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

2.6.5 薬物動態試験概要表

塩野義製薬株式会社

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略号及び用語定義一覧表

略号	英語
α_1-AGP	α_1-acid glycoprotein
ATAA	aminothiazole amide aldehyde
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time 0 to infinity
BCRP	breast cancer resistant protein
BDC	bile duct-cannulated
BLQ	below the lower limit of quantification
BSEP	bile salt export pump
$C_{2\ (5)\ min}$	the concentration 2 (5) minutes postdose
$C_{max,u}$	unbound maximum concentration in plasma
CL_{tot}	total clearance
CYP	cytochrome P450
D	detected
EC_{50}	concentration causing half maximal effect
E_{max}	maximal induction effect
F	female
HSA	human serum albumin
IC_{50}	50% inhibitory concentration
LC/MS/MS	high-performance liquid chromatography with tandem mass spectrometry
LC/MS^n	high-performance liquid chromatography with multistage mass spectrometry
LLOQ	lower limit of quantification
LSC	liquid scintillation counter
M	male
MATE	multidrug and toxin extrusion
mRNA	messenger RNA
N/A	not applicable
N.C.	not calculated
N.D.	not detected
N.S.	no sample
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCBA	pyrrolidine chlorobenzamide
P-gp	P-glycoprotein
PK	pharmacokinetic
QC	quality control
QWBA	quantitative whole-body autoradiography

略号	英語
Radio-HPLC	high performance liquid chromatography with radio-detector
RIS	relative induction score
RSD	relative standard deviation
S.D.	standard deviation
$t_{1/2,z}$	terminal elimination half-life
TK	toxicokinetic
UPLC/MS/MS	ultra-performance liquid chromatography with tandem mass spectrometry
Vd_{ss}	volume of distribution at steady state

2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験： 一覧表

Test Article: Cefiderocol sodium drug product

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Analytical Methods and Validation					
Radiolabeled compounds	[Thiazole-^{14}C]-cefiderocol sodium drug product	N/A	Shionogi & Co., Ltd.	R-649266-QB-020-N R-649266-QB-059-N	4.2.2.1-01 4.2.2.1-02
	[Catechol-^{14}C]-cefiderocol sodium	N/A	Shionogi & Co., Ltd.	R-649266-QB-005-N	4.2.2.1-03
	[Catechol-^{14}C]-cefiderocol sodium drug product	N/A	Shionogi & Co., Ltd.	R-649266-QB-005-N S-649266-QB-069-N, S-649266-QB-144-N	4.2.2.1-03, 4.2.2.1-04 4.2.2.1-05
	[Catechol-^{14}C]-triscefiderocol tetrakistosylate monosulfate hydrate	N/A	Shionogi & Co., Ltd.	S-649266-QB-144-N	4.2.2.1-05
Method for determination of cefiderocol in rat plasma by LC/MS/MS for TK analysis	Rat plasma	N/A	Shionogi & Co., Ltd.	R-649266-TB-026-N	4.2.2.1-07
Method for determination of cefiderocol in monkey plasma by LC/MS/MS for TK analysis	Monkey plasma	N/A	Shionogi & Co., Ltd.	R-649266-TB-026-N	4.2.2.1-07
Method for determination of cefiderocol in mouse plasma by LC/MS/MS for TK analysis	Mouse plasma	N/A	Shionogi & Co., Ltd.	S-649266-TB-134-N	4.2.2.1-08
Method for determination of cefiderocol in rat plasma by LC/MS/MS for TK analysis	Rat plasma	N/A	[redacted]	S-649266-TF-247-L	4.2.2.1-09
Method for determination of cefiderocol in mouse plasma by LC/MS/MS for PK analysis	Mouse plasma	N/A	Shionogi & Co., Ltd.	R-649266-TB-026-N	4.2.2.1-07
Method for determination of cefiderocol in rat plasma by LC/MS/MS for PK analysis	Rat plasma	N/A	Shionogi & Co., Ltd.	R-649266-TB-026-N	4.2.2.1-07

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Method for determination of cefiderocol in monkey plasma by LC/MS/MS for PK analysis	Monkey plasma	N/A	Shionogi & Co., Ltd.	R-649266-TB-026-N	4.2.2.1-07
Method for determination of cefepime in rat plasma by LC/MS/MS for PK analysis	Rat plasma	N/A	Shionogi & Co., Ltd.	R-649266-PB-038-N	4.2.2.1-06
Absorption					
Dose-linearity of cefiderocol after a single intravenous administration of cefiderocol sodium drug product	Rat (M)	Intravenous	Shionogi & Co., Ltd.	R-649266-PB-035-N	4.2.2.2-01
Dose-linearity and gender difference of cefiderocol after a single intravenous administration of cefiderocol sodium drug product	Monkey (M and F)	Intravenous	Shionogi & Co., Ltd.	R-649266-PB-034-N	4.2.2.2-02
Distribution					
Tissue distribution after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Pigmented rat (M)	Intravenous	[redacted] (UK)	S-649266-PF-079-L	4.2.2.3-01
Tissue distribution after a single intravenous administration of [thiazole-^{14}C]-cefiderocol sodium drug product	Rat (M and F),	Intravenous	[redacted] (UK)	R-649266-PF-036-L	4.2.2.3-02
Tissue distribution after repeated intravenous administrations of [thiazole-^{14}C]-cefiderocol sodium drug product	Rat (M)	Intravenous	[redacted] (UK)	S-649266-PF-189-L	4.2.2.3-03
Tissue distribution after a single intravenous administration of [thiazole-^{14}C]-cefiderocol sodium drug product	Pigmented rat (M)	Intravenous	[redacted] (UK)	R-649266-PF-036-L	4.2.2.3-02
In vitro protein binding of [thiazole-^{14}C]-cefiderocol	Mouse, Rat, Monkey, Human	In vitro	[redacted]	R-649266-PF-037-L	5.3.2.1-01
In vitro distribution of [thiazole-^{14}C]-cefiderocol to blood cells	Mouse, Rat, Monkey, Human	In vitro	[redacted]	R-649266-PF-037-L	5.3.2.1-01
Distribution to blood cells after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Pigmented rat (M)	Intravenous	[redacted] (UK)	S-649266-PF-079-L	4.2.2.3-01

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Distribution to blood cells after a single intravenous administration of [thiazole-^{14}C]-cefiderocol sodium drug product	Rat (M and F), Pigmented rat (M)	Intravenous	[redacted](UK)	R-649266-PF-036-L	4.2.2.3-02
Tissue distribution after a single intravenous administration of [thiazole-^{14}C]-cefiderocol sodium drug product	Pregnant rat (F)	Intravenous	Shionogi & Co., Ltd.	S-649266-PB-186-N	4.2.2.3-04
Excretion into milk after a single intravenous administration of [thiazole-^{14}C]-cefiderocol sodium drug product	Nursing rat (F)	Intravenous	Shionogi & Co., Ltd.	S-649266-PB-188-N	4.2.2.5-02
Metabolism					
Metabolite profiling of cefiderocol after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Rat (M)	Intravenous	GlaxoSmithKline (US)	[redacted]	4.2.2.4-01
Metabolite profiling of cefiderocol after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Monkey (M and F)	Intravenous	GlaxoSmithKline (US)	[redacted]	4.2.2.4-02
In vitro metabolism of [catechol-^{14}C]-cefiderocol	Mouse, Rat, Rabbit, Monkey, and Human hepatocytes	In vitro	GlaxoSmithKline (US)	[redacted]	5.3.2.2-01
In vitro inhibitory effects of cefiderocol on human CYP enzymes	Human liver microsomes	In vitro	[redacted]	S-649266-PF-065-L	5.3.2.2-02
In vitro CYP1A2, CYP2B6, and CYP3A4 induction by cefiderocol	Human hepatocytes	In vitro	[redacted]	S-649266-PF-135-N	5.3.2.2-03
In vitro CYP3A4 Induction by Cefiderocol	Human hepatocytes	In vitro	[redacted]	S-649266-PF-415-N	5.3.2.2-04
Excretion					
Urinary and fecal excretion after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Rat (M)	Intravenous	[redacted]	[redacted]	4.2.2.5-01
Urinary and fecal excretion after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Monkey (M and F)	Intravenous	[redacted]	[redacted]	4.2.2.5-03

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Urinary, biliary, and fecal excretion after a single intravenous administration of [catechol-^{14}C]-cefiderocol sodium drug product	Rat (M)	Intravenous	[redacted]	[redacted]	4.2.2.5-01
Pharmacokinetic Drug Interactions					
In vitro substrate assessments of cefiderocol for P-gp	Caco-2 cell systems	In vitro	[redacted]	S-649266-PF-067-N	5.3.2.2-05
In vitro substrate assessments of cefiderocol for human renal uptake transporters	OAT1, OAT3, or OCT2 expressing HEK293 cells	In vitro	[redacted]	S-649266-PF-074-N	5.3.2.2-07
In vitro substrate assessments of cefiderocol for human renal efflux transporters	MATE1 and MATE2-K expressing HEK293 cells	In vitro	[redacted]	S-649266-PF-128-N	5.3.2.2-06
In vitro inhibitor assessments of cefiderocol for human renal uptake transporters	OAT1, OAT3, or OCT2 expressing HEK293 cells	In vitro	[redacted]	S-649266-PF-074-N	5.3.2.2-07
In vitro inhibitor assessments of cefiderocol for human transporters	OATP1B1, OATP1B3, OCT1, MATE1, and MATE2-K expressing HEK293 cells, Caco-2 cell systems (P-gp and BCRP), or BSEP expressing vesicles	In vitro	[redacted]	S-649266-PF-127-N	5.3.2.2-08

BCRP = breast cancer resistant protein; BSEP = bile salt export pump; CYP = cytochrome P450; F = female; LC/MS/MS = high-performance liquid chromatography with tandem mass spectrometry; M = male; MATE = multidrug and toxin extrusion; N/A = not applicable; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; P-gp = P-glycoprotein; PK = pharmacokinetic; TK = toxicokinetic

2.6.5.2 分析方法及びバリデーション試験

2.6.5.2.1 [^{14}C]-セフィデロコルナトリウム塩製剤のロット番号，比放射能，放射化学的純度，化学的純度及び性状

Radiolabeled Position	Lot Number	Specific Radioactivity	Radiochemical Purity	Chemical Purity	Description	Study Number
Thiazole Ring	[redacted]	122 kBq/mg (3.31 µCi/mg)	≥ 96.5%	≥ 98.0%	Lyophilyzed powder	R-649266-QB-020-N
	[redacted]	123 kBq/mg (3.33 µCi/mg)	96.9%	99.5%	Lyophilyzed powder	R-649266-QB-020-N
	[redacted]	477 kBq/mg (12.9 µCi/mg)	≥ 95.8%	≥ 98.3%	Lyophilyzed powder	R-649266-QB-020-N R-649266-QB-059-N
	[redacted]	367 kBq/mg (9.93 µCi/mg)	98.2%	99.6%	Lyophilyzed powder	R-649266-QB-059-N
	[redacted]	400 kBq/mg (10.8 µCi/mg)	≥ 95.7%	≥ 98.4%	Lyophilyzed powder	R-649266-QB-059-N
	[redacted]	407 kBq/mg (11.0 µCi/mg)	97.3%	99.6%	Lyophilyzed powder	R-649266-QB-059-N
	[redacted]	122 kBq/mg (3.30 µCi/mg)	97.6%	99.4%	Lyophilyzed powder	R-649266-QB-059-N
	[redacted]	118 kBq/mg (3.19 µCi/mg)	97.3%	98.6%	Lyophilyzed powder	R-649266-QB-059-N
Catechol Moiety	[redacted]	90.7 kBq/mg (2.45 µCi/mg)	97.7%	99.2%	Lyophilyzed powder	R-649266-QB-005-N
	[redacted]	411 kBq/mg (11.1 µCi/mg)	95.5%	98.6%	White crystals	R-649266-QB-005-N
	[redacted]	124 kBq/mg (3.34 µCi/mg)	97.2%	99.0%	Lyophilyzed powder	R-649266-QB-005-N
	[redacted]	148 kBq/mg (4.01 µCi/mg)	98.2%	99.2%	Lyophilyzed powder	S-649266-QB-069-N
	[redacted]	119 kBq/mg (3.22 µCi/mg)	≥ 98.4%	≥ 99.5%	Crystals	S-649266-QB-144-N

2.6.5.2.2 LC/MS/MS によるラット及びサル血漿中セフィデロコル濃度測定法 (TK 評価用)

Test Site	Shionogi & Co., Ltd.							
LLOQ (μg/mL)	2.00							
Calibration Curve Range (μg/mL)	2.00 to 10000							
Matrix	Rat Plasma (Anticoagulant: heparin sodium)				Monkey Plasma (Anticoagulant: heparin sodium)			
LC/MS/MS System	1		2		1		2	
QC Levels (μg/mL) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	2.00 5.7 105 – –	6.00, 200, 8000 3.6 to 9.2 93.8 to 106.0 5.6 to 7.7 97.8 to 104.5	2.00 6.9 108.5 – –	6.00, 200, 8000 2.0 to 2.9 100.3 to 105.5 – –	2.00 7.4 102.0 – –	6.00, 200, 8000 5.0 to 9.8 91.5 to 96.7 – –	2.00 9.6 99.0 – –	6.00, 200, 8000 2.0 to 4.7 98.0 to 99.3 – –
Stability in Plasma	Stable after 3 freeze-thaw cycles at −20°C and −80°C, at least 6 days at −20°C and 63 days at −80°C, and at least 4 hours on ice				Stable after 3 freeze-thaw cycles at −20°C and −80°C, at least 8 days at −20°C and 58 days at −80°C, and at least 4 hours on ice			
Processed Extract Stability	Stable at least 24 hours at 4°C							
Study Number	R-649266-TB-026-N				R-649266-TB-026-N			
Study Number Supported	S-649266-TF-021-L, S-649266-TF-130-L, S-649266-TF-182-L, S-649266-TF-159-L, S-649266-TF-132-L, S-649266-TF-224-L				S-649266-TF-022-L, S-649266-TF-121-L, S-649266-TF-183-L			

QC = quality control; RSD = relative standard deviation; LLOQ = lower limit of quantification
–: No data

2.6.5.2.3 LC/MS/MS によるマウス血漿中セフィデロコル濃度測定法 (TK 評価用)

Test Site	Shionogi & Co., Ltd.			
Matrix	Mouse Plasma (Anticoagulant: heparin sodium)			
LLOQ (μg/mL)	2.00			
Calibration Curve Range (μg/mL)	2.00 to 10000			
LC/MS/MS System	1		2	
QC Levels (μg/mL) Within-run Precision (RSD, %) Within-run Accuracy (%) Between-run Precision (RSD, %) Between-run Accuracy (%)	2.00 2.7 to 5.1 98.0 to 111.0 6.2 104.5	5.99, 200, 7980 0.9 to 7.1 98.0 to 106.0 2.9 to 5.9 101.5 to 104.3	2.00 4.5 11.5 – –	5.99, 200, 7980 3.0 to 7.3 102.8 to 104.2 – –
Stability in Plasma	Stable after 3 freeze-thaw cycles at −20°C and −80°C, at least 6 days at −20°C and 63 days at −80°C, and at least 4 hours on ice			
Processed Extract Stability	Stable at least 24 hours at 4°C			
Study Number	S-649266-TB-134-N			
Study Number Supported	S-649266-TF-131-L			

–: No data

2.6.5.2.4 LC/MS/MS によるラット血漿中セフィデロコル濃度測定法 (TK 評価用)

Test Site	[redacted]	
Matrix	Rat Plasma (Anticoagulant: K_2EDTA)	
LLOQ (μg/mL)	2.00	
Calibration Curve Range (μg/mL)	2.00 to 2000	
QC Levels (μg/mL)	2.00	6.00, 75.0, 1600
Within-run Precision (RSD, %)	3.7 to 13.1	2.0 to 8.3
Within-run Accuracy (%)	98.0 to 113.5	97.0 to 108.7
Between-run Precision (RSD, %)	10.6	3.2 to 7.3
Between-run Accuracy (%)	7.0	100.8 to 106.9
Stability in Plasma	Stable after 3 freeze-thaw cycles at −70°C, at least 40 days at −70°C, and at least 6 hours on ice	
Processed Extract Stability	Stable at least 24 hours at 4°C	
Study Number	S-649266-TF-247-L	
Study Number Supported	S-649266-TF-274-L	

2.6.5.2.5 LC/MS/MS によるマウス，ラット及びサル血漿中セフィデロコル濃度測定法 (PK 評価用)

Test Site	Shionogi & Co., Ltd.					
Matrix	Mouse Plasma (Anticoagulant: heparin sodium)		Rat Plasma (Anticoagulant: heparin sodium)		Monkey Plasma (Anticoagulant: heparin sodium)	
LLOQ (μg/mL)	0.0500		0.100		0.100	
Calibration Curve Range (μg/mL)	0.0500 to 100		0.100 to 200		0.100 to 400	
QC Levels (μg/mL)	0.0500	0.150, 2.00, 80.0	0.100	0.300, 4.00, 160	0.100	0.300, 4.00, 160
Within-run Precision (RSD, %)	7.8	2.2 to 6.4	11.7	0.9 to 2.8	8.3	1.6 to 8.9
Within-run Accuracy (%)	10.0	−6.0 to 9.9	−8.0	−4.4 to 10.0	−3.9	−14.4 to 2.7
Dilution Factor	20		–		–	
Within-run Precision (RSD, %)	5.0		–		–	
Within-run Accuracy (%)	1.0		–		–	
Stability in Plasma	Stable after 3 freeze-thaw cycles at −80°C, at least 26 days at −80°C and at least 4 hours on ice		Stable after 3 freeze-thaw cycles at −80°C, at least 32 days at −80°C and at least 4 hours on ice		Stable after 3 freeze-thaw cycles at −80°C, at least 32 days at −80°C and at least 4 hours on ice	
Processed Extract Stability	Stable at least 24 hours at 4°C					
Study Number	R-649266-TB-026-N		R-649266-TB-026-N		R-649266-TB-026-N	
Study Number Supported	R-649266-EB-039-N, S-649266-EB-202-N, S-649266-PB-097-R		R-649266-PB-035-N S-649266-EB-157-N		R-649266-PB-034-N	

–: No data

2.6.5.2.6 LC/MS/MS によるマウス血漿中セフェピム濃度測定法 (TK 評価用)

Test Site	Shionogi & Co., Ltd.	
Matrix	Mouse Plasma (Anticoagulant: heparin)	
LLOQ (μg/mL)	0.500	
Calibration Curve Range (μg/mL)	0.500 to 5000	
QC Levels (μg/mL)	0.501	1.51, 15.1, 404
Within-run Precision (RSD, %)	4.6	0.6 to 3.3
Within-run Accuracy (%)	104.2	100.7 to 105.3
Between-run Precision (RSD, %)	–	2.1 to 2.6
Between-run Accuracy (%)	–	102.0 to 104.0
Dilution Factor	10	
Within-run Precision (RSD, %)	0.8	
Within-run Accuracy (%)	103.8	
Stability in Mouse Plasma	Stable after 3 freeze-thaw cycles at −80°C, at least 27 days at −80°C, and at least 4 hours on ice	
Processed Process Stability	Stable at least 24 hours at 4°C	
Study Number	R-649266-PB-038-N	
Study Number Supported	R-649266-EB-039-N	

–: No data

2.6.5.3 薬物動態試験： 吸収：単回投与

2.6.5.3.1 ラットにおけるセフィデロコルナトリウム塩製剤単回静脈内投与後のセフィデロコルの用量相関性

Test Article: Cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)		
Gender (M/F)/Number of Animals	M/4 per group		
Feeding Condition	Non-fasted		
Vehicle/Formulation	Saline/solution		
Method of Administration	Single intravenous administration (bolus)		
Dose (mg/kg) [a]	10, 30, 100		
Sample	Plasma (2, 5, 15, 30 minutes, 1, 2, 4, 6, 8 hours postdose)		
Analyte	Cefiderocol		
Assay	LC/MS/MS		
PK Parameters	10 mg/kg	30 mg/kg	100 mg/kg
$C_{2\ min}$ (µg/mL)	49.2 ± 2.6	157 ± 3	481 ± 12
$AUC_{0\text{-}inf}$ (µg·hr/mL)	19.2 ± 1.5	57.5 ± 2.4	174 ± 8
CL_{tot} (mL/hr/kg)	522 ± 41	522 ± 22	575 ± 24
$t_{1/2,z}$ (hr)	0.321 ± 0.007	0.338 ± 0.017	0.418 ± 0.024
Vd_{ss} (mL/kg)	206 ± 8	211 ± 3	235 ± 14
$AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 to infinity; $C_{2\ min}$ = the concentration 2 minutes postdose; CL_{tot} = total clearance; $t_{1/2,z}$ = terminal elimination half-life; Vd_{ss} = volume of distribution at steady state; S.D. = standard deviation Data are expressed as the mean ± S.D. of 4 individuals. LLOQ was set at 0.100 µg/mL. a As free form			
Study Number	R-649266-PB-035-N		
Location in CTD	4.2.2.2-01		

2.6.5.3.2 サルにおけるセフィデロコルナトリウム塩製剤単回静脈内投与後のセフィデロコルの用量相関性

Test Article: Cefiderocol sodium drug product

Species/Strain	Monkey/Cynomolgus			
Gender (M/F)/Number of Animals	M/3 per group, F/3 per group			
Feeding Condition	Non-fasted			
Vehicle/Formulation	Saline/solution			
Method of Administration	Single intravenous administration (2-minute infusion)			
Dose (mg/kg) [a]	M/10, 30, and 100, F/30			
Sample	Plasma (5, 15, 30 minutes, 1, 2, 4, 6, 8, and 24 hours postdose)			
Analyte	Cefiderocol			
Assay	LC/MS/MS			
PK Parameters	M			F
	10 mg/kg	30 mg/kg	100 mg/kg	30 mg/kg
$C_{5\ min}$ (μg/mL)	65.2 ± 4.9	180 ± 15	570 ± 9	182 ± 42
$AUC_{0\text{-}inf}$ (μg·hr/mL)	65.7 ± 4.0	207 ± 19	666 ± 34	200 ± 5
CL_{tot} (mL/hr/kg)	153 ± 9	145 ± 12	150 ± 8	150 ± 4
$t_{1/2,z}$ (hr)[b]	1.16 ± 0.13	1.19 ± 0.09	1.22 ± 0.05	1.18 ± 0.04
Vd_{ss} (mL/kg)	208 ± 13	205 ± 23	211 ± 9	203 ± 20
$C_{5\ min}$ = the concentration 5 minutes postdose Data are expressed as the mean ± S.D. of 3 individuals. LLOQ was set at 0.100 μg/mL. a As free form.				
Study Number	R-649266-PB-034-N			
Location in CTD	4.2.2.2-02			

2.6.5.4 薬物動態試験： 吸収：反復投与

反復投与時の吸収は，2.6.7 項に TK として記載している．

2.6.5.5 薬物動態試験： 分布

2.6.5.5.1 有色ラットにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の組織分布

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Harlan Long-Evans
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	148 kBq/mg (4.01 μCi/mg)
Sample	Plasma, Blood, Adrenal cortex, Adrenal medulla, Aortic wall, Bile ducts and contents, Bone marrow, Bone surface, Brain, Brown fat, Bulbo-urethral gland, Cerebrospinal fluid, Choroid plexus, Epididymis, Epimysium, Exorbital lachrymal gland, Fur (Pigmented), Harderian gland, Intra-orbital lachrymal gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mandibular lymph node, Meninges, Muscle, Myocardium, Nasal mucosa, Pancreas, Periodontal membrane, Pineal body, Pituitary gland, Preputial gland, Prostate, Salivary glands, Seminal vesicles, Skin (Non-pigmented), Skin (Pigmented), Spinal cord, Spleen, Testis, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Uveal tract/retina, White fat, Urinary bladder wall, Urinary bladder contents, Esophageal wall, Stomach mucosa (fundus), Stomach mucosa (non-fundus), Small intestinal mucosa, Caecum mucosa, Large intestinal mucosa, Rectum mucosa
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and blood, QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Plasma	120	25.5	0.204	0.032	N.D.	N.D.	N.D.	N.D.	N.C.
Blood	67.4	15.6	0.132	N.D.	N.D.	N.D.	N.D.	N.D.	N.C.
Adrenal cortex	19.2	3.91	0.217	0.166	BLQ	BLQ	BLQ	BLQ	N.C.
Adrenal medulla	28.1	5.40	0.203	0.106	BLQ	0.083	BLQ	BLQ	N.C.
Aortic wall	72.8	16.5	0.186	0.083	BLQ	BLQ	BLQ	BLQ	N.C.
Bile ducts and contents	72.6	23.5	N.S.	0.656	BLQ	BLQ	BLQ	BLQ	N.C.
Bone marrow	13.7	2.78	0.211	0.161	BLQ	0.078	BLQ	BLQ	83.1
Bone surface	30.1	3.91	0.192	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brain	0.696	0.543	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brown fat	19.2	3.51	0.095	0.098	BLQ	BLQ	BLQ	BLQ	N.C.
Bulbo-urethral gland	535	8.14	0.229	0.128	BLQ	1.44	BLQ	BLQ	N.C.
Cerebrospinal fluid	10.4	1.68	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Choroid plexus	5.14	1.61	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Epididymis	15.6	2.94	0.702	0.174	BLQ	BLQ	BLQ	BLQ	6.26
Epimysium	15.5	3.63	0.129	0.162	BLQ	BLQ	BLQ	BLQ	N.C.
Exorbital lachrymal gland	13.7	4.86	0.151	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Fur (Pigmented)	0.486	2.34	0.282	0.153	BLQ	BLQ	BLQ	BLQ	N.C.
Harderian gland	11.1	3.63	0.181	0.137	BLQ	BLQ	BLQ	BLQ	N.C.
Intra-orbital lachrymal gland	53.6	4.38	0.277	0.552	BLQ	BLQ	BLQ	BLQ	N.C.
Kidney cortex	220	146	17.4	10.3	2.75	1.27	0.177	BLQ	52.6
Kidney medulla	705	70.8	1.18	1.38	0.194	0.182	BLQ	BLQ	35.2
Lens of the eye	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Liver	16.7	5.70	0.715	0.335	0.138	0.103	BLQ	BLQ	42.6

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Lung	51.8	10.0	0.141	0.087	BLQ	0.116	BLQ	BLQ	N.C.
Mandibular lymph node	33.7	6.90	0.326	0.252	BLQ	BLQ	BLQ	BLQ	N.C.
Meninges	6.07	3.45	0.120	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Muscle	6.10	1.45	BLQ	0.085	BLQ	BLQ	BLQ	BLQ	N.C.
Myocardium	16.2	3.80	0.103	0.075	BLQ	BLQ	BLQ	BLQ	N.C.
Nasal mucosa	10.6	3.61	BLQ	0.112	BLQ	BLQ	BLQ	BLQ	N.C.
Pancreas	12.8	4.14	0.170	0.138	BLQ	BLQ	BLQ	BLQ	N.C.
Periodontal membrane	21.4	7.98	0.162	0.152	BLQ	BLQ	BLQ	BLQ	N.C.
Pineal body	16.1	2.53	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Pituitary gland	19.3	3.43	0.148	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Preputial gland	15.5	5.53	0.196	0.302	BLQ	BLQ	BLQ	BLQ	N.C.
Prostate	49.2	8.79	0.264	4.70	0.114	BLQ	BLQ	BLQ	N.C.
Salivary glands	22.8	5.07	0.191	0.105	BLQ	BLQ	BLQ	BLQ	N.C.
Seminal vesicles	11.2	1.10	BLQ	3.29	BLQ	BLQ	BLQ	BLQ	N.C.
Skin (Non-pigmented)	1.85	12.0	0.174	0.106	BLQ	BLQ	BLQ	BLQ	N.C.
Skin (Pigmented)	24.8	13.7	0.152	0.164	BLQ	BLQ	BLQ	BLQ	N.C.
Spinal cord	1.99	0.354	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Spleen	9.63	3.94	0.250	0.251	0.098	BLQ	BLQ	BLQ	45.3
Testis	4.82	2.03	0.098	0.107	BLQ	BLQ	BLQ	BLQ	N.C.
Thymus	6.40	1.70	0.085	0.082	BLQ	BLQ	BLQ	BLQ	N.C.
Thyroid gland	32.8	5.91	0.256	0.137	BLQ	BLQ	BLQ	BLQ	N.C.
Tongue	27.8	7.72	0.234	0.126	BLQ	BLQ	BLQ	BLQ	N.C.
Tooth pulp	16.5	5.66	0.220	0.128	BLQ	BLQ	BLQ	BLQ	N.C.
Trachea	47.0	9.83	0.101	0.154	BLQ	BLQ	BLQ	BLQ	N.C.
Uveal tract/retina	8.80	7.53	0.424	0.318	0.236	BLQ	BLQ	BLQ	83.2

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
White fat	0.440	BLQ	BLQ	0.093	BLQ	BLQ	BLQ	BLQ	N.C.
Urinary bladder wall	109	352	1.56	2.05	0.196	BLQ	BLQ	BLQ	19.8
Urinary bladder contents	140	1860	24.0	4.98	0.412	BLQ	BLQ	BLQ	11.6
Esophageal wall	27.1	6.93	0.282	0.117	BLQ	BLQ	BLQ	BLQ	N.C.
Stomach mucosa (fundus)	16.1	4.82	0.918	0.082	BLQ	BLQ	BLQ	BLQ	4.18
Stomach mucosa (non-fundus)	3.53	10.1	0.750	0.489	0.095	BLQ	BLQ	BLQ	21.7
Small intestinal mucosa	13.6	2.46	0.790	0.504	0.083	BLQ	BLQ	BLQ	19.9
Caecum mucosa	24.0	2.86	7.22	0.583	0.092	0.113	BLQ	BLQ	N.C.
Large intestinal mucosa	13.9	5.05	3.19	1.52	BLQ	0.168	0.151	BLQ	N.C.
Rectum mucosa	29.9	8.74	0.156	3.67	0.081	0.084	BLQ	BLQ	N.C.
BLQ = below the lower limit of quantification; LSC = liquid scintillation counter; N.C. = not calculated; N.D. = not detected; N.S. = no sample; QWBA = quantitative whole-body autoradiography When the plasma and blood concentrations of radioactivity were < 0.020 μg/g and < 0.047 μg/g, respectively, it was represented as N.D. When the concentrations of radioactivity in other tissues were < 0.075 μg/g, it was represented as BLQ. a As free form									
Study Number	S-649266-PF-079-L								
Location in CTD	4.2.2.3-01								

2.6.5.5.2 雄性ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の組織分布

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	122 kBq/mg (3.31 μCi/mg)
Sample	Plasma, Blood, Adrenal cortex, Adrenal medulla, Aortic wall, Bile ducts and contents, Bone marrow, Bone surface, Brain, Brown fat, Bulbo-urethral gland, Cerebrospinal fluid, Choroid plexus, Epididymis, Epimysium, Exorbital lachrymal gland, Fur, Harderian gland, Intra-orbital lachrymal gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mandibular lymph node, Meninges, Muscle, Myocardium, Nasal mucosa, Pancreas, Periodontal membrane, Pineal body, Pituitary gland, Preputial gland, Prostate, Salivary glands, Seminal vesicles, Skin, Spinal cord, Spleen, Testis, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Uveal tract/retina, White fat, Urinary bladder wall, Urinary bladder contents, Esophageal wall, Stomach mucosa (fundus), Stomach mucosa (non-fundus), Small intestinal mucosa, Caecum mucosa, Large intestinal mucosa, Rectum mucosa
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and blood, QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Plasma	97.8	13.7	1.95	0.965	0.345	0.132	N.D.	N.D.	30.3
Blood	64.9	7.97	1.10	0.517	0.199	0.089	N.D.	N.D.	32.8
Adrenal cortex	18.1	2.44	0.635	1.30	0.176	0.137	BLQ	BLQ	29.6
Adrenal medulla	29.7	2.72	1.01	0.388	0.151	0.141	BLQ	BLQ	42.6
Aortic wall	69.3	11.9	1.11	0.562	BLQ	BLQ	BLQ	BLQ	N.C.

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Bile ducts and contents	102	18.0	1.33	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Bone marrow	14.4	2.04	0.660	0.356	0.127	0.169	BLQ	BLQ	N.C.
Bone surface	25.9	2.58	0.678	0.470	BLQ	BLQ	BLQ	BLQ	N.C.
Brain	2.04	0.273	0.096	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brown fat	26.1	3.50	0.587	0.294	BLQ	0.106	BLQ	BLQ	N.C.
Bulbo-urethral gland	57.9	9.09	0.823	0.621	0.271	0.189	0.132	BLQ	289
Cerebrospinal fluid	36.7	6.03	0.940	0.471	BLQ	BLQ	BLQ	BLQ	N.C.
Choroid plexus	13.6	1.34	BLQ	0.171	BLQ	BLQ	BLQ	BLQ	N.C.
Epididymis	18.3	5.07	0.537	0.542	0.126	0.107	BLQ	BLQ	42.6
Epimysium	33.2	3.80	0.700	0.573	BLQ	BLQ	BLQ	BLQ	N.C.
Exorbital lachrymal gland	18.5	2.85	0.629	0.345	0.151	0.161	BLQ	BLQ	N.C.
Fur	BLQ	1.63	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Harderian gland	11.9	1.39	0.448	0.484	0.236	0.155	BLQ	BLQ	58.4
Intra-orbital lachrymal gland	21.6	2.75	0.416	0.332	0.268	0.117	BLQ	BLQ	66.6
Kidney cortex	259	49.5	25.4	16.7	8.86	5.10	1.99	0.221	159
Kidney medulla	426	31.7	1.56	0.806	1.59	2.56	1.08	BLQ	N.C.
Lens of the eye	0.235	0.168	BLQ	0.103	BLQ	BLQ	BLQ	BLQ	N.C.
Liver	14.8	2.57	0.829	0.618	0.200	0.133	BLQ	BLQ	41.3
Lung	53.3	5.67	1.04	0.494	0.202	0.122	BLQ	BLQ	38.5
Mandibular lymph node	18.9	2.23	0.553	0.256	0.245	0.151	BLQ	BLQ	126
Meninges	12.2	2.62	0.548	0.250	BLQ	BLQ	BLQ	BLQ	N.C.
Muscle	10.2	1.36	0.297	0.174	0.121	0.105	BLQ	BLQ	132
Myocardium	22.6	2.66	0.524	0.251	0.144	0.110	BLQ	BLQ	80.7
Nasal mucosa	10.9	2.89	0.360	0.242	0.142	0.105	BLQ	BLQ	66.3
Pancreas	21.7	2.52	0.549	0.273	0.178	0.128	BLQ	BLQ	87.9

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Periodontal membrane	41.5	5.38	0.823	0.417	BLQ	BLQ	BLQ	BLQ	N.C.
Pineal body	20.2	1.66	0.559	0.163	BLQ	BLQ	BLQ	BLQ	7.51
Pituitary gland	14.8	2.64	0.408	0.161	0.148	0.143	BLQ	BLQ	561
Preputial gland	25.1	2.56	1.25	0.580	0.276	0.156	BLQ	BLQ	40.4
Prostate	11.4	2.80	0.527	0.243	0.160	0.103	BLQ	BLQ	77.5
Salivary glands	20.2	3.14	0.553	0.326	0.184	0.119	BLQ	BLQ	54.3
Seminal vesicles	1.87	0.535	0.273	0.115	BLQ	BLQ	BLQ	BLQ	11.2
Skin	31.6	6.15	1.66	0.778	0.291	0.231	0.182	BLQ	441
Spinal cord	1.49	0.358	0.121	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Spleen	12.0	2.01	0.825	0.469	0.184	0.127	BLQ	BLQ	42.8
Testis	4.97	1.94	0.478	0.273	0.140	0.110	BLQ	BLQ	73.2
Thymus	8.09	1.51	0.235	0.210	0.139	0.134	BLQ	BLQ	132
Thyroid gland	23.2	4.70	0.797	0.671	0.115	0.208	BLQ	BLQ	N.C.
Tongue	21.7	4.23	0.593	0.365	0.151	0.120	BLQ	BLQ	49.5
Tooth pulp	69.9	5.07	1.15	0.608	0.148	0.221	BLQ	BLQ	N.C.
Trachea	33.3	4.37	0.699	0.131	N.S.	BLQ	BLQ	BLQ	5.07
Uveal tract/retina	15.2	7.00	1.19	0.411	0.208	0.260	BLQ	BLQ	N.C.
White fat	1.19	0.986	0.256	0.183	0.105	BLQ	BLQ	BLQ	52.9
Urinary bladder wall	542	910	N.S.	7.42	1.59	BLQ	BLQ	BLQ	N.C.
Urinary bladder contents	1370	1600	N.S.	1.38	0.706	0.702	BLQ	BLQ	N.C.
Esophageal wall	35.9	5.57	1.46	0.598	BLQ	BLQ	BLQ	BLQ	8.21
Stomach mucosa (fundus)	49.9	3.36	0.401	0.374	BLQ	BLQ	BLQ	BLQ	N.C.
Stomach mucosa (non-fundus)	27.7	5.49	0.656	0.316	BLQ	BLQ	BLQ	BLQ	N.C.
Small intestinal mucosa	24.8	2.58	0.490	0.451	0.144	BLQ	BLQ	BLQ	35.3
Caecum mucosa	34.7	3.98	1.40	1.92	0.186	BLQ	BLQ	BLQ	18.2

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Large intestinal mucosa	25.3	4.15	4.37	1.16	0.403	0.149	BLQ	BLQ	32.4
Rectum mucosa	42.6	4.43	4.62	1.31	0.244	0.168	BLQ	BLQ	24.5
When the plasma and blood concentrations of radioactivity were < 0.022 μg/g and < 0.039 μg/g, respectively, it was represented as N.D. When the concentrations of radioactivity in other tissues were < 0.092 μg/g, it was represented as BLQ. a As free form									
Study Number	R-649266-PF-036-L								
Location in CTD	4.2.2.3-02								

2.6.5.5.3 雌性ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の組織分布

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	F/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	122 kBq/mg (3.31 μCi/mg)
Sample	Plasma, Blood, Adrenal cortex, Adrenal medulla, Aortic wall, Bile ducts and contents, Bone marrow, Bone surface, Brain, Brown fat, Cerebrospinal fluid, Choroid plexus, Clitoris, Epimysium, Exorbital lachrymal gland, Fur, Harderian gland, Intra-orbital lachrymal gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mandibular lymph node, Meninges, Muscle, Myocardium, Nasal mucosa, Ovary, Pancreas, Periodontal membrane, Pineal body, Pituitary gland, Salivary glands, Skin, Spinal cord, Spleen, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Uterus, Uveal tract/retina, White fat, Urinary bladder wall, Urinary bladder contents, Esophageal wall, Stomach mucosa (fundus), Stomach mucosa (non-fundus), Small intestinal mucosa, Caecum mucosa, Large intestinal mucosa, Rectum mucosa
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and blood, QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Plasma	95.7	8.14	1.12	1.14	0.520	0.218	N.D.	N.D.	40.2
Blood	62.1	6.28	0.916	0.646	0.302	0.142	N.D.	N.D.	42.8
Adrenal cortex	18.7	1.94	0.513	0.237	0.204	0.174	BLQ	BLQ	215
Adrenal medulla	36.9	3.78	0.566	0.383	0.154	BLQ	BLQ	BLQ	35.4
Aortic wall	88.7	9.28	1.13	0.425	0.312	BLQ	BLQ	BLQ	N.C.
Bile ducts and contents	145	15.2	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Bone marrow	24.5	1.67	0.782	0.340	0.145	0.119	BLQ	BLQ	63.4
Bone surface	23.6	2.82	0.571	0.436	0.310	0.172	BLQ	BLQ	69.1
Brain	1.17	0.241	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brown fat	15.5	2.10	0.456	0.239	0.173	0.149	BLQ	BLQ	141
Cerebrospinal fluid	69.4	6.58	0.659	0.439	0.174	0.162	BLQ	BLQ	54.8
Choroid plexus	9.56	1.05	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Clitoris	4.07	2.74	1.26	0.532	0.137	0.121	BLQ	BLQ	34.0
Epimysium	39.2	10.0	0.705	0.619	0.206	0.222	BLQ	BLQ	60.2
Exorbital lachrymal gland	16.4	1.94	0.365	0.304	0.190	0.159	BLQ	BLQ	93.1
Fur	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Harderian gland	22.8	1.90	0.576	0.448	0.207	BLQ	BLQ	BLQ	44.4
Intra-orbital lachrymal gland	21.8	3.12	0.303	0.265	BLQ	BLQ	BLQ	BLQ	N.C.
Kidney cortex	332	40.9	21.4	16.3	8.46	6.71	3.15	1.02	258
Kidney medulla	706	35.1	7.79	1.05	0.619	0.202	0.585	BLQ	N.C.
Lens of the eye	0.232	0.209	0.118	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Liver	19.4	3.34	0.824	0.462	0.214	0.144	BLQ	BLQ	46.8
Lung	60.5	6.04	0.884	0.562	0.250	0.124	BLQ	BLQ	41.0
Mandibular lymph node	43.7	3.85	0.466	1.21	0.142	0.176	BLQ	BLQ	N.C.
Meninges	9.43	1.70	0.576	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Muscle	14.2	1.23	0.227	0.155	BLQ	BLQ	BLQ	BLQ	N.C.
Myocardium	26.8	BLQ	0.397	0.270	0.169	BLQ	BLQ	BLQ	56.4
Nasal mucosa	13.7	1.42	0.340	0.188	BLQ	BLQ	BLQ	BLQ	N.C.
Ovary	43.9	4.48	0.889	0.697	0.192	BLQ	BLQ	BLQ	28.9

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Pancreas	20.5	2.39	0.438	0.262	0.171	0.125	BLQ	BLQ	68.1
Periodontal membrane	39.2	4.57	0.868	0.400	0.461	0.193	BLQ	BLQ	N.C.
Pineal body	19.5	3.04	0.463	0.341	0.145	BLQ	BLQ	BLQ	39.3
Pituitary gland	21.1	2.06	0.317	0.326	0.262	BLQ	BLQ	BLQ	215
Salivary glands	27.7	2.60	0.452	0.328	0.148	0.166	BLQ	BLQ	N.C.
Skin	21.0	10.1	0.878	0.579	0.379	0.259	0.171	0.147	N.C.
Spinal cord	1.35	0.206	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Spleen	18.6	1.87	0.631	0.418	0.184	0.150	BLQ	BLQ	54.6
Thymus	10.0	0.942	0.271	0.193	0.148	BLQ	BLQ	BLQ	82.4
Thyroid gland	48.4	3.26	0.689	0.654	0.278	0.182	BLQ	BLQ	55.0
Tongue	30.3	2.40	0.379	0.323	0.142	0.151	BLQ	BLQ	77.4
Tooth pulp	43.2	5.29	1.43	0.519	0.270	BLQ	BLQ	BLQ	30.3
Trachea	34.4	4.38	0.466	0.300	0.119	BLQ	BLQ	BLQ	34.0
Uterus	63.6	3.15	1.12	0.726	0.295	0.143	BLQ	BLQ	38.7
Uveal tract/retina	23.5	6.44	0.465	0.376	0.266	BLQ	BLQ	BLQ	84.5
White fat	6.40	0.330	0.134	0.123	BLQ	BLQ	BLQ	BLQ	N.C.
Urinary bladder wall	930	344	34.5	0.814	0.470	N.S.	N.S.	BLQ	N.C.
Urinary bladder contents	1840	1010	9.78	0.515	0.232	N.S.	N.S.	BLQ	N.C.
Esophageal wall	38.9	4.16	0.830	0.559	0.388	BLQ	BLQ	BLQ	64.7
Stomach mucosa (fundus)	34.3	2.32	0.477	0.226	0.210	BLQ	BLQ	BLQ	N.C.
Stomach mucosa (non-fundus)	23.4	5.24	0.568	0.357	0.169	BLQ	BLQ	BLQ	39.0
Small intestinal mucosa	24.2	5.75	0.268	0.307	0.127	BLQ	BLQ	BLQ	54.3
Caecum mucosa	41.2	4.04	3.84	0.788	0.236	0.275	BLQ	BLQ	N.C.

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Large intestinal mucosa	35.6	2.52	BLQ	0.898	0.226	BLQ	BLQ	BLQ	N.C.
Rectum mucosa	54.4	4.72	0.546	1.69	0.292	N.S.	N.S.	BLQ	N.C.
When the plasma and blood concentrations of radioactivity were < 0.022 μg/g and < 0.036 μg/g, respectively, it was represented as N.D. When the concentrations of radioactivity in other tissues were < 0.118 μg/g, it was represented as BLQ. a As free form									
Study Number	R-649266-PF-036-L								
Location in CTD	4.2.2.3-02								

2.6.5.5.4 雄性ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤反復静脈内投与後の組織分布

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/solution
Method of Administration	Repeated intravenous administrations (bolus), once daily for 14 days
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	118 kBq/mg (3.19 μCi/mg)
Sample	Plasma, Blood, Adrenal cortex, Adrenal medulla, Aortic wall, Bile ducts, Bone marrow, Bone surface, Brain, Brown fat, Bulbo-urethral gland, Cerebrospinal fluid, Choroid plexus, Epididymis, Epimysium, Exorbital lachrymal gland, Fur, Harderian gland, Intra-orbital lachrymal gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mandibular lymph nodes, Meninges, Muscle, Myocardium, Nasal mucosa, Pancreas, Periodontal membrane, Pineal body, Pituitary gland, Preputial gland, Prostate, Salivary glands, Seminal vesicles, Skin, Spinal cord, Spleen, Testis, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Urinary bladder wall, Urine, Uveal tract/retina, White fat, Esophageal wall, Stomach mucosa (fundus), Stomach mucosa (non-fundus), Small intestinal mucosa, Caecum mucosa, Large intestinal mucosa and Rectum mucosa
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and QWBA for other tissues

Tissues		Radioactivity Concentration in Tissue (μg/g)												$t_{1/2,z}$ after 14th Administration (hr)
	Number of Administrations	1	7	13	14	14	14	14	14	14	14	14	14	
	Sampling Time	24 hr	24 hr	24 hr	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	168 hr	336 hr	840 hr	
Plasma		0.530	2.05	3.94	118	15.9	4.35	3.03	3.07	0.983	0.866	0.129	BLQ	65.4
Blood		BLQ	1.17	1.62	63.2	13.4	2.24	2.46	1.14	BLQ	BLQ	BLQ	BLQ	60.7
Adrenal cortex		BLQ	BLQ	0.859	19.7	5.16	1.73	1.70	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Adrenal medulla		BLQ	BLQ	1.37	31.4	7.98	2.56	2.58	1.14	0.694	0.817	BLQ	BLQ	81.5
Aortic wall		BLQ	1.81	2.78	26.6	16.2	2.88	4.03	1.51	1.49	2.45	0.699	0.919	N.C.
Bile ducts		BLQ	1.69	1.72	44.9	10.7	4.75	2.97	2.85	2.57	1.51	BLQ	BLQ	105
Bone marrow		BLQ	0.796	0.943	13.5	3.34	0.902	1.27	0.642	BLQ	BLQ	BLQ	BLQ	N.C.
Bone surface		BLQ	1.34	1.21	41.7	6.11	1.23	1.80	2.28	1.39	1.56	1.61	BLQ	N.C.
Brain		BLQ	BLQ	BLQ	1.18	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brown fat		BLQ	BLQ	0.831	25.6	4.76	1.21	1.19	BLQ	0.850	BLQ	BLQ	BLQ	214
Bulbo-urethral gland		BLQ	0.799	1.03	27.6	7.87	1.09	1.54	2.00	0.747	BLQ	BLQ	BLQ	N.C.
Cerebrospinal fluid		BLQ	0.991	1.38	24.4	5.52	1.78	1.63	BLQ	0.907	1.00	BLQ	BLQ	169
Choroid plexus		BLQ	BLQ	BLQ	14.8	4.47	BLQ	1.82	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Epididymis		BLQ	BLQ	BLQ	15.9	5.30	1.26	0.867	0.861	0.740	BLQ	BLQ	BLQ	N.C.
Epimysium		BLQ	0.937	2.32	19.0	6.62	2.54	2.23	0.719	2.45	1.19	0.870	BLQ	N.C.
Exorbital lachrymal gland		1.27	BLQ	1.82	18.2	1.79	2.54	1.38	1.17	0.848	0.901	BLQ	BLQ	208
Fur		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Harderian gland		BLQ	0.661	1.20	8.33	4.11	1.48	1.38	BLQ	BLQ	0.846	BLQ	BLQ	202
Intra-orbital lachrymal gland		BLQ	BLQ	1.46	17.4	4.55	1.35	1.83	1.01	0.668	0.904	BLQ	BLQ	N.C.
Kidney cortex		10.9	31.0	36.7	461	116	64.2	51.9	34.9	23.4	15.5	9.87	2.14	234
Kidney medulla		3.13	1.03	1.61	451	79.3	2.73	1.78	1.05	0.818	0.720	BLQ	BLQ	176
Lens of the eye		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.

Tissues		Radioactivity Concentration in Tissue (μg/g)												$t_{1/2,z}$ after 14th Administration (hr)
	Number of Administrations	1	7	13	14	14	14	14	14	14	14	14	14	
	Sampling Time	24 hr	24 hr	24 hr	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	168 hr	336 hr	840 hr	
Liver		BLQ	0.995	1.13	24.0	5.76	1.92	1.98	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Lung		BLQ	1.32	1.67	52.8	9.89	2.35	2.31	0.969	BLQ	0.749	BLQ	BLQ	92.7
Mandibular lymph nodes		BLQ	BLQ	1.29	22.3	6.17	1.28	0.944	BLQ	1.04	BLQ	BLQ	BLQ	N.C.
Meninges		BLQ	BLQ	BLQ	16.6	5.85	0.947	1.60	BLQ	0.756	1.08	BLQ	BLQ	N.C.
Muscle		BLQ	BLQ	BLQ	9.05	1.54	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Myocardium		BLQ	0.656	0.673	19.8	5.58	1.08	1.30	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Nasal mucosa		BLQ	BLQ	BLQ	19.7	3.22	0.920	1.04	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Pancreas		BLQ	BLQ	0.809	12.9	4.32	1.31	1.68	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Periodontal membrane		BLQ	1.25	2.79	28.9	8.12	1.92	2.75	1.18	0.871	1.31	0.848	BLQ	N.C.
Pineal body		BLQ	0.926	0.910	32.2	7.14	1.17	1.65	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Pituitary gland		BLQ	0.660	0.826	22.5	6.73	1.26	1.64	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Preputial gland		BLQ	BLQ	1.02	20.4	3.63	2.20	1.86	BLQ	BLQ	BLQ	BLQ	0.924	728
Prostate		BLQ	BLQ	0.869	12.2	2.23	BLQ	0.950	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Salivary glands		BLQ	0.820	1.26	24.1	6.67	1.31	1.43	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Seminal vesicles		BLQ	BLQ	BLQ	0.712	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Skin		BLQ	2.29	3.21	40.2	11.6	3.39	3.40	1.68	2.05	2.07	1.04	0.939	N.C.
Spinal cord		BLQ	BLQ	BLQ	1.04	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Spleen		BLQ	1.07	2.02	10.2	4.35	2.07	1.64	1.96	0.976	1.01	BLQ	BLQ	N.C.
Testis		BLQ	BLQ	0.725	8.62	2.32	0.971	0.982	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Thymus		BLQ	BLQ	BLQ	8.64	2.10	BLQ	0.728	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Thyroid gland		0.718	1.74	1.97	40.2	7.91	3.01	2.91	1.13	1.11	1.21	BLQ	BLQ	N.C.
Tongue		BLQ	BLQ	1.03	17.2	6.65	1.68	2.13	BLQ	0.651	1.12	BLQ	BLQ	N.C.
Tooth pulp		BLQ	1.02	3.32	39.5	7.30	2.35	2.83	1.55	0.950	1.05	BLQ	BLQ	106

Tissues		Radioactivity Concentration in Tissue (μg/g)												$t_{1/2,z}$ after 14th Administration (hr)
	Number of Administrations	1	7	13	14	14	14	14	14	14	14	14	14	
	Sampling Time	24 hr	24 hr	24 hr	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	168 hr	336 hr	840 hr	
Trachea		BLQ	1.20	1.91	33.6	5.27	1.84	2.16	BLQ	0.998	0.763	BLQ	BLQ	94.4
Urinary bladder wall		1.68	2.54	6.26	56.7	29.0	8.60	6.27	2.78	2.03	1.82	0.699	BLQ	134
Urine		2.28	2.85	9.25	1160	1680	10.2	7.28	3.60	BLQ	0.954	BLQ	BLQ	49.3
Uveal tract/retina		BLQ	1.27	3.69	32.2	12.4	3.87	4.30	2.19	0.682	1.75	1.16	0.968	N.C.
White fat		BLQ	BLQ	BLQ	3.40	1.23	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Esophageal wall		BLQ	BLQ	1.33	38.7	7.86	2.41	2.16	0.922	1.33	1.12	BLQ	0.760	1003
Stomach mucosa (fundus)		BLQ	BLQ	1.29	37.8	5.57	1.30	1.49	1.56	0.733	1.60	0.750	BLQ	N.C.
Stomach mucosa (non-fundus)		BLQ	BLQ	0.787	12.7	4.45	1.98	1.06	1.57	0.832	1.19	BLQ	BLQ	N.C.
Small intestinal mucosa		BLQ	0.675	1.29	23.7	2.93	1.23	1.51	BLQ	BLQ	0.743	BLQ	BLQ	182
Caecum mucosa		0.701	0.868	2.06	25.9	7.61	5.11	1.73	1.10	0.779	0.664	BLQ	BLQ	103
Large intestinal mucosa		2.03	1.69	1.59	22.1	5.05	1.18	3.02	1.48	1.18	0.743	BLQ	BLQ	75.1
Rectum mucosa		BLQ	0.907	2.38	36.6	7.14	2.80	2.86	1.39	1.25	1.32	0.686	BLQ	253
When the plasma and the other tissue concentrations of radioactivity were < 0.035 μg/g and < 0.641 μg/g, respectively, it was represented as BLQ. a As free form														
Study Number		S-649266-PF-189-L												
Location in CTD		4.2.2.3-03												

2.6.5.5.5 雄性有色ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の組織分布

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/LE/CpbHsd
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	122 kBq/mg (3.31 μCi/mg)
Sample	Plasma, Blood, Adrenal cortex, Adrenal medulla, Aortic wall, Bile ducts and contents, Bone marrow, Bone surface, Brain, Brown fat, Bulbo-urethral gland, Cerebrospinal fluid, Choroid plexus, Epididymis, Epimysium, Exorbital lachrymal gland, Fur (Pigmented), Harderian gland, Intra-orbital lachrymal gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mandibular lymph node, Meninges, Muscle, Myocardium, Nasal mucosa, Pancreas, Periodontal membrane, Pineal body, Pituitary gland, Preputial gland, Prostate, Salivary glands, Seminal vesicles, Skin (Non-pigmented), Skin (Pigmented), Spinal cord, Spleen, Testis, Thymus, Thyroid gland, Tongue, Tooth pulp, Trachea, Uveal tract/retina, White fat, Urinary bladder wall, Urinary bladder contents, Esophageal wall, Stomach mucosa (fundus), Stomach mucosa (non-fundus), Small intestinal mucosa, Caecum mucosa, Large intestinal mucosa, Rectum mucosa
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and blood, QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Plasma	112	18.2	2.07	1.52	0.654	0.355	0.032	N.D.	55.9
Blood	64.4	12.4	1.77	0.880	0.389	0.220	N.D.	N.D.	39.7
Adrenal cortex	23.1	4.37	1.94	0.606	0.335	0.123	0.277	BLQ	N.C.
Adrenal medulla	37.1	4.98	2.49	0.610	0.315	0.242	0.167	BLQ	316

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Aortic wall	65.9	14.3	1.40	0.468	0.423	0.212	0.128	BLQ	167
Bile ducts and contents	89.5	15.5	1.82	1.39	BLQ	BLQ	BLQ	BLQ	N.C.
Bone marrow	26.1	4.61	0.968	0.407	0.322	0.214	0.188	BLQ	N.C.
Bone surface	43.1	8.20	1.42	0.441	0.225	0.387	0.125	BLQ	N.C.
Brain	1.11	0.340	0.136	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Brown fat	16.8	3.99	0.985	0.373	0.155	0.193	0.124	0.131	N.C.
Bulbo-urethral gland	52.5	8.66	1.37	0.635	0.379	0.331	0.168	0.201	N.C.
Cerebrospinal fluid	11.0	2.38	0.865	0.467	0.137	BLQ	BLQ	BLQ	25.3
Choroid plexus	12.5	1.21	0.198	0.175	BLQ	BLQ	BLQ	BLQ	N.C.
Epididymis	21.6	5.08	1.19	0.188	0.298	0.203	BLQ	BLQ	N.C.
Epimysium	34.4	10.0	0.715	0.360	0.129	0.129	0.189	BLQ	N.C.
Exorbital lachrymal gland	22.9	4.26	0.803	0.392	0.217	BLQ	BLQ	BLQ	37.9
Fur (Pigmented)	6.84	0.626	0.491	BLQ	0.142	0.286	BLQ	BLQ	N.C.
Harderian gland	19.6	3.95	0.940	0.350	0.282	0.233	BLQ	BLQ	164
Intra-orbital lachrymal gland	19.7	3.94	1.37	0.259	0.220	0.445	BLQ	BLQ	N.C.
Kidney cortex	359	73.5	33.7	16.2	11.3	7.38	2.86	0.870	203
Kidney medulla	1060	115	4.01	4.94	2.06	0.918	0.350	0.154	298
Lens of the eye	BLQ	0.158	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Liver	25.1	5.80	1.46	0.527	0.310	0.215	BLQ	BLQ	74.2
Lung	56.2	9.67	1.37	0.638	0.336	0.253	BLQ	BLQ	71.9
Mandibular lymph node	23.0	4.36	0.787	0.378	0.325	0.236	BLQ	BLQ	141
Meninges	14.4	2.41	1.11	0.580	0.334	0.153	BLQ	BLQ	49.9
Muscle	9.75	1.20	0.345	0.162	0.133	0.166	BLQ	BLQ	N.C.
Myocardium	25.9	5.36	1.01	0.377	0.196	0.206	BLQ	BLQ	N.C.
Nasal mucosa	15.2	3.15	0.437	0.171	BLQ	BLQ	BLQ	BLQ	N.C.

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Pancreas	17.4	2.98	0.970	0.257	0.203	0.179	BLQ	BLQ	184
Periodontal membrane	40.0	8.84	1.28	0.624	0.347	0.179	0.131	BLQ	N.C.
Pineal body	40.6	10.2	0.782	0.227	BLQ	BLQ	0.153	BLQ	N.C.
Pituitary gland	20.9	2.76	0.822	0.336	0.184	0.124	BLQ	BLQ	66.8
Preputial gland	15.4	4.86	0.617	0.483	0.303	0.287	0.238	BLQ	770
Prostate	17.4	1.72	1.20	0.269	0.219	0.185	0.194	BLQ	N.C.
Salivary glands	21.6	4.58	0.837	0.313	0.182	0.271	0.122	BLQ	N.C.
Seminal vesicles	12.6	1.14	0.180	0.343	0.134	BLQ	BLQ	BLQ	N.C.
Skin (Non-pigmented)	61.9	13.1	2.14	0.679	0.461	0.485	0.254	0.152	458
Skin (Pigmented)	50.7	9.41	1.94	0.709	0.368	0.474	0.192	BLQ	189
Spinal cord	1.02	0.299	0.172	BLQ	BLQ	BLQ	BLQ	BLQ	N.C.
Spleen	14.8	3.16	1.17	0.558	0.306	0.192	0.154	BLQ	N.C.
Testis	10.5	2.52	0.576	0.354	0.194	0.177	0.129	BLQ	456
Thymus	11.1	1.67	0.463	0.189	BLQ	BLQ	BLQ	BLQ	8.38
Thyroid gland	28.6	5.68	1.11	0.565	0.353	0.385	0.128	BLQ	154
Tongue	35.1	4.58	1.39	0.359	0.200	0.201	BLQ	BLQ	N.C.
Tooth pulp	68.8	11.3	1.40	0.795	0.386	0.267	BLQ	BLQ	49.5
Trachea	31.1	6.12	0.786	0.462	0.330	0.132	BLQ	BLQ	48.5
Uveal tract/retina	49.2	11.4	1.25	0.544	0.367	0.200	0.175	BLQ	N.C.
White fat	1.74	0.173	0.246	BLQ	BLQ	BLQ	0.147	BLQ	N.C.
Urinary bladder wall	148	127	7.52	2.08	1.91	0.553	BLQ	BLQ	36.3
Urinary bladder contents	1550	1590	23.3	1.89	1.70	0.401	0.131	BLQ	79.9
Esophageal wall	32.9	10.3	2.16	0.724	0.398	0.387	0.121	BLQ	145
Stomach mucosa (fundus)	29.5	4.54	1.26	0.276	0.237	0.232	BLQ	BLQ	383

Tissues	Radioactivity Concentration in Tissue (μg/g)								$t_{1/2,z}$ (hr)
	0.083 hr	1 hr	6 hr	24 hr	72 hr	120 hr	336 hr	840 hr	
Stomach mucosa (non-fundus)	17.5	5.34	4.53	0.566	0.470	0.353	0.125	BLQ	142
Small intestinal mucosa	18.4	6.27	2.20	0.315	0.343	BLQ	BLQ	BLQ	N.C.
Caecum mucosa	31.5	5.08	7.47	3.72	0.673	0.251	0.152	BLQ	N.C.
Large intestinal mucosa	30.6	4.82	2.58	16.6	2.62	0.813	0.131	BLQ	66.3
Rectum mucosa	37.9	6.06	1.11	0.392	1.51	0.300	0.165	BLQ	N.C.
When the plasma and blood concentrations of radioactivity were < 0.025 μg/g and < 0.036 μg/g, respectively, it was represented as N.D. When the concentrations of radioactivity in other tissues were < 0.118 μg/g, it was represented as BLQ. a As free form									
Study Number	R-649266-PF-036-L								
Location in CTD	4.2.2.3-02								

2.6.5.6 薬物動態試験： タンパク結合

2.6.5.6.1 [Thiazole-^{14}C]-セフィデロコルの in vitro タンパク結合

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Test System	In vitro, plasma under fasted condition (Jcl:ICR mice [M], Crl:CD(Sprague Dawley) rats [M], cynomolgus monkeys [M], and human volunteers [M]), human serum protein solution (HSA, α_1-AGP, and γ-globulin)			
Radionuclide	^{14}C			
Specific Activity	122 kBq/mg (3.31 μCi/mg), 123 kBq/mg (3.33 μCi/mg)			
Concentration (μg/mL) [a]	1, 10, 100, 1000			
Method	Ultrafiltration Method, At 1800×*g* for 15 minutes at 37°C			
Incubation	At 37°C for 15 minutes			
Sample	Plasma, Human serum protein solution, Filtrate			
Analyte	Radioactivity			
Assay	LSC			
Species	Protein Binding Ratio in Plasma (%)			
	1 μg/mL	10 μg/mL	100 μg/mL	1000 μg/mL
Mouse (M) [b]	38.7 ± 1.1	32.9 ± 2.3	30.8 ± 0.3	24.1 ± 0.7
Rat (M)	51.9 ± 2.8	46.6 ± 4.1	41.6 ± 2.2	32.5 ± 0.7
Monkey (M)	62.3 ± 1.3	61.8 ± 2.1	61.0 ± 1.3	45.7 ± 1.3
Human (M)	60.4 ± 5.6	57.8 ± 6.7	51.8 ± 2.3	40.8 ± 2.9

α_1-AGP = α_1-acid glycoprotein; HSA = human serum albumin
Data are expressed as the mean ± S.D. of 3 individuals or 3 pools.
a As free form
b 3 batches of pooled plasma from 4 mice each

Purified protein	Protein Binding Ratio in Human Serum Protein Solution (%)			
	1 μg/mL	10 μg/mL	100 μg/mL	1000 μg/mL
4% HSA	67.6 ± 2.4	67.0 ± 1.2	73.7 ± 0.4	46.8 ± 1.2
0.08% α_1-AGP	2.4 ± 2.1	0.0 ± 0.0	0.1 ± 0.2	0.0 ± 0.0
1% γ-globulin	15.4 ± 3.8	14.5 ± 2.2	3.8 ± 0.3	8.4 ± 0.7
Data are expressed as the mean ± S.D. of triplicate assays.				
Study Number	R-649266-PF-037-L			
Location in CTD	5.3.2.1-01			

2.6.5.6.2 [Thiazole-^{14}C]-セフィデロコルの in vitro 血球移行性

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Test System	In vitro, blood under fasted condition (Jcl:ICR mice [M], Crl:CD(Sprague Dawley) rats [M], cynomolgus monkeys [M], and human volunteers [M])			
Radionuclide	^{14}C			
Specific Activity	122 kBq/mg (3.31 μCi/mg), 123 kBq/mg (3.33 μCi/mg)			
Concentration (μg/mL) [a]	1, 10, 100, 1000			
Incubation	At 37°C for 15 minutes			
Sample	Blood, Plasma			
Analyte	Radioactivity			
Assay	LSC			
Species	Distribution of Radioactivity to Blood Cells (%)			
	1 μg/mL	10 μg/mL	100 μg/mL	1000 μg/mL
Mouse [b] (M)	0.0 ± 0.0	0.6 ± 1.1	0.8 ± 1.4	7.4 ± 1.0
Rat (M)	0.0 ± 0.0	0.2 ± 0.3	4.0 ± 3.1	2.8 ± 2.4
Monkey (M)	0.3 ± 0.5	0.1 ± 0.2	4.2 ± 2.6	5.4 ± 1.8
Human (M)	2.1 ± 3.6	1.3 ± 2.3	4.6 ± 1.8	5.8 ± 2.9
Data are expressed as the mean ± S.D. of 3 individuals or 3 pools. a As free form b 3 batches of pooled blood from 4 mice each.				
Study Number	R-649266-PF-037-L			
Location in CTD	5.3.2.1-01			

2.6.5.6.3 有色ラットにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の血球移行性

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Harlan Long-Evans
Gender (M/F)/Number of Animals	M/1 per time point
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	148 kBq/mg (4.01 μCi/mg)
Sample	Blood, Plasma
Analyte	Radioactivity
Assay	LSC
Time (hr)	Distribution of Radioactivity to Blood Cells (%)
	Pigmented rat
0.083 hr	0
1 hr	0
6 hr	0
24 hr	N.C.
72 hr	N.C.
120 hr	N.C.
336 hr	N.C.
840 hr	N.C.
a As free form.	
Study Number	S-649266-PF-079-L
Location in CTD	4.2.2.3-01

2.6.5.6.4 ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の血球移行性

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(SD)	Rat/Crl:CD(Sprague Dawley)	Rat/LE/CpbHsd
Gender (M/F)/Number of Animals	M/1 per time point	F/1 per time point	M/1 per time point
Feeding Condition	Non-fasted		
Vehicle/Formulation	Saline/Solution		
Method of Administration	Single intravenous administration (bolus)		
Dose (mg/kg) [a]	30		
Radionuclide	^{14}C		
Specific Activity	122 kBq/mg (3.31 μCi/mg)		
Sample	Blood, Plasma		
Analyte	Radioactivity		
Assay	LSC		
Time (hr)	Distribution of Radioactivity to Blood Cells (%)		
	Albino rat (M)	Albino rat (F)	Pigmented rat (M)
0.083 hr	15.6	13.7	2.61
1 hr	0	24.8	19.3
6 hr	0	30.3	32.2
24 hr	0	0	1.55
72 hr	2.91	0	7.53
120 hr	22.9	18.6	16.1
336 hr	N.C.	N.C.	N.C.
840 hr	N.C.	N.C.	N.C.
a As free form			
Study Number	R-649266-PF-036-L		
Location in CTD	4.2.2.3-02		

2.6.5.7 薬物動態試験： 妊娠又は授乳動物における試験

2.6.5.7.1 妊娠ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の組織分布

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	F/1 per time point
Gestation Day	Day 18 of gestation
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity	122 kBq/mg (3.30 μCi/mg)
Sample	Plasma, Adrenal gland (cortex), Adrenal gland (medulla), Blood in the heart, Bone, Bone marrow, Brown fat, Cerebellum, Cerebrum, Cervical lymph node, Clitoral gland, Connective tissue, Exorbital lacrimal gland, Harderian gland, Kidney cortex, Kidney medulla, Lens of the eye, Liver, Lung, Mammary gland, Myocardium, Ovary, Pancreas, Parotid gland, Pineal body, Pituitary gland, Rectal mucosa, Skeletal muscle, Skin, Spinal cord, Spleen, Stomach mucosa, Sublingual gland, Submaxillary gland, Thymus, Thyroid, Trachea, Uterus, Vagina, White fat, Placenta, Yolk sac, Fetal blood in the heart, Fetal brain, Fetal kidney, Fetal liver, Fetal lung
Analyte	Radioactivity (cefiderocol equivalent)
Assay	LSC for plasma and QWBA for other tissues

Tissues	Radioactivity Concentration in Tissue (μg/g)					$t_{1/2}$ (hr)
	5 min	1 hr	6 hr	24 hr	48 hr	
Plasma	135	13.5	1.48	0.710	0.164	13.1
Adrenal gland (cortex)	22.0	2.85	0.489	0.235	0.0737 [b]	15.3
Adrenal gland (medulla)	37.0	5.52	0.777	0.514	0.176	19.3
Blood in the heart	78.3	8.43	0.817	0.416	BLQ	N.C.

Tissues	Radioactivity Concentration in Tissue (μg/g)					$t_{1/2}$ (hr)
	5 min	1 hr	6 hr	24 hr	48 hr	
Bone	2.50	0.576	BLQ	0.104 [b]	0.112 [b]	N.C.
Bone marrow	15.0	1.60	0.447	0.333	BLQ	N.C.
Brown fat	11.0	1.23	0.252	0.183	BLQ	N.C.
Cerebellum	1.28	0.185	BLQ	BLQ	BLQ	N.C.
Cerebrum	0.877	0.114 [b]	BLQ	BLQ	BLQ	N.C.
Cervical lymph node	25.7	3.11	0.664	0.380	0.0420 [b]	10.3
Clitoral gland	27.3	3.68	0.862	0.647	0.552	66.7
Connective tissue	36.0	15.7	1.42	0.813	0.338	20.2
Exorbital lacrimal gland	14.3	1.74	0.306	0.253	BLQ	N.C.
Harderian gland	17.6	2.25	0.424	0.192	BLQ	N.C.
Kidney cortex	180	30.5	15.7	11.8	8.17	44.6
Kidney medulla	155	20.4	6.06	1.22	0.694	13.8
Lens of the eye	0.592	BLQ	BLQ	BLQ	BLQ	N.C.
Liver	27.5	3.73	0.954	0.498	0.194	18.2
Lung	62.6	6.89	0.624	0.391	0.0479 [b]	11.1
Mammary gland	23.3	3.44	0.840	0.440	0.245	23.8
Myocardium	22.1	2.54	0.294	0.105 [b]	BLQ	N.C.
Ovary	20.5	2.70	0.594	0.137 [b]	BLQ	5.94
Pancreas	19.1	2.26	0.473	0.279	0.0388 [b]	11.4
Parotid gland	23.0	2.58	0.517	0.288	0.144 [b]	22.8
Pineal body	14.1	1.67	0.469	0.352	BLQ	N.C.
Pituitary gland	18.2	1.97	0.290	0.0885 [b]	BLQ	5.95
Rectal mucosa	63.1	6.92	0.642	1.70	0.997	N.C.
Skeletal muscle	7.76	0.863	0.0225 [b]	0.0214 [b]	0.0171 [b]	104
Skin	41.2	17.8	1.23	0.783	0.534	35.3

Tissues	Radioactivity Concentration in Tissue (μg/g)					$t_{1/2}$ (hr)
	5 min	1 hr	6 hr	24 hr	48 hr	
Spinal cord	0.925	0.131 [b]	BLQ	BLQ	BLQ	N.C.
Spleen	14.5	1.98	0.817	0.646	0.330	31.6
Stomach mucosa	23.3	2.16	0.526	0.184	0.0216 [b]	9.03
Sublingual gland	16.1	2.51	0.465	0.243	0.218	N.C.
Submaxillary gland	22.9	2.41	0.433	0.246	BLQ	N.C.
Thymus	15.8	1.47	0.352	0.224	BLQ	N.C.
Thyroid	31.9	3.62	1.29	0.371	0.166 [b]	14.4
Trachea	60.2	6.00	0.674	0.485	BLQ	N.C.
Uterus	93.7	8.70	1.49	1.07	0.552	29.1
Vagina	100	8.42	1.03	0.629	0.191	17.1
White fat	3.96	0.917	0.0865 [b]	BLQ	BLQ	N.C.
Placenta	46.0	4.44	0.959	0.588	0.201	18.4
Yolk sac	48.7	31.1	38.2	31.2	8.97	19.6
Fetal blood in the heart	0.516	0.581	0.369	0.0883 [b]	BLQ	N.C.
Fetal brain	0.0420 [b]	0.0832 [b]	0.0966 [b]	0.0786 [b]	BLQ	N.C.
Fetal kidney	0.456	0.788	0.539	0.373	0.127 [b]	19.8
Fetal liver	0.350	0.395	0.254	0.157 [b]	0.00696 [b]	7.87
Fetal lung	0.275	0.416	0.239	0.0782 [b]	BLQ	N.C.

When the concentrations of radioactivity in the tissues were < 0.172 μg/g, it was represented as BLQ.
a As free form
b The mean values were less than LLOQ because they were calculated from the each value including BLQ (BLQ is calculated as zero).
When quantitative data for 1 tissue were obtained from multiple sections, data are expressed as the mean value of each data. In the calculation of mean, BLQ was treated as zero. When the data on all sections were BLQ, the mean is expressed as "BLQ".

Study Number	S-649266-PB-186-N
Location in CTD	4.2.2.3-04

2.6.5.7.2 授乳ラットにおける [Thiazole-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の乳汁移行性

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)				
Gender (M/F)/Number of Animals	F/5				
Feeding Condition	Non-fasted				
Vehicle/Formulation	Saline/Solution				
Method of Administration	Single intravenous administration (bolus)				
Dose (mg/kg) [a]	30				
Radionuclide	^{14}C				
Specific Activity	122 kBq/mg (3.30 μCi/mg)				
Sample	Milk, Plasma				
Analyte	Radioactivity (cefiderocol equivalent)				
Assay	LSC				
Sample	Radioactivity Concentration (μg/mL)				
	5 min	1 hr	6 hr	24 hr	48 hr
Milk	1.99 ± 2.28 [b]	7.24 ± 3.15	1.84 ± 0.85	0.285 ± 0.160	0.245 ± 0.172
Plasma	123 ± 5	9.27 ± 2.04	1.09 ± 0.21	0.528 ± 0.077	0.281 ± 0.037
Milk/plasma Ratio	0.0159 ± 0.0180 [b]	0.835 ± 0.461	1.71 ± 0.84	0.535 ± 0.289	0.859 ± 0.551
Data are expressed as the mean ± S.D. of 5 individuals. a As free form b Data are expressed as the mean ± S.D. of 4 individuals.					
Study Number	S-649266-PB-188-N				
Location in CTD	4.2.2.5-02				

2.6.5.8 薬物動態試験： その他の分布試験

該当する試験なし.

2.6.5.9 薬物動態試験： 代謝：In vivo

2.6.5.9.1 ラットにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後のセフィデロコルの代謝物検索

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)
Gender (M/F)/Number of Animals	M/9 (intact rats) or 3 (BDC rats)
Feeding Condition	Non-fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Radio Activity	124 kBq (3.34 μCi)/mg
Sample [b]	Plasma, urine, and feces obtained from intact rats, bile obtained from BDC rats
Analyte	Radioactivity, cefiderocol, metabolites of cefiderocol
Assay	LSC, Radio-HPLC, LC/MS^n

Metabolites	Composition (% in plasma) [c]		Cumulative Excretion (% of dose) [c]		
	1 hr plasma	4 hr plasma	0–24 hr urine	0–4 hr bile	0–24 hr feces
Cefiderocol	37.8	7.6	76.7	0.10	0.08
PCBA	1.3	2.7	3.2	N.D.	3.76
M5	1.1	17.0	N.D.	0.32	N.D.
M23	N.D.	N.D.	N.D.	N.D.	0.11
M6	N.D	N.D.	N.D.	0.16	0.24
M7	1.0	2.1	N.D.		N.D.
M18	N.D.	N.D.	N.D.		N.D.
Cefiderocol catechol 3-methoxy	N.D.	3.5	N.D.	5.07	N.D.
M14	N.D.	N.D.	N.D.	0.16	N.D.

Metabolites	Composition (% in plasma) [c]		Cumulative Excretion (% of dose) [c]		
	1 hr plasma	4 hr plasma	0–24 hr urine	0–4 hr bile	0–24 hr feces
M15	N.D.	N.D.	N.D.		N.D.
M16	N.D.	N.D.	N.D.	0.12	N.D.
M20	N.D.	N.D.	N.D.	1.81	N.D.
A	17.0	7.0	N.D.	N.D.	N.D.
B	N.D.	6.4	N.D.	N.D.	N.D.
Sample preparation recovery	64 [d]	52 [d]	100.0 [e]	97.6 [e]	75.5 [d]

BDC = bile duct-cannulated; LC/MS^n = high-performance liquid chromatography with multistage mass spectrometry; Radio-HPLC = high performance liquid chromatography with radio-detector; PCBA = pyrrolidine chlorobenzamide

The speculated structures of metabolites are as follows; M5: a glucuronide of methylated PCBA, M6 and M23: methylated PCBA, M7: a sulfate of methylated PCBA, M14: a glucuronide of dimethylated and oxidized PCBA, M15: diglucuronide of methylated and oxidized PCBA, M16: a glucuronide of methylated and oxidized PCBA, M18: a sulfate of dimethylated and oxidized PCBA, M20: methylated cefiderocol, A and B: unknown.

a As free form
b The plasma, urine, bile, and feces samples were provided from excretion/pharmacokinetic study (Study Number: [redacted]).
c The data of the plasma were determined from the pooled sample of 3 animals at each time point, data of the urine and feces were determined from the sample of 3 intact animals, and data of the bile were determined from the sample of 3 BDC animals.
d Radioactivity recovery following extraction and concentration
e Radioactivity recovery following centrifugation

Study Number	[redacted]
Location in CTD	4.2.2.4-01

2.6.5.9.2 サルにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後のセフィデロコルの代謝物検索

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Cynomolgus Monkey
Gender (M/F)/Number of Animals	M/3 (intact monkeys) or F/3 (intact monkeys)
Feeding Condition	Fasted
Vehicle/Formulation	Saline/Solution
Method of Administration	Single intravenous administration (bolus)
Dose (mg/kg) [a]	30
Radionuclide	^{14}C
Specific Activity [a]	124 kBq (3.34 μCi)/mg
Sample [b]	Plasma, urine, and feces obtained from the same intact monkeys
Analyte	Radioactivity, cefiderocol, metabolites of cefiderocol
Assay	LSC, Radio-HPLC, LC/MS^n

Metabolites	Composition (% in plasma) [c]				Cumulative Excretion (% of dose) [c]			
	1 hr Plasma (M)	4 hr Plasma (M)	1 hr Plasma (F)	4 hr Plasma (F)	Urine [d] (M)	Urine [e] (F)	Feces [f] (M)	Feces [g] (F)
Cefiderocol	33.7	33.5	41.0	39.1	53.2	30.8	0.02	0.12
PCBA	1.91	BLQ	2.63	BLQ	16.2	19.8	2.64	4.97
M4	BLQ	BLQ	BLQ	N.D.	2.01	1.65	N.D.	N.D.
M6	N.D.	N.D.	N.D.	N.D.	1.08	0.73	0.85	1.73
M7	2.41	4.88	2.48	5.08	8.58	6.04	N.D.	N.D.
Cefiderocol catechol 3-methoxy	2.12	2.83	1.06	2.86	N.D.	N.D.	0.07	0.21
M12	N.D.	N.D.	N.D.	N.D.	1.38	1.09	N.D.	N.D.
M19	N.D.	N.D.	N.D.	N.D.	1.39	0.93	N.D.	N.D.
M23	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.13	0.32

Metabolites	Composition (% in plasma) [c]				Cumulative Excretion (% of dose) [c]			
	1 hr Plasma (M)	4 hr Plasma (M)	1 hr Plasma (F)	4 hr Plasma (F)	Urine [d] (M)	Urine [e] (F)	Feces [f] (M)	Feces [g] (F)
M24	N.D.	N.D.	N.D.	N.D.	BLQ	0.36	N.D.	N.D.
M25	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.13	0.14
A	18.8	14.9	16.2	16.9	N.D.	N.D.	N.D.	N.D.
Sample preparation recovery	59.4 [h]	57.9 [h]	65.5 [h]	65.3 [h]	99.3 [i]	99.6 [i]	86.3 [j]	90.4 [j]

The speculated structures of metabolites are as follows; M4: a sulfate of PCBA, M6 and M23: a methylated PCBA, M7 and M12: a sulfate of methylated PCBA, M19: an isomeric rearrangement of cefiderocol, M24: COOH and a net C_9H_7ON contained PCBA, M25: methylated cefiderocol, A: unknown.

a As free form

b The plasma, urine, and feces samples were provided from excretion/pharmacokinetic study (Study Number: [redacted]).

c The data of the plasma were determined from the pooled sample of 3 animals and data of the urine and feces were determined from the sample of 3 animals.

d The data were derived from 0-24 hr urine (Animal No. M01 and M03) and 0-48 hr urine (Animal No. M02).

e The data were derived from 0-24 hr urine (Animal No. F02 and F03) and 0-48 hr urine (Animal No. F01).

f The data were derived from 0-24 hr feces (Animal No. M01), 24-48 hr feces (Animal No. M03) and 24-72 hr feces (Animal No. M02).

g The data were derived from 0-24 hr feces (Animal No. F02 and F03) and 0-72 hr feces (Animal No. F01).

h Radioactivity recovery following extraction, evaporation and re-constitution

i Radioactivity recovery following centrifugation

j Radioactivity recovery following extraction, evaporation, re-constitution and centrifugation

Study Number	[redacted]
Location in CTD	4.2.2.4-02

2.6.5.10 薬物動態試験： 代謝：In vitro

2.6.5.10.1 肝細胞を用いた in vitro 代謝

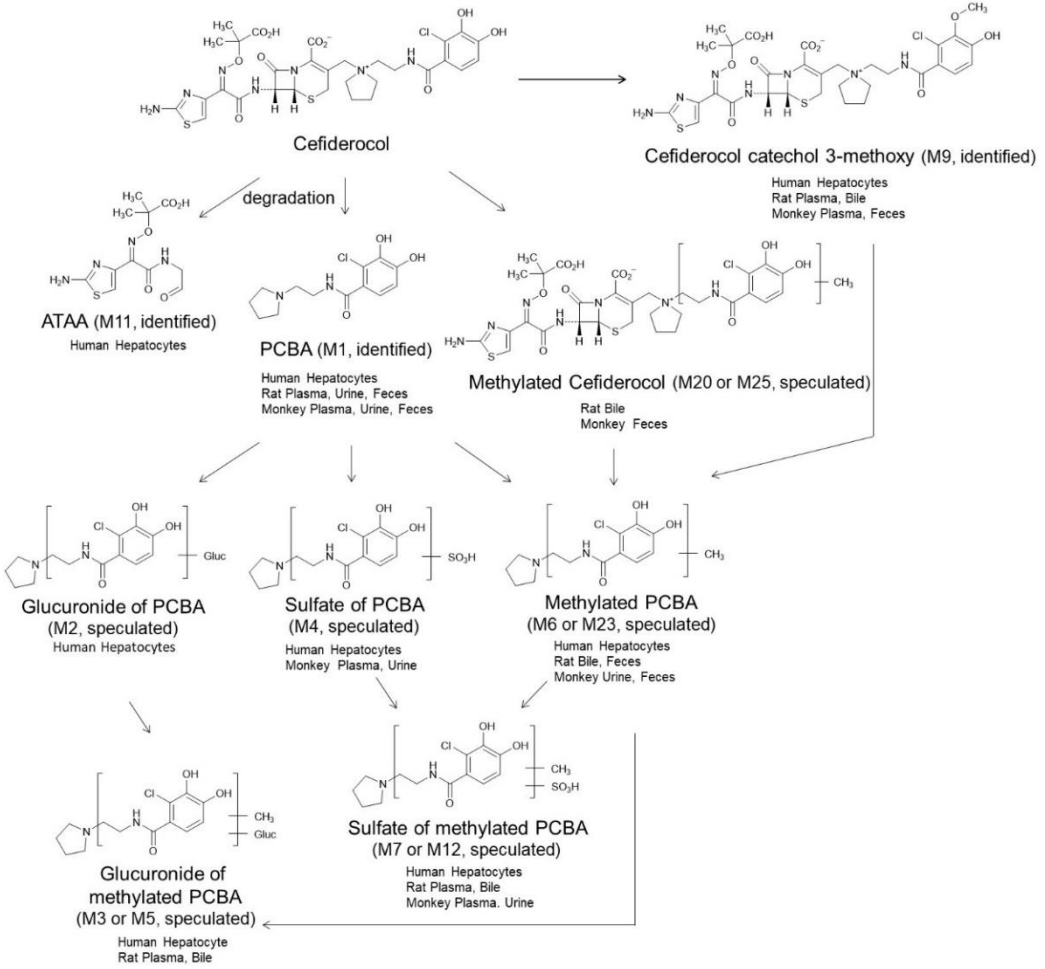
Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Test System	Fresh Crl:ICR(CD-1) mouse (M), Sprague Dawley rat (M), cynomolgus monkey (M), and human hepatocytes (M), and cryopreserved New Zealand rabbit (F) and human hepatocytes (pool of 10 donors; M/5 and F/5)
Incubation	At 37°C for 24 hours
Concentration (μmol/L)	15
Radionuclide	^{14}C
Specific Activity [a]	124 kBq (3.34 μCi)/mg
Sample	Reaction mixture after 24-hr incubation of [catechol-^{14}C]-cefiderocol with mouse, rat, rabbit, monkey or human hepatocytes
Analyte	Radioactivity, cefiderocol, metabolites of cefiderocol
Assay	LSC, Radio-HPLC, LC/MS^n

Metabolites	Mouse	Rat	Rabbit	Monkey	Fresh Human	Cryo Human	No Cell
Cefiderocol	D	D	D	D	D	D	D
PCBA	D	D	D	D	D	D	D
M2	D	D	D	N.D.	D	N.D.	N.D.
M3	D	D	D	N.D.	D	D	N.D.
M4	D	D	D	D	D	D	N.D.
M5	D	D	D	N.D.	D	D	N.D.
M6	D	D	N.D.	N.D.	D	D	N.D.
M7	D	D	N.D.	D	D	D	N.D.
M8	N.D.	N.D.	N.D.	D	D	D	N.D.
Cefiderocol catechol 3-methoxy	D	D	D	D	N.D.	D	N.D.
ATAA	D	D	D	D	D	D	D

Metabolites	Mouse	Rat	Rabbit	Monkey	Fresh Human	Cryo Human	No Cell
M12	N.D.	D	N.D.	N.D.	D	D	N.D.
M13	N.D.	N.D.	N.D.	D	N.D.	N.D.	N.D.
M14	N.D.	D	N.D.	N.D.	N.D.	N.D.	N.D.
M15	N.D.	D	N.D.	N.D.	N.D.	N.D.	N.D.
M16	N.D.	D.	N.D.	N.D.	N.D.	N.D.	N.D.
M19	D	D	D	D	D	D	D
ATAA = aminothiazole amide aldehyde; D = detected The speculated structures of metabolites are as follows; M2: a glucuronide of PCBA, M3 and M5: a glucuronide of methylated PCBA, M4: a sulfate of PCBA, M6 : a methylated PCBA, M7 and M12: a sulfate of methylated PCBA, M8: a sulfate of methylated, oxidized, and dehydrogenated PCBA, M13: a sulfate of oxidized and dehydrogenated PCBA, M14 : a glucuronide of dimethylated and oxidized PCBA, M15: a diglucuronide of methylated and oxidized PCBA, M16: a glucuronide of methylated and oxidized PCBA, M19: an isomeric rearrangement of cefiderocol. a As free form							
Study Number	[redacted]						
Location in CTD	5.3.2.2-01						

2.6.5.11 薬物動態試験： 推定代謝経路



PCBA = pyrrolidine chlorobenzamide; ATAA = aminothiazole amide aldehyde

2.6.5.12 薬物動態試験： 薬物代謝酵素の誘導／阻害

2.6.5.12.1 ヒト CYP 酵素に対するセフィデロコルの阻害作用

Test Article: Cefiderocol sodium drug product

Test System	Human liver microsomes (a pool of 50 individual)				
Concentration (μmol/L)	0 (control), 13.3, 39.9, 133, 399 and 1330 for all CYPs except for CYP2C8 0 (control), 133, 399, 1330, 2660 and 5320 for CYP2C8 only				
Substrates (Concentration)	Phenacetin (20 μmol/L) for CYP1A2, Bupropion (80 μmol/L) for CYP2B6, Paclitaxel (15 μmol/L) for CYP2C8, Diclofenac (10 μmol/L) for CYP2C9, S-Mephenytoin (20 μmol/L) for CYP2C19, Bufuralol (10 μmol/L) for CYP2D6, Chlorzoxazone (50 μmol/L) for CYP2E1, Testosterone (75 μmol/L) for CYP3A4, Nifedipine (25 μmol/L) for CYP3A4, Midazolam (5 μmol/L) for CYP3A4				
Incubation	At 37°C for 10 minutes				
Sample	Reaction mixture after incubation of substrate with human liver microsomes in the presence of cefiderocol sodium				
Analyte	Acetaminophen, Hydroxybupropion, 6α-Hydroxypaclitaxel, 4'-Hydroxydiclofenac, 4'-Hydroxy S-mephenytoin, 1'-Hydroxybufuralol, 6-Hydroxychlorzoxazone, 6β-Hydroxytestosterone, Oxidized nifedipine, 1'-Hydroxymidazolam				
Assay	UPLC/MS/MS				
CYP isoform	Direct Inhibition (0 minutes pre-incubation)		Time-dependent Inhibition (30 minutes pre-incubation)		Potential for Time-dependent Inhibition [a]
	IC_{50} (μmol/L)	% of Control at Maximum Concentration (%)	IC_{50} (μmol/L)	% of Control at Maximum Concentration (%)	
CYP1A2	> 1330	14.2	> 1330	6.36	None
CYP2B6	> 1330	15.1	> 1330	21.4	None
CYP2C8	> 5320	23.7	> 5320	30.1	None
CYP2C9	> 1330	27.8	> 1330	8.73	None
CYP2C19	> 1330	11.8	> 1330	16.9	None
CYP2D6	> 1330	7.13	> 1330	0.00	None
CYP2E1	> 1330	25.1	> 1330	6.98	None
CYP3A4 (Testosterone)	> 1330	12.2	> 1330	6.23	None

CYP3A4 (Nifedipine)	> 1330	23.2	> 1330	16.7	None
CYP3A4 (Midazolam)	> 1330	10.9	> 1330	0.00	None
IC_{50} = 50% inhibitory concentration; UPLC/MS/MS = ultra-performance liquid chromatography with tandem mass spectrometry a Time-dependent inhibition potential is indicated if the IC_{50} shift is >1.5-fold (0 and 30 minutes pre-incubation) Data are expressed as the mean of triplicate assays. Negative values are expressed as 0.00.					
Study Number	S-649266-PF-065-L				
Location in CTD	5.3.2.2-02				

2.6.5.12.2 ヒト CYP 酵素に対するセフィデロコルの誘導作用

Test Article: Cefiderocol sodium drug product

Test System	Primary cultures of cryopreserved human hepatocytes (3 Donors [Lot No. Hu8130, HUM4021, and HUM4016])
Exposure	72 hours
Concentration (μmol/L)	0 (control), 30, 100, 300, 1000, 3000
Positive and Negative Controls (Concentration)	Omeprazole (50 μmol/L) for prototypical inducer of CYP1A2, Phenobarbital (1000 μmol/L) for prototypical inducer of CYP2B6, Rifampicin (20 μmol/L) for prototypical inducer of CYP3A4, Flumazenil (20 μmol/L) for non-inducer
Substrates (Concentration)	Phenacetin (100 μmol/L) for CYP1A2, Bupropion (500 μmol/L) for CYP2B6, Midazolam (30 μmol/L) for CYP3A4/5
Sample	Reaction mixture after incubation of substrate with human hepatocytes which were exposed with cefiderocol or positive/negative control, Isolated RNA from human hepatocytes which were exposed with cefiderocol or positive/negative control
Analyte	Acetaminophen, Hydroxybupropion, 1'-Hydroxymidazolam, mRNA
Assay	LC/MS/MS, Quantitative real-time polymerase chain reaction

CYP isoform	Enzyme Activity							
	Test Article or Positive/Negative Controls	Concentration (μmol/L)	Fold Induction to the Corresponding Control			Percentages to the Positive Control (%)		
			Hu8130	HUM4021	HUM4016	Hu8130	HUM4021	HUM4016
CYP1A2	Cefiderocol	30	0.917	1.07	1.00	−0.386	0.112	0.0113
		100	0.955	1.20	1.03	−0.208	0.316	0.164
		300	1.16	1.52	0.948	0.743	0.827	−0.340
		1000	1.54	1.63	1.46	2.53	0.990	3.01
		3000	0.762	0.703	0.468	−1.11	−0.470	−3.49
	Omeprazole	50	27.8	80.7	13.2			
	Flumazenil	20	6.08	7.32	4.54	18.9	7.93	29.0
CYP2B6	Cefiderocol	30	1.00	1.32	0.716	0.00	4.03	−5.02
		100	0.985	1.59	0.757	−0.180	7.48	−4.30
		300	1.08	1.07	0.866	0.932	0.945	−2.37
		1000	1.03	0.890	0.916	0.301	−1.40	−1.49
		3000	0.536	0.373	0.188	−5.43	−7.95	−14.4
	Phenobarbital	1000	12.7	10.6	5.94			
	Flumazenil	20	1.84	1.24	1.04	7.13	2.45	0.824

CYP isoform	Enzyme Activity							
	Test Article or Positive/Negative Controls	Concentration (μmol/L)	Fold Induction to the Corresponding Control			Percentages to the Positive Control (%)		
			Hu8130	HUM4021	HUM4016	Hu8130	HUM4021	HUM4016
CYP3A4/5	Cefiderocol	30	0.986	1.85	1.38	−0.155	4.26	6.43
		100	0.972	2.14	1.15	−0.316	5.70	2.48
		300	1.17	2.80	0.825	1.92	8.99	−2.94
		1000	1.87	3.82	2.06	9.73	14.0	17.8
		3000	1.20	2.27	0.510	2.25	6.30	−8.23
	Rifampicin	20	10.0	27.3	6.18			
	Flumazenil	20	1.36	1.81	1.07	4.05	3.09	1.30

CYP isoform	mRNA							
	Test Article or Positive/Negative Controls	Concentration (μmol/L)	Fold Induction to the Corresponding Control			Percentages to the Positive Control (%)		
			Hu8130	HUM4021	HUM4016	Hu8130	HUM4021	HUM4016
CYP1A2	Cefiderocol	30	0.659	0.609	0.581	−1.23	−0.707	−0.283
		100	0.378	0.600	0.606	−2.24	−0.723	−0.267
		300	2.23	3.37	2.92	4.43	4.28	1.30
		1000	5.46	2.51	3.64	16.0	2.74	1.78
		3000	1.10	1.38	0.788	0.372	0.689	−0.143
	Omeprazole	50	28.8	56.3	149			
	Flumazenil	20	11.2	2.69	4.75	36.7	3.05	2.54
CYP2B6	Cefiderocol	30	0.563	0.998	0.496	−2.86	−0.00860	−5.29
		100	0.341	0.883	0.945	−4.31	−0.558	−0.574
		300	0.597	1.80	2.55	−2.63	3.84	16.3
		1000	0.494	1.72	2.13	−3.31	3.45	11.8
		3000	0.273	0.808	0.370	−4.75	−0.917	−6.62
	Phenobarbital	1000	16.3	21.9	10.5			
	Flumazenil	20	1.90	1.81	2.19	5.90	3.87	12.5

CYP isoform	mRNA							
	Test Article or Positive/Negative Controls	Concentration (μmol/L)	Fold Induction to the Corresponding Control			Percentages to the Positive Control (%)		
			Hu8130	HUM4021	HUM4016	Hu8130	HUM4021	HUM4016
CYP3A4	Cefiderocol	30	0.658	1.07	0.750	−5.62	0.0978	−0.607
		100	0.364	0.967	1.22	−10.4	−0.0446	0.527
		300	0.602	2.59	3.49	−6.53	2.15	6.04
		1000	1.12	2.75	4.15	2.01	2.36	7.65
		3000	0.837	0.231	0.825	−2.68	−1.04	−0.425
	Rifampicin	20	7.09	75.2	42.2			
	Flumazenil	20	1.91	1.01	0.910	14.9	0.0118	−0.219
mRNA = messenger RNA Data are expressed as the mean of triplicate assays. Hepatocytes from one donor (Lot Number Hu8130) were used in cytotoxicity assessment and cefiderocol showed cytotoxicity at the concentration of 5000 μmol/L or greater.								
Study Number	S-649266-PF-135-N							
Location in CTD	5.3.2.2-03							

2.6.5.12.3 ヒト CYP3A4 に対するセフィデロコルの誘導作用

Test Article: Cefiderocol sodium drug product

Test system:			Primary cultures of cryopreserved human hepatocytes (3 donors: Lot No. HC10-49, HC10-50, and HC7-25)					
Exposure:			72 hours					
Concentration (μmol/L):			0 (2% v/v saline), 10, 30, 100, 300, 1000, 3000					
Positive and negative controls (concentration):			Rifampin (20 μmol/L) for prototypical inducer of CYP3A4 and flumazenil (25 μmol/L) for negative control					
Sample:			Isolated RNA from human hepatocytes which were exposed with cefiderocol, negative or positive control.					
Analyte:			CYP3A4 mRNA					
Assay:			Quantitative real-time polymerase chain reaction					
Tabulated results:								
CYP Isoform	mRNA expression							
	Test article, negative or positive control	Concentration (μmol/L)	Fold change to the corresponding control			Percentages to the positive control (%)		
			HC10-49	HC10-50	HC7-25	HC10-49	HC10-50	HC7-25
CYP3A4	Cefiderocol	10	0.878	2.08	1.23	−0.648	1.53	0.358
		30	0.824	2.46	1.33	−0.932	2.07	0.519
		100	0.983	2.54	1.03	−0.0900	2.18	0.0498
		300	1.43	4.10	1.55	2.29	4.39	0.860
		1000	6.48	11.6	12.8	29.0	15.0	18.4
		3000	13.3	12.2	45.4	65.3	15.8	69.1
	Flumazenil	25	1.01	1.34	1.30	0.0529	0.485	0.472
	Rifampin	20	19.9	71.7	65.3	100	100	100
	mRNA EC_{50}, E_{max}, RIS and % decrease in AUC of midazolam Evaluation							
	Evaluation		HC10-49		HC10-50		HC7-25	
	EC_{50} (μmol/L)		1025		437		1310	
	E_{max} (fold change)		13.4		12.4		45.7	

	RIS (using $C_{max,u}$ of 64.7 µmol/L)	0.796	1.60	2.15
	% decrease in AUC of midazolam	83.0	79.3	86.2
AUC = area under the plasma concentration-time curve; $C_{max,u}$ = unbound maximum concentration in plasma; EC_{50} = concentration causing half maximal effect; E_{max} = maximal induction effect; RIS = relative induction score $RIS = E_{max} \times [I]/ (EC_{50} + [I])$ [I] = the $C_{max,u}$				
Study No.:	S-649266-PF-415-N			

2.6.5.13 薬物動態試験： 排泄

2.6.5.13.1 ラットにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の尿及び糞中排泄

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)		
Gender (M/F)/Number of Animals	M/3 (intact rats)		
Feeding Condition	Non-fasted		
Vehicle/Formulation	Saline/Solution		
Method of Administration	Single intravenous administration (bolus)		
Dose (mg/kg) [a]	30		
Radionuclide	^{14}C		
Specific Activity [a]	124 kBq (3.34 μCi)/mg		
Sample	Urine, Feces		
Analyte	Radioactivity		
Assay	LSC		
Sampling Time (hours)	Excretion of Radioactivity (% of dose)		
	Urine	Feces	Total [b]
4	73.0 ± 6.37	N/A	
8	10.2 ± 5.86	N/A	
24	5.94 ± 1.38	6.24 ± 1.09	
48	0.74 ± 0.21	0.55 ± 0.20	
72	0.20 ± 0.10	0.11 ± 0.05	
96	0.06 ± 0.02	0.05 ± 0.03	
120	0.03 ± 0.01	0.02 ± 0.03	
144	0.02 ± 0.01	0.01 ± 0.01	
168	0.01 ± 0.01	0.03 ± 0.05	
Total	90.2 ± 0.91	7.01 ± 1.19	98.65 ± 0.15
Data are expressed as the mean ± S.D. of 3 individuals. a As free form b Total excretion of radioactivity includes the sum of recovery in cage rinse, cage wash, cage wipe, carcass, and cage debris in addition to urine and feces.			
Study Number	[redacted]		
Location in CTD	4.2.2.5-01		

2.6.5.13.2 サルにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の尿及び糞中排泄

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Cynomolgus Monkey					
Gender (M/F)/Number of Animals	M/3 and F/3					
Feeding Condition	Fasted					
Vehicle/Formulation	Saline/Solution					
Method of Administration	Single intravenous administration (bolus)					
Dose (mg/kg) [a]	30					
Radionuclide	^{14}C					
Specific Activity	124 kBq (3.34 μCi)/mg					
Sample	Urine, Feces					
Analyte	Radioactivity					
Assay	LSC					
Sampling Time (hours)	Excretion of Radioactivity (% of dose)					
	M			F		
	Urine	Feces	Total [b]	Urine	Feces	Total [b]
4	68.2 ± 12.6	N/A		50.5 ± 9.24	N/A	
8	11.3 ± 5.74	N/A		6.34 ± 1.56	N/A	
24	4.67 ± 1.15	2.54 ± 3.12		4.20 ± 1.70	6.17 ± 4.61	
48	1.11 ± 0.84	2.01 ± 0.76		1.65 ± 1.51	1.33 ± 0.61	
72	0.41 ± 0.26	1.07 ± 1.50		0.19 ± 0.11	1.71 ± 2.18	
96	0.14 ± 0.09	0.33 ± 0.45		0.08 ± 0.02	0.57 ± 0.79	
120	0.09 ± 0.04	0.11 ± 0.11		0.04 ± 0.01	0.06 ± 0.02	
144	0.03 ± 0.02	0.06 ± 0.07		0.03 ± 0.01	0.03 ± 0.01	
168	0.05 ± 0.04	0.04 ± 0.04		0.02 ± 0.00	0.05 ± 0.03	
Total	86.0 ± 6.70	6.15 ± 1.61	96.7 ± 5.74	63.1 ± 10.9	9.92 ± 2.93	81.0 ± 15.0
Data are expressed as the mean ± S.D. of 3 individuals. a As free form b Total excretion of radioactivity includes the sum of recovery in cage rinse, cage wash, cage wipe, and cage debris in addition to urine and feces.						
Study Number	[redacted]					
Location in CTD	4.2.2.5-03					

2.6.5.14 薬物動態試験： 排泄：胆汁中

2.6.5.14.1 ラットにおける [Catechol-^{14}C]-セフィデロコルナトリウム塩製剤単回静脈内投与後の尿，糞及び胆汁中排泄

Test Article: [Catechol-^{14}C]-cefiderocol sodium drug product

Species/Strain	Rat/Crl:CD(Sprague Dawley)			
Gender (M/F)/Number of Animals	M/3 (BDC rats)			
Feeding Condition	Non-fasted			
Vehicle/Formulation	Saline/Solution			
Method of Administration	Single intravenous administration (bolus)			
Dose (mg/kg) [a]	30			
Radionuclide	^{14}C			
Specific Activity [a]	124 kBq (3.34 μCi)/mg			
Sample	Urine, Bile, Feces			
Analyte	Radioactivity			
Assay	LSC			
Sampling Time (hours)	Excretion of Radioactivity (% of dose)			
	Urine	Bile	Feces	Total [b]
4	61.9 ± 6.63	8.60 ± 1.33	N/A	
8	14.9 ± 2.64	0.12 ± 0.02	N/A	
24	9.02 ± 5.23	0.10 ± 0.02	0.37 ± 0.41	
48	1.08 ± 0.69	0.04 ± 0.00	0.79 ± 0.05	
72	0.19 ± 0.08	0.00 ± 0.01	0.38 ± 0.29	
96	0.05 ± 0.01	0.00 ± 0.00	0.08 ± 0.03	
Total	87.1 ± 2.39	8.86 ± 1.35	1.62 ± 0.25	99.71 ± 1.78
Data are expressed as the mean ± S.D. of 3 individuals. a As free form b Total excretion of radioactivity includes the sum of recovery in cage rinse, cage wash, cage wipe, cage debris, carcass, and cannula/jacket in addition to urine, bile and feces.				
Study Number	[redacted]			
Location in CTD	4.2.2.5-01			

2.6.5.15 薬物動態試験： 薬物相互作用

2.6.5.15.1 P-gp に対するセフィデロコルの基質評価

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Test System	Caco-2 cells			
Specific Activity	367 kBq/mg (9.93 µCi/mg)			
Concentration (µmol/L)	50, 100, 300			
Positive Control (Concentration)	[^{3}H]-Digoxin (1 µmol/L)			
Incubation	At 37°C for 3 hours			
Sample	Apical side solution, Basal side solution			
Analyte	Radioactivity			
Assay	LSC			
P-gp Substrate Assessment	Concentration (µmol/L)	Apparent Permeability (× 10^{-6} cm/sec)		Efflux Ratio [a]
		Apical to Basal	Basal to Apical	
[^{14}C]-Cefiderocol	50	0.0920 ± 0.0033	0.0930 ± 0.0075	1.0
	100	0.0811 ± 0.0033	0.106 ± 0.006	1.3
	300	0.0817 ± 0.0052	0.123 ± 0.001	1.5
[^{3}H]-Digoxin	1	1.08 ± 0.03	10.8 ± 0.6	10.0
Apparent permeability is expressed as the mean ± S.D. of triplicate assays. Efflux ratio was calculated by using the mean apparent permeability value of triplicate assays. a Efflux Ratio = the apparent permeability from basal to apical/the apparent permeability from apical to basal				
Study Number	S-649266-PF-067-N			
Location in CTD	5.3.2.2-05			

2.6.5.15.2 ヒト腎取り込み/排出トランスポーターに対するセフィデロコルの基質評価

Test Article: [Thiazole-^{14}C]-cefiderocol sodium drug product

Test System	Human renal uptake/efflux transporter (OAT1, OAT3, OCT2, MATE1, or MATE2-K) expressing HEK293 cells,
Specific Activity	400 kBq/mg (10.8 µCi/mg) for OAT1, OAT3, or OCT2 assessment, 407 kBq/mg (11.0 µCi/mg) for MATE1 or MATE2-K assessment
Concentration (µmol/L)	100
Positive Control (Concentration)	[^{3}H]*p*-Aminohippuric acid (1 µmol/L for OAT1 assessment), [^{3}H]Estrone-3-sulfate ammonium salt (0.05 µmol/L for OAT3 assessment), [^{14}C]Metformin (10 µmol/L for OCT2, MATE1, and MATE2-K assessment)
Inhibitors (Concentration)	Probenecid (300 µmol/L for OAT1 and OAT3 assessments), Quinidine (300 µmol/L for OCT2 assessment), Cimetidine (10 µmol/L for MATE1 assessment, 100 µmol/L for MATE2-K assessment)
Incubation	At 37°C for 2, 5, 15, or 30 minutes (for OAT1, OAT3, and OCT2 assessments), At 37°C for 2, 5, 10, or 15 minutes (for MATE1 and MATE2-K assessments)
Sample	Cell lysate
Analyte	Radioactivity
Assay	LSC

Uptake/Efflux Transporter	Inhibitor	Time (minutes)	Cleared Volume [a] (µL/mg protein)	
			Control	Transporter Expressing HEK293 Cells
OAT1	None	2	0.834 ± 0.338	0.277 ± 0.090
		5	0.403 ± 0.207	1.07 ± 0.47
		15	0.448± 0.049	0.446 ± 0.083
		30	1.05± 0.48	0.988 ± 0.158
	Probenecid	2	0.476 ± 0.056	0.375 ± 0.040
		5	0.500 ± 0.116	2.01 ± 0.62
		15	0.793± 0.131	0.949 ± 0.478
		30	0.497± 0.115	1.45 ± 0.62

Uptake/Efflux Transporter	Inhibitor	Time (minutes)	Cleared Volume [a] (μL/mg protein)	
			Control	Transporter Expressing HEK293 Cells
OAT3	None	2	0.834 ± 0.338	0.526 ± 0.140
		5	0.403 ± 0.207	0.667 ± 0.245
		15	0.448± 0.049	0.945 ± 0.222
		30	1.05± 0.48	0.835 ± 0.147
	Probenecid	2	0.476 ± 0.056	0.406 ± 0.169
		5	0.500 ± 0.116	0.927 ± 0.351
		15	0.793± 0.131	0.559 ± 0.162
		30	0.497± 0.115	0.648 ± 0.131
OCT2	None	2	0.0995 ± 0.0278	0.138 ± 0.045
		5	0.134 ± 0.039	0.206 ± 0.023
		15	0.294 ± 0.035	0.361 ± 0.085
		30	0.355 ± 0.010	0.381 ± 0.025
	Quinidine	2	0.119 ± 0.018	0.170 ± 0.034
		5	0.151 ± 0.060	0.172 ± 0.027
		15	0.256 ± 0.027	0.384 ± 0.120
		30	0.458 ± 0.035	0.497 ± 0.106
MATE1	None	2	0.389 ± 0.185	0.439 ± 0.172
		5	0.636 ± 0.074	0.591 ± 0.188
		10	0.705 ± 0.417	0.524 ± 0.034
		15	0.554 ± 0.061	0.564 ± 0.091
	Cimetidine	2	0.340 ± 0.044	0.283 ± 0.112
		5	0.445 ± 0.150	0.605 ± 0.118
		10	0.628 ± 0.040	0.550 ± 0.273
		15	0.881 ± 0.075	0.804 ± 0.181

Uptake/Efflux Transporter	Inhibitor	Time (minutes)	Cleared Volume [a] (μL/mg protein)	
			Control	Transporter Expressing HEK293 Cells
MATE2-K	None	2	0.324 ± 0.086	0.229 ± 0.017
		5	0.160 ± 0.022	0.326 ± 0.022
		10	0.266 ± 0.026	0.301 ± 0.034
		15	0.426 ± 0.097	0.437 ± 0.051
	Cimetidine	2	0.242 ± 0.076	0.567 ± 0.138
		5	0.300 ± 0.013	0.351 ± 0.090
		10	0.307 ± 0.047	0.359 ± 0.050
		15	0.362 ± 0.061	0.427 ± 0.083
Data are expressed as the mean ± S.D. of triplicate assays. a Cleared volume (μL/mg protein) = Uptake amount (dpm/well)/[Protein amount (mg protein/well) × Initial concentration (dpm/μL)]				
Study Number	S-649266-PF-074-N (for OAT1, OAT3, OCT2), S-649266-PF-128-N (for MATE1, MATE2-K)			
Location in CTD	5.3.2.2-07, 5.3.2.2-06			

2.6.5.15.3 ヒトトランスポーターに対するセフィデロコルの阻害評価

Test Article: Cefiderocol sodium drug product

Test System	Human transporter (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K) expressing HEK293 cells, Caco-2 cells, or BSEP expressing vesicles
Concentration (μmol/L)	0 (control), 30, 100, 300, 1000, 3000, 10000, or 30000 (OAT1, OAT3, and OCT2 assessments), or 0 (control), 10, 30, 100, 300, 1000, 3000, or 10000 (OATP1B1, OATP1B3, OCT1, MATE1, MATE2-K, BCRP, P-gp, and BSEP assessment)
Substrate (Concentration)	[^{3}H]*p*-Aminohippuric acid (1 μmol/L for OAT1 assessment), [^{3}H]Estrone-3-sulfate ammonium salt (0.05 μmol/L for OAT3 assessment, 0.1 μmol/L for BCRP assessment), [^{14}C]Metformin (10 μmol/L for OCT1, OCT2, MATE1, and MATE2-K assessments), [^{3}H]Estradiol 17β-D-glucuronide (0.05 μmol/L for OATP1B1 and OATP1B3 assessment), [^{3}H]Digoxin (1 μmol/L for P-gp assessment), [^{3}H]Taurocholic acid (2 μmol/L for BSEP assessment)
Inhibitors (Concentration)	Probenecid (300 μmol/L for OAT1, and OAT3 assessment), Quinidine (100 μmol/L for OCT1assessment, or 300 μmol/L for OCT2 assessment), Rifampicin (10 μmol/L for OATP1B1, and OATP1B3 assessment), Cimetidine (10 μmol/L for MATE1 assessment, or 100 μmol/L for MATE2-K assessment), Verapamil (30 μmol/L for P-gp assessment), Ko143 (1 μmol/L for BCRP assessment), Cyclosporin A (10 μmol/L for BSEP assessment)
Incubation	At 37°C for 0.5 minutes (for OAT1 assessment), 2 minutes (for OAT3, OCT2, OATP1B1, and OATP1B3 assessments), 5 minutes (for OCT1, MATE1, MATE2-K, and BSEP assessment), or 2 hours (Caco-2 cell systems)
Sample	Apical side solution, Basal side solution, Cell lysate
Analyte	Radioactivity
Assay	LSC

Transporters	Inhibitor	Concentrations (μmol/L)	Cleared Volume [a] (μL/mg protein)		% of Control [b]	IC_{50} (μmol/L)
			Control	Transporter Expressing HEK293 Cells		
OAT1	Cefiderocol	0	0.140 ± 0.048	21.9 ± 2.5	100.0	141
		30	0.149 ± 0.103	17.5 ± 0.3	79.7	
		100	0.0992 ± 0.0386	12.9 ± 0.5	58.8	
		300	0.0934 ± 0.0438	7.25 ± 0.19	32.9	
		1000	0.103 ± 0.025	2.89 ± 0.20	12.8	
		3000	0.128 ± 0.048	1.63 ± 0.16	6.9	
		10000	0.0524 ± 0.0079	0.458 ± 0.021	1.9	
		30000	0.0723 ± 0.0322	0.825 ± 0.127	3.5	
	Probenecid	300	0.147 ± 0.005	0.239 ± 0.061	0.4	
OAT3	Cefiderocol	0	1.00 ± 0.14	19.9 ± 2.4	100.0	292
		30	0.945 ± 0.236	15.8 ± 1.3	78.6	
		100	0.944 ± 0.062	14.0 ± 0.5	69.1	
		300	0.858 ± 0.138	9.84 ± 0.47	47.5	
		1000	0.981 ± 0.210	6.99 ± 0.21	31.8	
		3000	0.687 ± 0.104	3.74 ± 0.39	16.2	
		10000	0.691 ± 0.191	2.95 ± 0.08	12.0	
		30000	0.784 ± 0.108	2.00 ± 0.63	6.4	
	Probenecid	300	0.538 ± 0.116	1.40 ± 0.24	4.6	

Transporters	Inhibitor	Concentrations (μmol/L)	Cleared Volume [a] (μL/mg protein)		% of Control [b]	IC_{50} (μmol/L)
			Control	Transporter Expressing HEK293 Cells		
OCT1	Cefiderocol	0	1.38 ± 0.40	26.2 ± 2.9	100.0	1550
		10	1.15 ± 0.10	22.7 ± 1.8	86.8	
		30	1.44 ± 0.31	24.0 ± 2.1	90.9	
		100	1.21 ± 0.17	19.3 ± 2.2	72.9	
		300	1.36 ± 0.50	20.5 ± 1.4	77.1	
		1000	1.37 ± 0.22	20.8 ± 2.0	78.3	
		3000	1.15 ± 0.23	8.36 ± 0.34	29.0	
		10000	1.15 ± 0.14	2.98 ± 0.42	7.4	
	Quinidine	100	0.343 ± 0.130	0.937 ± 0.150	2.4	
OCT2	Cefiderocol	0	0.652 ± 0.011	112 ± 2	100.0	2170
		30	0.611 ± 0.023	94.0 ± 1.9	83.9	
		100	0.745 ± 0.090	103 ±5	91.8	
		300	0.598 ± 0.009	105 ±8	93.8	
		1000	0.518 ± 0.017	79.1 ± 2.3	70.6	
		3000	0.468 ± 0.089	47.4 ± 1.6	42.1	
		10000	0.275 ± 0.054	15.9 ± 0.3	14.0	
		30000	0.154 ± 0.011	3.99 ± 0.16	3.4	
	Quinidine	300	0.550 ± 0.158	1.77 ± 0.14	1.1	

Transporters	Inhibitor	Concentrations (μmol/L)	Cleared Volume [a] (μL/mg protein)		% of Control [b]	IC_{50} (μmol/L)
			Control	Transporter Expressing HEK293 Cells		
OATP1B1	Cefiderocol	0	0.578 ± 0.079	113 ± 10	100.0	4850
		10	0.785 ± 0.171	132 ± 6	116.7	
		30	0.638 ± 0.179	129 ± 8	114.2	
		100	0.651 ± 0.144	130 ± 9	115.1	
		300	0.653 ± 0.129	105 ± 3	92.8	
		1000	0.696 ± 0.017	93.1 ± 6.2	82.2	
		3000	0.568 ± 0.065	75.6 ± 8.1	66.7	
		10000	0.555 ± 0.053	29.9 ± 1.6	26.1	
	Rifampicin	10	0.672 ± 0.110	6.14 ± 0.55	4.9	
OATP1B3	Cefiderocol	0	0.578 ± 0.079	19.9 ± 2.3	100.0	2570
		10	0.785 ± 0.171	21.1 ± 1.3	105.1	
		30	0.638 ± 0.179	20.6 ± 1.5	103.3	
		100	0.651 ± 0.144	19.7 ± 1.3	98.6	
		300	0.653 ± 0.129	16.5 ± 0.4	82.0	
		1000	0.696 ± 0.017	14.3 ± 0.1	70.4	
		3000	0.568 ± 0.065	10.3 ± 0.4	50.4	
		10000	0.555 ± 0.053	4.30 ± 0.42	19.4	
	Rifampicin	10	0.672 ± 0.110	0.955 ± 0.079	1.5	

Transporters	Inhibitor	Concentrations (μmol/L)	Cleared Volume [a] (μL/mg protein)		% of Control [b]	IC_{50} (μmol/L)
			Control	Transporter Expressing HEK293 Cells		
MATE1	Cefiderocol	0	0.744 ± 0.190	23.9 ± 1.3	100.0	4730
		10	0.738 ± 0.038	19.9 ± 1.6	82.8	
		30	0.825 ± 0.175	21.3 ± 1.7	88.4	
		100	0.965 ± 0.191	19.7 ± 1.4	80.9	
		300	0.729 ± 0.125	21.1 ± 1.3	88.0	
		1000	0.913 ± 0.073	23.1 ± 2.0	95.8	
		3000	0.950 ± 0.039	16.5 ± 1.7	67.2	
		10000	0.786 ± 0.084	5.51 ± 0.34	20.4	
	Cimetidine	10	0.656 ± 0.113	1.80 ± 0.19	4.9	
MATE2-K	Cefiderocol	0	0.853 ± 0.010	21.7 ± 3.3	100.0	1230
		10	0.667 ± 0.026	22.0 ± 0.5	102.3	
		30	0.716 ± 0.053	22.3 ± 1.1	103.5	
		100	0.687 ± 0.043	22.5 ± 1.1	104.6	
		300	0.617 ± 0.050	14.9 ± 0.8	68.5	
		1000	0.713 ± 0.031	13.1 ± 0.7	59.4	
		3000	0.853 ± 0.016	7.00 ± 0.46	29.5	
		10000	0.642 ± 0.019	2.39 ± 0.07	8.4	
	Cimetidine	100	0.435 ± 0.034	4.25 ± 0.06	18.3	

Cleared volume is expressed as the mean ± S.D. of triplicate assays.

a Cleared volume (μL/mg protein) = Uptake amount (dpm/well)/[Protein amount (mg protein/well) × Initial concentration (dpm/μL)]

b % of Control = (Cleared volume of transporter expressing cells in the presence of cefiderocol or inhibitor − Cleared volume of control cells in the presence of cefiderocol or inhibitor)/(Cleared volume of transporter expressing cells in the absence of cefiderocol or inhibitor − Cleared volume of control cells in the absence of cefiderocol or inhibitor) × 100

Transporters	Inhibitor	Concentrations (μmol/L)	Apparent Permeability (× 10^{-6} cm/sec)		Efflux Ratio [a]	% of Control [b]	IC_{50} (μmol/L)
			Apical to Basal	Basal to Apical			
P-gp	Cefiderocol	0	0.491 ± 0.043	16.9 ± 1.3	34.4	100.0	>10000
		10	0.495 ± 0.032	16.7 ± 1.6	33.7	97.9	
		30	0.519 ± 0.042	17.5 ± 0.6	33.7	97.9	
		100	0.462 ± 0.098	17.6 ± 1.2	38.1	111.1	
		300	0.609 ± 0.043	18.2 ± 0.7	29.9	86.5	
		1000	0.551 ± 0.026	16.4 ± 0.9	29.8	86.2	
		3000	0.476 ± 0.030	15.1 ± 1.3	31.7	91.9	
		10000	0.564 ± 0.033	13.3 ± 0.9	23.6	67.7	
	Verapamil	30	3.99 ± 0.33	5.98 ± 0.44	1.5	1.5	
BCRP	Cefiderocol	0	1.02 ± 0.02	42.7 ± 1.5	41.9	100.0	4700
		10	1.04 ± 0.06	41.4 ± 1.2	39.8	94.9	
		30	0.966 ± 0.062	40.2 ± 1.0	41.6	99.3	
		100	1.12 ± 0.03	40.2 ± 2.3	35.9	85.3	
		300	1.10 ± 0.15	43.3 ± 1.0	39.4	93.9	
		1000	1.08 ± 0.05	40.6 ± 2.1	37.6	89.5	
		3000	1.37 ± 0.04	36.4 ± 1.9	26.6	62.6	
		10000	2.13 ± 0.29	25.6 ± 0.7	12.0	26.9	
	Ko143	1	5.17 ± 0.54	6.96 ± 0.57	1.3	0.7	

Apparent permeability is expressed as the mean ± S.D. of triplicate assays.
Efflux ratio was calculated by using the mean apparent permeability value of triplicate assays.
a Efflux Ratio = the apparent permeability from basal to apical/the apparent permeability from apical to basal
b % of Control = (Efflux ratio in the presence of cefiderocol or inhibitor − 1)/(Efflux ratio in the absence of cefiderocol or inhibitor − 1) × 100

Transporters	Inhibitor	Concentrations (μmol/L)	Cleared Volume [a] (μL/mg protein)		% of Control [b]	IC_{50} (μmol/L)
			AMP	ATP		
BSEP	Cefiderocol	0	36.9 ± 2.4	297 ± 10	100.0	>10000
		10	35.6 ± 5.9	291 ± 11	98.1	
		30	33.1 ± 1.5	310 ± 5	106.5	
		100	35.1 ± 3.5	317 ± 12	108.5	
		300	35.2 ± 1.6	266 ± 20	88.8	
		1000	36.6 ± 4.5	289 ± 38	96.9	
		3000	33.5 ± 1.7	251 ± 11	83.8	
		10000	31.2 ± 4.5	225 ± 4	74.6	
	Cyclosporin A	10	39.8 ± 1.8	69.7 ± 2.9	11.5	
Cleared volume is expressed as the mean ± S.D. of triplicate assays. a Cleared volume (μL/mg protein) = Uptake amount into vesicles (dpm)/[Protein content (mg protein) × Concentration in reaction mixture (dpm/μL)] b % of Control = (Cleared volume of vesicles in the presence of cefiderocol or inhibitor [ATP (+)] − Cleared volume of vesicles in the presence of cefiderocol or inhibitor [AMP (+)])/(Cleared volume of vesicles in the absence of cefiderocol or inhibitor [ATP (+)] − Cleared volume of vesicles in the absence of cefiderocol or inhibitor [AMP (+)]) × 100						
Study Number	S-649266-PF-074-N (for OAT1, OAT3, OCT2), S-649266-PF-127-N (for OCT1, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, BSEP)					
Location in CTD	5.3.2.2-07, 5.3.2.2-08					

2.6.5.16 薬物動態試験： その他

該当する試験なし.