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

2.6.3 薬理試験概要表

塩野義製薬株式会社

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略号及び用語定義一覧表

略号	英語
AUC_{total}	area under the concentration-time curves from the start of dosing to the last plasma sampling time after dosing
C_0	concentration at the completion of dosing
CAZ	ceftazidime hydrate
CD_{50}	dose levels to induce convulsions in 50% of mice (convulsive dose)
CEZ	cefazolin sodium hydrate
CFPM	cefepime dihydrochloride monohydrate
EEG	electroencephalogram
FOB	functional observation battery
GLP	Good Laboratory Practice
HEK-293 cell	human embryonic kidney-293 cell
hERG	human ether-à-go-go related gene
IC_{50}	50% inhibitory concentration
IPM	imipenem monohydrate
IPM/CS	imipenem monohydrate/cilastatin sodium
M	male
QTc	corrected QT interval
WBP	whole body plethysmography

2.6.3 薬理試験概要表

2.6.3.1 薬理試験：一覧表

Test Article: Cefiderocol sodium drug product

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location in CTD
Primary Pharmacodynamics					
Not Applicable					
Secondary Pharmacodynamics					
Effects of cefiderocol sodium drug product on various receptor, ion channel and transporter binding and enzyme assays	86 Receptors, channels, transporters and enzymes	In vitro	[redacted]	S-649266-EF-185-N	4.2.1.2-01
Safety Pharmacology: In vitro					
Cardiovascular System					
Effects of cefiderocol sodium drug product on myocardial action potential in isolated guinea pig papillary muscle	Guinea-pig papillary muscle	In vitro	[redacted]	R-649266-SF-030-L	4.2.1.3-02
Effects of cefiderocol sodium drug product on potassium currents in cells expressing hERG channels	HEK-293 cells expressing hERG channels	In vitro	[redacted]	R-649266-SF-031-L	4.2.1.3-03
Safety Pharmacology: In vivo					
Central nervous System					
Effects of cefiderocol sodium drug product on central nervous system in rats (modified FOB method)	Rat/Sprague Dawley	Intravenous	[redacted]	R-649266-SF-027-L	4.2.1.3-01
Cardiovascular System					
Effects of cefiderocol sodium drug product on cardiovascular system in monkeys (telemetry system)	Monkey/Cynomolgus monkey	Intravenous	[redacted]	R-649266-SF-028-L	4.2.1.3-05
Respiratory system					
Effects of cefiderocol sodium drug product on respiratory system in rats (WBP method)	Rat/Sprague Dawley	Intravenous	[redacted]	R-649266-SF-029-L	4.2.1.3-04
Follow up Safety Pharmacology					
Proconvulsive effect of cefiderocol sodium drug product following intracerebroventricular injection in mice	Mouse/ICR	Intracerebro-ventricular	Shionogi & Co., Ltd.	S-649266-SB-245-N	4.2.1.4-01
Effect of cefiderocol sodium drug product on electroencephalograms in Rats	Rat/Sprague Dawley	Intravenous	Shionogi & Co., Ltd.	S-649266-SB-246-N	4.2.1.4-02

FOB = functional observation battery; HEK-293 cell = human embryonic kidney-293 cell; hERG = human ether-à-go-go-related gene; [redacted]; WBP = whole body plethysmography

2.6.3.2 効力を裏付ける試験

全ての表及び図は 2.7.2.4 項に示す.

2.6.3.3 副次的薬理試験

2.6.3.3.1 各種受容体，イオンチャネル，トランスポーター及び酵素に及ぼすセフィデロコルの影響

Test Article: S-649266 sodium Drug Product

Receptors, channels, transporters, and enzymes	Receptor/transporter: Human recombinant (adenosine A_1, adenosine A_{2A}, adrenergic α_{1D}, adrenergic α_{2A}, adrenergic α_{2B}, adrenergic β_1, adrenergic β_2, norepinephrine transporter [NET], androgen [testosterone], angiotensin AT_1, bradykinin B_2, cannabinoid CB_1, cannabinoid CB_2, chemokine CCR_1, cholecystokinin CCK_1 [CCK_A], cholecystokinin CCK_2 [CCK_B], dopamine D_1, dopamine D_{2S}, dopamine D_{2L}, dopamine transporter (DAT), endothelin ET_A, estrogen ERα, $GABA_{B1A}$, glucocorticoid, glutamate [Metabotropic, $mGlu_5$], histamine H_1, histamine H_2, leukotriene [Cysteinyl $CysLT_1$], melanocortin MC_1, melanocortin MC_4, muscarinic M_1, muscarinic M_2, muscarinic M_3, muscarinic M_4, tachykinin NK1, , opiate δ_1 [OP1, DOP], opiate κ [OP2, KOP], opiate μ [OP3, MOP], potassium channel hERG, PPARγ, serotonin [5-Hydroxytryptamine] 5-HT_{1A}, serotonin 5-HT_{1B}, serotonin 5-HT_{2A}, serotonin 5-HT_{2B}, serotonin 5-$HT_{2C,}$ serotonin 5-HT_3, serotonin transporter [SERT], and vasopressin $V1_A$ receptors. Human cell line (neuropeptide Y Y_1, nicotinic acetylcholine, nicotinic acetylcholine α_1 [Bungarotoxin], and progesterone PR-B receptors). Human platelet (platelet activating factor [PAF]). Guinea Pig (adenosine transporter), Rat (adrenergic α_{1A}, adrenergic α_{1B}, Ca channel [Type L, Benzothiazepine], Ca channel [Type L, Dihydropyridine], Ca channel [Type L, Phenylalkylamine], Ca channel [Type N], GABA transporter, $GABA_A$ [Flunitrazepam, Central], $GABA_A$ [Ro-15-1788, Hippocampus], $GABA_A$ [Chloride Channel, TBOB], glutamate [AMPA], glutamate [Kainate], glutamate [NMDA Agonism], glutamate [NMDA Glycine], glutamate [NMDA Phencyclidine], glutamate [NMDA, Polyamine], glycine [Strychnine-Sensitive] receptors, and Sodium channel Site 2. Hamster (potassium channel [K_{ATP}]), Enzyme: Human recombinant (cholinesterase [Acetyl, ACES], cyclooxygenase-2 [COX-2], monoamine oxidase-A [MAO-A], monoamine oxidase-B [MAO-B], protein tyrosine kinase [Insulin Receptor], and protein tyrosine kinase [LCK]). Platelet; (cyclooxygenase-1 [COX-1], phosphodiesterase PDE3, Phosphodiesterase PDE4); Neutrophils; Peptidase (CTSG, Cathepsin G). Rabbit lung (peptidase (Angiotensin Converting Enzyme). Rat protein serine/threonine kinase (PKC, Non-Selective). Pig (ATPase, (Na^+/K^+, Heart).
Concentration (μmol/L)	100
Vehicle	1% Saline (cefiderocol sodium drug product) or 1% dimethyl sulfoxide (reference substances)
Reference substances (Concentration)	Listed in the table of Results
Evaluation items	Inhibition constant (K_i), Concentration that reduce the efficacy of the reference agonist by 50% of its maximum effect (IC_{50}), Functional binding constant (K_b), Percent of the maximal stimulation in the [^{35}S]-GTPγS binding (E_{max}), Effective concentration that produced 50% stimulation (EC_{50}) of the [^{35}S]GTPγS binding
Evaluation item	Inhibition effect (% inhibition) on radioligand binding to various receptors, channels, and transporters and on enzymes
Evaluation method for receptor, channel, and transporter	The percentage inhibition of cefiderocol sodium drug product or positive control on the binding of tracer to each receptor, channel, or transporter was calculated to assess the binding potency. The assay solution was prepared by diluting the membrane fractions prepared from each clone or tissue with the appropriate assay buffer. Each replacement article solution was added to tube for calculation of nonspecific binding, and 1% saline was added to tube for calculation of total binding. The solution of cefiderocol or positive control was added to tube for calculation of inhibition ratio. After addition of the assay buffer and tracer solution, the assay solution was added to each tube. The mixture was incubated under the appropriate conditions. The incubated mixture was filtered using a cell harvester or treated using dextran charcoal. The radioactivity of sample was counted using a liquid scintillation counter.

Evaluation method for enzyme	The percentage inhibition of cefiderocol or positive control on each enzyme reaction was calculated to assess the inhibitory potency. The enzyme solution was prepared from each tissue or clone. Assay medium or 1% saline was added to tube or well for measurement of background value and 100% activity. The solution of cefiderocol or positive control was added to the tube or well for calculation of inhibition ratio. The enzyme mixture was incubated under the appropriate conditions for each enzyme and the enzyme activity was measured by the appropriate method.
Calculation of inhibition percentage	Inhibition (%) = [1 − (B − N) / (B_0 − N)] × 100 B = average radioactivity, absorbance, or fluorescence intensity in the tube or well for calculation of inhibition percentage (individual value); B_0 = average radioactivity, absorbance, or fluorescence intensity in the tube or well for measurement of 100% activity (mean value); N = average radioactivity, absorbance, or fluorescence intensity in the tube or well for measurement of background value (mean value)

Assay Name	**Cefiderocol (Inhibition [%])**	**Reference Substances (Inhibition [%], concentration [µmol/L])**	**Assay Name**	**Cefiderocol (Inhibition [%])**	**Reference Substances (Inhibition [%], concentration [µmol/L])**
Cholinesterase, Acetyl, ACES	7	Physostigmine (94, 1)	$GABA_A$, Flunitrazepam, Central	7	Diazepam (81, 0.1)
Peptidase, Angiotensin Converting Enzyme	14	Captopril (95, 0.1)	$GABA_A$, Ro-15-1788, Hippocampus	2	Diazepam (85, 0.3)
ATPase, Na^+/K^+, Heart, Pig	2	Ouabain (94, 30)	$GABA_A$, Chloride Channel, TBOB	0	Picrotoxin (85, 3)
Peptidase, CTSG (Cathepsin G)	24	Chymostatin (98, 10)	$GABA_{B1A}$	−6	CGP-54626 (98, 0.1)
Cyclooxygenase COX-1	10	Indomethacin (99, 0.3)	Glucocorticoid	0	Dexamethasone (92, 0.03)
Cyclooxygenase COX-2	5	Rofecoxib (86, 0.1)	Glutamate, AMPA	−12	L-Glutamic acid (91, 3)
Monoamine Oxidase MAO-A	4	Clorgyline (98, 0.01)	Glutamate, Kainate	2	L-Glutamic acid (93, 3)
Monoamine Oxidase MAO-B	8	R(-)-Deprenyl (93, 0.1)	Glutamate, NMDA, Agonism	1	L-Glutamic acid (92, 3)
Phosphodiesterase PDE3	3	Cilostamide (75, 0.3)	Glutamate, NMDA, Glycine	1	MDL 105,519 (93, 0.1)
Phosphodiesterase PDE4	−9	Rolipram (82, 10)	Glutamate, NMDA, Phencyclidine	12	Dizocilpine ((+)-MK-801) (94, 0.03)
Protein Tyrosine Kinase, Insulin Receptor	5	Staurosporine (93, 3)	Glutamate, NMDA, Polyamine	−14	Ifenprodil (91, 0.3)
Protein Tyrosine Kinase, LCK	18	Staurosporine (99, 0.3)	Glutamate, Metabotropic, $mGlu_5$	12	L-Glutamic acid (88, 10)
Protein Serine/Threonine Kinase, PKC, Non-Selective	−3	Staurosporine (92, 0.01)	Glycine, Strychnine-Sensitive	13	(-)-Strychnine (84, 0.1)
Adenosine A_1	17	R(-)-PIA (77, 3)	Histamine H_1	12	Pyrilamine (95, 0.03)
Adenosine A_{2A}	5	CGS-21680 (95, 3)	Histamine H_2	0	Tiotidine (95, 0.3)
Transporter, Adenosine	−4	Nitrobenzylthioinosine (94, 0.01)	Leukotriene, Cysteinyl $CysLT_1$	−1	LTD_4 (91, 0.01)
Adrenergic α_{1A}	15	Prazosin (95, 0.003)	Melanocortin MC_1	−1	NDP-α-MSH (73, 0.0003)
Adrenergic α_{1B}	6	Prazosin (93, 0.003)	Melanocortin MC_4	−1	NDP-α-MSH (97, 0.003)
Adrenergic α_{1D}	−8	Prazosin (94, 0.01)	Muscarinic M_1	3	4-DAMP (97, 0.1)

Assay Name	Cefiderocol (Inhibition [%])	Reference Substances (Inhibition [%], concentration [µmol/L])	Assay Name	Cefiderocol (Inhibition [%])	Reference Substances (Inhibition [%], concentration [µmol/L])
Adrenergic α_{2A}	9	Yohimbine (95, 0.03)	Muscarinic M_2	2	4-DAMP (90, 0.3)
Adrenergic α_{2B}	0	Yohimbine (87, 0.1)	Muscarinic M_3	7	4-DAMP (97, 0.1)
Adrenergic β_1	−2	S(-)-Propranolol (69, 0.01)	Muscarinic M_4	3	4-DAMP (95, 0.3)
Adrenergic β_2	−10	S(-)-Propranolol (97, 0.01)	Tachykinin NK_1	9	L-703,606 (74, 0.03)
Transporter, Norepinephrine (NET)	−9	Desipramine (83, 0.01)	Neuropeptide Y Y_1	2	Neuropeptide Y (human, rat) (97, 0.003)
Androgen (Testosterone)	−1	Testosterone (90, 0.03)	Nicotinic Acetylcholine	3	Epibatidine (88, 0.001)
Angiotensin AT_1	−16	Saralasin (89, 0.01)	Nicotinic Acetylcholine α_1, Bungarotoxin	1	α-Bungarotoxin (84, 0.01)
Bradykinin B_2	2	Bradykinin (88, 0.01)	Opiate δ_1 (OP1, DOP)	−2	Naltrindole (93, 0.01)
Calcium Channel L-Type, Benzothiazepine	1	Diltiazem (85, 0.3)	Opiate κ (OP2, KOP)	3	U-69593 (89, 0.3)
Calcium Channel L-Type, Dihydropyridine	8	Nitrendipine (92, 0.003)	Opiate µ (OP3, MOP)	3	DAMGO (86, 0.3)
Calcium Channel L-Type, Phenylalkylamine	−3	Methoxyverapamil (D-600) (81, 0.3)	Platelet Activating Factor (PAF)	−18	PAF (75, 0.003)
Calcium Channel N-Type	−4	ω-Conotoxin GVIA (95, 0.0003)	Potassium Channel [K_{ATP}]	14	Glyburide (83, 0.1)
Cannabinoid CB_1	−3	R(+)-WIN-55,212-2 (77, 3)	Potassium Channel hERG	3	Astemizole (78, 0.03)
Cannabinoid CB_2	−2	R(+)-WIN-55,212-2 (89, 0.1)	PPARγ	1	Rosiglitazone (92, 0.3)
Chemokine CCR_1	13	MCP-3 (96, 0.03)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1A}$	7	Metergoline (93, 0.03)
Cholecystokinin CCK_1 (CCK_A)	3	Devazepide (L-364,718) (97, 0.01)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1B}$	−31	Serotonin (5-HT) (98, 3)
Cholecystokinin CCK_2 (CCK_B)	−19	Sincalide (97, 0.001)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2A}$	3	Ketanserin (93, 0.01)
Dopamine D_1	13	R(+)-SCH-23390 (97, 0.03)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2B}$	−1	Ketanserin (75, 3)
Dopamine D_{2L}	1	Spiperone (93, 0.003)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2C}$	3	SB242084 (98, 0.01)
Dopamine D_{2S}	3	Spiperone (93, 0.03)	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_3$	8	MDL 72222 (92, 0.3)
Transporter, Dopamine (DAT)	−11	GBR-12909 (90, 0.01)	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	−2	Fluoxetine (88, 0.1)
Endothelin ET_A	−6	Endothelin-1 (89, 0.001)	Sodium Channel, Site 2	−6	Dibucaine (86, 10)
Estrogen ERα	0	Diethylstilbestrol (97, 0.01)	Vasopressin V_{1A}	−7	(Arg^8)-Vasopressin (89, 0.003)

Assay Name	Cefiderocol (Inhibition [%])	Reference Substances (Inhibition [%], concentration [µmol/L])	Assay Name	Cefiderocol (Inhibition [%])	Reference Substances (Inhibition [%], concentration [µmol/L])
Transporter, GABA	10	NO-711 (92, 3)	Progesterone PR-B	−1	R-5020 (89, 0.003)
Study No. [Location in CTD]	S-649266-EF-185-N [4.2.1.2-01]				

2.6.3.4 安全性薬理試験コアバッテリー

2.6.3.4.1 In Vitro

Test Article: Cefiderocol sodium drug product

Organ Systems Evaluated	Test System	Method of Application	Concentration (mg/mL) [a]	No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Cardio-vascular system [b]	Guinea-pig papillary muscle	In vitro (Perfusion) [c]	0, 0.15, 0.5, 1.5	5	Yes	None	R-649266-SF-030-L/ 4.2.1.3-02
Cardio-vascular system [d]	HEK-293 cells expressing hERG channels	In vitro (Perfusion) [e]	0, 0.15, 0.5, 1.5	5	Yes	$IC_{50} \geq 1.5$ mg/L	R-649266-SF-031-L/ 4.2.1.3-03

GLP = Good Laboratory Practice; IC_{50} = 50% inhibitory concentration

a As free form

b Evaluation items were action potential amplitude, resting membrane potential, maximum rate of depolarization, action potential duration at 30% and 90% repolarization, and a difference in action potential duration between 90% and 30% repolarization.

c Cefiderocol sodium drug product was dissolved in external solution (perfusion solution), and applied to the specimens.

d Evaluation items were potassium current (hERG current).

e Cefiderocol sodium drug product was dissolved in Tyrode solution (perfusion solution), and applied to the cells.

2.6.3.4.2 In Vivo

Test Article: Cefiderocol sodium drug product

Organ Systems Evaluated	Species/ Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg) [a]	Gender and No. per Group	GLP Compliance	Noteworthy Findings	Study Number/ Location in CTD
Central nervous system (modified FOB method)	Rat/ Crl:CD(SD)	Intravenous administration for 30 minutes/animal (Physiological saline/ Solution)	0, 250, 500, 1000	6M	Yes	≥ 250: Chromaturia (red-brown) ≥ 500: Prone position, Increased volume of urine excretion 1000: Prone position Decrease in motor activity Decrease in rectal temperature	R-649266-SF-027-L/ 4.2.1.3-01
Cardio-vascular system (telemetry system) [b]	Monkey/ Cynomolgus monkey	Intravenous administration for 60 minutes /animal (Physiological saline/Solution)	0, 100, 300, 1000	4M	Yes	≥ 100: Chromaturia (reddish brown) ≥ 300: Vomiting and/or retching 1000: Prolongation of QT/QTc Elevation of blood pressure Decrease of body temperature Toxicokinetics	R-649266-SF-028-L/ 4.2.1.3-04
Respiratory System (WBP method) [c]	Rat/ Crl:CD(SD)	Intravenous administration for 30 minutes/animal (Physiological saline/ Solution)	0, 250, 500, 1000	8M	Yes	None	R-649266-SF-029-L/ 4.2.1.3-05

Toxicokinetics

Dose (mg/kg)	100	300	1000
C_0 (μg/mL)	316	907	2760
AUC_{total}	700	1980	6860

AUC_{total} = area under the concentration-time curves from the start of dosing to the last plasma sampling time after dosing; C_0 = plasma concentration at the completion of dosing; M = male; QTc = corrected QT interval

a As free form

b Evaluation items were blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram (PR interval, QRS duration, QT interval, and QTc), and intra-abdominal body temperature.

c Evaluation items were respiratory rate, tidal volume, and minute volume

2.6.3.5 安全性薬理フォローアップ試験

2.6.3.5.1 マウスの脳室内投与時の痙攣誘発作用

Test Article: Cefiderocol sodium drug product

Species/Strain	Mouse/Crl:CD1(ICR)
Gender (M/F) Number of Animals	M/10 per group
Feed Condition	Nonfasted
Vehicle/Formulation	Physiological saline/Solution
Method of Administration	Intracerebroventricular injection
Dose (μg/mouse) [a]	0, 5, 10, 25, 50, 100
Reference Substance (Vehicle/Formulation, Method of Administration/Dose)	CEZ (Physiological saline/Solution, Intracerebroventricular injection/10, 20, 30, and 40 μg/mouse) CFPM (Physiological saline/Solution, Intracerebroventricular injection/ 25, 40, 50, and 60 μg/mouse) CAZ (Physiological saline/Solution, Intracerebroventricular injection/ 60, 80, 100, and 120 μg/mouse) IPM (Physiological saline/Solution, Intracerebroventricular injection/ 1, 2.5, and 5 μg/mouse)
Treatment	Single administration
Evaluation Items	Incidence of convulsion (%), CD_{50}
Evaluation Method	Cefiderocol sodium drug product, CEZ, CFPM, CAZ, IPM, or physiological saline was injected into the lateral ventricle of conscious mice. The occurrences of clonic convulsions were observed for 20 minutes postdose. The CD_{50} for cefiderocol sodium drug product and reference substances were estimated using the logistic regression analysis.

Result				
Substances	**Doses (μg/mouse)** [a]	**Number of Animals**	**Incidence of Convulsion (%)**	**CD_{50} (μg/mouse) (95% two-sided confidence limits)**
Vehicle		10	0	
Cefiderocol sodium drug product	5	10	10	23.44 (14.83-36.00)
	10	10	0	
	25	10	70	
	50	10	70	
	100	10	100	
CEZ	10	10	0	19.34 (13.59-23.21)
	20	10	60	
	30	10	90	
	40	10	100	
CFPM	25	10	30	31.23 (19.32-38.54)
	40	10	70	
	50	10	90	
	60	10	90	
CAZ	60	10	0	88.20 (75.48-101.20)
	80	10	50	
	100	10	60	
	120	10	90	
IPM	1	10	0	3.83 (2.70-5.27)
	2.5	10	10	
	5	10	80	
Study Number [Location in CTD]		S-649266-SB-245-N [4.2.1.3-06]		

CAZ = ceftazidime hydrate; CD_{50} = dose levels to induce convulsions in 50% of mice (convulsive dose); CEZ = cefazolin sodium hydrate; CFPM = cefepime dihydrochloride monohydrate; IPM = imipenem monohydrate

a As free form

2.6.3.5.2 ラットの脳波及び行動試験

Test Article: Cefiderocol sodium drug product

Species/Strain		Rat/Crl:CD(SD)		
Gender (M/F) Number of Animals		M/6 to 8 per group		
Feed Condition		Nonfasted		
Vehicle/Formulation		Physiological saline/Solution		
Method of Administration		Intravenous administration for 30 minutes/animal		
Dose (mg/kg) [a]		0, 500, 750		
Positive control substance (Vehicle/Formulation, Method of Administration/Dose)		IPM/CS (Physiological saline/Solution, Intravenous administration for 30 minutes/animal/400/400 mg/kg)		
Treatment		Single administration		
Evaluation Items		EEG and behavior		
Evaluation Method		Electroencephalographic electrodes for recording cortical EEG were implanted into the dura matter over the frontal cortex and parietal cortex. A polyurethane tube filled with physiological saline containing heparin sodium was inserted into the femoral vein for injection of cefiderocol sodium drug product, IPM/CS, or vehicle. These surgical operations were conducted under anesthesia. Six to nine days after surgery, vehicle, cefiderocol sodium drug product, or IPM/CS was administered intravenously to rats. The effects of cefiderocol sodium drug product and IPM/CS on EEG and behavior were investigated from 0.5 hours before the start of administration to 4 hours postdose.		
Result				
Substances	**Doses (mg/kg)** [a]	**Number of Animals**	**EEG** [b]	**Behavior** [b]
Vehicle	–	8	No effects	No effects
Cefiderocol sodium drug product	500	6	No effects	No effects
	750	8	No effects	No effects
IPM/CS	400/400	8	Spike (7), Multiple spike-and slow-wave complex (5), Seizure discharge (3)	Wet dog shakes (1), Teeth chattering (1), Tremor (2), Twitch (3), Clonic convulsions (3)
Study Number [Location in CTD]		S-649266-SB-246-N [4.2.1.3-07]		

EEG = electroencephalogram; IPM/CS = imipenem monohydrate/cilastatin sodium

a As free form

b Parenthesis shows occurrence number of animals which exhibited electroencephalographic or behavioral changes.

2.6.3.6 薬力学的薬物相互作用試験

該当する試験なし.