臓（空胞化及びチモーゲン顆粒減少）に限られ、全身毒性を示す用量の投与（100 mg/kg/day 以上、5 日間）のみで認められた。当該変化は、全身性の一般毒性を反映したもので、毒性変化ではないと判断した。なお、XL184 を最長 6 ヵ月間連日投与したラット及びイヌにおける慢性毒性試験では、内分泌組織に対する毒性は観察されなかった。

XL184 投与に伴う筋骨格系毒性は、ラット及びイヌにおける 2 週間毒性の主要試験で、骨に認められたのみであった。XL184 投与ラット（5 mg/kg/day、14 日間）の骨における変化（骨端軟骨の肥厚）は軽微であり、休薬後に回復したことから、毒性変化ではないと判断した。XL184 投与イヌの骨における組織学的所見（遠位骨幹端の一次海綿骨萎縮に伴う成長停止）は、当該組織に対する XL184 の直接作用ではなく、全身毒性を示す用量の投与（100 mg/kg/day 以上、5 日間）により発現した食欲不振、脱水及び又はストレスに付随する二次変化と判断した。ラットにおける受胎能試験では、全身毒性を示す用量（2.5 mg/kg/day 以上）の投与により主に雄において、歯の外観に関する複数の変化（極度な白色化、欠損、過剰な長さ、不正咬合、切断又は上方への湾曲）が認められた。同様の歯の変化は、幼若ラット毒性試験でもみられた。骨形成に及ぼす XL184 の影響に関して、これら歯の変化の臨床的意義は不明である。ただし、XL184 を妊娠ラット及び妊娠ウサギに投与しても、対照群との比較において胎児骨格異常発現率の上昇はみられなかった。

XL184 に関連した皮膚の外観に対する影響は、イヌの慢性投与後に明らかにみられた。XL184 の 30 mg/kg/day を 1 日 1 回 10 日間投与後、20 mg/kg/day を 1 日 1 回 111 日間（雄）又は 161 日間（雌）投与した雌雄イヌにおいて、皮膚の変色（灰色）、被毛の変色（白色）、被毛の薄化、皮膚弾性の欠如及び皮膚の一部痂皮化が認められた。被毛及び皮膚の変色は軽度から重度の低色素沈着で、ヒトの白斑に類似しており、鼻孔や口唇、眼瞼辺縁まで広範に及んだ。皮膚の灰色化は、28 日間休薬後も回復せず、関連する織学的変化はなかった。したがって、当該所見の毒性学的意義は不明である。XL184 を慢性投与した雌雄イヌでは、皮膚の組織学的所見として軽微ないし軽度の角化亢進、表皮過形成及び表皮表面滲出物が認められたが、対照群及び投薬後に休薬した群では認められなかった。また、XL184 の 2 mg/kg/day を出生後 12 から 35 日に投与した幼若ラットでは、皮膚の変化として皮下付属器及び脂肪細胞の萎縮が認められた。

ラットで実施した毒性試験における臨床病理学的及び病理組織学的所見を踏まえると、XL184 投与は腎臓系の機能に対して毒性を示した。単回投与毒性の主要試験では、全身毒性及び／又は致死性を示す用量のみで腎機能障害が認められた。900 mg/kg/day 投与のラットでは、血清尿素窒素高値が腎組織の病理組織学的変化（尿細管上皮細胞の空胞化）と相関したが、当該変化と同時にクレアチニンの高値はみられなかった。したがって、これらの所見の一部又は全ては、消化管組織での著明な体液損失に伴う脱水による二次変化であると考えられた。ラットにおける 2 週間反復投与毒性の主要試験では、15 mg/kg/day を 14 日間投与したラットの腎組織に病理組織学的所見（尿細管変性及び糸球体基底膜肥厚）がみられ、臨床病理学的所見（尿潜血、血清尿素窒素の高値）と相関した。これらの所見は、XL184 の毒性による腎組織の一次変化を反映している可能性もあるが、全身毒性並びに消化管に関連した体液損失及び脱水などによる二次変化であり、毒性変化ではないと判断した。また、ラットにおける 2 週間反復投与毒性に関するもう 1 つの主要試験では、低用量であり全般的に良好な忍容性がみられた用量の投与（5 mg/kg/day、1 日 1 回 14 日間）において腎毒性がみられた。

腎臓で認められた所見は、腎臓重量の変化（軽度高値）及び組織学的所見（雌雄における軽微から中等度の糸球体基底膜の肥厚及び尿細管の変性）であった。休薬後の雌における好塩基性尿細管増加の頻度及び程度の軽度上昇は、投与終了時にみられた尿細管変性に対する再生反応と判断された。XL184 慢性投与ラット（1 mg/kg/day、180 日間）では、投与に関連した唯一の組織学的所見は腎臓組織でみられ、雌雄において慢性進行性腎症（CPN）の頻度及び／又は程度の軽度上昇が観察されたが、休薬により回復性が認められた。ラットでは、多くの生体異物が CPN 進行を加速することが示されている。本試験では、XL184 投与ラットの CPN の頻度及び／又は程度の上昇は、毒性変化ではないと判断したが、CPN 促進に関する主たる懸案は、長期試験での動物の生存性である。なお、XL184 を最長 6 ヵ月間連日投与したイヌにおける慢性毒性試験では、腎毒性は観察されなかった。

ラット及びイヌにおける非臨床安全性試験で、肝臓は XL184 の毒性の主な標的組織ではなかった。認められた所見は、非特異的な、投与に関連する全身毒性を全般的に反映した肝臓組織に関する血清生化学的検査値の高値及び／又は肝臓の病理組織学的変化であり、ほとんどの場合、休薬により回復性がみられた。XL184 の 50 mg/kg/day を 1 日 1 回 4 週間投与した rasH2 野生型マウスでは、ALT 高値（約 4 倍）がみられたが、肝臓組織に病理組織学的変化は認められなかった。XL184（100～900 mg/kg/day）単回投与から 3 日後のラットでは、用量依存的な ALT、AST、ALP、コレステロール及び総ビリルビン高値がみられたが、相関する肝臓の組織学的変化は認められなかった。XL184 の 2000 mg/kg/day 以上を投与したイヌでは、用量に依存しないコレステロール、AST 及び ALT 高値がみられた。2000 mg/kg/day 投与時の肝臓における病理組織学的所見（グリコーゲン減少）は、栄養状態不良を反映しており、消化管に対する XL184 関連毒性による二次変化と判断した。反復投与毒性の主要試験において XL184 投与ラット（1～15 、14 日間）では、用量依存的な ALT 及び AST 高値が認められた（4.2.3.2-4）。15 mg/kg/day 投与ラットでは、投与に関連する変化として、総蛋白及びアルブミン低値、並びに回復性のある病理組織学的変化の肝細胞肥大及び空胞化がみられたが、一次変化（肝毒性）ではなく、XL184 に関連した全身性の一般毒性による二次変化であり毒性変化ではないと判断された。また、XL184 の 100 mg/kg/day 以上を 5 日間投与したイヌで認められた所見〔回復性の ALT 及び AST 高値、回復性の血清クレアチニン及び尿素窒素低値、並びに胆嚢の病理組織学的変化（分泌物貯留）〕も、XL184 に関連した一次変化（肝毒性）ではなく、投与に関連した全身毒性が総合的に反映された二次変化と判断した。ラット及びイヌにおける慢性毒性試験で XL184 投与に付随した肝障害としては、ラット（0.1～1.0 mg/kg/day、180 日間）で用量依存的な ALT の軽微な高値（2 倍程度）のみがみられたが、相関する組織学的変化は認められなかった。

ラット又はイヌにおける単回及び反復投与毒性試験並びに単回投与による安全性薬理試験で、心血管系、呼吸器系又は中枢神経系の組織あるいは関連機能に、毒性学的に意義のある XL184 投与の影響 はみられなかった。XL184 投与イヌの心血管系又は中枢神経系の組織学的所見は、全身毒性を示す用量の投与（100 mg/kg/day：7 日間、1000 mg/kg/day：5 日間）による変化（脳及び脊髄における血管周囲性単核細胞浸潤を伴う神経膠症）のみであり、全身毒性、あるいは食欲不振、脱水及び／又はストレスに付随した二次変化と判断された。また、全身毒性を示す用量の投与（100 mg/kg/day：7 日間、300 mg/kg/day：6 日間）により数例のイヌでみられた眼の変化（角膜炎）も二次変化と判断した。ラット（5 又は 15 mg/kg/day、

14 日間）の下垂体における組織学的所見（好塩基性細胞の腫大及び空胞化）は毒性変化ではなく、主に副腎組織への XL184 関連毒性に起因する下垂体-副腎系の内分泌バランスの乱れを反映した二次変化と判断された。XL184 投与イヌで心電図の変化（QTc 間隔を含む）は認められなかった〔注：in vitro hERG チャネル阻害試験における XL184 の IC_{50} が高値（>30 μM）であったことと一致〕。XL184 投与に伴う肺組織の変化がまれにみられたが、非特異的反応（例：肺胞中隔及び肺胞腔の好中球及びマクロファージ集簇）と考えられ、全身毒性を示す用量のみで発現する二次変化と判断した。

臨床的に XL184 が遺伝毒性リスクを呈する可能性は低いと考えられる。XL184 は、大腸菌及びネズミチフス菌を用いた主要な復帰突然変異試験、ヒト末梢血リンパ球を用いた主要な in vitro 染色体異常試験、並びに in vivo マウス骨髄小核試験で陰性であった。また、XL184 の 2.0、5.0 又は 15.0 mg/kg/day を 26 日間投与した rasH2 トランスジェニックマウスにおいて、XL184 に関連する組織学的な腫瘍所見は認められなかった。XL-184 を 104 週間投与したラットにおける腫瘍形成は投与量依存的な良性褐色細胞腫の増加のみだった。褐色細胞腫及び副腎過形成の増加は、XL-184 と同様にグリア細胞株由来の神経栄養因子受容体（RET）をターゲットとするチロシンキナーゼ阻害薬であるスニチニブのラットを用いた 2 年がん原性試験でも報告されている。げっ歯類を用いた長期反復毒性試験において、黒色真菌症を増加させる化学物質に共通項は同定されておらず、このタイプの腫瘍をヒトで増加させる報告もない（Greim et al, 2009）。rasH2 トランスジェニックマウスを用いた 26 週間がん原性試験においてカボザンチニブは発がん性を示さなかった（Cometriq USPI）。従って、前臨床試験で評価したカボザンチニブの発がん性は類似薬理ターゲットを持つ抗がん剤の結果と一致するものの、ラットで認められた腫瘍形成がヒトで認められるかは不確かである。発がん作用が認められた際、低用量（0.1 mg/kg/day）でのラットにおける曝露量は日本人がん患者にカボザンチニブ 60 mg（FBE）を連日投与したときの定常状態の血漿中曝露量（$AUC_{0\text{-}24}$）の約 0.07 倍である。

主要な発生毒性試験では、妊娠ラットへの XL184 投与（妊娠 6 から 17 日）により、低用量／曝露量〔NOEL：0.01 mg/kg/day（$AUC_{0\text{-}48}$ = 168 ng·hr/mL）；推定上、臨床的に XL184 FBE 60 mg を連日投与したときの定常期の血漿中曝露量の 1%未満〕において胚・胎児生存率の低下がみられたが、評価した最高用量〔NOEL：0.1 mg/kg/day（$AUC_{0\text{-}48}$ = 1,490 ng·hr/mL）〕で、胚・胎児の成長への影響、並びに胎児の外表、内臓及び骨格の変異又は異常は認められなかった。ラットにおける用量設定試験（非主要試験）では 0.6 mg/kg/day 投与により、XL184 に関連した発育異常として、胎児水腫、口蓋／口唇裂、皮膚形成不全及び曲尾／痕跡尾などの外表異常が観察された。妊娠ウサギへの XL184 投与（妊娠 6 から 21 日）では、評価した最高用量〔NOEL：3.0 mg/kg/day（$AUC_{0\text{-}48}$ = 4,240 ng·hr/mL）；推定上、臨床的定常期の血漿中曝露量の約 0.1 倍〕において、胚・胎児の生存率及び成長への影響、並びに外表及び骨格の変異又は異常は認められなかったが、胎児の内臓異常（脾臓の小型化、肺中葉の矮小化又は欠損）がみられた。

XL184 の 0、0.03、0.1 又は 0.3 mg/kg/day を妊娠後期（妊娠 10 日）から離乳時（哺育 20 日）まで連日強制経口投与した妊娠期及び哺育期のラット（F0）、並びに F1 出生児の出生前及び出生後の発生に対し、被験物質に関連する毒性はみられなかった。主要な幼若動物毒性試験として、幼若ラットに XL184 の 2 mg/kg/day を投与した出生後 12 から 35 日又は出生後 12

から 70 日のいずれかあるいは両方のコホートで、途中死亡、並びに体重、摂餌量及び器官重量（脾臓、子宮、卵巣、精巣）の低値、また、複数の組織（骨、リンパ系組織、消化管、卵巣、精巣、子宮など）で組織学的変化が認められた。少し日齢が進んだ出生後 21 から 35 日又は出生後 21 から 70 日の幼若ラットに投与した試験では、XL184 の 2 mg/kg/day 投与により死亡はみられなかったものの、出生後 12 日から投与したときと同様の被験物質関連毒性が観察された。XL184 の 1 mg/kg/day 投与では、いずれの試験においても被験物質に関連した死亡はみられなかった。これらの結果から、2 mg/kg/day 投与で被験物質に関連した死亡が認められた出生後 12 日の幼若ラット（2 歳未満の幼児に相当）は、2 mg/kg/day 投与で被験物質に関連した途中死亡が認められなかった出生後 21 日の幼若ラット（2 歳超の幼児に相当）より、XL184 の毒性に対する感受性が高いことが示唆された。

XL184 は、Balb/c マウス由来線維芽細胞株 3T3 を用いた in vitro 光毒性試験において陰性であった。

ラットにおけるトキシコキネティクス評価では、XL184（100～900 mg/kg/day）単回経口投与時、全身薬物曝露パラメータ値（C_{max} 及び AUC_{0-t}）は用量に比例して増加せず、その増加は用量比を下回った。ラットにおける連日反復経口投与では、投与 14 及び 178 日後の AUC_{0-t} は用量にほぼ比例して増加した（用量範囲はそれぞれ、1～15 mg/kg/day 及び 0.1～1 mg/kg/day）。また、最長 6 ヵ月の連日反復投与では、中等度の蓄積が示された。イヌでは XL184（400～2000 mg/kg/day）単回経口投与時、C_{max} 及び AUC_{0-t} は用量に比例して増加せず、その増加は用量比を下回り、血中への吸収の飽和の可能性が示唆された。最長 14 日間の連日反復投与では、10～100 mg/kg/day の用量範囲における C_{max} 及び AUC_{0-24} の増加は用量比を上回り、100～1000 mg/kg/day の用量範囲におけるそれらの増加は用量比を下回った。XL184 を最長 6 ヵ月連日投与したイヌでは、0.2～5 mg/kg/day の用量範囲における曝露量は、用量にほぼ比例して増加し、蓄積の程度は軽微であった（増加は 2 倍以下）。

主代謝物 EXEL-1644 に関する主要な 2 週間反復投与試験では、EXEL-1644 を 30 mg/kg/day まで皮下投与した雌雄ラットにおいて、被験物質に関連する死亡、並びに毒性として一般状態の変化や臨床病理学的及び剖検所見はみられなかった。当該用量での血漿中曝露量は、XL184 の臨床用量〔60 mg/日（FBE）〕を投与後の定常期にみられる代謝物曝露量の約 3.5 倍以上（AUC_{0-24}：雄で 692,000 ng·hr/mL、雌で 460,000 ng·hr/mL）と推定される。

以上のように、非臨床安全性評価により、XL184 の経口曝露に伴う毒性は概して、用量依存性を示し、臨床的に観察可能であり、投与中止によって自然に回復することが示唆された。ただし、非臨床試験では雌雄動物の受胎能や胚・胎児の生存及び発生に対して毒性がみられたことから、XL184 の投与により、これら非臨床所見に関連した副作用が発現する可能性を認識しておく必要がある。非臨床試験において胚・胎児への毒性は、日本人がん患者に 60 mg（FBE）の XL184 を連日投与したときの定常期の 1%程度の血漿中曝露量（母動物）で認められた。

2.6.6.10 図表

2.6.6.11 参考文献一覧

[1] Greaves 2007.

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2.6.7 毒性試験概要表

2.6.7.1 毒性試験：一覧表

毒性試験の一覧表　　被験物質：XL184

試験の種類	動物種及び系統	投与方法	投与期間	投与量 (mg/kg)[a]	GLP 適用	実施施設	添付資料番号	区分
Single-dose toxicity	Crl:CD®(SD) rats	Gavage	—	0, 500, 1000, 2000	No	Exelixis Inc.	4.2.3.1-1	参考
	Crl:CD®(SD) rats	Gavage	—	0, 100, 300, 900	Yes	[redacted]	4.2.3.1-2	評価
	Beagle dog	Gavage	—	30, 60, 120, 240, 480	No		4.2.3.1-3	参考
	Beagle dog	Gavage	—	0, 400, 1000, 2000	Yes		4.2.3.1-4	評価
Repeat-dose toxicity	001178-W (wild type) RasH2 mice	Gavage	28 Days	5[b]	No		4.2.3.2-2	参考
	001178-W (wild type) RasH2 mice	Gavage	28 Days	0, 5, 15, 50	Yes		4.2.3.2-1	評価
	Crl:CD®(SD) rats	Gavage	8 Days	0, 1, 3, 10, 30, 100	No	Exelixis Inc.	4.2.3.2-3	参考
	Crl:CD®(SD) rats	Gavage	14 Days	0, 1, 5, 15	Yes	[redacted]	4.2.3.2-4	評価
	Crl:CD®(SD) rats	Gavage	14 Days	0, 1, 5	Yes		4.2.3.2-5	評価
	Crl:CD®(SD) rats	Gavage	26 Weeks	0, 0.1, 0.3, 1	Yes		4.2.3.2-6	評価
	Beagle dog	Gavage	1 Day 4 Days	2000 500	No		4.2.3.2-7	参考
	Beagle dog	Gavage	14 Days 5-7 Days	0, 10 100, 300, 1000	Yes		4.2.3.2-8	評価
	Beagle dog	Gavage	26 Weeks	0, 0.2, 1, 5	Yes		4.2.3.2-9	評価
	Beagle dog	Gavage	26 Weeks	30/20	Yes		4.2.3.2-10	評価

2.6.7.1 毒性試験：一覧表（続き）

毒性試験の一覧表（続き）　　被験物質：XL184

試験の種類	動物種及び系統	投与方法	投与期間	投与量 (mg/kg)[a]	GLP 適用	実施施設	添付資料番号	区分
Genotoxicity	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	No	[redacted]	4.2.3.3.1-1	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.3.1-2	評価
	Mouse lymphoma cell culture	In vitro	—	0-500 µg/plate	No		4.2.3.3.1-3	参考
	Human lymphocytes	In vitro	—	0-525 µg/mL	Yes		4.2.3.3.1-4	評価
	CD-1 mice	Gavage	Single dose	0, 500, 1000, 2000	Yes		4.2.3.3.2-1	評価
Carcinogenicity	001178-T (hemizygous) RasH2 mice	Gavage	26 Weeks	2, 5, 15	Yes		4.2.3.4.2-1	評価
	HSD: Sprague Dawley rats	Gavage	104 Weeks	0.1, 0.3, 1.0	Yes		4.2.3.4.1-1	評価
Reproductive and developmental toxicity	Crl:CD®(SD) rats	Gavage	See footnote[d]	0, 1, 2.5, 5	Yes		4.2.3.5.1-1	評価
	Crl:CD®(SD) rats	Gavage	F: GD 6-17	0-7.5	No		4.2.3.5.2-1	参考
	Crl:CD®(SD) rats	Gavage	F: GD 6-17	0, 0.01, 0.03, 0.1	Yes		4.2.3.5.2-2	評価
	Crl:CD®(SD) rats	Gavage	F: GD 10-21 F: GD 14-21	0, 0.1, 0.3, 1, 3 0.1, 0.3, 1, 3	No		4.2.3.5.3-1	参考
	Crl:CD®(SD) rats	Gavage	F: GD 10-PND 20	0, 0.03, 0.1, 0.3	Yes		4.2.3.5.3-2	評価
	Crl:WI (Han) rats	Gavage	PND 12-35	0, 0.3, 1, 3/2	No		4.2.3.5.4-1	参考
	Crl:WI (Han) rats	Gavage	PND 21-35 PND 21-70	0, 0.3, 1, 2 0, 0.3, 1, 2	Yes		4.2.3.5.4-2	評価
	Crl:CD®(SD) rats	Gavage	PND 12-35 PND 12-70	0, 1, 2 0, 1, 2	Yes		4.2.3.5.3-2	評価
	NZW rabbits	Gavage	7 days	0-30	No		4.2.3.5.2-3	参考
	NZW rabbits	Gavage	F: GD 7-20	0, 0.3, 1, 3	Yes		4.2.3.5.2-4	評価

2.6.7.1 毒性試験：一覧表（続き）

毒性試験の一覧表（続き）　　被験物質：XL184

試験の種類	動物種及び系統	投与方法	投与期間	投与量 (mg/kg)[a]	GLP 適用	実施施設	添付資料番号	区分
Local tolerance[e]	—	—	—	—	—	—		
Metabolite	Hsd:SD rats	Subcutaneous Injection	14 Days	0, 3, 10, 30[c]	Yes	[redacted]	4.2.3.7.5-1	評価
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.5-2	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.5-3	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	No		4.2.3.7.5-4	参考
Impurity	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.6-1	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.6-2	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.6-3	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	Yes		4.2.3.7.6-4	参考
	S. typhimurium, E. coli	In vitro	—	0-5000 µg/plate	No		4.2.3.7.6-5	参考
Phototoxicity	3T3 fibroblast cells	In vitro	—	0-100 µg/mL	Yes		4.2.3.7.7-1	評価

F, female; GD, gestational day; PND, postnatal day; GLP, Good Laboratory Practice; NZW, New Zealand white; SD, Sprague Dawley.

a. dose underlined = no-observed-adverse effect level

b. XL184 (5 mg/kg PO) in combination with EXEL-1644 (20 mg/kg SC)

c. Test article EXEL1644 only

d. 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.

e. Study not conducted.

2.6.7.2 トキシコキネティクス試験：一覧表（臨床曝露との比較に用いた主要試験を記載）

Overview of Toxicokinetics Studies[a]				Test Article: XL184	
試験の種類	試験系	投与方法	投与量 (mg/kg)	GLP 適用	添付資料番号
Single-dose toxicity	Rat	Gavage	500, 1000, 2000	No	4.2.3.1-1
Single-dose toxicity	Rat	Gavage	100, 300, 900	Yes	4.2.3.1-2
Repeat-dose toxicity	Mouse	Gavage	5[a]	No	4.2.3.2-2
Repeat-dose toxicity	Mouse	Gavage	0, 5, 15, 50	Yes	4.2.3.2-1
Repeat-dose toxicity	Rat	Gavage	1, 3, 10, 30, 100	No	4.2.3.2-3
Repeat-dose toxicity	Rat	Gavage	1, 5, 15	Yes	4.2.3.2-4
Repeat-dose toxicity	Rat	Gavage	1, 5	Yes	4.2.3.2-5
Repeat-dose toxicity	Rat	Gavage	0.1, 0.3, 1	Yes	4.2.3.2-6
Reproductive/fertility	Rat	Gavage	1, 2.5, 5	Yes	4.2.3.5.1-1
Embryotoxicity/teratogenicity	Rat	Gavage	0.01, 0.03, 0.1	Yes	4.2.3.5.2-2
Reproductive/juvenile	Rat	Gavage	0, 0.3, 1, 3/2	No	4.2.3.5.4-1
Reproductive/juvenile	Rat	Gavage	0, 0.3, 1, 2	Yes	4.2.3.5.4-2
Reproductive/juvenile	Rat	Gavage	0, 1, 2	Yes	4.2.3.5.3-1
Reproductive/pre-, post-natal	Rat	Gavage	0, 0.03, 0.1, 0.3	Yes	4.2.3.5.3-1
Reproductive/pre-, post-natal	Rat	Gavage	0, 0.1, 0.3, 1, 3	No	4.2.3.5.3-2
Single-dose toxicity	Dog	Gavage	30, 60, 120, 240, 480	No	4.2.3.1-3
Single-dose toxicity	Dog	Gavage	400, 1000, 2000	Yes	4.2.3.1-4
Repeat-dose toxicity	Dog	Gavage	500, 2000	No	4.2.3.2-7
Repeat-dose toxicity	Dog	Gavage	10,100, 300, 1000	Yes	4.2.3.2-8
Repeat-dose toxicity	Dog	Gavage	0.2, 1, 5	Yes	4.2.3.2-9
Repeat-dose toxicity	Dog	Gavage	30/20	Yes	4.2.3.2-10
Embryotoxicity/teratogenicity	Rabbit	Gavage	0.3, 1, 3	Yes	4.2.3.5.2-4

GLP, Good Laboratory Practice

a. XL184 (5 mg/kg PO) in combination with EXEL-1644 (20 mg/kg SC)

2.6.7.3 トキシコキネティクス試験：成績の一覧表（臨床曝露との比較に用いた主要試験を記載）

Test Article: XL184	Steady-State AUC (ng·hr/mL)							
Daily Dose (mg/kg/day)	Mice		Rats		Dogs		Female Rabbits	Humans
	Male	Male	Male	Female	Male	Female		
0.1	—	—	2,632[a]	4,753[a]	—	—	—	—
0.2	—	—	—	—	291[b]	338[b]	—	—
0.3	—	—	7,851[a]	14,416[a]	—	—	274[c]	—
1	—	—	29,736[a] 10,978[d]	44,086[a]	2,027[b]	2,011[b]	984[c]	—
3	—	—	—	—	—	—	4,240[c]	—
5	36,200[g]	21,500[g]	52,152[d]	—	7,757[b]	6,327[b]	—	—
10	—	—	—	—	8,406[g]	11,408[g]	—	—
15	104,000[g]	74,700[g]	512,771[d]	—	—	—	—	—
20	—	—	—	—	18,800[h]	24,800[h]	—	—
60 mg/day	—	—	—	—	—	—	—	37,513[e]

AUC, area under the plasma concentration time curve.

a. 4.2.3.2-6, a 6-month study.

b. 4.2.3.2-9, a 6-month study.

c. 4.2.3.5.2-4, an embryotoxicity/teratogenicity study.

d. 4.2.3.2-4, a 14-day study.

e. 5.3.5.4-1 (Clinical Study Report XL184-014), XL184 tablet form dose in Japanese patients: 60 mg FBE (n=26) on Day19

f. 4.2.3.2.-1, a 28-day study

g. 4.2.3.2-8, a 14-day study.

h. 4.2.3.2-10, a 6-month study.

2.6.7.4 毒性試験：使用ロットの一覧

Drug Substance					Test Article: XL184	
		規格設定された不純物(by Area) 規格値:				
ロット番号	純度 (%)	Dimer RRT 0.97-0.98 (≤.43%)1-5A	RRT 1.15-1.16 (≤.19%)	Ortho-fluoro XL184 (≤.2%) 1-5D	添付資料番号	試験の種類
[redacted]	NA	NA	NA	NA	4.2.3.1-3	Single-dose oral range-finding study in dogs
	NA	NA	NA	NA	4.2.3.2-7	5-Day oral range-finding study in dogs
	99.3	0.29	<LOQ	ND	4.2.3.1-2	Single-dose oral study in rats
					4.2.3.1-4	Single-dose oral study in dogs
					4.2.3.2-4	2-Week oral study in rats
					4.2.3.3.1-2	Ames test
					4.2.3.3.1-4	Human lymphocytes assay in vitro
	99.0	0.43	0.18	ND	4.2.3.2-8	2-Week oral study in dogs
					4.2.3.2-9	6-Month oral study in dogs
					4.2.3.2-6	6-Month oral study in rats
					4.2.3.2-10	6-Month oral study in dogs
	98	0.05	0.06	0.21	4.2.3.2-5	2-Week oral study in rats
	94.9	ND	ND	ND	4.2.3.3.2-1	Micronucleus test in mice
					4.2.3.5.1-1	Fertility and early embryonic development in rats
					4.2.3.5.2-1	Embryofetal development range-finder in rats
					4.2.3.5.2-2	Embryofetal development in rats
					4.2.3.5.2-3	Embryofetal development range-finder in rabbits
					4.2.3.5.2-4	Embryofetal development in rabbits
					4.2.3.7.7-1	Phototoxicity
	102.0	<LOQ	Not Detected	Not Detected	4.2.3.5.4-2	Reproductive/juvenile rat
					4.2.3.5.4-1	Juvenile rat
	100.0	<LOQ	ND	ND	4.2.3.2-1	4-week oral study in mice
	100.0	<LOQ	ND	ND	4.2.3.5.3-2	Reproductive/pre-, post-natal; juvenile rat
	99.9%	<LOQ	ND	ND	4.2.3.4.1-1	Carcinogenicity, rat
	99.9%	<LOQ	ND	ND	4.2.3.4.2-1	Carcinogenicity, rasH2 mouse

LOQ, limit of quantitation; NA, not available; ND, not determined; RRT, relative retention time.

2.6.7.5 単回投与毒性試験

Single-Dose Toxicity				Test Article: XL184			
動物種 及び系統	投与方法 (媒体/投与形態)	投与量 (mg/kg)	動物数 及び性/群	最大非致死量 (mg/kg)	概略致死量 (mg/kg)	特記すべき所見	添付資料番号
Rat/ Crl:CD®(SD)	Gavage (water for injection)	0. 500, 1000, 2000	2F	500	1000	≥ 500: Body weight loss ≥ 1000: Died/sacrificed 72-144 hr post-dose	4.2.3.1-1
	Gavage (EPW)	0, 100, 300, 900	5M 5F	300 100	900 300	300: 1/5F died (Day 4 post-dose); inflammation in lung; necrosis/ inflammation in adrenal cortex. 900: 5/5M, 5/5F died by Day 3 post-dose; degeneration/ necrosis in GI tract, adrenal gland, bone marrow; depletion/necrosis in lymphoid tissues; necrosis in lung, male reproductive tissues; vacuolation in kidney, pancreas.	4.2.3.1-2
Dog/ Beagle	Gavage (EPW)	30, 60, 120, 240, 480	2M total (escalating dose)	480	>480	≥ 120: fecal changes 240: MTD	4.2.3.1-3
	Gavage (EPW)	0, 400, 1000, 2000	2M 2F	2000	>2000	2000: excess salivation	4.2.3.1-4

EPW, ethanol: polyethylene glycol 400: water, 5:45:50 (v/v/v); F, female; GI, gastrointestinal; M, male; MTD, maximum tolerated dose; SD, Sprague Dawley.

2.6.7.6 反復投与毒性試験：用量設定試験

Repeat-Dose Toxicity, Nonpivotal Studies					Test Article: XL184		
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 及び性/群	無毒性量 (mg/kg)	特記すべき所見	添付資料番号
001178-W (wild type) RasH2 mice	Gavage (EPW)	28 Days	5[a]	12/sex	Not Available	No test article-related systemic tissue toxicity; injection site erythema and associated macroscopic/microscopic changes, however, slight decrease in body weight was observed transiently.	4.2.3.2-2
Rat/ Crl:CD®(SD)	Gavage (Water for injection)	8 Days	0, 1, 3, 10, 30, 100	6F	Not determined	≥ 10: submucosal edema in stomach; ≥ 1: follicular necrosis in ovaries, inflammation in stomach 100: Died/sacrificed (6/6F on Dosing Day 5)	4.2.3.2-3
Dog/ Beagle	Gavage (EPW)	4 Days 1 Day	500 2000	2M	Not determined	≥ 500: vomitus, abnormal feces, decreased body weights/food consumption; Necrosis of surface epithelium usually accompanied by submucosal inflammation (500) in GI tract; lymphoid necrosis (500) and hyperplasia (2000) in lymphoid tissues, germ cell degeneration in testes.	4.2.3.2-7

EPW, ethanol: polyethylene glycol 400: water, 5:45:50 (v/v/v); F, female; GI, gastrointestinal; M, male; NOAEL, no observable adverse effect level; PO, oral dosing; SC, subcutaneous; SD, Sprague Dawley.

2.6.7.7 反復投与毒性試験

2.6.7.7A 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

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		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Mouse/RasH2 (001178-W [Wild Type])	Duration of Dosing: 28 Days	Study Number: [redacted] Study No. [redacted] (4.2.3.2-1)
Initial Age: 8 to 9 weeks old	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: None		
Maximum Tolerated Dose: 15 mg/kg/day		

Daily Dose (mg/kg)	0 (Control)		5		15		50	
No. of Animals	M:12	F:12	M:12	F:12	M:12	F:12	M:12	F:12
Toxicokinetics: AUC_{0-24} (ng·hr/mL)								
Day 1	ND	ND	36400	20300	46600	66300	218000	189000
Day 14	ND	ND	36700	16100	95400	69800	150000	235000
Day 28	ND	ND	36200	21500	104000	74700	131000	99000
Noteworthy findings:								
Died or sacrificed moribund	0	0	0	0	0	0	0	0
Body weight[a] (%)	29.8 g	22.7 g	-4	-2	-5	-4	-10	-6

2.6.7.7A 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 (continued)

Daily Dose (mg/kg)	0 (Control)		5		15		50	
No. of Animals	M:12	F:12	M:12	F:12	M:12	F:12	M:12	F:12
Food consumption[a] (%)	25.8 g/mice/ Days 22-29	26.5 g/mice/ Days 22-29	0	-18	8	10	21*	-17
Clinical observations								
White discoloration of hair coat (primarily around nose)	-	-	-	-	-	-	+	+
Hematology								
Reticulocyte count ($\times 10^3/\mu L$)	286.8	248.9	217.8*	217.0	130.4*	171.8	223.1	119.1
Serum chemistry								
ALT (IU/L)	29	34	50	37	75	49	125*	112
ALP (IU/L)	71	120	70	134	91	144	93	167*
Organ weights[b] (%)								
Spleen	0.0751 g	0.0854 g	-21*	-14	-26*	-21*	-25*	-31*
Heart	0.1624 g	0.1354 g	-19*	-7	-12*	-17*	-24*	-18*
Testis	0.2768 g	NA	-4	NA	-9	NA	-57*	NA
Ovary	NA	0.0260 g	NA	-5	NA	-19	NA	-35
Histopathology								
No. examined (U)[c]	6	6	6	6	6	6	6	6
Thymus: lymphocytic depletion/necrosis,	0	0	0	0	3 (++) 1(++++)	0	2 (++) 1 (+++) 3 (++++)	2 (+) 3 (++)
Spleen: lymphocytic depletion	2 (++)	2 (+)	4 (++)	1 (+)	3 (++) 3 (+++)	4 (+) 2 (++)	1 (++) 1 (+++) 4 (++++)	1 (++) 2 (+++) 3 (++++)

2.6.7.7A 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 (continued)

Daily Dose (mg/kg)	0 (Control)		5		15		50	
No. of Animals	M:12	F:12	M:12	F:12	M:12	F:12	M:12	F:12
Histopathology (continued)								
No. examined (U)[c]	6	6	6	6	6	6	6	6
Glandular stomach: decreased parietal/chief cells, fundus	0	0	0	0	0	0	1 (+) 3 (++) 2 (+++)	2 (++) 4 (+++)
Glandular stomach, epithelial hyperplasia, fundus	0	0	0	0	0	3 (+)	2 (++) 3 (+++) 1 (++++)	5 (+++) 1 (++++)
Glandular stomach, epithelial hyperplasia, pylorus	0	0	0	0	0	1 (++)	3 (+++) 3 (++++)	2 (+++) 4 (++++)
Glandular stomach, mucus cell metaplasia, pylorus	0	0	0	0	0	0	3 (+++) 3 (++++)	2 (+++) 4 (++++)
Glandular stomach, epithelial hyperplasia, gastroduodenal junction	0	0	0	0	0	0	3 (++) 2 (+++) 1 (++++)	1 (+) 1 (++) 1 (+++) 3 (++++)
Glandular stomach, chronic active inflammation, gastroduodenal junction	0	0	0	0	0	0	2 (+) 2 (++) 2 (+++)	6 (+)
Pancreas, zymogen depletion	0	0	0	0	0	0	1 (+) 4 (++) 1 (+++)	0

2.6.7.7A 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 (continued)

Daily Dose (mg/kg)	0 (Control)		5		15		50	
No. of animals	M:12	F:12	M:12	F:12	M:12	F:12	M:12	F:12
No. examined (U)[c]	6	6	6	6	6	6	6	6
Marrow (femur): hypocellularity	1 (+)	0	3 (+) 1 (++)	2 (+) 1 (++)	1 (+) 3 (++) 2 (+++)	1 (+) 3 (++) 2 (+++)	4 (++) 2 (+++)	1 (+) 2 (++) 3 (+++)
Marrow (femur): congestion/hemorrhage	0	0	3 (+) 1 (++)	3 (+)	1 (+) 5 (++)	2 (+) 2 (++) 1 (+++)	1 (+) 3 (++) 1 (+++) 1 (++++)	1 (+) 4 (++) 1 (+++)
Marrow (sternum): hypocellularity	0	0	4 (+)	4 (++)	3 (++) 2 (+++) 1 (++++)	4 (++) 2 (+++)	2 (+) 1 (++) 2 (+++) 1 (++++)	2 (++) 4 (+++)
Marrow (sternum): congestion/hemorrhage	0	0	4 (+)	4 (+) 1 (++)	2 (++) 4 (+++)	2 (+) 3 (++) 1 (+++)	1 (+) 3 (++) 2 (++++)	4 (++) 2 (+++)
Testis, seminiferous tubule degeneration/atrophy	0	NA	0	NA	3 (+)	NA	3 (++) 2 (+++) 1 (++++)	NA
Ovary, hypoplasia	NA	0	NA	1 (+)	NA	4 (+) 1 (++)	NA	2 (+++) 4 (++++)
Uterus, hypoplasia	NA	0	NA	0	NA	1 (++) 1 (+++)	NA	1 (++) 5 (+++)

2.6.7.7A 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 (continued)

Daily Dose (mg/kg)	0 (Control)		5		15		50	
Post-dose evaluation: No. evaluated	M:6	F:6	M:6	F:6	M:6	F:6	M:6	F:6
No. examined (U)[c]	6	5(1)	6	6	6	6	6	6
Glandular stomach: decreased parietal/chief cells, fundus	0	0	0	0	0	1 (+)	0	0
Glandular stomach, epithelial hyperplasia, fundus	0	0	0	0	0	1 (+)	1 (+) 1 (++) 1 (+++)	2 (+) 1 (++)
Glandular stomach, epithelial hyperplasia, pylorus	0	0	0	0	0	0	1 (+) 3 (++) 1 (+++) 1 (++++)	3 (++) 2 (+++)
Glandular stomach, mucus cell metaplasia, pylorus	0	0	0	0	0	0	0	2 (+) 1 (++)
Glandular stomach, epithelial hyperplasia, gastroduodenal junction	0	0	0	0	0	0	1 (+)	0
Glandular stomach, chronic active inflammation, gastroduodenal junction	0	0	0	0	0	0	1 (+) 2 (++)	1 (++)
Spleen: lymphocytic depletion	3 (++)	1 (+)	2 (++)	0	1 (++)	2 (+) 1 (++)	4 (++)	4 (+)
Ovary, hypoplasia	NA	0	NA	0	NA	1 (+)	NA	2 (+) 1 (++)

2.6.7.7A 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 (continued)

Daily Dose (mg/kg)	0 (Control)		5		15		50	
Post-dose evaluation: No. evaluated	M:6	F:5(1)	M:6	F:6	M:6	F:6	M:6	F:6
No. examined (U)[c]	6	6	6	6	6	6	6	6
Uterus, hypoplasia	NA	0	NA	0	NA	3 (+) 1 (++) 1 (+++)	NA	1 (+) 1 (++) 1 (+++)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; U, unscheduled sacrifice.; NA, not applicable; ND, not determined.

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

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

a. At end of dosing or recovery period. 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. Both absolute and relative weights differed from controls in the direction indicated. Number indicates percentage difference for the absolute weights.

c. Number reflects scheduled sacrifice or (U) unscheduled sacrifice.

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period

Report Title: 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period				Test Article: XL184 (Lot No. [redacted])				
Species/Strain: Rat/Crl:CD®(SD)		Duration of Dosing: 14 Days		Study Number: [redacted] Study No. [redacted] (4.2.3.2-4)				
Initial Age: 46 to 53 days old		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: None								
No Observable Adverse Effect Level: 1 mg/kg/day								
Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of Animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Toxicokinetics: AUC_{0-24} (ng·hr/mL)								
Day 1	ND	ND	9,940	ND	41,920	ND	135,549	ND
Day 14	ND	ND	10,978	ND	52,152	ND	512,771	ND
Noteworthy findings:								
Died or sacrificed moribund	0	0	0	0	0	0	3	9
Body weight[a] (%)	356 g	238 g	-1	-3	-5	0	-27*	-24*
Food consumption[a] (%)	230 g/rat/Week 2	172 g/rat/Week 2	0	-7	-13*	-11*	-57*	-54*

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of Animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Clinical observations								
Hunched posture, thin, nonformed/liquid feces, clear discharge-eyes, cold to touch, brown scrotum [male only] , rough haircoat	-	-	-	-	-	-	+	+
Head tremors, squinted eyes irregular respiration, yellow and/or brown (hindlimb, perineal)	-	-	-	-	-	-	-	+
Hematology								
Erythrocyte count ($\times 10^6/\mu L$)	-	7.14	-	7.51*	-	6.89	-	5.62*
Hemoglobin (g/dL)	14.5	14.9	15.0	15.3	15.5*	14.8	15.1	11.7*
Hematocrit (%)	-	46.1	-	47.3	-	44.5*	-	34.6*
MCV (fL)	66.1	64.7	65.5	63.0	67.7	64.6	63.5*	61.7*
MCHC (g/dL)	31.2	32.2	31.7*	32.4	32.1*	33.3*	33.1*	33.8*
Reticulocyte count ($\times 10^3/\mu L$)	226.0	171.1	202.7	158.1	215.6	157.0	37.4*	62.6*
Platelet count ($\times 10^3/\mu L$)	1142	1229	1088	1093	998	854*	441*	273*
White blood cell count ($\times 10^3/\mu L$)	7.55	-	7.08	-	6.16	-	5.63*	-
Absolute eosinophil count ($\times 10^3/\mu L$)	0.06	0.06	0.06	0.09	0.04*	0.06	0.01*	0.02*
Prothrombin time (sec)	-	15.7	-	15.8	-	15.5	-	17.1*
APTT (sec)	19.4	18.4	18.1*	18.0	17.5*	17.3*	20.9	22.7*

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Serum chemistry								
Glucose (mg/dL)	-	102	-	97	-	101	-	70*
Creatinine (mg/dL)	-	0.6	-	0.7	-	0.6	-	0.4*
Urea nitrogen (mg/dL)	16	16	16	17	17	20*	27*	27*
Total protein (g/dL)	6.7	7.1	6.7	7.0	6.4	6.6	5.0*	3.7*
Albumin (g/dL)	4.4	4.8	4.4	4.8	4.2*	4.3*	2.8*	1.9*
Globulin (g/dL)	-	2.2	-	2.3	-	2.3	-	1.8*
Albumin-to-globulin ratio	1.9	2.2	2.0	2.1	1.9	1.9*	1.3*	1.0*
Cholesterol (mg/dL)	53	54	52	55	64	89*	148*	75*
AST (IU/L)	138	147	159	155	227*	254*	437*	532*
ALT (IU/L)	35	29	41*	41*	132*	190*	267*	307*
ALP (IU/L)	241	-	259	-	236	-	121*	-
Calcium (mg/dL)	11.2	11.1	11.1	11.1	11.0	11.0	9.9*	8.9*
Phosphorus (mg/dL)	9.5	-	9.0	-	9.2	-	8.0*	-
Potassium (mmol/L)	5.9	5.4	5.6	5.5	5.4*	5.1	4.9*	4.6*
Chloride (mmol/L)	-	103	-	102	-	103	-	106*

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Urinalysis								
Occult blood	-	-	-	-	-	-	+	+
Protein	-	-	-	-	-	-	+	+
Urobilinogen	-	-	-	-	-	-	+	+
Potassium (mmol)	1.34	-	1.79*	-	1.58	-	0.99*	-
Organ weights[b] (%)								
Liver	11.17 g	7.78 g	-10	-12*	-21*	-17*	-37*	-40*
Kidney	2.97 g	-	-6	-	-6	-	-23*	-
Spleen	0.71 g	-	-3	-	-14	-	-21*	-
Thymus	0.54 g	0.55 g	-2	-9	-30*	-23*	-48*	-65*
Lung	1.53 g	1.21 g	-7	-4	-12	-6	-11*	-21*
Heart	1.24 g	0.90 g	-2	-3	-6	-4	-32*	-27*
Pituitary	0.01 g	0.02 g	+8	-11	-3	-12	-25*	-46*
Adrenal	0.07 g	0.08 g	-4	-11	-6	-4	+50	+74*
Prostate	0.87 g	NA	-3	NA	-6	NA	-36*	NA
Ovary	NA	0.15 g	NA	-1	NA	-26*	NA	-52*
Gross pathology								
No. examined	10	10	10	10	10	10	8	4
Adrenal cortex: large	0	0	0	0	0	0	3	3
Adrenal cortex: diffusely red, and/or mottled	0	0	0	0	0	0	8	4
Thyroid: diffusely light	0	0	0	0	0	0	2	1
Stomach: large	0	0	0	0	0	0	2	0
Stomach: red focus or area	0	0	0	0	0	0	3	3
Duodenum: large	0	0	0	0	0	0	7	3
Seminal vesicle: small	0	NA	0	NA	2	NA	5	NA

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of Animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Histopathology								
No. examined (U)[c]	10	10	10	10	10	10	8 (3)	4 (9)
Thymus: lymphocytic necrosis, minimally-severe	0	0	0	0	4	7	8 (3)	4 (9)
Spleen: lymphocytic necrosis, minimally-severe	0	0	0	0	0	1	7 (2)	4 (4)
Ileum, lymphocytic necrosis, minimally-severe	0	0	0	0	1	4	2 (2)	0 (4)
Glandular stomach: acute inflammation	0	0	0	0	0	0	0 (2)	1 (2)
Duodenum: acute inflammation	0	0	0	0	0	0	7 (3)	4 (9)
Bile duct: acute, subacute or chronic active inflammation	0	0	0	0	0	0	6 (2)	4 (4)
Jejunum acute or subacute inflammation	0	0	0	0	0	0	0 (0)	1 (1)

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
No. of animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
No. examined (U)[c]	10	10	10	10	10	10	8 (3)	4 (9)
Adrenal: cortical necrosis	0	0	0	0	0	0	2 (3)	4 (9)
Adrenal: angiectasis	0	0	0	0	0	0	8 (2)	4 (9)
Kidney: glomerular basement membrane thickening	0	0	0	0	4	3	3 (3)	3 (7)
Pancreas: acinar cell degeneration/necrosis	0	0	0	0	0	0	7 (2)	3 (7)
Pancreas: subacute inflammation	0	0	0	0	0	0	4 (2)	3 (6)
Marrow (femur): depletion, minimal	0	0	0	0	7	4	8 (3)	4 (9)
Marrow (sternum): depletion, minimal	0	0	0	0	10	2	8 (3)	4 (9)
Liver, hepatocellular hypertrophy	0	0	8	4	8	7	8 (3)	3 (9)
Pituitary: basophil hypertrophy	0	0	0	0	4	0	8 (3)	2 (8)
Pituitary: basophil degeneration/necrosis	0	0	0	0	0	0	8 (1)	1 (2)

2.6.7.7B 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 28-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5		15	
Post-dose evaluation: No. evaluated	M:5	F:5	M:0	F:0	M:0	F:0	M:4	F:2
Body weight[a] (%)	461 g	291 g	NA	NA	NA	NA	-17*	-21*
Adrenal: cortical necrosis	0	0	NA	NA	NA	NA	1	0
Kidney: tubular epithelial regeneration, bilateral	0	0	NA	NA	NA	NA	4	0
Liver, bile duct hyperplasia	0	0	NA	NA	NA	NA	4	2
Pituitary, basophil hypertrophy	1	0	NA	NA	NA	NA	4	0

ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NA, not applicable; ND, not determined; SD, Sprague Dawley; U, unscheduled sacrifice.

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

* $P \leq 0.05$, Dunnett's Test. (Two simple T-Test for recovery phase)

a. At end of dosing or recovery period. 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. Both absolute and relative weights differed from controls in the direction indicated. Number indicates percentage difference for the absolute weights.

c. Number reflects scheduled sacrifice or (U) unscheduled sacrifice.

2.6.7.7C 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 14-Day Recovery Period

Report Title: 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 14-Day Recovery Period			Test Article: XL184 (Lot No. [redacted])			
Species/Strain: Rat/Crl:CD®(SD)	Duration of Dosing: 14 Days		Study Number: [redacted] Study No. [redacted] (4.2.3.2-5)			
Initial Age: 42 to 48 days old	Duration of Post-Dose: 14 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: None						
No Observable Adverse Effect Level: 1 mg/kg/day						
Daily Dose (mg/kg)	0 (Control)		1		5	
No. of Animals	M:15	F:15	M:10	F:10	M:15	F:15
Toxicokinetics: AUC_{0-24} (ng·hr/mL)						
Day 1	ND	ND	6,780	ND	36,200	ND
Day 14	ND	ND	ND	ND	ND	ND
Noteworthy findings:						
Died or sacrificed moribund	0	0	0	0	0	0
Body weight (%)[a]	310 g	194 g	-3	-1	-3	-1
Food consumption (%)[a]	175 g/rat/Days 8-13	118 g/rat/Days 8-13	-2	+3	-2	+1
Clinical observations	-	-	-	-	-	-

2.6.7.7C 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 14-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5	
No. of Animals	M:15	F:15	M:10	F:10	M:15	F:15
Ophthalmoscopy	-	-	-	-	-	-
Hematology						
Erythrocyte count ($\times 10^6/\mu L$)	7.47	7.62	7.59	7.70	7.29	7.19*
Hemoglobin (g/dL)	15.4	15.4	16.0	15.9	16.1*	15.2
MCV (fL)	60.5	57.6	61.3	58.9	63.8*	59.2
MCH (pg)	20.6	20.3	21.1*	20.7	22.1*	21.2*
Reticulocytes ($\times 10^3/\mu L$)	310.6	210.0	295.5	180.2	254.0*	183.6
White blood cell count ($\times 10^3/\mu L$)	8.40	6.21	6.61	5.67	6.16*	5.36
Neutrophil count ($\times 10^3/\mu L$)	1.01	0.77	0.81	0.54	0.62	0.41*
Platelet count ($\times 10^3/\mu L$)	1366	1344	1182*	1187	1173*	1038*
Serum chemistry						
AST (IU/L)	143	146	154	147	182	202*
ALT (IU/L)	30	34	46*	41	110*	180*
Total Protein (g/dL)	6.1	6.4	6.0	6.4	5.8	5.8*
Albumin (g/dL)	4.1	4.4	4.1	4.5	4.0	3.8*
Cholesterol (mg/dL)	65	60	61	66	64	98*
Urinalysis						
Urine volume (mL)	10.0	7.5	18.4	6.7	7.5	4.2
Urine specific gravity	1.038	1.029	1.030	1.033	1.045	1.052*

2.6.7.7C 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 14-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5	
No. of Animals	M:15	F:15	M:10	F:10	M:15	F:15
Organ weights (%)[b]						
Kidney (g)	2.499	1.599	-3	+2	-1	+12*
Liver (g)	8.985	5.898	-7	-4	-10	-7
Thymus (g)	0.591	0.524	-6	-1	-12	-29*
Gross pathology						
Adrenal, mottled	0	0	0	0	0	1
Histopathology, no. evaluated	M:10	F:10	M:10	F:10	M:10	F:10
Bone, femur, thickened physis	0	0	1 (+)	0	4 (++) 6 (+++)	1 (++) 9 (+++)
Bone marrow, femur, hypocellularity	0	1 (+)	0	0	5 (+) 5 (++)	1 (+) 4 (++) 5 (+++)
Kidney, glomerular basement membrane thickening	0	0	0	0	7 (+)	6 (+) 1 (++) 1 (+++)
Kidney, tubular degeneration	0	0	0	0	2 (+)	1 (+) 1 (++)
Adrenal cortex, dilated sinusoids	0	0	0	0	0	2 (+)
Adrenal cortex, necrosis	0	0	0	0	0	2 (+) 3 (++)

2.6.7.7C 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Rats with a 14-Day Recovery Period (continued)

Daily Dose (mg/kg)	0 (Control)		1		5	
No. of Animals	M:15	F:15	M:10	F:10	M:15	F:15
Ovary, corpora lutea, hypoplasia	NA	1 (+)	NA	0	NA	1 (+) 7 (++)
Ovary, corpora lutea, necrosis	NA	0	NA	0	NA	3 (+) 1 (++)
Pituitary, hypertrophy and vacuolation, basophils, pars distalis	0	0	0	0	2 (+)	0
Thymus, lymphocyte, necrosis	2 (+)	0	3 (+)	2 (+)	8 (+)	8 (+) 2 (++)
Post-dose evaluation: No. evaluated	M:5	F:5	M:0	F:0	M:5	F:5
Body weight (%)[a]	387 g	232 g	NA	NA	-8	-17*
Food consumption (%)[a]	200 g/rat/Days 22-27	136 g/rat/Days 22-27	NA	NA	-13*	-25
MCV (fL)	58.6	59.1	NA	NA	62.4*	63.2*
MCH (pg)	19.8	20.3	NA	NA	21.0*	21.6*
Kidney, tubular basophilia	3 (+)	1 (+)	NA	NA	3 (+)	3 (+) 1 (++)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; NA, not applicable; ND, not determined; SD, Sprague Dawley.

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

* $P \leq 0.05$, Dunnett's Test. (Two simple T-Test for recovery phase)

a. At end of dosing or recovery period (Day 28 [Day 14 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. Both absolute and relative weights differed from controls in the direction indicated. Number indicates percentage difference for the absolute weights.

2.6.7.7D A Six Month Oral Toxicity Study with Recovery in Rats

Report Title: XL184: A Six Month Oral Toxicity Study with Recovery in Rats		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Rat/Crl:CD®(SD)	Duration of Dosing: 26 Weeks	Study Number: [redacted] Study No. [redacted] (4.2.3.2-6)
Initial Age: Approx. 6 weeks	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: None		
No Observable Adverse Effect Level: 0.3 mg/kg/day		

Daily Dose (mg/kg)	0 (Control)		0.1		0.3		1.0	
No. of Animals	M:26	F:26	M:20	F:20	M:20	F:20	M:26	F:26
Toxicokinetics: AUC_{0-24} (ng·hr/mL)								
Day 1	ND	ND	656	1,149	1,826	3,359	8,356	10,187
Day 28	ND	ND	1,208	1,952	3,669	6,753	15,239	18,580
Day 178	ND	ND	2,632	4,753	7,851	14,416	29,736	44,086
Noteworthy findings:								
Died or sacrificed moribund	1	2	0	0	0	0	1	2
Body weight[a] (%)	627 g	344 g	0	0	-4	0	-3	-10*
Food consumption[a] (%)	25.9 g/rat/day	18.7 g/rat/day	-1	-4	-3	+1	+1	0

2.6.7.7D A Six Month Oral Toxicity Study with Recovery in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		0.1		0.3		1.0	
No. of Animals	M:26	F:26	M:20	F:20	M:20	F:20	M:26	F:26
Clinical observations								
Broken teeth	-	+	+	+	+	-	+	+
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology								
Erythrocyte count ($\times 10^6/\mu L$)	9.08	8.19	8.82	8.17	8.87	7.96	8.45*	7.52*
MCHC (g/dL)	30.88	31.54	30.12	30.60*	30.22	30.94	31.32	31.88
MCV (fL)	55.77	58.96	58.39*	60.42	59.44*	61.52*	60.39*	63.61*
MCH (pg)	17.19	18.57	17.58	18.49	17.96*	19.04	18.89*	20.22*
Serum chemistry								
ALT (IU/L)	33.7	41.8	37.8	51.6	42.6	51.2	61.4*	70.1*
Total protein (g/dL)	7.06	8.12	7.04	8.16	6.99	8.09	6.63*	7.50*
Albumin (g/dL)	3.53	4.35	3.51	4.40	3.47	4.34	3.30*	3.93*
Globulin (g/dL)	3.53	3.79	3.54	3.79	3.52	3.77	3.32*	3.56*
Albumin: globulin ratio	1.00	1.14	1.00	1.16	0.97	1.15	0.99	1.11
Urinalysis	-	-	-	-	-	-	-	-
Organ weights[a] (%)								
Spleen (g)	0.924	0.562	-8	-4	-10	-8	-13*	-8

2.6.7.7D A Six Month Oral Toxicity Study with Recovery in Rats (continued)

Daily Dose (mg/kg)	0 (Control)		0.1		0.3		1.0	
No. of Animals	M:26	F:26	M:20	F:20	M:20	F:20	M:26	F:26
Testes (g)	3.737	NA	-3	NA	-9	NA	-14*	NA
Thymus (g)	0.315	0.249	-5	-18	-14	-16	-19	-27*
Uterus + cervix (g)	NA	0.664	NA	+29	NA	+23	NA	+12
Gross pathology	-	-	-	-	-	-	-	-
Histopathology[b], no. evaluated	M:19 (1)	F:18 (2)	M:20	F:20	M:20	F:20	M:19 (1)	F:18 (2)
Kidney, nephropathy, chronic progressive [bilateral lesions]	15 (+) [9/15]	6 (+) [2/6]	14 (+) [10/14]	4(+) [1/4]	13 (+) [9/13]	5 (+) [2/5]	(1)(+) 14 (+) 4 (++) [16/19]	10 (+) 2 (++) [11/12]
Post-dose evaluation: No. evaluated	M:6	F:6	M:0	F:0	M:0	F:0	M:6	F:6
Kidney, nephropathy, chronic progressive [bilateral lesions]	5 (+) [4/5]	1 (+) [1/1]	NA	NA	NA	NA	4 (+) 1 (++) [4/5]	4 (+) 1 (++) [4/5]

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; SD, Sprague Dawley; U, unscheduled sacrifice.; NA, not applicable; ND, not deteremined

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

* $P \leq 0.05$, Dunnett's Test or Welch's t-test with a Bonferroni connection.

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 scheduled sacrifice or (U) unscheduled sacrifice.

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period

Report Title: 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28-Day Recovery Period		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Dog/Beagle	Duration of Dosing: 14 Days	Study Number: [redacted] Study No. [redacted] (4.2.3.2-8)
Initial Age: Approx. 4.5 months	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: None		
No Observable Adverse Effect Level: 10 mg/kg/day		

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Toxicokinetics: AUC_{0-24} (µg·hr/mL)														
Day 1	ND	ND	199.6	135.2	464.9	310.6	447.4	431.9	0	0	6.1	7.2	237.4	222.1
Day 14[g]	ND	ND	115.4	63.0	ND	ND	ND	ND	0	0	8.4	11.4	ND	ND
Noteworthy findings:														
Died or sacrificed moribund	0	0	3	3	2	2	5	4	0	0	0	0	0	1
Body weight (%)[h]	7.24 kg	6.44 kg	-19	-13	-21	-22	-24	-20	9.00 kg	7.80 kg	+1	-1	-14	-12
Food consumption (%)	259 g/ dog/day	209 g/ dog/day	-72*	-55*	NE	NE	NE	NE	300 g	266 g	+6	-4	NE	NE

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Clinical observations														
Thin and/or dehydrated	-	+	+	+	+	+	+	+	-	-	-	-	+	+
Liquid, discolored, and/or nonformed feces	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Clear and/or cloudy discharge, eyes	+	+	+	+	+	+	+	+	-	+	-	+	+	+
Emesis	-	-	+	+	+	+	+	+	+	+	+	+	+	+
Hypoactive	-	-	+	+	+	+	+	+	-	-	-	-	+	+
Hematology[i]														
Erythrocyte count ($\times 10^6/\mu L$)	6.16	5.99	7.35*	7.20*	7.13*	7.40*	7.30	7.72	5.90	5.72	5.70	6.45	7.21	7.47
Hemoglobin (g/dL)	12.9	12.5	14.9*	14.7*	14.7*	14.8*	16.2	17.0	12.7	12.1	12.1	12.9	15.1	15.9
Hematocrit (%)	39.9	38.7	44.3*	45.3*	44.2*	45.6*	46.4	48.5	38.0	35.8	35.7	38.6	43.3	44.8
MCV (fL)	64.8	-	60.3*	-	62.0*	-	63.5	-	64.3	62.7	62.6	59.8	60.0	60.1
MCHC (g/dL)	32.3	-	33.8*	-	33.2	-	34.8	-	33.4	33.7	33.7	33.4	34.9	35.5
Reticulocyte count ($\times 10^3/\mu L$)	66.4	57.0	4.8*	7.3*	4.4*	6.8*	8.3	7.2	41.5	48.7	29.2	26.6	4.5	9.7
Lymphocyte count ($\times 10^3/\mu L$)	4.76	-	2.99*	-	2.87*	-	1.98	-	3.79	-	2.78	-	2.90	-

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Serum chemistry[j]														
Creatinine (mg/dL)	0.8	0.8	0.6*	0.7	0.6*	0.6*	0.5	0.6	0.8	0.8	0.8	0.9	0.7	0.7
Urea nitrogen (mg/dL)	17	-	8*	-	9*	-	10		11	11	12	12	10	10
Total protein (g/dL)	5.2	5.1	6.1	6.4*	6.2	5.7	6.1	6.1	5.4	5.4	5.5	5.2	6.2	5.4
Albumin (g/dL)	3.1	3.1	3.2	3.3	3.3	3.0	3.2	3.3	3.2	3.3	3.1	3.3	3.1	3.1
Globulin (g/dL)	2.2	2.1	2.9*	3.1*	2.9*	2.7*	3.0	2.8	2.2	2.1	2.4	2.0	3.1	2.3
Albumin-to-globulin ratio	1.4	1.5	1.1	1.1	1.2	1.1	1.1	1.2	1.5	1.6	1.3	1.7	1.0	1.3
Cholesterol (mg/dL)	198	197	309	337	326	280	342	289	178	184	182	159	332	254
AST (IU/L)	36	33	43	71*	45	70*	77	71	25	31	38	42	60	41
ALT (IU/L)	28	21	36	65*	44*	75*	63	78	26	19	30	30	59	56
Phosphorus (mg/dL)	8.8	8.0	6.2*	7.3	6.2*	5.8*	7.1	5.9	7.5	7.0	7.1	6.6	5.9	6.0
Chloride (mmol/L)	111	111	97*	105*	102*	103*	99	100	111	111	112	111	102	104
Sodium (mmol/L)	146	145	135*	141	137*	138*	130	130	145	145	146	146	135	135
Urinalysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Organ weights (%)[k]														
Spleen (g)	ND	ND	ND	ND	ND	ND	ND	ND	27.5	44.9	-22	-46	-31	ND
Thymus (g)	ND	ND	ND	ND	ND	ND	ND	ND	15.7	11.1	-46	-18	-46	ND
Gross pathology	-	-	-	-	-	-	-	-	-	-	-	-	-	-

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Histopathology;[l] No. evaluated	(5)	(5)	(3)	(3)	(2)	(2)	(5)	(4)	3	3	2	2	0	(1)
Bone, femur, atrophy primary spongiosa	(0)	(0)	(3)	(3)	(2)	(2)	(4)	(4)	0	0	0	0	0	(1)
Bone marrow, hypocellularity	(0)	(0)	(3)	(3)	(2)	(2)	(5)	(4)	0	0	0	0	0	(0)
Brain, gliosis and/or perivascular mononuclear cell infiltrate	(0)	(0)	(1)	(1)	(0)	(0)	(0)	(1)	1	0	0	0	0	(0)
Spinal cord, gliosis and/or perivascular mononuclear cell infiltrate	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(2)	0	0	0	0	0	(0)
Gallbladder, accumulation of secretion	(0)	(0)	(3)	(3)	(2)	(2)	(4)	(2)	0	0	0	0	0	(1)
Spleen, lymphocyte depletion/necrosis	(0)	(0)	(2)	(2)	(2)	(0)	(3)	(0)	0	0	0	0	0	(1)
Thymus, lymphocyte depletion/necrosis	(0)	(0)	(3)	(3)	(2)	(2)	(5)	(4)	0	0	0	0	0	(1)
Mesenteric lymph nodes, lymphocyte, depletion/necrosis	(0)	(0)	(2)	(2)	(2)	(0)	(5)	(3)	0	0	0	0	0	(1)
Stomach, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)	0	0	0	0	0	(0)

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Stomach, dilated glands with cell debris	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	0	0	0	0	0	(0)
Stomach, hemorrhage	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	0	0	0	0	0	(0)
Duodenum, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(0)	(0)	(1)	(1)	(0)	(1)	0	0	0	0	0	(0)
Duodenum, dilated glands with cell debris	(0)	(0)	(2)	(2)	(1)	(2)	(5)	(2)	3	2	1	1	0	(0)
Duodenum, inflammation, acute	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	0	0	0	0	0	(0)
Duodenum, hemorrhage	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	0	0	0	0	0	(0)
Jejunum, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(1)	0	0	0	0	0	(1)
Jejunum, dilated glands with cell debris	(0)	(0)	(1)	(0)	(0)	(0)	(3)	(0)	0	0	0	0	0	(0)
Jejunum, inflammation, acute	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	0	0	0	0	0	(0)
Jejunum, lymphocyte/macrophage, infiltrate	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	0	0	0	0	0	(0)

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Ileum, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(3)	(2)	(2)	(2)	(5)	(4)	0	0	0	0	0	(1)
Ileum, inflammation, acute	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(2)	0	0	0	0	0	(0)
Ileum, epithelium, necrosis	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	0	0	0	0	0	(0)
Ileum, epithelium, hyperplasia	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	0	0	0	0	0	(0)
Ileum, lymphocyte/macrophage, infiltrate	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	0	0	0	0	0	(0)
Colon, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(3)	(1)	(1)	(2)	(3)	(4)	0	0	0	0	0	(1)
Colon, dilated glands with cell debris	(0)	(0)	(1)	(0)	(1)	(0)	(3)	(1)	0	0	0	0	0	(0)
Colon, inflammation, acute	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(0)	0	0	0	0	0	(0)
Cecum, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(1)	(2)	(1)	(2)	(4)	(4)	0	0	0	0	0	(1)

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Cecum, dilated glands with cell debris	(0)	(0)	(1)	(1)	(1)	(1)	(4)	(2)	0	0	0	1	0	(0)
Cecum, inflammation, acute	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	0	0	0	0	0	(1)
Cecum, hemorrhage	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	0	0	0	0	0	(0)
Rectum, Peyer's patch, lymphocyte, depletion/necrosis	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(2)	0	0	0	0	0	(0)
Rectum, dilated glands with cell debris	(0)	(0)	(0)	(2)	(1)	(0)	(3)	(0)	0	1	0	0	0	(0)
Rectum, hemorrhage	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	0	0	0	0	0	(0)
Pancreas, acinar cell, vacuolization	(0)	(0)	(3)	(1)	(2)	(1)	(5)	(4)	0	0	0	0	0	(0)
Eye, keratitis	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	0	0	0	0	0	(0)
Post-dose evaluation: No. evaluated	0	0	0	0	1	1	0	1	0	0	0	0	2	1
Duodenum, dilated glands with cell debris	0	0	0	0	1	0	0	1	0	0	0	0	0	1
Cecum, dilated glands with cell debris	0	0	0	0	1	1	0	0	0	0	0	0	1	0

2.6.7.7E 14-Day Oral Gavage Toxicity and Toxicokinetic Study with XL184 in Dogs with a 28 Day Recovery Period (continued)

Daily Dose (mg/kg)	Phase 1								Phase 2[a]					
	0 (Control)[b]		100[c]		300[d]		1000[e]		0 (Control)		10		100[f]	
No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5	M:3	F:3	M:2	F:2	M:2	F:2
Cecum, jejunum, ileum, colon, Peyer's patch, lymphocyte depletion/necrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Spleen, thymus, mesenteric lymph node, lymphocyte, depletion/necrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pancreas, increased apoptosis	0	0	0	0	1	1	0	0	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NE, not evaluated; ND, not determined; U, unscheduled sacrifice.

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

* $P \leq 0.05$, Dunnett's Test. or two sample t-test.

a. Due to clinical signs of toxicity observed during the in-life period, dosing of the initial treatment cohorts (Phase 1) was terminated prior to 14 days and additional cohorts (Phase 2) were subsequently included in the study.

b. Dogs were dosed for 7 days due to clinical signs of toxicity, and then provided a 2-week non-dosing period prior to reassignment to Phase 2 cohorts (0 and 100 mg/kg/day).

c. Dogs were dosed for only 7 days due to clinical signs of toxicity.

d. Dogs were dosed for only 6 days due to clinical signs of toxicity; 1 male and 1 female were designated to receive a 4-week recovery.

e. Dogs were dosed for only 5 days due to clinical signs of toxicity; 1 males and 1 female were designated to receive a 4-week recovery.

f. Dogs were dosed for only 5 days due to clinical signs of toxicity, and then designated to receive a 4-week recovery; values presented reflect end of dosing data (except organ weight and histopathology).

g. Day 7 data for Phase 1 cohort (100 mg/kg/day).

h. At end of dosing or recovery period. For controls, group means are shown. For treated groups, percentage differences from time-matched control values are shown. Statistical significance is based on actual data (not on the percentage differences).

i. Day 6 data for Phase 1 cohort (1000 mg/kg/day) and Day 6, 7 and 34 for Phase 2 cohort (100 mg/kg/day).

j. Day 6 data for Phase 1 cohort (1000 mg/kg/day) and Day 6, 7 and 34 for Phase 2 cohort (100 mg/kg/day).

k. Both absolute and relative weights differed from controls in the direction indicated. Number indicates percentage difference for the absolute weights.

l. Number reflects scheduled sacrifice or (U) unscheduled sacrifice.

2.6.7.7F A Six Month Oral Toxicity Study with Recovery in Dogs

Report Title: XL184: A Six Month Oral Toxicity Study with Recovery in Dogs		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Dog/Beagle	Duration of Dosing: 180 Days	Study Number: [redacted] Study No. [redacted] (4.2.3.2-9)
Initial Age: Approx. 5.5-6 months	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: None		
No Observable Adverse Effect Level: 5.0 mg/kg/day		

Daily Dose (mg/kg)	0 (Control)		0.2		1.0		5.0	
No. of Animals	M:7	F:7	M:4	F:4	M:4	F:4	M:7	F:7
Toxicokinetics: AUC_{0-24} (ng·hr/mL)								
Day 1	ND	ND	309	206	1200	1408	4768	3323
Day 28	ND	ND	252	242	2244	1362	8251	3994
Day 180	ND	ND	285	323	2027	2012	7757	6327
Noteworthy findings:								
Died or sacrificed moribund	0	0	0	0	0	0	0	0
Body weight[a] (%)	11.2 kg	8.8 kg	-3	-4	-3	+7	-7	+2
Food Consumption[a] (%)	299 g/dog/day	259 g/dog/day	-1	+15	+8	-18	-11	-7
Clinical observations	-	-	-	-	-	-	-	-

2.6.7.7F A Six Month Oral Toxicity Study with Recovery in Dogs (continued)

Daily Dose (mg/kg)	0 (Control)		0.2		1.0		5.0	
No. of Animals	M:7	F:7	M:4	F:4	M:4	F:4	M:7	F:7
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology								
Eosinophil count ($\times 10^3/\mu L$)	0.249	0.336	0.243	0.188	0.260	0.218	0.120*	0.179
Serum chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-
Organ weights [a] (%)								
Testes (g)	13.61	NA	+2	NA	-18	NA	-33*	NA
Ovaries (g)	NA	1.53	NA	-41	NA	-34	NA	-54*
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology, no. evaluated	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Epididymides, oligospermia/germ cell debris, bilateral	0	NA	0	NA	1 (++)	NA	1 (++) 1 (+++)	NA
Testes, hypospermatogenesis, bilateral	0	NA	0	NA	1 (++)	NA	1 (+) 1 (+++)	NA
Ovaries, corpus luteum absent	NA	0	NA	2	NA	1	NA	2

2.6.7.7F A Six Month Oral Toxicity Study with Recovery in Dogs (continued)

Daily Dose (mg/kg)	0 (Control)		0.2		1.0		5.0	
No. of Animals	M:7	F:7	M:4	F:4	M:4	F:4	M:7	F:7
Post-dose evaluation: No. evaluated	M:3	F:3	M:0	F:0	M:0	F:0	M:3	F:3
Testes (g)	14.19	NA	NA	NA	NA	NA	-38*	NA
Ovaries (g)	NA	0.84	NA	NA	NA	NA	NA	+21
Epididymides, oligospermia/germ cell debris, bilateral	0	NA	NA	NA	NA	NA	1 (++)	NA
Testes, hypospermatogenesis, bilateral	0	NA	NA	NA	NA	NA	1 (++)	NA

AUC, area under the plasma drug concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male.; NA, not applicable

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

* $P \leq 0.05$, Dunnett's Test or Welch's t-test with a Bonferroni correction.

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).

2.6.7.7G XL184: A Six Month Oral Toxicity Study with Recovery in Dogs

Report Title: XL184: A Six Month Oral Toxicity Study with Recovery in Dogs		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Dog/Beagle	Duration of Dosing: 180 Days	Study Number: [redacted] Study No. [redacted] (4.2.3.2-10)
Initial Age: Approx. 5-6.5 months	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: None		
No Observable Adverse Effect Level: Not Determined		

Daily Dose (mg/kg)	0 (Control)		30 mg/kg × 10 days 11 Non-Dosing Days 20 mg/kg × 111 (M) or 161 (F) Days	
No. of Animals	M:4	F:4	M:6	F:6
Toxicokinetics: AUC_{0-24} (ng·hr/mL)				
Day 1	ND	ND	24900	34800
Day 22	ND	ND	18700	18400
Day 132 (M) or Week 26 (F)	ND	ND	18800	24800
Noteworthy findings:				
Died or sacrificed moribund	0	0	2	1
Body weight (%)[a]	9.17 kg	7.77 kg	-19*	-5

2.6.7.7G XL184: A Six Month Oral Toxicity Study with Recovery in Dogs (continued)

Daily Dose (mg/kg)	0 (Control)		30 mg/kg × 10 days 11 Non-Dosing Days 20 mg/kg × 111 (M) or 161 (F) Days	
No. of Animals	M:4	F:4	M:6	F:6
Food consumption (%)[a]	191 g/dog/day	193 g/dog/day	-64*	-37
Clinical observations				
Feces, soft	-	-	+	+
Lacrimation	-	-	-	+
Hair discolored, white	-	-	+	+
Skin, scabbed area	-	-	+	+
Skin discolored, gray	-	-	+	+
Ophthalmoscopy	-	-	-	-
Electrocardiography	-	-	-	-
Hematology				
Erythrocyte count ($\times 10^6/\mu L$)	7.39	7.50	6.37	7.14
Hemoglobin (g/dL)	17.05	17.13	14.60	15.90
Hematocrit (%)	50.40	51.15	43.95	47.92
Reticulocyte count ($\times 10^3/\mu L$)	27.73	57.76	10.38*	12.72*
Serum Chemistry				
AST (IU/L)	24.0	24.5	41.3	29.2
ALT (IU/L)	29.0	27.0	73.8	27.0
Total protein (g/dL)	5.88	5.98	4.53	4.68*

2.6.7.7G XL184: A Six Month Oral Toxicity Study with Recovery in Dogs (continued)

Daily Dose (mg/kg)	0 (Control)		30 mg/kg × 10 days 11 Non-Dosing Days 20 mg/kg × 111 (M) or 161 (F) Days	
No. of Animals	M:4	F:4	M:6	F:6
Albumin (g/dL)	3.18	3.15	2.05*	2.14*
Globulin (g/dL)	2.70	2.83	3.00	2.65
Albumin-to-globulin ratio	1.20	1.15	0.90	0.90
Urinalysis				
Proteinuria	-	-	+	-
Organ weights (%)[a]				
Testes (g)	11.4	NA	-58	NA
Ovaries (g)	NA	1.00	NA	-54
Gross pathology	-	-	-	-
Histopathology [b], no. evaluated	M:2	F:2	M:4	F:4
Testes, hypospermatogenesis, bilateral	-	NA	1 (+++), 1 (1) (++++)	NA
Ovaries, corpus luteum absent	NA	-	NA	3
Epididymides, oligospermia	-	NA	3	NA
Thymus, lymphoid depletion	-	-	1 (2) (+++)	(1) (+++)
Uterus, fewer glands	NA	-	NA	3 (NR)
Mammary, reduced glandular tissue	NA	-	NA	4 (NR)

2.6.7.7G XL184: A Six Month Oral Toxicity Study with Recovery in Dogs (continued)

Daily Dose (mg/kg)	0 (Control)		30 mg/kg × 10 days 11 Non-Dosing Days 20 mg/kg × 111 (M) or 161 (F) Days	
No. of Animals	M:4	F:4	M:6	F:6
Post-dose evaluation: No. evaluated	M:2	F:2	M:2	F:2
Body weight (%)[a]	9.80 kg	7.75 kg	-19	0
Food consumption (%)[a]	241 g/dog/day	229 g/dog/day	-21	+24
Clinical observations				
Lacrimation	-	-	-	+
Hair discolored, white	-	-	+	+
Skin, scabbed area	-	-	+	-
Skin, discolored, gray	-	-	+	+
Organ weights (%)[a]				
Testes (g)	16.3	NA	-63	NA
Ovaries (g)	NA	0.90	NA	-18
Gross pathology	-	-	-	-
Histopathology [b], no. evaluated	M:2	F:2	M:2	F:2
Testes, hypospermatogenesis, bilateral	-	NA	2 (+++)	NA

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the drug plasma concentration time curve; EtOH, ethanol; F, female; GLP, Good Laboratory Practice; M, male.; NA, not applicable; NR, not reported; U, unscheduled sacrifice.

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

* $P \leq 0.05$, 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 scheduled sacrifice or (U) unscheduled sacrifice.

2.6.7.8 *In Vitro* 遺伝毒性試験

2.6.7.8A *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with XL184

Report Title: *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with XL184			Test Article: XL184 (Lot No. [redacted])
Test for Induction of: Reverse mutation in bacterial cells		No. of Independent Assays: 2	Study Number: [redacted] Study No. [redacted] (4.2.3.3.1-2)
Strains: S. typhimurium and E. coli		No. of Replicate Cultures: 3	
Metabolizing System: Aroclor-induced rat liver S9		No. of Cells Analyzed/Culture: NA	
Vehicles:	For Test Article: DMSO	For Positive Controls: DMSO	GLP Compliance: Yes
Treatment: Plate incorporation for 52±4 hr			Date of Treatment: [redacted] 20[redacted]
Cytotoxic Effects: None			
Genotoxic Effects: None			

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay #1 TA98	Revertant Colony Counts TA 100	(Mean±SD) TA1535	TA1537	WP2*uvr*A
Without activation	DMSO	50 µL/plate	9±5	100±7	15±4	9±5	17±9
	XL184	33.3	14±2	75±8	17±5	8±3	10±2
		100	11±2	90±19	12±3	8±3	7±2
		333	6±2	78±15	8±3	7±2	5±2
		1000	8±7	73±21	9±6	3±1	6±3
		3330	2±1	65±14	8±1	3±1	4±1
		5000	1±0	43±9	7±3	2±2	3±2
	2-nitrofluorene	1	323±62				
	Sodium azide	2		987±102	700±33		
	ICR-191	2				530±79	
	4-nitroquinoline-N-oxide	1					309±42

2.6.7.8A Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with XL184 (continued)

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Revertant Colony Counts (Mean±SD) Assay #1 TA98	TA 100	TA1535	TA1537	WP2*uvr*A
With activation	DMSO	50 µL/plate	25±7	111±6	15±1	13±5	18±2
	XL184	33	23±4	119±9	14±4	11±1	14±5
		100	24±2	105±9	12±6	7±4	19±3
		333	23±3	113±10	11±3	11±3	16±6
		1000	14±2	107±4	9±4	5±1	9±1
		3330	8±3	86±8	5±2	4±2	8±2
		5000	4±3	86±4	8±1	2±2	5±1
	Benz(a)pyrene	2.5	477±16				
	2-amino-anthracene	2.5		1160±223	146±27	213±38	
	2-amino-anthracene	25					114±41

GLP, Good Laboratory Practice; NA, not applicable; SD, standard deviation.

2.6.7.8B XL184: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes

Report Title: XL184: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes			Test Article: XL184 (Lot No. [redacted])
Test for Induction of: Chromosome Aberrations		No. of Independent Assays: 2	Study Number: [redacted] Study No. [redacted] (4.2.3.3.1-4)
Strains: Primary human lymphocytes		No. of Replicate Cultures:2	
Metabolizing System: Aroclor-induced rat liver S9		No. of Cells Analyzed/Culture: 100	
Vehicles:	For Test Article: DMSO	For Positive Controls: DMSO	GLP Compliance: Yes
Treatment: Continuous treatment for 3 h with and without S9; cultures harvested ~22 h from initiation of treatment			Date of Treatment: [redacted] 20[redacted]
Cytotoxic Effects: Dose-related decreases in mitotic indices			
Genotoxic Effects: None			

Metabolic Activation	Test Article	Concentration or Dose Level (μg/mL)	Mitotic Index Reduction (% of Vehicle Control)	No. of Polyploid Cells/200 Cells Scored	No. of Endoreduplication Cells/200 Cells Scored	% Cells with Chromosome Aberrations	% Cells with Chromosome Aberrations + % Cells with Gaps
Without activation	DMSO	10 μL/mL	0	0.0	0.0	0.5	2.0
	XL184	180	45	0.0	0.0	1.5	1.5
		257	47	0.5	0.0	0.5	1.0
		368	40	0.5	0.0	0.5	2.0
		525	58	0.0	0.0	0.0	1.0
	Mitomycin C	1	-	0.0	0.0	19.3*	26.7
With activation	DMSO	10 μL/mL	0	0.0	0.0	0.0	0.5
	XL184	88.2	-	0.0	0.0	0.5	3.0
		126	4	1.0	0.0	1.0	4.0
		180	41	1.5	0.0	0.5	1.5
		257	46	0.5	0.0	0.5	2.5
	Cyclophosphamide	25.0	-	0.0	0.0	23.2*	38.6

GLP, Good Laboratory Practice. * Significantly greater than vehicle control, $P \leq 0.01$.

2.6.7.9 *In Vivo* 遺伝毒性試験

2.6.7.9A *In Vivo* Mouse Bone Marrow Micronucleus Assay

Report Title:XL184: In Vivo Mouse Bone Marrow Micronucleus Assay		Test Article: XL184 (Lot No. [redacted])
Test for Induction of: Bone marrow micronuclei	Treatment Schedule: One dose	Study Number [redacted] Study No. [redacted] (4.2.3.3.2-1)
Species/Strain: Mice/CD-1 (ICR)	Sampling Time: 24 and 48 h	
Age: Approx. 9 weeks	Method of Administration: Oral gavage	
Cells Evaluated: Polychromatic erythrocytes	Vehicle/Formulation: Aqueous solution or suspension	GLP Compliance: Yes
No. of Cells Analyzed/Animal: At least 2000 per mouse		Date of Dosing: [redacted] 20[redacted]
Special Features: Toxicokinetic cohorts (3 mice/dose level) for plasma exposure determination (1 h post-dose)		
Toxic/Cytotoxic Effects: None		
Genotoxic Effects: None		
Evidence of Exposure: Dose-related increase in exposure (mean±SD at 2000 mg/kg: 35,900±23,600 ng/mL)		

Test Article	Dose (mg/kg)	No. of Animals	Harvest Time	% Micronucleated PCEs (mean±SD)	Ratio PCE: NCE (mean±SD)
Vehicle control[a]	20 mL/kg	5 M	24 h post-dose	0.05±0.06	0.58±0.09
		5 M	48 h post-dose	0.04±0.04	0.60±0.10
Positive control cyclophosphamide	80	5 M	24 h post-dose	1.54±0.065*	0.73±0.15
XL184	500	5 M	24 h post-dose	0.03±0.03	0.71±0.13
	1000	5 M	24 h post-dose	0.04±0.04	0.75±0.12
	2000	5 M	24 h post-dose	0.05±0.04	0.73±0.14
	2000	5 M	48 h post-dose	0.00±0.00**	0.72±0.12

GLP, Good Laboratory Practice; M, male; NCE, normochromatic erythrocyte; PCE, polychromatic erythrocytes; SD, standard deviation.

* Significantly greater than corresponding vehicle control, $P \leq 0.01$.

** Significantly less than corresponding vehicle control, $P \leq 0.05$.

a. Vehicle (ethanol:polyethylene glycol 400: water, 5:45:50, v/v/v).

2.6.7.10 がん原性試験

2.6.7.10A 26-Week Oral Gavage Carcinogenicity Study with Cabozantinib (S)-Malate in 001178 T (Hemizygous) RasH2 Mice

Report Title: 26-Week Oral Gavage Carcinogenicity Study with Cabozantinib (S)-Malate in 001178 T (Hemizygous) RasH2 Mice		Test Article: XL184 (Lot No. [redacted])
Species/Strain: Mice, 001178-T (hemizygous) RasH2	Duration of Dosing: 26 Weeks	Study No. [redacted] Study No. [redacted] (4.2.3.4.2-1)
Initial Age: 10-11 weeks	Method of Administration: oral gavage	Location in CTD: Vol. Page
Date of First Dose: [redacted] 20[redacted]	Vehicle/Formulation: Ethanol (EtOH, 200 proof):polyethylene glycol (PEG) 400:reverse osmosis (RO) water, 5:45:50 (v:v:v).	
GLP Compliance: Yes	Treatment of Controls: 2 control groups: EtOH:PEG400:RO water, 5:45:50 (v:v:v) and RO water only	
Basis for High-Dose Selection: 15 mg/kg/day considered MTD in GLP 4-week repeat-dose toxicity study in RasH2 Mice (Exelixis Study No. XL184-NC-032)		
Special Features: Positive Control: N-methyl-N-nitrosourea (vehicle: acidified physiological saline (150 mM sodium chloride and 15 mM sodium citrate in RO water adjusted to pH 4.5±0.1 with 1 N hydrochloric acid) as a single 75 mg/kg IP dose on Day 1		

Daily Dose (mg XL184/kg/day)	0 (XL184 Vehicle Control)		2.0		5.0		15.0		75 mg/kg NMNU	
Gender	M	F	M	F	M	F	M	F	M	F
Toxicokinetics: AUC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Number of Animals At Start	25	25	25	25	25	25	25	25	20	20
Died/Sacrificed Moribund	1	3	0	5	1	0	9	3	16	15
Terminal Sacrifice	24	22	25	20	24	25	16	22	4	5

2.6.7.10A 26-Week Oral Gavage Carcinogenicity Study with Cabozantinib (S)-Malate in 001178 T (Hemizygous) RasH2 Mice (continued)

Daily Dose (mg XL184/kg/day)	0 (XL184 Vehicle Control)		2.0		5.0		15.0		75 mg/kg NMNU	
Gender	M	F	M	F	M	F	M	F	M	F
Survival (%) [a]	96	88	100	80	96	100	64	88	20	25
Body Weight (%)[a]	18%	14%	14%	8%	8%	5%	-4%*	-3%*	15%	22%
Food Consumption (%) [b]	-22%	22%	-18%	15%	-22%	-25%	-11%	-12%	0%	13%
Neoplastic Lesions/Tissue (No. of Animals with Neoplastic Lesion): [c]										
Carcinoma, squamous cell (malignant), tongue	0	0	0	1	0	0	0	0	NR	NR
Adenoma, bronchio-alveolar (benign), lung	1	2	2	0	1	0	0	0	NR	NR
Carcinoma, bronchio-alveolar (malignant), lung	2	0	1	0	0	0	0	2	NR	NR
Carcinoma, squamous cell (malignant), stomach (non-glandular)	1	0	0	0	0	0	0	0	6/16	1/14
Hemangiosarcoma (malignant), whole body	2	2	3	3	1	2	4	2	2	0
Lymphoma, (malignant), whole body	0	0	0	1	0	0	1	0	7	8
Sarcoma (malignant), skeletal muscle (# animals examined)	NA	NA	1 (1)	0 (2)	NA	NA	0 (1)	NA	NR	NR
Gross Pathology:										
Stomach, glandular region, raised area	0	0	0	0	0	1	0	2	NR	NR

2.6.7.10A 26-Week Oral Gavage Carcinogenicity Study with Cabozantinib (S)-Malate in 001178 T (Hemizygous) RasH2 Mice (continued)

Daily Dose (mg XL184/kg/day)	0 (XL184 Vehicle Control)		2.0		5.0		15.0		75 mg/kg NMNU	
Gender	M	F	M	F	M	F	M	F	M	F
Duodenum, large	0	0	0	0	0	0	2	0	NR	NR
Histopathology – Non-Neoplastic Lesions [c]										
Spleen, lymphocyte depletion, marginal zone, diffuse	0	0	0	0	0	0	4 (++) 12 (+++)	3 (++) 10 (+++)	NR	NR
Stomach, hyperplastic, epithelium, glandular region	0	0	0	0	0	0	4 (++)	5 (++) 2 (+++)	NR	NR
Duodenum, hyperplastic, epithelium, diffuse	0	0	0	0	0	0	2 (+++)	0	NR	NR
Pancreas, depletion, zymogen	0	0	0	0	0	0	4 (+) 1(++)	0	NR	NR

+, minimal; ++, slight; +++, moderate; GLP, good laboratory practice; MTD, maximum tolerated dose; NA, Not applicable; NC, not calculated; NMNU, N-methyl-N-nitrosourea; NR, incidence not specifically reported in positive control group.

Note: microscopic findings in animals given the positive control article reflected a clear carcinogenic response characterized by the occurrence of numerous neoplasms consistent with expected MNU-related neoplasms that included malignant lymphoma at multiple sites, squamous cell papilloma of the skin, squamous cell carcinoma of the nonglandular stomach (males: 6/16; females: 1/14), and papilloma of the nonglandular stomach (males: 10/16; females: 12/14). Neoplasms were present in all animals given the positive control article.

a. at terminal sacrifice (Day 183) or % difference (Day 183/Day 1).

b. % difference (Week 26-27/Week 1-2).

c. No. evaluated per group = 25, unless otherwise noted.

* $p<0.05$.

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats

2.6.7.10 Carcinogenicity

Report Title: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats

Test Article: XL184

Study No. [redacted]

Species/Strain: HSD:Sprague Dawley Rats
Initial Age: 6 to 7 weeks

Date of First Dose (Males): [redacted] 20[redacted]
Date of First Dose (Females): [redacted] 20[redacted]
Special Features: None

Duration of Dosing: up to 104 weeks
Method of Administration: Oral gavage
Vehicle Control Article: Ethanol (EtOH, 200 proof):polyethylene glycol (PEG) 400:reverse osmosis (RO) water, 5:45:50 (v:v:v)
Control Article: Reverse osmosis (RO) water

4.2.3.4.1-1
Location in CTD: Vol. Page

GLP Compliance: Yes

Sex	Male					Female				
Daily Dose (mg/kg/day)[a]	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Number of Toxicokinetic Animals	3	3	9	9	9	3	3	9	9	9
Dosing Phase										
Toxicokinetics:										
Week 3										
$AUC_{0\text{-last}}$ (ng·hr/mL)	LLOQ	LLOQ	1460	4440	16100	LLOQ	LLOQ	2310	6260	20500
C_{max} (ng/mL)	LLOQ	LLOQ	107	349	1400	LLOQ	LLOQ	119	364	1650
Week 26										
$AUC_{0\text{-last}}$ (ng·hr/mL)	LLOQ	LLOQ	2160	7140	22100	LLOQ	LLOQ	3530	10000	29600
C_{max} (ng/mL)	LLOQ	LLOQ	171	492	1530	LLOQ	LLOQ	203	766	1860
Noteworthy Findings:										
Died or Sacrificed Moribund	27	29	34	32	35	24	26	25	25	35
Survival to Terminal Sacrifice (%)[b]	47	42	32	37	0	52	48	51	50	30
Clinical Observations[c]										
Teeth, malocclusion	2	4	0	3	20	0	0	2	7	39
Teeth, missing	0	0	0	2	4	0	0	0	0	11
Teeth, white appearance	0	0	0	0	8	0	0	0	0	49
Feces, liquid	2	0	4	4	13	1	0	5	2	8
Feces, nonformed	21	2	38	28	26	2	0	30	44	26
Appearance, thin	3	3	8	5	12	3	8	6	3	7

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Body Weight (%)[d,e]										
Week 94	566 g	6.5*	0.9	-1.2	-8.7*	338 g	4.7	-1.5	-3.8	-8.6
Week 98	563 g	6.6	1.2	-3.2	NA	340 g	4.7	-1.8	-3.8	-7.4
Week 105	518 g	7.3	1.5	-4.2	NA	NA	NA	NA	NA	NA
Food Consumption (%)[d,f]										
Week 10 to 11	-	-	-	-	-	15 g	0.0	-6.7	-6.7	-13.3*
Week 11 to 12	-	-	-	-	-	16 g	-6.3	-12.5	-12.5	-12.5*
Week 13 to 14	-	-	-	-	-	16 g	-6.3	-12.5*	-6.3	-12.5*
Week 21 to 22	-	-	-	-	-	16 g	-6.3	-12.5*	-6.3	-12.5*
Week 33 to 34	-	-	-	-	-	15 g	0.0	0.0	0.0	-13.3*
Week 41 to 42	-	-	-	-	-	15 g	0.0	-6.7	0.0	-13.3*
Week 45 to 46	-	-	-	-	-	15 g	6.7	-6.7	0.0	-6.7*
Week 49 to 50	-	-	-	-	-	15 g	6.7	0.0	0.0	-6.7*
Week 53 to 54	-	-	-	-	-	15 g	0.0	-6.7	-6.7	-6.7*
Mass Observations[g]	-	-	-	-	-	-	-	-	-	-
Clinical Pathology	-	-	-	-	-	-	-	-	-	-
Macroscopic Observations										
Kidney, discolored	1	2	6	3	9	1	0	0	1	4
Tooth, discolored, other	0	0	0	0	5	0	0	0	0	28
Tooth, discolored, upper	0	0	0	0	0	0	0	0	0	1
Tooth, discolored, lower	0	0	0	0	0	0	0	0	0	1
All teeth, discolored	0	0	0	0	5	0	0	0	0	30
Uterus, abnormal contents	NA	NA	NA	NA	NA	8	0	3	5	15
Uterus, large	NA	NA	NA	NA	NA	5	0	6	5	16

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Neoplastic Lesions										
Adrenal Gland, Medulla										
Benign Pheochromocytoma	11	12	19	17	24	6	4	4	11	13
Malignant Pheochromocytoma	3	2	3	2	4	1	0	0	0	0
Complex Malignant Pheochromocytoma	0	0	1	0	0	0	0	0	0	1
Hyperplasia	9	9	10	8	8	6	2	10	11	14
Nonneoplastic Findings										
Kidney										
Cyst	3	2	13	10	13	0	0	0	0	2
Vacuolation, tubule cell										
Minimal	0	0	1	0	1	0	0	1	0	0
Slight	1	0	7	4	7	0	0	0	0	0
Moderate	0	0	2	1	1	0	0	0	0	0
Marked	0	0	0	1	0	0	0	0	0	0
Nephropathy, chronic progressive										
Minimal	3	2	0	0	3	19	38	30	24	16
Slight	9	12	9	8	2	20	9	10	17	13
Moderate	18	18	15	11	12	1	0	5	5	5
Marked	19	16	15	20	16	1	0	0	2	7
Severe	1	2	10	10	16	0	0	0	0	0
Mineralization										
Minimal	3	1	0	2	0	5	4	2	4	7
Slight	0	0	2	2	1	1	0	0	1	5
Moderate	0	0	0	0	1	0	0	0	0	1
Mineralization, pelvis										
Minimal	0	0	0	0	0	8	15	6	8	9
Slight	0	0	0	0	0	4	1	5	3	5

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Moderate	0	0	0	0	0	1	0	1	0	9
Tooth, Other (Incisors)[h]										
Degeneration/necrosis, odontoblasts										
Minimal	10	13	6	7	4	2	0	NA	1	3
Slight	1	1	9	8	12	0	0	NA	0	12
Moderate	0	0	0	2	11	0	0	NA	0	12
Marked	0	0	0	0	2	0	0	NA	0	6
Degeneration/necrosis, enamel organ										
Minimal	0	0	2	3	6	0	0	NA	0	11
Slight	0	0	0	1	4	0	0	NA	0	15
Moderate	0	0	0	0	3	0	0	NA	0	4
Marked	0	0	0	0	0	0	0	NA	0	1
Alteration, dentin matrix										
Minimal	4	3	6	6	6	0	0	NA	0	7
Slight	1	0	5	5	7	0	0	NA	0	7
Moderate	0	0	1	1	10	0	0	NA	0	12
Marked	0	0	0	0	2	0	0	NA	0	8
Femur										
Trabecular thickness, increased										
Minimal	5	14	7	6	9	20	8	6	17	14
Slight	1	1	0	0	2	5	1	10	7	9
Moderate	0	0	0	0	0	0	0	1	0	5
Sternum										
Trabecular thickness, increased										
Minimal	6	3	7	14	25	10	4	16	21	17
Slight	0	0	0	0	12	4	0	17	11	17
Moderate	0	0	0	0	1	0	0	2	0	5

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Liver										
Karyomegaly/multinucleated hepatocytes										
Minimal	0	0	0	0	0	0	1	0	1	8
Slight	0	0	0	0	0	0	0	0	3	2
Moderate	0	0	0	0	0	0	0	0	2	0
Pigment										
Minimal	4	1	2	1	2	6	8	6	8	4
Slight	0	0	0	0	0	1	1	2	4	5
Moderate	0	0	0	0	1	0	1	1	2	13
Marked	0	0	0	0	0	0	1	0	1	7
Severe	0	0	0	0	0	0	0	0	0	2
Uterus										
Dilation										
Minimal	NA	NA	NA	NA	NA	1	0	1	0	0
Slight	NA	NA	NA	NA	NA	3	0	1	1	0
Moderate	NA	NA	NA	NA	NA	3	4	1	2	6
Marked	NA	NA	NA	NA	NA	3	0	3	4	10
Severe	NA	NA	NA	NA	NA	2	0	2	1	1

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Stomach, Glandular										
Inflammation, vessel										
Minimal	0	5	1	1	1	1	0	0	0	2
Slight	0	1	1	1	0	1	0	0	1	4
Moderate	1	2	1	0	0	0	0	0	2	1
Marked	0	0	0	0	0	0	0	1	0	0
Mineralization										
Minimal	0	0	0	0	1	0	1	0	0	1
Slight	0	0	0	1	1	0	0	0	0	3
Moderate	0	0	2	0	3	0	0	0	0	0
Marked	0	0	0	1	1	0	0	0	0	1
Tongue										
Inflammation, vessell										
Minimal	1	3	5	7	2	1	0	1	1	5
Slight	4	6	4	6	7	0	0	1	4	3
Moderate	2	3	2	4	5	0	0	0	3	2
Marked	1	1	0	0	1	0	0	1	0	0
Mineralization, vessel										
Minimal	6	5	8	8	12	4	0	4	6	10
Slight	2	0	0	1	1	1	0	0	0	7
Moderate	0	0	0	0	1	0	0	0	0	3

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Lymph Node, Mesenteric										
Inflammation, vessel										
Minimal	0	1	0	0	2	0	0	0	0	2
Slight	2	0	1	1	1	0	0	0	3	2
Moderate	0	0	0	4	3	0	0	0	0	2
Marked	1	0	0	0	1	0	0	0	0	1
Severe	0	0	0	0	0	0	0	1	1	0
Mineralization										
Minimal	0	0	0	0	1	0	0	0	0	1
Slight	2	0	1	1	3	0	0	0	0	7
Moderate	0	0	2	0	4	0	0	0	0	11
Marked	0	0	0	0	3	0	0	0	1	0
Testis										
Inflammation, vessel										
Minimal	1	1	1	2	2	NA	NA	NA	NA	NA
Slight	3	5	13	8	8	NA	NA	NA	NA	NA
Moderate	4	6	5	9	12	NA	NA	NA	NA	NA
Marked	1	5	3	4	6	NA	NA	NA	NA	NA
Severe	0	1	0	1	0	NA	NA	NA	NA	NA
Duodenum										
Inflammation, vessel										
Minimal	0	1	0	1	1	1	0	0	1	3
Slight	0	0	0	0	0	0	0	0	2	2
Moderate	0	0	0	0	0	0	0	0	0	1

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Colon										
Inflammation, vessel										
Minimal	0	3	0	1	2	0	0	1	1	0
Slight	0	2	0	0	4	1	0	1	3	4
Moderate	0	0	0	1	0	0	0	0	1	3
Marked	1	0	0	0	0	0	0	0	0	0
Cecum										
Inflammation, vessel										
Minimal	0	1	1	5	2	0	0	0	2	3
Slight	1	2	0	0	7	0	0	3	2	5
Moderate	0	1	0	1	0	0	0	0	2	2
Marked	0	1	0	0	0	0	0	0	0	0
Rectum										
Inflammation, vessel										
Minimal	0	0	1	0	2	0	0	0	0	0
Slight	0	4	0	2	3	1	0	1	2	0
Moderate	1	3	0	0	1	0	0	1	1	5
Marked	0	1	0	0	0	0	0	1	3	2
Pancreas										
Inflammation, vessel										
Minimal	0	2	1	1	4	0	0	0	1	1
Slight	0	2	0	1	5	0	0	0	2	0
Moderate	1	2	2	3	0	1	0	0	2	4
Marked	0	1	0	0	0	0	0	1	1	1
Severe	0	1	0	0	0	0	0	0	0	0

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

Sex	Male					Female				
Daily Dose (mg/kg/day)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)	0 (Control 1)	0 (Control 2)	0.1 (Low)	0.3 (Mid)	1.0 (High)
Number of Carcinogenicity Animals at Study Start	50	50	50	50	50	50	50	50	50	50
Histopathology										
Number of Animals Examined	50	50	50	50	50	50	50	50	50	50
Nonneoplastic Findings (continued)										
Muscle, Biceps Femoris										
Degeneration										
Minimal	7	4	4	3	2	0	3	0	0	0
Slight	4	4	1	1	1	1	0	0	0	0
Moderate	1	1	0	0	0	0	0	0	0	0
Eye										
Hypertrophy/hyperplasia, corneal epithelium										
Minimal	6	4	3	0	3	0	0	0	0	0
Slight	8	7	6	4	0	0	0	0	0	0
Moderate	2	6	2	2	2	0	0	0	0	0
Marked	1	1	0	1	1	0	0	0	0	0
Inflammation, cornea										
Minimal	7	6	2	3	0	0	0	0	0	0
Slight	9	7	4	1	4	0	0	0	0	0
Moderate	2	5	4	2	2	0	0	0	0	0
Marked	0	0	2	0	0	0	0	0	0	0
Vascularization, cornea										
Minimal	1	2	1	2	0	0	0	0	0	0
Slight	10	5	7	1	1	0	0	0	0	0
Moderate	5	9	5	1	3	0	0	0	0	0

2.6.7.10B 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats (continued)

- = No noteworthy findings; $AUC_{(0\text{-last})}$ = Area under the plasma concentration-time curve from time 0 to 24 hours postdose; C_{max} = Maximum observed XL184 concentration; GLP = Good Laboratory Practices; LLOQ = Lower Limit of Quantitation; NA = Not applicable.

* = Statistically significant based on actual data (not on percent difference); $p \leq 0.05$.

a. Animals in Group 1 were dosed with the vehicle control article only; animals in Group 2 received the control article.

b. Adjusted for accidental deaths. Surviving Group 5 males were sacrificed on Day 669 (Week 96), all females were sacrificed on Day 690 (Week 99), and all surviving males were sacrificed on Day 729 (Week 105).

c. Clinical observations are presented as the number of animals affected.

d. For controls, group means are shown. For treated groups, percent difference from controls is shown.

e. Body weights shown are the % difference from controls at the respective sacrifices (see footnote b).

f. Food consumption intervals that were statistically significant compared with controls are presented.

g. No differences in the incidence of masses were noted during palpable mass examinations.

h. Teeth were not examined for females administered 0.1 mg/kg/day.

2.6.7.11 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)	Gestation Days 6-17	0, 0.03, 0.1, 0.6, 1, 2.5, 5, 7.5	6 F	≥ 5 mg/kg/day: maternal toxicity (decreased maternal body weight, decreased food consumption, lethality) ≥ 1 mg/kg/day: decreased embryo/fetal viability (100% implantation loss) 0.6 mg/kg/day: decreased embryo/fetal viability (16.6% postimplantation loss and external malformations) 0.1 mg/kg/day: embryo/fetal NOAEL	4.2.3.5.2-1
Rabbit/Hra (NZW) SPF	Oral gavage (EPW)	Gestation Days 7-20	0, 0.5, 2.5, 7.5, 15, 30	6 F	≥ 7.5 mg/kg/day: maternal toxicity (decreased maternal body weight, decreased food consumption, lethality); decreased fetal viability ≥ 2.5 mg/kg/day; decreased fetal weights; increased fetal soft tissue variations 0.5 mg/kg/day: fetal NOAEL	4.2.3.5.2-3

EPW, ethanol: polyethylene glycol 400: water, 5:45:50 (v/v/v); F, female; NOAEL, no observable adverse effect level; NZW, New Zealand white; SD, Sprague Dawley; SPF, specific pathogen free.

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

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

Report Title: Oral Gavage Study of Fertility, Early Embryonic Development to Implantation, and Toxicokinetics with XL184 in Rats			Test Article: XL184 (Lot No. [redacted])	
Design similar to ICH 4.1.1? Yes	Duration of Dosing: M:10 week minimum (28 days prior to mating and throughout mating period); F: at least 14 days prior to mating, throughout the mating period, and through Gestation Day 7		Study Number: [redacted] Study No. [redacted] (4.2.3.5.1-1)	
Species/Strain: Rat/Crl:CD(SD)	Day of Mating: Day 0			
Initial Age: 9 weeks	Day of C-Section: Gestation Day 13			
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral gavage		GLP Compliance: Yes	
Special Features: Sperm count and motility	Vehicle/Formulation: ethanol:polyethylene glycol 400:water (5:45:50, v/v/v)			
No Observable Adverse Effect Level: F_0 Males: 1 mg/kg/day F_0 Females: 2.5 mg/kg/day F_1 Litters: <1 mg/kg/day				
Daily Dose (mg/kg)	0 (Control)	1	2.5	5.0
Males, no. evaluated	N = 22	N = 22	N = 22	N = 22
Toxicokinetics: AUC_{0-24} (ng·hr/mL)				
Day 1	ND	10700	25700	50800
Day 28	ND	17200	40600	102000
Day 70	ND	20700	52600	ND[a]
No. died or sacrificed moribund	0	0	2	22