2.6.5.2 分析方法及びバリデーション試験

Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Method Utilized	Noteworthy Findings (Precision and Accuracy Validation)[a]	Study Number
Mouse	XL184	0.5-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-6
Rat	XL184	5.0-2500 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-1
Rat	XL184	1.0-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-7
Rat	XL184	0.5-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-8 4.2.2.1-9
Rat	EXEL-1644	1.0-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-10
Dog	XL184	1.0-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-2
Dog	XL184	0.5-1000 ng/mL	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-3
Dog	XL184、EXEL-5162	5.0-2500 ng/mL for XL184 1.0-500 ng/mL for EX-5162	Plasma drug concentration analysis	LC/MS/MS	Intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-4
Dog	XL184、EXEL-5162, EXEL-1646, EXEL-5366, p-FA	1.0-400 ng/mL for XL184, EXEL-5162 and EXEL-5366 2.0-800 ng/mL for EX-1646 and p-FA	Plasma drug concentration analysis	LC/MS/MS	Inter- and intra-assay precision (≤ ±15% RSD) and accuracy (≤ ±15% DMT)	4.2.2.1-5

[a] RSD: Relative standard deviation, DMT: Deviation of the mean from theoritical

2.6.5.3 薬物動態試験：単回投与後の吸収

			Test Article: XL184		
			Study No. 4.2.2.2-2		
Species	Dog	Dog	Dog	Dog	Dog
Test Article Lot No.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (M/F)/Number of animals:	M/5	M/5	M/5	M/5	M/5
Feeding condition:	Fasted	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation:	Suspension, ethanol, PEG400, water (5, 45, 50)	Capsule (dry powder formulation)	Capsule (melt 1 formulation)	Capsule (melt 2 formulation)	Capsule (liquid formulation)
Method of Administration:	Gavage	Gavage	Gavage	Gavage	Gavage
Dose (mg):	50 (5 mg/mL)	50 (2 x 25)	50 (2 x 25)	50 (2 x 25)	50 (2 x 25)
Sample:	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte:	XL184	XL184	XL184	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:					
Tmax (hr)	2.6	2.8	2.2	2.2	0.9
Cmax (ng/mL)	441	739	729	654	943
AUC (ng·hr/mL)	3,220	6,090	5,240	4,630	6,100
(Time for calculation - hr)	(0-48 hrs)	(0-48 hrs)	(0-48 hrs)	(0-48 hrs)	(0-48 hrs)
T1/2 (hr)	4.5	4.17	4.14	4.26	4.22

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

	Test Article: XL184-	
	Study No. 4.2.2.2-3	
Species	Dog	Dog
Test Article Lot No.	[redacted]	[redacted]
Gender (M/F)/Number of animals:	M/5	M/5
Feeding condition:	Fed	Fed
Vehicle/Formulation:	Solution; ethanol, PEG400, water (10, 45, 45)	Capsule (dry powder formulation)
Method of Administration:	IV	Gavage
Dose (mg):	50	50 (2 x 25)
Sample:	Plasma	Plasma
Analyte:	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS
PK parameters:		
Tmax (hr)	ND	ND
Cmax (ng/mL)	2,460	814
AUC (ng·hr/mL)	13,600	6,530
(Time for calculation - hr)	(0-72 hrs)	(0-48 hrs)
T1/2 (hr)	5.74	8.05
BA(%)	-	50.6

ND : not determined, -: not culculated

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

	Test Article: XL184		
	Study No. 4.2.2.2-4		
Species	Dog	Dog	Dog
Test Article Lot No.	[redacted]	[redacted]	[redacted]
Gender (M/F)/Number of animals:	M/8	M/8	M/8
Feeding condition:	Fed	Fed	Fed
Vehicle/Formulation:	Solution, ethanol, PEG400, water (10, 45, 45)	Suspension, ethanol, PEG400, water (5, 45, 50)	Capsule (dry powder formulation)
Method of Administration:	IV	Gavage	Gavage
Dose (mg):	50	50	50 (2 x 25)
Sample:	Plasma	Plasma	Plasma
Analyte:	XL184	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:			
Tmax (hr)	0.5	3.13	2.25
Cmax (ng/mL)	2,350	668	760
AUC (ng·hr/mL)	11,500	5,820	6,300
(Time for calculation - hr)	(0-72 hrs)	(0-48 hrs)	(0-48 hrs)
T1/2 (hr)	5.5	6.58	5.47
BA(%)	-	50.6	54.8

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

		Test Article: XL184		
		Study No. 4.2.2.2-5		
Species	Dog[a]	Dog[a]	Dog[a]	Dog[a]
Test Article Description	Girindus, 10% drug load	Torcan, 35% drug load	Torcan, 50% drug load	Girindus, 50% drug load
Gender (M/F)/Number of animals:	M/11	M/11	M/11	M/11
Feeding condition:	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation:	Capsule (dry powder formulation)	Capsule (dry powder formulation)	Capsule (dry powder formulation)	Capsule (dry powder formulation)
Method of Administration:	Gavage	Gavage	Gavage	Gavage
Dose (mg):	100 (4 x 25)	100 (1 x 100)	100 (1 x 100)	100 (1 x 100)
Sample:	Plasma	Plasma	Plasma	Plasma
Analyte:	XL184	XL184	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:				
Tmax (hr)	3.27	3.09	3.45	3.09
Cmax (ng/mL)	1,810	1,490	1,510	1,620
AUC (ng·hr/mL)	14,500	11,200	10,600	12,100
(Time for calculation - hr)	(0-72 hrs)	(0-72 hrs)	(0-72 hrs)	(0-72 hrs)
T1/2 (hr)	7.41	7.02	7.28	7.08

[a] Dogs pretreated with pentagastrin (6 µg/kg) via subcutaneous injection (24µg/mL, 0.25 mL/kg) 30 minutes prior to XL184 Administration.

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

	Test Article: XL184		
	Study No. 4.2.2.2-6		
Species	Dog	Dog[a]	Dog[b]
Test Article Lot No.	[redacted]	[redacted]	[redacted]
Gender (M/F)/Number of animals:	M/11	M/11	M/11
Feeding condition:	Fasted	Fasted	Fasted
Vehicle/Formulation:	Capsule (dry powder formulation)	Capsule (dry powder formulation)	Capsule (dry powder formulation)
Method of Administration:	Gavage	Gavage	Gavage
Dose (mg):	100	100	100
Sample:	Plasma	Plasma	Plasma
Analyte:	XL184	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:			
Tmax (hr)	2.41	2.27	3.27
Cmax (ng/mL)	1340	1310	1210
AUC (ng·hr/mL)	9,630	9,390	8,560
(Time for calculation - hr)	(0-72 hrs)	(0-72 hrs)	(0-72 hrs)
T1/2 (hr)	7.08	7.45	7.59
Gastric pH	7.08	8.16	4.49

[a] Dogs pretreated with famotidine (2 x 20 mg tablets) 3 hrs prior to XL184 administration; [b] Dogs pretreated with pentagastrin (6 µg/kg) via subcutaneous injection (24µg/mL, 0.25 mL/kg) 30 min prior to XL184 administration

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

			Test Article: XL184	
			Study No.4.2.2.2-7	
Species	Dog	Dog[a]	Dog[b]	Dog[c]
Test Article Lot No.	[redacted]	[redacted]	[redacted]	[redacted]
Gender (M/F)/Number of animals:	M/37	M/37	M/37	M/37
Feeding condition:	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation:	Capsule (dry powder formulation)	Capsule (dry powder formulation)	Capsule (dry powder formulation)	Capsule (dry powder formulation)
Method of Administration:	Gavage	Gavage	Gavage	Gavage
Dose (mg):	50 (2 x 25)	50 (2 x 25)	50 (2 x 25)	50 (2 x 25)
Sample:	Plasma	Plasma	Plasma	Plasma
Analyte:	XL184	XL184	XL184	XL184
Assay:	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:				
Tmax (hr)	2.04	1.81	1.91	1.78
Cmax (ng/mL)	771	1,060	927	863
AUC (ng·hr/mL)	5,440	6,330	5,810	5,720
(Time for calculation - hr)	(0-72 hrs)	(0-72 hrs)	(0-72 hrs)	(0-72 hrs)
T1/2 (hr)	6.24	5.75	6.04	6.59

[a]N-2 lot; [b]N-1lot; [c]N-1/N-2 mixture

2.6.5.3 薬物動態試験：単回投与後の吸収（続き）

	Test Article: XL184					
	Study No. 4.2.2.2-8					
Species	Dog		Dog		Dog	
Test Article Lot No.	[redacted]		[redacted]		[redacted]	
Gender (M/F)/Number of animals:	M/6		M/6		M/6	
Feeding condition:	Fasted		Fasted		Fasted	
Vehicle/Formulation:	Capsule		Tablet 1		Tablet 2	
Method of Administration:	Gavage		Gavage		Gavage	
Dose (mg):	100 (2x50mg)		100 (1x100mg)		100 (1x100mg)	
Sample:	Plasma		Plasma		Plasma	
Assay:	LC/MS/MS		LC/MS/MS		LC/MS/MS	
Analyte:[a]	XL184	EXEL-5162	XL184	EXEL-5162	XL184	EXEL-5162
PK parameters:						
Tmax (hr)	1.4	1.8	1.8	2.0	1.9	2.4
Cmax (ng/mL)	1560	93.9	1640	98.1	1670	110
AUC (ng·hr/mL)	8,900	453	11,100	540	10,400	570
(Time for calculation - hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)

[a] EXEL-5162 is the *N*-oxide metabolite of XL184; NS (not specified)

2.6.5.4 薬物動態試験：反復投与後の吸収

Pharmacokinetics: Absorption after Repeated Dose —Male Mice							Test Article: XL184 (Lot No. [redacted])		
Report Title: 4-Week Oral Gavage Dose Range Finding Toxicity and Toxicokinetic Study with Cabozantinib S-Malate in 001178-W (Wild Type) Mice with a 4-Week Recovery Phase (GLP-Compliant)							Study No. 4.2.3.2-1		
Species:	Mice, rasH2								
Gender/Number:	Male (24/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	5.0			15.0			50.0		
	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28
PK parameters:									
Tmax (hr)	2.00	4.00	2.00	2.00	4.00	8.00	4.00	4.00	8.00
Cmax (ng/mL)	2,680	3,590	3,380	9,380	7,250	6,310	19,000	13,300	9,270
AUC (ng·hr/mL)	36,400	36,700	36,200	46,600	95,400	104,000	218,000	150,000	131,000
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Female Mice							Test Article: XL184 (Lot No. [redacted])		
Report Title: 4-Week Oral Gavage Dose Range Finding Toxicity and Toxicokinetic Study with Cabozantinib S-Malate in 001178-W (Wild Type) Mice with a 4-Week Recovery Phase (GLP-Compliant)							Study No. 4.2.3.2-1		
Species:	Mice, rasH2								
Gender/Number:	Female (24/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	5.0			15.0			50.0		
	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28
PK parameters:									
Tmax (hr)	2.00	4.00	4.00	2.00	1.00	4.00	8.00	8.00	8.00
Cmax (ng/mL)	2,500	2,140	2,330	4,710	5,010	6,970	12,100	16,200	7,300
AUC (ng·hr/mL)	20,300	16,100	21,500	66,300	69,800	74,700	189,000	235,000	99,000
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Rat			Test Article: XL184 (Lot No. [redacted])			
Report Title: 14-Day Oral Gavage Toxicity And Toxicokinetic Study With XL184 in Rats with a 28-Day Recovery Period (GLP-Compliant)			Study No. 4.2.3.2-4			
Species:	Rat					
Gender/Number:	Male (10-15/dose level)					
Feeding condition:	Nonfasted					
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)					
Method of Administration:	Gavage					
Sample:	Plasma					
Analyte:	XL184					
Assay:	LC/MS/MS					
Dose (mg/kg/day):	1.0		5.0		15.0	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
PK parameters:						
Tmax (hr)	6.00	6.00	6.00	6.00	6.00	12.00
Cmax (ng/mL)	831	853	3,053	4,690	8,513	26,733
AUC (ng·hr/mL)	9,940	10,978	41,920	52,152	135,549	512,771
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	NC	9.62	NC	16.0	NC	21.5

NC = not calculated

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose — Male Rat (Juvenile)			Test Article: XL184 (Lot No. [redacted])			
Report Title: XL184: 3 Week (Nominal) Oral (Gavage) Administration Dose Range Finding Toxicity Study in the Juvenile Rat			Study No. 4.2.3.5.4-1			
Species:	Rat (Juvenile)					
Gender/Number:	Male (27/dose level)					
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)					
Method of Administration:	Gavage					
Sample:	Plasma					
Analyte:	XL184					
Assay:	LC/MS/MS					
Dose (mg/kg/day):	0.3		1.0		3.0/2.0[a]	
Postnatal Day (PND)	PND 12	PND 35	PND 12	PND 35	PND 12	PND 35[a]
PK parameters:						
Tmax (hr)	24.00	4.00	24.00	6.00	24.00	2.00
Cmax (ng/mL)	361	474	1,350	1,330	3,730	1,460
AUC (ng·hr/mL)	7,190	7,500	22,500	18,100	66,600	18,200
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

[a] Dose was reduced to 2 mg/kg/day from 3 mg/kg/day after 9 doses; starting on PND 20

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose — Female Rat (Juvenile)					Test Article: XL184 (Lot No. [redacted])	
Report Title: XL184: 3 Week (Nominal) Oral (Gavage) Administration Dose Range Finding Toxicity Study in the Juvenile Rat					Study No. 4.2.3.5.4-1	
Species:	Rat (Juvenile)					
Gender/Number:	Female (27/dose level)					
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)					
Method of Administration:	Gavage					
Sample:	Plasma					
Analyte:	XL184					
Assay:	LC/MS/MS					
Dose (mg/kg/day):	0.3		1.0		3.0/2.0[a]	
Postnatal Day (PND)	PND 12	PND 35	PND 12	PND 35	PND 12	PND 35[a]
PK parameters:						
Tmax (hr)	24.00	1.00	24.00	4.00	24.00	4.00
Cmax (ng/mL)	356	486	1,160	1,870	3,400	1,600
AUC (ng·hr/mL)	7,510	8,600	20,600	23,900	64,100	20,900
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

[a] Dose was reduced to 2 mg/kg/day from 3 mg/kg/day after 9 doses; starting on PND 20

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Rat (Juvenile)							Test Article: XL184 (Lot No. [redacted])		
Report Title: XL184: 3 or 7 Week (nominal) Oral (Gavage) Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (GLP-Compliant)							Study No. 4.2.3.5.4-2		
Species:	Rat (Juvenile)								
Gender/Number:	Male (9/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.3			1.0			2.0		
Postnatal Day (PND)	PND 21	PND 35	PND 70	PND 21	PND 35	PND 70	PND 21	PND 35	PND 70
PK parameters:									
Tmax (hr)	6.00	4.00	6.00	6.00	2.00	6.00	6.00	4.00	4.00
Cmax (ng/mL)	314	377	554	983	1,110	1,390	2,040	2,250	2,750
AUC (ng·hr/mL)	6,000	5,490	7,680	20,000	15,900	22,900	37,300	31,500	40,200
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Female Rat (Juvenile)							Test Article: XL184 (Lot No. [redacted])		
Report Title: XL184: 3 or 7 Week (nominal) Oral (Gavage) Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (GLP-Compliant)							Study No. 4.2.3.5.4-2		
Species:	Rat (Juvenile)								
Gender/Number:	Female (9/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.3			1.0			2.0		
Postnatal Day (PND)	PND 21	PND 35	PND 70	PND 21	PND 35	PND 70	PND 21	PND 35	PND 70
PK parameters:									
Tmax (hr)	6.00	2.00	6.00	6.00	4.00	4.00	4.00	4.00	6.00
Cmax (ng/mL)	371	464	623	1,040	1,420	1,700	2,310	2,380	3,160
AUC (ng·hr/mL)	6,880	7,800	10,100	20,200	20,500	31,300	46,400	41,700	53,000
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male and Female Rat (Juvenile)					Test Article: XL184 (Lot No. [redacted])			
Report Title: Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib S-malate (XL184) in Rats (GLP-Compliant)					Study No. 4.2.3.5.3-2			
Species:	Rat (Juvenile)							
Gender/Number:	Male (15/dose level), Female (15/dose level)							
Feeding condition:	Nonfasted							
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)							
Method of Administration:	Gavage							
Sample:	Plasma							
Analyte:	XL184							
Assay:	LC/MS/MS							
Dose (mg/kg/day):[a]	1.0				2.0			
	Male		Female		Male		Female	
Postnatal Day (PND)	PND 35 (n=10)	PND 70[c] (n=10)	PND 35 (n=11)	PND 70 [c] (n=12)	PND 35 (n=8)	PND 70[c] (n=9)	PND 35 (n=9)	PND 70[c] (n=13)
PK parameters: Cmax (ng/mL)[b]	939 (540)	671 (157)	900 (389)	844 (157)	1297 (548)	1197 (636)	1246 (375)	1689 (797)

[a] Groups of juvenile rats (15/sex/dose level/cohort) received vehicle only (ethanol:PEG400:water, 5:45:50, v/v/v) or XL184 via oral gavage at doses of 1 and 2 mg/kg/day from PND 12 to 35 [cohort 1] and PND 12 to 70 [cohort 2]. [b] Mean (SD), Single plasma PK samples were taken at approximately 24 hours post final dose; [c] Plasma samples taken Dosing Days 70-73 (approximately 24 hours post final dose)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Rat							Test Article: XL184 (Lot No. [redacted])		
Report Title: XL184: A Six-Month Oral Toxicity Study with Recovery in Rats (GLP-Compliant)							Study No. 4.2.3.2-6		
Species:	Rat								
Gender/Number:	Male (12/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.1			0.3			1.0		
	Day 1	Day 28	Day 178	Day 1	Day 28	Day 178	Day 1	Day 28	Day 178
PK parameters:									
Tmax (hr)	6	3	3	3	3	3	6	3	3
Cmax (ng/mL)	54.9	90	165	168	367	523	687	1,530	2,590
AUC (ng·hr/mL)	656	1,209	2,632	1,826	3,669	7,851	8,356	15,242	29,736
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	10.2	13.7	NC	10.5	12.8	26.1	8.33	9.99	22.8

NC = not calculated

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose — Female Rat							Test Article: XL184 (Lot No. [redacted])		
Report Title: XL184: A Six-Month Oral Toxicity Study with Recovery in Rats (GLP-Compliant)							Study No. 4.2.3.2-6		
Species:	Rat								
Gender/Number:	Female (12/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.1			0.3			1.0		
	Day 1	Day 28	Day 178	Day 1	Day 28	Day 178	Day 1	Day 28	Day 178
PK parameters:									
Tmax (hr)	3	6	6	6	6	3	6	6	6
Cmax (ng/mL)	87.4	145	298	283	441	881	754	1,230	2,740
AUC_{0-t} (ng·hr/mL)	1,149	1,953	4,753	3,359	6,757	14,416	10,187	18,603	44,086
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	13.2	NC	NC	18.0	17.8	NC	18.3	20.7	NC

NC = not calculated

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Rat			Test Article: EXEL-1644 (6-desmethyl amide cleavage product sulfate; Lot No. [redacted])			
Report Title: 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase (GLP-Compliant)			Study No. 4.2.3.7.5-1			
Species:	Rat					
Gender/Number:	Male (9/dose level)					
Feeding condition:	Nonfasted					
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)					
Method of Administration:	Subcutaneous Injection					
Sample:	Plasma					
Analyte:	EXEL-1644					
Assay:	LC/MS/MS					
Dose (mg/kg/day):	3.0		10.0		30.0	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
PK parameters:						
Tmax (hr)	4.00	2.00	4.00	2.00	2.00	2.00
Cmax (ng/mL)	4,820	8,290	34,900	50,500	101,000	104,000
AUC (ng·hr/mL)	72,000	104,000	323,000	323,000	759,000	692,000
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	NC	NC	9.73	9.72	8.87	8.79

NC = not calculated

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Female Rat			Test Article: EXEL-1644 (6-desmethyl amide cleavage product sulfate; Lot No. [redacted])			
Report Title: 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase (GLP-Compliant)			Study No. 4.2.3.7.5-1			
Species:	Rat					
Gender/Number:	Female (9/dose level)					
Feeding condition:	Nonfasted					
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)					
Method of Administration:	Subcutaneous Injection					
Sample:	Plasma					
Analyte:	EXEL-1644					
Assay:	LC/MS/MS					
Dose (mg/kg/day):	3.0		10.0		30.0	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
PK parameters:						
Tmax (hr)	2.00	2.00	2.00	2.00	2.00	2.00
Cmax (ng/mL)	4,690	10,600	35,000	38,600	112,000	99,300
AUC (ng·hr/mL)	67,800	95,300	248,000	214,000	585,000	460,000
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	NC	NC	13.9	7.51	9.21	8.17

NC = not calculated

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Dog			Test Article: XL184 (Lot No. [redacted])	
Report Title: 14-Day Oral Gavage Toxicity And Toxicokinetic Study With XL184 in Dogs with a 28-Day Recovery Period (GLP-Compliant)			Study No. 4.2.3.2-8	
Species:	Dog			
Gender/Number:	Male (2-3/dose level)			
Feeding condition:	Nonfasted			
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)			
Method of Administration:	Gavage			
Sample:	Plasma			
Analyte:	XL184			
Assay:	LC/MS/MS			
Dose (mg/kg/day):	10[a]		100[b]	
	Day 1	Day 14	Day 1	Day 7
PK parameters:				
Tmax (hr)	4.50	3.75	6.00	5.00
Cmax (ng/mL)	651	824	12,967	8,507
AUC (ng·hr/mL)	6,125	8,406	199,566	115,408
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	4.83	6.02	5.06	7.81

[a] N=2, [b] N=3.

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Female Dog			Test Article: XL184 (Lot No. [redacted])	
Report Title: 14-Day Oral Gavage Toxicity And Toxicokinetic Study With XL184 in Dogs with a 28-Day Recovery Period (GLP-Compliant)			Study No. 4.2.3.2-8	
Species:	Dog			
Gender/Number:	Female (2-3/dose level)			
Feeding condition:	Nonfasted			
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)			
Method of Administration:	Gavage			
Sample:	Plasma			
Analyte:	XL184			
Assay:	LC/MS/MS			
Dose (mg/kg/day):	10[a]		100[b]	
	Day 1	Day 14	Day 1	Day 7
PK parameters:				
Tmax (hr)	3.00	2.25	4.25	2.25
Cmax (ng/mL)	640	1,400	10,163	7,127
AUC (ng·hr/mL)	7,172	11,408	135,198	63,010
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	5.17	6.01	4.65	6.76

[a] N=2, [b] N=3.

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Male Dog				Test Article: XL184 (Lot No. [redacted])					
Report Title: XL184: A Six-Month Oral Toxicity Study with Recovery in Dogs (GLP-Compliant)				Study No. 4.2.3.2-9					
Species:	Dog								
Gender/Number:	Male (4-7/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.2[a]			1.0[a]			5.0[b]		
	Day 1	Day 28	Day 180	Day 1	Day 28	Day 180	Day 1	Day 28	Day 180
PK parameters:									
Tmax (hr)	2.13	1.5	2.5	1.5	0.875	1	2.71	1.57	1.29
Cmax (ng/mL)	60.3	46.9	33.8	173	299	317	635	724	706
AUC (ng·hr/mL)	309	252	285	1,200	2,244	2,027	4,768	8,251	7,757
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	6.08	6.68	4.89	5.93	17.1	8.53	15.1	9.62	12.6

[a] N=4 (N= 3 for $T_{1/2}$ Day 180 at 1 mg/kg/day), [b] N=7 (N=5 for $T_{1/2}$ Day 1 at 5 mg/kg/day)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Pharmacokinetics: Absorption after Repeated Dose —Female Dog				Test Article: XL184 (Lot No. [redacted])					
Report Title: XL184: A Six-Month Oral Toxicity Study with Recovery in Dogs (GLP-Compliant)				Study No. 4.2.3.2-9					
Species:	Dog								
Gender/Number:	Female (4-7/dose level)								
Feeding condition:	Nonfasted								
Vehicle/Formulation:	Ethanol, PEG400, water (5, 45, 50)								
Method of Administration:	Gavage								
Sample:	Plasma								
Analyte:	XL184								
Assay:	LC/MS/MS								
Dose (mg/kg/day):	0.2[a]			1.0[a]			5.0[b]		
	Day 1	Day 28	Day 180	Day 1	Day 28	Day 180	Day 1	Day 28	Day 180
PK parameters:									
Tmax (hr)	1.25	0.75	1.25	0.625	1	0.75	1.57	1.93	1.21
Cmax (ng/mL)	45.6	52.1	73.4	345	234	426	559	536	1,008
AUC (ng·hr/mL)	206	242	323	1,408	1,362	2,012	3,323	3,994	6,327
(Time for calculation - hr)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)	(0-24 hrs)
T1/2 (hr)	3.61	6.01	5.09	6.34	6.65	9.97	6.26	7.02	8.58

[a] N=4, [b] N=7 (N=5 for $T_{1/2}$ Day 28 and N=6 for $T_{1/2}$ Day 180 at 5 mg/kg/day)

2.6.5.5 薬物動態試験：分布

	Test Article: [^{14}C]XL84				
	Study No. 4.2.2.3-3				
Species: Rat, pigmented (Long-Evans)					
Gender (M/F)/Number of animals: Adult male, n=12					
Feeding Condition: Fasted					
Vehicle/Formulation: ethanol:PEG400:water (5:45:50)					
Method of Administration: Gavage					
Dose (mg/kg): 10 mg/kg (100 µCi/kg) target dose					
Radionuclide: ^{14}C					
Specific Activity: 30.4 µci/mg					
Analyte/Assay (unit): Concentrations of radioactivity expressed as µg equivalents of XL184 per gram tissue sample (µg equiv/g)					
Sampling Times (1 rat/sample time): 0.5 hr, 1.0 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr, 2 days, 4 days, 5 days, 7 days and 28 days post-dose					
Tissues/Organs	Cmax[a]	Tmax[b]	$T_{1/2}$ [c]	AUCall[d]	T/B[e]
Adipose (brown)	17.231	2.0	8.4	257.123	1.50
Adipose (white)	17.890	2.0	8.0	215.099	1.25
Adrenal gland	17.396	2.0	113.0	594.557	3.46
Blood (cardiac)	10.519	2.0	15.9	171.650	1.00
Bone	0.556	2.0	ND	9.270	0.05
Bone marrow	7.728	2.0	9.5	143.673	0.84
Brain (entire)	0.788	2.0	13.6	17.761	0.10
Cecum	10.197	8.0	19.2	210.761	1.23
Epididymis	5.057	8.0	8.5	110.725	0.65
Eye (entire)	33.673	24.0	79.9	4953.409	28.86
Eye (lens)	0.405	24.0	ND	14.168	0.08
Eye (uveal tract)	196.935	24.0	201.6	31433.832	183.13
Heart (myocardium)	7.791	2.0	9.8	157.229	0.92
Kidney (entire)	10.072	8.0	15.9	244.759	1.43
Liver	24.061	2.0	18.7	454.556	2.65
Lung	13.227	2.0	15.0	219.768	1.28
Pituitary gland	9.563	8.0	15.37	238.557	1.39
Prostate gland	3.008	12.0	9.48	73.944	0.43
Seminal vesicles	1.722	2.0	15.96	38.462	0.22

[a] (µg equivalents/g tissue); [b] (hr); [c] (hr); [d] area under the curve for all observed time points (µg equiv·hr /g); [e] tissue to blood AUC ratio; ND not determined

2.6.5.5 薬物動態試験：分布（続き）

	Test Article: [^{14}C]XL84				
	Study No. 4.2.2.3-3				
Species: Rat, pigmented (Long-Evans)					
Gender (M/F)/Number of animals: Adult male, n=12					
Feeding Condition: Fasted					
Vehicle/Formulation: ethanol:PEG400:water (5:45:50)					
Method of Administration: Gavage					
Dose (mg/kg): 10 mg/kg (100 µCi/kg) target dose					
Radionuclide: ^{14}C					
Specific Activity: 30.4 µci/mg					
Analyte/Assay (unit): Concentrations of radioactivity expressed as µg equivalents of XL184 per gram tissue sample (µg equiv/g)					
Sampling Times (1 rat/sample time): 0.5 hr, 1.0 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr, 2 days, 4 days, 5 days, 7 days and 28 days post-dose					
Tissues/Organs	Cmax[a]	Tmax[b]	$T_{1/2}$ [c]	AUCall[d]	T/B[e]
Skeletal muscle	5.575	8.0	9.86	107.250	0.62
Skin (non-pigmented)	4.785	12.0	8.70	108.639	0.63
Skin (pigmented)	7.654	24.0	ND	225.713	1.31
Small intestine	29.934	4.0	8.11	398.161	2.32
Spinal cord	0.704	8.0	10.97	14.924	0.09
Spleen	5.902	2.0	9.19	122.911	0.72
Stomach (gastric mucosa)	16.029	2.0	15.93	201.287	1.17
Testis	2.117	8.0	9.95	53.543	0.31
Thymus	4.731	8.0	8.69	107.560	0.63
Thyroid	6.669	2.0	8.66	131.265	0.76
Urinary bladder	6.430	2.0	9.86	85.166	0.50

[a] (µg equivalents/g tissue); [b] (hr); [c] (hr); [d] area under the curve for all observed time points (µg equiv·hr/g); [e] tissue to blood AUC ratio; ND not determined

2.6.5.6 薬物動態試験：蛋白結合

			Test Article: XL184
Study System: *In vitro*			
Target entity, Test System and Method: Plasma, Equilibrium dialysis			
Species	Conc. Tested (μmol/L)	% Bound	Study No.
Mouse	1.0 - 10	>99.9 – 99.8	4.2.2.3-1
Rat	0.2 - 10	>99.9	4.2.2.3-1
Human	0.2 - 10	>99.9 – 99.7	4.2.2.3-1

2.6.5.6 薬物動態試験：蛋白結合（続き）

			Test Article: EXEL-1644
Study System: *In vitro*			
Target entity, Test System and Method: Plasma, Equilibrium dialysis			
Species	Conc. Tested (µmol/L)	% Bound	Study No.
Mouse	125 - 500	98.793 – 96.937	4.2.2.3-2
Rat	125 - 500	99.966 – 99.729	4.2.2.3-2
Human	125 - 500	99.996 – 99.950	4.2.2.3-2

Note: concentration-dependent binding (decreasing with increasing EXEL-1644 concentration)

2.6.5.6 薬物動態試験：蛋白結合（続き）

			Test Article: XL184
Study System: *In vivo*			
Target entity, Test System and Method: Plasma, Equilibrium dialysis			
Species	Dose (mg/kg)	Bound Mean (%)	Study No.
Mouse	30	99.3± 0.54	4.2.2.3-1
	100	99.8± 0.05	
Rat	100	>99.9± 0.02	4.2.2.3-1
	300	>99.9± 0.01	

Note: mean (± SD) values reflect individual analyses performed on samples taken at 0.5, 1, 2, and 4 hrs post single oral dose

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

			Test Article: XL184	
Placental transfer			Study No. 4.2.3.5.2-2	
Species: Rat, Crl: CD (SD)				
Gestation day/Number of animals: Daily dosing gestation days 6-17; maternal blood sampling (3 dams/time point/dose level);				
Vehicle/Formulation: ethanol:PEG400:water (5:45:50)				
Method of Administration: Gavage				
Analyte: XL184				
Assay: LC/MS/MS				
Dose (mg/kg):	0.0	0.01	0.03	0.1
Plasma Concentration (ng/mL)				
Dam[a]:	0	5.76±1.21	17.5±8.20	61.0±7.31
Fetus[b]:	0	1.31±0.28	3.57±0.14	11.1±1.38

[a] Maternal mean blood concentration at 24 hrs post final (Gestation Day 17) dose; [b] Fetal mean [n=6 fetuses/0.0 and 0.1 mg/kg, n=5 fetus/0.01 and 0.03 mg/kg] blood concentration on Gestation Day 18 (sample taken approximately 24 hrs post final maternal dose)

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験（続き）

			Test Article: XL184	
Placental transfer			Study No. 4.2.3.5.2-4	
Species: Rabbit, New Zealand White				
Gestation day/Number of animals: Daily dosing gestation days 7-20; maternal blood sampling (3 dams/time point/dose level);				
Vehicle/Formulation: ethanol:PEG400:water (5:45:50)				
Method of Administration: Gavage				
Analyte: XL184				
Assay: LC/MS/MS				
Dose (mg/kg):	0.0	0.3	1.0	3.0
Plasma Concentration (ng/mL)				
Dam[a]:	0	4.97±2.23	14.5±6.59	56.9±17.7
Fetus[b]:	0	1.79±0.635	6.19±2.54	15.1±2.10

[a] Maternal mean blood concentration at 24 hrs post final (Gestation Day 20) dose; [b] Fetal mean [n=3 fetuses/dose level] blood concentration on Gestation Day 21 (sample taken approximately 24 hrs post final maternal dose)

2.6.5.8 薬物動態試験：その他の分布試験

実施していない

2.6.5.9 薬物動態試験：*In Vitro* における代謝

		Test Article: XL184	
		Study No. 4.2.2.3-1	
Study System: NADPH-supplemented liver (mouse, rat, human) microsomal fractions			
Species:	Mouse	Rat	Human
Time:	4 hr	4 hr	4 hr
Concentration:	10 µmol/L	10 µmol/L	10 µmol/L
	% of Total	% of Total	% of Total
Compounds			
Parent	87.8	96.5	75.9
M-1	4.38	1.94	9.72
M-4	1.53	0.61	7.84
M-6	2.88	0.96	6.57
M-10	1.38	Not detected	Not detected
M-11	2.06	Not detected	Not detected

Refer to Section 2.6.5.11 for proposed metabolite structures.

2.6.5.9 薬物動態試験：*In Vitro* における代謝（続き）

		Test Article: [^{14}C]XL184
		Study No. 4.2.2.4-5
Study System: recombinant human CYP. Concentration of [^{14}C]XL184: 5 µmol/L, Incubation time: 60 min.		
CYP isoform	Metabolite formation rate (pmol/min/mg protein)	% of control
Vector treated control without NADPH[a]	13.4	NA
Vector treated control[a]	16.8	125
CYP1A1[a]	31.2	232
CYP1A2[a]	25.2	188
CYP2B6[a]	23.2	173
CYP2C8[a]	20.1	149
CYP2C19[a]	22.6	168
CYP2D6[a]	27.6	205
CYP2E1[a]	17.0	126
CYP3A4[a]	535	3980
Vector treated contro without NADPH[b]	14.3	NA
Vector treated control[b]	19.1	134
CYP2A6[b]	15.3	107
CYP2C9[b]	19.3	135

[a]: Assay performed in phosphate buffer.

[b]: Assay performed in tris buffer.

NA: Not applicable.

2.6.5.9 薬物動態試験：*In Vitro* における代謝（続き）

			Test Article: [^{14}C]XL184
			Study No. 4.2.2.4-5
Study System: human hepatic microsomes (1.0 mg protein/mL). Concentration of [^{14}C]XL184: 5 µmol/L			
	Metabolite formation rate (pmol/min/mg protein)		
CYP isoform	Without antibody (control)	With antibody	% of control
CYP1A2	8.50	10.9	128
CYP2A6	8.43	10.9	129
CYP2B6	8.58	10.6	124
CYP2C8	9.02	9.33	103
CYP2C9	8.73	7.26	83.1
CYP2C19	8.39	10.6	126
CYP2D6	8.91	10.6	119
CYP2E1	8.04	10.8	134
CYP3A4	8.59	1.63	19.0

2.6.5.9 薬物動態試験：*In Vitro* における代謝（続き）

		Test Article: EXEL-5526、EXEL-1744
		Study No. 4.2.2.4-6
Study System: purified sulfotransferase isoenzymes		
Compounds	Relative Order for Formation of EXEL-1646	Relative Order for Formation of EXEL-1644
EXEL-5526 (0.762 μmol/L)	SULT1A1 > SULT1A2 > SULT2A1	NE
EXEL-5526 (7.62 μmol/L)	SULT2A1 > SULT1A1 > SULT1A2 > SULT1A3	NE
EXEL-1744 (1.31 μmol/L)	NE	SULT1A1 > SULT1A2 > SULT1A3 > SULT1E1
EXEL-1744 (13.1 μmol/L)	NE	SULT1A3 > SULT1A1 > SULT1A2 > SULT2A1 > SULT1E1

Note: EXEL-5526 and EXEL-1744 are the non-sulfate conjugated precursors of sulfate conjugates EXEL-1646 and EXEL-1644, respectively.

NE: Not evaluated.

2.6.5.10 薬物動態試験：*In Vivo* における代謝

							Test Article: XL184	
Gender (M/F)/Number of animals:			Mouse: F/20, Rat: M/4					
Feeding Condition:			-					
Vehicle/Formulation:			Saline					
Method of Administration:			Gavage					
Dose (mg/kg):			Mouse: 100 mg/kg, Rat: 300 mg/kg					
			% of Compound in Sample					
Species	Sample	Sampling Time	XL184	M1	M4	M5	M9	Study No.
Mouse	Plasma	4 hr	66.1	5.85	1.16	15.1	8.22	4.2.2.3-1
Rat	Plasma	4 hr	89.8	2.51	2.39	0.72	2.22	4.2.2.3-1

Eight metabolites (M1, M2, M3, M4, M5, M7, M8, and M9) were detected in mouse plasma with metabolites M5 and M9 being the most abundant. Seven metabolites (M1, M2, M3, M4, M5, M8, and M9) were detected in rat plasma with metabolites M4 and M9 being the most abundant. Refer to Section 2.6.5.11 for proposed metabolite structures. [g] M1 identified in this study as XL184-*N*-Oxide (m/z 518; refer to Section 2.6.5.11)

2.6.5.10 薬物動態試験：*In Vivo* における代謝（続き）

rasH2 mouse (male)						Test Article: XL184	
						Study No. 4.2.2.4-7	
Gender/Number of animals/ Dose Levels: 8 males/dose level (10, 30 or 100 mg/kg daily via oral gavage for 5 consecutive days)							
Vehicle/Formulation: ethanol :PEG400 :water (5 :45 :50)							
Method of Analysis: LC/MS/MS of plasma samples post-dosing Day 5							
Dose (mg/kg):	Mean PK Parameter Value[a]	XL184	EXEL-5162	EXEL-5366	EXEL-1646	EXEL-1644	p-FA
10	$t_{1/2}$ (hr)	8.25	5.38	8.64	3.48	NC	NC
	T_{max} (hr)	8.00	4.00	8.00	2.00	8.00	NC
	Cmax (ng/mL)	2,680	91.0	64.8	10.60	17.1	0.00
	AUC_{last} (ng·hr/mL)	31,000	901	732	47.3	254	NC
	$\%AUC_{analyte}/AUC_{XL184}$	NC	2.9	2.36	0.15	0.82	0.00
	$\%AUC_{analyte}/AUC_{total}$	94.1	2.74	2.22	0.14	0.77	0.00
30	$t_{1/2}$ (hr)	6.37	4.23	6.88	3.51	NC	NC
	T_{max} (hr)	8.00	6.00	8.00	2.00	8.00	1.00
	Cmax (ng/mL)	8,720	411	259	56.80	61.0	7.89
	AUC_{last} (ng·hr/mL)	120,000	5,280	3,680	337.0	994	35.00
	$\%AUC_{analyte}/AUC_{XL184}$	NC	4.4	3.07	0.28	0.83	0.03
	$\%AUC_{analyte}/AUC_{total}$	92.1	4.05	2.82	0.26	0.76	0.03
100	$t_{1/2}$ (hr)	10.9	7.42	14.3	6.02	NC	8.18
	T_{max} (hr)	8.00	4.00	8.00	2.00	12.0	0.50
	Cmax (ng/mL)	18,500	1,520	754	330.0	318	22.10
	AUC_{last} (ng·hr/mL)	320,000	20,000	13,000	3,030	5,250	355.0
	$\%AUC_{analyte}/AUC_{XL184}$	NC	6.3	4.06	0.95	1.64	0.11
	$\%AUC_{analyte}/AUC_{total}$	88.5	5.53	3.59	0.84	1.45	0.10

[a] Sample time (0-24 hrs post-dose);$t_{1/2}$, terminal half-life; T_{max}, time of observed Cmax; Cmax, observed maximum concentration; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; $\%AUC_{analyte}/AUC_{XL184}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of parent XL184); $\%AUC_{analyte}/AUC_{total}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of total AUC [sum of $AUC_{0.5\text{-}last}$ of XL184 and 5 metabolites]); refer to Section 2.6.5.11 for analyte structures; NC, not calculated

2.6.5.10 薬物動態試験：*In Vivo* における代謝（続き）

rasH2 mouse (female)						Test Article: XL184 Study No. 4.2.2.4-7	
Gender/Number of animals/ Dose Levels: 8 females/dose level (10, 30 or 100 mg/kg daily via oral gavage for 5 consecutive days)							
Vehicle/Formulation: ethanol :PEG400 :water (5 :45 :50)							
Method of Analysis: LC/MS/MS of plasma samples post-dosing Day 5							
Dose (mg/kg):	Mean PK Parameter Value[a]	XL184	EXEL-5162	EXEL-5366	EXEL-1646	EXEL-1644	p-FA
10	$t_{1/2}$ (hr)	3.39	2.77	3.28	5.97	NC	NC
	T_{max} (hr)	8.00	4.00	8.00	4.00	4.00	NC
	Cmax (ng/mL)	1,780	97.0	50.1	25.40	6.03	0.00
	AUC_{last} (ng·hr/mL)	20,800	1,060	582	181.0	49.5	NC
	$\%AUC_{analyte}/AUC_{XL184}$	NC	5.1	2.80	0.87	0.24	0.00
	$\%AUC_{analyte}/AUC_{total}$	91.7	4.68	2.57	0.80	0.22	0.00
30	$t_{1/2}$ (hr)	3.82	3.11	3.77	10.50	NC	10.70
	T_{max} (hr)	8.00	8.00	8.00	2.00	0.500	8.00
	Cmax (ng/mL)	6,200	344	189	87.80	25.9	12.10
	AUC_{last} (ng·hr/mL)	73,100	3,670	2030	638.0	367	83.60
	$\%AUC_{analyte}/AUC_{XL184}$	NC	5.0	2.78	0.87	0.50	0.11
	$\%AUC_{analyte}/AUC_{total}$	91.5	4.59	2.54	0.80	0.46	0.10
100	$t_{1/2}$ (hr)	6.44	4.73	8.59	7.22	NC	7.07
	T_{max} (hr)	12.0	12.0	12.0	12.00	12.0	4.00
	Cmax (ng/mL)	16,700	1,990	597	584.00	132	30.60
	AUC_{last} (ng·hr/mL)	2,65000	25,700	9,100	7,090	1,530	461.0
	$\%AUC_{analyte}/AUC_{XL184}$	NC	9.7	3.43	2.68	0.58	0.17
	$\%AUC_{analyte}/AUC_{total}$	85.8	8.32	2.95	2.30	0.50	0.15

[a] Sample time (0-24 hrs post-dose);$t_{1/2}$, terminal half-life; T_{max}, time of observed Cmax; Cmax, observed maximum concentration; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; $\%AUC_{analyte}/AUC_{XL184}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of parent XL184); $\%AUC_{analyte}/AUC_{total}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of total AUC [sum of $AUC_{0.5\text{-}last}$ of XL184 and 5 metabolites]); refer to Section 2.6.5.11 for analyte structures; NC, not calculated

2.6.5.10 薬物動態試験：*In Vivo* における代謝（続き）

CD-1 mouse (male and female)						Test Article: XL184 Study No. 4.2.2.4-7		
Gender/Number of animals/ Dose Levels: 8/sex/dose level (30 mg/kg daily via oral gavage for 5 consecutive days)								
Vehicle/Formulation: ethanol :PEG400 :water (5 :45 :50)								
Method of Analysis: LC/MS/MS of plasma samples post-dosing Day 5								
Dose (mg/kg):	Gender	Mean PK Parameter Value[a]	XL184	EXEL-5162	EXEL-5366	EXEL-1646	EXEL-1644	p-FA
30	Male	$t_{1/2}$ (hr)	2.12	2.14	4.09	NC	NC	NC
		T_{max} (hr)	4.00	4.00	4.00	2.00	6.00	NC
		Cmax (ng/mL)	4,600	467	164	55.20	41.9	0.00
		AUC_{last} (ng·hr/mL)	39,400	3,350	1,110	178.0	560	NC
		$\%AUC_{analyte}/AUC_{XL184}$	NC	8.5	2.82	0.45	1.42	0.00
		$\%AUC_{analyte}/AUC_{total}$	88.3	7.51	2.49	0.40	1.26	0.00
30	Female	$t_{1/2}$ (hr)	3.17	3.42	6.43	14.70	NC	NC
		T_{max} (hr)	2.00	6.00	6.00	0.50	6.00	0.50
		Cmax (ng/mL)	4,420	712	127	106.0	18.1	5.89
		AUC_{last} (ng·hr/mL)	36,500	4,160	869	526	146	7.46
		$\%AUC_{analyte}/AUC_{XL184}$	NC	11.4	2.38	1.44	0.40	0.02
		$\%AUC_{analyte}/AUC_{total}$	86.5	9.86	2.06	1.25	0.35	0.02

[a] Sample time (0-24 hrs post-dose);$t_{1/2}$, terminal half-life; T_{max}, time of observed Cmax; Cmax, observed maximum concentration; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; % $AUC_{analyte}/AUC_{XL184}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of parent XL184); % $AUC_{analyte}/AUC_{total}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of total AUC [sum of $AUC_{0.5\text{-}last}$ of XL184 and 5 metabolites]); refer to Section 2.6.5.11 for analyte structures; NC, not calculated

2.6.5.10 薬物動態試験：*In Vivo* における代謝（続き）

SD rat (male and female)							Test Article: XL184 Study No. 4.2.2.4-7	
Gender/Number of animals/ Dose Levels: 9/sex/dose level (10 mg/kg daily via oral gavage for 5 consecutive days)								
Vehicle/Formulation: ethanol :PEG400 :water (5 :45 :50)								
Method of Analysis: LC/MS/MS of plasma samples post-dosing Day 5								
Dose (mg/kg):	Gender	Mean PK Parameter Value[a]	XL184	EXEL-5162	EXEL-5366	EXEL-1646	EXEL-1644	p-FA
10	Male	$t_{1/2}$ (hr)	NC	NC	NC	NC	NC	NC
		T_{max} (hr)	4.00	8.00	8.00	8.00	8.00	NC
		Cmax (ng/mL)	13,400	381	53.3	1,140	9.16	0.00
		AUC_{last} (ng·hr/mL)	232,000	6,750	897	21,700	155	0.00
		$\%AUC_{analyte}/AUC_{XL184}$	NC	2.9	0.39	9.4	0.07	0.00
		$\%AUC_{analyte}/AUC_{total}$	88.7	2.6	0.34	8.3	0.06	0.00
10	Female	$t_{1/2}$ (hr)	NC	NC	NC	NC	NC	NC
		T_{max} (hr)	12.0	6.00	6.00	6.00	12.0	NC
		Cmax (ng/mL)	20,500	231	48.1	359	5.15	0.00
		AUC_{last} (ng·hr/mL)	396,000	4,520	973	7,340	88.7	0.00
		$\%AUC_{analyte}/AUC_{XL184}$	NC	1.1	0.25	1.9	0.02	0.00
		$\%AUC_{analyte}/AUC_{total}$	96.8	1.1	0.24	1.8	0.02	0.00

[a] Sample time (0-24 hrs post-dose);$t_{1/2}$, terminal half-life; T_{max}, time of observed Cmax; Cmax, observed maximum concentration; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; % $AUC_{analyte}/AUC_{XL184}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of parent XL184); % $AUC_{analyte}/AUC_{total}$, (ratio of $AUC_{0.5\text{-}last}$ of analyte to$AUC_{0.5\text{-}last}$ of total AUC [sum of $AUC_{0.5\text{-}last}$ of XL184 and 5 metabolites]); refer to Section 2.6.5.11 for analyte structures; NC, not calculated

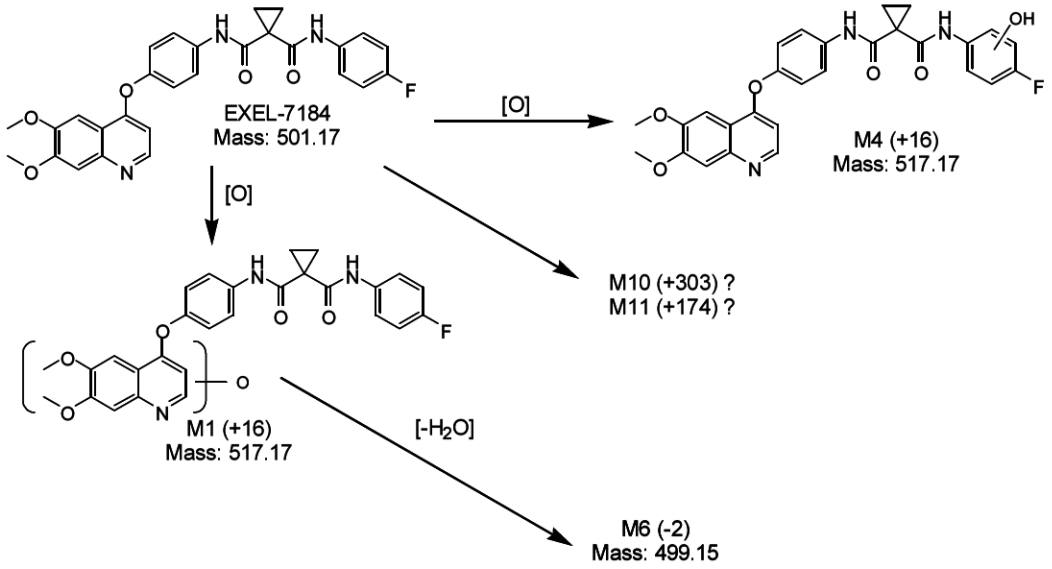
2.6.5.10 薬物動態試験：*In Vivo* における代謝（続き）

Dog					Test Article: XL184	
					Study No. 4.2.2.4-9	
Gender/Number of animals/ Dose Levels: 6 /sex (20 mg/kg)[a]						
Vehicle/Formulation: ethanol :PEG400 :water (5 :45 :50)						
Method of Analysis: LC/MS/MS of plasma samples following single 20 mg/g oral dose						
Dose (mg/kg):	Mean PK Parameter Value[b]	XL184	EXEL-5162	EXEL-5366	EXEL-1646	p-FA
20	Tmax (hr)	2.25	2.58	2.58	2.0	3
	Cmax (ng/mL)	2,140	97.1	44.0	8.95	3.66
	AUC_{last} (ng·hr/mL)	16,600	657	355	36.9	18.4
	$\%AUC_{analyte}/AUC_{XL184}$	NC	4.08	2.03	0.24	0.09
	$\%AUC_{analyte}/AUC_{total}$	93.96	3.72	2.01	0.21	0.10

[a] Animals previously dose at 30 mg/kg/day for 10 days, then provided a 11 day non-dosing period prior to re-initiating dosing at 20 mg/kg starting study Day 22 (4.2.3.2-10); [b] Data reflect mean combined male and female values; sample time (0-24 hrs post-dose); T_{max}, time of observed Cmax; Cmax, observed maximum concentration; AUC_{last}, area under the plasma concentration-time curve from time 0 hr to the last observable concentration above the limit of quantitation; $\%AUC_{analyte}/AUC_{XL184}$, (ratio of AUC_{last} of analyte to AUC_{last} of parent XL184); $\%AUC_{analyte}/AUC_{total}$, (ratio of AUC_{last} of analyte to AUC_{last} of total AUC [sum of AUC_{last} of XL184 and 4 metabolites]); refer to Section 2.6.5.11 for analyte structures; NC, not calculated; plasma concentrations of metabolite EXEL-1644 were not measured in this study.

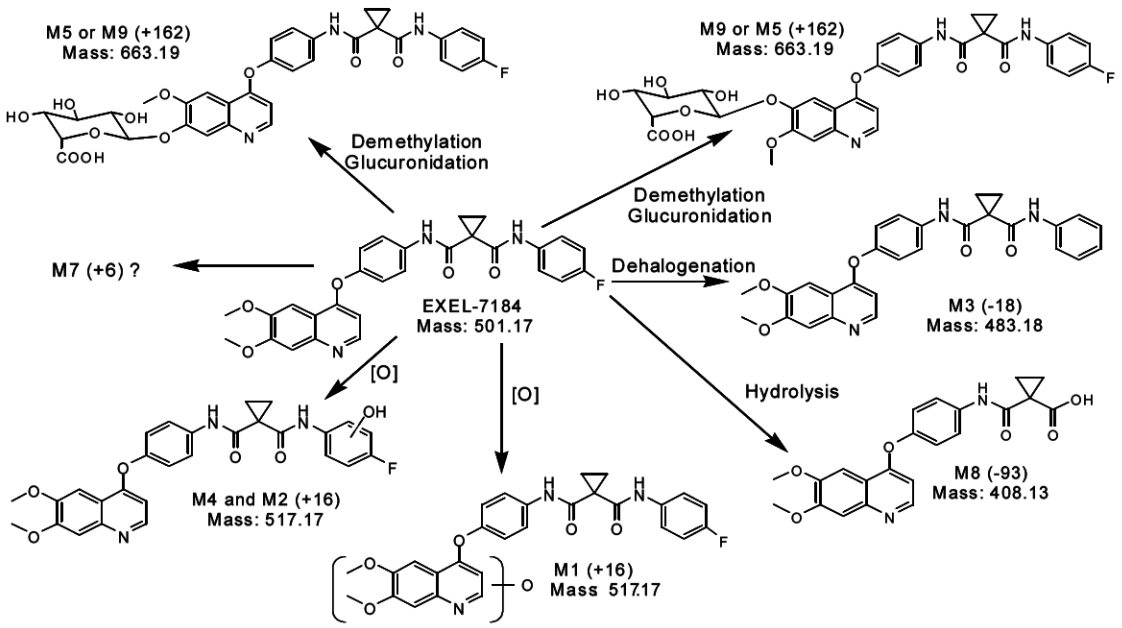
2.6.5.11 薬物動態試験：推定代謝経路

In vitro	
Study No. 4.2.2.3-1	Test Article: XL184 (EXEL-7184)



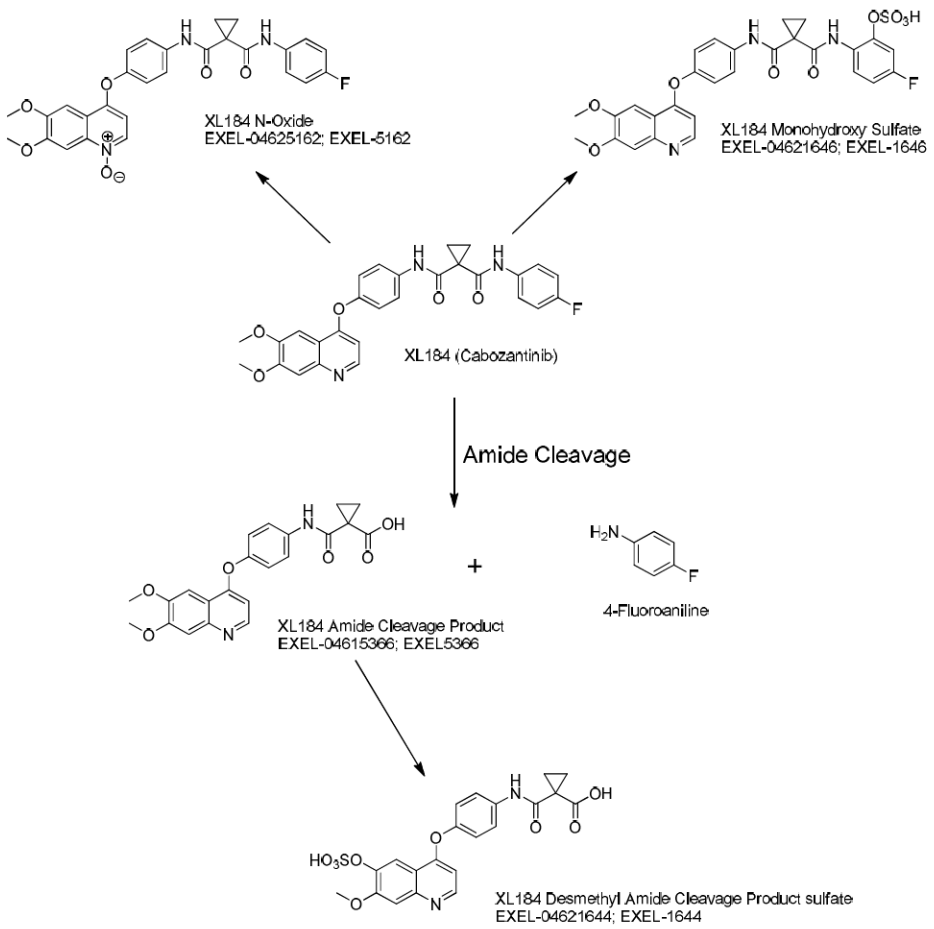
2.6.5.11 薬物動態試験：推定代謝経路（続き）

Pharmacokinetics: Possible Metabolic Pathways in Vivo— Mice and Rats	
Study No. 4.2.2.3-1	Test Article: XL184 (EXEL-7184)



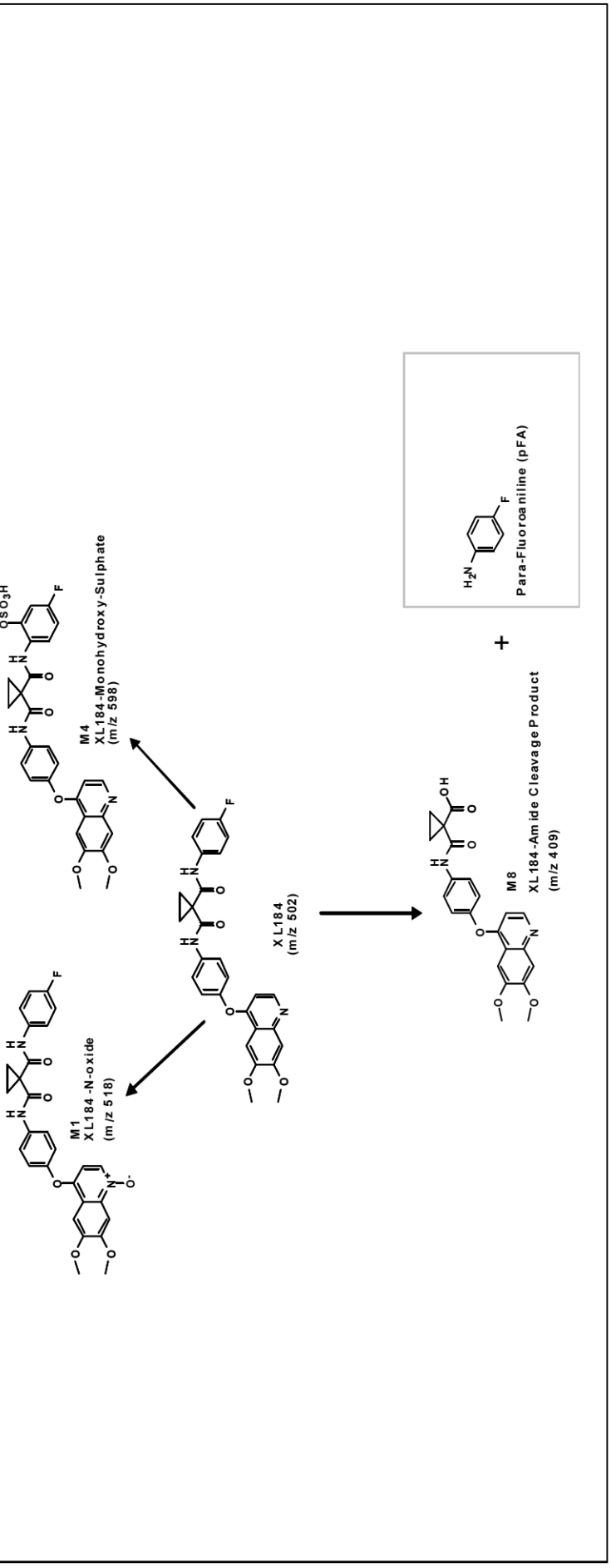
2.6.5.11 薬物動態試験：推定代謝経路（続き）

Pharmacokinetics: Possible Metabolic Pathways in Vivo—Mice and Rats	
Note: Pathways associated with formation of primary XL184 metabolites present in human plasma Study No. 4.2.2.4-7	Test Article: XL184



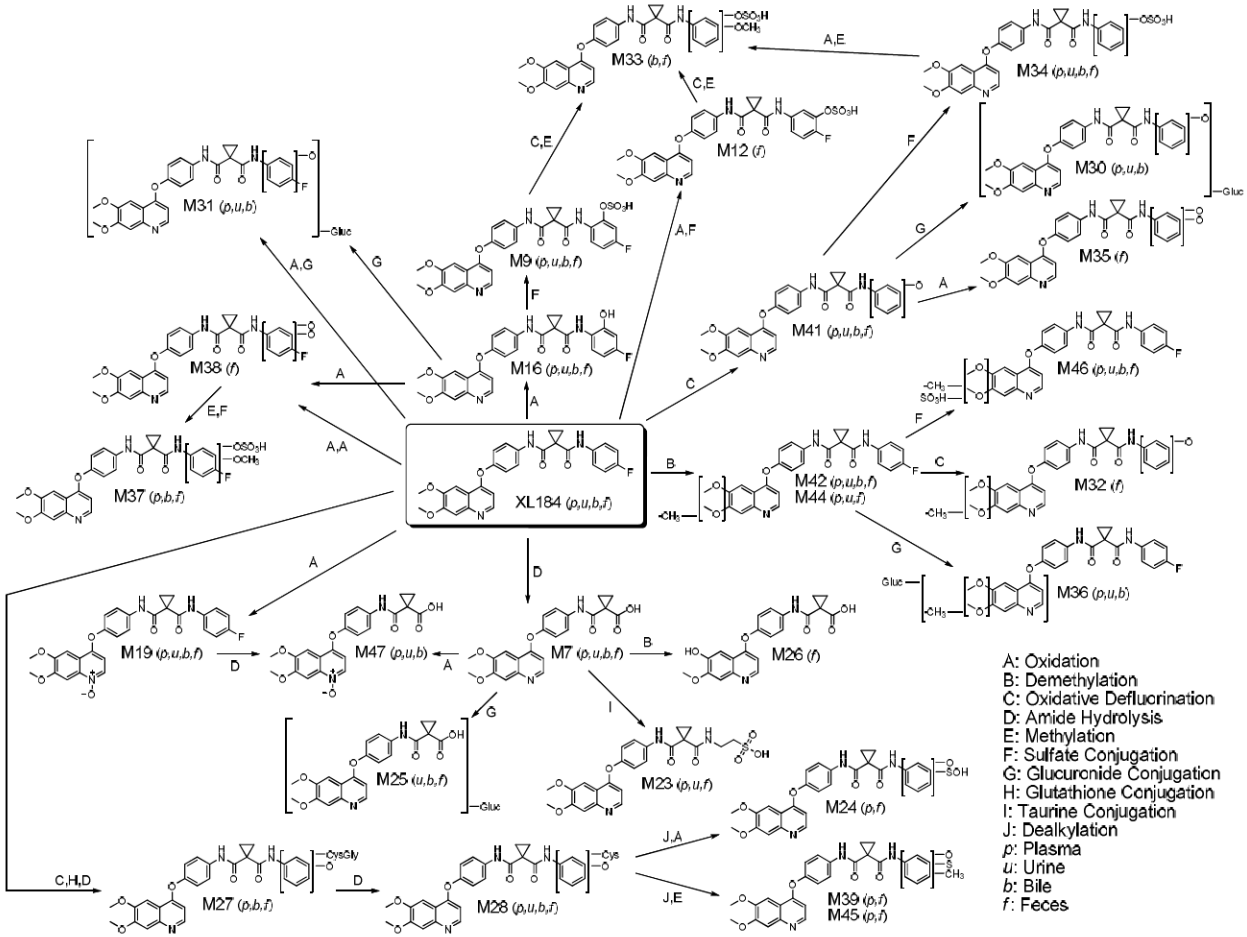
2.6.5.11 薬物動態試験：推定代謝経路（続き）

Pharmacokinetics: Possible Metabolic Pathways in Vivo—Rat and Dog	
Study No. 4.2.2.4-9	Test Article: XL184



2.6.5.11 薬物動態試験：推定代謝経路（続き）

Pharmacokinetics: Possible Metabolic Pathways in Vivo—Dogs	
Study No. 4.2.2.4-10	Test Article: XL184



2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害

	Test Article: XL184	
	Study Nos. [a] 4.2.2.2-1; [b] 4.2.2.4-1; [c] 4.2.2.4-2	
Type of Study: In vitro inhibition of cytochrome (CYP) enzymes in human liver microsomal preparations by XL184		
Method: [a] HPLC; or [b, c] LC/MS/MS;		
Tabulated Results:		
	IC_{50} (µmol/L)	K_i (µmol/L)[b]
CYP1A2	>100[b] - >200[a]	NE
CYP2C8	3.8[b] – 6.4[a]	4.6
CYP2C9	6.1[a] – 40[b]	10.4
CYP2C19	6.2[a] – 59[b]	28.8
CYP2D6	>100[b] - >200[a]	NE
CYP2B6	10.1[c]	NE
CYP3A	$>20_{MDZ}$[a] - >100[b] $>200_{TEST}$[a] – 272[b]	282_{MDZ}

MDZ (midazolam); TEST (testosterone); NE (not evaluated)

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

	Test Article: EXEL-1644	
	Study Nos. 4.2.2.4-3	
Type of Study: In vitro inhibition of cytochrome (CYP) enzymes in human liver microsomal preparations by EXEL-1644		
Method: LC/MS/MS		
Tabulated Results:		
	IC_{50} (µmol/L)	K_i (µmol/L)
CYP1A2	>100	NE
CYP2C8	5.59	1.1
CYP2C9	31.4	32.5
CYP2C19	>100	NE
CYP2D6	>100	NE
CYP2B6	>100	NE
CYP3A	$>100_{MDZ}$ $>100_{TEST}$	NE

MDZ, midazolam; TEST, testosterone; NE, not evaluated.

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

				Test Article: XL184		
				Study No. 4.2.2.2-1		
Type of Study: Induction of cytochrome (CYP) isozyme-specific mRNA in fresh human hepatocytes preparations (n= 2 separate incubations/donors) by XL184 (0.1-30 µmol/L)						
Method: mRNA (quantitative PCR analysis)						
Tabulated Results: Fold Induction Range relative to vehicle control value after Treatment with XL184						
	CYP1A1			CYP1A2		
	Donor 1	Donor 2	Average	Donor 1	Donor 2	Average
XL184:						
0.1µmol/L	0.81	0.97	0.89	0.93	1.08	1.01
0.3µmol/L	1.18	1.15	1.16	1.19	1.41	1.30
1.0µmol/L	1.43	1.08	1.26	1.89	1.69	1.79
3.0µmol/L	1.43	0.94	1.19	2.53	1.53	2.03
10µmol/L	1.46	0.60	1.03	3.54	1.55	2.54
30µmol/L	21.20	3.26	12.23	4.63	2.09	3.36
β-NF:						
0.1µmol/L	1.08	0.77	0.93	1.22	0.63	0.93
0.3µmol/L	1.80	0.93	1.37	2.05	0.82	1.43
1.0µmol/L	6.20	1.27	3.74	5.53	1.58	3.55
3.0µmol/L	12.16	2.74	7.45	9.18	3.92	6.55
10µmol/L	20.11	4.90	12.51	16.37	6.92	11.64

Positive control: β-NF (β-naphthoflavone);

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

	Test Article: XL184
	Study No. 4.2.2.2-1

Type of Study: Induction of cytochrome (CYP) isozyme-specific mRNA in fresh human hepatocytes preparations (n= 2 separate incubations/donors) by XL184 (0.1-30 µmol/L)

Method: mRNA (quantitative PCR analysis)

Tabulated Results: Fold Induction Range relative to vehicle control value after Treatment with XL184

	CYP2C8			CYP2C9			CYP2C19			CYP3A4		
	Donor 1	Donor 2	Average	Donor 1	Donor 2	Average	Donor 1	Donor 2	Average	Donor 1	Donor 2	Average
XL184:												
0.1µmol/L	1.10	0.96	1.03	0.82	1.02	0.92	1.12	1.00	1.06	1.06	2.70	1.88
0.3µmol/L	1.37	1.18	1.27	1.13	1.16	1.14	1.35	1.09	1.22	1.06	3.89	2.47
1.0µmol/L	2.01	1.24	1.63	1.68	1.38	1.53	1.30	1.35	1.32	2.11	9.38	5.74
3.0µmol/L	2.24	1.16	1.70	1.55	1.25	1.40	1.11	1.33	1.22	3.57	18.49	11.03
10µmol/L	2.06	1.22	1.64	1.81	1.34	1.57	1.36	1.75	1.56	7.34	55.36	31.35
30µmol/L	0.30	0.65	0.47	0.86	1.04	0.95	1.19	1.56	1.38	1.42	6.47	3.95
RIF:												
0.1µmol/L	0.89	1.47	1.18	1.64	1.31	1.47	0.92	1.46	1.19	1.92	70.54	36.23
0.3µmol/L	0.69	1.94	1.31	1.83	1.73	1.78	0.60	2.53	1.57	2.87	250.40	126.64
1.0µmol/L	1.46	2.67	2.07	1.95	1.92	1.94	1.16	3.31	2.23	5.13	467.30	236.21
3.0µmol/L	1.41	2.73	2.07	2.23	1.87	2.05	1.00	3.57	2.29	7.76	525.08	266.42
10µmol/L	1.28	3.14	2.21	2.44	1.55	2.00	0.98	4.21	2.59	8.15	731.70	369.93

Positive control: RIF (rifampicin);

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

		Test Article: XL184	
		Study No. 4.2.2.4-4	
Type of Study: Induction of cytochrome (CYP) isozyme-specific mRNA and enzyme-related activities in fresh human hepatocytes preparations (n= 3 separate incubations) by XL184 (0-20 µmol/L)			
Method: in situ enzyme activity analysis (LC/MS/MS)			
Tabulated Results: Summary of Enzyme Activity (Fold Induction Range Relative to Vehicle Control; n=3) after Treatment with XL184			
	CYP1A2	CYP2B6	CYP3A4
3-MC	68.6-129.5	1.1-2.4	0.6-0.8
PB	4.1-11.4	6.8-20.4	5.3-16.4
RIF	2.3-11.6	3.0-9.0	5.8-21.2
XL184: 0.5 µmol/L 5 µmol/L 20 µmol/L	 2.5- 4.4 3.7-4.9 1.5-4.1	 1.0-1.6 0.9-2.5 0.9-1.6	 1.0-1.4 1.1-1.6 0.4-0.9

Positive controls: 3-MC (3-methylcholanthrene; 2 µmol/L); PB (Phenobarbital;1000 µmol/L); RIF (rifampicin;10 µmol/L)

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

						Test Article: XL184			
						Study No. 4.2.2.4-4			
Type of Study: Induction of cytochrome (CYP) isozyme-specific mRNA and enzyme-related activities in fresh human hepatocytes preparations (n= 3 separate incubations) by XL184 (0-20 µmol/L)									
Method: mRNA (quantitative PCR)									
Tabulated Results: Summary of mRNA Content (Fold Induction Relative to Vehicle Control) after Treatment with XL184									
	CYP1A2			CYP2B6			CYP3A4		
	Prep #1	Prep #2	Prep #3	Prep #1	Prep #2	Prep #3	Prep #1	Prep #2	Prep #3
3-MC	233	388	228	2.73	1.43	3.58	0.371	0.167	1.21
PB	2.13	3.13	1.55	28.7	28.1	67.2	10.6	29.4	77.4
RIF	2.28	4.96	1.56	9.17	13.3	22.9	11.0	30.7	55.4
XL184:									
0.5 µmol/L	4.42	13.6	3.44	2.11	1.41	1.77	1.75	0.961	1.93
5 µmol/L	7.46	13.5	3.62	4.28	3.46	3.47	4.84	4.93	9.25
20 µmol/L	4.94	5.64	3.29	3.14	4.03	5.13	4.33	10.2	19.2

Positive controls: 3-MC (3-methylcholanthrene;2 µmol/L); PB (Phenobarbital;1000 µmol/L); RIF (rifampicin;10 µmol/L)

2.6.5.13 薬物動態試験：累積排泄

				Test Article:[^{14}C]XL184		
Species:	Rat			Rat		
Gender (M/F)/Number of Animals:	Male, n=3			Female, n=3		
Feeding Condition:	Fasted			Fasted		
Vehicle/Formulation:	ethanol:PEG400:water (5:45:50)			ethanol:PEG400:water (5:45:50)		
Method of Administration:	Gavage			Gavage		
Dose (mg/kg):[a]	10			10		
Analyte:[b]	TRA[b]			TRA[b]		
Assay:	LSC			LSC		
Cumulative Excretion[c]: 0-Time (hr)	Urine	Feces	Total	Urine	Feces	Total
0-6	1.69	-	1.69	0.89	-	0.89
0-12	3.31	-	3.31	2.41	-	2.41
0-24	5.34	28.67	34.01	5.12	20.95	26.07
0-48	7.81	59.17	66.98	8.48	44.56	53.04
0-72	8.60	75.42	84.02	10.31	56.15	66.46
0-96	8.91	84.24	93.15	11.14	61.99	73.13
0-120	9.01	85.21	94.22	11.52	71.78	83.30
0-144	9.05	85.52	94.57	11.71	81.18	92.89
0-168	9.06	85.64	94.70	11.81	82.05	93.86
Study Number	4.2.2.5-1					

[a] 10 mg/kg XL184 Free form (83 µCi [^{14}C]XL184/kg); [b] total radioactivity analysis; [c] % of administered dose

2.6.5.14 薬物動態試験：胆汁中排泄

						Test Article: [^{14}C]XL184				
Species:	Rat					Dog				
Gender (M/F)/Number of Animals:	Male, n= 3 BDI and 6 BDC					Male, n= 3 BDI and 3 BDC				
Feeding Condition:	Fasted					Fasted				
Vehicle/Formulation:	ethanol:PEG400:water (5:45:50)					ethanol:PEG400:water (5:45:50)				
Method of Administration:	Gavage					Gavage				
Dose (mg/kg):[a]	50					100				
Analyte:	TRA[b]					TRA[b]				
Assay:	LSC					LSC				
Collection time:	0-120 hr					0-168 hr				
Cumulative Excretion[c]:	Urine	Feces	Bile	Cage Rinse	Total	Urine	Feces	Bile	Cage Rinse	Total
Bile Duct Intact (BDI)	2.44 ± 0.261	84.6 ± 4.65	NA	0.880 ± 0.203	92.5 ± 1.30	1.88 ± 1.39	86.2 ± 4.37	NA	1.91 ± 1.33	92.6 ± 1.08
Bile Duct Cannulated (BDC)	7.44 ± 4.63	45.8 ± 6.95	29.1 ± 5.48	1.69 ± 1.06	91.6 ± 1.89	0.679 ± 0.264	73.3 ± 4.96	14.5 ± 7.71	1.10 ± 1.28	91.7 ± 4.29
Study Number	4.2.2.4-10 (dog) and 4.2.2.4-8 (rat)									

[a] Radioactive dose(rat: 750 µCi [^{14}C]XL184/kg; dog: 50 µCi [^{14}C]XL184/kg); [b] total radioactivity; [c] % of administered dose

2.6.5.15 薬物動態試験：薬物相互作用

	Test Article: XL184
	Study No. 4.2.2.2-1
Type of Study: Evaluation of XL184 as a possible substrate and/or inhibitor of P-gp transporter in MDCK-MDR1 cells, and permeability across MDCK cells in vitro	
Method: Substrate assay: XL184 (1-10 μmol/L) tested in bidirectional assay (LC-MS/MS analyte measurement) in the absence or presence of known P-gp inhibitor GF120918. Inhibitor assay: XL184 (0.3-30 μmol/L) was incubated with known P-gp substrate (digoxin; 5 μmol/L)	
Tabulated Results: XL184 was a demonstrated P-gp inhibitor (IC_{50} = 7.0 μmol/L), but is not a P-gp substrate. XL184 showed high permeability (P_{app}: 70-110 nm/sec)	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: XL184
	Study No. 4.2.2.6-2
Type of Study: The objective of this study was to determine if XL184 is a substrate and/or an inhibitor of key human transporters, including organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP)2, and bile salt export pump (BSEP).	
Method: Test systems were: (1) Chinese hamster ovary (CHO) cells, stably transfected individually with empty vector pCMV6, OAT1-pCMV6, OAT3-pCMV6, OCT1-pCMV6, OCT2-pCMV6, OATP1B1-pCMV6, and OATP1B3-pCMV6; (2) Caco-2 cells for P-gp and BCRP assays; and (3) inside-out human BSEP and MRP2 membranes prepared from transfected insect cells (Sf9). Substrate evaluations utilized [^{14}C]XL184 (final concentrations: 1 and 10 µmol/L for OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3; 2 and 10 µmol/L for BSEP) or XL184 (final concentrations: 2 and 10 µmol/L for MRP2) in the presence of transporter-specific inhibitors. Inhibitor evaluations utilized un-labeled XL184 (final concentrations: 5 and 15 µmol/L [uptake transporters] or 5 and 50 µmol/L [efflux transporters]) in the presence of transporter-specific substrates.	
Results: The results obtained from the study indicate that XL184 is likely a substrate of MRP2, but not of the other transporters. XL184 (5 and 15 µmol/L) showed no inhibition of OAT1, OCT1, OATP1B1, OATP1B3, and MRP2; weak inhibition of OCT2 and BSEP (estimated IC_{50} values >15 µmol/L); and strong inhibition of OAT3 (estimated IC_{50} value <5 µmol/L, although not concentration dependent). XL184 (5 and 50 µmol/L) showed weak inhibition of P-gp and BCRP (estimated IC_{50} values >50 µmol/L).	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: XL184
	Study No. 4.2.2.6-3
Type of Study: The objective of this study was to determine the inhibition potential of XL184 towards human drug transporters MATE1 and MATE2-K.	
Method: The test system was transfected MDCK-II cells. XL184 was evaluated at a single final concentration of 5 μmol/L.	
Results: XL184 (at a final concentration of 5 μmol/L) inhibited the transport of the probe substrates of MATE1 and MATE2-K by 39.9% and 30.6%, respectively, compared with the vehicle control.	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: XL184
	Study No. 4.2.2.6-4
Type of Study: The objective of this study was to determine IC_{50} values for XL184 toward human drug transporters OAT3, MATE1, and MATE2-K-mediated transport.	
Method: The test system was transfected MDCK-II cells. XL184 was studied over the concentration range of 0.1 – 20 μmol/L; the limit of solubility of XL184 in the assay medium was approximately 20 μmol/L.	
Results: The maximum inhibition of OAT3, MATE1 and MATE2-K were 41.0%, 62.8% and 75.0%, respectively. Due to lack of sufficient inhibition of OAT3, the IC_{50} for this drug transporter could not be determined. The IC_{50} values determined for MATE1 and MATE2-K were 5.94 and 3.12 μmol/L, respectively.	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: EXEL-1644
	Study No. 4.2.2.6-7
Type of Study: The objective of this study was to determine if XL184 metabolite EXEL-1644 is a substrate of key human transporters, including organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP)2, and bile salt export pump (BSEP).	
Method: The drug transporters evaluated were: (1) OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 in transfected MDCK-II cell monolayers; (2) P-gp in MDCK-MDR1 cell monolayers; (3) BCRP in the Caco-2 cell monolayers; and (4) MRP2 and BSEP in transfected insect cell Sf9 membrane vesicles. EXEL-1644 was studied at 1, 3 and 10 μmol/L without inhibitor, and at 3 μmol/L in the presence of reference inhibitor for each transporter. The amount of EXEL-1644 transported was determined by LC/MS/MS.	
Results: EXEL-1644 appears to be a substrate for transporters OAT3, OATP1B1, OATP1B3, BCRP and MRP2, but does not appear to be a substrate of transporters OAT1, OCT1, OCT2 or BSEP. It was unclear whether EXEL-1644 is a P-gp substrate due to detection limitations with this specific assay.	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: EXEL-1644
	Study No. 4.2.2.6-5
Type of Study: Metabolite EXEL-1644 was evaluated in vitro as a potential inhibitor of clinically-relevant human drug transporters. The drug transporter panel evaluated initially consisted of BCRP, BSEP, MRP2, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2-K. A follow up study was conducted in the same assay system to determine the IC_{50} values of EXEL-1644 against the transport of probe substrate by OAT1, OAT3 and OATP1B1.	
Method: The test system was transfected MDCK cells, MDCK-II cells, Caco-2 cells and membrane vesicles. EXEL-1644 was evaluated at a single concentration (10 µmol/L) for inhibition of movement of transporter-specific radio-labeled probe substrates across transfected MDCK-II cell monolayers. The transport of each substrate was determined by radiometric detection. EXEL-1644 was studied in the concentration range of 0.1 – 20 µmol/L for IC_{50} determinations.	
Results: 10 µmol/L EXEL-1644 inhibited the transport of the probe substrates of OAT1, OAT3, OCT2 and OATP1B1 by 83.4%, 89.9%, 26.7% and 67.7%, respectively. Lower but statistically significant inhibition was observed for BSEP and MRP2 (10.9% and 6.37%, respectively). No inhibition was observed for transport of the probe substrates of BCRP, P-gp, MATE1, MATE2-K, OCT1 and OATP1B3. The IC_{50} values for OAT1, OAT3 and OATP1B1 were determined to be 4.27 µmol/L, 4.33 µmol/L and 6.06 µmol/L, respectively.	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: : EXEL-1644
	Study No. 4.2.2.6-6
Type of Study: The objective of this study was to determine IC_{50} values of EXEL-1644 for human transporters OCT1, OCT2, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, BSEP and MRP2.	
Method: The test system was transfected MDCK cells, MDCK-II cells, Caco-2 cells and membrane vesicles. EXEL1644 was studied over the concentration range of 1 – 250 µmol/L	
Results: The inhibition of OCT1, OCT2, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, BSEP and MRP2 at maximum concentration was 19.3%, 27.3%, 93.0%, 84.5%, 73.6%, 43.0%, 4.20%, 78.1% and 77.5%, respectively. Due to lack of sufficient inhibition of OCT1, OCT2, BCRP and P-gp, the IC_{50} values could not be determined for these transporters. The IC_{50} values determined for OATP1B3, MATE1, MATE2-K, BSEP and MRP2 were 20.6, 16.7, 65.3, 50.0 and 78.5 µmol/L, respectively.	

2.6.5.15 薬物動態試験：薬物相互作用（続き）

	Test Article: EXEL-1644
	Study No. 4.2.2.6-8
Type of Study: The objective of this study was to determine if EXEL-1644 was a substrate of human transporter BCRP	
Method: The test system was Sf9 insect cell vesicles transfected with ABC transporter BCRP. EXEL1644 was studied over the concentration range of 1 – 10 µmol/L, in the presence and absence of known inhibitors of BCRP.	
Results: EXEL-1644 was shown to be a substrate of human transporter BCRP in transfected Sf9 insect cell vesicles.	

2.6.5.16 薬物動態試験：その他

実施していない