 (35)	129.10†† [b] 149.5 (40) 144.2 (43) 270.7 (44)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Hematology [a]	**Neut count (10^3/μL)**	**Day −16**		4.220						3.710 6.45 (42)
		Day −8		3.413						3.887 5.08 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13.00 (42)
	Neut ratio (%)	**Day −16**		37.19						36.91 42.2 (42)
		Day −8		38.47						42.79 37.5 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	70.8 (42)
	APTT (s)	**Day −16**		20.16						19.97 17.9 (42)
		Day −8		20.14						20.37 18.2 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	24.6 (42)
	Fbg (mg/dL)	**Day −16**		168.61						170.23 158.6 (42)
		Day −8		176.06						170.57 145.8 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	361.2 (42)
Blood Chemistry [a]	**AST (IU/L)**	**Day −16**	27.3	32.9		32.0		30.8	28.0 29 (32)	36.1 31 (40) 55 (42) 42 (43)
		Day −8	32.9	30.1		28.5		29.3	32.7 33 (32)	34.9 30 (40) 33 (42) 40 (43)
		Day 41	–	36.3	–	37.3	–	39.5	–	82.3[††] 121 (40) 129 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	130 (42)
		Day 90	32.0	28.6	–	42.0	–	33.8	48.3 105 (32)	73.2[†† b] 97 (40) 113 (43)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Blood Chemistry [a]	**LD (IU/L)**	**Day −16**		391.3						348.0 394 (42)
		Day −8		352.0						391.1 376 (42)
		Day 76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	954 (42)
	CK (IU/L)	**Day −16**		533.0				182.3 185 (28)		177.4 160 (43)
		Day −8		220.4				175.3 233 (28)		252.0 179 (43)
		Day 41	–	262.1	–	–	–	792.3 2693 (28)	–	–
		Day 90	–	137.1	–	–	–	1487.3 5318 (28)	–	700.5 [b] 2203 (43)
	TG (mg/dL)	**Day −16**	28.7	43.0	43.8	48.8	23.5 29 (24)	66.0	31.3 27 (31)	46.3 35 (38) 67 (39) 42 (41) 57 (44)
		Day −8	22.6	33.6	33.8*	57.5	22.8 27 (24)	50.0	27.7 41 (31)	31.0 27 (38) 35 (39) 36 (41) 42 (44)
		Day 41	–	36.0	–	55.5	–	65.5	–	117.0†† 107 (38) 177 (39) 137 (41) 183 (44)
		Day 90	27.3	59.1	52.3†		61.8† 102 (24)		63.3†† 114 (31)	105.7 [b] 123 (38) 184 (41)

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Organ Weight [a]										
Scheduled necropsy	**No. Examined**		4	4	4	4	4	4	4	4
	Liver	**Absolute**	66.45 g	58.63 g		60.55		71.50 86.3 (30)	90.33 114.9 (32)	82.43** 93.7 (39) 89.6 (43)
		Relative	16.965 g/ 1 kg BW	20.168 g/ 1 kg BW	17.765	20.595	19.518*	23.165 25.92 (30)	23.433** 24.82 (32)	26.445** 26.03 (39) 27.65 (43)
	Kidney	**Absolute (total, g)**	13.05 g (total)	11.03 g (total)	14.38	12.23	16.35	13.73 16.6 (30)	22.28** 24.8 (32) 21.2 (34) 26.0 (37)	16.18** 16.0 (41) 17.1 (43)
		Relative	3.340 g/ 1 kg BW (total)	3.788 g/ 1 kg BW (total)	3.953	4.135	4.298*	4.448 4.98 (30)	5.815** 5.36 (32) 5.79 (34) 5.39 (36) 6.72 (37)	5.220** 5.33 (41) 5.28 (43) 5.44 (44)
Necropsied on Day 76 [c]	**No. Examined**		0	0	0	0	0	0	0	1
	Liver	**Absolute**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	93.5 g
		Relative	N/A	N/A	N/A	N/A	N/A	N/A	N/A	29.22 g/ 1 kg BW
	Kidney	**Absolute**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16.8 g (total)
		Relative	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.25 g/ 1 kg BW (total)
Macropathology [d]										
Scheduled necropsy	**No. Examined**		4	4	4	4	4	4	4	4
	Injection site	**Thickening subcutaneous tissue**	0	0	0	0	1	0	2	0
Necropsied on Day 76 [c]	**No. Examined**		0	0	0	0	0	0	0	1
	Injection site (tail)	**Excoriation**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Histopathology [d]										
Scheduled necropsy	**No. Examined**		4	4	4	4	4	4	4	4
Kidney	**Hyaline droplet, proximal tubule**	**Very slight**	0	0	3	3	0	2	0	0
		Slight	0	0	1	1	4	2	4	4
Injection site	**Inflammation, chronic**	**Very slight**	0	0	0	0	1	0	0	0
		Slight	0	0	0	0	0	0	2	0
	Thrombus, with thickening, vascular intima		0	1	0	0	1	0	3	3
Femoral bone marrow	**Hyperplasia**	**Slight**	0	0	0	0	0	1	0	1
	Atrophy, adipose tissue	**Slight**	0	0	0	0	0	0	1	0
Sternal bone marrow	**Hyperplasia**	**Slight**	0	0	0	0	0	1	0	1
Lung	**Thrombus**		0	0	0	0	0	0	0	1
Liver	**Change, clear, hepatocyte**	**Very slight**	0	0	0	0	0	0	1	0
	Hypertrophy, Kupffer cell	**Very slight**	0	0	0	0	0	0	1	0
Adrenal	**Hypertrophy, with lipid depletion, zona fasciculata**	**Slight**	0	0	0	0	0	0	1	0
Heart	**Atrophy, adipose tissue**	**Slight**	0	0	0	0	0	0	1	0
Skin (back, interscapular)	**Atrophy, adipose tissue**	**Slight**	0	0	0	0	0	0	1	0
Lymph node (mesenteric)	**Atrophy**	**Slight**	0	0	0	0	0	0	1	0
Thymus	**Atrophy**	**Moderate**	0	0	0	0	0	0	1	0
Necropsied on Day 76 [c]	**No. Examined**		0	0	0	0	0	0	0	1
Kidney	**Hyaline droplet, proximal tubule**	**Slight**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Injection site	**Necrosis**	**Slight**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
	Thrombus, with thickening, vascular intima		N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Lung	**Thrombus**		N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Liver	**Hypertrophy, Kupffer cell**	**Very slight**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1

Daily Dose (mg/kg, as free form)			0 (Control)		100		300		1000	
Lymph node (mesenteric)	Histiocytosis, sinus	Very slight	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Lymph node (sub-mandibular)	Histiocytosis, sinus	Very slight	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Postdose Evaluation - Noteworthy Findings										
No. Evaluated			**M: 3**	**F: 3**	**M: 0**	**F: 0**	**M: 0**	**F: 0**	**M: 3**	**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	–	–
Ophthalmology			–	–	N/A	N/A	N/A	N/A	–	–
Urinalysis			–	–	N/A	N/A	N/A	N/A	–	–
Hematology			–	–	N/A	N/A	N/A	N/A	–	–
Blood Chemistry			–	–	N/A	N/A	N/A	N/A	–	–
Organ Weight			–	–	N/A	N/A	N/A	N/A	–	–
Macropathology			–	–	N/A	N/A	N/A	N/A	–	–
Histopathology [d]										
Kidney	Hyaline droplet, proximal tubule	Very slight	0	0	N/A	N/A	N/A	N/A	1	1
Injection site	Recanalization, organizing thrombus		0	0	N/A	N/A	N/A	N/A	1	2
Lung	Thrombus		0	0	N/A	N/A	N/A	N/A	1	0

APTT = activated partial thromboplastin time; LD = lactate dehydrogenase

−, No noteworthy findings

* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)

† $p < 0.05$ vs control (Dunnett-type test [Miller's test])

‡ $p < 0.05$, ‡‡ $p < 0.01$ vs control (Fisher's exact test)

a Group means are shown. Numeral in parenthesis represents animal number with the finding, and values with animal numbers are individual values.

b n = 6

c One female (animal No. 42) at 1000 mg/kg/day was necropsied on Day 76 because dosing could not be continued due to loss of vessel patency at all injection sites.

d Number of animals with findings. Numeral in parenthesis represents animal number with the finding

e Data on fresh urine collected before dosing or preserved urine

f Data on fresh urine collected after the end of dosing. Only color and urinary sediment were examined.

2.6.7.8 In vitro 遺伝毒性試験

2.6.7.8.1 細菌を用いる復帰突然変異試験

Test Article: Cefiderocol sodium drug product

Report Title: Reverse Mutation Test of RSC-649266 (GSK2696266) sodium Drug Product with Bacteria		
Test for Induction of: Gene mutation	**No. of Independent Assays:** 2	**Study No.** R-649266-TB-011-L
Strains: *Salmonella typhimurium* and *Escherichia coli*	**No. of Replicate Cultures:** 2	**Location in CTD:** 4.2.3.3-01
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 10% in metabolic activation system (S9 mix)	**No. of Cells Analyzed/Cultured:** −	**GLP Compliance:** Yes
Vehicles: **For Test Article:** Physiological saline	**For Positive Controls:** DMSO	**Date of Treatment:** Sep – Oct 20[redacted]
Treatment: Preincubation method (37°C, 20 min) and incubation for 48 hours (37°C)		
Cytotoxic Effects: Refer to the following table		
Genotoxic Effects: None		

Metabolic Activation	**Test Article**	**Dose Level** [a] **(µg/plate)**	**First mutation test**				
			Revertant Colony Counts (Mean of 2 plates)				
			Base-pair Substitution Type			**Frameshift Type**	
			TA100	**TA1535**	**WP2*uvrA***	**TA98**	**TA1537**
Without Activation	Negative control (physiological saline)	100 µL/plate	141	13	46	17	10
	Cefiderocol sodium drug product	0.153	123	12	41	19	8
		0.305	143	10	22	17	10
		0.610	142	6	33	21	8
		1.22	120	5	29	17	5
		2.44	86	4 [b]	24	19	1 [b]
		4.88	25 [b]	0 [b]	14 [b]	8	0 [b]
		9.77	7 [b]	N/A	6 [b]	3 [b]	N/A
		19.5	0 [b]	N/A	2 [b]	0 [b]	N/A
	AF-2 [c]	0.01	724		258		
		0.1				534	
	NaN_3 [c]	0.5		243			
	9AA [c]	80					634

Metabolic Activation	**Test Article**	**Dose Level**[a] (μg/plate)	**First mutation test**				
			Revertant Colony Counts (Mean of 2 plates)				
			Base-pair Substitution Type			**Base-pair Substitution Type**	
			TA100	**TA1535**	WP2*uvrA*	**TA98**	**TA1**
With Activation	Negative control (physiological saline)	100 μL/plate	133	11	50	28	10
	Cefiderocol sodium drug product	0.153	138	11	49	29	11
		0.305	131	9	49	28	12
		0.610	145	10	42	31	8
		1.22	138	10	35	26	7
		2.44	130	7	12[b]	24	1[b]
		4.88	106	2[b]	10[b]	15	2[b]
		9.77	35[b]	N/A	4[b]	4[b]	N/A
		19.5	11[b]	N/A	2[b]	1[b]	N/A
	2AA[c]	0.5				466	
		1	998				
		2		269			156
		10			787		

Metabolic Activation	Test Article	Dose Level[a] (µg/plate)	Second mutation test				
			Revertant Colony Counts (Mean of 2 plates)				
			Base-pair Substitution Type			Frameshift Type	
			TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without Activation	Negative control (physiological saline)	100 µL/plate	132	11	46	23	14
	Cefiderocol sodium drug product	0.153	145	13	40	30	16
		0.305	152	13	42	23	12
		0.610	139	9	29	22	13
		1.22	135	8	34	26	9
		2.44	102	5	25	25	2[b]
		4.88	47[b]	0[b]	13[b]	21	0[b]
		9.77	8[b]	N/A	5[b]	2[b]	N/A
		19.5	0[b]	N/A	0[b]	2[b]	N/A
	AF-2[c]	0.01	947		176		
		0.1				499	
	NaN_3[c]	0.5		252			
	9AA[c]	80					501
With Activation	Negative control (physiological saline)	100 µL/plate	135	11	45	34	20
	Cefiderocol sodium drug product	0.153	157	10	49	34	17
		0.305	166	9	44	34	20
		0.610	143	12	30	34	12
		1.22	121	11	31	33	8
		2.44	115	3[b]	12[b]	25	6[b]
		4.88	84	3[b]	4[b]	22	1[b]
		9.77	46[b]	N/A	2[b]	8[b]	N/A
		19.5	12[b]	N/A	0[b]	2[b]	N/A
	2AA[c]	0.5				448	
		1	1079				
		2		338			154
		10			873		

AF-2 = 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide; NaN_3 = sodium azide; 2AA = 2-aminoanthracene; 9AA = 9-aminoacridine hydrochloride; DMSO = dimetyl sulfoxide

a As free form
b Cytotoxicity (decrease in the number of revertant colonies)
c Positive control

2.6.7.8.2 ほ乳類の培養細胞を用いる染色体異常試験

Test Article: Cefiderocol sodium drug product

Report Title: Chromosomal Aberration Test of RSC-649266 (GSK2696266) sodium Drug Product in Cultured TK6 Cells		
Test for Induction of: Chromosomal aberration	**No. of Independent Assays:** 1	**Study No.** R-649266-TF-012-L
Strains: TK6 cell	**No. of Replicate Cultures:** 2	**Location in CTD:** 4.2.3.3-02
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 1.5 vol%	**No. of Cells Analyzed/Cultured:** 100 for structural aberrations, 100 for polyploid cells	**GLP Compliance:** Yes
Vehicles: For Test Article: Physiological saline	**For Positive Controls:** Physiological saline	**Date of Treatment:** Oct 20[redacted]
Treatment: Short-term treatment for 4 hours and recovery time for 20 hours with and without S9 mix, 24-hour continuous treatment without S9 mix		
Cytotoxic Effects: The IC_{50} were calculated to be 2499, 3182 and 476 µg/mL in short-term treatment for 4 hours without and with S9 mix, and 24-hour continuous treatment, respectively.		
Genotoxic Effects: Positive in the 24-hour continuous treatment without S9 mix		

Metabolic Activation	Treatment – Recovery (hour)	Test Article	Concentration [a] (µg/mL)	Relative Cell Growth (% of control)	Aberrant Cells [b] (%)	Polyploid Cells [c] (%)
Without Activation	4–20	Negative control (physiological saline)	10 vol%	100	1.5	0.0
		Cefiderocol sodium drug product	1800	60.7	0.0	2.0
			3000	59.9	1.0	0.5
			5000	48.5	1.5	0.0
		Mitomycin C [d]	0.25	58.4	36.0	1.5
With Activation	4–20	Negative control (physiological saline)	10 vol%	100	0.5	1.5
		Cefiderocol sodium drug product	1800	76.1	2.0	1.0
			3000	69.6	1.0	0.5
			5000	63.2	3.0	1.5
		Cyclophosphamide [d]	8.00	55.1	30.0	1.0
Without Activation	24–0	Negative control (physiological saline)	10 vol%	100	0.5	0.5
		Cefiderocol sodium drug product	84.0	85.7	2.0	0.0
			140	82.7	4.0*	2.0
			233	87.9	5.0*	2.0
			389	75.1	12.7* † [e]	2.1 [e]
		Mitomycin C [d]	0.07	69.2	36.0*	0.5

IC_{50} = 50% inhibitory concentration
* $p < 0.025$ vs control (Fisher's exact test), † $p < 0.025$: Significant correlation with dosage levels (Cochran-Armitage trend test)

a As free form
b Incidence of cells with aberrations except gap per 200 analyzed cells
c Incidence of polyploid cells per 200 analyzed cells
d Positive control
e The number of analyzed mitotic cells were 157 for structural chromosomal aberration and 190 for polyploidy respectively because of an extreme decrease in the number.

2.6.7.8.3 マウスリンフォーマ試験

Test Article: Cefiderocol sodium drug product

Report Title: Mouse Lymphoma Assay of RSC-649266 (GSK2696266) sodium Drug Product		
Test for Induction of: Gene mutation and chromosomal aberration	**No. of Independent Assays:** 1	**Study No.** R-649266-TF-014-L
Strains: Mouse lymphoma cell line (L5178Y *tk*$^{+/-}$ 3.7.2C)	**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 Plates/Culture:** 4 plates for the negative control, 2 plates for the test article and positive control	**GLP Compliance:** Yes
Vehicles: For Test Article: Physiological saline	**For Positive Controls:** Physiological saline	**Date of Treatment:** Oct 20[redacted]
Treatment: Short-term treatment for 3 hours with and without S9 mix, 24-hour continuous treatment without S9 mix		
Cytotoxic Effects: RTG was 39.6% at 5000 µg/mL in the short-term treatment without S9 mix, 30.7% at 5000 µg/mL in the short-term treatment with S9 mix, and 22.0% at 400 µg/mL in the 24-hour continuous treatment.		
Genotoxic Effects: Positive in the short-term treatment with S9 mix		

Metabolic Activation	**Treatment (hour)**	**Test Article**	**Concentration [a] (µg/mL)**	**RS0 [b] (%)**	**RSG [c] (%)**	**RTG [d] (%)**	**MF [e] (×10^{-6})**
Without Activation	3	Negative control (physiological saline)	10 vol%	100	100	100	122.2
		Cefiderocol sodium drug product	156	103.6	83.5	91.0	170.3
			313	97.1	90.3	109.9	123.1
			625	117.5	92.2	102.0	138.9
			1250	115.1	91.8	93.0	224.7
			2500	95.8	86.9	87.0	194.4
			5000	68.6	46.4	39.6	209.8
		Methyl methanesulfonate [f]	10	120.1	96.2	93.5	436.2
With Activation	3	Negative control (physiological saline)	10 vol%	100	100	100	144.1
		Cefiderocol sodium drug product	78.1	109.2	103.1	102.1	134.8
			156	133.8	112.3	111.6	157.3
			313	118.8	94.5	95.5	180.4
			625	130.7	99.0	91.8	196.8
			1250	85.6	66.4	64.7	219.7
			2500	86.5	45.8	49.0	267.1
			5000	65.1	34.0	30.7	321.3
		Cyclophosphamide [f]	3	57.1	29.9	31.5	555.4

Metabolic Activation	Treatment (hour)	Test Article	Concentration [a] (μg/mL)	RS0 [b] (%)	RSG [c] (%)	RTG [d] (%)	MF [e] (×10^{-6})
Without Activation	24	Negative control (physiological saline)	10 vol%	100	100	100	143.7
		Cefiderocol sodium drug product	100	104.7	117.5	119.2	139.3
			200	95.3	122.1	103.5	145.8
			300	78.5	81.9	68.3	151.5
			400	56.6	30.8	22.0	345.6
			500	23.5	12.0	4.2	700.7 [g]
			600	5.8	7.4	1.3	483.2 [g]
			700	0.3	5.7	0.1	N.C.
			800	0.3	5.7	0.0	N.C.
		Methyl methanesulfonate [f]	5	96.3	111.5	78.6	809.1

N.C. = Not calculated
Significant difference from negative control (modified Dunnett test, $p < 0.05$) and correlation with dosage levels (trend test, $p < 0.05$) in the MF was noted in the short-term treatment with S9 mix.
Significant difference from negative control (modified Dunnett test, $p < 0.05$) in the MF was noted in the 24-hour continuous treatment without S9 mix.

a As free form
b Relative survival on day 0
c Relative suspension growth
d Relative total growth
e Mutant frequency
f Positive control
g Excluded from evaluation because RTG was less than 10%.

2.6.7.8.4 ほ乳類培養細胞を用いた HPRT 遺伝子突然変異試験

Test Article: Cefiderocol sodium drug product

Report Title: HPRT Gene Mutation Test of S-649266 (GSK2696266) sodium Drug Product with Cultured Mammalian Cells		
Test for Induction of: Gene mutation	**No. of Independent Assays:** 1	**Study No.** S-649266-TF-071-L
Strains: Chinese hamster lung (V79) cells	**No. of Replicate Cultures:** 2	**Location in CTD:** 4.2.3.3-04
Metabolizing System: Phenobarbital and 5,6-benzoflavone induced rat liver S9, 5 vol%		**GLP Compliance:** Yes
Vehicles: For Test Article: Physiological saline	**For Positive Controls:** DMSO	**Date of Treatment:** Apr 20[redacted]
Treatment: Four hours with and without S9 mix		
Cytotoxic Effects: None		
Genotoxic Effects: None		

Metabolic Activation	Test Article	Concentration [a] (μg/mL)	Cell Survival [b] (% of control)	Plating Efficiency [c] (%)	Mutation Frequency [d] (10^{-5})
Without Activation	Negative control (physiological saline)	1 vol%	100.0	100.0	0.61 [f]
	Cefiderocol sodium drug product	63	99.0	115.0	0.57
		125	101.3	114.6	0.26
		250	99.7	110.4	0.00
		500	101.3	132.6	0.29
	Ethyl methanesulfonate [e]	1000	97.0	100.4	114.61 [g, h]
With Activation	Negative control (physiological saline)	1 vol%	100.0	100.0	0.59 [f]
	Cefiderocol sodium drug product	63	100.8	100.1	0.33
		125	102.0	110.3	0.21
		250	100.3	103.1	0.27
		500	101.2	112.5	0.05
	N-nitrosodimethylamine [e]	2000	99.0	98.7	40.67 [g, h]

a As free form
b The relative optical density (OD590) measured
c The relative number of colonies of 100 cells plated on day 6 after treatment
d The relative number of $6TG^r$ (6-thioguanine resistant) colonies of 10^5 cells plated on day 6 after treatment
e Positive control
f Mutation frequency calculated by the formulation of (the average number of $6TG^r$ colonies per dish × $1/10^5$) × (100/plating efficiency)
g The mutation frequency was three times higher than that of the negative controls.
h The mutation frequency was higher than historical control data of negative controls with and without S9 mix (range: 0-3.3 and 0-3.7 × 10−5, respectively, obtained from 46 experiments).

2.6.7.9 In vivo 遺伝毒性試験

2.6.7.9.1 ラットの小核試験

Test Article: Cefiderocol sodium drug product

Report Title: Micronucleus Test of RSC-649266 (GSK2696266) sodium Drug Product with Rat Bone Marrow Cells		
Test for Induction of: Bone marrow micronuclei	**Treatment Schedule:** 2 days (Once daily)	**Study No.** R-649266-TF-013-L
Species/Strain: Rat/Crl:CD(SD)	**Sampling Time:** 24 hours after final dosing	**Location in CTD:** 4.2.3.3-05
Age at dosing: 8 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes	**GLP Compliance:** Yes
Cell Evaluated: Immature erythrocytes	**Vehicle/Formulation:** Physiological saline/solution	**Date of Dosing:** 27 – 28 Sep 20[redacted]
No. of Cells Evaluated/Animal: 2000		
Special Features: None		
Toxic/Cytotoxic Effects: Death, decrease in locomotor activity and convulsion were observed in 2000 mg/kg/day group.		
Genotoxic Effects: None		
Evidence of Exposure: None		

Test Article	Dose [a] (mg/kg/day)	Gender and No. per Group	Ratio of IE (%) [b]	Frequency of MNIE (%) [c]
Negative control (physiological saline)	0	5M	44.5 ± 6.8	0.11 ± 0.07
Cefiderocol sodium drug product	500	5M	37.0 ± 4.2	0.09 ± 0.05
	1000	5M	45.5 ± 6.3	0.17 ± 0.08
	2000	3M	37.1 ± 8.3	0.15 ± 0.13
Mitomycin C [d]	2	5M	41.1 ± 9.6	3.71 ± 1.11*

* $p < 0.025$ vs negative control (Kastenbaum and Bowman test)

a As free form
b Number of immature erythrocytes/500 erythrocytes per animal, mean ± standard deviation
c Number of micronucleated immature erythrocytes/2000 immature erythrocytes per animal, mean ± standard deviation
d Positive control, single intravenous injection

2.6.7.9.2 ラットを用いたコメットアッセイ

Test Article: Cefiderocol sodium drug product

Report Title: Comet Assay of RSC-649266 (GSK2696266) sodium Drug Product in Rats		
Test for Induction of: DNA damage in the liver	**Treatment Schedule:** 2 days (Once daily)	**Study No.** R-649266-TF-052-L
Species/Strain: Rat/Crl:CD(SD)	**Sampling Time:** 3 hours after final dosing	**Location in CTD:** 4.2.3.3-06
Age at dosing: 8 weeks	**Method of Administration/Dosing Duration:** Intravenous/30 minutes	**GLP Compliance:** Yes
Cell Evaluated: Percentage of DNA fragments present in the tail (tail % intensity)	**Vehicle/Formulation:** Physiological saline/solution	**Date of Dosing:** 17 – 18 Jan 20[redacted]
No. of Cells Evaluated/Animal: 100		
Special Features: None		
Toxic/Cytotoxic Effects: None		
Genotoxic Effects: None		
Evidence of Exposure: None		

Test Article	Dose [a] (mg/kg/day)	Gender and No. per Group	Tail % intensity [b]
Negative control (physiological saline)	0	5M	0.80 ± 0.43
Cefiderocol sodium drug product	500	5M	0.66 ± 0.36
	1000	5M	0.88 ± 0.57
	1500	5M	1.10 ± 0.21
Ethyl methanesulfonate [c]	200	5M	17.88 ± 5.11

a As free form
b Mean ± standard deviation
c Positive control

2.6.7.10 生殖発生毒性試験： 重要な試験以外の試験

Test Article: Cefiderocol sodium drug product

Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Duration of Dosing**	**Doses [a] (mg/kg/day)**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in CTD**
Rat/ Crl:CD(SD)	Intravenous (Physiological saline/Solution)	G6-17	0, 500, 1000	7F (Pregnant)	Dams: 1000: Loose stool (G21). ≥500: Tendency of decreased body weight gain (from end of the dosing period). Embryos and Fetuses: ≥500: Tendency of decreased fetal body weight	R-649266-TB-006-R/ 4.2.3.5-06

<table>
<tr><th>Species/
Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td>Rabbit/
New Zealand White</td><td>Intravenous (Physiological saline/Solution)</td><td>G7-19</td><td>0, 10, 50, 100, 300, 1000</td><td>6–7F (Pregnant)</td><td>
<u>Dams:</u>
≥50:
Mortality: One female was found dead on G23, and 4, 2, 4 and 2 females were euthanized between G11 and 21 in the 50, 100, 300, and 1000 mg/kg/day, respectively. The other survived animals were prematurely terminated until G25.
Other findings: Abnormal feces, fecal stained fur, thin body condition, ears cold to touch, discoloration at the ear and the injection site, red substance in cage pan, swollen/red vaginal area, mild dehydration, body weight losses (within −6% based on G7), suppressed food consumption (within −64% based on G7-10), edematous cecum and/or mesentery, numerous red areas on the cecum, cloudy and red fluid in the thoracic cavity, and small liver.
10:
Scant and soft or liquid feces, body weight loss (−1 % based on G7), suppressed food consumption (within – 9% based on G7-10)
<u>Embryos and Fetuses:</u>
10:
A decrease in mean fetal body weight (−5% for male and −7% for female compared with each control group)
<u>Toxicokinetics:</u>
Mean value of 2 or 3 pregnant female rabbits
<table>
<tr><th>Daily dose (mg/kg/day)</th><th>Day</th><th>C_{max} (μg/mL)</th><th>AUC_{0-t} (μg·hr/mL)</th></tr>
<tr><td>10</td><td>11</td><td>27.2</td><td>49.9</td></tr>
<tr><td>50</td><td>11</td><td>145</td><td>274</td></tr>
<tr><td>100</td><td>11</td><td>197</td><td>435</td></tr>
<tr><td>300</td><td>11</td><td>580</td><td>1010</td></tr>
<tr><td>1000</td><td>11</td><td>1410</td><td>3415</td></tr>
</table>
</td><td>[redacted]/
4.2.3.5-07</td></tr>
</table>

<table>
<tr><th>Species/
Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th colspan="4">Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td rowspan="5">Mouse/
Crl:CD1[ICR]</td><td rowspan="5">Subcutaneous (Physiological saline/Solution)</td><td rowspan="5">G6-15</td><td rowspan="5">0, 500, 1000, 2000
(0, 250, 500, 1000 b.i.d.)</td><td rowspan="5">9F
(Pregnant)</td><td colspan="4">Dams:
No noteworthy findings
Embryos and Fetuses:
No noteworthy findings
Toxicokinetics:
Mean value of 3 non-pregnant female mice</td><td rowspan="5">[redacted]/
4.2.3.5-08</td></tr>
<tr><td>Daily dose (mg/kg/day)</td><td>Day</td><td>C_{max} (μg/mL)</td><td>AUC_{0-t} (μg·hr/mL)</td></tr>
<tr><td>500</td><td>5</td><td>226</td><td>341</td></tr>
<tr><td>1000</td><td>5</td><td>250</td><td>639</td></tr>
<tr><td>2000</td><td>5</td><td>458</td><td>1010</td></tr>
</table>

<table>
<tr><th>Species/
Strain</th><th>Method of Administration (Vehicle/ Formulation)</th><th>Duration of Dosing</th><th>Doses [a] (mg/kg/day)</th><th>Gender and No. per Group</th><th>Noteworthy Findings</th><th>Study Number/ Location in CTD</th></tr>
<tr><td rowspan="15">Juvenile Rat/
Crl:CD(SD)</td><td rowspan="11">Subcutaneous (Physiological saline/Solution)</td><td rowspan="11">PND7-13</td><td rowspan="11">0, 200, 600, 2000</td><td rowspan="11">8M, 8F in the control, 48M, 48F in the 200, 600 and 2000 mg/kg/day groups</td><td>2000:
Death (One female, PND10)
≥600:
Clonic convulsion
Toxicokinetics:
Mean value of 4 rats</td><td rowspan="11">S-649266-TF-258-R/ 4.2.3.5-09</td></tr>
<tr><td><table>
<tr><th rowspan="2">Daily dose (mg/kg/day)</th><th rowspan="2">PND</th><th colspan="2">C_{max} (μg/mL)</th><th colspan="2">AUC_{0-6hr} (μg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">200</td><td>7</td><td>353</td><td>320</td><td>867</td><td>811</td></tr>
<tr><td>13</td><td>338</td><td>333</td><td>616</td><td>606</td></tr>
<tr><td rowspan="2">600</td><td>7</td><td>751</td><td>815</td><td>2140</td><td>2480</td></tr>
<tr><td>13</td><td>779</td><td>815</td><td>1550</td><td>1660</td></tr>
<tr><td rowspan="2">2000</td><td>7</td><td>2010</td><td>2200</td><td>8320</td><td>9380</td></tr>
<tr><td>13</td><td>2140</td><td>1870</td><td>4770</td><td>4560</td></tr>
</table></td></tr>
<tr><td rowspan="4">Intravenous (Physiological saline/Solution)</td><td rowspan="4">PND28-34</td><td rowspan="4">0, 100, 300, 600</td><td rowspan="4">4M, 4F in the control, 24M, 24F in the 100, 300, 600 mg/kg/day groups</td><td>600:
Tendency of decreased body weight gain (female, PND29 to 30)
≥100:
Red urine
Toxicokinetics:
Mean value of 4 rats</td></tr>
<tr><td><table>
<tr><th rowspan="2">Daily dose (mg/kg/day)</th><th rowspan="2">PND</th><th colspan="2">C_0 (μg/mL)</th><th colspan="2">AUC_{0-6hr} (μg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">100</td><td>28</td><td>270</td><td>276</td><td>133</td><td>132</td></tr>
<tr><td>34</td><td>305</td><td>272</td><td>154</td><td>127</td></tr>
<tr><td rowspan="2">300</td><td>28</td><td>992</td><td>917</td><td>481</td><td>445</td></tr>
<tr><td>34</td><td>868</td><td>866</td><td>445</td><td>430</td></tr>
<tr><td rowspan="2">600</td><td>28</td><td>1700</td><td>1780</td><td>877</td><td>865</td></tr>
<tr><td>34</td><td>1720</td><td>1790</td><td>876</td><td>866</td></tr>
</table></td></tr>
</table>

AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing

a As free form

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

2.6.7.11.1 ラット受胎能及び着床までの初期胚発生に関する試験

Test Article: Cefiderocol sodium drug product

Report Title: Intravenous Study for Effects of S-649266 sodium Drug Product on Fertility and Early Embryonic Development to Implantation in Rats		
Design similar to ICH 4.1.1 ?: Yes	**Duration of Dosing:** 4 weeks before mating, through the mating period (2 weeks), until the day before necropsy (males); 2 weeks before mating, through the mating period (2 weeks), until G7 (females)	**Study No.** S-649266-TF-159-L
Species/Strain: Rat/Crl:CD(SD)		**Location in CTD:** 4.2.3.5-01
Initial Age: M: 11 weeks, F: 12 weeks		
Day of Mating: G0	**Day of Caesarean Section:** G15	**GLP Compliance:** Yes
Date of First Dose: M: 10 Sep 20[redacted] F: 24 Sep 20[redacted]	**Method of Administration/Dosing Duration:** Intravenous/30 minutes	
Special Features: None	**Vehicle/Formulation:** Physiological saline/solution	
NOAEL: F0 Males: 1000 mg/kg/day F0 Females: 1000 mg/kg/day F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg, as free form)		**0 (Control)**	**100**	**300**	**1000**
F0 Males					
No. Males Evaluated		**20**	**20**	**20**	**20** [a]
Noteworthy Findings					
Died or Sacrificed Moribund		0	0	0	0
Clinical Observation [b]	**Abnormalities (crust, trauma, blackening, and/or loss) at the injection site (tail)**	0	0	0	9
	Chromaturia (pale red)	0	0	20	20
Body Weight (%) [c]	**Day 18 (Pre-Pairing)**	404.6 g	−1	−4*	−4*
	Day 22 (Pre-Pairing)	410.9 g	−1	−3	−4*
	Day 25 (Pre-Pairing)	417.9 g	–2	–4*	–5**
	Day 29	422.7 g	−2	−4	−5**
	Day 32	420.1 g	0	−3	−4
	Day 36	430.9 g	−1	−3	−4*
	Day 39	436.5 g	0	−3	−4*
	Day 43	442.3 g	−1	−3	−4*
	Day 46	447.3 g	−1	−3	−5*
	Day 50	456.1 g	−2	−4	−5*

Daily Dose (mg/kg, as free form)			0 (Control)	100	300	1000
	Day 53		458.2 g	−1	−3	−5*
	Day 58		465.9 g	–2	–4	–6**
Body Weight Gain (g)	Day 1-8 (Pre-Pairing)		7.1	7.9	−0.1**	3.3
	Day 1-15 (Pre-Pairing)		20.9	22.0	8.0**	10.3**
	Day 1-18 (Pre-Pairing)		25.2	22.9	10.7**	10.9**
	Day 1-22 (Pre-Pairing)		31.5	29.0	18.2**	14.9**
	Day 1-25 (Pre-Pairing)		38.5	32.8	22.7**	18.5**
	Day 1-29		43.3	35.3	27.9	21.3††
	Day 1-32		40.7	40.1	27.2	23.6†
	Day 1-36		51.5	49.0	39.1	33.4††
	Day 1-39		57.1	56.2	44.8	38.8†
	Day 1-43		62.9	61.4	51.4	43.9†
	Day 1-46		67.9	66.1	55.1	47.1††
	Day 1-50		76.7	70.8	59.8	52.8††
	Day 1-53		78.8	74.2	63.3	54.8††
	Day 1-58		86.5	78.3	67.1	60.7†
Food Consumption (%) [c]	Day 2 (Pre-Pairing)		23.5 g/day	–17**	–23**	–24**
	Day 5 (Pre-Pairing)		23.2 g/day	1	–10*	–15**
Reproductive Organ Weight [d]			–	–	–	–
Macropathology [b]	Injection site (tail)	Crust, trauma, black discoloration, and/or loss	0	0	0	6
	Cecum	Dilatation	0	0	9	16
Sperm Analysis [e]			–	–	–	–
Mean No. Days Prior to Copulation			3.4	2.4	2.8	3.3
No. of Males Copulated (%, Copulation)			20 (100.0)	19 (95.0)	20 (100.0)	20 (100.0)
No. of Fertile Males (%, Fertility)			19 (95.0)	19 (100.0)	19 (95.0)	19 (95.0)
F0 Females						
No. Females Evaluated			20	20	20	20
No. Died or Sacrificed Moribund			0	0	0	0
Clinical Observation [b]	Pre-Copulating Periods					
	Abnormality (crust) at the injection site (tail)		0	0	0	1
	Chromaturia (pale red)		0	0	20	20
	Pregnancy Periods					
	Abnormalities (crust, trauma, and/or blackening) at the injection site (tail)		0	0	0	2
	Chromaturia (pale red)		0	0	20	20

Daily Dose (mg/kg, as free form)			0 (Control)	100	300	1000
Body Weight	Pre-Pairing Period		–	–	–	–
	Pregnancy Period		–	–	–	–
Body Weight Gain	Pre-Pairing Period [f]		–	–	–	–
	Pregnancy Period [g]		–	–	–	–
Food Consumption (%) [c]	Day 2 (Pre-Pairing)		15.5 g/day	–10	–14**	–13*
	Day 5 (Pre-Pairing)		16.7 g/day	2	–7	–16**
Macropathology [b]	Injection site (tail)	Crust and trauma	0	0	0	2
Mean No. Estrus/14 days			3.4	3.3	3.3	3.3
Mean Days of Estrous Cycle			3.99	4.22	4.07	4.28††
Mean No. Days Prior to Copulation			3.4	2.4	2.8	3.3
No. of Females Sperm-Positive (%, Copulation)			20 (100.0)	19 (95.0)	20 (100.0)	20 (100.0)
No. of Pregnant Females (%, Fertility)			19 (95.0)	19 (100.0)	19 (95.0)	19 (95.0)
Mean No. Corpora Lutea			14.7	14.4	13.8	14.3
Mean No. Implantations			14.1	13.3	12.8	13.2
Mean % Implantations			96.2	91.3	92.8	92.4
Mean % Pre-implantation Loss			3.9	8.7	7.2	7.6
Embryos						
No. Litters Evaluated			19	19	19	19
Mean No. Live Embryos			13.2	12.5	11.9	12.4
Mean % Embryonic Viability Rate			93.3	93.7	91.0	93.7
Mean No. Post-implantation Loss			0.9	0.8	0.9	0.8
Mean % Post-implantation Loss			6.7	6.3	9.1	6.4

Day 1 = the first day of dosing
−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)
† $p < 0.05$, †† $p < 0.01$ vs control (Dunnett-type test)

a Two animals were euthanized because the test substance could not be administered due to marked irritative changes observed at the injection site (tail) on Day 49 or 55 of dosing.
b Numerals represent number of animals with the finding
c For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
d Testes, epididymides, and ventral prostate
e Sperm activity, motile sperm rate, sperm count, and abnormal sperm rate
f Based on body weight on Day 1 of dosing
g Based on body weight on Day 0 of gestation

2.6.7.12 生殖発生毒性試験： 胚・胎児発生に関する試験

2.6.7.12.1 ラット胚・胎児発生に関する試験

Test Article: Cefiderocol sodium drug product

Report Title: Intravenous Study for Effects of S-649266 sodium Drug Product on Embryo-Fetal Development in Rats		
Design similar to ICH 4.1.3. ?: Yes	**Duration of Dosing:** G6–17	**Study No.** S-649266-TF-132-L
Species/Strain: Rat/Crl:CD(SD)	**Day of Mating:** G0	**Location in CTD:** 4.2.3.5-02
Initial Age: 12–13 weeks	**Day of Caesarean section:** G20	**GLP Compliance:** Yes
Date of First Dose: 08 Jan 20[redacted]	**Method of Administration/Dosing Duration:** Intravenous/30 minutes	
Special Features: None	**Vehicle/Formulation:** Physiological saline/Solution	
NOAEL: F0 dams: 300 mg/kg/day for general toxicity and 1000 mg/kg/day for maternal reproductive function F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg, as free form)			**0 (Control)**	**100**	**300**	**1000**
Dams						
Toxicokinetics [a]						
No. Evaluated			**4**	**5**	**5**	**5**
Cefiderocol	**C_0 (µg/mL)**	**G6**	N.C.	242	693	2300
		G17	N.C.	249	748	2010
	AUC_{total} (µg·hr/mL)	**G6**	N.C.	195	563	1930
		G17	N.C.	195	601	1600
Noteworthy Findings						
No. Pregnant			**19**	**18**	**19**	**20**
No. Died or Sacrificed Moribund			0	0	0	0
No. Aborted or with Total Resorption Loss			0	0	0	0
Clinical Observation [b]	**Abnormalities (blackening, trauma, and/or loss) at the injection site (tail)**		0	0	0	2
	Chromaturia (pale red)		0	14	19	20
Body Weight (%) [c]	**G18**		362.9 g	–1	–1	–4*
	G19		378.8 g	–1	–1	–4*

Daily Dose (mg/kg, as free form)			0 (Control)	100	300	1000
Body Weight Gain (g)	G6–11		14.4	15.0	13.7	9.5*
	G6–12		19.5	19.2	16.8	14.0*
	G6–13		23.9	21.9	22.1	16.0**
	G6–14		27.4	26.7	25.9	21.6
	G6–15		33.2	33.2	32.5	24.9**
	G6–16		42.2	40.2	40.4	33.0**
	G6–17		52.8	50.8	51.9	43.0**
	G6–18		67.4	63.5	64.2	54.3**
	G6–19		83.3	80.4	80.6	69.5**
	G6–20		99.4	96.1	97.4	85.6**
Food Consumption (%) [c]	G7		23.0 g/day	–18**	–23**	–21**
	G8		22.9 g/day	–14**	–18**	–21**
	G9		22.5 g/day	–3	–6	–20**
	G10		21.3 g/day	6	2	–12*
Macropathology [b]	Injection site (tail)	Black discoloration, trauma, and/or loss	0	0	0	2
	Cecum	Dilatation	0	0	1	10
Mean No. Corpora Lutea			14.8	14.4	14.9	14.7
Mean No. Implantations			14.0	14.2	14.3	13.6
Mean % Implantation			94.8	98.4	95.9	91.1
F1 Litters						
No. Litters Evaluated			19	18	19	20
Total No. Live Fetuses			249	237	262	253
Mean No. Live Fetuses			13.1	13.2	13.8	12.7
Mean % Fetal Viability			93.9	92.6	96.3	92.8
Mean No. Embryo/Fetus Deaths			0.9	1.1	0.5	0.9
Mean % Post-implantation Loss			6.2	7.5	3.7	7.3
Fetal Sex Ratio (Male/Male + Female)			0.507	0.461	0.513	0.490
Mean Fetal Body Weight (g)		Male	4.00	3.93	3.91	3.88
		Female	3.82	3.66	3.73	3.63*
Mean Placental Weight (g)		Male	0.51	0.49	0.49	0.51
		Female	0.49	0.47	0.48	0.48

Daily Dose (mg/kg, as free form)	0 (Control)	100	300	1000
Placental Malformations	–	–	–	–
External Malformations	–	–	–	–
Visceral Malformations	–	–	–	–
Skeletal Malformations	–	–	–	–
Degree of Ossification [d]	–	–	–	–

–, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)

a Group means are shown.
b Numerals represent number of animals with the finding
c For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
d Number of sternebrae and sacral and caudal vertebrae

2.6.7.12.2 マウス胚・胎児発生に関する試験

Test Article: Cefiderocol sodium drug product

Report Title: Subcutaneous Study for Effects of S-649266 sodium Drug Product on Embryo-Fetal Development in Mice		
Design similar to ICH 4.1.3.?: Yes	**Duration of Dosing:** G6–15	**Study No.** S-649266-TF-131-L
Species/Strain: Mouse/Crl:CD1(ICR)	**Day of Mating:** G0	**Location in CTD:** 4.2.3.5-03
Initial Age: 12-14 weeks	**Day of Caesarean section:** G18	**GLP Compliance:** Yes
Date of First Dose: 04 Dec 20[redacted]	**Method of Administration:** Subcutaneous	
Special Features: None	**Vehicle/Formulation:** Physiological saline/Solution	
NOAEL: F0 dam: 500 mg/kg/day for general toxicity and 2000 mg/kg/day for maternal reproductive function F1 litter: 2000 mg/kg/day		

Daily Dose [a] (mg/kg, as free form)			**0 (Control)**	**500**	**1000**	**2000**
Dams						
Toxicokinetics [b]						
No. Evaluated			**3-4**	**3-5**	**3-5**	**3-5**
Cefiderocol	**C_{max} (µg/mL)**	**G6**	N.C.	327	469	784
		G15	N.C.	366	609	1340
	AUC [c] (µg·hr/mL)	**G6**	N.C.	580	1020	2300
		G15	N.C.	654	1330	2320
Noteworthy Findings						
No. Pregnant			**18**	**18**	**18**	**17**
No. Died or Sacrificed Moribund			0	0	0	0
No. Aborted or with Total Resorption Loss			0	0	0	0
Clinical Observation [d]	**Injection site, crust**		0	0	2	11
	Chromaturia (red)		0	0	10	17
Body Weight			–	–	–	–
Body Weight Gain			–	–	–	–
Food Consumption			–	–	–	–
Macropathology [d]	**Injection site**	**Crust**	0	0	0	9
		Subcutaneous hemorrhage	0	0	4	10
	Cecum	**Dilatation**	0	3	17	17
Mean No. Corpora Lutea			13.8	11.5	9.3††	10.5††
Mean No. Implantations			13.2	11.2	8.2**	9.8*
Mean % Implantation			94.5	96.4	86.1†	91.6

Daily Dose [a] (mg/kg, as free form)		0 (Control)	500	1000	2000
F1 Litters					
No. Litters Evaluated		**18**	**18**	**18**	**17**
Total No. Live Fetuses		219	183	133	154
Mean No. Live Fetuses		12.2	10.2	7.4**	9.1*
Mean % Fetal Viability		92.6	92.2	88.9	92.9
Mean No. Embryo/Fetus Death		1.0	1.0	0.8	0.8
Mean % Post-implantation Loss		7.4	7.8	11.1	7.2
Fetal Sex Ratio (Male/Male + Female)		0.511	0.463	0.503	0.516
Mean Fetal Body Weight (g)	**Male**	1.34	1.32	1.40	1.35
	Female	1.30	1.28	1.35	1.33
Mean Placental Weight (g)	**Male**	0.121	0.112	0.131	0.130
	Female	0.116	0.109	0.128	0.123
Placental Malformations		–	–	–	–
External Malformations		–	–	–	–
Visceral Malformations		–	–	–	–
Skeletal Malformations		–	–	–	–
Degree of Ossification [e]		–	–	–	–

–, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)
† $p < 0.05$, †† $p < 0.01$ vs control (Dunnett-type test)

a Doses were divided into 2 equal daily doses of 250, 500 or 1000 mg/kg/dose, given approximately 6 hours apart.
b Group means are shown.
c Doubled the $AUC_{0\text{-}5hr}$ after the first dosing
d Numerals represent number of animals with the finding
e Number of sternebrae, sacro-caudal vertebrae

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

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

Test Article: Cefiderocol sodium drug product

Report Title: Intravenous Study for Effects of S-649266 sodium Drug Product 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-649266-TF-190-L
Species/Strain: Rat/Crl:CD(SD)	**Method of Administration/Dosing Duration:** Intravenous/30 minutes	**Location in CTD:** 4.2.3.5-04
Initial Age: 12 to 13 weeks	**Vehicle/Formulation:** Physiological saline/Solution	
Date of First Dose: 10 Mar 20[redacted]	**Litters Culled/Not Culled:** Culled to 4/sex/litter	**GLP Compliance:** Yes
Special Features: None		
NOAEL: F0 dam: 300 mg/kg/day for general toxicity and 1000 mg/kg/day for maternal reproductive function F1 litters: 1000 mg/kg/day		

Daily Dose (mg/kg, as free form)			**0 (Control)**	**100**	**300**	**1000**
F0 Females						
Noteworthy Findings						
No. Pregnant			**22**	**21**	**20**	**21**
No. Died or Sacrificed Moribund			0	0	0	0
No. Total Litter Loss			0	0	0	0
Clinical Observation [a]						
Gestation Period	**Abnormality (crust) at the injection site (tail)**		0	0	0	2
	Chromaturia (pale red)		0	9	20	21
Lactation Period	**Abnormalities (crust, blackening, and/or loss) at the injection site (tail)**		0	0	0	3
	Chromaturia (pale red)		0	1	20	21
Body Weight (%) [b]		**G19**	404.7 g	–2	–3	–4*
		G20	420.1 g	–2	–3	–5*
		Lactation Period	–	–	–	–
Body Weight Gain (g)		**G6–16**	49.8	45.5	44.4	41.6*
		G6–17	62.5	57.3	55.2	52.4**
		G6–18	78.2	73.0	70.6	64.4**
		G6–19	93.7	86.6	85.6	76.8**
		G6–20	109.1	101.6	100.3	89.6**
		Lactation Period	–	–	–	–

Daily Dose (mg/kg, as free form)			0 (Control)	100	300	1000
Food Consumption (%) [b]		G7	23.4 g/day	–16**	–20**	–25**
		G8	23.1 g/day	–3	–15**	–16**
		G9	22.8 g/day	–1	–9†	–12††
		G10	24.0 g/day	–3	–13**	–13**
		G11	23.8 g/day	–2	–8	–9*
		G12	24.2 g/day	0	–5	–7
		G13	25.2 g/day	–1	–7	–7
		G14	25.0 g/day	0	–6	–5
		G15	25.5 g/day	–3	–4	–11**
		G16	26.8 g/day	–3	–5	–10*
		G17	27.5 g/day	–3	–9*	–8
		G18	28.0 g/day	–5	–7	–15**
		G19	27.0 g/day	–3	–5	–7*
		G20	26.3 g/day	–4	–8	–16**
		Lactation Period	–	–	–	–
Macropathology [a]	Injection site (tail)	Black discoloration and loss	0	0	0	1
	Cecum	Dilatation	0	0	0	11
Mean Duration of Gestation (days)			21.91	22.07	22.08	22.17*
No. Delivery (%, Gestation Index) [c]			22 (100.0)	21 (100.0)	20 (100.0)	21 (100.0)
Abnormal Parturition			–	–	–	–
F1 Litters (Pre-weaning)						
No. Litters Evaluated			22	21	20	21
Mean No. Pups/Litter			14.3	13.8	15.0	13.8
Mean No. Live Born Pups/Litter			14.1	13.6	14.9	13.7
Mean Pup Sex Ratio (Male/Male + Female)			0.48	0.53	0.54	0.44
Mean No. Stillborn Pups/Litter			0.2	0.2	0.2	0.1
Delivery Index (%) [d]			92.82	93.33	94.82	93.41
Birth Index (%) [e]			91.67	91.99	93.91	92.80
Mean % Postnatal Survival to Day 4 after birth			99.45	97.86	99.11	99.72
Mean % Postnatal Survival to Weaning			100.00	100.00	99.38	100.00
External Malformations			–	–	–	–
Pup Clinical Observation			–	–	–	–
Mean Pup Body Weights			–	–	–	–
Functional Development [f]			–	–	–	–
Physical Development [g]			–	–	–	–
Pup Macropathology			–	–	–	–

Daily Dose (mg/kg, as free form)		0 (Control)	100	300	1000
F1 Males (Post-weaning)					
No. Males Evaluated (R, B)		**44 (22, 22)**	**42 (21, 21)**	**40 (20, 20)**	**40 (21, 19)**
No. Died or Sacrificed Moribund		0	0	0	0
Clinical Observation		–	–	–	–
Body Weights		–	–	–	–
Open Field Test	**4 to 5 Weeks of Age**	–	–	–	–
Water Maze Test	**6 to 7 Weeks of Age**	–	–	–	–
Genital Development (Cleavage of the Balano-Preputial Gland)		–	–	–	–
Mean No. of Days Prior to Copulation		3.1	3.7	3.4	3.0
No. Males Copulated (%, Copulation Rate)		21/22 (95.5)	19/21 (90.5)	19/20 (95.0)	21/21 (100.0)
No. Fertile Males (%, Fertility Rate)		20/21 (95.2)	16/19 (84.2)	18/19 (94.7)	20/21 (95.2)
Macropathology		–	–	–	–
F1 Females (Post-weaning)					
No. Females Evaluated (R, B)		**44 (22, 22)**	**42 (21, 21)**	**40 (20, 20)**	**42 (21, 21)**
No. Died or Sacrificed Moribund		0	0	0	0
Clinical Observation		–	–	–	–
Body Weights	**Pre-Pairing Period**	–	–	–	–
	Gestation Period	–	–	–	–
Open Field Test	**4 to 5 Weeks of Age**	–	–	–	–
Water Maze Test	**6 to 7 Weeks of Age**	–	–	–	–
Macropathology		–	–	–	–
Genital Development (Vaginal Opening)		–	–	–	–
Mean No. Estrus/2 Weeks		3.5	3.3	3.4	3.3
Mean Days of Estrous Cycle		4.20	4.26	4.18	4.15
Mean No. Days Prior to Copulation (Copulatory Interval)		3.1	3.7	3.4	3.0
No. Females that Copulated (%, Copulatory Index)		21/22 (95.5)	19/21 (90.5)	19/20 (95.0)	21/21 (100.0)
No. Pregnant Females (%, Fertility Index)		20/21 (95.2)	16/19 (84.2)	18/19 (94.7)	20/21 (95.2)
Mean No. Corpora Lutea		14.6	14.4	14.9	15.6
Mean No. Implantations		13.8	13.5	14.4	14.9
Mean % Pre-implantation Loss		6.7	6.3	6.2	5.0

Daily Dose (mg/kg, as free form)	0 (Control)	100	300	1000
F2 Embryos				
Number Evaluated	**20**	**16**	**18**	**20**
Mean No. Live Conceptuses/Litter	13.3	12.9	13.3	13.8
Mean % Post-implantation Loss	4.5	4.5	13.3	7.6

B = for behavioral evaluations; R = for reproductive function observations
−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)
† $p < 0.05$, †† $p < 0.01$ vs control (Dunnett-type test)

a Numerals represent number of animals with the finding
b For the controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is calculated based on actual data (not on the percentage differences).
c (Number of pregnant animals that delivered live pups / number of pregnant animals) × 100
d (Number of newborns/number of implantation sites) × 100
e (Number of live newborns/number of implantation sites) × 100
f Righting reflex, negative geotaxis, pupillary reflex, Preyer's reflex and pain response
g Pinna detachment, incisor eruption and eyelid opening

2.6.7.14 幼若ラットを用いた試験

2.6.7.14.1 幼若ラットにおける 3 週間反復皮下及び静脈内投与毒性試験

Test Article: Cefiderocol sodium drug product

Report Title: 3-Week Subcutaneous and Intravenous Toxicity Study of S-649266 sodium Drug Product in Juvenile Rats			
Species/Strain: Rat/Crl:CD(SD)	**Duration of Dosing:** 3 weeks	**Duration of Postdose:** 4 weeks	**Study No.** S-649266-TF-274-L
Initial Age: Cohort 1: PND 7, Cohort 2: PND 28	**Method of Administration/Dosing Duration:** Cohort 1: Subcutaneous injection, Cohort 2: Intravenous injection		**Location in CTD:** 4.2.3.5-05
Date of First Dose: Cohort 1: 24 May 20[redacted] Cohort 2: 14 Jun 20[redacted]	**Vehicle/Formulation:** Physiological saline/Solution		**GLP Compliance:** Yes
Special Features: None			
NOAEL: Cohort 1: 1000 mg/kg/day, Cohort 2: 600 mg/kg/day			

Cohort 1										
Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**1000**	
Toxicokinetics [a]										
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_{max} (µg/mL)**	**PND 7**	N.C.	N.C.	154	134	391	542	1110	1150
		PND 21	N.C.	N.C.	87.5	121	307	418	950	867
		PND 27	N.C.	N.C.	149	188	409	468	606	605
	$AUC_{0\text{-}6hr}$ (µg·hr/mL)	**PND 7**	N.C.	N.C.	357	341	1000	1020	3790	3060
		PND 21	N.C.	N.C.	153	193	370	508	1320	1300
		PND 27	N.C.	N.C.	179	192	552	561	839	828
Noteworthy Findings										
No. Evaluated			**M: 22**	**F: 22**	**M: 12**	**F: 12**	**M: 12**	**F: 12**	**M: 22**	**F: 22**
No. Died or Sacrificed Moribund			0	0	0	0	0	0	0	0
Clinical Observation [b]	**Tremors**		0	0	0	0	0	0	17	1
	Lies down on side or back immediately following dosing		0	0	0	0	0	0	16	17
	Vocalization		0	0	0	0	0	0	17	13
	Decreased respiration rate		0	0	0	0	0	0	7	0
	Partial closure of left eye		0	0	0	0	0	0	7	18
	Partial closure of right eye		0	0	0	0	0	0	7	18
Body Weight			–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–
Tibial Length			–	–	–	–	–	–	–	–

Cohort 1										
Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**1000**	
Crown Rump Length			–	–	–	–	–	–	–	–
Functional Observational Battery			–	–	–	–	–	–	–	–
Urinalysis			–	–	–	–	–	–	–	–
Hematology			–	–	–	–	–	–	–	–
Blood Chemistry			–	–	–	–	–	–	–	–
Organ Weight (%) [c]	**No. Examined**		12	12	12	12	12	12	12	12
	Kidney	**Absolute**	1.27 g	1.14 g	+7.9	+6.1	+10.2	+10.5	+11.0	+14.9*
		Relative to final body weight	1.231 g/100 g	1.228 g/100 g	+6.7*	+5.0	+10.2**	+9.4**	+14.4**	+15.1**
		Relative to brain weight	74.868 g/100 g	69.624 g/100 g	+9.0	+7.2	+10.8*	+13.1*	+12.7**	+18.4**
Macropathology [b]	**No. Examined**		12	12	12	12	12	12	12	12
	Injection site (scapular region)	**Red discoloration**	0	0	0	0	0	2	7	6
Histopathology [b]	**No. Examined**		12	12	12	12	12	12	12	12
Kidney	**Alteration, proximal tubule**	**Minimal**	0	0	0	2	2	2	4	12
		Mild	0	0	0	0	0	0	2	0
	Hyperplasia, proximal tubule	**Minimal**	0	0	1	0	1	0	0	0
		Mild	0	0	0	0	0	0	1	0
		Marked	0	0	0	0	0	0	1	0
Injection site (scapular region)	**Cavitation**	**Mild**	N/A	N/A	1	0	0	3	1	1
		Moderate	N/A	N/A	0	0	0	1	7	5
		Marked	N/A	N/A	0	0	0	0	1	2
		Severe	N/A	N/A	0	0	0	0	0	1
	Hemorrhage	**Minimal**	N/A	N/A	0	0	0	1	1	1
		Mild	N/A	N/A	2	1	3	3	0	1
		Moderate	N/A	N/A	0	0	0	0	8	3
		Marked	N/A	N/A	0	0	0	1	0	4
		Severe	N/A	N/A	0	0	0	0	0	1
	Inflammation, chronic	**Minimal**	N/A	N/A	1	0	2	3	0	0
		Mild	N/A	N/A	0	1	0	1	1	2
		Moderate	N/A	N/A	0	0	0	0	8	1
		Marked	N/A	N/A	0	0	0	1	0	6
		Severe	N/A	N/A	0	0	0	0	0	1

Cohort 1								
Daily Dose (mg/kg, as free form)	**0 (Control)**		**100**		**300**		**1000**	
Postdose Evaluation								
No. Evaluated	**M: 10**	**F: 10**	**M: 0**	**F: 0**	**M: 0**	**F: 0**	**M: 10**	**F: 10**
No. Died or Sacrificed Moribund	0	0	N/A	N/A	N/A	N/A	0	0
Clinical Observation	0	0	N/A	N/A	N/A	N/A	0	0
Body Weight	–	–	N/A	N/A	N/A	N/A	–	–
Food Consumption	–	–	N/A	N/A	N/A	N/A	–	–
Tibial Length	–	–	N/A	N/A	N/A	N/A	–	–
Crown Rump Length	–	–	N/A	N/A	N/A	N/A	–	–
Mean Age at Preputial Separation/Vaginal Patency	–	–	N/A	N/A	N/A	N/A	–	–
Functional Observational Battery	–	–	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	–	–
Macropathology	–	–	N/A	N/A	N/A	N/A	–	–
Histopathology	–	–	N/A	N/A	N/A	N/A	–	–

Cohort 2										
Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**600**	
Toxicokinetics [a]										
No. Evaluated			**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Cefiderocol	**C_0 (μg/mL)**	**PND 28**	N.C.	N.C.	278	294	837	798	1780	1970
		PND 48	N.C.	N.C.	389	321	1150	1060	2170	2220
	$AUC_{0\text{-}6hr}$ (μg·hr/mL)	**PND 28**	N.C.	N.C.	117	127	365	362	687	711
		PND 48	N.C.	N.C.	172	132	465	375	904	760
Noteworthy Findings										
No. Evaluated			**M: 22**	**F: 22**	**M: 12**	**F: 12**	**M: 12**	**F: 12**	**M: 22**	**F: 22**
No. Died or Sacrificed Moribund			0	2 [d]	0	0	0	0	1 [e]	0
Clinical Observation [b]										
Time of dose	**Wet red material around nose**		0	2	0	2	1	2	6	3
	Dried red material around nose		1	0	0	0	0	1	8	7
	Wet clear material around mouth		1	3	3	4	2	4	6	9
	Wet red material around mouth		0	0	0	2	0	2	3	5
0-5 minutes postdose	**Wet red material around nose**		3	1	1	2	0	3	6	4
	Dried red material around nose		1	0	0	1	3	4	7	7
	Wet clear material around mouth		0	1	0	0	0	0	2	2
1 hour postdose	**Dried red material around nose**		0	0	0	0	0	0	0	3
Body Weight			–	–	–	–	–	–	–	–
Food Consumption			–	–	–	–	–	–	–	–
Tibial Length			–	–	–	–	–	–	–	–
Crown Rump Length			–	–	–	–	–	–	–	–
Mean Age at Preputial Separation/Vaginal Patency			–	–	–	–	–	–	–	–
Functional Observational Battery			–	–	–	–	–	–	–	–
Auditory Startle Response			–	–	–	–	–	–	–	–
Motor Activity			–	–	–	–	–	–	–	–
Learning and Memory			–	–	–	–	–	–	–	–
Urinalysis			–	–	–	–	–	–	–	–
Hematology			–	–	–	–	–	–	–	–
Blood Chemistry			–	–	–	–	–	–	–	–

Cohort 2										
Daily Dose (mg/kg, as free form)			**0 (Control)**		**100**		**300**		**600**	
Organ Weight (%) [c]	**No. Examined**		12	12	12	12	12	12	12	12
	Kidney	**Absolute**	2.29 g	–	+7.0	–	+11.8*	–	+12.2*	–
		Relative to final body weight	0.978 g/100 g	–	+4.7	–	+7.5*	–	+9.3**	–
		Relative to brain weight	117.573 g/100 g	–	+6.2	–	+12.3*	–	+12.6*	–
Macropathology	**No. Examined**		12	12	12	12	12	12	12	12
	Noteworthy Findings		–	–	–	–	–	–	–	–
Histopathology [b]	**No. Examined**		12	12	12	12	12	12	12	12
Kidney	**Hyaline droplet, proximal tubule**	**Minimal**	0	0	0	0	0	0	4	0
		Mild	0	0	0	0	0	0	3	0
Postdose Evaluation										
No. Evaluated			**M: 10**	**F: 10**	**M: 0**	**F: 0**	**M: 0**	**F: 0**	**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			–	–	N/A	N/A	N/A	N/A	–	–
Food Consumption			–	–	N/A	N/A	N/A	N/A	–	–
Tibial Length			–	–	N/A	N/A	N/A	N/A	–	–
Crown Rump Length			–	–	N/A	N/A	N/A	N/A	–	–
Mean Age at Preputial Separation/Vaginal Patency			–	–	N/A	N/A	N/A	N/A	–	–
Functional Observational Battery			–	–	N/A	N/A	N/A	N/A	–	–
Auditory Startle Response			–	–	N/A	N/A	N/A	N/A	–	–
Motor Activity			–	–	N/A	N/A	N/A	N/A	–	–
Learning and Memory			–	–	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	–	–
Macropathology			–	–	N/A	N/A	N/A	N/A	–	–
Histopathology			–	–	N/A	N/A	N/A	N/A	–	–

−, No noteworthy findings
* $p < 0.05$, ** $p < 0.01$ vs control (Dunnett's test)

a Group means are shown.
b Number of animals with findings

c For controls, group means (absolute weights, relative weights to 100 g body weights or relative to 100 g brain weight) are shown. For treated groups, percent differences from absolute or relative control are shown. Statistical significance is calculated based on actual absolute or relative data (not on the percentage differences from absolute or relative control).
d Two main study females in the control group were found dead on PND 29 or 36
e One main study male in the 600 mg/kg/day group was found dead on PND 31. No cause of death could be determined following macroscopic and microscopic examination, and therefore the death was considered to be related to the dose administration procedures, and not the test article.

2.6.7.15 局所刺激性試験

該当する試験なし

2.6.7.16 その他の毒性試験

2.6.7.16.1 モルモット抗原性試験

Test Article: Cefiderocol sodium drug product

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/animal)	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Guinea pig/ Slc:Hartley	Immunization: Subcutaneous (Physiological saline with or without FA/Solution or Emulsion) Challenge in ASA test: Intravenous (Physiological saline/Solution) Elicitation in PCA test: Intravenous (Physiological saline/Solution)	Immunization: Five times a week for 3 weeks (without FA) Challenge in ASA test: Single dose (31days after the last immunization) Elicitation in PCA test: Single dose	Immunization: 10 [a] Challenge in ASA test: 10 [a] (cefiderocol sodium drug product alone) or 4 [b] (cefiderocol-GSA) Elicitation in PCA test: 10 [a] (cefiderocol sodium drug product alone) or 1 [b] (cefiderocol-GSA)	Immunization: 10F Challenge in ASA test: 5F/5F: cefiderocol sodium drug product alone/cefiderocol-GSA as elicitor Recipient in PCA test: 3F	Yes	ASA test: No anaphylaxis reactions in any animal elicited by cefiderocol sodium drug product alone or cefiderocol-GSA. PCA test: No anaphylaxis reactions in any animal elicited by cefiderocol sodium drug product alone or cefiderocol-GSA. ELISA: No antibody against cefiderocol was detected in any of the sera collected from the immunized animals 28 days after the last immunization.	R-649266-TB-025-L/ 4.2.3.7-01

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/animal)	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Guinea pig/ Slc:Hartley		Immunization: Twice a week for 3 weeks (with FA) Challenge in ASA test: Single dose (31days after the last immunization) Elicitation in PCA test: Single dose	Immunization: 1 [a] Challenge in ASA test: 10 [a] (cefiderocol sodium drug product alone) or 4 [b] (cefiderocol-GSA) Elicitation in PCA test: 10 [a] (cefiderocol sodium drug product alone) or 1 [b] (cefiderocol-GSA)	Immunization: 10F Challenge in ASA test: 5F/5F: cefiderocol sodium drug product alone/cefiderocol-GSA as elicitor Recipient in PCA test: 3F		ASA test: Slight anaphylaxis reactions (chewing, scratching, hyperemia of ear, and/or piloerection) in 2 out of 5 animals elicited by cefiderocol sodium drug product alone and in 2 out of 5 animals elicited by cefiderocol-GSA. PCA test: Positive reactions were generated by 3 out of 10 sera from the animals elicited by cefiderocol sodium drug product. ELISA: Antibodies against cefiderocol (antibody titer, 10^1 to 10^3) were detected in 8 of 10 sera collected from the immunized animals 28 days after the last immunization.	

ELISA = enzyme-linked immunosorbent assay; GSA = guinea pig serum albumin

a As free form

b As a conjugate of cefiderocol with GSA

2.6.7.16.2 調製検体溶液の色調に関する予備検討

Test Article: Cefiderocol sodium

Treatment/Evaluation	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Cefiderocol sodium aqueous solution (0.05, 0.15, 0.5, 1.5, and 5 mg/mL) was mixed with $FeCl_3$, $MgCl_2$, $CaCl_2$, and $ZnCl_2$ aqueous solution (0.05, 0.15, 0.5, 1.5, and 5 mmol/L for $FeCl_3$ aqueous solution; 0.05, 0.15, 0.5, and 1.5 mmol/L for $MgCl_2$, $CaCl_2$, and $ZnCl_2$ aqueous solutions). Color alteration was grossly observed under acidic and basic condition. The absorption spectrum of cefiderocol sodium aqueous solution (0.5 mmol/L) when mixed with $FeCl_3$ aqueous solution was measured.	No	Reddish coloration of cefiderocol sodium solution were observed in the presence of $FeCl_3$, but not observed in the presence of $MgCl_2$, $CaCl_2$, and $ZnCl_2$ under basic condition.	[redacted]/4.2.3.7-03

2.6.7.16.3 尿試験紙検査に及ぼす影響

Test Article: Cefiderocol sodium drug product

Treatment/Evaluation	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Cefiderocol sodium drug product solutions with physiological saline (0.05, 0.5, 5, 10, and 50 mg/mL) were assessed by urinary test paper under several pH conditions (not adjusted, 7.0 to 8.0, 8.0 to 9.0, and > 9.0).	No	Positive reactions for occult blood and ketone body were observed at 5 mg/mL or above, and positive reactions for protein were observed at 10 mg/mL or above.	R-649266-TB-044-R/ 4.2.3.7-04

2.6.7.16.4 不純物の細菌を用いる復帰突然変異試験

Test Article	Test System	Treatment	Doses (µg/plate)	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
不純物1*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	7.71 to 5000	Yes	Negative	S-649266-TF-153-L/ 4.2.3.7-05
不純物2*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	6.86 to 5000	Yes	Negative	S-649266-TF-154-L/ 4.2.3.7-06
不純物3*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	6.86 to 5000	Yes	Negative	S-649266-TF-155-L/ 4.2.3.7-07
不純物4*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	7.63 to 5000	Yes	Negative	S-649266-TF-156-L/ 4.2.3.7-08
出発物質B*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-168-L/ 4.2.3.7-09
中間体B*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-169-L/ 4.2.3.7-10
中間体A*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-170-L/ 4.2.3.7-11
不純物5*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-171-L/ 4.2.3.7-12
不純物6*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-212-L/ 4.2.3.7-13
不純物7*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-217-L/ 4.2.3.7-14
不純物8*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-218-L/ 4.2.3.7-15
不純物9*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-219-L/ 4.2.3.7-16
不純物10*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	6.86 to 5000	Yes	Negative	S-649266-TF-241-L/ 4.2.3.7-17
不純物11*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	6.86 to 5000	Yes	Negative	[redacted]/ 4.2.3.7-18

＊新薬承認情報提供時に置換

Test Article	Test System	Treatment	Doses (µg/plate)	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
出発物質A*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	3.91 to 5000	Yes	Positive (all tester strains, ±S9)	[redacted]/ 4.2.3.7-19
不純物19*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	1.2 to 5000	No	Positive (TA100, ±S9)	[redacted]/ 4.2.3.7-20
不純物12*	*S. typhimurium*	Plate incorporation method and incubation for 48 hours (37°C)	16.7 to 5000	Yes	Negative	[redacted]/ 4.2.3.7-28
不純物20*	*S. typhimurium* and *E. coli*	Plate incorporation method	50 to 5000	No	Positive (WP2*uvrA*, ±S9. TA1535, −S9)	Ames-295 and Ames-332/ 4.2.3.7-29
不純物13*	*S. typhimurium*	Plate incorporation method and incubation for 48 hours (37°C)	50 to 5000	Yes	Negative	[redacted]/ 4.2.3.7-30
不純物14*	*S. typhimurium* and *E. coli*	Plate incorporation method and incubation for 72 hours (37°C)	150 to 5000 (*S. typhimurium*) 15 to 5000 (*E. coli*)	No	Negative	Ames-2064/ 4.2.3.7-31
不純物15*	*S. typhimurium* and *E. coli*	Plate incorporation method and incubation for 72 hours (37°C)	150 to 5000 (*S. typhimurium*) 15 to 5000 (*E. coli*)	No	Negative	Ames-2065/ 4.2.3.7-32
不純物16*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-280-L/ 4.2.3.7-21
不純物21*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Positive (WP2*uvrA*, ±S9)	S-649266-TF-281-L/ 4.2.3.7-22
不純物17*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-282-L/ 4.2.3.7-23
出発物質C*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-283-L/ 4.2.3.7-24
不純物22*	*S. typhimurium* and *E. coli*	Plate incorporation method and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Positive (TA100 and TA1535, ±S9)	S-649266-TF-284-L/ 4.2.3.7-25
出発物質D*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	4.88 to 5000	Yes	Negative	S-649266-TF-285-L/ 4.2.3.7-26
不純物18*	*S. typhimurium* and *E. coli*	Preincubation method (37°C, 20 min.) and incubation for 48 hours (37°C)	78.1 to 5000	Yes	Negative	S-649266-TF-335-L/ 4.2.3.7-27
[redacted]						

＊新薬承認情報提供時に置換



2.6.7.16.5 有色ラット光毒性試験

Test Article: Cefiderocol sodium drug product

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses [a] (mg/kg/day)	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Rat/Crlj: LE	Intravenous administration for 30 minutes/animal (Physiological saline/ Solution)	3 days	0, 600, 1000	5F (0 mg/kg/day) 10F (600, 1000 mg/kg/day)	Yes	No skin reactions indicating phototoxicity	S-649266-TB-214-L/ 4.2.3.7-02

a As free form

2.6.7.16.6 In vitro 溶血性試験

Test Article: Cefiderocol sodium drug product

Species/ Strain	Method of Administration (Vehicle/Formulation)	Concentrations [a] (mg/mL)	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Rat blood, Monkey blood	In vitro (Physiological saline/Solution)	0, 15, 25, 50	No	Rat: slight haemolysis at 25 mg/mL, no hemolysis at ≤ 12.5 mg/mL Monkey: no haemolysis	[redacted]/ 4.2.3.7-33
Rabbit blood	In vitro (Physiological saline/Solution)	0, 6, 30, 50	No	No haemolysis	[redacted]/ 4.2.3.7-35
Human blood	In vitro (Physiological saline/Solution)	0, 10, 20, 40, 50	No	No haemolysis	[redacted]/ 4.2.3.7-34

a As free form