2.6.7.12A Oral Gavage Study of Fertility, Early Embryonic Development to Implantation, and Toxicokinetics with XL184 in Rats (continued)

Daily Dose (mg/kg)	0 (Control)	1	2.5	5.0
Males	N = 22	N = 22	N = 22	N = 22
Clinical observations				
Thin or pale appearance	-	-	-	++
Fecal changes (soft, liquid, few)	-	-	+++	+++
Teeth (malocclusion, missing, extremely white)	-	-	+++	-
Rough hair coat	-	-	++	+++
Necropsy observations				
Intestines, thickened	-	-	-	++
Kidneys, enlarged or dilated	-	-	+	-
Body weight (%)[a]	569 g	-3	-12**	NR
Food consumption (%)[a]	32.6 g/day	-3	-24**	ND
Mean No. days prior to mating	NR	NR	NR	NR
No. of males that mated	21	22	21	19
No. of fertile males	20	21	0	0
Sperm motility (%)[a]	87	+8	+3	0
Sperm count[a]	1256	-21	-35*	-54*
Females, no. evaluated	N = 22	N = 22	N = 22	N = 22
Toxicokinetics: AUC_{0-24} (ng·hr/mL)				
Day 1	ND	15300	35400	71200
Day 14	ND	22100	60400	116000

2.6.7.12A Oral Gavage Study of Fertility, Early Embryonic Development to Implantation, and Toxicokinetics with XL184 in Rats (continued)

Daily Dose (mg/kg)	0 (Control)	1	2.5	5.0
Females	N = 22	N = 22	N = 22	N = 22
Toxicokinetics: AUC_{0-24} (ng·hr/mL)				
Gestation Day 7	ND	19300	73200	148000
No. died or sacrificed moribund	0	0	0	3
Clinical observations				
Teeth (extremely white)	-	-	++	++
Fecal changes (soft, liquid, few)	-	-	-	++
Yellow or red haircoat	-	-	+	++
Rough hair coat	-	-	-	++
Necropsy observations				
Intestines, thickened	-	-	-	++
Premating body weight (%)[a]	249 g	+1	+1	0
Gestation body weight (%)[a]	331 g	-3	ND	ND
Premating food consumption (%)[a]	22 g/day	+1	0	-6
Gestation food consumption (%)[a]	28 g/day	-3	ND	ND
Mean No. estrous cycles/14 days	NR	NR	NR	NR
Mean No. days prior to mating	NR	NR	NR	NR
No. of females sperm positive	NR	NR	NR	NR

2.6.7.12A Oral Gavage Study of Fertility, Early Embryonic Development to Implantation, and Toxicokinetics with XL184 in Rats (continued)

Daily Dose (mg/kg)	0 (Control)	1	2.5	5.0
Females	N = 22	N = 22	N = 22	N = 22
No. of pregnant females	20	21	0	0
No. aborted or with total resorption of litter	0	0	0	0
Mean No. corpora lutea	15.5	18.0*	ND	ND
Mean No. implantations	15	14.6	ND	ND
Mean % preimplantation loss	3.3	18**	ND	ND
Mean No. live conceptuses	14.2	5.5	ND	ND
Mean No. resorptions	0.8	9.1	ND	ND
No. dead conceptuses	0	0	ND	ND
Mean % postimplantation loss	5.7	62*	ND	ND

AUC, area under the plasma drug concentration time curve; F, female; GLP, Good Laboratory Practice; ICH, International Conference on Harmonisation; M, male; ND, not determined; NR, not reported; SD, Sprague Dawley.

(-), No noteworthy findings. Observed finding or increased incidence or severity above control group: minimal (+), slight (++), moderate (+++).

*, ** $P \leq 0.05$, 0.01, Dunnett's Test.

a. At end of dosing or phase (Males: 10 week minimum [28 days prior to mating and throughout mating period]; Females: at least 14 days prior to mating, throughout the mating period, and through Gestation Day 7). For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

2.6.7.13 生殖発生毒性試験

2.6.7.13A Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rats

Report Title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rats		Test Article: XL184 (Lot No. [redacted])
Design similar to ICH 4.1.3? Yes	Duration of Dosing: Gestation Days 6 through 17	Study Number: [redacted] Study No. [redacted] (4.2.3.5.2-2)
	Day of Mating: Day 0	
Species/Strain: Rat/Crl:CD(SD)	Day of C-Section: Gestation Day 21	
Initial Age:12 weeks	Method of Administration: Oral Gavage	
Date of First Dose: [redacted] 20[redacted]	Vehicle/Formulation: ethanol: polyethylene glycol 400:water (5:45:50, v/v/v)	GLP Compliance: Yes
Special Features: Fetal plasma drug analysis		

No Observable Adverse Effect Level:
F_0 Females: 0.1 mg/kg/day
F_1 Litters: 0.01 mg/kg/day (viability); 0.1 mg/kg/day (growth and development)

Daily Dose (mg/kg)[a]	0 (Control)	0.01	0.03	0.1
Dams/Does: Toxicokinetics: AUC_{0-24} (ng·hr/mL)[b]				
Gestation Day 6	-	132	364	1360
Gestation Day 17	-	168	469	1490
No. pregnant	25	25	25	25
No. died or sacrificed moribund	0	0	0	0
No. aborted or with total resorption of litter	0	0	0	0
Clinical observations	-	-	-	-
Necropsy observations	-	-	-	-

2.6.7.13A Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rats (continued)

Daily Dose (mg/kg)[a]	0 (Control)	0.01	0.03	0.1
Body weight (%)[c]	361 g	-1	+2	+2
Food consumption (%)[c]	28.9 g	-1	+1	+3
Mean No. corpora lutea	14.4	13.9	14.1	14.4
Mean No. implantations	13.3	12.6	13.1	13.2
Mean % preimplantation loss	7.4	9.1	6.7	7.7
Litters:				
Fetal plasma drug concentration (Gestation Day 18 [1 day post final maternal XL184 dose]) (mean ng/mL)	0	1.3	3.6	11.1
No. litters evaluated	25	25	25	25
No. live fetuses	12.9	12.4	12.5	12.5
Mean No. resorptions	0.4	0.2	0.6	0.8
No. of litters with dead fetuses	0	0	0	0
Mean % postimplantation loss	2.9	2.2	4.5	5.9
Mean fetal body weight (g)	5.37	5.44	5.53	5.33
Fetal sex ratios (M:F)	52:48	48:52	45:55	51:49
Fetal anomalies:				
Gross external malformations				
Total fetal incidence (%)	0.3	0.0	0.0	0.3
Total litter incidence (%)	4.0	0.0	0.0	4.0
Visceral malformations				
Total fetal incidence (%)	0.0	0.6	0.0	0.7
Total litter incidence (%)	0.0	4.0	0.0	4.0

2.6.7.13A Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rats (continued)

Daily Dose (mg/kg)[a]	0 (Control)	0.01	0.03	0.1
Skeletal malformations				
Total fetal incidence (%)	1.2	1.3	0	0.6
Total litter incidence (%)	8.0	8.0	0.0	4.0
Total affected fetuses (litters)[d]	2 (2)	3 (3)	0 (0)	2 (2)

AUC, area under the plasma drug concentration time curve; F, female; GLP, Good Laboratory Practice; ICH, International Conference on Harmonisation; M, male; SD, Sprague Dawley.

(-), No noteworthy findings.

a. Main study cohorts (25 females/dose level).

b. Toxicokinetic cohorts (six pregnant rabbits/dose level).

c. At end of in-life phase (body weight: Gestation Day 21; food consumption: Gestation Days 4-21). For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

d. Total fetuses evaluated: n = 323 (0.0 mg/kg), 310 (0.01 mg/kg), 313 (0.03 mg/kg), 312 (0.1 mg/kg); total litters evaluated: n = 25/dose level.

2.6.7.13B Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rabbits

Report Title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rabbits				Test Article: XL184 (Lot No. [redacted])
Design similar to ICH 4.1.3? Yes	Duration of Dosing: Gestation Days 7 through 20			Study Number: [redacted] Study No. [redacted] (4.2.3.5.2-4)
	Day of Mating: Day 0			
Species/Strain: Rabbit/Hra (NZW) SPF	Day of C-Section: Gestation Day 29			
Initial Age: 5.5 months	Method of Administration: Oral Gavage			
Date of First Dose: [redacted] 20[redacted]	Vehicle/Formulation: ethanol: polyethylene glycol 400:water (5:45:50, v/v/v)			GLP Compliance: Yes
Special Features: Fetal plasma drug analysis				
No Observable Adverse Effect Level: F_0 Females: 3.0 mg/kg/day F_1 Litters: 3.0 mg/kg/day (viability and growth); 1.0 mg/kg/day (developmental toxicity/teratology)				
Daily Dose (mg/kg)[a]	0 (Control)	0.3	1.0	3.0
Dams/Does: Toxicokinetics: AUC_{0-24} (ng·hr/mL)[b]				
Gestation Day 7	-	255	1020	3560
Gestation Day 20	-	274	984	4240
No. pregnant	17	20	18	18
No. died or sacrificed moribund	0	0	0	0
No. aborted or with total resorption of litter	0	0	0	0
Clinical observations	-	-	-	-
Necropsy observations	-	-	-	-

2.6.7.13B Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rabbits (continued)

Daily Dose (mg/kg)[a]	0 (Control)	0.3	1.0	3.0
Body weight (%) [c]	3705 g	+1	-2	+1
Food consumption (%) [c]	136 g	+1	-10	+1
Mean No. corpora lutea	9.5	10.2	10.1	10.3
Mean No. implantations	8.8	9.5	9.1	9.0
Mean % preimplantation loss	7.7	6.7	9.4	12.7
Litters:				
Fetal plasma drug concentration (Gestation Day 21 [1 day post final maternal XL184 dose]) (mean ng/mL)	0	1.79	6.19	15.1
No. litters evaluated	17	20	18	18
No. live fetuses	8.4	9.4	8.9	8.4
Mean No. resorptions	0.4	0.2	0.2	0.6
No. of litters with dead fetuses	0	0	0	0
Mean % postimplantation loss	4.3	1.3	2.2	6.3
Mean fetal body weight (g)	40.51	39.12	37.48	37.23
Fetal sex ratios (M:F)	59:41	42:58	54:46	41:59
Fetal anomalies:				
Gross external malformations				
Total fetal incidence (%)	0.7	0.0	0.6	0.7
Total litter incidence (%)	5.9	0.0	5.6	5.6
Visceral malformations				
Spleen, reduced	0	1	0	7*

2.6.7.13B Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics with XL184 in Rabbits (continued)

Daily Dose (mg/kg)[a]	0 (Control)	0.3	1.0	3.0
Total fetal incidence (%)	0	0.5	0	4.6*
Total litter incidence (%)	0	5.0	0	5.6
Skeletal malformations				
Total fetal incidence (%)	2.1	0.5	0.6	1.3
Total litter incidence (%)	12	5.0	5.6	11
Total affected fetuses (litters)[d]	5 (4)	2 (1)	4 (4)	12 (5)

AUC, area under the plasma drug concentration time curve; F, female; GLP, Good Laboratory Practice; ICH, International Conference on Harmonisation; M, male; NZW, New Zealand white; SPF, specific pathogen free.

(-) No noteworthy findings.

* $P \leq 0.05$, Dunnett's Test.

a. Main study cohorts (20 females/dose level).

b. Toxicokinetic cohorts (three pregnant rabbits/dose level).

c. At end of in-life phase (body weight: Gestation Day 29; food consumption: Gestation Days 4-29). For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

d. Total fetuses evaluated: n = 142 (0.0 mg/kg), 187 (0.3 mg/kg), 160 (1.0 mg/kg), 152 (3.0 mg/kg); total litters evaluated: n = 17 (0.0 mg/kg), 20 (0.3 mg/kg), 18 (1.0 mg/kg), 18 (3.0 mg/kg).

2.6.7.13C 生殖発生毒性試験：予備試験

Nonpivotal Studies				Test Article: XL184 (Lot No. [redacted])		
動物種 及び系統	投与方法 (媒体/投与形態)	投与期間	投与量 (mg/kg)	動物数/群	特記すべき所見	添付資料番号
Rat/Crl:CD(SD)	Oral gavage (EPW)	GD 10-21 or 14-21	0, 0.1, 0.3, 1, 3	6/sex	0.3 mg/kg: GD 10-21: NOAEL 1 mg/kg: GD 10-21: decreased mean fetal weight, high incidence menigo-encephalocele and short tail; GD 14-21: NOAEL 3 mg/kg: GD 10-21: total litter loss (increased early resorptions, pre- and post-implantation loss);GD 14-21: decreased fetal weight, increased malformations (anasarca, micrognathia, bent tail)	4.2.3.5.3-1

EPW, ethanol: GD, gestation day; polyethylene glycol 400: water, 5:45:50 (v/v/v); NOAEL, no observable adverse effect level; SD, Sprague Dawley.

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

2.6.7.14A Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats

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			Test Article: XL184 (Lot No. [redacted])	
Design similar to ICH 4.1.2? Yes, except F_0 females initiated dosing on GD 10 rather than at implantation (GD 6-7) [a]	Duration of Dosing: Mated F_0 females GD 10 to LD 20		Study No. [redacted] Study No. [redacted] (4.2.3.5.3-2)	
	Day of Mating: Pre-mated F_0 females (approximately 11-12 weeks of age); F_1 males and females (approximately 12 days of age)			
Species/Strain: Rat/Cr:CD (SD)	Method of Administration: Oral Gavage		Location in CTD: Vol. Page	
Initial Age: GD 10	Vehicle/Formulation: EtOH: polyethylene glycol (PEG) 400:reverse osmosis water (5:45:50)			
Date of First Dose: [redacted] 20[redacted]	Litters Culled/Not Culled: Yes		GLP Compliance: Yes	
Special Features:				
No Observed Adverse Effect Level				
F_0 Females: 0.3 mg/kg/day				
F_1 Males: 0.3 mg/kg/day				
F_1 Females: 0.3 mg/kg/day				
Daily Dose (mg/kg)	0 (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
F_0 Females: Toxicokinetics (LD 21) [b] mean ng/mL [range] (number of animals sampled)	ND	8.5 ng/mL [5.3-15.6] (n=23)	30.1 ng/mL [14.7-60.8] (n=25)	71.4 ng/mL [48-129] (n=22)
Daily Dose (mg/kg) (n= 25 F_0 mated females/group)	0 (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
No. Pregnant	24	25	25	24

2.6.7.14A Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg) (n= 25 F0 mated females/group)		0 (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
No. Died or Sacrificed Moribund		2	1	0	2
No. Aborted or with Total Res. of Litter		1	0	0	2
Clinical Observations		-	-	-	-
Necropsy Observations		-	-	-	-
Gestation Body Weight (%) [c]		363 g	101%	101%	100%
Lactation Body Weight (%) [d]		310 g	100%	100%	101%
Gestation Food Consumption (%) [c]		60.6 g	104%	108%	105%
Lactation Food Consumption (%) [d]		256 g	105%	102%	103%
Mean Duration of Gestation (days)		23	23	23	23.1
Abnormal Parturition		NR	NR	NR	NR
F_1 Litters: (Preweaning)	Daily Dose	0 mg/kg/day	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
	No. Litters Evaluated	24	25	25	24
	Mean No. of Implantations	NR	NR	NR	NR
	Mean No. Pups/Litter	11.54	11.20	10.88	11.54
	Mean No. Liveborn Pups/Litter	11.46	11.20	10.88	11.42
	No. of Litters with Stillborn Pups	0.08	0.00	0.00	0.13
	Postnatal Survival to Day 4 (%)	100	98	100	99
	Postnatal Survival to Weaning (total # of pups)	183	182	198	176
	No. of Total Litter Losses	0	0	0	0
	Pup Body Weight/Litter (mean g M/F) [d]	48.23/47.02	49.68/48.57	49.36/48.27	49.20/48.82
	Pup Sex Ratios (mean% males/litter) (Day0)	53	54	52	44
	Pup Clinical Signs	-	-	-	-
	Pup Necropsy Observations	-	-	-	-

2.6.7.14A Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

F_1 Males: (Postweaning)	Daily Dose	0 mg/kg/day	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
	No. Evaluated Postweaning Per Litter	1/litter (23 total)	1/litter (23 total)	1/litter (25 total)	1/litter (22 total)
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change (%) [e]	455 g	104%	100%	104%
	Food Consumption (%) [e]	481.4 g	116%	104%	101%
	Preputial Separation	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	NR	NR	NR	NR
	No. of Males that Mated (%) [g]	96	96	92	91
	No. of Fertile Males (%) [h]	96	91	84	86
F_1 Females: (Postweaning)	Daily Dose	0 mg/kg/day (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
	No. Evaluated Postweaning	1/litter (23 total)	1/litter (23 total)	1/litter (25 total)	1/litter (22 total)
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Premating Body Weight Change (%) [e]	271 g	99%	99%	100%
	Gestation Body Weight Change (%) [f]	351 g	97%	97%	99%
	Premating Food Consumption (%) [e]	336.8 g	111%	106%	99%
	Gestation Food Consumption (%) [f]	73.4 g	98%	98%	104%
	Mean Age of Vaginal Patency (days)	NR	NR	NR	NR
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	NR	NR	NR	NR
	No. of Females Sperm-Positive	22	23	23	21

2.6.7.14A Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

F1 Females: (Postweaning)	Daily Dose	0 mg/kg/day (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
	No. of Pregnant Females	22	22	21	20
	Mean No. Corpora Lutea	17.5	17.2	17.3	17.8
	Mean No. Implantations	16.8	15.5	15.9	16.5
	Mean % Preimplantation Loss	4.0	9.8	9.2	7.1
	Mean No. Early Resorptions	0.5	0.5	0.6	0.6
F_2 Litters:	Daily Dose	0 mg/kg/day (Control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day
	Mean No. Live Conceptuses/pregnant female	16.3	15.0	15.3	15.9
	Mean No. Late Resorptions	0	0	0	0
	Pregnant with Total Litter Loss	0	0	0	0
	No. Dead Conceptuses	NR	NR	NR	NR
	Mean % Postimplantation Loss	3.1	3.1	3.6	3.7
	Fetal Body Weights (g)	ND	ND	ND	ND
	Fetal Sex Ratios (% males)	ND	ND	ND	ND
	Fetal Anomalies	ND	ND	ND	ND

(-) no significant test article-related findings observed; GD, Gestation Day; LD, Lactation Day; ND, not determined; NR, not reported.

a. Dosing initiated at GD 10 rather than at implantation (GD 6-7) to avoid increased post-implantation loss observed at subclinical plasma exposures in F0 female rats dosed at 0.03 mg/kg/day starting on GD 6 and continuing through GD 17 in the definitive embryo-fetal development study (4.2.3.5.3-2).

b. PK plasma sample taken from F0 females on LD 21

c. GD 20 (body weights) or GD 19-20 (food consumption)

d. LD 21 (body weights) or LD 17-21(food consumption)

e. Day 56 (body weights) or Days 49-56 (food consumption)

f. GD 13 (body weights) or GD 10-13 (food consumption)

g. Mating Index (%) = (number of males mating with at least 1 female/Number of males cohabited with at least 1 female)x100

h. Fertility Index (%) = (number of males impregnating at least 1 female/Number of males cohabited with at least 1 female)x100

2.6.7.15 新生児を用いた試験

Nonpivotal Studies				Test Article: XL184 (Lot No. [redacted])		
動物種 及び系統	投与方法 (媒体/投与形態)	投与期間	投与量 (mg/kg)	動物数/群	特記すべき所見	添付資料番号
Rat/ Crl:WI (Han)	Oral gavage (EPW)	PND 12-35	0, 0.3, 1, 3	9/sex	3/2 mg/kg: Unscheduled deaths starting PND 18 at 3 mg/kg/day; dose reduced to 2 mg/kg/day PND 20; decreased body weights, teeth changes 1 mg/kg: Decreased body weights, teeth changes 0.3 mg/kg: NOAEL	4.2.3.5.4-1

EPW, ethanol: polyethylene glycol 400: water, 5:45:50 (v/v/v); NOAEL, no observable adverse effect level; PND Postnatal Day(s).

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods

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		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Rat/Crl:WI (Han)	Duration of Dosing: Postnatal Days (PND) 21-35 or 21-70	Study Number: [redacted] Study No. [redacted] (4.2.3.5.4-2)
Initial Age: PND 21	Duration of Post-Dose: 28 Days	
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral Gavage	
	Vehicle/Formulation: EtOH: polyethylene glycol (PEG) 400:reverse osmosis water (5:45:50)	GLP Compliance: Yes
Special Features: Many study treatment cohorts PND 21-35 (15/sex/dose); PND 21-70 (10/sex/group); Recovery cohorts (both 10/sex/dose)		
No Observable Adverse Effect Level: 0.3 mg/kg/day (PND 21-35 and 21-70 cohorts)		

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Toxicokinetics: AUC_{0-24} (ng·hr/mL)								
Day 1	0	0	6,000	6,880	20,000	20,200	37,300	46,400
Day 35	0	0	5,490	7,800	15,900	20,500	31,500	41,700
Day 70	0	0	7,680	10,100	22,900	31,300	40,200	53,000
Noteworthy findings:								
Died or sacrificed moribund	2	0	0	0	0	2	0	0
Body weight (%)[a, b]	127.0 g (298.3 g)	113.9 g (193.1 g)	-1 (0)	-2 (-2)	-5 (+4)	-5 (-2)	-10 (-9)	-9 (-5)

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (continued)

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Food consumption (%)[a, b]	104.5 g/rat/wk (160.9 g/rat/wk)	92.5 g/rat/wk (108.2 g/rat/wk)	-1 (0)	0 (-3)	-3 (0)	0 0	-11 (+6)	-8 (-1)
Clinical observations	-	-	-	-	-	-	-	-
Teeth abnormalities[b]	-	-	-	-	+ (+)	+ (+)	+ (+)	+ (+)
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology[b]								
Erythrocyte count ($\times 10^6/\mu L$)	7.28 (8.59)	7.22 (8.16)	7.13 (8.43)	7.37 (8.32)	7.31 (8.46)	7.34 (8.40)	7.20 (8.52)	7.52 (8.25)
Hemoglobin (g/dL)	13.9 (16.0)	14.0 (15.2)	14.2 (15.8)	14.3 (15.4)	14.9* (17.1*)	15.3* (16.3*)	15.4* (17.2*)	15.8* (16.6*)
Reticulocytes ($10^9/L$)	738.9 (236.2)	637.8 (212.3)	720.9 (240.6)	572.9 (192.7)	522.28 (202.8)	488.9* (172.1)	589.4* (271.9)	526.3* (189.4)
MCHC (g/dL)	30.5 (32.9)	31.3 (33.3)	31.0 (32.9)	31.2 (33.0)	31.8* (33.1)	32.1* (33.2)	32.2* (32.3)	32.0 (32.9)
MCV (fL)	62.6 (56.5)	61.9 (56.0)	64.4 (57.1)	62.1 (56.2)	64.1 (61.2*)	64.8 (58.6*)	66.3 (62.6*)	66.0* (61.5*)
MCH (pg)	19.1 (18.6)	19.4 (18.7)	20.0 (18.8)	19.4 (18.6)	20.4* (20.2*)	20.8* (19.5)	21.4* (20.2*)	21.1* (20.2*)

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (continued)

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Serum chemistry								
ALT (IU/L)	71 (49)	66 (31)	88 (48)	75 (36)	92 (54)	96 (48*)	93 (57)	92 (58*)
Total protein (g/dL)	58 (61)	59 (59)	61* (60)	61 (59)	60 (58*)	63* (59)	58 (56*)	58 (57)
Albumin (g/dL)	41 (41)	42 (43)	44* (41)	45 (43)	43 (38*)	44 (41)	42 (38*)	42 (35*)
Globulin (g/dL)	17 (19)	17 (16)	17 (19)	17 (16)	17 (20)	19 (18)	16 (19)	16 (22*)
Albumin: globulin ratio	2.4 (2.2)	2.6 (2.7)	2.6 (2.2)	2.7 (2.7)	2.5' (1.9)	2.4 (2.3*)	2.6 (2.0)	2.6 (1.7*)
Urinalysis	-	-	-	-	-	-	-	-
Organ weights (%)[a, b]								
Spleen (g)	0.359 (0.518)	0.318 (0.405)	-2 (0)	-8 (-11)	-17* (-2)	-27* (-8)	-24* (+4)	-31* (-7)
Kidney (g)	1.076 (2.005)	0.995 (1.267)	+2 (-5)	0 (0)	0 (-3)	-6* (+2)	-3 (-5)	-8* (+3)
Thymus (g)	0.464 (0.515)	0.408 (0.426)	0 (+6)	+5 (+6)	-2 (+3)	-4 (+2)	-19* (-12)	-11 (-12)
Liver (g)	3.880 (8.649)	3.675 (5.453)	-1 (+4)	-5 (-7)	-6* (-3)	-10* (-10)	-4 (-20*)	-12* (-10)

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (continued)

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Organ weights (%)[a, b]								
Heart (g)	0.488 (0.870)	0.452 (0.607)	-3 (-5)	-3 (-10*)	-3 (-3)	-10* (-3)	-7* (+4)	-12* (-2)
Ovary (g)	-	0.040 (0.082)	-	-8 (-1)	-	-25* (+12)	-	-25* (+4)
Gross pathology	-	-	-	-	-	-	-	-
DEXA bone analysis[b]								
Area (cm^2)	1.08 (1.59)	0.97 (1.35)	-10* (+1)	+14* (-2)	-10* (+2)	+10* (-4)	-2 (-5)	+13* (-9*)
Bone (femur) mineral content (g)	0.10 (0.31)	0.09 (0.26)	0 (0)	+11* (-4)	-10 (0)	0 (-4)	-20* (-16*)	0* (-19*)
Bone (femur) mineral density (g/cm^2)	0.091 (0.198)	0.096 (0.191)	+12* (-1)	-7* (0)	+4 (-3)	-11* (-1)	-15* (-12*)	-20* (-10*)
Histopathology , no. evaluated PND 21-35 Cohort	M:15	F:15	M:15	F:15	M:15	F:15	M:15	F:15
No. evaluated for spleen	M:13	F:15	M:15	F:15	M:15	F:14	M:15	F:15
Spleen, hematopoiesis	2 (++) 11 (+++)	1 (+) 7 (++) 7 (+++)	4 (++) 11 (+++)	3 (+) 8 (++) 4 (+++)	1 (+) 6 (++) 8 (+++)	3 (+) 8 (++) 3 (+++)	7 (++) 8 (+++)	5 (+) 8 (++) 2 (+++)
No. evaluated for uterus	M:0	F:15	M:0	F:15	M:0	F:14	M:0	F:15
Uterus, immature	NE	3	NE	3	NE	5	NE	7
Uterus, increased mucus cells	NE	2 (+)	NE	2 (+)	NE	(4 (+) 1 (++)	NE	1 (+) 5 (++) 1 (+++)

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (continued)

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
No. evaluated for ovary	M:0	F:15	M:0	F:15	M:0	F:14	M:0	F:15
Ovary, pubescent	NE	2	NE	2	NE	7	NE	8
Histopathology , no. evaluated PND 21-70 Cohort	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
No. evaluated for spleen	M:10	F:10	M:0	F:10	M:0	F:9	M:10	F:10
Spleen, hematopoiesis	6 (+) 3 (++)	7 (+) 1 (++)	NE	1 (+) 8 (++) 1 (+++)	NE	5 (+) 4 (++)	6 (+) 4 (++)	3 (+) 6 (++)
No. evaluated for liver	M:10	F:10	M:1	F:10	M:0	F:9	M:10	F:10
Liver, pigment	-	-	-	-	NE	1 (+) 1 (++)	-	4 (+) 1 (++)
No. evaluated for mandibular lymph node	M:10	F:10	M:2	F:10	M:9	F:9	M:10	F:10
Mandibular lymph node, lymphoid hyperplasia	1 (++)	2 (+)	-	1 (+) 1 (++)	1 (+) 1 (++)	1 (+)	-	2 (+) 3 (++) 1 (+++)
Post-dose evaluation:								
Histopathology , no. evaluated PND 21-35 Cohort	M:10	F:10	M:0	F:0	M:0	F:0	M:10	F:10
No. evaluated for spleen	M:10	F:10	M:0	F:0	M:0	F:0	M:10	F:10
Spleen, hematopoiesis	7 (+) 2 (++)	8 (+) 1 (++)	NE	NE	NE	NE	8 (+) 1 (++)	8 (+)
Histopathology , PND 21-70 Cohort	M:10	F:10	M:0	F:0	M:0	F:0	M:10	F:10
No. of evaluated for spleen	M:0	F:10	M:0	F:0	M:0	F:0	M:1	F:10
Spleen, hematopoiesis	NE	8 (+) 1 (++)	NE	NE	NE	NE	1 (+)	6 (+)

2.6.7.15A XL184: 3 or 7 Week (nominal) Oral (Gavage)Administration Toxicity Study in the Juvenile Rat with 4 and 12 Week Treatment-free Periods (continued)

Daily Dose (mg/kg)	0 (Control)		0.3		1.0		2.0	
No. of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
No. of evaluated for liver	M:3	F:10	M:0	F:0	M:0	F:0	M:4	F:10
Liver, pigment	-	-	NE	NE	NE	NE	-	5 (+) 1 (++)
No. of evaluated for mandibular lymphoid	M:2	F:10	M:0	F:0	M:0	F:0	M:3	F:10
Mandibular lymph node, lymphoid hyperplasia	-	1 (++)	NE	NE	NE	NE	1 (+++)	1 (+) 3 (++)

ALT, alanine aminotransferase; AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NE, not evaluated; PND Postnatal Day(s).

(-), No noteworthy findings. Observed finding or increased incidence or severity above control group: minimal (+), slight (++), moderate (+++).

* $P \leq 0.05$, Dunnett's Test.

a. At end of dosing or recovery period (Day 208 [Day 28 post-dose]). For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

b. Number reflects PND 21-35 or (PND 21-70) cohort values.

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats

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		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Rat/Crl:CD (SD)	Duration of Dosing: Postnatal Days (PND) 12-35 or 12-70 (Juvenile arm cohorts)	Study Number: [redacted] Study No. [redacted] (4.2.3.5.3-2)
Initial Age: PND 12	Duration of Post-Dose: 28 Days	
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral Gavage	
	Vehicle/Formulation: EtOH: polyethylene glycol (PEG) 400:reverse osmosis water (5:45:50)	GLP Compliance: Yes
Special Features: Juvenile toxicity treatment cohorts (n= 15/sex/dose at 0, 1.0 and 2.0 mg/kg/day) PND 12-35 (Groups 5-7, respectively) and PND 12-70 (Groups 8-10, respectively [Designated by *]); Recovery cohorts (both 5/sex/dose) sacrificed PND 63 and PND 98, respectively; pre- and postnatal cohort data provided Table 2.6.7.14.2.		
No Observable Adverse Effect Level: Not determined (<1.0 mg/kg/day (PND 12-35 and 12-70 cohorts)		

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
No. of Animals	M:15	F:15	M:15	F:15	M:15	F:15
Toxicokinetics: [a,b] mean ng/mL (range) [n]						
Day 35	NE	NE	939 (233-1900 [10]	900 (262-1580) [11]	1297 (551-2210) [8]	1246 (810-1770) [9]
Day 70	NE	NE	695 (496-946) [9]*	854 (567-1120) [11]*	1324 (821-1680) [5]*	1750 (839-2870) [10]*
Noteworthy findings:						
Died or sacrificed moribund	0 0*	0 0*	0 0*	0 0*	7 6*	6 2*

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
No. of Animals	M:15	F:15	M:15	F:15	M:15	F:15
Body weight (%)[a, c]	160 g 429 g*	137 g 262 g*	-32# -19*	-26# -8*#	-63# -58*#	-59# -34*#
Food consumption (%)[a, c]	255.6 g/rat/wk 471.5 g/rat/wk*	199.8 g/rat/wk 292.6 g/rat/wk*	-39# -23*	-22 -10*	-70# -61*#	+69# -43*#
Clinical observations	- 	- 	+ +*	+ +*	++ ++	++ ++
Teeth abnormalities	- 	- 	- -*	- -*	- +*	- +*
Ophthalmoscopy	NE	NE	NE	NE	NE	NE
Hematology	NE	NE	NE	NE	NE	NE
Serum chemistry	NE	NE	NE	NE	NE	NE
Urinalysis	NE	NE	NE	NE	NE	NE
Organ weights (%)[a, c]	M:10	F:10	M:10	F:10	M:10	F:10
Spleen (g)	0.5577 -*	0.4304 -*	-43 -*	-38 -*	-72 -*	-61 -*
Uterus (g)	NA NA*	0.2085 -*	NA NA*	-68 -*	NA NA*	-84 -*

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
No. of Animals	M:10	F:10	M:10	F:10	M:10	F:10
Ovary (g)	NA NA*	0.0584 -*	NA NA*	-45 -*	NA NA*	-59 -*
Testis (g)	1.3119 -*	NA NA*	-16 -*	NA NA*	-64 -*	NA NA*
Gross pathology	-	-	-	-	-	-
DEXA bone analysis[a]						
Area (cm2)	0.84 2.00*	0.81 1.58*	-56# -12*#	-64# -6*	-93# -50*#	-91# -37*#
Bone (femur) mineral content (g)	0.09 0.38*	0.09 0.32	-54# -18*#	-67# -12*#	-89# -68*#	-100# -56*#
Bone (femur) mineral density (g/cm^2)	0.111 0.19*	0.113 0.20*	-13# -10*#	-14# -10*#	-28# -37*#	-30# -35*#
Histopathology , no. evaluated[d] PND 12-35 Cohort	M:10	F:10	M:10	F:11	M:8	F:9
Spleen, lymphocyte depletion/decreased extramedullary hematopoiesis	-	1 /1 (+)	0 / 2 (+) 0 / 2 (++) 0 / 2 (+++)	1 / 1 (+) 0 / 1 (++) 0 / 4 (+++)	3 / 3 (+) 1 / 3 (++)	3 / 2 (+) 0/ 4 (++) 1 / 0 (+++)
Uterus, immature	NA	0	NA	9	NA	8
Adrenal, congestion, hemorrhage	-	-	-	-	2 (+) 3 (++)	3 (+) 2 (++)

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
Histopathology , no. evaluated [d] PND 12-35 Cohort, cont.	M:10	F:10	M:10	F:11	M:8	F:9
Ovary, immature	NA	2	NA	11	NA	9
Thymus, lymphocyte depletion, necrosis	-	-	-	-	3 (+) 1 (++)	2 (+) 1 (+++)
Duodenum, cystic dilatation/hyperplasia of Brunner's gland	-	-	-	2 / 1 (+)	1 / 1 (+) 2 / 3 (++) 2 / 3 (+++) 2 / 0 (++++)	1 / 0 (+) 1 / 1 (++) 3 / 4 (+++) 3 / 1 (++++)
Duodenum, inflammation	-	-	-	-	1 (+) 1 (++) 1 (+++)	2 (+) 3 (++) 1 (+++) 1 (++++)
Colon, epithelial hyperplasia,	-	-	-	-	2 (+) 4 (++)	3 (+) 4 (++)
Cecum, epithelial hyperplasia,	-	-	-	-	3 (++) 1 (+++)	3 (+) 2 (++) 2 (+++)
Skin-subcutis, atrophy in adnexa/adipose tissue	-	-	-	-	0 / 1 (+) 2 / 1 (++) 6 / 0 (+++)	0 / 1 (+) 4 / 1 (++) 5 / 0 (+++)

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
Histopathology , no. evaluated [d] PND 12-35 Cohort, cont.	M:10	F:10	M:10	F:11	M:8	F:9
Bone (femur), physeal hypertrophy/decreased cortical bone	-	-	3 / 0 (+)	1 / 0 (+)	0 / 0 (+) 2 / 4 (++) 5 / 2 (+++)	2 / 5 (++) 5 / 3 (+++)
Bone marrow (femur), hypocellularity	-	-	5 (+) 4 (++)	8 (+) 3 (++)	2 (++) 6 (+++)	2 (++) 7 (+++)
Testes, delayed maturation	0	NA	-	NA	8	NA
Vagina, immature	NA	1	NA	10	NA	8
Kidney, chronic progressive nephropathy	4 (+)	1 (+)	-	-	2 (+)	4 (+)
Lymph node, lymphocytic depletion	-	-	-	-	2 (+) 3 (++)	1 (+) 2 (++)
Histopathology , no. evaluated [d] PND 12-70 Cohort	M:10	F:11	M:10	F:12	M:9	F:13
Spleen, lymphocyte depletion/increased extramedullary hematopoiesis	-	-	-	0 / 2 (+)	2 / 2 (+) 2 / 2 (++)	3 / 3 (+) 2 / 1 (++)
Uterus, immature	NA	0	NA	-	NA	2
Adrenal, vacuolation/congestion-hemorrhage	-	-	-	-	1 / 0 (+)	0 / 1 (+) 0 / 2 (++)

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
Histopathology , no. evaluated [d] PND 12-70 Cohort	M:10	F:11	M:10	F:12	M:9	F:13
Vagina, immature	NA	0	NA	-	NA	3
Thymus, lymphocyte depletion, necrosis	-	-	-	-	4 (+)	5 (+)
Duodenum, cystic dilatation/hyperplasia of Brunner's gland	-	-	1 / 1 (+)	1 / 0 (+)	2 / 3 (++) 1 / 4 (+++) 5 / 1 (++++)	1 / 3 (+) 2 / 2 (++) 6 / 7 (+++) 3 / 0 (++++)
Duodenum, inflammation	-	-	-	-	3 (++) 3 (+++)	2 (++) 3 (+++)
Colon, epithelial hyperplasia,	-	-	-	-	2 (+)	2 (+)
Cecum, epithelial hyperplasia,	-	-	-	-	2 (+) 1 (++)	-
Bone (femur), physeal hypertrophy/decreased cortical bone	-	-	-	-	4 / 2 (+) 2 / 5 (++) 1 / 0 (+++)	4 / 4 (+) 7 / 2 (++)
Bone marrow (femur), hypocellularity	-	-	3 (+)	3 (+)	4 (+) 2 (++) 2 (+++)	7 (+) 3 (++) 1 (+++)
Testes, degeneration/atrophy seminiferous tubules	-	NA	-	NA	3 (++++) 2 (+++++)	NA

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
Histopathology , no. evaluated [d] PND 12-70 Cohort	M:10	F:11	M:10	F:12	M:9	F:13
Ovary, immature	NA	0	NA	-	NA	3
Kidney, chronic progressive nephropathy	2 (+)	1 (+)	6 (+) 2 (+++)	4 (+) 2 (++)	4 (+) 1 (+++)	1 (+) 4 (+++) 1 (++++)
Kidney, glomerulonephritis	-	-	2 (+) 1 (+++) 1 (++++)	3 (+) 1 (++) 1 (+++)	1 (+) 1 (++) 5 (+++) 1 (++++)	2 (+) 1 (++) 4 (+++) 3 (++++)
Liver, hepatocyte pigment	-	-	-	3 (+)	3 (+) 1 (++)	7 (+) 2 (++)
Epididymus, reduced luminal sperm	-	NA	-	NA	1 (++) 1 (+++) 1 (++++) 4 (+++++)	NA
Post-dose evaluation (recovery):						
DEXA bone analysis no. evaluated [c] PND 12-35 Cohort PND 12-70 Cohort*	 M:5 M:4*	 F:5 F:4*	 M:4 M:3*	 F:4 F:3*	 M:0[e] M:0*[e]	 F:0[e] F:0*[e]
Area (cm^2) 	1.80 2.28*	1.49 1.76*	-8 -2*	-3 -5*	NE NE*	NE NE*
DEXA bone analysis no. evaluated [c] PND 12-35 Cohort PND 12-70 Cohort*	 M:5 M:4*	 F:5 F:4*	 M:4 M:3*	 F:4 F:3*	 M:0[e] M:0*[e]	 F:0[e] F:0*[e]

2.6.7.15B Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function and Juvenile Arm with Cabozantinib (S)-Malate (XL184) in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		1.0		2.0	
Histopathology , no. evaluated [d] PND 12-70 Cohort	M:10	F:11	M:10	F:12	M:9	F:13
Bone mineral content (g)	0.33 0.53*	0.29 0.39*	-12 -6*	-14[#] -2*	NE NE*	NE NE*
Bone mineral density (g/cm^2)	0.185 0.233*	0.192 0.222*	-6 0*	-9[#] +2*	NE NE*	NE NE*
Histopathology , no. evaluated [c] PND 12-35 Cohort PND 12-70 Cohort*	 M:5 M:4*	 F:5 F:4*	 M:4 M:3*	 F:4 F:3*	 M:0[e] M:0*[e]	 F:0[e] F:0*[e]
Kidney, glomerulonephritis	- -*	- -	- 2*	- -	NE NE	NE NE

(-), No noteworthy findings; ALT, alanine aminotransferase; AUC, area under the plasma drug concentration time curve; F, female; GLP, Good Laboratory Practice; M, male; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; SD, Sprague Dawley; U, unscheduled sacrifice.; NA, not applicable; NE, not evaluated

Observed finding or increased incidence or severity above control group: (+) minimal, (++) slight, (+++) moderate, (++++) marked, (+++++) severe.

a. Number reflects PND12-35 or (PND21-70)[designated by *] cohort values

b. TK sample taken approximately 24 hrs post final dose;

c. At end of dosing periods (PND35[Groups 5-7] or PND 70 [Groups 8-10] or recovery periods (PND 63 or 98, respectively). For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

d. Histopathology data for animals at scheduled sacrifice dates only (PND35[Groups 5-7] or PND 70 [Groups 8-10];

e. Histopathology not performed due to high n number of unscheduled deaths in these cohorts

* $P \leq 0.05$, Dunnett's Test.

2.6.7.16 局所刺激性試験

XL184 was administered clinically as an oral capsule to subjects with advanced MTC in the pivotal Phase 3 study XL184-301. In GLP compliant nonclinical safety studies, XL184 was administered formulated as an oral suspension. In these rodent and non-rodent nonclinical single-dose and repeat-dose toxicity studies of up to 6-months duration, XL184-mediated gastro-intestinal tract (local) toxicity was characterized by clinical signs, gross macroscopic and histopathologic evaluations. Based on these extensive nonclinical evaluations, the Sponsor determined that no additional local tolerance studies were required to estimate clinical risk of treatment-related gastro-intestinal tract toxicity.

2.6.7.17 その他の毒性試験

2.6.7.17A 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase

Report Title: 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase		Test Article: EXEL-1644 (Lot No. [redacted])
Species/Strain: Rat/Hsd:Sprague Dawley®SD®	Duration of Dosing: 14 Days	Study No. [redacted] Study No. [redacted] (4.2.3.7.5-1)
Initial Age: 7-8 weeks	Duration of Postdose: 28 Days	
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Subcutaneous Injection	
	Vehicle/Formulation: EtOH: polyethylene glycol (PEG) 400: reverse osmosis water (5:45:50)	GLP Compliance: Yes
Special Features: None		
No Observed Adverse Effect Level: 30 mg/kg/day		

Daily Dose (mg/kg)	0 (Control)		3		10		30	
Number of Animals	M: 15	F: 15	M: 10	F: 10	M: 10	F: 10	M: 15	F: 15
Toxicokinetics: $AUC_{0\text{-}inf}$ (ng·hr/mL)								
Day 1	NE	NE	72000	67800	323000	248000	759000	585000
Day 15	NE	NE	104000	95300	323000	214000	692000	460000
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%)[a]	310 g	208 g	-3	-1	-2	+1	-1	0
Food Consumption (%)[a]	129 g/rat/ Days 8-15	98 g/rat/ Days 8-15	+2	+4	+6	+9	0	+2

2.6.7.17A 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase (continued)

Daily Dose (mg/kg)	0 (Control)		3		10		30	
Number of Animals	M: 15	F: 15	M: 10	F: 10	M: 10	F: 10	M: 15	F: 15
Clinical Observations								
Injection site erythema/edema	+	+	+	+	+	+	+	+
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry								
Total protein (g/dL)	6.1	-	6.2	-	6.3	-	5.9*	-
Albumin (g/dL)	4.0	-	4.0	-	4.0	-	3.8*	-
Phosphorous (mg/dL)	8.9	-	8.9	-	9.5	-	8.3*	-
Triglycerides (mg/dL)	42	-	33	-	28*	-	28*	-
Urinalysis	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology								
discoloration, scab, and/or thickening in subcutaneous injection sites	+	+	+	+	+	+	+	+
Histopathology								
Subcutaneous injection sites (n=4/animal): epidermal hyperplasia, ulceration, and exudate; dermal fibrosis; subcutis hemorrhage, necrosis, chronic inflammation, and fibrosis; and/or adnexal atrophy	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable

2.6.7.17A 2-Week Toxicity and Toxicokinetic Subcutaneous Injection Study with EXEL-1644 in Rats with a 4-Week Recovery Phase (continued)

Daily Dose (mg/kg)	0 (Control)		3		10		30	
Number of Animals	M: 15	F: 15	M: 10	F: 10	M: 10	F: 10	M: 15	F: 15
Histopathology (continued) Mandibular lymph node, lymphoid hyperplasia	3 (+) 0 (++) 1 (+++) 0 (++++) 0 (+++++)	5 (+) 2 (++) 0 (+++) 0 (++++) 0 (+++++)	NE	NE	NE	NE	4 (+) 4 (++) 0 (+++) 0 (++++) 0 (+++++)	4 (+) 1 (++) 2 (+++) 1 (++++) 1 (+++++)
Postdose Microscopic Evaluation: Number Evaluated	M: 5	F: 5	M: 0	F: 0	M: 0	F: 0	M: 5	F: 5
Subcutaneous injection sites (n=4/animal): epidermal hyperplasia, ulceration, and exudate; dermal fibrosis; subcutis chronic inflammation, and fibrosis; and/or adnexal atrophy	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable	NE	NE	NE	NE	Incidence: variable; Severity: variable	Incidence: variable; Severity: variable
Mandibular lymph node, lymphoid hyperplasia	5 (variable, generally moderate-severe)	5 (variable, generally moderate-severe)	NE	NE	NE	NE	5 (variable, generally moderate-severe)	4 (variable, generally moderate-severe)

AUC, area under the plasma drug concentration curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; NE, not evaluated; SD, Sprague Dawley.

(-), No noteworthy findings. Observed finding or increased incidence or severity above control group: minimal (+), slight (++), moderate (+++), marked (++++), severe (+++++).

* $P \leq 0.05$, Dunnett's Test.

a. At end of dosing. For controls, group means are shown. For treated groups, percentage differences from controls are shown. Statistical significance is based on actual data (not on the percentage differences).

2.6.7.17B 不純物の毒性試験

Test Article: Impurities of XL184						
Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	添付資料番号
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	BMS-927982 (N-oxide of XL-184) non-mutagenic	4.2.3.7.5-2
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	SQ-008953 (4-Fluoroaniline) mutagenic	4.2.3.7.5-3
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	EXEL1644 non-mutagenic EXEL1646 non-mutagenic	4.2.3.7.5-4
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	BMS-655335 (XL184-1-1) mutagenic	4.2.3.7.6-1
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	BMS-908145 (XL184-1-4) mutagenic	4.2.3.7.6-2
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	BMS-908148 (XL184-1-2) non-mutagenic	4.2.3.7.6-3
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	BMS-908146 (XL184-2-2) non-mutagenic	4.2.3.7.6-4
S. typhimurium, E. coli	In vitro	-	0-5000 µg/plate	—	EXEL-01229114 mutagenic EXEL-04621743 mutagenic	4.2.3.7.6-5

2.6.7.17C 光毒性試験

動物種及び系統	投与方法	投与期間	投与量 (mg/kg)	動物数及び性/群	特記すべき所見	添付資料番号
3T3 fibroblast cells	In vitro	-	0-100 µg/mL	—	XL184 non-phototoxic	4.2.3.7.7-1