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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203,756
Supporting document/s:	IND (b) (4) IND (b) (4) IND 113,446
Applicant's letter date:	May 29, 2012
CDER stamp date:	May 29, 2012
Product:	Cabozantinib (S)-malate (Cometriq)
Indication:	Medullary Thyroid Cancer (MTC)
Applicant:	Elelixis, Inc., San Francisco, CA
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 2)
Reviewer:	Margaret Brower, Ph.D.
Supervisor/ Team Leader:	Whitney S. Helms, Ph.D.
Division Director:	John K. Leighton, Ph.D. DABT (Patricia Keegan, M.D.)
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1 Executive Summary

1.1 Introduction

NDA 203,756 has been submitted as a full New Drug Application (NDA) for cabozantinib, indicated for the treatment of patients with medullary thyroid cancer. Cabozantinib is a new molecular entity that is a kinase inhibitor with activity at multiple kinases including RET kinase, mesenchymal epithelial transition factor (MET), and vascular endothelial cell growth factor receptors (VEGFR). The proposed clinical dose of 140 mg (freebase equivalent weight) is administered orally as a capsule once daily. Nonclinical pharmacology, pharmacokinetic, and toxicology studies have been submitted to support the approval of cabozantinib for the proposed indication.

1.2 Brief Discussion of Nonclinical Findings

Cabozantinib is a small molecule tyrosine kinase inhibitor (TKI) which primarily targets RET kinase, mesenchymal epithelial transition factor (MET), and the vascular endothelial cell growth factor receptor 2 (VEGFR2) with *in vitro* IC_{50} values of 9.8, 1.8, and 0.035 nM, respectively. Two additional VEGF receptor kinases (VEGFR1 and VEGFR3) have also found to be inhibited with IC_{50} values of 12.2 and 6.0 nM. Additional targets include FLT3, TIE2, AXL, TRKB, and KIT with IC_{50} values of 14.4, 14.3, 7.7, and 4.6 nM, respectively. In mouse xenograft models, treatment with XL184 was found to inhibit RET phosphorylation in medullary thyroid cells in a dose-dependent manner, with maximal inhibition (84 and 89%) at doses of 100 and 300 mg/kg, respectively. Multiple murine tumor models were examined in an attempt to define the activity of XL184, including tumor growth inhibition, tumor cell metastasis, and survival. Rodents implanted with cell lines C6 (rat glioma), MDA-MB-231 (human breast carcinoma), H441 (human lung carcinoma), and TT (human MTC) were studied. In each of the tumor models, significant tumor growth inhibition (TGI) and/or tumor regression was observed; histological evaluation of tumor tissue following XL184 treatment indicated a decrease in microvessel density. The N-oxide and acid metabolites of XL184 (EXEL-5162 and EXEL-5366) were significantly less active against primary targets of XL184 in biochemical and cellular assays when compared to the parent drug. The pharmacological activity of other XL184 metabolites was not determined.

XL184 did not inhibit hERG channel activity when tested at concentrations of 1, 10, and 30 μM in safety pharmacology studies. In dogs, XL184 administered at 150 or 1000 mg/kg had no effect on cardiovascular parameters. In agreement with these safety pharmacology studies, cardiovascular toxicity was not commonly observed in rodents or non-rodents administered cabozantinib for up to 6 months, although, cardiac inflammation was noted in a single female dog administered 20 mg/kg for the 6 month period. In other safety pharmacology studies in rats, behavioral and physiological changes were not observed following single doses of XL184 up to 300 mg/kg. In a separate study, a single dose of 900 mg/kg XL184 to conscious rats had no effects on respiratory parameters.

The parent drug cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* rat micronucleus assay. Six process impurities and two metabolites were assayed for mutagenicity, but were not tested for induction of chromosomal aberrations.

Neither the process impurities [redacted] (b) (4) nor the XL184 N-oxide and EXEL-5366 metabolites were found to be mutagenic. Four of the six process impurities in the drug substance were identified as genotoxic: [redacted] (b) (4) The proposed release/stability acceptance criteria for [redacted] (b) (4) are [redacted] (b) (4), respectively, for drug substance, and [redacted] (b) (4), respectively, for drug product. Based on XL184 lot #0804672, used for clinical and nonclinical studies, the previous clinical intake of these impurities on a daily basis exceeded the expected intake at the proposed limits. At the specification proposed, none of the impurities exceeds an intake of (b) (4) µg/day at the recommended dose of cabozantinib. The (b) (4) µg intake level represents a low safety risk in this patient population; the currently proposed acceptability criteria for the genotoxic impurities present in cabozantinib are, therefore, considered acceptable.

It should be noted that as a result of revised purity/impurity methodology, the Applicant has indicated that stability specifications of genotoxic and non-genotoxic impurities will equal release specifications. The proposed release/stability specification of a single non-genotoxic impurity ([redacted] (b) (4) is [redacted] (b) (4), which exceeds the ICH Q3B(R2) qualification threshold. Based on a nonclinical lot tested in the 6-month repeat-dose toxicology study in dogs, the clinical intake of the impurity at this limit is qualified.

Pharmacokinetics of cabozantinib were studied in mice, rats, dogs, and monkeys. In patients treated with 175 mg XL184 L-malate capsules, the C_{max} (Day 19) was 2220 ng/mL, with an AUC of 37850 ng·h/mL (Day 19); the plasma half-life was approximately 55 hours, with time to steady state at 15 days following daily dosing. Cabozantinib was well absorbed in animal models, as well as humans. Drug accumulation was observed over time following 6 months of repeat dose administration in rats and dogs. Pharmacokinetics in dogs were more similar to those seen clinically with drug half lives between 6 and 7 hours. In patients administered cabozantinib, systemic exposures were generally dose proportional over 5 days of administration with plasma drug accumulation between 4.7 to 6.9 fold.

Distribution studies in rats showed that high concentrations of cabozantinib were found at early time points in GI contents and bile, liver, adrenal gland, adipose tissue, and stomach. At later time points, concentrations were high in the eye and small intestine. Interestingly, only selective tissues were also target sites of toxicity. Even though the drug was found to accumulate in the eye and eye uveal tissue, no associated ocular toxicity findings have been observed clinically or nonclinically, with the exception of ocular keratitis in dogs administered toxic levels of XL184 (100 to 1000mg/kg, Study XL184-NC-006). Disposition studies indicated elimination primarily in the feces (82-85%) with 9-12% in urine following oral administration.

The pharmacokinetics of XL184 and selected metabolites M1 (XL184-N-oxide), M4 (XL184-monohydroxy-sulfate), M8 (XL184-amide cleavage product), and para-fluoroaniline (pFA) were compared in rats and dogs administered XL184 in repeat-dose rat and dog studies and humans administered a single 175 mg oral dose of XL184 in the healthy volunteer mass balance study XL184-012. When measured quantitatively using validated LC-MS/MS, dogs and rats were exposed to the 4 metabolites at low levels compared to human exposure. The mean percentage AUC of metabolite relative to AUC of XL184 in humans was 43% for M4, 15% for M1, and 10% for M8. The pFA level was below the limit of quantitation. The primary isozyme for drug metabolism is CYP3A4; XL184 inhibits the enzymatic activity of CYP2C8, CYP2C9 and CYP2C19. Concomitant strong inducers of inhibitors of CYP3A4 should be used with caution,

as well as substances that induce, inhibit, or are substrates of CYP2C8, CYP2C9, and CYP2C19. Cabozantinib is highly bound to human plasma proteins *in vitro.*

Target organs of cabozantinib-mediated toxicity in rats and dogs dosed up to 6 months included the gastrointestinal tract, reproductive system, kidney, liver/gall bladder, hematopoietic/lymphoid system, endocrine tissues, skin, and dentin. Target organs and dose limiting toxicities were generally consistent for shorter and longer periods of dosing. With the exception of reproductive toxicity (which has not been studied in humans), all other targets have also been noted clinically.

Gastrointestinal toxicity was observed in rodents and non-rodents administered cabozantinib for 14 days. Marked gastrointestinal histopathology (necrosis and degeneration of all organs of the gastrointestinal tract) was exhibited in rats administered doses ≥5 mg/kg, and in dogs administered doses ≥100 mg/kg, with significant associated systemic toxicity (emesis, hypoactivity, anorexia, dehydration, decreased body weight, and moribund sacrifice). Histological findings were reversible following recovery in rats, but not in dogs. Gastrointestinal histopathology was not observed at doses studied in the 6-month studies in either species even though exposures in rats based on AUC were 0.7 to 1.2-fold those measured in patients administered 175 mg XL184 daily, with reported nausea, diarrhea, emesis, mucositis, GI perforation, GI fistula, and GI ulcers. Dogs administered ≥20mg/kg/day for 6 months exhibited clinical signs of gastrointestinal toxicity (depressed food consumption and body weight, emaciation, dehydration, and abnormal feces), but correlating gastrointestinal histopathology (rectal hemorrhage) in only a single female decedent. Gastrointestinal tract toxicity is a pharmacological class finding of VEGF inhibitors, which may reflect the role of VEGF in maintaining mucosal homeostasis. Hematopoietic and immunological findings, characterized by dose-related red and white cell depletion, hypocellularily in bone marrow and lymphoid depletion and necrosis of the thymus, spleen, mesenteric lymph nodes and gastrointestinal tract was primarily observed in rats administered higher doses of cabozantinib (≥5 mg/kg). Hematopoietic depletion was observed in dogs administered ≥20 mg/kg/day, although associated immunological depletion and histopathology as described above was reported at doses ≥100 mg/kg.

Rats administered 5 mg/kg cabozantinib for 14 days exhibited renal degeneration. When rats were dosed for 6 months, chronic progressive nephropathy with bilateral hydronephrosis was observed at doses ≥0.1 mg/kg, and persisted following recovery. Dogs were less sensitive, and the incidence and severity of renal toxicity in dogs was less pronounced compared to rodents. Renal degeneration was observed in a single male administered 5 mg/kg cabozantinib for 6 months, and mineralization of the kidney was observed in 3 of 3 female dogs administered 30/20mg/kg cabozantinib in a 2nd 6-month repeat dose study. Elevated urinary proteins have been seen clinically in patients in the XL184-301 Phase 3 trial.

Cabozantinib-related hepatotoxic changes were generally reflective of treatment-related systemic toxicity in rats and dogs, characterized by significant elevations in liver enzymes; similar increases have been noted clinically. Liver hypertrophy was observed in rats administered doses of 1 to 15 mg/kg cabozantinib for 14 days. Adverse liver findings were not observed histologically in rats following 6 months of dosing, although liver enzymes were increased at all doses studied (0.1 to 1 mg/kg/day). Endocrine tissue toxicity was primarily exhibited as adrenal gland changes in rats administered doses of 5 and 15 mg/kg for 14 days in two separate studies. Adrenal necrosis was dose related, but was not observed in surviving animals following recovery. Degeneration and necrosis of the pancreas and pituitary observed in rats was considered to be secondary to general drug-related systemic, or adrenal changes,

respectively. Thyroid findings were not observed in animal models; altered thyroid indices have been reported with other multi-kinase RTK inhibitors, and would be an expected finding of cabozantinib.

In contrast to other VEGF inhibitors, changes in epiphyseal growth plates were not observed following treatment with cabozantinib, although atrophy of the femur was observed in dogs administered doses ≥100 mg/kg/day for 14 days; this finding was not observed following recovery, and was considered to be secondary to the systemic toxicity observed in these animals. Changes in dentin (broken teeth, whitening of teeth) were observed in rats dosed for 6 months; the incidence of these changes was highest in female rats administered XL184 at the 1 mg/kg dose level, and increased with prolonged exposure. Changes in tooth appearance (malocclusion, excessively long, white teeth curved upward) were also observed in the fertility study in male and female rats administered 1 to 5 mg/kg/day. Cutaneous toxicity was observed only in dogs administered 20 mg/kg/day for 6 months. Gray skin (exhibited on the nose, lips, and eyelids), and white haircoat hypopigmentation was not resolved following recovery. These findings were not associated with a microscopic correlate, although a dermal histopathologic hyperkeratosis, hyperplasia and exudate was noted in these animals. Changes in skin and hair appearance have been reported in patients administered cabozantinib (e.g. pigmentary changes, pruritis, dry skin), and are consistent with skin reactions observed with other VEGF inhibitors. Drug-related phototoxicity was not observed *in vitro*.

Male and female fertility may be compromised with XL184 treatment. These findings are consistent with the pharmacologic effects of XL184, and the inhibition of VEGF-induced angiogenesis.

Reproductive and developmental toxicology studies were conducted in rats and rabbits to assess the effects of XL184 on fertility and embryofetal development. In the rodent fertility study, there was a total loss of fertility at doses ≥2.5mg/kg/day (approximately 1.5 times the human exposure by AUC at the recommended dose); at this dose male rats administered XL184 exhibited dose related reduction in reproductive organ weights with correlative reductions in sperm counts and concentration and females exhibited prolongation of diestrus. Increased pre- and post-implantation loss and reduction in the number of viable fetuses was also observed in females administered 1mg/kg cabozantinib daily (approximately 0.58 times the human exposure by AUC at the recommended dose). Effects on male and female reproductive organs were also observed following repeat dose administration of 6 months in dogs of both genders. Dogs were the more sensitive species; the lowest dose which resulted in adverse findings in reproductive organs of males and females (hypospermatogenesis and absence of corpora lutea) was 1 mg/kg/day. Rats administered doses of cabozantanib up to 1 mg/kg/day for 6 months did not exhibit reproductive findings, although ovarian necrosis was observed in females administered 5 mg/kg/day for 14 days. Male and female fertility may be compromised with XL184 treatment. These findings are consistent with the pharmacologic effects of XL184, and the inhibition of VEGF-induced angiogenesis.

Administration of XL184 to pregnant rats during the period of organogenesis resulted in embryo-fetal lethality at doses ≥0.03mg/kg/day as evidenced by increased implantation loss, and increased intrauterine deaths ($AUC_{0\text{-}48h}$ = 168ng.h/mL; <1% of clinical steady-state plasma exposures). Cardiac anomalies (septal defects of the ventricle) were observed at 0.01 and 0.1mg/kg and the total number of skeletal variations were significantly increased in XL184 fetuses compared to controls in the absence of maternal toxicity. XL184 administration to pregnant rabbits during the period of organogenesis resulted in limited signs of maternal toxicity and embryo-fetal viability, but the incidence of visceral variation and malformations was

increased in F_1 fetuses, including splenic size reduction and missing lung lobe at 3mg/kg (approximately 0.11 times the exposure by AUC at the recommended human dose). XL184 caused embryo-fetal toxicities in rat and rabbit models at maternal exposures significantly lower than the equivalent human exposure at the recommended dose of 140 mg/day. Prenatal/postnatal development studies have not been conducted; (b) (4) Though the Applicant proposed Pregnancy Category (b) (4), based on their interpretation of the animal data, the reproductive and developmental toxicology studies suggest that administration of cabozantinib may impair fertility and pose a risk for fetal toxicity. Pregnancy category D is recommended.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. The non-clinical studies submitted to this NDA provide sufficient information to support the use of cabozantinib in the treatment of progressive metastatic medullary thyroid cancer.

1.3.2 Additional Non-Clinical Recommendations

Based on the expected extended survival (5 years or longer after first exposure to cabozantinib), and extended dosing duration of the medullary thyroid cancer patient population, carcinogenicity studies will be required for cabozantinib. In general, carcinogenicity is a safety concern with chronic drug exposure. In addition, cabozantinib is a kinase inhibitor, and other kinase inhibitors have demonstrated carcinogenicity in nonclinical carcinogenicity studies. Based on these considerations, two rodent carcinogenicity studies, a long-term (2-year) rat study and a mouse study, need to be conducted to assess the carcinogenic potential for cabozantinib.

Based on the expected extended survival, and extended dosing duration of this patient population, as well as the pharmacological mechanism of action (e.g. inhibition of MET and VEGF pathways which may result in altered bone development in neonates), a pre/post-natal developmental toxicity study will need to be conducted with cabozantinib. Cabozantinib has been reported to cause osteonecrosis of the jaw in patients administered the drug at 175mg/day. (b) (4)

The clinical level of the M4 metabolite (monohydroxy sulfate) significantly exceeds the level of exposure of this metabolite in animal models. An *in vitro* mutagenicity assay will be required to determine the genetic toxicity of this metabolite.

1.3.3 Labeling

A separate labeling review will be provided.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number: 1140909-48-3

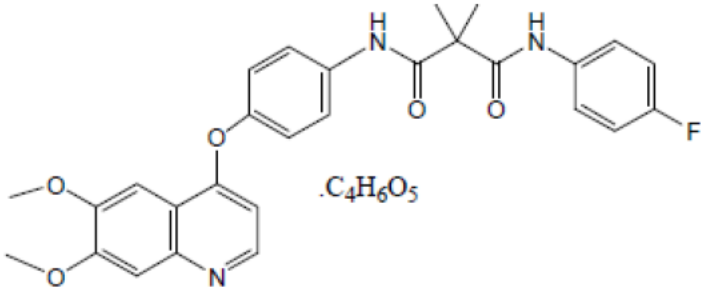
2.1.2 Generic Name: None

2.1.3 Code Name: XL184, EXEL-7184, EXEL-02977184

2.1.4 Chemical Name:
N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamine, (2S)-hydroxybutanedioate

2.1.5 Molecular Formula/Molecular Weight: $C_{28}H_{24}FN_3O_5.C_4H_6O_5$/635.6 Daltons (L-malate salt)

2.1.6 Structure



2.1.7 Pharmacologic class: Tyrosine kinase inhibitor

2.2 Relevant IND/s: IND (b) (4) IND (b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Cabozantinib is manufactured and packaged by (b) (4); drug product lots were manufactured at the commercial manufacturing site by (b) (4) (b) (4) Each 1.267 mg of cabozantinib as the malate salt is equivalent to 1mg of cabozantinib. The capsule strength used in clinical studies was 25 mg as salt-based weight which corresponds to 19.7 mg as freebase. This capsule strength equals the commercially proposed 20 mg capsule. Drug product capsules will be manufactured containing 20 mg or 80 mg freebase cabozantinib. The 80 mg capsule corresponds to 78.9 mg freebase clinical dosage strength. Differences between the clinical

(19.7 and 78.9 mg), and commercial (20 and 80mg) dosage strengths are not considered clinically relevant. Information regarding the (b) (4) is discussed in Section 2.6. Proposed Clinical Population and Dosing Regimen. Comparative plasma pharmacokinetics of the free base and salt forms are reviewed in Section 5 Pharmacokinetics.

Cabozantinib (S)-malate exists (b) (4) All batches of the drug product were primarily (b) (4) with the exception of lot L0208700 (80 mg capsule) which contained a (b) (4). A clinical bioequivalence study was conducted comparing the (b) (4) (Study XL184-016). All other cabozantinib capsules administered non-clinically and clinically were the (b) (4).

Process B is denoted as the proposed commercial manufacturing process. XL184 lots used for non-clinical studies, as well as clinical administration manufactured between 2004 and 2008 (nonclinical lots EGI759-90A and P163-183-1, nonclinical + clinical lot P172-27-1, and clinical lots P188-144-1 and 80-4001) were denoted as Process A. Additional information on differences between manufacturing processes was not available.

Composition of Cabozantinib (drug product) 20mg and 80mg capsules

Ingredient	Function	Batch formula (wt %)		Theoretical quantity (mg/unit dose)	
		20mg	80mg	20mg	80mg
Cabozantinib (S)-malate	Active ingredient	(b) (4)			
(b) (4) (silicified microcrystalline cellulose)		(b) (4)			
(b) (4) (croscarmellose sodium)					
(b) (4) (sodium starch glycolate)					
(b) (4) (fumed silica)					
Stearic acid					

(b) (4)

The Applicant described 2 container closure systems for commercial packaging for the capsule formulation. The multiple cavity blister card will contain 20 mg and 80 mg capsules in card configurations providing 140 mg, 100 mg, or 60 mg weekly dosages. The bottle packaging will provide sixty 20 mg capsules.

2.3.2 Comments on Novel Excipients

Excipients are compendial and meet the US Pharmacopeia/ National Formulary requirements.

2.3.3 Impurities/Degradants – Comments and Qualification

Four genotoxic impurities were identified in the drug substance; (b) (4) are process impurities as well as degradants, while (b) (4) are process impurities, but not degradants. Ames assays have been conducted for all genotoxic impurities. The genetic toxicology section of this NDA reviews studies conducted with genotoxic and non-genotoxic impurities and indicates: 1) (b) (4) is mutagenic in *S.typhimurium* strain TA1537 in both the presence and absence of metabolic activation. 2) (b) (4) in combination with (b) (4) is mutagenic in the presence of metabolic activation in *S.typhimurium* strains TA98 and TA100. 3) (b) (4) was mutagenic in the absence of activation in strains *S.typhimurium* TA1535 and *E.coli* WP2 *uvrA*. The clastogenicity potential of the impurities was not tested.

The two degradation products (b) (4) and (b) (4) identified as genotoxic impurities, were monitored in release testing and stability studies. The proposed acceptance criteria for (b) (4) is (b) (4) corresponding to an intake of (b) (4) µg/day at a cabozantinib dose of 140 mg/day. The proposed acceptance criteria for (b) (4) is (b) (4), this limit corresponds to an intake o (b) (4) µg/day at the 140 mg (b) (4) dose of cabozantinib. (b) (4) an impurity and metabolite of XL184, has been combined with (b) (4) in the proposed specification limit of (b) (4). Batch levels of (b) (4) are documented as ND (not detectable), and plasma levels are below the limit of quantitation (<2ng/mL) in patients administered 175 mg cabozantinib. The combination of the 2 impurities has not increased the proposed specification limit. (b) (4) is a process impurity of XL184 which is documented as ND in batch analyses of clinical and nonclinical batches, even though the impurity is indicated to be a source material for the (b) (4) manufacturing process. The proposed specification for this impurity is (b) (4) which would result in a daily intake of (b) (4) µg (b) (4) at the recommended daily dose of cabozantinib.

In an October 23, 2012 telecon, the Applicant stated that the proposed acceptance criteria release and stability limits of cabozantinib genotoxic and non-genotoxic impurities are equal (see table below). The proposed impurity limits are the result of revised purity/impurity methodology in place since July, 2011, which are proposed to continue to be used for the commercial production of cabozantinib. The proposed release/stability acceptance criteria for (b) (4) (b) (4) + (b) (4) and (b) (4) are (b) (4), respectively, for drug substance (DS), and (b) (4), respectively, for drug product (DP). These purity/impurity methodologies have been reviewed and approved by the product review chemist, Mike Adams, Ph.D.

Genotoxic impurity (GTI) levels using revised impurity methodology

Impurity	Proposed specification limits at release and end of shelf life (stability)	Impurity levels from clinical batch #0804672 (175 mg salt basis)	Impurity intake at proposed clinical dose (140mg freebase)	Limit Acceptability
[redacted]				Accepted
				Accepted
				Accepted

Even though the genotoxic impurities noted above exceed a theoretical threshold of toxicologic concern of 1.5 µg/day, this threshold is based on a lifetime risk for the development of cancer and, as stated in ICH S9, a strict adherence to this limit may not be appropriate for a drug developed to treat patients with cancer. At the drug product specifications proposed, none of the impurities exceeds an intake o (b) (4) µg/day at the recommended dose of cabozantinib. The (b) (4) µg intake level represents a low safety risk for this patient population. Thus, the currently proposed acceptability criteria for the genotoxic impurities/degradants present in cabozantanib are considered acceptable from a pharmacology/toxicology perspective.

Previous stability data indicated that when stability results of the 20 mg drug capsules were compared in different container closure systems (bottle vs blister card), levels of (b) (4) were comparatively higher at the same temperature and humidity (40º C, 75% RH) with bottle storage ((b) (4) ppm) compared to with blister card storage (b) (4) ppm). Levels were lower with 80 mg capsule storage. Accelerated storage conditions are not usually considered in setting impurity specification, and updated methodology tightened the impurity limits as stated above. Stability data are acceptable at 25ºC/60% RH for up to 24 months.

Individual non-genotoxic impurities specified in cabozantanib ((b) (4) (retention time (RRT) (b) (4) and an unnamed impurity at RRT (b) (4) are below or NMT (b) (4), which is within the ICH Q3B(R2) qualification threshold of 0.2%. The proposed release/stability specification of a separate impurity, (b) (4) (RRT (b) (4) is (b) (4) which exceeds the ICH Q3B(R2) qualification threshold. The daily intake for this impurity resulting from the proposed clinical dose of 140 mg (b) (4) (b) (4) mg/m^2 based on a 70 kg adult) is (b) (4) mg/m^2/day. The nonclinical batch (batch # 163-183-1) used for the 6-month rat and dog repeat-dose toxicology studies contained (b) (4) At the highest dose administered to dogs for 6 months in which there was no mortality (5 mg/kg), the animal impurity intake was (b) (4) mg/m^2/day, which is above the proposed intake of the impurity in humans at the proposed clinical dose. Based on this calculation, (b) (4) is qualified at (b) (4)

The individual proposed release/stability acceptability criteria for unspecified impurities is NMT (b) (4), which is below the ICH Q3B(R2) qualification threshold.

2.3.4 Metabolites

Metabolic profiling evaluations of clinical plasma samples have identified 4 metabolites of XL184 which exceed levels of the same metabolites in plasma samples of rodent and non-rodents administered XL184 in repeat-dose studies up to 6 months. In addition, these metabolic levels may be greater than 10% of the parent drug exposure at steady state. These XL184 metabolites include an N-oxide, a monohydroxy sulfate, a half dimer, and a mono-demethyl half dimer. The N-oxide metabolite (EXEL-5162) and an acid metabolite (EXEL-5366) are not considered to be pharmacologically active (see Pharmacology study XL184-Disc-002). Other metabolites have not been tested for activity. The Applicant has cited ICH S9 when indicating that no further testing of the drug metabolites is planned or warranted for treatment of advanced cancer. As indicated in the Genetic Toxicology section of this NDA, an Ames bioassay has been conducted on a single metabolite (XL184 N-oxide), and was not found to be mutagenic.

Metabolite profiling in human plasma, urine and feces is ongoing. No data on metabolite accumulation in plasma upon repeat XL184 dosing is available.

Metabolite	Percent AUC of metabolite to AUC of XL184	
	Rat/dog 6-month[a]	Clinical study[b]
N-oxide	2.0 - 4.0	15
Monohydroxy sulfate	0.24 - 7.0	43
Half dimer amide	0.5 – 2.0	10
Mono-demethyl half dimer	-	NA[c]
Para-fluoroaniline (p-FA or 4-FA)[d]	<1.0	<LOQ

[a] Study report XL184-NC-029
[b] Mass balance study in normal healthy volunteers administered single oral dose; Study report XL184-012.
[c] Metabolite identified in human plasma but not quantified (NA= not available).
Metabolic profiling in human plasma, urine and feces, as well as metabolic accumulation of additional XL184 metabolites identified in human plasma (including mono-demethyl half dimer, half dimer methyl ester, and mono-demethyl glucuronides) are not currently available.
(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Patient dose and schedule: The proposed clinical dose of 140 mg (freebase equivalent weight) is administered orally as a capsule once daily. The Phase 1/2, and 3 cabozantinib dose administered to patients was 175 mg/day (L-malate salt weight; 138 mg freebase equivalent weight). Efficacy for the drug was primarily based on the Phase 3 trial conducted in 330 patients with metastatic or locally advanced medullary thyroid cancer (MTC). The difference between the clinical and commercial doses is not considered to be clinically relevant (1 mg XL184 as freebase = 1.267 mg as L-malate salt).

Clinical study XL184-004 in normal volunteers evaluated the effect of food (high fat) on the plasma pharmacokinetics of XL184. C_{max} and AUC values of XL184 were found to increase by 41 and 57%, respectively, following a high fat meal compared to fasted conditions. The drug should be administered under fasted conditions (fasting 2h before and 1h following each dose).

In the clinic XL184 exhibits a long half-life, ~5-fold accumulation in plasma at steady state and moderately high steady-state variability for C_{max} between individuals. The T_{max} ranged from 2 to 5h post-dose. The Applicant noted that dose-normalized plasma exposures were indicated to be ~2-fold higher for the cabozantinib capsule formulation relative to the cabozantinib powder in bottle formulation, although absolute bioavailability was not evaluated.

Efficacy studies conducted in patients with thyroid cancer indicated that cabozantinib extended the median PFS by 7.2 months (cabozantinib 11.2 months, placebo 4 months).

(b) (4)

Note: (b) (4) .

2.7 Regulatory Background:

IND (b) (4) for cabozantinib was initially submitted to the division in June, 2005. Cabozantinib was granted orphan drug status for medullary thyroid carcinoma on November 29, 2010, and fast tract designation on April 8, 2011. (b) (4) the new IND 113,446 for the MTC application was created. A conditionally acceptable status for the proposed name Cometriq was documented by the Agency on December 6, 2011.

During the pre-NDA meeting with the Applicant on December 20, 2011, the Agency indicated the following:

1. The nonclinical package needed to support the approval of cabozantinib in the MTC patient population may be more in line with ICH M3(R2)* for the advanced or metastatic medullary thyroid cancer patient population. (*Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals)
2. A pre-postnatal developmental toxicity study and a carcinogenicity assessment may be needed as per ICH M3(R2).
3. Postmarketing requirements/commitments, including carcinogenicity assessments, should be provided in module one of the NDA submission.

The Applicant indicated that pre-postnatal developmental toxicity studies were not planned, and were not needed according to the shortened prognosis (median overall survival of 21 months in placebo arm and mean PFS of 11.2 months in cabozantinib arm) in patients with advanced MTC. The Applicant also indicated that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat this advanced cancer population, according to ICH S9 and ICH S1A. The Agency noted that the exclusion of pre/post developmental toxicity and carcinogenicity studies would be an NDA review issue.

In Module 2.4 of the NDA, the Applicant stated that carcinogenicity evaluation of XL184 has not been conducted based on:

1) Absence of genotoxicity in both *in vitro* and *in vivo* bioassays
2) Lack of pre-neoplastic lesions in repeat-dose toxicity studies in rats and dogs
3) Lack of demonstrated carcinogenic potential in the RTKi product class
4) Intended patient population with shortened life expectancy

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Study #	Study Name
XL184-Disc-001	*In vitro* biochemical characterizations of EXEL-02977184 (EXEL-7184, XL184)
XL184-Disc-002	*In vitro* characterizations of 2 major XL184 metabolites (EXEL-5162 and EXEL-5366)
XL184-Disc-003	Crystal structure of the kinase domain of c-MET bound to EXEL-02977184
XL184-Disc-005	Studies on the effect of EXEL-02977184 on the proliferation of human and murine tumor cell lines
XL184-Disc-007	Studies of the effect of EXEL-02977184 on tube formation and migration in human and murine endothelial cell lines
XL184-Disc-009	In vivo pharmacodynamic study with EXEL-02977184 in TT xenograft tumors
XL184-Disc-010	*In vivo* pharmacodynamic study with EXEL-02977184 in mouse lung following intravenous administration of VEGF
XL184-Disc-011	*In vivo* pharmacodynamic study with EXEL-02977184 in BaF3/FLT3-ITD pre-B lymphoblastic xenograft tumors
XL184-Disc-012	*In vivo* pharmacodynamic study with EXEL-02977184 in Calu6/KIT AC(D10C)xenograft tumors
XL184-Disc-013	*In vivo* pharmacodynamic study with EXEL-02977184 in mouse liver following intravenous administration of hepatocyte growth factor (HGF)
XL184-Disc-014	*In vivo* pharmacodynamic study with EXEL-02977184 in H441 xenograft tumors
XL184-Disc-015	*In vivo* pharmacodynamic study with EXEL-02977184 in mouse lung
XL184-Disc-017	*In vivo* efficacy study with EXEL-029977 in MDA MB-231 xenograft dose response study
XL184-Disc-023	*In vivo* efficacy study with EXEL-029977 in rat C6 glioma tumors: low dose response study
XL184-Disc-024	*In vivo* efficacy study with EXEL-029977 in H441 xenograft rumors: dose response study
XL184-Disc-025	*In vivo* efficacy study with EXEL-029977 in TT medullary thyroid xenograft tumors: dose response study
XL184-Disc-026	*In vivo* efficacy study with EXEL-029977 in an experimental model of lung metastisis

Safety Pharmacology

XL184-Disc-027	Electrophysiology study of EXEL-02977184 on hERG potassium channel by manual patch clamp
XL184-NC-007	Effects on general activity and behavior in the rat following oral administration
XL184-NC-008	Measurement of respiratory parameters in the freely moving conscious rat using whole body plethysmography
XL184-NC-009	Cardiovascular effects in the conscious dog using the ITS radiotelemetry system

Pharmacokinetics

XL184-Disc-029	Single dose pharmacokinetic profile of EXEL-02977184 in female CD rats
XL184-Disc-031	Single dose pharmacokinetic profile of EXEL-02977184 in female CD rats
XL184-Disc-034	Single dose pharmacokinetic profile of EXEL-02977184 in male cynomolgus monkeys
XL184-NC-017	Comparative bioavailability study of intravenous and oral dosage forms in beagle dogs
BMS-907351	Quantitative tissue distribution of drug-related material using whole body autoradiography following a single oral dose of [^{14}C]BMS-907351 to male Sprague Dawley rats and Long-Evans rats and human radiation dosimetry prediction
XL184-Disc-035	Protein binding, stability, and biotransformation of EXEL-02977184
CRL-20000504	Mass balance of radioactivity after oral administration of [^{14}C]BMS-907351 to male and female Sprague Dawley rats
XL184-MBA00472	BMS-907351: Pharmacokinetics following oral administration to non-naïve male Beagle dogs
XL184-NC-029	Pharmacokinetics of selected XL184 metabolites in rats, dogs and humans
XL184-Disc-036	Non-GLP *in vivo* toxicity evaluation of EXEL-02977184 in female CD rats following sub-chronic oral gavage administration
XL184-Disc-037	*In vitro* ADME properties of EXEL-02977184

General Toxicology

XL184-NC-003	Single dose toxicology study in the Sprague Dawley rat
XL184-NC-004	Single dose toxicology study in the Beagle dog
XL184-NC-005	14-day oral gavage toxicity and toxicokinetic study with XL184 in rats with a 28-day recovery period
XL184-NC-014	14-day oral gavage toxicity and toxicokinetic study with XL184 in rats with a 14-day recovery period
XL184-NC-013	XL184: A six month oral toxicity study with recovery in rats
XL184-NC-006	14-day oral gavage toxicity and toxicokinetic study with XL184 in dogs with a 28-day recovery period
XL184-NC-012	XL184:A six-month oral toxicity study with recovery in dogs
XL184-NC-018	XL184:A six-month oral toxicity study with recovery in dogs

Genetic Toxicology

XL-184-NC-010	*Salmonella-Escherichia coli*/Mammalian-microsome reverse mutation assay with a confirmatory assay with XL184
XL-184-NC-011	Chromosomal Aberrations in cultured human peripheral blood lymphocytes
XL-184-NC-019	*In vivo* mouse bone marrow micronucleus assay
(b) (4)	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*
(b) (4)	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*
(b) (4)	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*
(b) (4)	
(b) (4)	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*
(b) (4)	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*
BMS-927982	Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Reproductive Toxicology and Special Toxicology studies

XL184-NC-020	Oral gavage study of fertility, early embryonic development in implantation, and toxicokinetics with X184 in rats
XL184-NC-022	Reproductive and developmental toxicity – effects on embryofetal development in rats

XL184-NC-024	Oral gavage study for effects on embryo-fetal development and toxicokinetics with XL184 in rabbits
XL184-NC-028	Evaluation of *in vitro* phototoxicity on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay

Studies Not Reviewed

Pharmacology

XL184-Disc-004	Effects of EXEL-02977184 on cellular phosphorylation levels in human and murine cells
XL184-Disc-006	Studies of the effects of EXEL-02977184 on the migration and invasion behavior of murine tumor cells
XL184-Disc-008	Cell-based studies of EXEL-02977184 on anchorage dependent growth on murine and human tumor cell lines
XL184-Disc-018	*In vivo* efficacy study with EXEL-02977184 in MDA MB-231 xenograft tumors::tumor regression study
XL184-Disc-019	*In vivo* efficacy study with EXEL-02977184 in B16F10 lung tumors: an experimental tumor metastasis model
XL184-Disc-020	*In vivo* efficacy study with EXEL-02977184 in BaF3/FLT3/ ITD pre-B lymphocyte tumors: dose response
XL184-Disc-021	*In vivo* efficacy study with EXEL-02977184 in rat C6 glioma tumors: dose response
XL184-Disc-022	*In vivo* efficacy study with EXEL-02977184 in rat C6 glioma tumors: single dose study
XL184-TM-001	Combined inhibition of VEGF and c-MET signaling suppresses tumor invasion and metastasis and prolongs survival
XL184-TM-002	Targeting MET with XL184 to reverse EGFR tyrosine kinase inhibitor (TKI) resistance in NSCLC : Impact of pre-clinical studies on clinical trial design
XL184-TM-003	Activated MET is a molecular prognosticator and protential therapeutic target for malignant peripheral nerve sheath tumors
XL184-TM-004	c-MET: A new cancer stem cell marker and therapeutic target for pancreatic cancer

Pharmacokinetics

XL184-BA-VR-069-00	Method validation of method BA-M-069: Bioanalytical determination of XL184 in rabbit plasma by LC/MS/MS
XL184-BA-VR-060-00	Method validation of method BA-M-060: Bioanalytical determination of XL184 in dog plasma by LC/MS/MS
7359-217	Validation of a method for the determination of XL184 in dog plasma
XL184-BA-VR-021-00	Cross validation method BA-M-021/00: Bioanalytical determination of XL184 in rat plasma by LC/MS/MS
7359-216	Validation of a method for the determination of XL184 in rat plasma
S10115-TRA1	Quantitative determination of BMS-907351 and its metabolite in rat plasma by LC/MS/MS
TNJS09272	Quantitative determination of BMS-907351 and its metabolite in dog plasma by LC/MS/MS
XL184-BA-VR-083-00	Validation report of method BMS-021/00 for the determination of XL184 and 4 metabolites in rat plasma
XL184-BA-VR-082-00	Validation report of method BMS-021/00 for the determination of XL184 and 4 metabolites in dog plasma
XL184-BA-SR-159-00	Bioanalytical study report for XL184 mono-demethyl amide cleavage half dimer for protocol XL184-NC-018 and XL184-NC-020
XL184-Disc-037	In vitro absorption, distribution, metabolism and excretion properties of EXEL-02977184
XL184-Disc-028	Single ascending dose pharmacokinetic profile of EXEL-02977184 in female athymic nude mice

XL184-Disc-030	Single ascending dose pharmacokinetic profile of EXEL-02977184 in female CD rats
XL184-Disc-032	Single ascending dose oral gavage plasma concentration time profile of EXEL-02977184 in male beagle dogs
XL184-Disc-033	Single dose pharmacokinetics profile of EXEL-02977184 in male beagle dogs
XL184-NC-025	Collection of samples for determination of pharmacokinetics of various capsule formulations of XL184 following single oral doses to beagle dogs pretreated with pentagastrin
XL184-NC-026	Collection of samples for determination of pharmacokinetics of various capsule formulations of XL184 following single oral doses to beagle dogs pretreated with famotidine or pentagastrin
XL184-NC-015	Comparative bioavailability of 4 solid oral dosage forms in beagle dogs
XL184-NC-016	Comparative bioavailability of intravenous and oral dosage forms in beagle dogs
7350-420	Inhibitory potential of XL184 on human hepatic cytochromes P450
3200-1224-1800	In vitro assessment of BMS-907351 as an inducer of human cytochrome P450 expression in primary human hepatocytes
BMS-PGP	Testing of BMS-907351 in the Caco-2-P-gp assay suite

General toxicology

XL184-Disc-038	In vivo toxicity of EXEL-02977184 in female CD rats after single dose administration
XL184-NC-001	Non-GLP single dose oral gavage toxicity and toxicokinetic study in Beagle dogs

3.3 Previous Reviews Referenced

IND (b) (4) 1995, D.Y.Lee Ham, Ph.D. summary review noted but not utilized in the completion of this review.
IND (b) (4) (b) (4)

4. Pharmacology

4.1 Primary Pharmacology

Study tile	Study no.	Study report location
In vitro biochemical characterizations of EXEL-02977184 (EXEL-7184, XL184)	XL184-Disc-001	Electronic submission, M4.2.1.1
Crystal structure of the kinase domain of c-MET bound to EXEL-02977184	XL184-Disc-003	

XL184 (cabozantinib) is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs), which binds to a region of the kinase domain (including the ATP-binding site) in a reversible manner promoting a pseudo-inactivation of the kinase loop. The sponsor has documented the primary drug targets as MET, vascular endothelial growth factor receptor 2 (VEGFR2/KDR), and RET with IC_{50} values of 1.8, 0.035, and 9.8nM, respectively. Two additional VEGF receptor kinases, VEGFR1 and VEGFR3 are inhibited with IC_{50} values of 12.2 and 6.0nM, respectively. Additional targets of XL184 include FLT3, TIE2, AXL, TRKB, and KIT with IC_{50} values of 14.4, 14.3, 7.7, and 4.6nM, respectively. The drug has demonstrated limited inhibitory activity on serine/threonine protein kinases.

In order to determine kinase specificity, EXEL-7184 (XL184) was tested against a panel of receptor tyrosine kinases, serine/threonine kinases, and protein kinases. (Tables and figure below are excerpted from the sponsor's submission).

Table 4: Inhibition of Tyrosine Kinases by EXEL-7184

Kinase	IC_{50} ± SEM (nM)
Receptor Tyrosine Kinase	
Met	1.8 ± 0.2
Ron	121 ± 8
KDR	0.035 ± 0.007
Flt-1	12.2 ± 0.7
Flt-4	6.0 ± 0.6
RET	9.8 ± 2.3
KIT	4.6 ± 0.5
FLT-3	14.4 ± 0.8
PDGFRβ	234 ± 1.1
TIE-2	14.3 ± 2.8
c-Abl	>500
Alk	139 ± 23
EphA4	319 ± 14
EphB4	248 ± 30
ErbB2	>500[a]
InsR	1140 ± 21
IGF1R	1240 ± 140
Axl	7[b]
TrkB	7[b]
EGFR, FGFR1	>2000[a]
Non-Receptor Tyrosine Kinase	
Fyn	365 ± 55
Blk	101[b]
Lyn	45[b]
Yes	83[b]
Fes	1000[b]
FAK	460 ± 31
BTK	114 ± 11
Jak2, Jak3, Src, ZAP70	>500[a]
LCK	>5000[a]
ITK	>10,000[a]

Table 5: Inhibition of RET Wild Type and Mutants by EXEL-7184

RET Wild Type and Mutants	IC_{50} ± SEM (nM)
RET	9.8 ± 2.3
RET_M918T	27 ± 5
RET_V804L	>5000
RET_Y791F	1170 ± 80

Table 6: Inhibition of MET Wild Type and Mutant Enzymes by EXEL-7184

MET Wild Type and Mutants	IC_{50} (nM)
MET	1.8
MET_D1246N	11.8
MET_H1112Y	37.5
MET_K1262R	14.6
MET_L1213V	61.2
MET_M1149T	31.8
MET_M1268T	39.0
MET_V1110I	26.4
MET_V1238I	39.7
MET_Y1248H	3.8

Table 7: Inhibition of Wild Type KIT and FLT-3 and Mutants by EXEL-7184

KIT or FLT-3 Wild Type and Mutants	IC_{50} ± SEM (nM)
KIT	4.6± 0.5
KIT_D816V	2400 ± 500
KIT_T670I	4.8 ± 0.6
FLT-3	14.4 ± 0.8
FLT-3_D835Y	6900 ± 100

Sixty serine/threonine kinase were evaluated for inhibition by XL184; only 2 were found to have IC_{50}s under 500 nM.

Table 8: Inhibition of Serine-Threonine Kinases by EXEL-7184

Serine-Threonine Kinase	IC_{50} ± SEM (nM)
SAPK4 (p38δ)	141[a]
MAP2K1 (MEK1)	390 ± 40
p38α	8000 ± 1000
ROCK1	>500[b]
c-Raf	260 ± 30[c]
AMPK, Bmx, CamKII, CamKIV, CDK1/cyclinB, CDK2/cyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5/p35, CDK6/cyclin D3, CDK7/cyclin H/MAT1, GSK3α, IKKα, IKKβ, JNK1α1, JNK2α2, JNK3, MAPK1, MAPK2, MKK4, MKK6, MKK7β, MSK1, PAK2, PRK2, Akt2, Akt3, PKCα, PKCγ, PKCδ, PKCε, PKCη, PKCι, PKCθ, PKD2, PRAK, PRK2, RSK1, RSK2, RSK3, SGK, SAPK3 (p38γ).	>1000[a]
p38β	>5000[b]
Akt1, Chk1, CK2, EMK, MAP4K3, MAPKAPK2, p70S6K, PAK4, PIM1, PKA, PDK1, STK24	>10,000[b]

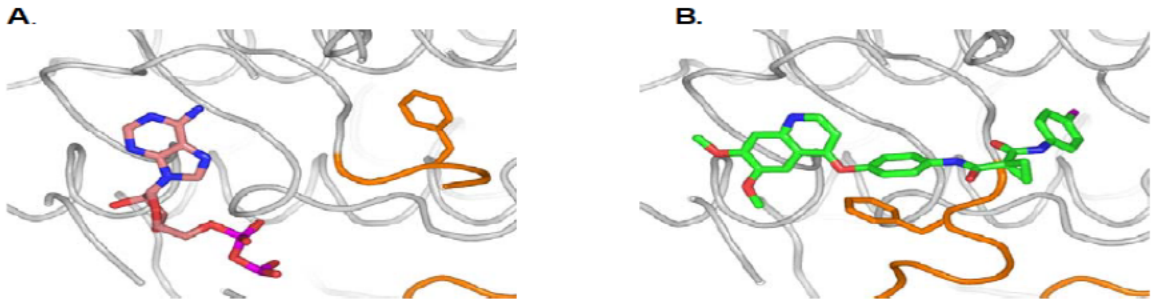
Experimental conditions and protein information are detailed in Table 1 and Table 2.

[a] Assays performed by (b) (4)

[b] Highest concentration tested.

[c] The assay uses c-RAF and its substrate MAP2K1. The inhibition observed is likely largely due to inhibition of MAP2K1.

The structure of the kinase domain of XL184 bound to MET kinase was determined by X-ray crystallography. Since XL184 occupies an area that is larger than ATP, the molecule occupies an area that includes the ATP-binding site as well as other catalytic regions. XL184 binds between the two lobes of the kinase domain causing reorganization of the activation loop, and placing the kinase in an unactivated conformation. The phenylalanine reorients and forms a stabilized interaction with the phenyl ring of XL184. Hydrogen bonding and nonspecific hydrophobic interactions are indicated to be responsible for the binding, blocking nucleotide binding, and inhibiting the kinase. To a lesser extent, the structure was also found to be an ATP-competitive inhibitor of KDR, TIE-2, and FLT-3. Studies with the MET, VEGFR2 and TIE-2 kinase domains indicate that this binding is fully reversible. No further information was provided.



(A) The structure of c-Met bound to ADP compared with (B) the structure of c-Met bound to EXEL-02977184. In both figures the activation loop is shown in orange, with the sidechain of Phe 1223 of the activation loop "DFG" in sticks.

Table 3: K_i Determinations and Kinetic Constants for EXEL-7184 Against Selected Kinases

Parameters	Met	KDR	TIE-2	FLT-3
ATP-competitive	Yes	Yes	Yes	Yes
K_M (μM) (ATP)[a]	52	1	5	10
K_i (nM)	2.3	0.05	15	9.4
k_{off} (sec^{-1})	~3.4×10^{-4}	~9.6×10^{-5}	>6×10^{-3}	ND
$t_{1/2}$ (min)[b]	~34	~120	<2 min	ND

ND, not determined.
[a] Apparent ATP KM values with details in Methods (Section 4.2.2).
[b] Half-life of the E-I complex is estimated using the relationship $t_{1/2} = 0.693/k_{off}$.

Study title: In vitro characterizations of 2 major XL184 metabolites (EXEL-5162 and EXEL-5366)
Study no: XL184-Disc-002
Study location: Electronic submission, M4.2.1.1

The N-oxide and acid metabolites of XL184 (EXEL-5162 and EXEL-5366) were significantly less active against primary targets of XL184 in biochemical and cellular assays when compared to the parent drug. The pharmacological activity of other XL184 metabolites was not determined. (See table below excerpted from the sponsor's submission).

In a cellular mechanistic assay that measures Met autophosphorylation in PC-3 cells, EXEL-5162 had an IC_{50} of 2.0μM while EXEL-5366 was inactive (IC_{50}>30μM). In comparison, the parent drug exhibited an IC_{50} of 7.8nM in the same assay. When the anti-proliferation activity of the metabolites was compared, ELEX-5162 indicated moderate to minimal activity against EBC-1 cells (IC_{50}=3.0μM), Hs 746T cells (IC_{50}=3.0μM) and MKN-45 cells (IC_{50}=25μM), with inactivity against TT cells (IC_{50}>30μM). EXEL-5366 was inactive against all four cell lines. In comparison, the parent drug exhibited IC_{50} values of 13, 9.9, 149, and 94nM against EBC-1 cells, Hs 746T cells, MKN-45 cells, and TT cells, respectively.

Table 1: Inhibition of Kinases by EXEL-5162 and EXEL-5366

Protein Kinase	EXEL-5162 IC_{50} (nM)	EXEL-5366 IC_{50} (nM)	XL184 IC_{50} (nM)
Met	190	5000	1.8
KDR	140	>10000 [a]	0.035
Flt-3	530	>3600 [a]	14.4
Akt1	>3600 [a]	>3600 [a]	>10000 [a]
Aurora B	>3600 [a]	>3600 [a]	n.d.
c-Kit	>3600 [a]	>3600 [a]	4.6
Cdc7	>3600 [a]	>3600 [a]	n.d.
Cdk1/CyclinB	>3600 [a]	>3600 [a]	>1000 [a]
c-Raf-1	>3600 [a]	>3600 [a]	260
EGFR	>3600 [a]	>3600 [a]	>2000 [a]
ErbB2	>3600 [a]	>3600 [a]	>500 [a]
FGFR1	>3600 [a]	>3600 [a]	>2000 [a]
Flt-1	>3600 [a]	>3600 [a]	12.2
PKA	>3600 [a]	>3600 [a]	>10000 [a]
InsR	>3600 [a]	>3600 [a]	1140
Jak2	>3600 [a]	>3600 [a]	>500 [a]
Map2K1	>3600 [a]	>3600 [a]	390
P70S6K	>3600 [a]	>3600 [a]	>10000 [a]
PDGFRβ	>3600 [a]	>3600 [a]	234
PDK1	>3600 [a]	>3600 [a]	>10000 [a]
Pim1	>3600 [a]	>3600 [a]	>10000 [a]
PKCβII	>3600 [a]	>3600 [a]	n.d.
Src	>3600 [a]	>3600 [a]	>500 [a]
Vps34	>3600 [a]	>3600 [a]	n.d.

n.d., not determined.

Study title: Studies on the effect of EXEL-02977184 on the proliferation of human and murine tumor cell lines
Study no: XL184-Disc-005
Study location: Electronic submission, M4.2.1.1

XL184 was found to inhibit cellular proliferation in multiple tumor types with IC_{50} values between 3nM and 787nM. In cells demonstrating a reliance on signaling through MET, XL184 inhibition ranged from 13 to 149nM (see table below excerpted from the sponsor's submission).

Table 3: Relative MET Gene Copy Number in Tumor Cell Lines

Cell Line	MET Relative Copy Number	Tissue and Pathology
C32	5	Skin, melanoma
EBC-1	9.8	Lung, squamous cell carcinoma
MKN-45	8.5	Gastric, adenocarcinoma
NCI-H1573	5.3	Lung, adenocarcinoma
OE33	8.7	Esophageal, adenocarcinoma
SNU-5	25	Gastric, carcinoma

Study title: Studies of the effect of EXEL-02977184 on tube formation and migration in human and murine endothelial cell lines
Study no: XL184-Disc-007
Study location: Electronic submission, M4.2.1.1

The effect of XL184 on endothelial tube formation, function and cell migration was assessed in *in vitro* models. XL184 reduced endothelial cellular migration in response to VEGF, HGF, and angiopoietin-1 with IC_{50} values of 12 to 23nM.

Table 2: EXEL-7184 Inhibits Wound-Induced Endothelial Cell Migration

	Growth Factor		
Endothelial Cell Type	VEGF IC_{50} (nM)	HGF IC_{50} (nM)	Ang1 IC_{50} (nM)
HMVEC-L	12 (n[a] = 3)	19 (n = 3)	23 (n = 2)
MS1	6 (n = 2)	41 (n = 3)	ND

ND, not determined.
[a] Number of assay replicates.
Table excerpted from sponsor's submission

Study title: In vivo pharmacodynamic study with EXEL-02977184 in TT xenograft tumors
Study no: XL184-Disc-009
Study location: Electronic submission, M4.2.1.1

Treatment with XL184 was found to inhibit RET phosphorylation in TT medullary thyroid cells in a dose-dependent manner, with maximal inhibition (84 and 89%) at xenograft mouse doses of 100 and 300mg/kg, respectively. Plasma concentratons of 49-66µM XL184 resulted in 84-89% inhibition. It appeared that a steady-state plasma concentration greater than 10uM was required to maintain maximal RET inhibition.

Figure 3: Dose-Response Relationship for Inhibition of Phosphorylation of Ret by EXEL-7184 in TT Xenograft Tumors (4 hours Post-Dose)

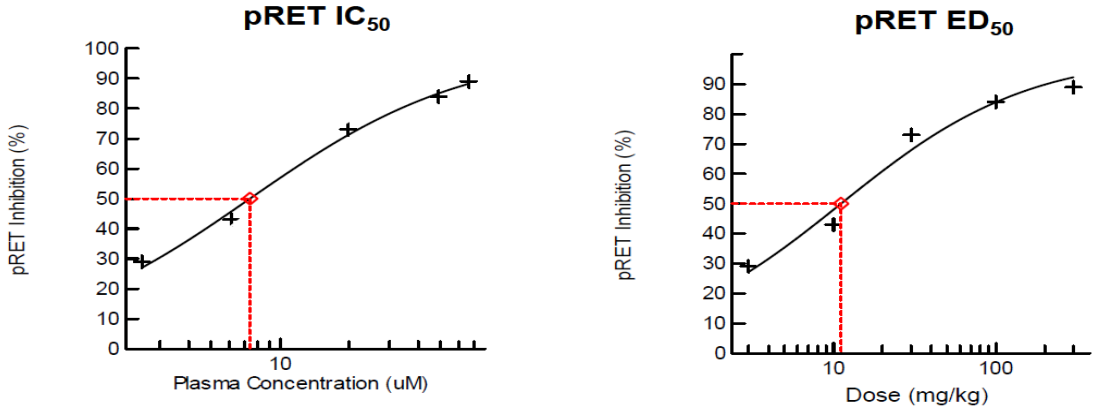


Table 2: Summary of Plasma and Tumor Lysate Concentrations of EXEL-7184 (4 hours Post-Dose)

Group	Dose (mg/kg)	EXEL-7814 (µM)		pRet (% Control)	pRet (% Inhibition)[a]
		Plasma Mean ± SD	Tumor Mean ± SD		
Vehicle	10 mL/kg	na	na	100	0
EXEL-7184	3	2.51 ± 0.50	1.13 ± 0.21	71	29
EXEL-7184	10	6.15 ± 1.70	2.57 ± 0.88	57	43
EXEL-7184	30	19.8 ± 6.51	9.33 ± 3.48	27	73
EXEL-7184	100	49.0 ± 5.86	23.3 ± 5.22	16	84
EXEL-7184	300	66.4 ± 15.2	38.6 ± 20.7	11	89

Table and figures excerpted from sponsor's submission

XL184-Disc-010	***In vivo* pharmacodynamic study with EXEL-02977184 in mouse lung following intravenous administration of VEGF**
XL184-Disc-011	***In vivo* pharmacodynamic study with EXEL-02977184 in BaF3/FLT3-ITD pre-B lymphoblastic xenograft tumors**
XL184-Disc-012	***In vivo* pharmacodynamic study with EXEL-02977184 in Calu6/KIT AC(D10C)xenograft tumors**
XL184-Disc-013	***In vivo* pharmacodynamic study with EXEL-02977184 in mouse liver following intravenous administration of hepatocyte growth factor (HGF)**
XL184-Disc-014	***In vivo* pharmacodynamic study with EXEL-02977184 in H441 xenograft tumors**
XL184-Disc-015	***In vivo* pharmacodynamic study with EXEL-02977184 in mouse lung**

Study location: Electronic submission, M4.2.1.1

In a number of mouse xenograft studies, the effects of XL184 on the growth of established human tumors were studied. Mice with established human cell lines from liver (H441, liver tissue +HGF), lung + VEGF, medullary thyroid cells, BaF3/FLT-3 ITD, and Calu6/KITD10C, were administered a single dose of XL184, with cells harvested up to 96 hours post-dose.

Single dose in vivo target modulation xenograft studies

		Dose Response				Duration of Action		
Target	Tissue or Cell Line	Maximum Inhibition (%)	Estimated ED_{50} (mg/kg)	Estimated IC_{50} µM	Estimated IC_{50} ng/mL	Dose (mg/kg)	Maximum Inhibition (%)	Sustained Inhibition[a] (hours)
MET	Liver (+HGF)	97	5	2	1000	100	99	10
	H441	96	9	7	3500	100	92	8
VEGFR2	Lung (+VEGF)	98	26	2	1000	100	99	10
RET	TT	89	11	8	4000	100	79	< 24
TIE-2	Lung	84	86	24	12000	100	58	4
FLT-3	BaF3 / FLT-3 ITD	89	≤1	≤0.48	≤240	30	86	24
KIT	Calu6 / KIT D10C	47	≥100	≥19	≥95000	ND	ND	ND

[a] Continuous inhibition of >50%.ED50 = dose associated with 50% inhibition of receptor phosphorylation, HGF = hepatocyte growth factor, IC50 = concentration associated with 5-% inhibition of receptor phosphorylation,

Table excerpted from sponsor's submission

XL184-Disc-017	***In vivo* efficacy study with EXEL-029977 in MDA MB-231 xenograft dose response study**
XL184-Disc-023	***In vivo* efficacy study with EXEL-029977 in rat C6 glioma tumors: low dose response study**
XL184-Disc-024	***In vivo* efficacy study with EXEL-029977 in H441 xenograft rumors: dose response study**
XL184-Disc-025	***In vivo* efficacy study with EXEL-029977 in TT medullary thyroid xenograft tumors: dose response study**
XL184-Disc-026	***In vivo* efficacy study with EXEL-029977 in an experimental model of lung metastisis**

Study location: Electronic submission, M4.2.1.1

Multiple murine tumor models were examined in an attempt to further define the activity of XL184, including tumor growth inhibition, tumor cell metastasis, and survival. Rodents with cell lines C6 (rat glioma), MDA-MB-231 (human breast carcinoma), H441 (human lung carcinoma), and TT (human MTC) were studied (see table below). XL184 was administered daily; steady state exposure of ~1500-2400ng/mL were needed for >90% tumor growth inhibition. In each of the tumor models, significant TGI and/or tumor regression was observed; histological evaluation of tumor tissue following XL184 treatment indicated a decrease in microvessel density. The drug half-life was significantly shorter in mice (~3.5h) compared to rats or humans (~13h in rats and 80-172h in humans).

Table 12: Summary of In Vivo Solid Tumor Growth Inhibition Studies (Continuous Dosing Regimens)

Tumor Model	Dose and Duration	TGI (%)	Tumor Regression (%)	XL184 Plasma Exposure (C_{avg})[a] (ng/mL)
C6 glioma (rat)	1 mg/kg/d x 12d	92	--	1234
C6 glioma (rat)	3 mg/kg/d x 12d	>100	62	1979
C6 glioma (rat)	10 mg/kg/d x 12d	>100	85	7827
MDA-MB-231 (mouse)	1 mg/kg/d x 14d	39	--	28
MDA-MB-231 (mouse)	3 mg/kg/d x 14d	55	--	179
MDA-MB-231 (mouse)	10 mg/kg/d x 14d	86	--	514
MDA-MB-231 (mouse)	30 mg/kg/d x 14d	99	--	1544
MDA-MB-231 (mouse)	60 mg/kg/d x 14d	>100	18	3017
TT (mouse)	1 mg/kg/d x 14d	5	--	56
TT (mouse)	3 mg/kg/d x 14d	12	--	355
TT (mouse)	10 mg/kg/d x 14d	50	--	802
TT (mouse)	30 mg/kg/d x 14d	100	--	2382
TT (mouse)	60 mg/kg/d x 14d	>100	20[b]	7847
H441 (mouse)	1 mg/kg/d x 14d	31	--	43
H441 (mouse)	3 mg/kg/d x 14d	56	--	134
H441 (mouse)	10 mg/kg/d x 14d	58	--	505
H441 (mouse)	30 mg/kg/d x 14d	97	--	1944
H441 (mouse)	60 mg/kg/d x 14d	>100	33	3256

Table excerpted from sponsor's submission

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted.

4.3 Safety Pharmacology

XL184 did not inhibit hERG channel activity when tested at 1, 10, and 30 μM. In dogs, XL184 administered at 150 or 1000 mg/kg had no effect on cardiovascular parameters. Behavioral and physiological changes were not observed following single doses of XL184 up to 300 mg/kg; 900 mg/kg was lethal. In a separate safety pharmacology study, a single dose of 900 mg/kg XL184 to conscious rats had no effects on respiratory parameters.

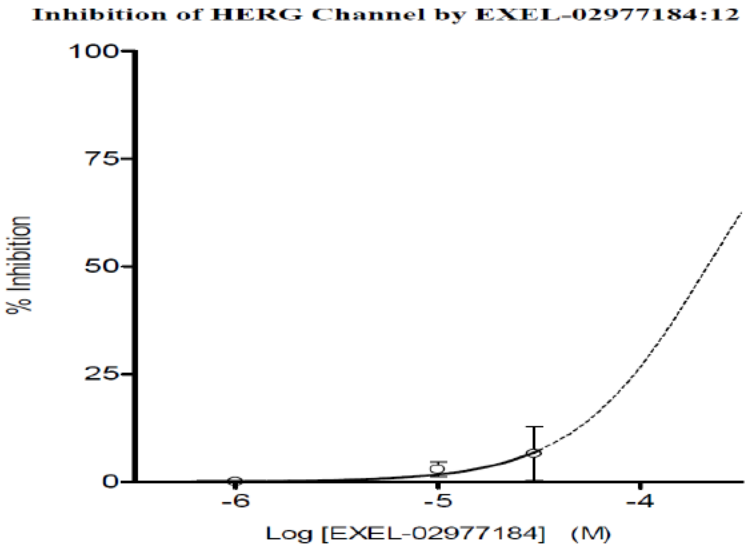
Study title: Electrophysiology study of EXEL-02977184 on hERG potassium channel by manual patch clamp

Study no.:	EXEL-02977184
Study report location:	Electronic submission , M4.2.1.3
Conducting laboratory and location:	Exelixis Research and Development, San Francisco, CA
Date of study initiation:	June 2, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	XL184, batch # EGI759-90A, 99.3% pure

<u>Key Study Findings:</u>

● EXEL-02977184 did not inhibit hERG channel activity when tested up to 30 μM.

Results:
hERG potassium channel inhibition was evaluated by manual patch-clamp electrophysiology using Chinese hamster ovary (CHO) cells expressing hERG channels. At 1 and 10 µM, the drug inhibited hERG channel activity by 0 and 2.9%. At 30 µM, EXEL-02977184 showed inhibition of 6.5% compared to DMSO controls. (Figure excerpted from sponsor's submission).



Study title: XL184: Cardiovascular effects in the conscious dog using the ITS radiotelemetry system

Study no.:	XL184-NC-009
Study report location:	Electronic submission , M4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 8, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XL184, batch # EGI759-90A, 99.3% pure

Key Study Findings:
- No changes in QTc prolongation noted by study laboratory
- ↑13% arterial BP, ↑22% diastolic pressure at 1000mg/kg

Methods

Doses:	150mg/kg (nominal), 1000mg/kg (see below)
Frequency of dosing:	weekly
Route of administration:	Oral gavage
Dose volume:	Not indicated
Formulation/Vehicle:	Ethanol:PEG400:water (5:45:50)
Species/Strain:	Beagle dog
Number/Sex/Group:	1M/dose
Age:	2-3y
Weight:	9.8-12.9kg
Satellite groups:	None
Unique study design:	▲Study was performed in conscious dogs which had been previously used for similar study (4w washout between studies) ▲Same animals administered vehicle and separate dose levels separated by 7-day washout period between each treatment until each animal received all doses in ascending order. ▲Konigsberg sensors surgically implanted for measurement of aortic blood pressure (AOP), left ventricular pressure (LVP), and Lead II ECG ▲Parameters measured: -Systolic, diastolic, and mean arterial BP -Heart rate -Left ventricular pressure + dP/dt_{max} -RR, QRS, PR, QT, QTcf intervals, height of R wave of ECG complex -Activity above baseline

	Week/Compound/Dose (mg XL184 /kg)			
	Week 1	Week 2	Week 3	Week 4
1M	0	150	1000	not dosed
2M	0	150	1000	not dosed
3M	150	0	* 175	1000
4M	150	0	* 175	1000

* The low dose formulation for week 3 dosing was incorrectly prepared, resulting in a dose level of 175 mg/kg. All low dose animals will be grouped as having received a nominal dose of 150 mg/kg.

Note: Study documentation indicates that a “system crash” occurred (assumed to be monitoring) at week 1 following dosing (0-2h post dose. As a result, dogs 3 and 4 were re-dosed at week 3 in order to obtain a complete data set. In addition, as noted in the footnote above, the LD was incorrectly prepared, and animals were administered 175 mg/kg. Regardless, LD data was grouped as a dose of 150 mg/kg.

Parameter	150mg/kg	1000mg/kg
Mortality	None	
Clinical observations	Emesis at 1000mg/kg	
EKG	▲ Decrease in heart rate in dosed and control animals during dark cycle reflected as increase in RR interval ▲ QT prolongation not noted by study laboratory	

Study title: XL184: Effects on general activity and behaviour in the rat following oral administration

Study no.: XL184-NC-007
Study report location: Electronic submission , M4.2.1.3
Conducting laboratory and location: (b) (4)
Date of study initiation: December 7, 2004
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: XL184, batch # EGI759-90A, 99.3% pure

Key Study Findings:
- Single dose NOAEL of 300 mg/kg for general activity and behavior

Methods

Doses: 100, 300, 900mg/kg
Frequency of dosing: Single dose
Route of administration: Oral gavage
Dose volume: 10mL/kg
Formulation/Vehicle: Ethanol:PEG400:water (5:45:50)
Species/Strain: Wistar rats
Number/Sex/Group: 6M/group
Age: 6w
Weight: 175-205g
Satellite groups: Toxicokinetics
Unique study design: ▲Irwin's observations performed at 30, 60, 120, 240, 300min, and 24h post dose, and held for 7d recovery.

Results: No behavioral or physiological changes observed at 100 or 300 mg/kg XL184. Signs of toxicity were observed beginning at day 4 in animals administered 900mg/kg. One of 6 HD animals died, and 3 additional animals were sacrificed moribund. The remaining 2 animals administered 900 mg/kg exhibited uncoordinated gait, piloerection, and decreased body tone, abnormal breathing, hypothermia, ptosis, and apathy. Histopathological examination indicated marked distension of bladder, hemorrhagic jejunum and inflated dark lungs in one animal sacrificed moribund. The mean C_{max} and $AUC_{0\text{-}24h}$ at 900 mg/kg were 78467 ng/mL and 1349932 ng.hr/mL, respectively.

Study title: XL184: Measurement of respiratory parameters in the freely moving conscious rat using whole body plethysmography

Study no.:	XL184-NC-008
Study report location:	Electronic submission , M4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 1, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XL184, batch # EGI759-90A, 99.3% pure

Key Study Findings:

● No significant changes in respiratory parameters were exhibited in conscious rats administered single doses up to 900 mg/kg.

Methods

Doses:	100, 300, 900mg/kg
Frequency of dosing:	Single dose
Route of administration:	Oral gavage
Dose volume:	10mL/kg
Formulation/Vehicle:	Ethanol:PEG400:water (5:45:50)
Species/Strain:	Wistar rats
Number/Sex/Group:	6M/group
Age:	6w
Weight:	175-205g
Satellite groups:	None
Unique study design:	None

5. Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption:

XL184-Disc-029	**Single dose pharmacokinetic profile of EXEL-02977184 in female CD rats**
XL184-Disc-031	**Single dose pharmacokinetic profile of EXEL-02977184 in female CD rats**

Study location: M4.2.2.2

In single dose absorption studies in rats, alternative salt forms of XL184 were compared to the free base form. Groups of 3 CD-1 rats were administered a 3 mg/kg dose of XL184 in solution in the maleic, malic, phosphate or hydrochloride salt form. In a separate experiment, a single 5 mg/kg dose was administered to rats in solution in the free base, hydrochloride and bisulphate salt forms. The drug was either formulated in ethanol:PEG400:Solutol:water, or dosed as a dry powder in a gelatin capsule via gavage.

Oral exposure ($AUC_{0\text{-}inf}$) of XL184 for the 5 mg/kg dose of the free base was increased compared to the hydrochloride and bisulphate salt (see tables) through oral bioavailability was similar for the free base and hydrochloride salt (111 and 92%, respectively). Oral exposure ($AUC_{0\text{-}inf}$) of XL184 for the 3 mg/kg oral capsule was similar for the maleic, malic and hydrochloride salts. Oral bioavailability of the capsule dose was most similar between the maleic and hydrochloride salts (74-79%).
Reviewers comment: The XL184 free base should have been added to Study XL184-Disc-031 in order to provide a direct comparison between the free base and the salts tested.

Pharmacokinetics of XL184 salt forms following single iv or oral doses in rats

Study Report XL184-Disc-029	Free Base		Hydrochloride		Bisulphate	
Dose (mg/kg)	5	5	5	5	5	5
Route	IV	PO	IV	PO	IV	PO
Formulation	EPSW	EPSW	EPW	EPW	EPW	EPW
t_{max} (h)	0.25	4.0	0.25	4.0	1.0	2.0
C_{max} (µM)	18.7	14.6	16.5	15.2	14.4	9.14
$t_{1/2}$	10.9	14.1	8.8	9.0	9.5	10.9
$AUC_{0\text{-}t}$ (µM•h)	196	192	169	153	155	192
$AUC_{0\text{-}inf}$ (µM•h)	259	288	202	186	117	153
CL (L/kg/h)	0.038	NA	0.045	NA	0.043	NA
V_{dss} (L/kg)	0.6	NA	0.6	NA	0.6	NA
%F	—	111	—	92	—	79.6
$AUC_{0\text{-}t}$/Dose (µM•h/mg/kg)	39.3	38.6	33.9	30.6	30.9	23.3

$AUC_{0\text{-}t}$, area under the plasma concentration-time curve during the experimental time period (t = 24h); $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$/Dose, dose-normalized $AUC_{0\text{-}t}$; C_{max}, observed maximum plasma concentration; CL, clearance after IV administration; EPSW, Ethanol:PEG400:Solutol®:water (5:35:5:55; v:v:v:v); EPW, ethanol:PEG400:water (5:45:50; v:v:v) solution; %F, oral bioavailability; IV, intravenous; NA, not applicable; PO, oral; $t_{1/2}$, terminal phase half-life; t_{max}, observed time to reach C_{max}; V_{dss}, steady-state volume of distribution; Water, water formulation.
Note: XL184 limit of quantitation (LOQ) = 0.004 µM.

Study Report XL184-Disc-031	Maleic			Malic			Phosphate			Hydrochloride		
Dose (mg/kg)	3	3	3	3	3	3	3	3	3	3	3	3
Route	IV	PO	PO	IV	PO	PO	IV	PO	PO	IV	PO	PO
Formulation	EPW	EPW	Cap	EPW	EPW	Cap	EPW	EPW	Cap	EPW	EPW	Cap
t_{max} (h)	2.00	4.00	4.00	1.00	4.00	4.00	1.00	4.00	4.00	0.50	4.00	4.00
C_{max} (µM)	13.3	8.79	8.22	12.4	8.53	12.2	13.6	6.26	8.35	20.3	14.5	11.7
$t_{1/2}$	12.8	16.3	11.4	13.9	13.0	12.7	12.1	12.2	13.3	12.2	15.1	13.7
AUC_{0-t} (µM•h)	151	117	120	151	99.7	135	130	75.3	106	198	151	145
AUC_{0-inf} (µM•h)	154	122	122	154	102	138	132	76.6	108	200	155	148
CL (L/kg/h)	0.039	—	—	0.039	—	—	0.045	—	—	0.030	NA	NA
V_{dss} (L/kg)	0.61	—	—	0.61	—	—	0.65	—	—	0.41	NA	NA
%F	—	79.7	79.1	—	65.9	89.6	—	58	82	NA	78	74
AUC_{0-t}/Dose (µM•h/mg/kg)	50.3	39.1	40.0	50.4	33.2	45.1	43.4	25.1	35.3	65.9	50.3	48.4

AUC_{0-t}, area under the plasma concentration-time curve during the experimental time period (t = 72h); AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}/Dose, dose-normalized AUC_{0-t}; Cap, soft gelatin capsule; CL, clearance after IV administration; C_{max}, observed maximum plasma concentration; EPW, ethanol:PEG400:water (5:45:50; v:v:v) solution; %F, oral bioavailability; IV, intravenous; NA, not applicable; PO, oral; $t_{1/2}$, terminal phase half-life; t_{max}, observed time to reach C_{max}; V_{dss}, steady-state volume of distribution; Water, water formulation.
Note: XL184 limit of quantitation (LOQ) = 0.004 µM.

(Tables excerpted from sponsor's submission)

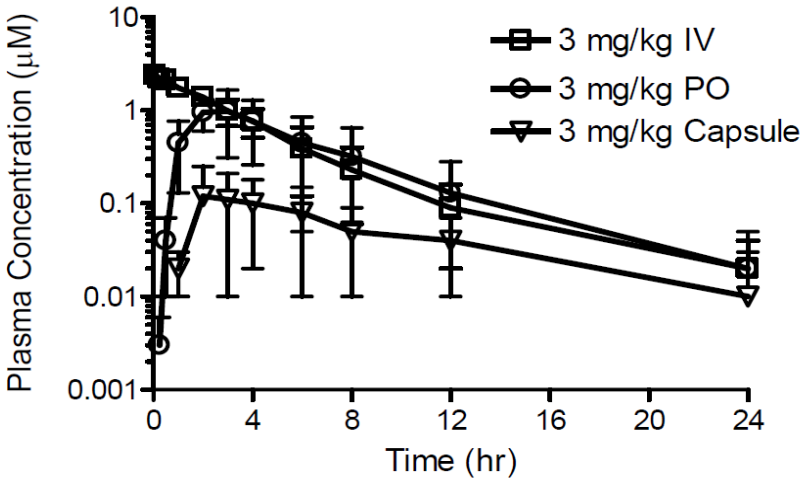
Study title: Single dose pharmacokinetic profile of EXEL-02977184 in male cynomolgus monkeys
Study no.: XL184-Disc-034
Study report location: M4.2.2.2

A single dose absorption study was performed in groups of male cynomolgus monkeys (3 monkeys/group) over 24 hours, comparing a 3 mg/kg iv dose to oral gavage and capsule administration of the hydrochloride salt form of XL184. Systemic exposure and bioavailability of the capsule form was markedly lower compared to the liquid oral dose. Intravenous administration of XL184 resulted in a volume of distribution of 2.7 L/kg indicating significant extravascular distribution. Half-life of the liquid and capsule dosage forms was 4 and 6 h, respectively.

Study Report XL184-Disc-034	Dose (mg/kg)		
	3	3	3
Route	IV	PO	PO
Formulation	EPW	EPW	Capsule
t_{max} (hours)	0.08	3.0	2.0
C_{max} (µM)	2.51	0.98	0.12
$t_{1/2}$ (hours)	3.92	4.18	6.07
AUC_{0-t} (µM•h)	8.74	6.46	1.12
AUC_{0-inf} (µM•h)	8.65	6.33	1.09
CL (L/kg/h)	0.64	—	—
Vdss (L/kg)	2.67	—	—
%F	—	73	13
AUC_{0-t}/Dose (µM•h/mg/kg)	2.91	2.15	0.37

AUC_{0-t}, area under the plasma concentration-time curve during the experimental time period (t = 24 h); AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}/Dose, dose-normalized AUC_{0-t}; C_{max}, observed maximum plasma concentration; CL, clearance after IV administration; EPW, Ethanol:PEG400:water (5:45:50, v:v:v); %F, oral bioavailability; IV, intravenous; PO, oral; $t_{1/2}$, terminal phase half-life; t_{max}, observed time to reach C_{max}; V_{dss}, steady-state volume of distribution.
Limit of quantitation (LOQ) = 0.004 µM.

Figure 1: Mean (± SD) Plasma Concentration-Time Profiles of EXEL-7184 in Male Cynomolgus Monkeys Following Single-Dose Administration (IV, PO and Gelatin Capsule)



(Table and figure excerpted from sponsor's submission)

Title: XL184: Comparative bioavailability study of intravenous and oral dosage forms in beagle dogs
Study no.: XL184-NC-017
Study report location: M4.2.2.2

A comparative bioavailability study of intravenous, and oral (L-Malate dry powder in 25-mg gelatin capsules, oral aqueous formulation, and iv bolus formulation) 50 mg doses of XL184 was conducted in beagle dogs; dogs were administered for 3 doses of XL184 separated by a 1-week washout. Absolute bioavailability values for the capsule and aqueous suspension formulations were approximately equivalent (54.8% and 50.6%, respectively). Relative bioavailability of the capsule vs. suspension formulation was 108%; the C_{max} for the capsule was 110% of that of the aqueous suspension. Mean terminal half-life values for all treatment groups were similar, ranging from 5.5 to 6.6 hours.

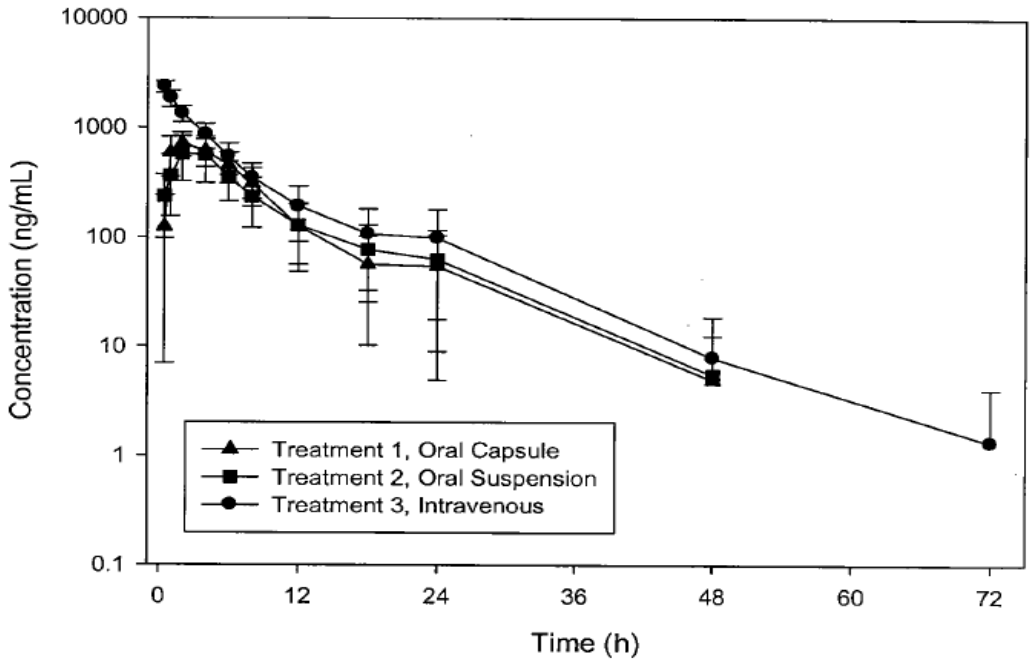


Table 3-1: Mean Pharmacokinetic Parameters of XL184 from Intravenous (IV) and Oral (PO) Dosage Formulations after Administration of XL184 to Male Beagle Dogs

Treatment No.	Subject	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
1	N	8	8	8	8	8
(PO Capsule)	Mean	5.47	2.25	760	6300	6420
	SD	2.2	1.16	197	2480	2530
	CV%	40.1	51.8	26	39.4	39.4
2	N	8	8	8	8	8
(PO Aqueous)	Mean	6.58	3.13	668	5820	5930
	SD	2.1	1.64	283	2430	2460
	CV%	31.9	52.5	42.4	41.8	41.4
3	N	8	8	8	8	8
(IV)	Mean	5.5	0.5	2350	11500	11600
	SD	2.17	0	286	3620	3610
	CV%	39.4	0	12.2	31.5	31.2

$AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to the last observable concentration above the limit of quantitation; C_{max}, observed maximum plasma concentration; CV, coefficient of variation; SD, standard deviation; $t_{1/2}$, terminal phase half-life; t_{max}, time to reach the maximum plasma concentration.

(Table and figure excerpted from sponsor's submission)

The repeat-dose administration pharmacokinetics/toxicokinetics of XL184 are discussed in section 5.2.

Distribution:

Study title: Quantitative tissue distribution of drug-related material using whole-body autoradiography following a single oral does of [^{14}C]BMS-907351 (10 mg/kg) to male Sprague Dawley and Long-Evans rats and human radiation dosimetry prediction.
Study no.: BMS-907351
Study report location: M4.2.2.3

The concentration of total reactivity of BMS-907351 (XL184) was measured in plasma and selected tissues following a single oral administration of 10 mg freebase/kg [^{14}C]BMS-907351 to male Sprague-Dawley and Long-Evans rats using quantitative whole-body autoradiography. In addition, a prediction of human radiation dosimetry was performed. The highest concentrations of drug-derived radioactivity at T_{max} (>100 µg equiv/g) were found in the alimentary canal contents and bile of pigmented rats. The highest concentration of radioactivity in tissues at T_{max} were found in the eye and eye uveal tract, small intestine, Harderian gland, liver, white adipose tissue, adrenal gland, brown adipose tissue and stomach. The highest concentration in blood was observed at 2 hours post-dose; [^{14}C]BMS-907351 was detectable 5 days following dosing. Maximum concentrations of radioactivity (C_{max}) were observed at 2 hours and 1 hour post-dose in pigmented and albino rats, respectively. Low concentrations were observed in the CNS. Generally similar patterns of tissue distribution were observed in albino and pigmented rats, although concentrations in ocular tissues were higher in pigmented rats. Distribution of metabolites was not measured. See tables below excerpted from sponsor's submission. Predicted human dosimetry is not discussed below.

Placental transfer studies with XL184 were not conducted, although measurable levels of XL184 were observed in fetal tissue following maternal administraton in rats and rabbits (see Section 9, Reproductive and developmental toxicology).

Table 7: Tissue to Blood AUC Ratios in Male Pigmented Rats After Single PO Dose of [^{14}C]BMS-907351 at 10 mgkg

Tissue	AUCall (µg equiv•h/g)	Tissue:Blood AUC Ratio
Adipose (brown)	257.1230	1.50
Adipose (white)	215.0993	1.25
Adrenal Gland	594.5565	3.46
Blood (cardiac)	171.6498	1.00
Bone	9.2700	0.05
Bone Marrow	143.6733	0.84
Brain (cerebellum)	17.8095	0.10
Brain (cerebrum)	16.3493	0.10
Brain (entire)	17.7608	0.10
Brain (medulla)	15.1835	0.09
Cecum	210.7605	1.23
Epididymis	110.7245	0.65
Esophagus	114.5240	0.67
Eye (entire)	4953.4085	28.86
Eye (lens)	14.1680	0.08
Eye (uveal tract)	31433.8323	183.13
Harderian Gland	526.7145	3.07
Heart (myocardium)	157.2288	0.92
Kidney (entire)	244.7588	1.43
Large Intestine	165.4650	0.96
Liver	454.5560	2.65
Lung	219.7675	1.28
Lymph Node	114.6773	0.67
Pancreas	207.9748	1.21
Pituitary Gland	238.5568	1.39
Prostate Gland	73.9435	0.43
Renal Cortex	251.4278	1.46
Renal Medulla	238.9788	1.39

Table 7 (cont'd): Tissue to Blood AUC Ratios in Male Pigmented Rats After a Single PO Dose of [^{14}C]BMS-907351 at 10 mgkg

Tissue	AUCall (µCi•h/g)	Tissue:Blood AUC Ratio
Salivary Gland	233.0895	1.36
Seminal Vesicles	38.4615	0.22
Skeletal Muscle	107.2503	0.62
Skin (non-pigmented)	108.6385	0.63
Skin (pigmented)	225.7130	1.31
Small Intestine	398.1613	2.32
Spinal Cord	14.9243	0.09
Spleen	122.9110	0.72
Stomach (gastric mucosa)	201.2873	1.17
Testis	53.5430	0.31
Thymus	107.5598	0.63
Thyroid	131.2650	0.76
Urinary Bladder	85.1655	0.50

(Table excerpted from sponsor's submission)

Study title: Protein binding, stability, and biotransformation of EXEL-02977184
Study no.: XL184-Disc-035
Study report location: M4.2.2.3

In vitro and *in vivo* models were used to define protein binding of XL184. At a concentration of 1 to 10 µM in mouse plasma, 0.2 to 10 µM in rat plasma, and 0.2 to 10 µM in human plasma, XL184 was highly protein bound *in vitro* (99.8 to 99.9%). *In vivo* binding of XL184 following oral gavage dosing of 30 and 100 mg/kg in mice and 100 and 300 mg/kg in rats indicated protein binding of 99.3 to 99.9% in both species (see table below). This study also attempted to characterize biotransformation products of XL184, which is discussed under metabolism.

Table 5: In Vivo Protein Binding of EXEL-7184 in Mouse and Rat Plasma Determined by Equilibrium Dialysis

Species	Dose (mg/kg)	Time Interval (hours)	Bound (%)	Bound Mean (%)
Mouse	30	0.5	99.8 ± 0.05	99.3 ± 0.54
		1	99.7 ± 0.04	
		2	99.7 ± 0.05	
		4	98.0 ± 2.03	
	100	0.5	99.7 ± 0.09	99.8 ± 0.05
		1	99.9 ± 0.05	
		2	99.8 ± 0.02	
		4	99.8 ± 0.03	
Rat	100	0.5	>99.9	>99.9 ± 0.02
		1	99.9 ± 0.02	
		2	99.9 ± 0.01	
		4	99.9 ± 0.02	
	300	0.5	>99.9	>99.9 ± 0.01
		1	99.9 ± 0.01	
		2	99.9 ± 0.01	
		4	99.9 ± 0.01	

(Table excerpted from sponsor's submission)

Metabolism:

Study title: Protein binding, stability, and biotransformation of EXEL-02977184
Study no.: XL184-Disc-035
Study report location: M4.2.2.4

Biotransformation products of XL184 were characterized both *in vitro* and *in vivo* in mice and rats. *In vivo*, mouse plasma metabolites M5 and M9 were present in higher concentrations, while in rat plasma, M4 and M9 were most abundant. As a percentage of the parent drug, the *in vivo* metabolites accounted for up to approximately 10% and 34% in rat and mouse plasma, respectively (Table 7 excerpted from sponsor's submission).

When mouse liver fractions were incubated up to 4 hours with XL184 and NADPH, 5 metabolites (M1, M4, M6, M10, and M11), representing ~12% of total drug conversion resulted, compared to 5% of drug conversion following incubation with rat liver fractions (M1, M4, and M6), and 24% conversion following incubation with human liver microsomal fractions (M1, 14, and M6) (Table 23 excerpted from sponsor's submission). No peaks were observed in the absence of NADPH. These data indicate that XL184 does not appear to be extensively metabolized *in vitro*.

Table 7: Summary of Relative Percentage of In Vivo Metabolites of EXEL-7184 Following Oral Gavage

Plasma	Time (hours)	M1[a] (%)	M2 (%)	M3 (%)	M4 (%)	M5 (%)	M7 (%)	M8 (%)	M9 (%)	EXEL-7184 (%)
Mouse[b]	0.5	3.04	0.54	0.27	0.43	8.46	0.65	0.42	3.75	82.4
	1	4.23	0.61	0.28	0.45	9.87	0.84	0.78	4.30	78.6
	2	5.14	0.38	0.37	1.02	16.5	1.43	1.37	7.72	66.0
	4	5.85	0.49	0.35	1.16	15.1	1.41	1.29	8.22	66.1
Rat[c]	0.5	0.82	0.64	0.54	0	0.83	0	0	1.45	95.7
	1	2.25	0.79	0.44	0.64	1.99	0.35	0.35	3.23	90.0
	2	2.37	0.81	0.44	2.23	1.34	0.15	0.79	2.41	89.5
	4	2.51	1.00	0.49	2.39	0.72	0.03	0.86	2.22	89.8

[a] The relative percentage of metabolites were estimated based upon the assumption that the parent and metabolites have the same UV extinction coefficient.
[b] 100-mg/kg dose.
[c] 300-mg/kg dose.

Table 23: Summary of Relative Percentage of XL184 Metabolites of Generated In Vitro Using Hepatic Microsomal Preparations from Different Species (Study Report XL184-Disc-035)

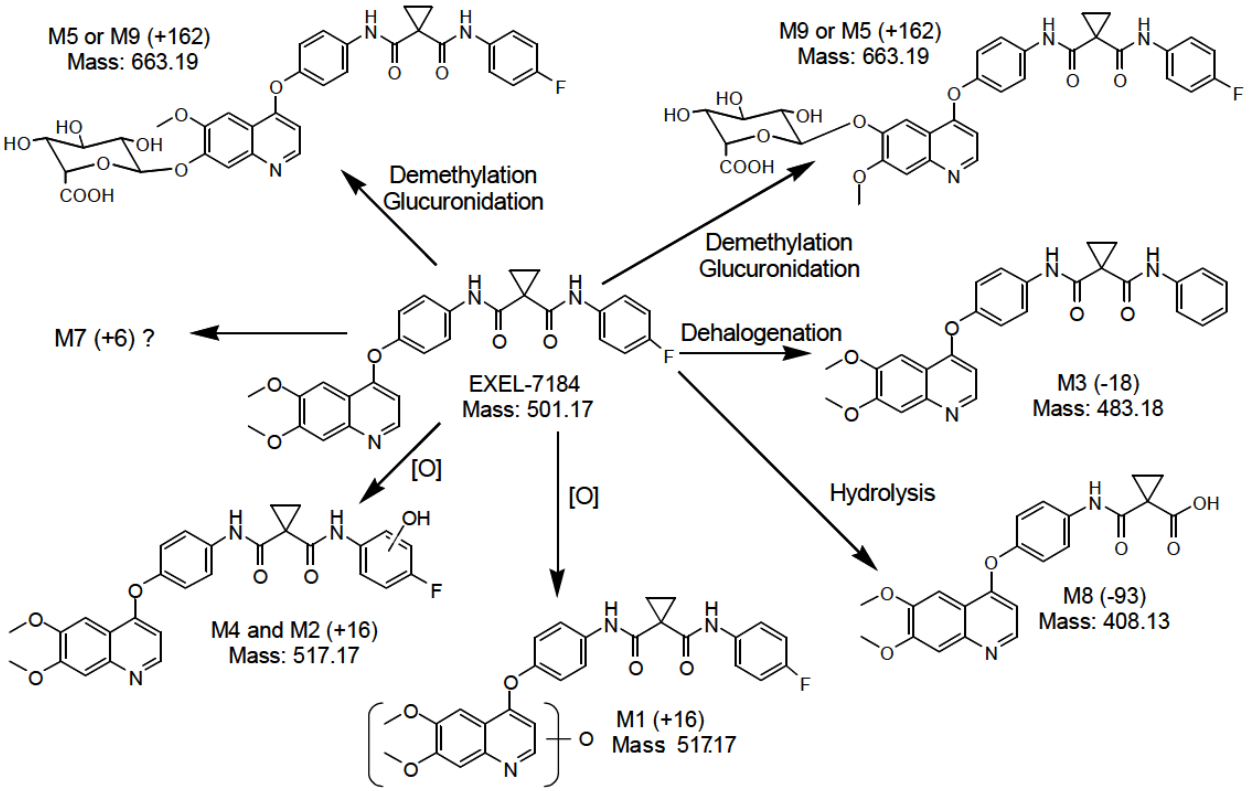
Study Report XL184-Disc-035

Hepatic Microsomal Preparations (Species)	Incubation Time (h)	M1[a] (%)	M4 (%)	M6 (%)	M10 (%)	M11 (%)	XL184 (%)	Total (%)
Human	0	0	0	0	NA	NA	100	100
	0.5	3.15	4.29	2.34	NA	NA	90.2	100
	1	4.74	4.20	3.94	NA	NA	87.1	100
	2	7.27	7.45	6.03	NA	NA	79.2	100
	4	9.72	7.84	6.57	NA	NA	75.9	100
Mouse	0	0	0	0	0	0	100	100
	0.5	2.41	0.84	1.63	1.68	0.34	93.1	100
	1	3.24	1.29	2.74	2.17	1.04	89.5	100
	2	4.44	1.59	3.14	1.80	1.81	87.2	100
	4	4.38	1.53	2.88	1.38	2.06	87.8	100
Rat	0	0	0	0	NA	NA	100	100
	0.5	0.78	0.39	0.43	NA	NA	98.4	100
	1	1.12	0.55	0.65	NA	NA	97.7	100
	2	1.67	0.55	0.76	NA	NA	97.7	100
	4	1.94	0.61	0.96	NA	NA	96.5	100

NA, not applicable.
[a] The relative percentage of metabolites was estimated based upon the assumption that the parent and metabolites have the same UV extinction coefficient (ie, 254 nm).

(Tables and figure excerpted from sponsor's submission)

The proposed *in vivo* biotransformation schema for XL184 as defined in this study is presented below.



CRL-20000504	Mass balance of radioactivity after oral administration of [14C]BMS-907351 to male and female Sprague-Dawley rats
XL184-MBA00472	BMS-907351: Pharmacokinetics following oral administration to non-naïve male Beagle dogs

				% of Compound in Sample					
Species	**Sample**	**Sampling Time or Period**	**Mean PK Parameter Value**	**Parent**	**M1**	**M4**	**M5**	**M9**	**Study No.**
Mouse[b,d]	Plasma	4 hr		66.1	5.85	1.16	15.1	8.22	XL184-Disc-035
Rat[b,d]	Plasma	4 hr		89.8	2.51	2.39	0.72	2.22	XL184-Disc-035
Rat[a,c,e,g]	Plasma	0-168 hrs post-dose	Cmax (ng/mL) Tmax (h) AUC0-t (ng.h/mL)	11657 4-6 168884	338 4-6 3192	-	-	-	CRL-20000504
Dog [c,f,g]	Plasma	0-72 hrs post-dose	Cmax (ng/mL) Tmax (h) AUC0-t (ng.h/mL)	1560 1.4 8900	93.9 1.8 453	-	-	-	XL184-MBA00472

In separate studies ([redacted] (b) (4) scientific reports), metabolite M1 (N-oxide metabolite) was compared to metabolites M4, M5, and M9, and found at significantly higher concentrations (see table above excerpted from sponsor's submission).

Comparative metabolic profiling in rats, dogs and humans:
Metabolic profiling of clinical plasma samples have identified four metabolites of XL184 (an N-oxide; a monohydroxy sulfate; a half dimer; and a monodemethyl half dimer) that are present at >10% of parent drug systemic exposure at steady state. Human exposures to these four metabolites exceed those measured in plasma samples from rat and dog species administered XL184 in repeat dose studies. Based on the intended treatment population of advanced MTC for XL184, the Applicant cites ICH S9 when indicating that separate evaluations of human metabolites are not required for treatment indications of advanced cancer patient populations. No additional nonclinical testing of the drug metabolites is intended.

Genetic toxicity assays of metabolites are reviewed under section 7, Genetic Toxicology, of this NDA. The XL184 N-oxide metabolite was not mutagenic at concentrations ranging from 40 to 5000 µg/plate; precipitation was observed at concentrations >158 µg/plate (study #BMS-927982). Para-fluoroaniline (p-FA) (b) (4) was a positive mutagen in tester strain TA98 under conditions of metabolic activation ((b) (4) p-FA levels are below the limits of quantitation (<2ng/mL) in the plasma of patients administered a dose of 175 mg cabozantinib.

Study title: Pharmacokinetics of selected XL184 metabolites in rats, dogs and humans
Study No: XL184-NC-029 (incorporating toxicokinetic results from studies XL184-NC-018, XL184-NC-020, and XL184-012 (fertility study in rats, 6-month dog studies).
Study location: 4.2.2.4

The pharmacokinetics of XL184 and selected metabolites M1 (XL184-N-oxide), M4 (XL184-monohydroxy-sulfate), M8 (XL184-amide cleavage product), and para-fluoroaniline (pFA) were compared in rats and dogs administered XL184 in repeat-dose rat and dog studies and in humans administered a single 175 mg oral dose of XL184 in a healthy volunteer mass balance study XL184-012 (see tables below).

When measured quantitatively using validated LC-MS/MS, dogs and rats were exposed to the 4 metabolites at low levels compared to human exposure. The mean percentage AUC of metabolite relative to AUC of XL184 in humans was 43% for M4, 15% for M1, and 10% for M8. The pFA level was below the limit of quantitation. Interspecies differences in metabolite exposures as compared below are, however, not definitive, as the studies reflect variations in study duration and dose levels, and do not account for parameters which may affect results (e.g. interspecies differences in accumulation, drug related toxicities, non-linear pharmacokinetics).

Table 3-3: Summary Statistics of PK Parameters of XL184 and Selected Metabolites in Humans after a Single XL184 Dose of 175 mg (Exelixis Study XL184-012)

XL184				
Statistics	**T_{max} (hr)**	**C_{max} (µg/mL)**	**AUC_{last} (µg × hr/mL)**	
N	8	8	8	
Mean	1.6	1.3	67.2	
Median	1.5	1.3	69.1	
SD	0.7	0.2	6.9	
%CV	45.8	19.1	10.2	
M4 Monohydroxy Sulfate Metabolite				
Statistics	**T_{max} (hr)**	**C_{max} (µg/mL)**	**AUC_{last} (µg × hr/mL)**	**% ($AUC_{Metabolite\ Sulfate}/AUC_{XL184}$)**
N	8	8	8	8
Mean	21.9	0.236	28.9	43.0
SD	14.0	0.067	10.7	14.3
Median	24.0	0.248	28.4	45.3
CV%	64.2	28.2	37.0	33.4
M1 N-Oxide Metabolite				
Statistics	**T_{max} (hr)**	**C_{max} (µg/mL)**	**AUC_{last} (µg × hr/mL)**	**% ($AUC_{Metabolite\ N\text{-}oxide}/AUC_{XL184}$)**
N	8	8	8	8
Mean	13.1	0.12	10.1	15.0
SD	11.6	0.03	3.22	3.8
Median	13.5	0.12	9.33	14.5
CV%	88.6	28.3	31.7	25.4
M8 Half-dimer Amide Cleavage Metabolite				
Statistics	**T_{max} (hr)**	**C_{max} (µg/mL)**	**AUC_{last} (µg × hr/mL)**	**% ($AUC_{Metabolite\ half\text{-}dimer}/AUC_{XL184}$)**
N	8	8	8	8
Mean	16.4	0.053	6.54	9.9
SD	8.52	0.017	1.69	3.2
Median	19	0.050	6.46	9.4
CV%	52.0	32.6	25.8	32.3

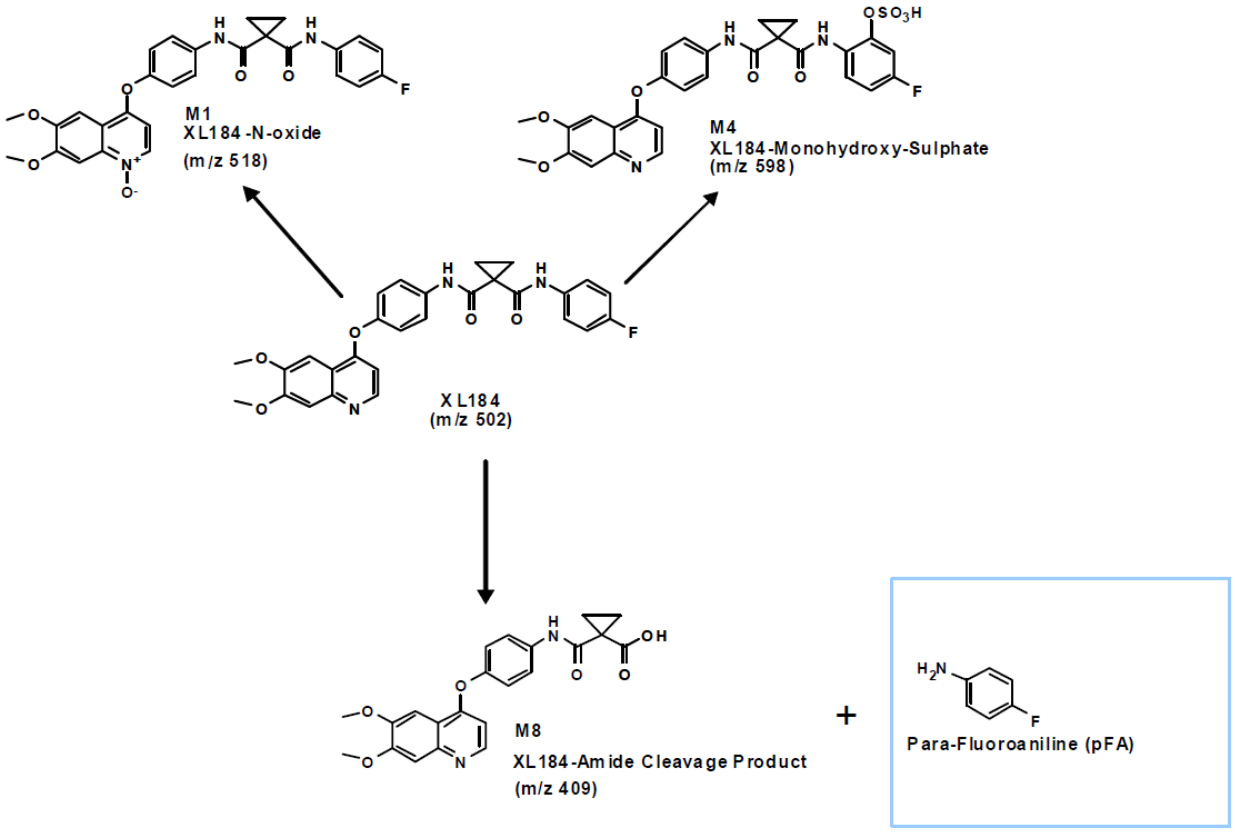
$AUC_{0\text{-}last}$, area under the plasma concentration-time curve from time 0 to the last observable concentration above the limit of quantitation; % ($AUC_{metabolite}/AUC_{XL184}$), (ratio $AUC_{0\text{-}last}$ of metabolite to $AUC_{0\text{-}last}$ of XL184)×100; C_{max}, observed maximum plasma concentration; t_{max}, time to reach the maximum plasma concentration.

Table 3-4: Summary PK Statistics (AUC Values) of XL184 and Selected Metabolites in Rats, Dogs, and Humans

Day	Dose (mg/kg)	XL184 AUC (ng×hr/mL)	M4 Sulfate AUC (ng×hr/mL)	M1 N-oxide AUC (ng×hr/mL)	M8 Half-dimer AUC (ng×hr/mL)	pFA AUC (ng×hr/mL)	% ($AUC_{M4,sulfate}/AUC_{XL184}$)	% ($AUC_{M1,N\text{-}oxide}/AUC_{XL184}$)	% ($AUC_{M8,Half\text{-}dimer}/AUC_{XL184}$)	% (AUC_{pFA}/AUC_{XL184})
					Rat					
D70	1	18800	1250	579	93	BLOQ	6.65	3.08	0.49	BLOQ
D70	2.5	46800	2690	1520	205	BLOQ	5.75	3.25	0.44	BLOQ
GD7	1	19100	152	338	20	BLOQ	0.80	1.77	0.10	BLOQ
GD7	2.5	68300	836	1370	129	BLOQ	1.22	2.01	0.19	BLOQ
					Dog					
22	20	16600	36.9	657	355	18.4	0.24	4.08	2.03	0.09
					Human					
1	Single dose 175 mg	67200	28900	10133	6544	BLOQ	43.0	15.0	9.90	BLOQ

AUC, area under the plasma concentration-time curve from time 0 to the last observable concentration above the limit of quantitation; % ($AUC_{metabolite}/AUC_{XL184}$), (ratio $AUC_{0\text{-}last}$ of metabolite to $AUC_{0\text{-}last}$ of XL184)×100; BLOQ, below the lower limit of quantification; GD, gestational day.

Comparative *in vivo* metabolic pathways for rats and dogs (Note: This is similar to the biotransformation pathway presented in Study-Disc-035 above).



(Tables and figure excerpted from sponsor's submission)

CYP induction *in vivo*

Study title: Non-GLP *in vivo* toxicity evaluation of EXEL-02977184 in female CD rats following sub-chronic oral gavage administration
Study no.: XL184-Disc-036

CYP induction following exposure to XL184 was studied in hepatic fractions of female CD rats administered doses of 1, 3, 10, 30, or 100mg/kg/day for up to 8 days. CYP induction was measured by both total protein and mRNA content. CYP1A1 protein content increased by 1.5-fold in rats administered 100mg/kg, while CYP3A levels increased by ~ 1.5 to 1.7-fold at doses ≥ 3 mg/kg. CYP2B was generally consistent, and unaffected. mRNA analysis indicated increased levels for CYP1A1 at 30 and 100 mg/kg, although induction was variable. CYP3A23 mRNA levels increased ~5-fold at 100 mg/kg. (Figures excerpted from sponsor's submission).

Figure 5: Hepatic CYP450 Content in Female CD Rats after Sub-Chronic 8 D Exposure to EXEL-7184

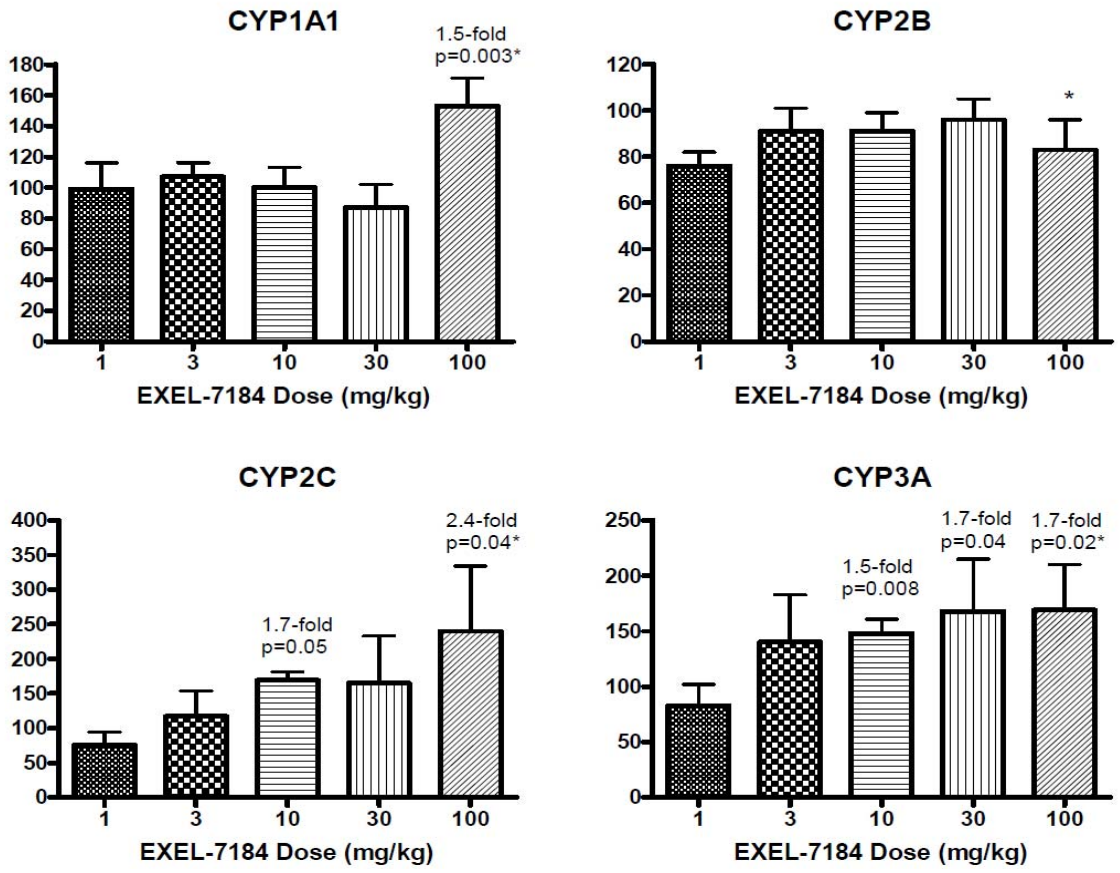
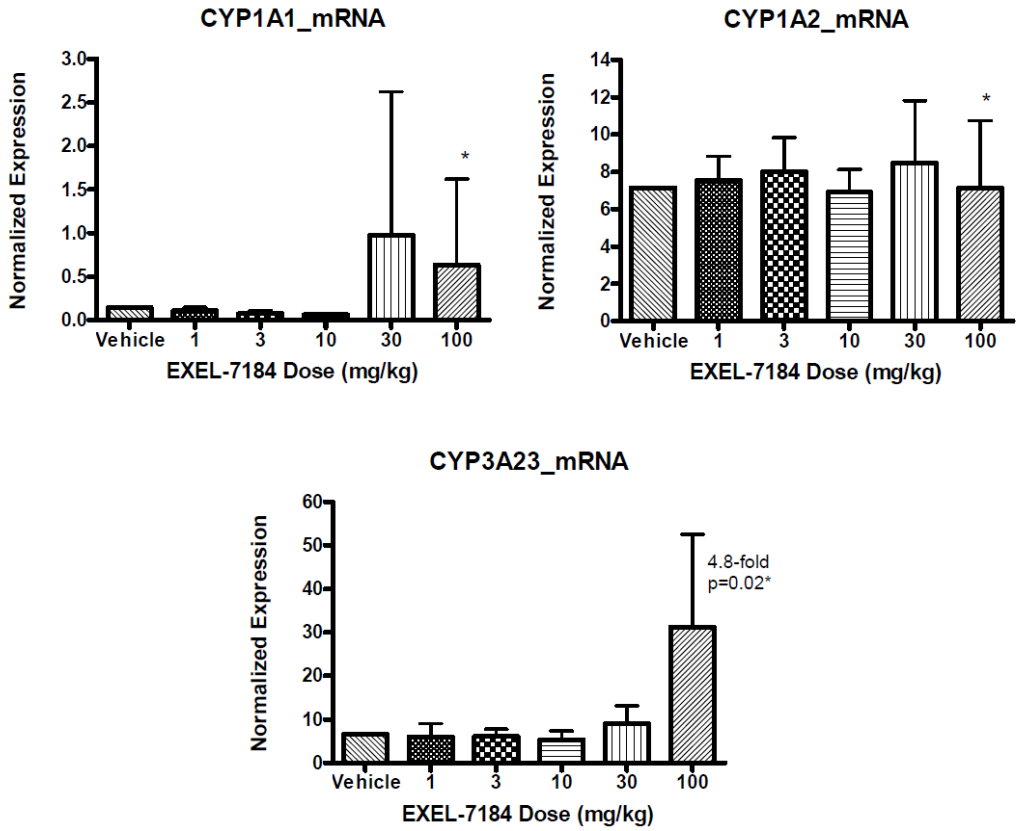


Figure 6: Hepatic CYP450 mRNA Content in Female Rats after Sub-Chronic 8 Day Exposure to EXEL-7184



Excretion

Study title: Mass balance of radioactivity after oral administration of [^{14}C]BMS-907351 to male and female Sprague-Dawley rats
Study no.: CRL-200000504
Study report location: M4.2.2.5

Following an oral dose of 10 mg/kg [^{14}C] XL184 to male and female Sprague-Dawley rats (80.5-81.4 µCi/kg), drug-related radioactivity was eliminated primarily in feces. Mean recoveries through 168 hours post dose were 85.6% in feces and 9.1% in urine in males and 82.1% in feces and 11.8% in urine in females.

Cmulative Excretion[c]: 0-Time (h)	Urine	Feces	Total	Urine	Feces	Total
0 – 6	1.69	-	1.69	0.89	-	0.89
0-12	3.31	-	3.31	2.41	-	2.41
0-24	5.34	28.67	34.02	5.12	20.95	26.07
0-48	7.81	59.17	66.98	8.48	44.56	53.04
0-72	8.60	75.42	84.02	10.31	56.15	66.46
0-96	8.91	84.24	93.15	11.14	61.99	73.13
0-120	9.01	85.21	94.22	11.52	71.78	83.30
0-144	9.05	85.52	94.57	11.71	81.18	92.89
0-168	9.06	85.64	94.70	11.81	82.05	93.86

(Table excerpted from sponsor's submission)

Drug-Drug Interaction

Study title: *In vitro* ADME properties of EXEL-02977184
Study no.: XL184-Disc-037
Study report location: M4.2.2.6

XL184 was demonstrated to be a P-gp inhibitor with an IC_{50} of 2.7 - 7.0μM, but is not a P-gp substrate.

Toxicokinetics

Toxicokinetics associated with repeat dosing in animal models were reviewed with associated studies (see General Toxicology). In general, XL184 exhibited time-dependent differences in pharmacokinetics between single-dose and multiple-dose administration within dose and gender groups.

Comparative toxicokinetics of cabozantinib

Test Article: XL184	Steady-State AUC (ng•h/mL)					
Daily Dose (mg/kg/day)	Rats		Dogs		Female Rabbits	Humans
	Male	Female	Male	Female		
0.1	2,632[a]	4,753[a]	—	—	—	—
0.2	—	—	291[c]	338[c]	—	—
0.3	7,851[a]	14,416[a]	—	—	274[e]	—
1	29,736[a] 10,978[b]	44,086[a]	2,027[c]	2,011[c]	384[e]	—
1.79	—	—	—	—	—	29,100[f]
2.5	—	—	—	—	—	37,850[g]
3	—	—	—	—	4,240[e]	—
5	52,152[b]	—	7,757[c]	6,327[c]	—	—
10	—	—	8,406[d]	11,408[d]	—	—
15	512,771[b]	—	—	—	—	—

AUC, area under the plasma concentration time curve.
[a] Study XL184-NC-013, a 6-month study.
[b] Study XL184-NC-005, a 14-day study.
[c] Study XL184-NC-012, a 6-month study.
[d] Study XL184-NC-006, a 14-day study.
[e] Study XL184-NC-024, an embryotoxicity/teratogenicity study.
[f] Clinical Study Report XL184-201 as of July 2010. XL184 dose: 125 mg (n=6)
[g] Clinical Study XL184-001, XL184 capsule form dose: 175 mg (n=26).

Pharmacokinetic summary of XL184 in animal models (3mg/kg single dose unless otherwise indicated)

	Mouse	Rat	Dog	Monkey
$AUC_{0-\infty}$ (μM·h)	10.3[c]	132	8.69	6.33
%F	42	82	87	73
%F (SOD)[b]	- -	87 -	18 54.8[e]	13 -
t_{max} (h)	0.5	4.0	3.0	3.0
Plasma $t_{1/2}$ (h)	3.6	12.9	4.88	4.18
CL (L/kg/h)	0.229[d]	0.034	0.56	0.64
Vd_{ss} (L/kg)	0.93[c]	0.61	2.10	2.67
Intrinsic CL (mL/min/mg)	0.022	0.011	0.016	0.018
Plasma Protein Binding (%):	99.9 (in vitro) 99.3-99.9 (in vivo)	99.9 (in vivo) >99.9 (in vivo)	99.9 (in vitro human plasma)	
CYP inhibition:	K_i: CYP2C8 (4.6 μM); CYP2C9 (10.4 μM); CYP2C19 (28.8 μM); IC_{50}: $CYP3A_{midazolam}$ (272 μM); IC_{50} values could not be determined for CYP1A2, CYP2D6, $CYP3A_{testosterone}$			
CYP Induction Potential:	CYP3A4 (moderate); CYP1A1, CYP1A2 (minimal-none); CYPB6, CYP2C8, CYP2C9 (none);			
XL184 CYP Substrate Specificity:	CYP3A4 (major pathway); CYP2C9 (minor pathway?): CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1 (none);			
Route of Elimination (rat total ^{14}C):	Feces: 82.5% (females) - 85.6% (males) Urine: 11.8% (females) - 9.1% (males)			
P-gp IC_{50}:	2.7 - 7.0 μM			

Area under the plasma concentration-time curve extrapolated from zero time to infinity ($AUC_{0-\infty}$); absolute bioavailability (%F); time of maximal plasma concentration (T_{max}); terminal plasma half-life ($T_{1/2}$); plasma clearance (CL); volume of distribution at steady-state (Vd_{ss})

[a] Data reflect mean values following a single oral gavage dose (3 mg XL184 HCl salt/kg) in aqueous vehicle (EtOH:PEG 400:H_2O; 5:45:50, v:v:v) unless otherwise indicated; [b] solid oral dosing (SOD) capsule form neat drug substance unless otherwise noted; [c] water vehicle; [d] cremaphor vehicle; [e] clinical capsule prototype formulation (XL184 L-malate salt)

(Tables excerpted from sponsor's submission)

6. General Toxicology

6.1 Single-Dose Toxicity

Study No.	Species/strain	Dose (mg/kg)	#M or F /group	HNSTD	Lethal dose	Findings
XL184-NC-003	Rat/Crl:CD(SD)	0, 100, 300, 900	5M 5F	100 (M+F)	300(M+F)	♦MD: Mortality 1/5M, 4/5F; lung inflammation, adrenal necrosis/inflammation ♦HD: Mortality 5/5M, 5/5F; necrosis/degeneration of GI tract, adrenal, BM; necrosis/depletion lymphoid tissues; necrosis of lung, male reproductive tissues, kidney/pancreas vacuolation
XL184-NC-004	Dog/Beagle	0, 400, 1000, 2000	2M 2F	2000	>2000	♦HD: 1F death due to drug aspiration (gavage error); salivation, eye discharge, emesis, soft feces; hepatic glycogen accumulation

Study report location: M4.2.3.1

Note: Only GLP compliant single dose toxicity studies are included in above table; all animals were dosed via gavage.

6.2 Repeat-Dose Toxicity

Study title: 14-day oral gavage toxicity and toxicokinetic study with XL184 in rats with a 28-day recovery period

Study no.: XL184-NC-005
Study report location: Electronic submission, M4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: November 16, 2004
GLP compliance: Y
QA statement: Y
Drug, lot #, and % purity: XL184-(L)-Malate; lot #EG1759-90A; 99.3 % pure

Key study findings:
● STD_{40} = 15 mg/kg (90 mg/m^2); NOAEL = <1.0 mg/kg (6 mg/m^2)
● Changes in clinical pathology consistent with hematopoietic, hepatic, gastrointestinal or renal toxicity.
● Histopathological targets: gastrointestinal tract, adrenal, bone marrow, lymphoid tissues (thymus, spleen, ileum), and pancreas
● Post-recovery target sites included kidney, liver, and bile duct
● Cited impurity qualification ((b) (4)) at proposed DP specification; documentation unavailable for verification.

Note: The Certificate of Analysis report for the drug lot did not report individual impurities; therefore, the individual impurities documented as qualified by the study could not be verified

Methods

Doses:	1, 5, 15 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	10mL/kg/dose
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	Control + HD: 15/sex/dose; LD, MD: 10/sex/dose
Age:	6.5-7.5 weeks
Weight:	M: 311g; F: 218g
Satellite groups:	Toxicokinetics: 12M/dose
Unique study design:	Recovery period of 28d
Deviation from study protocol:	# of HD recovery animals reduced to provide adequate HD animals for terminal sacrifice D16

Parameter	1 mg/kg		5 mg/kg		15 mg/kg	
	M	F	M	F	M	F
Mortality					**4**	**9**
Clinical observations	HD: ♦ hunched posture, emaciation, hypoactivity, soft or no feces, ocular discharge, hypothermia, irregular respiration, rough haircoat, head tremors					
Body weight[a]					↓10	
Food consumption			↓13	↓11	↓57	↓54
Ophthalmoscopy	UR					
Hematology[a]						
Erythrocyte count						↓21
Hemoglobin/Hematocrit						↓22/↓25
Reticulocyte count					↓83	↓64
Platelet count					↓62	↓78
Clinical chemistry[a]						
BUN					↑68	↑68
Cholesterol				↑64	↑179	↑38
AST			↑64	↑72	↑216	↑260
ALT			↑2.7 fold	↑5.5 fold	↑6.5 fold	↑9 fold
ALP						
Urinalysis	UR					
Organ weights – absolute[a]						
Liver		↓12	↓21	↓17	↓37	↓40
Kidney					↓23	
Spleen			↓14		↓21	
Thymus			↓30	↓23	↓48	↓65
Lung			↓22		↓22	↓21
Heart					↓32	↓27
Pituitary					↓25	↓46
Adrenal						↑74
Prostate					↓36	
Ovary				↓26		↓52
Gross pathology (15d)	HD: Adrenal: large, diffusely red; Stomach: large, red focus; Duodenum: large					
Histopathology	See histopathology table					
Toxicokinetics						
AUC_{0-24} (ng.h/mL) /Day 1	9940		41,920		135,549	
/Day 14	10,978		52,152		512,771	

[a] Percent compared to concurrent control
Abbreviations: UR = unremarkable, M = males, F = females

Histopathology (Terminal necropsy D15)

Organ/finding	1 mg/kg (N)		5 mg/kg (N)		15 mg/kg [N(decedents)]	
	M (10)	F (10)	M (10)	F (10)	M [7(4)]	F [4(9)]
Thymus/*necrosis (min-severe)*			4	7	8(3)	4(9)
Spleen/*necrosis (min-severe)*				1	7(2)	4(4)
Ilium/*necrosis (min-severe)*			1	4	2(2)	0(4)
Stomach/*inflammation*					0(2)	1(2)
Duodenum/*inflammation*					7(3)	4(9)
Jejunum/*inflammation*					1(0)	1(1)
Adrenal/*necrosis*					2(3)	4(9)
/*angiectasis*					8(2)	4(9)
Pancreas/*necrosis*					7(2)	3(7)
Bone marrow/*depletion*			10	2	8(3)	4(9)
Liver/*hypertrophy*	8	4	8	7	8(3)	3(8)
Pituitary/*necrosis*					8(1)	1(2)

Abbreviations: min = minimal, M = male, F = female
Note: Grading of finding not reported for all organs

Histopathology (Recovery sacrifice)

Organ/finding	control		15mg/kg (N)	
	M (5)	F (5)	M (4)	F (2)
Kidney/tubular epithelial regeneration			4	2
Liver, bile duct hyperplasia			4	2
Pituitary/hypertrophy	1	1	4	

Study title: 14-day oral gavage toxicity and toxicokinetic study with XL184 in rats with a 14-day recovery period

Study no.: XL184-NC-014
Study report location: Electronic submission, M4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: March 31, 2006
GLP compliance: Y
QA statement: Y
Drug, lot #, and % purity: XL184-(L)-Malate; lot# P172-27-1; 99.2% pure

Key study findings:
● Elevated AST and ALT, and reduction in reticulocyte and platelet counts at 5 mg/kg comparable to definitive 14-day rat study above.
● Histopathological findings including renal degeneration (exhibited in 7 of 15M and 8 of 15F), adrenal and ovarian necrosis, and bone marrow hypocellularity were exhibited at 5 mg/kg. Ovarian necrosis/ hypoplasia (observed in 8 of 15F) was not observed in study # XL184-NC-005 reviewed above.
● Findings normalized following recovery; NOAEL = 1.0 mg/kg
● Cited impurity qualification ((b) (4)) at proposed DP specification; documentation unavailable for verification.

Note: The Certificate of Analysis report for the drug lot did not report individual impurities; therefore, the individual impurities documented as qualified by the study could not be verified.

Note: Observed pituitary hypertrophy at 5 mg/kg was considered to be a response to adrenal changes, and thymic necrosis in all dosed rodents was considered to be a stress response.

Methods

Doses:	1, 5 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg/dose
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	Control + HD: 15/sex/dose; LD: 10/sex/dose
Age:	6.5-7.5 weeks
Weight:	M: 310g; F: 194g
Satellite groups:	Toxicokinetics: males only
Unique study design:	Recovery period of 14d
Deviation from study protocol:	None
Reason for conducting study:	Qualification of drug lot containing (b) (4) impurity

Study title: **XL184: A six month oral toxicity study with recovery in rats**

Study no.:	XL184-NC-013
Study report location:	Electronic submission, M4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 6, 2005
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot #P163-183-1; 99.0% pure

Key study findings:

●STD_{10}=1.0 mg/kg (6 mg/m2)

●3 deaths at HD in main study animals (52 total); 3 deaths at HD in TK animals (24 total) = 6/76 deaths at HD

● Primary target site: kidney; chronic progressive nephropathy exhibited at all doses following dosing and persisted following recovery

● Broken teeth/white teeth observed at all doses; incidence highest in females at HD, and increased with prolonged exposure

● Drug accumulation, gender effect, and XL184 half-life of 8-26h

Methods

Doses:	0.1, 0.3, 1 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	1mL/kg/dose
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	Control + HD: 26/sex/dose; LD, MD: 20/sex/dose
Age:	6 weeks
Weight:	M: 184-214g; F: 156-183g
Satellite groups:	Toxicokinetics: 9 animals/sex/dose (3 additional animals/sex/group were dosed as replacement animals)
Unique study design:	Recovery period of 28d Histopathological tissue examination for all dose groups following dosing, and control and HD following recovery
Deviation from study protocol:	None
Justification of dose levels:	XL184-NC-005:14 day oral gavage toxicity and toxicokinetic study with XL184 in rats with a 28-day recovery

Dosing formulations were reported to be stable for 7-14 days at 71 to 104% of initial Day 0 formulations (see table below). A stability retest of formulation at Week 19 was reported to be less variable; tabulated data were not provided. The sponsor has indicated that the formulated test material is stable for up to 14 days at room temperature.

Stability

Week	Dose Level (mg/kg/day)	Nominal Concentration (mg/mL)	Mean Found Concentration (mg/mL) (Day)			Mean % Recovery (Day)		
			0[a]	7	14	0[a,b]	7[c]	14[c]
11	0.1	0.1000	0.0986	0.0920	0.0869	98.6	93.3	88.2
	1.0	1.0000	1.0302	0.7740	0.7319	103.0	75.1	71.0
19	0.1	0.1000	0.1070	0.1064	0.1050	107.0	99.5	98.1
	1.0	1.0000	1.0040	1.0062	1.0408	100.4	100.2	103.7

[a]Day 0 is defined as the date that formulations were prepared.
[b]Values were calculated from the nominal concentration.
[c]Day 7 and 14 mean % recovery values were calculated from the respective Day 0 value.

Dosing groups

Main study[a]	Dose level (mg/kg)	Number of animals	
		Males	Females
	0	26	26
	0.1	20	20
	0.3	20	20
	1	26	26
Toxicokinetics[b]	0	12	12
	0.1	12	12
	0.3	12	12
	1	12	12

[a] Following the dosing period, 6 animals/sex from control and HD groups were held for 28-day recovery

[b] Toxicokinetics groups = 9 rats/sex/dose (3 additional animals/sex/group were dosed as replacement animals)

Observation	Time of assessment
Mortality	2x/d
Clinical observations	Weekly
Body weight	Weekly for 13w; monthly thereafter
Food consumption	Weekly for 13w; monthly thereafter
Ophthalmoscopy	Pretest and prior to terminal and recovery sac
Hematology	Pretest, 1 and 3 months postdose, terminal and recovery sacrifice
Clinical chemistry	
Urinalysis	
Organ weights	D182
Toxicokinetics	Predose and 0.5, 1, 3, 6, 9, 12, and 24h following dosing on days 1, 28, 178
Gross pathology	D28/D178
Histopathology	D28/D178

Parameter	0.1 mg/kg		0.3 mg/kg		1.0 mg/kg	
	M	F	M	F	M	F
Mortality	♦Control M:D162 – urogenital inflammation/obstruction/calculi) Control F: D147 – dosing error Control F: D162 – accidental injury (nose fracture) ♦ HDF: D159 – urogenital inflammation/obstruction/calculi) HDF: D40 – dosing error HDM: D176 – undetermined ♦ 3 HD TK animals: D28, 106, 179 – undetermined **3HD deaths main study; 3HD deaths TK animals**					
Clinical observations	LD, MD and HD: ♦ Broken teeth/white teeth: Incidence higher in F compared to M, higher at HD, and increased with prolonged exposure (highest in both gender between weeks 15 and 26).					
Body weight[a] (26w)						↓10
Food consumption	UR					
Ophthalmoscopy	UR					
Hematology[a] (26w)	UR					
Coagulation	UR					
Clinical chemistry[a]						
AST(4w)						↑15
AST(12w)					↑14	↑17
AST (26w)					↑22	↑29
ALT (4w)			↑15	↑15	↑51	↑59
ALT(12w)			↑20	↑16	↑57	↑62
ALT (26w)	↑12	↑23	↑26	↑24	↑82	↑67
Creatine kinase (12w)					↑27	↑56
Creatine kinase (26w)					↑30	↑60
Cholesterol (12w)			↑22		↑24	
Cholesterol (26w)			↑18	↑13	↑37	↑21
Alk phos (Recovery)					↑46	
Urinalysis	UR					
Organ weights – absolute[a] (26w)						
Spleen			↓10		↓13	
Testis			↓9		↓14	
Thymus		↓18	↓14	↓16	↓19	↓27
Uterus + cervix		↑29		↑23		↑12
Gross pathology (26w)	UR					
Histopathology	See histopathology tables					
Toxicokinetics	See toxicokinetics table					

[a] Percent compared to concurrent control
Abbreviations: UR = unremarkable, M = males, F = females

Histopathology (Terminal necropsy D28)

Organ/finding	0.1 mg/kg (N)		0.3 mg/kg (N)		1.0 mg/kg (N)	
	M (20)	F (20)	M (20)	F (20)	M (19)	F (18)
Kidneys/chronic progressive nephropathy (min-mild)[a]	14	4	13	5	18	12
/hydronephrosis, bilateral (mild-severe)	1	1				
Nose/metaplasia, (min)[b]					3	
Thymus/hemorrhage (min-mild)					1	
Testes/degeneration (severe)			1			
Urinary bladder/hyperplasia, inflammation (mild)		1				
Uterus/cervix/metaplasia (min)[c]						2

[a] Control incidence: control M: 15 of 19; control F: 6 of 18
[b] Control incidence: control M: 1 of 19
[c] Control incidence: control F: 1 of 18
Abbreviations: min = minimal, M = male, F = female

Recovery Necropsy

Organ/finding	control (N)		1.0 mg/kg (N)	
	M (6)	F (6)	M (6)	F (6)
Kidneys/chronic progressive nephropathy (minimal)		1		4
Kidneys/chronic progressive nephropathy (mild)			1	1

Toxicokinetics following administration of XL184 at days 1, 28, and 178

Dose/Gender/Day			Normalized C_{max} (ng/ml)	Normalized AUC_{γ} (hr.ng/ml)	Accumulation Ratio (Day 178/D1) AUC	C_{max}	CL (L/hr/kg)	$t_{1/2}$ (h)
0.1 mg/kg	M	D1	549	8197			0.12	10.2
		D28	900	12076			0.083	13.7
		D178	1650	26324	3.2	3.0	0.038	N/D
	F	D1	874	17110			0.058	13.2
		D28	1450	19517			0.05	N/D
		D178	2980	47533	2.8	3.4	0.021	N/D
0.3 mg/kg	M	D1	560	7559			0.13	10.5
		D28	1223	12230			0.082	12.8
		D178	1743	26171	3.5	3.1	0.038	26.1
	F	D1	943	17921			0.056	18
		D28	1470	22509			0.04	17.8
		D178	2937	48052	2.7	3.1	0.021	N/D
1 mg/kg	M	D1	678	9654			0.10	8.3
		D28	1530	15239			0.066	10
		D178	2590	29736	3.1	3.8	0.034	22.8
	F	D1	754	17332			0.058	18.3
		D28	1230	18580			0.05	20.7
		D178	2740	44086	2.5	3.6	0.023	N/D

Abbreviations: AUCγ= Exposure from time zero to last observable concentration at end of dosing interval. N/D= not determined (e.g. mortality)

A gender effect was observed following exposure of XL184; normalized C_{max} and AUC were higher in females compared to males. In addition, drug accumulation was observed at days 28 and 178 with both AUC and C_{max} following repeated drug administration. Drug half-life was between 8 and 26 hours, and appeared to increase with repeated drug administration for the MD and HD, although several half-life calculations were not provided.

Study title: **14-day oral gavage toxicity and toxicokinetic study with XL184 in dogs with a 28-day recovery period**

Study no.:	XL184-NC-006
Study report location:	Electronic submission, M4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 3, 2005
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot #P163-183-1; 99.0% pure

Key study findings:

● Administration of 100, 300, or 1000 mg/kg (Phase 1) was lethal following 5-7 days of dosing; study terminated.
● Administration of 100 mg/kg (Phase 2) was lethal following 5 days of dosing; animals reassigned to 4 weeks recovery
● Clinical biochemical findings consistent with drug-related dehydration, stress, inflammation and anorexia
● Target organs: bone, bone marrow, spleen, thymus, pancreas, lymph nodes, gastrointestinal organs; findings persisted following recovery in surviving animals
● Toxicokinetics unreliable due to limited data

Methods

Doses:	0, 100, 300, 1000 mg/kg (phase 1); 0, 10, 100 mg/kg (phase 2)
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	Phase 1: 15 mL/kg; Phase 2: 1mL/kg (see explanation below)
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Beagle dog
Number/Sex/Group:	See table below
Age:	4.5 months
Weight:	M: 7.4 kg; F: 6.4 kg
Satellite groups:	Recovery: control + 1000 mg/kg (2 dogs/sex/group)
Unique study design:	Recovery period of 28d Dosing duration 14 days as indicated in protocol modified due to mortality and clinical signs of toxicity
Deviation from study protocol:	Phase 2 initiated due to excessive mortality and toxicity; dosing durations modified (see note)
Justification of dose levels:	Dose range-finding study in dogs (Study #XL184-NC-002)

Note: Phase 1 terminated following dosing for 5-7 days due to excessive mortality; vehicle control dogs from Ph 1 were dosed for 7 days, and were reassigned to Ph 2 control and 100mg/kg groups following a 2 week rest.

Dogs administered 100, 300, and 1000 mg/kg during Ph 1 were limited to 7, 6, and 5 days of dosing, respectively. Dogs administered 100 mg/kg during Ph 2 were limited to 5 days of dosing also due to clinical signs of toxicity, and were reassigned to 4 weeks of recovery.

Phase 2 animals were dosed at a 1mL/kg dose volume compared to 15 mL/kg in Phase 1 in order to evaluate the effect of the high dose volume on appetite and toxicity at 100mg/kg/day.

Dosing groups

Main study – Phase 1	Dose level (mg/kg)	Number of animals	
		Males	Females
	0	5	5
	100	3	3
	300	3	3
	1000	5	5
Main study – Phase 2	0	3	3
	10	2	2
	100	2	2

Phase 1: Controls + 100 mg/kg groups dosed for 7 days; 300 mg/kg group dosed for 6 days; 1000 mg/kg dosed for 5 days (2M + 2F of 1000 mg/kg group originally designated as recovery animals with necropsy 28d following final dose)
Phase 2: Controls + 10 mg/kg dosed for 14 days and sacrificed following 48h toxicokinetic blood collection; 100 mg/kg dosed for 5 days only followed by 4 weeks of recovery

Observation	Time of assessment
Mortality	2x/d
Clinical observations	2X/d
Body weight	Day 1, 5, 8, 12, 15 of dosing phase 1 and 2, and weekly during recovery
Food consumption	Weekly
Ophthalmoscopy	Not conducted
EKG	Not conducted
Hematology	Phase 1: Prior to dosing, days 6 (1000 mg/kg group) and 7 (all groups), prior to recovery(day 36) Urine collection prior to dosing, day 7, prior to recovery Phase 2: Days 6 (100 mg/kg group) and 7 (all surviving dogs), prior to scheduled sacrifice (day 16; ~48h following final dose of additional dosing phase), prior to recovery (day 34)
Clinical chemistry	
Urinalysis	
Organ weights	Protocol specified organs collected at necropsy times documented below
Toxicokinetics	Predose, 0.25, 0.75, 1.5, 3, 6, 12, 24, 48h postdose
Gross pathology	Phase 1: LD sacrifice D9, MD + HD sacrificed D7(with exception of 2dogs/group); remaining animals sacrificed following 28d recovery Phase 2: LD sacrificed D14 HD sacrificed following 28d recovery
Histopathology	

Phase 1

Parameter	100 mg/kg (N = 3)		300 mg/kg (N = 3)		1000 mg/kg (N = 5)	
	M	F	M	F	M	F
Mortality	3	3	2	2	5	4
Clinical observations	Severe dehydration, emaciation, emesis, hypoactiivty, clear/cloudy eye discharge, liquid/discolored feces					
Body weight[a] (day 5)	↓19	↓13	↓21	↓22	↓24	↓20
Food consumption	↓72	↓55	-	-	-	-
Hematology *(day6/7)*[a]						
Reticulocytes	↓99	↓99	↓99	↓99	↓99	↓99
Clinical chemistry *(day6/7)*[a]						
Total protein	↑17	↑25	↑19	↑12	↑17	↑20
Globulin	↑32	↑48	↑32	↑29	↑36	↑33
AST	↑19	↑115	↑25	↑112	↑113	↑115
ALT	↑29	↑3-fold	↑57	↑3.6-fold	↑125	↑3.7-fold
ALP	UR	UR	UR	UR	↑40	↑22
Cholesterol	↑56	↑71	↑65	↑42	↑72	↑47
Urinalysis	UR					
Organ weights	Not measured					
Gross pathology	None reported					
Histopathology	See histopathology tables					
Toxicokinetics	See toxicokinetics table					

[a] Percent compared to concurrent control
Dash = not measured

Phase 2

Parameter	10 mg/kg (N=2)		100 mg/kg (N=2)	
	M	F	M	F
Mortality				1
Clinical observations	100 mg/kg: Severe dehydration, emaciation, emesis, hypoactiivty, liquid/discolored feces 10mg/kg: Soft feces, emesis			
Body weight[a] (day 15)	UR	UR	↓17	↓22
Food consumption			↓77	-
Hematology *(day 7HD, day 16 LD)*[a]				
Reticulocytes	↓30	↓45	↓99	↓98
Clinical chemistry *(day 7HD, day 16 LD)*[a]				
Total Protein	UR	UR	↑15	UR
Globulin	UR	UR	↑48	↑10
Cholesterol	UR	UR	↑87	↑32
AST	↑52	↑35	↑140	↑32
ALT	↑15	↑58	↑126	↑194
Urinalysis	UR			
Organ weights – absolute[a]				
Spleen	↓22	↓46	↓31	-
Thymus	↓46	↓18	↓46	-
Gross pathology	UR			
Histopathology	See histopathology tables			
Toxicokinetics	See toxicokinetics table			

[a] Percent compared to concurrent control
Dash = not measured; UR = unremarkable

Hematology and clinical chemistry findings were consistent with drug-related findings of dehydration, stress, inflammation and anorexia.

Toxicokinetics

Phase 1	Dose (mg/kg/day)	Gender	C_{max}/dose (ng/mL)	AUC_{0-24h}/Dose (ng.hr/mL)	$t_{1/2}$
	Single dose				
Day 1	100 (N=3)	M	130	1996	5
		F	102	1352	4.7
	300 (N=3)	M	88.3	1550	NA
		F	63.7	1035	8
	1000 (N=5)	M	25.1	447	NA
		F	25.1	432	9.5
Day 7	Multiple Dose				
	100 (N=3)	M	85.1	1154	7.8
		F	71.3	630	6.8
Phase 2	Single Dose				
Day 1	10 (N=2)	M	65.1	613	4.8
		F	64	717	5.2
	100 (N=2; $t_{1/2}$ based on N=1)	M	157	2374	7.6
		F	135	2221	10
Day 14	Multiple Dose				
	10 (N=2)	M	82.4	841	6
		F	140	1141	6

Reviewer comment: As a result of drug lethality and intra- and intergroup variability in numbers of animals available for toxicokinetics, tabulated results should not be considered definitive.

As a result of the limited animal numbers, it is difficult to reach conclusions regarding toxicokinetics. Half-life values increased with increase in dose and with multiple dosing. Exposure appeared to be slightly increased in males during Phase 1, but this pattern was not consistent during Phase 2. In phase 2, AUC and C_{max} appeared to increase following multiple dosing indicating drug accumulation during Phase 2 at 10 mg/kg, although drug accumulation was not observed at 100mg/kg during Phase 1. In addition, drug exposure at 100 mg/kg on Day 1 was higher during Phase 2 compared to Phase 1.

Histopathology (Phase 1)

Organ/finding	100 mg/kg[a] (N)		300 mg/kg[b] (N)		1000 mg/kg[c] (N)	
	M (3)	F (3)	M (2)	F (2)	M (5)	F (4)
Bone (femur)/atrophy	3	3	2	2	4	4
Bone marrow (femur, sternum) /hypocellularity	3	3	2	2	5	4
Brain/gliosis	1	1				1
Spinal cord/gliosis		1				2
Spleen/necrosis, lymphocyte depletion	2	2	2		3	
Thymus/necrosis, lymphocyte depletion	3	3	2	2	5	4
Mesenteric lymph n /necrosis, lymphocyte depletion	2	2	2		5	3
Stomach, Peyer's patch/necrosis, lymphocyte depletion	1				1	1
Stomach/hemorrhage					1	1
Duodenum, Peyer's patch/necrosis, lymphocyte depletion	1	2	1	2	4	4
/dilated glands with cellular debris	1	1	1	1	4	2
Jejunum, Peyer's patch/necrosis, lymphocyte depletion				1	2	1
Jejunum/acute inflammation		1				
Duodenum/ acute inflammaiton						1
Ileum, Peyer's patch/necrosis, lymphocyte depletion	3	2	2	2	5	4
/acute inflammation	1				1	2
Colon, Peyer's patch/necrosis, lymphocyte depletion	3	1	1	2	3	4
/acute inflammation					1	1
Cecum, Peyer's patch/necrosis, lymphocyte depletion	1	2	1	2	4	4
Cecum/acute inflammation or hemorrhage				1		2
Cecum/dilated glands with cellular debris	1	1	1	1	4	2
Rectum, Peyer's patch/necrosis, lymphocyte depletion	1				1	2
Pancreas/vacuolization	3	1	2	1	5	4
Eye/keratitis				1	1	1
Recovery sacrifice (N)			1	1	1	1
Duodenum/gland dilation, cellular debris			1			1
Cecum/gland dilation, cellular debris			1	1		
Large intestine/necrosis, lymphocyte depletion				1		
Spleen, thymus, mesenteric lymph node/necrosis, lymphocyte depletion				1		
Pancreas/increased apoptosis			1	1		

Note: Due to excessive mortality, Phase 1 was terminated following 5-7 days of dosing. Controls used for phase 1 were reassigned to phase 2 following a 2 week rest period.
Note 2: Degree of histopathological findings not indicated in study report
[a] Dogs dosed for 7 day period.
[b] Dogs dosed for 6 day period; 1M, 1F held for 4-week recovery
[c] Dogs dosed for 5 day period; 1M, 1F held for 4-week recovery

Histopathology (Phase 2)

Organ/finding	10 mg/kg (N)		100 mg/kg[a] (N)	
	M (2)	F (2)	M (0)	F (1)
Bone (femur)/atrophy				1
Spleen/necrosis, lymphocyte depletion				1
Thymus/necrosis, lymphocyte depletion				1
Jejunum, Peyer's patch/necrosis, lymphocyte depletion				1
Ileum, Peyer's patch/necrosis, lymphocyte depletion				1
Colon, Peyer's patch/necrosis, lymphocyte depletion				1
Cecum/acute inflammation or hemorrhage				1
Cecum/dilated glands with cellular debris		1		1
Recovery sacrifice (N)	2	2	2	1
Cecum/gland dilation, cellular debris		1	1	

[a] Due to signs of morbidity, dogs were dosed for 5 days and reassigned to 4 weeks of recovery.

Study title: **XL184: A six month oral toxicity study with recovery in dogs**

Study no.: XL184-NC-012
Study report location: Electronic submission, M4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: September 8, 2005
GLP compliance: Y
QA statement: Y
Drug, lot #, and % purity: XL184-(L)-Malate; lot #P163-183-1; 99.0% pure

Key study findings:

● Testicular hypoplasia and hypospermatogenesis at doses ≥1mg/kg following dosing, finding continued to be exhibited following recovery of HD (5 mg/kg)

● A gender effect was observed with generally increased drug exposure (Cmax and AUC) in males compared to females; gender effects were variable depending upon the duration of dosing.

Methods

Doses:	0.2, 1.0, 5.0 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	1mL/kg/dose
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Beagle dog
Number/Sex/Group:	Control + HD: 7/sex/dose; LD, MD: 4/sex/dose
Age:	5.5-6 months
Weight:	M: 7.4-10 kg; F: 6.7-8.5 kg
Satellite groups:	Toxicokinetics (see table below)
Unique study design:	Recovery period of 28d (3control and HD dogs/sex) Dosing duration 180 days (26w)
Deviation from study protocol:	None
Justification of dose levels:	Study XL184-NC-006 - 14 day study in dogs

Note: The analytical method used to test stability of drug substance was not available until study week 8, therefore, stability could not be verified until study week 10. The test material was stored at room temperature from 7-19 days to establish stability.

Dosing groups

Main study[a]	Dose level (mg/kg)	Number of animals	
		Males	Females
	0	7	7
	0.2	4	4
	1.0	4	4
	5.0	7	7
Toxicokinetics	0	7	7
	0.2	4	4
	1.0	4	4
	5.0	7	7

[a] Following the dosing period, 3 animals/sex from control and HD groups were held for 28-day recovery

Observation	Time of assessment
Mortality	2x/d
Clinical observations	Pretest, weekly thereafter
Body weight	Pretest, weekly thereafter
Food consumption	Weekly
Ophthalmoscopy	Pretest and prior to terminal and recovery sac
EKG	Pretest, during w26 (predose and 2h post dose), prior to recovery sacrifice
Hematology	Pretest, 1 and 3 months postdose, terminal and recovery sacrifice
Clinical chemistry	
Urinalysis	
Bone marrow	Control, HD dogs, terminal + recovery sacifice
Organ weights	D180, D208
Toxicokinetics	Predose and 0.5, 1, 3, 6, 9, 12, and 24h following dosing on days 1, 28, 180
Gross pathology	D180, D208
Histopathology	D180, D208

Parameter	0.2 mg/kg		1.0 mg/kg		5.0 mg/kg	
	M	F	M	F	M	F
Mortality	None					
Clinical observations	Alopecia, skin discoloration					
Body weight[a] (26w)	UR					
Food consumption				↓18	↓11	↓7
Ophthalmoscopy	UR					
EKG	UR					
Hematology[a]						
Reticulocytes (4w/12w/26w)			↓28/UR/UR		↓47/↓33/UR	UR/UR/↑30
Eosinophils (4w/12w/26w)			↓23/↓45/↓52	UR/↓43/↓47		
Coagulation	UR					
Clinical chemistry[a]	UR					
Urinalysis	UR					
Organ weights – absolute[a] (26w)						
Testis			↓18		↓33	
Ovaries		↓42		↓35		↓54
Gross pathology (180d)	UR					
Histopathology (180d, 208d)	See histopathology tables					
Toxicokinetics	See toxicokinetics table					

[a] Percent compared to concurrent control
Abbreviations: UR = unremarkable, M = males, F = females

Histopathology (Terminal necropsy: 180d)

Organ/finding	0.2 mg/kg (N)		1.0 mg/kg (N)		5.0 mg/kg (N)	
	M (4)	F (4)	M (4)	F (4)	M (4)	F (4)
Kidneys/degeneration					1	
Epididymides/oligospermia, germ cell debris			1		2	
Testes/hypoplasia (min-mild)			1		1	
/hypospermia (min-moderate)			1		2	
Ovaries/absence of corpora lutea		2		1		2
Skin/exudate, fibrosis, hyperplasia (mild)						1

Abbreviations: min = minimal, M = male, F = female

Recovery Necropsy: 208d

Organ/finding	control (N)		5.0 mg/kg (N)	
	M (3)	F (3)	M (3)	F (3)
Epididymides/oligospermia, germ cell debris			1	
Salivary gland (mandibular)/lymphocytic infiltration (min)			1	1
Salivary gland (parotid)/lymphocytic infiltration (min)			2	
Salivary gland (sublingual)/lymphocytic infiltration (min)			2	
Testes/hypoplasia,hypospermatogenesis (min-mild)			1	
Thyroid/lymphocytic infiltration (min)				1

Toxicokinetics following administration of XL184 at days 1, 28, and 180

Dose/Gender/Day			Normalized C_{max} (ng/ml)	Normalized AUC_{∞} (hr.ng/ml)	Accumulation Ratio AUC	C_{max}	CL (L/hr/kg)	$t_{1/2}$ (h)
0.2 mg/kg	M	D1	301	1650			0.64	6.1
		D28	234	1294	0.78	0.78	0.83	5.7
		D180	169	1454	0.88	0.56	0.72	4.9
	F	D1	228	1077			1.0	3.6
		D28	261	1277	1.19	1.14	0.86	6.0
		D180	367	1688	1.56	1.60	0.64	5.1
1.0 mg/kg	M	D1	173	1291			0.90	5.9
		D28	299	2244	1.74	1.73	0.52	17.1
		D180	317	2027	1.57	1.83	0.62	8.5
	F	D1	345	1509			0.74	6.3
		D28	234	1362	0.90	0.68	0.87	6.7
		D180	426	2011	1.33	1.23	0.53	10.0
5.0 mg/kg	M	D1	127	1194			0.86	15.1
		D28	145	1650	1.38	1.14	0.80	9.6
		D180	141	1551	1.29	1.11	0.92	12.6
	F	D1	112	699			1.7	6.3
		D28	107	799	1.14	0.96	1.4	7.0
		D180	202	1265	1.81	1.80	0.93	8.6

Abbreviations: N/D= not determined (e.g. mortality) Accumulation ratios = D28/D1 and D180/D1
Note: Sporadic missing exposure indices were exhibited in males and females.

Absorption was rapid at all dose levels (T_{max} ~0.6 to 2.7h on days 1, 28 and 180). Accumulation of XL184 was low following repeat daily drug administration for 28 and 180 days compared to day 1. A gender effect was observed with generally increased exposure (Cmax and AUC) in males compared to females. Gender effects were variable depending upon the duration of dosing. Total mean drug half-life ranged between 3 and 17 hours, but was generally between 6 and 7 hours. Clearance was marginally higher in females. Dose dependency was exhibited in males and females (see table below).

Non-normalized C_{max} and AUC following administration of XL184 at days 1, 28, and 180

Dose/Gender/Day			C_{max} (ng/ml)	AUC_{∞} (hr.ng/ml)
0.2 mg/kg	M	D1	60	330
		D28	47	259
		D180	34	291
	F	D1	46	215
		D28	52	255
		D180	73	338
1.0 mg/kg	M	D1	173	1291
		D28	299	2244
		D180	317	2027
	F	D1	345	1509
		D28	234	1362
		D180	426	2011
5.0 mg/kg	M	D1	635	5969
		D28	724	8251
		D180	706	7757
	F	D1	559	3495
		D28	536	3994
		D180	1008	6327

Study title: **XL184: A six month oral toxicity study with recovery in dogs (2nd revised final report)**

Study no.:	XL-184-NC-018
Study report location:	Electronic submission, M4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 18, 2008
Study completion and revision dates:	Study completed: July 23, 2009 1st revised final report: November 1, 2011 2nd revised final report: November 4, 2011
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot #P163-183-1; 99.0% pure

Key study findings:

● Lethality at 30 mg/kg; dose lowered to 20 mg/kg

● Immature development of reproductive organs of males and females, including hypospermia/oligospermia of testes and epididymides, absence of corpora lutea, and and reduction in glandular tissue of ovaries, uterus, and mammary glands.

● Gray skin and white haircoat hypopigmentation; not resolved following recovery. Findings not associated with microscopic correlate, although dermal histopathologic hyperkeratosis, hyperplasia and exudate noted in these same animals

Methods

Doses:	30/20 mg/kg (30 mg/kg for days 1-10; 20 mg/kg for days 22-132 for M, and days 22-182 for F).
Frequency of dosing:	Daily for 10 d, followed by 11 non-dosing days, and continued daily dosing for 111 (males) to 161 (females) gender-specific days
Route of administration:	Oral gavage
Dose volume:	3 mL/kg/dose
Formulation/Vehicle:	EtOH: polyethylene glycol(PEG) 400: reverse osmosis water (5:45:50)
Species/Strain:	Beagle dog
Number/Sex/Group:	Control: 4/sex; 30/20mg/kg: 6/sex
Age:	5.5-6 months
Weight:	M: 7.3-8.2kg; F: 5.9-7.0kg
Satellite groups:	Toxicokinetics
Unique study design:	Recovery period of 28d (2 dogs/sex/group) Dosing duration 130-170 days
Deviation from study protocol:	None
Reasoning for lowering doses	Excessive BW loss (↓11% in M, 9% in F from D1 weights)+ inability to maintain hydration

Note 1: The analytical method used to test stability of drug substance was not available until study week 8, therefore, stability could not be verified until study week 10. The test material was stored at room temperature from 7-19 days to establish stability.

Note 2: XL 184 suspension at nominal concentration (XL 184 + vehicle) weeks 1-2: 10 mg/mL; weeks 3-26: 6.67 mg/mL)

Note 3: Suspension of dosing also occurred for 3M administered 30/20 mg/kg/day XL 184 from days 127-129, and 2F from days 78-92, and 133-134, respectively.

Observation	Time of assessment
Mortality	2x/d
Clinical observations	Pretest, weekly thereafter
Body weight	Pretest, weekly thereafter
Food consumption	Weekly
Ophthalmoscopy	Prior to terminal and recovery sacrifice
EKG	Pretest, during w26 (predose and 2h post dose), prior to recovery sacrifice
Hematology	Pretest, day 11, week 13, and all surviving animals prior to terminal and recovery sacrifice
Clinical chemistry	
Urinalysis	
Organ weights	Post dose: D132M/183F
Toxicokinetics	Predose and 1, 2, 4, 6, 8, 12, and 24h following dosing on days 1, and 22, and predose and 1, 2, 4, 6, 8, 12 24 and 48h from recovery animals following final dose on D132 for M and D182 for F (Note: Deviation of sample collection was noted for a single dosed F#117; reasoning and data inclusion data were not provided)
Gross pathology	Post dose: D132M/183F
Histopathology	Post dose: D132M/183F

Parameter	Control		30/20 mg/kg (N=6)	
	M	F	M	F
Mortality [a]			2 (D71, 119)	1 (D135)
Clinical observations	30 mg/kg: Red, mucoid feces (> incidence in F) 20 mg/kg: Abnormal feces, emaciation, mild-severe discoloration of haircoat (white) and skin (gray – nose, lips, eyelids), alopecia, loss of skin elasticity, scabbing, hypothermia, lacrimation, interdigital cysts (M affected to > extent). Decedents: Inability to maintain hydration and body weight			
Body weight[b] (post dose: M,d126; F,d175; post recovery)			↓19; ↓19	UR; UR
Food consumption[b] (post dose: M,d126; F,d175; post recovery)			↓64-68; ↓21	↓37; ↑24
Ophthalmoscopy	UR			
EKG	UR			
Hematology[b] (post dose; post recovery)				
Erythrocyte count			↓14; ↓16	
Hgb			↓15; ↓17	
Hct			↓13; ↓14	
Reticulocyte count (absolute)			↓63; ↓36	↓78; ↑128
Platelets			↑60; ↑48	↑55; ↑14
Clinical chemistry[b] (day 11)				
AST			↑120	↑64
ALT			↑34	↑39
Sorbitol dehydrogenase			↑4-fold	↑1.6-fold
Urinalysis[b]				
Volume (terminal)[c]			↓49	↓22
Organ weights – absolute[b] (post dose; post recovery)				
Testis			↓57.8; ↓63.2	
Epididymides			↓15; ↓14	
Ovaries				↓53.6; ↓17.9
Gross pathology	Gray discoloration (mild – moderate) of skin and head following dosing and recovery.			
Histopathology	See table below			
Toxicokinetics	See table below			

[a] F sacrificed 4d prior to scheduled terminal sac due to deteriorating condition
[b] Percent compared to concurrent controls
[c] Sponsor considered volume reduction within the limits of physiological variation, which is questionable. Sponsor also reported increased occurrence and magnitude of proteinuria in M at dosing termination, although parameter not tabulated.
Abbreviations: UR = unremarkable, M = males, F = females

Parameters of decedents:
Similar to above data for hematology and liver indices; in addition, total protein and albumin moderately to markedly decreased and calcium decreased as secondary to decrease in albumin.

Histopathology (Decedents)

Organ/finding	30/20 mg/kg	
	M (N=2)	F (N=1)
Testes/hypospermatogenesis, bilateral (moderate-severe)	1	
Epididymides/oligospermia	Noted for 3 dosed M in study findings, although not included in tabulation	
Prostate/immature	1	
Ovaries/corpus luteum absent	See table and notation below	
Uterus/ reduced glandular tissue		
Mammary/reduced glandular tissue		
Thymus/lymphoid depletion	2	1
Spleen/lymphoid depletion	1	1
Colon, rectum/hemorrhage (minimal)		1
Skin/hyperplasia		1

Abbreviations: M = male, F = female

Histopathology (Terminal necropsy)

Organ/finding	30/20 mg/kg	
	M (N=2)	F (N=3)
Testes/hypospermatogenesis, bilateral (moderate-severe)	2	
Epididymides/oligospermia	Noted for 3 dosed M in study findings, although not included in tabulation	
Ovaries/corpus luteum absent	See table and notation below	
Uterus/ reduced glandular tissue		
Mammary/reduced glandular tissue		
Thymus/lymphoid depletion	1	
Skin/hyperkeratosis; exudate; hyperplasia	1	1
Kidney/mineralization[a]		3

[a] Note 2 control F with mineralization of kidney
Note: Single M noted with immature testes, prostate and epididymides (not included in tabulation).
Abbreviations: M = male, F = female

Changes in ovary/estrous cycle of females administered XL184

Ovarian change	Control (N=2)	30/20mg/kg (N=4)
Diestrus	1	
Proestrus		1
Estrus		
Metestrus		
Anestrus	1	
Quiescent		4

Study findings documented ovaries of treated females as quiescent (could not be staged) characterized by small size, lack of corpora lutea, and reduced numbers of secondary antral follicles. Uteri from these animals were small with few glands, and mammary tissue also exhibited marked reduction in glandular tissue. It appears that XL 184 delayed sexual maturity in these animals. Interestingly, these findings were not recorded in tabulation of histological data; this may be a consequence of the revised study report. Even though this is a revised and final study report, the reproductive data appears that it may be incomplete in the recovery histological tabulation submitted with the study.

Recovery Necropsy: 208 d

Organ/finding	30/20 mg/kg	
	M (N=2)	F (N=3)
Testes/hypospermatogenesis, bilateral (moderate)	2	
Heart/inflammation (mild)		1
Kidney/mineralization (minimal)		2

Toxicokinetics following administration of XL184 at days 1, 22, and recovery

Dose/Gender/Day			Normalized C_{max} (ng/ml)	Normalized AUC_{∞} (hr.ng/ml)	$t_{1/2}$ (h)
30 mg/kg[a]	M	D1	112	830	6.9
	F	D1	124	1160	5
20 mg/kg[b]	M	D22	113	936	6.4
		D132	130	941	6.1
	F	D22	129	920	5
		D182	125	1240	7.7

[a] N= 6
[b] N=4 for males, and 4-5 for females

Exposure was higher in females compared to males on day 1 and following recovery, although there was little or no drug accumulation following multiple dosing. Mean terminal half-life was 5 to 7 hours, and was longer in males except following recovery.

7. Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: ***Salmonella-Escherichia coli*/Mammalian-microsome reverse mutation assay with a confirmatory assay with XL184**

Study no.: XL-184-NC-010
Study report location: Electronic submission; M4.2.3.3
Conducting laboratory and location: (b) (4)
Date of study initiation: October 1, 2004
GLP compliance: Y (with exception[a])
QA statement: Y
Drug, lot #, and % purity: XL-184, lot # EG1759-90A/DMSO; purity not provided

[a] Dosing preparations were not analyzed for stability, homogeneity, or concentration

Key study findings:

● XL184 was not mutagenic at doses up to 5000 µg/plate in presence or absence of metabolic activation.

Methods: Initial + confirmatory study performed

Strains:	TA98, TA100, TA1535, TA1537, *E.coli* WP2*uvr*A (see table and comment below)
Concentrations in definitive study:	33.3, 100, 333, 1000, 3330, 5000 µg/plate in presence and absence of metabolic activation
Basis of concentration selection:	Rangefinding study with tester strains TA100 and WP2*uvr*A
Negative control:	DMSO
Positive control:	See below
Vehicle:	DMSO
Incubation & sampling time:	Incubation determined by monitoring of culture target density (0.5×10^9 cell/mL); removed from incubation and harvested at target density

Table III. Tester Strain Genotypes

Tester Strain	*his*/*trp* Mutation	Additional Mutations		Plasmid
		Repair	LPS	
TA98	*his*D3052	*uvr*B	*rfa*	pKM101
TA100	*his*G46	*uvr*B	*rfa*	pKM101
TA1535	*his*G46	*uvr*B	*rfa*	–
TA1537	*his*C3076	*uvr*B	*rfa*	–
WP2*uvr*A	*trp*	*uvr*A	–	–

Note: Tester strains contained 2 additional mutations (in addition to histidine or tryptophan operons) to enhance sensitivity.

Table I. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	–	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

Study validity (excerpted from sponsor's submission):

Tester Strain Integrity
rfa Wall Mutation
To demonstrate the presence of the *rfa* wall mutation, *Salmonella typhimurium* tester strain cultures exhibited sensitivity to crystal violet.

pKM101 Plasmid
To demonstrate the presence of the pKM101 plasmid, cultures of tester strains TA98 and TA100 exhibited resistance to ampicillin.

Characteristic Number of Spontaneous Revertants
To demonstrate the requirement for histidine (*Salmonella typhimurium*) or tryptophan (*Escherichia coli*), the tester strain cultures exhibited a characteristic number of spontaneous revertants per plate when plated along with the vehicle under selective conditions. The acceptable ranges for the mean vehicle controls were as follows:

TA98	8	-	60
TA100	60	-	240
TA1535	4	-	45
TA1537	2	-	25
WP2*uvr*A	5	-	40

Tester Strain Culture Density
To demonstrate that appropriate numbers of bacteria are plated, the density of tester strain cultures was greater than or equal to 0.5×10^9 bacteria per mL and/or had reached a target density demonstrated to produce cultures with at least 0.5×10^9 bacteria per mL.

Positive Control Values in the Absence of S9 Mix
To demonstrate that the tester strains were capable of identifying a mutagen, the mean value of a positive control for a respective tester strain exhibited at least a 3-fold increase over the mean value of the vehicle control for that strain.

Positive Control Values in the Presence of S9 Mix (S9 Mix Integrity)
To demonstrate that the S9 mix was capable of metabolizing a promutagen to its mutagenic form(s), the mean value of the positive control for a respective tester strain in the presence of the S9 mix exhibited at least a 3-fold increase over the mean value of the vehicle control for that strain.

An acceptable positive control in the presence of S9 mix for a specific strain was evaluated as having demonstrated both the integrity of the S9 mix and the ability of the tester strain to detect a mutagen.

Cytotoxicity
A minimum of three non-toxic doses were required to evaluate assay data. Cytotoxicity is detectable as a decrease in the number of revertant colonies per plate and/or by a thinning or disappearance of the bacterial background lawn. A thinning of the bacterial

Results

Cytotoxicity was not observed in range-finding or mutagenicity studies. XL184 was not mutagenic at doses up to 5000 µg/plate in the presence or absence of metabolic activation.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title: **Chromosomal Aberrations in cultured human peripheral blood lymphocytes**

Study no.:	XL 184-NC-011
Study report location:	Electronic submission; M4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 27, 2004
GLP compliance:	Y (with exception[a])
QA statement:	Y
Drug, lot #, and % purity:	XL184; lot # A017777101, A019779001; purity not provided

[a] Dosing preparations were not analyzed for stability, homogeneity, or concentration

Key study findings:

● XL184 did not induce an increase in chromosomal aberrations, polyploidy, or endoreduplication at doses of 88.2 to 257µg/mL.

Methods: Initial + confirmatory assay performed

Test system:	Human whole blood from healthy volunteers
Concentrations in definitive study:	See below
Basis of concentration selection:	Initial chromosomal aberration assay
Negative control:	Cells + culture media (RMPI 1640)
Positive control:	Mitomycin C; cyclophosphamide
Vehicle:	DMSO
Incubation & sampling time:	37°; 22h harvest corresponding to ~1.5X cell cycle division

The highest dose tested in the assay (750 µg/mL) was above the solubility limit for the drug. Initial assay concentrations of 5.09, 7.27, 10.4, 14.8, 21.2, 30.3, 43.2, 61.8, 88.2, 126, 180, 257, 368, 525, and 750 µg/mL were tested with and without metabolic activation.
Without metabolic activation, a precipitate was observed following dosing at ≥126 µg/mL. Reductions in the mitotic indices were observed in cultures treated from 126 to 750 µg/mL. Based on the initial assay, the confirmatory chromosomal aberration assay was conducted at doses of 14.8, 21.2, 30.3, 43.2, 61.8, 88.2, 116, 155, 207, 276, 368, 420, 525, 600, and 750 µg/mL without metabolic activation and 30.3, 43.2, 61.8, 88.2, 126, 180, 257, 368, 525, and 750 µg/mL with metabolic activation. Treatment periods were for ~22 and ~3h without and with metabolic activation, respectively; cultures were harvested at ~22h from initiation of treatment.

Chromosomal aberrations were analyzed from cultures treated with 88.2, 126, 180, and 257 µg/mL.

Study validity (excerpted from sponsor's submission):

Acceptable Controls. The negative and vehicle control cultures must contain less than approximately 5% cells with aberrations. The positive control result must be significantly higher ($p \leq 0.01$) than the vehicle controls.

Acceptable High Dose. If the aberration results are negative and there is no significant reduction (approximately ≥50%) in mitotic index, the assay must include the highest applicable dose, (a target dose of 5 mg/mL or 10 mM) or a dose exceeding solubility limit in culture medium.

Acceptable Number of Doses. The assay must include at least three analyzable concentrations.

Assay Evaluation Criteria
The following factors were taken into account in evaluation of the test article data:

- The number and percentages of aberrant cells excluding gaps (-g).
- The number and percentages of aberrant cells including gaps (+g).
- Evidence of a dose-response relationship.

The experimental unit is the cell, and therefore the percentage of cells with structural aberrations was the basis for evaluation. Statistical analysis employed a Cochran-Armitage test for linear trend and Fisher's Exact Test (Thakur *et al.*, 1985) to compare the percentage of cells with aberrations in treated cells to the results obtained for the vehicle controls.

Statistical analysis was also performed for cells exhibiting polyploidy and/or endoreduplication in order to indicate significant ($p \leq 0.01$) increases in these events as indicators of possible induction of numerical aberrations.

Evaluation of a Positive Response. A test article was considered positive for inducing chromosomal aberrations if a significant increase (the difference was considered significant when $p \leq 0.01$) in the number of cells with chromosomal aberrations was observed at one or more concentrations. The linear trend test evaluated the dose responsiveness. If a significant increase was seen at one or more concentrations, a dose-response should be observed.

Evaluation of a Negative Response. A test article was considered negative for inducing chromosomal aberrations if no significant increase was observed in the number of cells with chromosomal aberrations at any of the concentrations.

Equivocal Evaluation. Although most assays give clearly positive or negative results, in rare cases the data set would preclude making a definitive judgment about the activity of the test article. Results might remain equivocal or questionable regardless of the number of times the assay is repeated.

Results (Table excerpted from sponsor's submission):

Table 8: Chromosomal Aberrations in Human Lymphocytes - With Metabolic Activation - 3-Hour Treatment, ~22-Hour Harvest

Assay No.: 26511-0-449OECD Trial No.: C1 Date: 12/29/04 Lab No.: CY122804 Test Article: XL184

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: gaps	simple breaks	chte	chre	mab	Totals[c] g-	Totals[c] g+	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		1	1				1	1	
			B	100		100	0	0		2	2				2	4	
			Total	200		200				3	3				3	5	
			Average	%	--		0.0	0.0		1.5	1.5				1.5	2.5	
Vehicle:	DMSO	10.0 µL/mL	A	100		100	0	0			1				1	1	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				1	2				2	3	
			Average	%	0		0.0	0.0		0.5	1.0				1.0	1.5	
Positive:	CP	25.0 µg/mL	A	75		100	0	0		1	16	4	1		18	18	
			B	50		100	0	0			19	4		1	21	21	
			Total	125		200				1	35	8	1	1	39	39	
			Average	%	--		0.0	0.0	-	0.8	28.0	6.4	0.8	0.8	31.2	31.2	+
Test Article		88.2 µg/mL	A	100		100	0	0							0	0	
			B	100		100	0	0		1	1	1			2	3	
			Total	200		200				1	1	1			2	3	
			Average	%	27		0.0	0.0	-	0.5	0.5	0.5			1.0	1.5	-
		126 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0							0	0	
			Total	200		200				1					0	1	
			Average	%	33		0.0	0.0	-	0.5					0.0	0.5	-
		180 µg/mL	A	100		100	0	0							0	0	
			B	100		100	0	0							0	0	
			Total	200		200									0	0	
			Average	%	20		0.0	0.0	-						0.0	0.0	-
		257 µg/mL	A	100		100	3	0			2				2	2	
			B	100		100	0	0			1				1	1	
			Total	200		200					3				3	3	
			Average	%	50		1.5	0.0	-		1.5				1.5	1.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

XL184 did not induce an increase in chromosomal aberrations, polyploidy, or endoreduplication at doses of 88.2 to 257ug/mL.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: ***In vivo* mouse bone marrow micronucleus assay**

Study no.: XL-184-NC-019; 8201025

Study report location: Electronic submission, M4.2.3.3

Conducting laboratory and location: (b) (4)

Date of study initiation: December 18, 2008

GLP compliance: Y (with exceptions[a])

QA statement: Y

Drug, lot #, and % purity: XL184; lot# 0804672; purity 94.9%

[a] Bioanalytical and toxicokinetic analyses were conducted in accordance with FDA and OECD standards (not MHLW regulations), but were not distributed to (b) (4) study director management.

Key study findings:

● XL184 did not induce increases in micronucleated PCEs at doses up to 2000mg/kg.

Methods

Doses in definitive study:	500, 1000, 2000 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Oral gavage
Dose volume:	20 mL/kg
Formulation/Vehicle:	XL184 formulated in polyethylene glycol (PEG) 400:Ethanol:Reverse osmosis water (45:5:50)
Species/Strain:	CD-1 (ICR) mice
Number/Sex/Group:	See below
Satellite groups:	Toxicokiinetics: 3 males/group
Basis of dose selection:	Range-finding study in mice
Negative control:	Vehicle as noted above
Positive control:	Cyclophosphamide

Note: The stability of the dose formulation and vehicle was established for 13 days under refrigerated conditions and 30 days under frozen conditions.

Target Dose Level (mg/kg)	Stock Concentration (mg/mL)	Dosing Volume (mL/kg)	Route of Administration	Animals/Harvest Timepoint 24 Hour Male	48 Hour Male	Toxicokinetic Animals[a] Male
Positive Control, 80	8	10	Oral Gavage	5	-	-
Vehicle Control, 0	0	20	Oral Gavage	5	5	3
500	25	20	Oral Gavage	5	-	3
1000	50	20	Oral Gavage	5	-	3
2000	100	20	Oral Gavage	5	5	3

Vehicle Control = PEG400:Ethanol:RO Water (45:5:50)
Positive Control = Cyclophosphamide
a Three animals/timepoint were bled for possible measurement of plasma levels at 1 hour postdose.

Study validity (excerpted from sponsor's submission):

Slide Analysis
Slides prepared from the bone marrow collected from five animals per group at the designated harvest timepoints were scored for micronuclei and the PCE to NCE cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined by scoring the number of PCEs and NCEs observed while scoring at least 500 erythrocytes per animal.

The criteria for the identification of micronuclei were those of Schmid (1976). Micronuclei were darkly stained and generally round, although almond- and ring-shaped micronuclei occasionally occurred. Micronuclei were sharp bordered and generally between one-twentieth and one-fifth the size of the PCEs. The unit of scoring was the micronucleated cell, not the micronucleus; thus, the occasional cell with more than one micronucleus was counted as one micronucleated PCE, not two (or more) micronuclei.

The staining procedure permitted the differentiation by color of PCEs and NCEs (bluish-gray and red, respectively).

The historical background frequency of micronucleated cells was expressed as percentage micronucleated cells based on the number of PCEs analyzed. The historical background frequency of micronuclei in the mouse strains at this laboratory is about 0.0 to 0.4%, which is within the range of the published data (Salamone and Mavournin, 1994).

Statistical Evaluation
The following statistical methods were used to analyze the micronucleus data.

- Assay data analysis was performed using an analysis of variance (Winer, 1971) on untransformed proportions of cells with micronuclei per animal and on untransformed PCE:NCE ratios when the variances were homogeneous. Ranked proportions were used for heterogeneous variances.
- If the analysis of variance was statistically significant ($p \leq 0.05$), Dunnett's t-test (Dunnett, 1955; 1964) was used to determine which dose groups, if any, were

statistically significantly different from the vehicle control. Analyses were performed separately for each sampling time.

The 500, 1000, and 2000 mg/kg dose groups, as well as the positive control group, were compared with the vehicle control group at the 5% probability level.

Statistical significance is designated throughout the text of this report by the term *significant*. Statistical analysis programs are referenced accordingly in the appropriate section of this report.

Data Presentation
Individual animal data are summarized by dose group for the different timepoints and are presented in the Tables section of the report.

Assay Acceptance Criteria
Acceptable Controls
The vehicle control group mean must lie within the historical control range and will usually be less than 0.4% micronucleated PCEs.

There must be a statistically significant elevation of the mean of the positive control group relative to the vehicle control group, and the positive control response must be consistent with historical positive control data.

Acceptable High Dose
Generally the high dose should reach the limit dose or produce some indication of toxicity, e.g., toxic signs and/or mortality in the test article dosed animals and/or a reduction in the PCE:NCE ratio. If there are solubility constraints, the highest dose tested will be the solubility limit or higher doses if a well-dispersed suspension is obtained that does not settle out rapidly.

Assay Evaluation Criteria
The criteria for a positive response is the detection of a statistically significant increase in micronucleated PCEs for at least one dose level, and a statistically significant dose-related response. A test article that does not induce both of these responses is considered negative. Statistical significance is not the only determinant of a positive response; the Study Director also considers the biological relevance of the results in the final evaluation.

Results:

XL184 did not induce signs of clinical toxicity following single dose administration of 500-2000 mg/kg. In addition, XL184 did not induce increases in micronucleated PCEs at doses tested. (Table excerpted from sponsor's submission)

Table 1: Micronucleus Assay – Summary Table

Assay No.: 30350-0-455OECD
Test Article: XL184
Initiation of Dosing: 07 January 2009

Treatment	Dose	Harvest Time	% Micronucleated PCEs Mean ± SD Male		Ratio PCE:NCE Mean ± SD Male	
Controls						
Vehicle	VC 20 mL/kg	24	0.05	± 0.06	0.58	± 0.09
		48	0.04	± 0.04	0.60	± 0.10
Positive	CP 80 mg/kg	24	1.54	± 0.65 *	0.73	± 0.15
Test Article	500 mg/kg	24	0.02	± 0.03	0.71	± 0.13
	1000 mg/kg	24	0.04	± 0.04	0.75	± 0.12
	2000 mg/kg	24	0.05	± 0.04	0.73	± 0.14
		48	0.00	± 0.00 **	0.72	± 0.12

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
** Significantly less than the corresponding vehicle control, $p \leq 0.05$.
VC = Polyethylene glycol 400:Ethanol:Reverse osmosis water (45:5:50)
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte

7.4 Genetic Toxicity Studies – Impurities and Metabolites

Genetic toxicology - Impurities

Study #	Study name	Impurity studied
(b) (4)	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	(b) (4)
(b) (4)	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	(b) (4)
(b) (4)	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	(b) (4)
(b) (4)		
(b) (4)	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	(b) (4)
(b) (4)	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	(b) (4)

Genetic toxicology - Metabolites

BMS-927982	**Ames reverse mutation study in *Salmonella typhimurium* and *E.coli***	**XL184 n-oxide**

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.: (b) (4)
Study report location: Electronic submission, M4.2.3.3
Conducting laboratory and location: (b) (4)
Date of study report: July 27, 2009
GLP compliance: Y
QA statement: Y
Positive controls: Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

- (b) (4) was mutagenic in the presence of metabolic activation.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group.
The mutagenic activity of the test article was assessed by applying the following criteria:
• *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay

outside the historical control range).
• *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
• *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.
For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:
(b) (4) ((b) (4) a process impurity and degradant of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E. coli* strain WP2 *uvr*A with and without metabolic activation. Eight concentrations of the impurity, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Precipitation was observed at concentrations ≥1280 µg/plate, and completely obscured evaluations at 5000 µg; toxicity was not observed. Increases in TA98 and TA100 mean revertant counts were observed in the presence of metabolic activation when compared to negative controls.

Table 3 (b) (4) **Confirmatory Assay in the Absence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †
			x_1	x_2	x_3	mean	SD	x_1	x_2	x_3	
TA1535	DMSO	0	23	22	28	**24**	3				1.0
	160	0	27	18	20	**22**	5				0.9
	320	0	20	15	19	**18**	3				0.7
	640	0	13	26	22	**20**	7	ppt	ppt		0.8
	1280	0	20	23	23	**22**	2	ppt	ppt	ppt	0.9
	2560	0	18	21	27	**22**	5	ppt	ppt	ppt	0.9
	5000	0	19	14	17	**17**	3	pobl	pobl	pobl	0.7
TA1537	DMSO	0	14	10	7	**10**	4				1.0
	320	0	15	15	10	**13**	3				1.3
	640	0	7	11	11	**10**	2				0.9
	1280	0	12	12	17	**14**	3	ppt	ppt	ppt	1.3
	2560	0	15	11	13	**13**	2	ppt	ppt	ppt	1.3
	5000	0	14	9	12	**12**	3	pobl	pobl	pobl	1.1
TA98	DMSO	0	31	43	25	**33**	9				1.0
	320	0	45	43	40	**43**	3				1.3
	640	0	28	38	40	**35**	6				1.1
	1280	0	47	26	39	**37**	11	ppt	ppt	ppt	1.1
	2560	0	29	42	62	**44**	17	ppt	ppt	ppt	1.3
	5000	0	31	37	28	**32**	5	pobl	pobl	pobl	1.0
TA100	DMSO	0	157	142	143	**147**	8				1.0
	320	0	153	132	137	**141**	11				1.0
	640	0	131	153	140	**141**	11				1.0
	1280	0	124	159	149	**144**	18	ppt	ppt	ppt	1.0
	2560	0	144	142	140	**142**	2	pobl	pobl	pobl	1.0
	5000	0	106	122	112	**113**	8	pobl	pobl	pobl	0.8
WP2 *uvrA*	DMSO	0	35	46	31	**37**	8				1.0
	320	0	57	34	35	**42**	13				1.1
	640	0	44	35	43	**41**	5				1.1
	1280	0	59	44	38	**47**	11	ppt	ppt	ppt	1.3
	2560	0	50	42	35	**42**	8	ppt	ppt	ppt	1.1
	5000	0	38	37	32	**36**	3	pobl	pobl	pobl	1.0

Table 4 [redacted] (b) (4) **Confirmatory Assay in the Presence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants x_1	x_2	x_3	mean	SD	Plate observations * x_1	x_2	x_3	Fold response †	
TA1535	DMSO	+	22	26	21	**23**	3				1.0	
	160	+	25	26	17	**23**	5				1.0	
	320	+	25	37	18	**27**	10				1.2	
	640	+	17	39	24	**27**	11	ppt	ppt	ppt	1.2	
	1280	+	20	23	21	**21**	2	ppt	ppt	ppt	0.9	
	2560	+	25	17	34	**25**	9	ppt	ppt	ppt	1.1	
	5000	+	22	20	20	**21**	1	pobl	pobl	pobl	0.9	
TA1537	DMSO	+	16	17	17	**17**	1				1.0	
	320	+	28	33	33	**31**	3				1.9	
	640	+	19	30	30	**26**	6				1.6	
	1280	+	6	20	12	**13**	7	ppt	ppt	ppt	0.8	
	2560	+	19	27	24	**23**	4	ppt	ppt	ppt	1.4	
	5000	+	23	23	23	**23**	0	pobl	pobl	pobl	1.4	
TA98	DMSO	+	54	43	53	**50**	6				1.0	
	40	+	63	68	66	**66**	3				1.3	
	80	+	103	90	98	**97**	7				1.9	
	160	+	99	94	115	**103**	11				2.1	+
	320	+	128	105	70	**101**	29				2.0	+
	640	+	104	105	98	**102**	4				2.0	+
	1280	+	133	95	105	**111**	20	ppt	ppt	ppt	2.2	+
	2560	+	104	98	91	**98**	7	ppt	ppt	ppt	2.0	+
	5000	+	105	98	103	**102**	4	pobl	pobl	pobl	2.0	+

Strain	Conc. (µg/plate)	S9	Number of revertants x_1	x_2	x_3	mean	SD	Plate observations * x_1	x_2	x_3	Fold response †	
TA100	DMSO	+	152	153	145	**150**	4				1.0	
	40	+	193	194	184	**190**	6				1.3	
	80	+	295	283	279	**286**	8				1.9	
	160	+	361	357	366	**361**	5				2.4	+
	320	+	377	333	358	**356**	22				2.4	+
	640	+	413	403	348	**388**	35				2.6	+
	1280	+	401	367	397	**388**	19	ppt	ppt	ppt	2.6	+
	2560	+	327	214	341	**294**	70	ppt	ppt	ppt	2.0	+
	5000	+	323	346	310	**326**	18	pobl	pobl	pobl	2.2	+
WP2 *uvrA*	DMSO	+	49	62	70	**60**	11				1.0	
	320	+	72	46	50	**56**	14				0.9	
	640	+	48	41	62	**50**	11				0.8	
	1280	+	57	48	56	**54**	5	ppt	ppt	ppt	0.9	
	2560	+	51	37	46	**45**	7	ppt	ppt	ppt	0.7	
	5000	+	47	42	31	**40**	8	pobl	pobl	pobl	0.7	

Tables above excerpted from sponsor's submission.

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.:	(b) (4)
Study report location:	Electronic submission, M4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study report:	July 27, 2009
GLP compliance:	Y
QA statement:	Y
Positive controls:	Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

- (b) (4) was mutagenic in the absence and presence of metabolic activation.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group.
The mutagenic activity of the test article was assessed by applying the following criteria:

- *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay outside the historical control range).
- *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
- *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.

For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:

(b) (4) ((b) (4) a process impurity and degradant of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E. coli* strain WP2 *uvr*A with and without metabolic activation. Eight concentrations of the impurity, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Precipitation was observed at concentrations ≥1280 µg/plate. Toxicity as indicated by a substantial reduction in revertant colony counts was observed with most of the

strains in the absence and presence of metabolic activation. Increases in TA1537 mean revertant counts were observed in the absence and presence of metabolic activation when compared to negative controls.

Table 3 [redacted] (b) (4) **- Confirmatory Assay in the Absence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †	
			x_1	x_2	x_3	**mean**	SD	x_1	x_2	x_3		
TA1535	DMSO	0	33	25	19	**26**	7				1.0	
	160	0	9	28	17	**18**	10				0.7	
	320	0	19	18	26	**21**	4				0.8	
	640	0	20	22	20	**21**	1				0.8	
	1280	0	23	20	18	**20**	3	ppt	ppt		0.8	
	2560	0	10	17	15	**14**	4	ppt	ppt	ppt	0.5	T
	5000	0	12	8	11	**10**	2	ppt	ppt	ppt	0.4	T
TA1537	DMSO	0	9	11	11	**10**	1				1.0	
	320	0	5	14	9	**9**	5				0.9	
	640	0	11	16	9	**12**	4				1.2	
	1280	0	28	44	45	**39**	10				3.8	+
	2560	0	132	115	113	**120**	10	ppt	ppt	ppt	12	+
	5000	0	108	48	72	**76**	30	ppt	ppt	ppt	7.4	+
TA98	DMSO	0	42	32	27	**34**	8				1.0	
	320	0	36	35	24	**32**	7				0.9	
	640	0	41	31	36	**36**	5				1.1	
	1280	0	53	42	36	**44**	9				1.3	
	2560	0	22	34	35	**30**	7	ppt	ppt	ppt	0.9	
	5000	0	28	39	44	**37**	8	ppt	ppt	ppt	1.1	
TA100	DMSO	0	136	135	136	**136**	1				1.0	
	320	0	143	119	121	**128**	13				0.9	
	640	0	149	153	135	**146**	9				1.1	
	1280	0	146	128	132	**135**	9	ppt	ppt		1.0	
	2560	0	98	66	68	**77**	18	ppt	ppt	ppt	0.6	
	5000	0	95	114	111	**107**	10	ppt	ppt	ppt	0.8	
WP2 *uvrA*	DMSO	0	45	41	40	**42**	3				1.0	
	160	0	37	38	40	**38**	2				0.9	
	320	0	45	40	34	**40**	6				0.9	
	640	0	46	38	38	**41**	5				1.0	
	1280	0	34	29	32	**32**	3	ppt	ppt	ppt	0.8	
	2560	0	29	16	18	**21**	7	ppt	ppt	ppt	0.5	T
	5000	0	18	24	18	**20**	3	ppt	ppt	ppt	0.5	T

Table 4 [redacted] (b) (4) **- Confirmatory Assay in the Presence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †	
			x_1	x_2	x_3	**mean**	SD	x_1	x_2	x_3		
TA1535	DMSO	+	31	34	24	**30**	5				1.0	
	320	+	31	19	32	**27**	7				0.9	
	640	+	26	28	8	**21**	11				0.7	
	1280	+	19	23	22	**21**	2	ppt	ppt	ppt	0.7	
	2560	+	17	20	13	**17**	4	ppt	ppt	ppt	0.6	
	5000	+	15	16	12	**14**	2	ppt	ppt	ppt	0.5	T
TA1537	DMSO	+	17	14	18	**16**	2				1.0	
	320	+	11	9	15	**12**	3				0.7	
	640	+	12	20	22	**18**	5				1.1	
	1280	+	66	48	44	**53**	12	ppt	ppt	ppt	3.2	+
	2560	+	55	44	40	**46**	8	ppt	ppt	ppt	2.8	
	5000	+	49	35	59	**48**	12	ppt	ppt	ppt	2.9	
TA98	DMSO	+	38	45	41	**41**	4				1.0	
	320	+	38	43	40	**40**	3				1.0	
	640	+	48	44	40	**44**	4				1.1	
	1280	+	36	51	37	**41**	8	ppt	ppt	ppt	1.0	
	2560	+	32	30	38	**33**	4	ppt	ppt	ppt	0.8	
	5000	+	57	30	50	**46**	14	ppt	ppt	ppt	1.1	
TA100	DMSO	+	150	124	156	**143**	17				1.0	
	160	+	168	147	170	**162**	13				1.1	
	320	+	124	123	145	**131**	12				0.9	
	640	+	154	144	147	**148**	5				1.0	
	1280	+	131	123	106	**120**	13	ppt	ppt	ppt	0.8	
	2560	+	36	41	31	**36**	5	ppt	ppt	ppt	0.3	T
	5000	+	38	48	41	**42**	5	ppt	ppt	ppt	0.3	T
WP2 *uvrA*	DMSO	+	55	50	40	**48**	8				1.0	
	320	+	42	58	43	**48**	9				1.0	
	640	+	37	38	50	**42**	7				0.9	
	1280	+	41	52	29	**41**	12				0.8	
	2560	+	22	23	35	**27**	7	ppt	ppt	ppt	0.6	
	5000	+	25	32	37	**31**	6	ppt	ppt	ppt	0.6	

Tables above excerpted from sponsor's submission

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.:	(b) (4)
Study report location:	Electronic submission, M4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study report:	April 15, 2010
GLP compliance:	Y
QA statement:	Y
Positive controls:	Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

- (b) (4) was mutagenic in the presence of metabolic activation.
- The level of the impurity is < LOQ (b) (4)) at the 175 mg clinical dose as documented in clinical pharmacokinetic studies.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group.
The mutagenic activity of the test article was assessed by applying the following criteria:

- *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay outside the historical control range).
- *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
- *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.

For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:

(b) (4) ((b) (4) a process impurity (b) (4) of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E.*

coli strain WP2 *uvr*A with and without metabolic activation. Eight concentrations of the impurity, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Toxicity and test article precipitation were not observed. Significant dose-related increases in TA98 revertant counts were observed at concentrations ≥1280 µg/plate in the presence of metabolic activation when compared to negative controls.

Table 4 [redacted] (b) (4) **Confirmatory Assay in the Presence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of Revertants					Plate Observations *			Fold Response †	
			x_1	x_2	x_3	Mean	SD	x_1	x_2	x_3		
TA1535	DMSO	+	20	26	17	**21**	5				1.0	
	320	+	19	14	22	**18**	4				0.9	
	640	+	33	22	26	**27**	6				1.3	
	1280	+	23	18	23	**21**	3				1.0	
	2560	+	11	24	23	**19**	7				0.9	
	5000	+	26	11	27	**21**	9				1.0	
TA1537	DMSO	+	23	19	12	**18**	6				1.0	
	320	+	22	18	25	**22**	4				1.2	
	640	+	17	16	18	**17**	1				0.9	
	1280	+	25	19	15	**20**	5				1.1	
	2560	+	20	24	24	**23**	2				1.3	
	5000	+	15	19	24	**19**	5				1.1	
TA98	DMSO	+	47	43	44	**45**	2				1.0	
	320	+	60	63	70	**64**	5				1.4	
	640	+	63	73	70	**69**	5				1.5	
	1280	+	109	141	129	**126**	16				2.8	+
	2560	+	142	171	185	**166**	22				3.7	+
	5000	+	212	215	240	**222**	15				5.0	+
TA100	DMSO	+	166	158	139	**154**	14				1.0	
	320	+	160	123	136	**140**	19				0.9	
	640	+	130	138	152	**140**	11				0.9	
	1280	+	158	186	162	**169**	15				1.1	
	2560	+	183	180	166	**176**	9				1.1	
	5000	+	166	203	189	**186**	19				1.2	
WP2 *uvrA*	DMSO	+	59	69	46	**58**	12				1.0	
	320	+	40	40	57	**46**	10				0.8	
	640	+	61	48	50	**53**	7				0.9	
	1280	+	53	52	55	**53**	2				0.9	
	2560	+	63	56	53	**57**	5				1.0	
	5000	+	58	50	53	**54**	4				0.9	

Table excerpted from sponsor's submission

Study title: Mutagenicity of [redacted] (b) (4) in E. coli WP2uvrA/pKM101 and its relevance to oxidative DNA damage

Scientific publication: [redacted] (b) (4)
Study report location: Electronic submission, M4.2.3.3
Conducting laboratory and location: [redacted] (b) (4)
Date of study report: 1998
GLP compliance: N/A
QA statement: N/A
Drug, lot #, and % purity: [redacted] (b) (4); no further data provided

Key study findings:

- [redacted] (b) (4) was mutagenic to an altered form of *E.coli* with a higher sensitivity to oxidative mutagens.

Results: [redacted] (b) (4) has been reported to induce DNA cleavage in mouse lymphoma cells, CHO cells and human lymphoblastoid cells, although the mutagenicity of the chemical has not been detected by reverse mutation assays. *E.coli* WP2*uvr*A/pKM101 has a higher sensitivity to oxidative mutagens with an AT base pair at the mutation site. [redacted] (b) (4) was found to be mutagenic to *E.coli* WP2*uvr*A/pKM101, although the mutagenicity was suppressed with the addition of dimethylsulfoxide or catalase. The study authors have suggested that induction of the mutagenicity of the chemical requires involvement of an active oxygen species.

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.: [redacted] (b) (4)
Study report location: Electronic submission, M4.2.3.3
Conducting laboratory and location: [redacted] (b) (4)
Date of study report: July 27, 2009
GLP compliance: Y
QA statement: Y
Positive controls: Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

- [redacted] (b) (4) was not mutagenic in the presence or absence of metabolic activation.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using

Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group. The mutagenic activity of the test article was assessed by applying the following criteria:

- *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay outside the historical control range).
- *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
- *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.

For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:

(b) (4) a process impurity of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E. coli* strain WP2 *uvr*A with and without metabolic activation. Eight concentrations of the impurity, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Toxicity and test article precipitation were not observed. When compared to negative controls, XL 184-1-1 was not mutagenic in the presence or absence of metabolic activation when tested up to 5000 µg/plate.

Table 3 [redacted] (b) (4) **Confirmatory Assay in the Absence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †
			x_1	x_2	x_3	**mean**	SD	x_1	x_2	x_3	
TA1535	DMF	0	22	23	15	**20**	4				1.0
	320	0	19	34	13	**22**	11				1.1
	640	0	22	15	20	**19**	4				1.0
	1280	0	23	30	28	**27**	4				1.4
	2560	0	15	29	29	**24**	8				1.2
	5000	0	23	22	34	**26**	7				1.3
TA1537	DMF	0	9	12	10	**10**	2				1.0
	320	0	13	10	6	**10**	4				0.9
	640	0	10	21	6	**12**	8				1.2
	1280	0	13	15	12	**13**	2				1.3
	2560	0	9	10	10	**10**	1				0.9
	5000	0	10	14	13	**12**	2				1.2
TA98	DMF	0	30	35	45	**37**	8				1.0
	320	0	31	36	35	**34**	3				0.9
	640	0	35	36	38	**36**	2				1.0
	1280	0	28	27	48	**34**	12				0.9
	2560	0	34	31	35	**33**	2				0.9
	5000	0	36	36	28	**33**	5				0.9
TA100	DMF	0	161	148	157	**155**	7				1.0
	320	0	154	195	186	**178**	22				1.1
	640	0	181	162	150	**164**	16				1.1
	1280	0	167	170	172	**170**	3				1.1
	2560	0	143	155	142	**147**	7				0.9
	5000	0	172	137	154	**154**	18				1.0
WP2 *uvrA*	DMF	0	69	39	40	**49**	17				1.0
	320	0	55	43	47	**48**	6				1.0
	640	0	45	44	45	**45**	1				0.9
	1280	0	38	43	50	**44**	6				0.9
	2560	0	45	28	45	**39**	10				0.8
	5000	0	34	40	33	**36**	4				0.7

Table 4 [redacted] (b) (4) **Confirmatory Assay in the Presence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †	
			x_1	x_2	x_3	**mean**	SD	x_1	x_2	x_3		
TA1535	DMF	+	29	18	30	**26**	7				1.0	
	320	+	34	45	23	**34**	11				1.3	
	640	+	22	15	22	**20**	4				0.8	
	1280	+	28	35	29	**31**	4				1.2	
	2560	+	27	17	20	**21**	5				0.8	
	5000	+	30	16	16	**21**	8				0.8	
TA1537	DMF	+	18	10	7	**12**	6				1.0	
	320	+	16	15	14	**15**	1				1.3	
	640	+	21	19	29	**23**	5				2.0	
	1280	+	22	19	22	**21**	2				1.8	
	2560	+	17	7	21	**15**	7				1.3	
	5000	+	16	17	16	**16**	1				1.4	
TA98	DMF	+	46	47	52	**48**	3				1.0	
	320	+	43	54	63	**53**	10				1.1	
	640	+	62	55	72	**63**	9				1.3	
	1280	+	80	75	69	**75**	6				1.5	
	2560	+	73	79	65	**72**	7				1.5	
	5000	+	68	54	54	**59**	8				1.2	
TA100	DMF	+	161	181	182	**175**	12				1.0	
	320	+	183	219	204	**202**	18				1.2	
	640	+	169	165	163	**166**	3				0.9	
	1280	+	190	192	182	**188**	5				1.1	
	2560	+	144	139	139	**141**	3				0.8	
	5000	+	178	143	157	**159**	18				0.9	
WP2 *uvrA*	DMF	+	71	61	77	**70**	8				1.0	
	320	+	55	72	70	**66**	9				0.9	
	640	+	51	56	69	**59**	9				0.8	
	1280	+	56	65	51	**57**	7				0.8	
	2560	+	44	47	58	**50**	7				0.7	
	5000	+	38	37	28	**34**	6				0.5	A

Tables excerpted from sponsor's submission

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.:	(b) (4)
Study report location:	Electronic submission, M4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study report:	August 4, 2009
GLP compliance:	Y
QA statement:	Y
Positive controls:	Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

- (b) (4) was not mutagenic in the presence or absence of metabolic activation.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group.
The mutagenic activity of the test article was assessed by applying the following criteria:

- *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay outside the historical control range).
- *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
- *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.

For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:

(b) (4) a process impurity of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E. coli* strain WP2 *uvr*A with

and without metabolic activation. Eight concentrations of the impurity, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Test article precipitation was not observed. Slight toxicity was observed with TA1535 at 5000 µg/plate. When compared to negative controls, [redacted] (b) (4) was not mutagenic in the presence or absence of metabolic activation when tested at levels up to 5000 µg/plate.

Table 3 [redacted] (b) (4) **Confirmatory Assay in the Absence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants x_1	x_2	x_3	**mean**	SD	Plate observations * x_1	x_2	x_3	Fold response †	
TA1535	DMSO	0	21	14	23	**19**	5				1.0	
	160	0	26	18	9	**18**	9				0.9	
	320	0	12	15	26	**18**	7				0.9	
	640	0	24	22	22	**23**	1				1.2	
	1280	0	10	10	12	**11**	1				0.6	
	2560	0	17	8	7	**11**	6				0.6	
	5000	0	12	9	5	**9**	4				0.4	T
TA1537	DMSO	0	15	9	10	**11**	3				1.0	
	320	0	7	15	14	**12**	4				1.1	
	640	0	11	9	12	**11**	2				0.9	
	1280	0	12	11	10	**11**	1				1.0	
	2560	0	10	12	14	**12**	2				1.1	
	5000	0	7	8	11	**9**	2				0.8	
TA98	DMSO	0	59	53	73	**62**	10				1.0	
	320	0	46	71	67	**61**	13				1.0	
	640	0	55	60	63	**59**	4				1.0	
	1280	0	68	79	65	**71**	7				1.1	
	2560	0	64	68	55	**62**	7				1.0	
	5000	0	62	53	80	**65**	14				1.1	
TA100	DMSO	0	150	129	131	**137**	12				1.0	
	320	0	115	135	115	**122**	12				0.9	
	640	0	110	144	139	**131**	18				1.0	
	1280	0	110	113	123	**115**	7				0.8	
	2560	0	92	99	128	**106**	19				0.8	
	5000	0	44	122	106	**91**	41				0.7	
WP2 *uvrA*	DMSO	0	30	38	48	**39**	9				1.0	
	320	0	50	38	35	**41**	8				1.1	
	640	0	45	36	48	**43**	6				1.1	
	1280	0	41	44	43	**43**	2				1.1	
	2560	0	39	34	34	**36**	3				0.9	
	5000	0	17	28	30	**25**	7				0.6	

Table 4 (b) (4) **Confirmatory Assay in the Presence of S9 Mix**

Strain	Conc. (µg/plate)	S9	Number of revertants x_1	x_2	x_3	**mean**	SD	Plate observations * x_1	x_2	x_3	Fold response †
TA1535	DMSO	+	26	25	20	**24**	3				1.0
	320	+	22	24	18	**21**	3				0.9
	640	+	18	15	32	**22**	9				0.9
	1280	+	11	25	27	**21**	9				0.9
	2560	+	14	21	15	**17**	4				0.7
	5000	+	14	15	20	**16**	3				0.7
TA1537	DMSO	+	13	10	7	**10**	3				1.0
	320	+	7	17	14	**13**	5				1.3
	640	+	14	14	11	**13**	2				1.3
	1280	+	14	19	9	**14**	5				1.4
	2560	+	9	12	17	**13**	4				1.3
	5000	+	10	11	15	**12**	3				1.2
TA98	DMSO	+	60	61	77	**66**	10				1.0
	320	+	79	60	69	**69**	10				1.1
	640	+	74	81	92	**82**	9				1.2
	1280	+	60	68	72	**67**	6				1.0
	2560	+	88	88	84	**87**	2				1.3
	5000	+	64	63	62	**63**	1				1.0
TA100	DMSO	+	139	146	139	**141**	4				1.0
	320	+	165	137	127	**143**	20				1.0
	640	+	146	155	141	**147**	7				1.0
	1280	+	158	136	126	**140**	16				1.0
	2560	+	119	118	126	**121**	4				0.9
	5000	+	149	115	110	**125**	21				0.9
WP2 *uvrA*	DMSO	+	51	46	45	**47**	3				1.0
	320	+	54	50	52	**52**	2				1.1
	640	+	50	59	40	**50**	10				1.0
	1280	+	60	60	59	**60**	1				1.3
	2560	+	38	47	46	**44**	5				0.9
	5000	+	39	37	18	**31**	12				0.7

Tables excerpted from sponsor's submission

Study title: Ames reverse mutation study in *Salmonella typhimurium* and *E.coli*

Study no.:	BMS-927982
Study report location:	Electronic submission, M4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study report:	February 10, 2010
GLP compliance:	Y
QA statement:	Y
Positive controls:	Sodium azide, 9-aminoacridine, 2-nitrofluorene, 4-nitroquinoline N-oxide, 2-aminoanthracene, benzopyrene

Key study findings:

●. XL184 n-oxide (BMS 927982), a metabolite of cabozantinib, was not mutagenic in the absence of metabolic activation. Testing was not performed in the presence of metabolic activation since the metabolite is not further metabolized *in vivo*.

Study validation (excerpted from study submission):

The plates from at least 5 non-toxic dose levels of the test article were assessed for revertant colonies in each experiment. The remaining plates from the lowest dose levels were evaluated, and the data are included in the study notebook (not reported herein). Means and standard deviations for appropriate dose levels were calculated using Microsoft® Excel 2000/2003. The mean number of revertant colonies for all treatment groups was compared with those obtained for the concurrent vehicle control group.
The mutagenic activity of the test article was assessed by applying the following criteria:

- *Positive*: If treatment with the test article produced a dose-related increase in revertant colony numbers at least twice the concurrent vehicle control levels with bacterial strains TA98, TA100 and WP2 *uvrA*, (3-fold for TA1535 and TA1537) either in the presence or absence of S9 mix, the test article was considered to show evidence of mutagenic activity in the test system (provided mean value(s) lay outside the historical control range).
- *Negative:* If treatment with the test article did not produce a dose-related increase in revertant colony numbers at least twice the concurrent vehicle controls levels with strains TA98, TA100, and WP2 *uvrA* (3-fold for strains TA1535 and 1537) the test article was considered to show no evidence of mutagenic activity in the test system.
- *Equivocal:* If the results obtained failed to satisfy the criteria for a clear positive or negative response, the results were considered equivocal. It was acceptable to conclude an equivocal response if no clear conclusion could be made. Note that the reproducibility of any apparent effect was taken into account in making any clear conclusion.

For an assay to be considered valid, the mean revertant colony counts of the vehicle/negative controls for each strain had to lie close to or within the current historical control range of the laboratory. All positive control articles (with S9 where required) had to produce increases in revertant colony numbers indicative of a positive response. No invalid assay results were obtained in this study.

Results:

XL 184 n-oxide (BMS 927982), a metabolite of cabozantinib, was evaluated to determine the potential for induction of frameshift and/or base-pair substitution mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, as well as *E. coli* strain WP2 *uvr*A without metabolic activation. Testing was performed only in the absence of metabolic activation

since the metabolite in not further metabolized *in vivo*. Eight concentrations of the metabolite, ranging from 1.58 to 5000 µg/plate) were tested, with the confirmatory assay using concentrations from 40 to 5000 µg/plate. Test article precipitation was observed at concentrations ≥158 µg/plate; toxicity was not observed at any concentration. When compared to negative controls, XL184 n-oxide was not mutagenic in the absence of metabolic activation when tested at levels up to 5000 µg/plate.

Table 2 BMS-927982 - Confirmatory Assay

Strain	Conc. (µg/plate)	S9	Number of revertants x_1	x_2	x_3	mean	SD	Plate observations * x_1	x_2	x_3	Fold response †
TA1535	DMSO	0	26	11	23	**20**	8				1.0
	320	0	18	20	20	**19**	1	ppt	ppt	ppt	1.0
	640	0	19	16	21	**19**	3	ppt	ppt	ppt	0.9
	1280	0	16	13	23	**17**	5	ppt	ppt	ppt	0.9
	2560	0	13	24	22	**20**	6	ppt	ppt	ppt	1.0
	5000	0	10	17	16	**14**	4	ppt	ppt	ppt	0.7
TA1537	DMSO	0	15	15	12	**14**	2				1.0
	320	0	17	18	29	**21**	7	ppt	ppt	ppt	1.5
	640	0	15	27	18	**20**	6	ppt	ppt	ppt	1.4
	1280	0	20	14	14	**16**	3	ppt	ppt	ppt	1.1
	2560	0	8	10	7	**8**	2	ppt	ppt	ppt	0.6
	5000	0	12	11	11	**11**	1	ppt	ppt	ppt	0.8
TA98	DMSO	0	37	31	32	**33**	3				1.0
	320	0	16	34	39	**30**	12	ppt	ppt	ppt	0.9
	640	0	33	29	31	**31**	2	ppt	ppt	ppt	0.9
	1280	0	30	25	25	**27**	3	ppt	ppt	ppt	0.8
	2560	0	27	23	16	**22**	6	ppt	ppt	ppt	0.7
	5000	0	26	19	21	**22**	4	ppt	ppt	ppt	0.7
TA100	DMSO	0	141	115	141	**132**	15				1.0
	320	0	120	131	107	**119**	12	ppt	ppt	ppt	0.9
	640	0	136	115	132	**128**	11	ppt	ppt	ppt	1.0
	1280	0	131	122	129	**127**	5	ppt	ppt	ppt	1.0
	2560	0	126	122	99	**116**	15	ppt	ppt	ppt	0.9
	5000	0	130	115	131	**125**	9	ppt	ppt	ppt	0.9
WP2 uvra	DMSO	0	41	49	40	**43**	5				1.0
	320	0	42	27	41	**37**	8	ppt	ppt	ppt	0.8
	640	0	46	51	44	**47**	4	ppt	ppt	ppt	1.1
	1280	0	42	35	45	**41**	5	ppt	ppt	ppt	0.9
	2560	0	43	30	36	**36**	7	ppt	ppt	ppt	0.8
	5000	0	39	45	44	**43**	3	ppt	ppt	ppt	1.0

Table excerpted from Sponsor's submission

8. Carcinogenicity – None

The applicant is depending on overall survival results from clinical study XL-184-301 to determine the need for non-clinical carcinogenicity studies. Based on the expected extended survival of the MTC patient population, P/T will require a PMR for completion of these studies.

9. Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: **Oral gavage study of fertility, early embryonic development in implantation, and toxicokinetics with X184 in rats**

Study no.:	XL184-NC-020
Study report location:	Electronic submission, M4.2.3.5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 23, 2009
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot# 0804672, purity: 94.9%

Key Study Findings:

● Lethality at high dose (5 mg/kg); all surviving males and females without confirmed mating sacrificed early at day 39.

● Males administered 2.5 or 5 mg/kg XL184 were not fertile, and exhibited a dose-related decrease in sperm counts and reproductive organ weights. The copulation index was similar between control and low- and mid-dosed animals.

● No pregnancies were observed in females mated with males administered 2.5 or 5 mg/kg XL184.

● Pre-and post-implantation loss was significantly increased in females administered 1 mg/kg XL184 compared to concurrent control females.

● The number of viable fetuses were significantly reduced in females administered 1 mg/kg XL184.

Methods

Doses:	1, 2.5, 5 mg/kg
Frequency of dosing:	Males: 28 d prior to mating and throughout mating prior to sacrifice (10 week duration) Females: 14 d prior to mating, throughout mating period and through gestation D7 Females not confirmed for mating: Dosing continued for 7 d following completion of 3-week breeding period
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol:polyethylene glycol 400: water (5:45:50)
Species/Strain:	Crl:CD(SD) rat
Number/Sex/Group:	22/sex/group
Age at initiation:	9 weeks
Animal weight:	M: 301-362g; F: 188-251g
Satellite groups:	Toxicokinetics (3/sex/group) Note: The # of animals used for toxicokinetics was inconsistently reported (3 vs 9 rats/sex/dose for XL184 treated animals)
Study design:	Mating phase = 21 days Day of mating confirmation (sperm or copulatory plug = GD (gestation day) 0 Day of C-section: GD13 (Uterus examined for # of live and dead fetuses, and resorptions. Ovaries examined for # of corpora lutea.) Males necropsied and evaluated for reproductive capacity.
Deviation from study protocol:	Due to toxicities observed in HD rats, all surviving males, as well as all females without confirmed mating exhibiting toxicities sacrificed on day 39

Observation	Time or description of assessment
Mortality	2X/d
Clinical Observations	2X/d
Body weights	2X/week
Food consumption	M: weekly during pre-mating; following D46: 2X/week at time of BW measurement F: 2X/week during pre-mating F confirmed for mating:GD 0, 3, 7, 10, 13
Estrous cycle determination	Vaginal smears assessed for stage of estrus during 14-day premating
Mating confirmation	Daily inspection for presence of retained or dropped copulatory plug, or vaginal sperm
Toxicokinetics	Blood collection: M: D1, 28, 70; F: D1, 14, GD 7
Cesarean section	GD13: Uterus of each gravid animal examined for # and placement of uterine implantation sites, # of live fetuses, and # of early or late resorptions Ovaries examined for # corpora lutea
Organ weights	Epididymis, prostate, seminal vesicles, testes
Male reproductive assessment	1st 10 surviving M /group evaluation for sperm motility + total sperm count

Abbreviations: GD = gestation day; M = males; F = females; d = day

Results

Observations	M (mg/kg)			F (mg/kg)		
	1	2.5	5	1	2.5	5
Mortality		2	22			3
Clinical observations	Decedent M and F: Emaciation, pale, soft/liquid/absence of feces, teeth (malocclusion, missing, extremely white), rough hair coat, discolored hair coat, hypoactivity, hunched posture, ataxia HD surviving F: discolored hair coat, rough hair coat, pale, emaciation, hunched posture, few/soft/absence of feces, hypoactivity, extremely white teeth MD surviving M: pale, teeth (malocclusion, missing, extremely white, bottom teeth excessively long, top teeth curved inward), rough/discolored hair coat, soft/liquid/discolored/absence of feces, emaciation. One LD M also exhibited malocclusion of teeth. MD surviving F: discolored hair coat, extremely white teeth LD F: no noted observations					

Summary of mating and fertility (N=22/group)

Males (mg/kg)	Control	1	2.5	5
Mean # days prior to mating	Not recorded			
# of males mating	21	22	21	19
Male/Female copulation index (%)	95	100	95	86
Male/Female fertility index (%)	91	95	0	0
Sperm motility (%) (post dose)[a]	87	↑8	↑3	UR
Sperm count (%) (post dose)[a]	1256	↓21	↓35	↓55
Body weight[a] (D38-42)			↓12-14	↓17-29
Food consumption [a] (D38-study termination)		UR	↓24-37	ND
Organ weights (absolute)				
Testes		↓10	↓15	↓35

Epididymis			↓11	↓24
Prostate				↓29
Seminal vesicles				↓28
Cauda epididymis				↓25
Gross pathology	MD: Kidneys pale/enlarged (incidence: 3 of 22) HD: Intestines thickened (incidence: 16 of 22); stomach distended (2 of 22); adrenal large/discolored (incidence: 2 of 22) MD/HD: Testis, epididymis, seminal vesicle small; prostate, seminal vesicle gelatinous			
Females				
Premating body weight (d14)[a]	UR			
Premating food consumption[a] (d14)				↓11
Gross pathology	HD: Intestines: thickened and distended 13 of 22HD F)			
Gestation body weight[a]	UR for LD compared to control dams at GD 13; F at MD and HD not determined			
Gestation food consumption[a]	UR for LD compared to control dams at GD 13; F at MD and HD not determined			
# pregnant females	20 (91%)	21 (95%)	0	0
# aborted or total resorption of litter	0	0	0	0
Mean # corpora lutea	15.5	18	ND	ND
Mean # implantations	15	14.6	ND	ND
# pregnant at C-section	19	21	0	0
Dams with viable fetuses	19	16	0	0
Dams with no viable fetuses	0	5	0	0
Mean % pre-implantation loss	3.3	18	ND	ND
Mean # live births	14.2	5.5	ND	ND
Mean # total resorptions Early resorptions Late resorptions	0.8 0.7 0.1	9.1 8.0 1.1	ND	ND
Mean # dead fetuses	0	0	ND	ND
Mean % post-implantation loss	5.7	62	ND	ND

[a] Percent compared to concurrent controls

Abbreviations: UR = unremarkable; GD = gestational day; LD = low dose; MD = mid dose; HD = high dose; ND = not determined

Notes: 1. Mean # of estrous cycles, mean # of days prior to mating and # of females sperm positive were not reported.
2. Several parameters were inconsistently reported (written summary of data vs tabulated data).

Total sperm count and concentration were reduced in a dose related manner, as were reproductive organ weights of these animals. There were no pregnancies in females mated with MD and HD males. Sperm motility was similar in males from all dosed groups.

There were no successful matings at the MD or HD. The incidence of prolonged diestrus was dose related, and found at all doses.

Table 5-1: Toxicokinetic Parameters of XL184 after Single or Daily Administration of XL184 at 1, 2.5 or 5 mg/kg to Male and Female Rats

Sex	Day	Dose (mg/kg)	Group	$t_{1/2,z}$ (h)	t_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng*h/mL)	AR C_{max} (%)	AR AUC_{0-24} (%)
Females	1	1.0	6	17.8	6.00	1130	15300	NC	NC
		2.5	7	NR	4.00	2500	35400	NC	NC
		5.0	8	18.5	4.00	3880	71200	NC	NC
Females	14	1.0	6	26.6	4.00	1650	22100	146	144
		2.5	7	21.4	4.00	4160	60400	166	171
		5.0	8	27.6	4.00	6670	116000	172	163
Females	GD7	1.0	6	22.4	4.00	1170	19300	104	126
		2.5	7	NR	8.00	5380	73200	215	207
		5.0	8	NR	2.00	11600	148000	299	208
Males	1	1.0	6	8.77	6.00	862	10700	NC	NC
		2.5	7	12.6	4.00	2460	25700	NC	NC
		5.0	8	15.4	4.00	4090	50800	NC	NC
Males	28	1.0	6	11.7	8.00	949	17200	110	161
		2.5	7	14.7	4.00	3610	40600	147	158
		5.0	8	NR	6.00	7260	102000	178	201
Males	70	1.0	6	17.7	2.00	1260	20700	146	193
		2.5	7	9.45	6.00	3880	52600	158	205

NC, not calculated; NR, not reported because terminal elimination phase could not be well determined; AR, Accumulation Ratio

Table excerpted from sponsor's submission

In general, exposure increased approximately dose proportionally or greater than dose proportionally with increasing dose; during gestation day 7, exposure increased greater than dose proportionally. Terminal half-life ranged from 8.8 to 17.7 hours for males, and 17.8 to 27.6 hours for females. Following repeated dosing, there was a small but dose related accumulation, with the largest accumulation found in MD and HD females at gestation day 7.

9.2 Embryonic Fetal Development

Study title: **Reproductive and developmental toxicity – effects on embryofetal development in rats**

Study no:	XL184-NC-022
Study report location:	Electronic submission, M4.2.3.5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 1, 2009
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot# 0804672, purity: 94.9%

Key Study Findings:

● Embryo-fetal toxicity at ≥0.03 mg/kg as evidenced by dose-related increase in post-implantation loss, and intrauterine deaths.
● # of live fetuses and fetal body weights similar between control and dosed groups
● Not maternal toxic at doses tested

● External anomalies observed in single 0.1mg/kg fetus considered minimal and within historical control incidence, although cardiac anomalies were observed at 0.01 and 0.1 mg/kg (LD and HD)
● Skeletal anomalies generally not dose related, but observed in a small number of fetuses at all dose groups, and total number of skeletal variations were significantly increased in XL184 fetuses compared to controls.
● XL184 is considered to exhibit embryo-fetal toxicity and is mildly teratogenic in rats at 0.01, 0.03 and 0.1 mg/kg.

Methods

Doses:	0, 0.01, 0.03, 0.1
Frequency of dosing:	Daily from GD 6-17
Dose volume:	5mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol:polyethylene glycol 400: water(5:45:50)
Species/Strain:	Crl:CD(SD) rat
Number/Sex/Group:	25F/group
Age at initiation:	9 weeks
Animal body weight:	M: 301-362g; F: 188-251g
Satellite groups:	Toxicokinetics: 6F/group
Study design:	Day of mating: D0 Day of C-section: GD 21
Deviation from study protocol:	None

Dams

Daily dose (mg/kg)	0	0.01	0.03	0.1
# Pregnant	25	25	25	25
Toxicokinetics/ AUC_{0-24} (ng.h/mL) GD6	0	132	364	1360
/ AUC_{0-24} (ng.h/mL) GD17	0	168	469	1490
Plasma concentration (ng/mL) ~24h following dosing GD17 - dams	0	5.8	17.5	61
Plasma concentration (ng/mL) ~24h following final maternal dosing, GD18 - fetuses	0	1.3	3.6	11.1
Mortality	None			
# with total resorption of litter or aborted	None			
Clinical observations	UR			
Terminal BW (GD21) [a]	361g	UR change from control		
Gravid Uterine Weight (g)	97.2	92.7	95.1	96.9
Corrected BW (g)	264	264.3	273.8	271.7
Net BW change from day 4 (g)	36	35	46	39
FC (GD4-21) [a]	29g	UR change from control		
Mean # corpora lutea	14.4	13.9	14.1	14.4
Mean # implantations	13.3	12.6	13.1	13.2
Mean % preimplantation loss	7.4	9.1	6.7	7.7
Gross pathology *Kidney*/cyst *Uterus*/red fluid (attributed to ↑ number of late resorptions in dam)				 1 1

[a] % compared to concurrent controls; BW and FC measured in animals with live fetuses only
Abbreviations: MD=mid-dose; HD=high-dose; FC=food consumption; BW=body weight; UR = unremarkable; GD = gestation day

Litters

Dose (mg/kg)	control	0.01	0.03	0.1
Fetal plasma drug concentraton (GD18; mean ng/mL)[a]	0	1.3	3.6	11.1
# Litters evaluated	25	25	25	25
Mean # Live fetuses[b]	13	12	12	12
Mean # Resorptions	0.4	0.2	0.6	0.8
Mean # Dead fetuses/litter	0	0	0	0
Mean % pre-implantation loss	7.4	9.1	6.7	7.7
Mean % post-implantation loss	2.9	2.2	4.5	5.9
Mean fetal BW (g)	5.4	5.4	5.5	5.3
Fetal sex ratios (M:F) (%)	52:48	48:52	45:55	51:49

[a]GD 18 = 1 day post final maternal XL184 dose
[b] Number of fetuses documented as fraction; rounded off to next higher number of live fetuses

Fetal anomalies, malformations and variations

Dose (mg/kg)	control	0.01	0.03	0.1
External anomalies – Total affected fetuses(litters); presented as %				
# Fetuses examined	323	310	313	312
# Litters evaluated	25	25	25	25
Hindlimbs malrotated[a]				0.3 (4)
Filamentous tail[a]				0.3 (4)
Anal atresia[a]				0.3 (4)
Viseral anomalies - Total affected fetuses(litters); presented as %				
# fetuses examined	163	155	156	153
# Litters evaluated	25	25	25	25
Heart/ventricular septal defect		0.6 (4)		0.7 (4)
Absent aortic arch				0.7 (4)
Skeletal anomalies - Total affected fetuses(litters); presented as %				
# fetuses examined	160	155	157	159
# Litters evaluated	25	25	25	25
Incomplete ossification of skull		0.6 (4)	0.6 (4)	
Accessory bone(s) in skull				0.6 (4)
25 presacral vertebrae	0.6 (4)	1.3 (4)		
< 4 caudal vertebrae ossified	0.6 (4)			0.6 (4)
Bipartite vertebral centrum	0.6 (4)	1.3 (8)	2.5 (16)	3.8 (24)
Hemicentrum				0.6 (4)
Sternebrae; incomplete ossification				
; No ossification 5th	1.9 (12)	2.6 (12)		1.3 (8)
; incomplete ossification 5th/ 6th	4.4 (16)	7.1 (32)	2.5 (12)	2.5 (12)
; other sternebrae incomplete ossification	0.6 (4)		0.6 (4)	
; sternebrae extra ossification site				0.6 (4)
; 5th/6th sternebrae bipartite		0.6 (4)		0.6 (4)
14th rudimentary rib(s)	1.2 (8)	1.9 (12)	10** (32)*	6.3* (20)
13th rudimentary rib(s)	1.2 (8)	3.9 (16)	0.6 (4)	3.1 (8)
Total fetal skeletal variations	9.4 (40)	17* (52)	16* (56)	16* (56)
Absent vertebrae				0.6 (4)
Centrum absent				0.6 (4)

Split sternebrae	0.6 (4)	1.3 (8)		
Major fusion of sternebrae		0.6 (4)		
Absent rib				0.6 (4)
Total fetal skeletal malformations	1.2 (8)	1.3 (8)		0.6 (4)

* = Significant at P≤0.05; ** = Significant at P≤0.01
[a] All external variations found in one fetus of litter B54178

Note: Fetal anomalies were not noted in above table if incidence occurred in only controls, or if incidence occurred equally in control and LD animals, without findings at higher doses.

Study title: **Oral gavage study for effects on embryo-fetal development and toxicokinetics with XL184 in rabbits**

Study no:	XL184-NC-024
Study report location:	Electronic submission, M4.2.3.5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 15, 2009
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	XL184-(L)-Malate; lot# 0804672, purity: 94.9%

Key Study Findings:
● Limited signs of maternal toxicity (reduced/soft feces at ≥0.3 mg/kg, depressed FC at 1 mg/kg)
● Post-implantation loss and resorptions minimally increased at 3 mg/kg.
● Number of live fetuses similar in dosed and control litters
● Fetal body weights mildly depressed at mid- and high-dose
● Increased incidence of visceral anomalies generally not dose related, but observed in a small number of fetuses at all dose groups; incidence of visceral variations and malformations significantly increased at 0.3 and 3 mg/kg
● Significant incidence of splenic size reduction and missing lung lobe at 3 mg/kg
● Total number of skeletal variations was similar in XL184 fetuses compared to controls although several significantly increased findings
● XL184 is not considered to exhibit embryo-fetal lethality in rabbits at doses tested, but is teratogenic at doses ≥0.3 mg/kg.

Methods

Doses:	0, 0.3, 1, 3 mg/kg
Frequency of dosing:	Daily from GD 6-17
Dose volume:	mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol:polyethylene glycol 400: water(5:45:50)
Species/Strain:	Hra:(NZW)SPF rabbits
Number/Sex/Group:	20F/group
Age at initiation:	5.5 months
Animal body weight:	F: 2952-4286g main study; 3039-3581g toxicokinetics group
Satellite groups:	Toxicokinetics: 3F/group
Study design:	Day of mating: D0 (mated at animal supplier; main study F received D3); tk rabbits received D2 Day of C-section: GD 29
Deviation from study protocol:	Single HD F removed from study on GD9 due to difficulties in gavage tube placement; no microscopic lesions were exhibited; rabbit was not pregnant

Abbreviations: tk = toxicokinetics

Dams

Daily dose (mg/kg)	0	0.3	1.0	3.0
# Pregnant	17	20	18	18
Toxicokinetics/ AUC_{0-24} (ng.h/mL) GD7	0	255	1020	3560
/ AUC_{0-24} (ng.h/mL) GD20	0	274	984	4240
Plasma concentration (ng/mL) ~24h following dosing GD20 - dams	0	5.0	15.5	59.9
Plasma concentration (ng/mL) ~24h following final maternal dosing GD21 - fetuses	0	1.8	6.2	15.1
Mortality	None			
# with total resorption of litter or aborted	None			
Clinical observations	♦ Increased incidence of fecal changes (few, none, or soft) in XL184 treated dams ♦ Minimal incidence of alopecia			
Terminal BW (GD29) [a]	3705g	UR change from control		
Gravid Uterine Weight (g)	488.7	525.4	503.4	452.1
Corrected BW (g)	3216.5	3217.9	3217.4	3291.9
Net BW change from day 4 (g)	-99	-37	-128	-20
FC (GD4-29) [a]	136g	LD and HD food consumption UR; MD food consumption ↓10%		
Mean # corpora lutea	9.5	10.2	10.1	10.3
Mean # implantations	8.8	9.5	9.1	9.0
Mean % preimplantation loss	7.7	6.7	9.4	12.7
Gross pathology	UR			

[a] % compared to concurrent controls; BW and FC measured in animals with live fetuses only
MD: mid-dose; HD: high-dose; FC: food consumption; BW: body weight; UR = unremarkable; GD = gestation day

Litters

Dose (mg/kg)	control	0.3	1.0	3.0
Fetal plasma drug concentraton (GD21; mean ng/mL)[a]	0	1.79	6.2	15.1
# Litters evaluated	20	20	20	20
Mean # Live fetuses[b]	8.4	9.4	8.9	8.4
Mean # Resorptions	0.4	0.2	0.2	0.6
Mean # Dead fetuses/litter	0	0	0	0
Mean % post-implantation loss	4.3	1.3	2.2	6.3
Mean fetal BW (g)	40.5	39.1	37.5	37.2
Fetal sex ratios (M:F) (%)	59:41	42:58	54:46	41:59

[a]GD 21 = 1 day post final maternal XL184 dose
[b] Number of fetuses documented as fraction; rounded off to next higher number of live fetuses

Fetal anomalies, malformations and variations

Dose (mg/kg)	control	0.3	1.0	3.0
External anomalies – Total affected fetuses(litters); presented as %				
# Fetuses examined	142	187	160	152
# Litters evaluated	17	20	18	18
Swollen hind paw				5.9 **(17)
Gastroschisis			0.6 (5.6)	
Rudimentary tail				0.7 (5.6)
Viseral anomalies - Total affected fetuses(litters); presented as %				
# fetuses examined	142	187	160	152
# Litters evaluated	17	20	18	18
Thoracic cavity fluid				1.3 (11)
Left carotid arises from innominate artery	4.9 (24)	15**(30)	8.1 (33)	12*(44)
Absent innominate artery			0.6 (5.6)	
Atrium enlarged		0.5 (5)		
Intermediate lobe of lung missing	2.1 (18)	1.6 (15)	4.4 (33)	15**(50)*
Lungs small			0.6 (5.6)	0.7 (5.6)
Stomach distended				0.7 (5.6)
Gonadal cyst				0.7 (5.6)
Accessory subclavian	2.8 (12)	1.1 (10)	2.5 (11)	2.6 (22)
Total visceral variations	9.9 (41)	19*(50)	14 (67)	26**(72)
Edema		0.5 (5)		
Lens opacity			0.6 (5.6)	
Stenosis of ascending aorta				0.7 (5.6)
Dilation of pulmonary trunk		0.5 (5)		
Marked dilation of aortic arch				0.7 (5.6)
Interrupted aortic arch			0.6 (5.6)	
Diaphragmatic hernia			0.6 (5.6)	
Spleen reduced in size		0.5 (5)		4.6**(5.6)
Gall bladder adenosis		0.5 (5)		1.3 (5.6)
Total visceral malfomations	0.7 (5.9)	0.5 (5)	1.9 (17)	7.2**(22)
Skeletal anomalies - Total affected fetuses(litters); presented as %				
# fetuses examined	142	187	160	152
# Litters evaluated	17	20	18	18
Angulated hyoid wing	1.4 (12)	2.1 (20)	0.6 (5.6)	5.9*(39)
Unossified hyoid wing(s)		0.5 (5)		
Unossified hyoid body	0.7 (5.9)	2.1 (15)	1.9 (17)	2.6 (5.6)
Accessory bone in skull	0.7 (5.9)	1.1 (10)	0.6 (5.6)	

26 presacral vertebrae	13 (29)	2.7**(20)	12 (39)	7.2 (33)
< 16 caudal vertebrae ossified	3.5 (12)	4.8 (25)	8.8*(39)	19**(56)**
Incomplete ossification of vertebral centrum			0.6 (5.6)	2.6 (17)
Hemicentrum(a)		0.5 (5)	0.6 (5.6)	5.3**(22)
Unosified vertebral centrum(a)			0.6 (5.6)	1.3 (11)
Bipiartite vertebral centum(a)			1.2 (11)	2 (17)
Misaligned or bipartite distal caudal vertebra(e)			0.6 (5.6)	0.7 (5.6)
Scapula misshapen		0.5 (5)		
Sternebrae; incomplete ossification				
; No ossification 5th	11 (35)	21*(60)	14 (50)	19*(72)*
; incomplete ossification 5th/ 6th	15 (71)	25*(85)	15 (61)	18 (78)
; 6th sternebrae unossified	4.2 (24)	8 (30)	5.6 (33)	
; sternebrae asymmetrically ossified with minor fusion				0.7 (5.6)
Sternebra(e) misshapen			0.6 (5.6)	
13th rudimentary rib(s)	19 (59)	16 (70)	22 (89*)	7.2**(28)
13th unilateral full rib	6.3 (35)	3.7 (35)	5 (44)	3.3 (22)
13th full rib	35 (88)	28 (75)	26 (72)	17**(61)
17th cervical rib				1.3 (11)
Talus unossified	0.7 (5.9)	0.5 (5)	1.2 (11)	2 (11)
Long bone bent		0.5 (5)		
Total fetal skeletal variations	75 (100)	76 (100)	75 (100)	72 (100)
Misaligned, fused, and/or absent vertebrae				0.7 (5.6)
Total fetal skeletal malformations	2.1 (12)	0.5 (5)	0.6 (5.6)	1.3 (11)

* = Significant at P≤0.05; ** = Significant at P≤0.01

Note: Fetal anomalies were not noted in above table if incidence occurred in only controls, or if incidence occurred equally in control and LD animals, without findings at higher doses.

The Applicant indicated that low XL184 dose ranges were evaluated in developmental toxicity studies in rats and rabbits in order to avoid maternal toxicity observed at higher doses in pilot studies.
The above studies indicate that XL184 caused embryo-fetal toxicities in rat and rabbit models at maternal exposures significantly lower than the equivalent human exposure at the recommended dose of 140 mg/day (freebase).

9.3 Prenatal/Postnatal Development

A prenatal/postnatal development study has not been conducted, but will be required under a post marketing requirement. (b) (4) Administration of XL184 inhibits both MET and VEGFR pathways, and these pathways have been reported to have important roles in osteoclast and osteoblast function in developing bone[1].

[1] (Aftab, TD and McDonald, DM. 2011. MET and VEGF: synergistic targets in castration-resistant prostate cancer. Clin Trnsl Oncol. 13: 704-10.

10. Special Toxicology Studies

Study title: Evaluation of *in vitro* phototoxicity on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay

Study no.:	XL184-NC-028
Study report location:	Electronic submission, M4.2.3.7
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	December, 2010
GLP compliance:	Y
QA statement:	Y
Test material, batch number, purity:	XL184 (L)-Malate, batch # 0804672, purity 94.9%

Key Study findings:

● XL184 (L)-Malate was not phototoxic *in vitro* when tested up to a precipitation concentration of 31.6 µg/mL.

Summary and Results:

Balb/c 3T3 fibroblast cells were treated for 1 hour with concentrations of XL184 ranging from 0.032 to 100 µg/mL prior to irradiation. One set of plates was exposed to 5 J/cm^2 UV-A, with comparative plates kept in darkened conditions for the same period. Approximately 20 hours following irradiation and incubation, cytotoxicity was assessed by the neutral Red uptake assay. Chlorpromazine was used as the positive control.

Concentration-related cytotoxicity (decreased cell survival as indicated by a decrease in Neutral Red uptake) was observed at a XL184 concentration of 10 µg/mL in the absence and presence of UV-A light. The two highest concentrations tested (31.6 and 100 µg/mL) were excluded from analysis due to the presence of precipitation both in the absence and presence of UV-A.

Table 1: IC_{50} and PIF calculations

Test article	IC_{50} absence of UV-A (µg/mL)	IC_{50} presence of UV-A (µg/mL)	PIF Value
XL184 (L)-Malate	5.445	4.280	1.272
Chlorpromazine	19.791	0.525	37.697*

* PIF > 6, therefore positive control response was acceptable.

Table excerpted from the sponsor's submission.

Validation criteria (excerpted from sponsor's submission):

The assay was considered valid if the following criteria were met:

1. Irradiated vehicle controls showed a viability of approximately 80% of the non-irradiated vehicle control
2. OD_{540} in the untreated unirradiated controls > 0.4
3. The positive controls showed a clearly cytotoxic response in the presence of UV-A light, compared to the response seen in the absence of UV-A light, such that the PIF for the positive control was > 6.

Evaluation criteria (excerpted from sponsor's submission):

1. The test article was considered 'phototoxic' in this assay if PIF values of > 5 were obtained
2. The test article was considered 'non-phototoxic' in this assay if PIF values of < 2 were obtained
3. The test article was considered equivocal 'probably phototoxic' in this assay if PIF values of >2 and <5 were obtained.

Local tolerance studies were not conducted.

11. Integrated Summary and Safety Evaluation

Pharmacology

In vitro and *in vivo* studies were conducted to investigate the pharmacologic and anti-tumor activity of cabozantinib. The drug was tested in multiple *in vitro* enzyme assays to evaluate the potency and selectivity of the compound by determining the IC_{50} values for various protein kinases. Results indicated primary targets as RET kinase, mesenchymal epithelial transition factor (MET), and the vascular endothelial cell growth factor receptor 2 (VEGFR2) with IC_{50} values of 9.8, 1.8, and 0.035 nM, respectively. Two additional VEGF receptor kinases (VEGFR1 and VEGFR3) were also inhibited with IC_{50} values of 12.2 and 6.0nM. Additional targets include FLT3, TIE2, AXL, TRKB, and KIT with IC_{50} values of 14.4, 14.3, 7.7, and 4.6 nM, respectively. In xenograft mouse models, treatment with XL184 was found to inhibit RET phosphorylation in medullary thyroid cells in a dose-dependent manner, with maximal inhibition (84 and 89%) at doses of 100 and 300 mg/kg, respectively. Based on these data, the pharmacological classification of cabozantinib is a kinase inhibitor.

Multiple murine tumor models were examined in an attempt to define the activity of XL184, including tumor growth inhibition, tumor cell metastasis, and survival. Rodents implanted with cell lines C6 (rat glioma), MDA-MB-231 (human breast carcinoma), H441 (human lung carcinoma), and TT (human MTC) were studied. In each of the tumor models, significant tumor growth inhibition (TGI) and/or tumor regression was observed; histological evaluation of tumor tissue following XL184 treatment indicated a decrease in microvessel density. The N-oxide and acid metabolites of XL184 (EXEL-5162 and EXEL-5366) were significantly less active against primary targets of XL184 in biochemical and cellular assays when compared to the parent drug. The pharmacological activity of other XL184 metabolites was not determined.

Safety Pharmcology

Both *in vitro* and in *vivo* safety pharmacology studies were conducted to assess the effects of cabozantinib on cardiovascular, behavioral,general physiological, and respiratory function. XL184 did not inhibit hERG potassium channel activity when tested at 1, 10, and 30 µM using manual patch-clamp electrophysiology using Chinese hamster ovary cells expressing hERG channels. In dogs, XL184 administered at 150 or 1000 mg/kg had no effect on cardiovascular parameters. In rats, behavioral and physiological changes were not observed following single doses of XL184 up to 300 mg/kg. In a separate safety pharmacology study, a single dose of 900mg/kg XL184 to conscious rats had no effects on respiratory parameters.

Genotoxic and Non-genotoxic impurities

Four genotoxic impurities were identified in the drug substance; ((b) (4) and (b) (4) (b) (4) and (b) (4) (b) (4) and (b) (4) are process impurities as well as degradants, while (b) (4) and (b) (4) are process impurities, but not degradants; 4-fluoroaniline is a human metabolite. The proposed release/stability acceptance criteria for (b) (4) (b) (4) + (b) (4) and (b) (4) are (b) (4) respectively, for drug substance (DS), and (b) (4), respectively, for drug product (DP). Based on XL184 lot #0804672, used during clinical trials and nonclinical studies, the previous clinical intake of these impurities on a daily basis exceeded the expected intake at the proposed limits for the commercial product.

Genotoxic impurity (GTI) levels using revised impurity methodology

Impurity	Proposed specification limits at release and end of shelf life (stability)	Impurity levels from clinical batch #0804672 (175 mg salt basis)	Impurity intake at proposed clinical dose (140mg freebase)	Limit Acceptability
(b) (4)	(b) (4)			Accepted
(b) (4) + (b) (4)				Accepted
(b) (4)				Accepted

[a] ND in clinical batch used for qualification of genotoxic impurities (GTIs)

As a result of revised purity/impurity methodology, the Applicant has indicated that stability specification of genotoxic and non-genotoxic impurities will equal release specification. The XL184 lot used to support acceptability of proposed genotoxic impurity limits (lot # 0804672) is a batch manufactured using process B-1. The lot was used for a clinical study, as well as for reproductive toxicology testing (fertility and embryofetal development) of rats and rabbits (Studies XL184-NC-020, XL184-NC-022, and XL184-NC-024), and the mouse micronucleus assay (XL184-NC-019).

Even though the genotoxic impurities noted above exceed a theoretical threshold of toxicologic concern of 1.5 µg/day, this threshold is based on a lifetime risk for the development of cancer and, as stated in ICH S9, a strict adherence to this limit may not be appropriate for a drug

developed to treat patients with cancer. At the drug product specifications proposed, none of the impurities exceeds an intake o (b) (4)/day at the recommended dose of cabozantinib. The (b) (4) intake level represents a low safety risk for this patient population. Thus, the currently proposed acceptability criteria for the genotoxic impurities/degradants present in cabozantanib are considered acceptable.

Ames assays have been conducted for all genotoxic impurities. Results indicated: 1) (b) (4) is mutagenic in *S.typhimurium* strain TA1537 in both the presence and absence of metabolic activation. 2) (b) (4) in combination with (b) (4) is mutagenic in the presence of metabolic activation in *S.typhimurium* strains TA98 and TA100. 3) (b) (4) was mutagenic in the absence of activation in strains *S.typhimurium* TA1535 and *E.coli* WP2 *uvrA*. The clastogenicity potential of the impurities was not tested.

The proposed release/stability specification of a non-genotoxic impurity, (b) (4) (b) (4) which exceeds the ICH Q3B(R2) qualification threshold. The clinical intake per day for this impurity at the proposed clinical dose of 140 mg freebase (b) (4) mg/m^2 based on a 70kg adult) is (b) (4) mg/m^2/day. The nonclinical batch (batch # 163-183-1) used for 6-month rat and dog repeat-dose toxicology studies contained (b) (4). At the highest dose administered to dogs for 6 months in which there was no mortality (5 mg/kg), the animal impurity intake was (b) (4) mg/m^2/day, which is above the proposed intake of the impurity in humans at the proposed clinical dose. Based on this calculation, (b) (4) is qualified at (b) (4). Other individual non-genotoxic impurities specified in cabozantanib ((b) (4) (retention time (RRT) (b) (4) and an unnamed impurity at RRT (b) (4) are below or NMT (b) (4), which is within the ICH Q3B(R2) qualification threshold of 0.2%.

Pharmacokinetics

Pharmacokinetics of cabozantinib were studied in mice, rats, dogs, and monkeys. In human patients treated with 175 mg XL184 L-malate capsules, the C_{max} (Day 19) was 2220 ng/mL, with an AUC of 37850 ng·h/mL (Day 19); the plasma half-life was approximately 55 hours, with time to steady state at 15 days following daily dosing. Cabozantinib was well absorbed in animal models, as well as human subjects.

When the oral bioavailability of XL184 free base was compared to its salt forms (maleic, malic, phosphate, and hydrochloride) in rats, the bioavailability of the cabozantanib was most similar between the maleic and hydrochloride forms. The maleic salt form has been developed for commercial use in the patient population with MTC, and has been administered to these patients in clinical trials. Bioavailability of the capsule and aqueous suspension formulations were similar in dogs administered 50 mg weekly for 3 weeks, but the capsule formulation was lower in monkeys administered a single comparative dose. The relative bioavailability of the capsule formulation was higher in humans (~2-fold) compared to dogs; the basis of the inter-species differences is unknown.

Drug accumulation was observed over time following 6 months of repeat dose administration in rats along with a gender effect in which females exhibited higher exposure. Drug half-life was between 8 and 26 hours in this species; exposure was less than dose proportional at lower dose levels (between 0.1 to 1 mg/kg). Similarly, in dogs dosed for 6 months, XL184 plasma exposures also increased less than dose proportionally at lower dose levels (between 0.2 to 5 mg/kg), although overall drug accumulation was low. A gender effect was observed in dogs with generally increased exposure in males compared to females, but was variable dependent on duration of dosing; the drug half-life was generally between 6 and 7 hours. Dose-normalized exposure was significantly higher in rats compared to dogs following a single dose

administration. In patients administered cabozantinib, systemic exposures were generally dose proportional over 5 days of administration with plasma drug accumulation between 4.7 to 6.9 fold, with no gender effects (Clinical Study XL184-001).

Distribution studies in rats showed that high concentrations of cabozantinib were found at early time points in GI contents and bile, liver, adrenal gland, adipose tissue, and stomach. At later time points, concentrations were high in the eye and small intestine. Interestingly, only selective tissues were also target sites of toxicity. Even though the drug was found to accumulate in the eye and eye uveal tissue, no associated ocular toxicity findings have been observed clinically or nonclinically, with the exception of ocular keratitis in dogs administered toxic levels of XL184 (100 to 1000 mg/kg, Study XL184-NC-006). Disposition studies indicated elimination primarily in the feces (82-85%) with 9-12% in urine following oral administration.

The pharmacokinetics of XL184 and selected metabolites M1 (XL184-N-oxide), M4 (XL184-monohydroxy-sulfate), M8 (XL184-amide cleavage product), and para-fluoroaniline (pFA) were compared in rats and dogs administered XL184 in repeat-dose rat and dog studies and humans administered a single 175 mg oral dose of XL184 in the healthy volunteer mass balance study XL184-012. When measured quantitatively using validated LC-MS/MS, dogs and rats were exposed to the 4 metabolites at low levels compared to human exposure. The mean percentage AUC of metabolite relative to AUC of XL184 in humans was 43% for M4, 15% for M1, and 10% for M8. The pFA level was below the limit of quantitation. The primary isozyme for drug metabolism is CYP3A4; XL184 inhibits the enzymatic activity of CYP2C8, CYP2C9 and CYP2C19. Concomitant strong inducers of inhibitors of CYP3A4 should be used with caution, as well as substances that induce, inhibit, or are substrates of CYP2C8, CYP2C9, and CYP2C19. Cabozantinib is highly bound to human plasma proteins *in vitro.*

General Toxicology

Target organs of cabozantinib-mediated toxicity were exhibited in rats and dogs dosed up to 6 months, and included the gastrointestinal tract, reproductive system, kidney, liver/gall bladder, hematopoietic/lymphoid system, endocrine tissues, skin, and dentin. Target organs and dose limiting toxicities were generally consistent for shorter and longer periods of dosing.

Gastrointestinal toxicity was observed in rodents and non-rodents administered cabozantinib for 14 days. Marked gastrointestinal histopathology (necrosis and degeneration of all organs of the gastrointestinal tract) was exhibited in rats administered doses ≥5 mg/kg, and in dogs administered doses ≥100 mg/kg, with significant associated systemic toxicity (emesis, hypoactivity, anorexia, dehydration, decreased body weight, and moribund sacrifice). Histological findings were reversible following recovery in rats, but not in dogs. Gastrointestinal histopathology was not observed at doses studied in the 6-month studies in either species even though exposures in rats based on AUC were 0.7 to 1.2-fold those measured in patients administered 175 mg XL184 daily, with reported nausea, diarrhea, emesis, mucositis, GI perforation, GI fistula, and GI ulcers. Dogs administered ≥20 mg/kg/day for 6 months exhibited clinical signs of gastrointestinal toxicity (depressed food consumption and body weight, emaciation, dehydration, and abnormal feces), but correlating gastrointestinal histopathology (rectal hemorrhage) in only a single female decedent. Gastrointestinal tract toxicity is a pharmacological class finding of VEGF inhibitors, which may reflect the role of VEGF in maintaining mucosal homeostasis. Hematopoietic and immunological findings, characterized by dose-related red and white cell depletion, hypocellularily in bone marrow and lymphoid depletion and necrosis of the thymus, spleen, mesenteric lymph nodes and gastrointestinal tract was primarily observed in rats administered higher doses of cabozantinib (≥5mg/kg). Hematopoietic

depletion was observed in dogs administered ≥20 mg/kg/day, although associated immunological depletion and histopathology as described above was reported at doses ≥100 mg/kg.

Rats administered 5 mg/kg for 14 days exhibited renal degeneration. When rats were dosed for 6 months, chronic progressive nephropathy with bilateral hydronephrosis was observed at doses ≥0.1 mg/kg, and persisted following recovery. Dogs were less sensitive, and the incidence and severity of renal toxicity in dogs was less pronounced compared to rodents. Renal degeneration was observed in a single male dog administered 5 mg/kg cabozantinib for 6 months, and mineralization of the kidney was observed in 3 of 3 female dogs administered 30/20 mg/kg cabozantinib in a 2nd 6-month repeat dose study.

Cabozantinib-related hepatotoxic changes were generally reflective of treatment-related systemic toxicity in rats and dogs, characterized by significant elevations in liver enzymes. Liver hypertrophy was observed in rats administered doses of 1 to 15 mg/kg cabozantinib for 14 days. Liver histopathology was not observed in rats following 6 months of dosing, although liver enzymes were increased at all doses studied (0.1 to 1 mg/kg/day). Endocrine tissue toxicity was primarily exhibited as adrenal gland changes in rats administered doses of 5 and 15mg/kg for 14 days in two separate studies. Adrenal necrosis was dose related, and was partially reversible. Degeneration and necrosis of the pancreas and pituitary observed in rats was considered to be secondary to general drug-related systemic, or adrenal changes, respectively. Even though clinical reports of patients administered cabozantinib have included abnormal thyroid function test results, thyroid findings were not observed in animal models. Altered thyroid indices have been reported with other multi-kinase RTK inhibitors, and would be an expected finding of cabozantinib.

In contrast to other VEGF inhibitors, changes in epiphyseal growth plates were not observed following treatment with cabozantinib, although atrophy of the femur was observed in dogs administered doses ≥100 mg/kg/day for 14 days; this finding was not observed following recovery, and was considered to be secondary to the systemic toxicity observed in these animals. Changes in dentin (broken teeth, whitening of teeth) were observed in rats dosed for 6 months; the incidence of these changes was highest in female rats administered XL184 at the 1 mg/kg dose level, and increased with prolonged exposure. Changes in tooth appearance (malocclusion, excessively long, white teeth curved upward) were also observed in the fertility study in male and female rats administered 1 to 5 mg/kg/day. Cutaneous toxicity was observed only in dogs administered 20 mg/kg/day for 6 months. Gray skin (exhibited on the nose, lips, and eyelids), and white haircoat hypopigmentation was not resolved following recovery. These findings were not associated with microscopic correlates, although a dermal histopathologic hyperkeratosis, hyperplasia and exudate was noted in these animals. Drug-related phototoxicity was not observed *in vitro*. Changes in skin and hair appearance have been reported in patients administered cabozantinib (e.g. pigmentary changes, pruritis, dry skin), and are consistent with skin reactions observed with other VEGF inhibitors.

In agreement with the cardiovascular safety pharmacology studies, cardiovascular toxicity was not commonly observed in rodents or non-rodents administered cabozantinib for up to 6 months, although cardiac inflammation was noted in a single female dog administered 20 mg/kg for the 6 month dosing period.

Genetic Toxicology

The parent drug cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* rat micronucleus assay. Six process impurities were assayed for mutagenicity; impurities were not tested for induction of chromosomal aberrations. Process impurities (b) (4) (b) (4) (b) (4) and (b) (4) were found to be genotoxic. At (b) (4) µg intake level for these GTIs at the proposed clinical dose of cabozantinib, these impurities represent a low safety risk for this patient population. Process impurities (b) (4) and (b) (4) were not genotoxic. The XL184 N-oxide and EXEL-5366 metabolites were tested for mutagenicity, and found to be negative. Metabolites were not tested for clastogenicity.

Carcinogenicity

Carcinogenicity studies with cabozantinib have not been studied.

Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were conducted in rats and rabbits to assess the effects of XL184 on fertility and embryofetal development. In the rodent fertility study, male and female rats were each administered cabozantinib limiting the interpretation of the effects on male and female fertility independently. At doses ≥ 2.5 mg/kg/day, there was total loss of fertility. Male rats administered XL184 doses of ≥ 2.5 mg/kg/day exhibited dose related reductions in reproductive organ weights with correlative reductions in sperm counts and concentration; at the same dose level, female rats exhibited prolongation of diestrus. The dose of 2.5 mg/kg in rats is approximately 1.5 times the recommended human dose on an AUC basis. Increased pre- and post-implantation loss and reduction in the number of viable fetuses was also observed in females administered 1 mg/kg/day. Effects on male and female reproductive organs were also observed following repeat dose administration of 6 months in dogs of both genders. Dogs were the more sensitive species; the lowest dose which resulted in adverse findings in reproductive organs of males and females (hypospermatogenesis and absence of corpora lutea) was 1 mg/kg/day. Rats administered doses of cabozantanib up to 1 mg/kg/day for 6 months did not exhibit reproductive findings, although ovarian necrosis was observed in females administered 5mg/kg/day for 14 days.

Administration of XL184 to pregnant rats during the period of organogenesis resulted in embryo-fetal lethality at doses ≥0.03 mg/kg/day as evidenced by increased implantation loss, and increased intrauterine deaths ($AUC_{0\text{-}48h}$ = 168 ng.h/mL; <1% of clinical steady-state plasma exposures). Cardiac anomalies (septal defects of the ventricle) were observed at 0.01 and 0.1 mg/kg and the total number of skeletal variations were significantly increased in XL184 fetuses compared to controls in the absence of maternal toxicity. XL184 administration to pregnant rabbits during the period of organogenesis resulted in limited signs of maternal toxicity and embryo-fetal viability, but the incidence of visceral variation and malformations was increased in F_1 fetuses, including splenic size reduction and missing lung lobe at 3 mg/kg (approximately 0.11 times the exposure by AUC at the recommended human dose). XL184 caused embryo-fetal toxicities in rat and rabbit models at maternal exposures significantly lower than the equivalent human exposure at the recommended dose of 140 mg/day.

Prenatal/postnatal development studies have not been conducted; (b) (4)

(b) (4)

The reproductive and developmental toxicology studies suggest that administration of cabozantinib may impair fertility and pose a risk for fetal toxicity. Pregnancy category D is recommended. This is not in agreement with the Applicant recommendation of category (b) (4) based on their data interpretation (lack of embryo-fetal growth, and lack of fetal external, soft tissue or skeletal malformations or variations in rats or rabbits at the highest dose tested).

Special Toxicology

XL184 (L)-Malate was not phototoxic *in vitro* when tested up to a precipitation concentration of 31.6 µg/mL. Local tolerance studies were not conducted.

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/s/

MARGARET E BROWER
11/06/2012

WHITNEY S HELMS
11/06/2012
I concur with Dr. Brower's conclusion that there are no pharmacology/toxicology issues that would prevent the approval of this drug in the intended patient population.

JOHN K LEIGHTON
11/06/2012

MEMORANDUM

Date: November 5, 2012
From: Whitney S. Helms, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology
For the Division of Oncology Products 2
To: File for NDA #203756
Cabozantinib (COMETRIQ)
Re: Approvability of Pharmacology and Toxicology

In NDA 203756, Exelixis has submitted clinical trial data to support the use of cabozantinib for the treatment of patients with medullary thyroid cancer. Non-clinical studies examining the pharmacology and toxicology of cabozantinib provided to support this indication were reviewed in detail by Margaret Brower, Ph.D. The application included studies of orally administrated cabozantinib in rats, dogs, mice, and rabbits that investigated the drug's pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (*in vivo* and *in vitro*), and reproductive toxicity.

The pharmacology studies submitted to this NDA demonostrate that cabozantinib is a kinase inhibitor targeting primarily tyrosine kinases. "Kinase inhibitor" is an existing established pharmacological class and this designation is reflected in the indication statement in the Highlights Section of the label for cabozantinib. Like other approved kinase inhibitors, cabozantinb targets a number of enzymes at concentrations that could be achieved clinically including MET, RET, VEGFR-1,-2, and -3, Tie2, Flt-3, Axl, TrkB, and KIT. In addition to biochemical inhibition, the Applicant provided data showing that cabozantinib was able to inhibit *in vitro* proliferation of a variety of tumor cell lines including some with mutations leading to MET overexpression. Incubation with cabozantinib *in vitro* also led to reduced endothelial cellular migration in response to VEGF and HGF in a wound induced endothelial tube formation model. Xenograft models using various tumors including thyroid tumors demonstrated the inhibitory activity of cabozantinib *in vivo*. In one xenograft experiment using a medullary thyroid tumor, the Applicant demonstrated a dose dependent decrease in RET phosphorylation following cabozantinib administration.

During the course of drug development, comparison of human and animal metabolites showed there were 4 major metabolites of cabozantinib present at levels ≥ 10% of total exposure of the parent drug. Three of these, M1, M4, and M8, had greater exposure in humans compared to animals. The M1 and M8 metabolites were examined further to assess their contribution to the activity of cabozantinib. Neither metabolite had significant activity in biochemical inhibition studies. The M1 metabolite was also negative in a bacterial reverse mutation assay (Ames)assay. As the tested metabolites had no significant pharmacologic activity *in vitro*, no further testing was conducted. The third metabolite, M4, showed the biggest difference between animal and human exposure being present in humans at levels of up to 43% of the total cabozantinib exposure while the highest exposure in animals was only up to 7%. Because this metabolite was

present at high levels in humans, as a postmarketing requirement the Applicant will be asked to conduct an *in vitro* mutagenicity assay with M4.

Safety pharmacology studies were performed to examine the effects of cabozantinib on the cardiovascular, respiratory, and central nervous system. Cabozantinib did not significantly inhibit hERG channel activity in *in vitro* assays suggesting low potential for QTc prolongation. No significant QTc changes were noted in an *in vivo* cardiovascular study conducted in dogs administered weekly doses of cabozantinib, although at the high dose of 1000 mg/kg dogs displayed increases in blood pressure (≥10%). Hypertension has been reported clinically. There were also no common cardiovascular toxicities noted in 6-month general toxicology studies conducted in rats or dogs. In rats there were no clear behavioral or physiologic effects following administration of cabozantinib at doses up to 300 mg/kg or on respiratory parameters at doses up to 900 mg/kg.

Target organs for cabozantinib-mediated toxicity identified in toxicology studies conducted using both rats and dogs included the liver, kidney, adrenal gland, gastrointestinal tract, and hematopoietic/lymphoid system. Skin toxicity was also observed in dogs. Signs of toxicity in all of these organs/systems have been observed clinically. Findings of alterations in dentin (broken teeth, malocclusion, excessively long, white teeth curved upward) were observed primarily in rats and have been observed with other compounds that inhibit VEGFR signaling. These findings may be more relevant to a pediatric patient population. Changes in pigmentation of the skin and teeth (whitening) were observed nonclinically and have been reported in humans. In rats there were findings of kidney toxicity in both 14-day and 6-month studies. These findings included renal degeneration, chronic progressive nephropathy, and bilateral hydronephrosis. Dogs appeared less senstitive to cabozantinib-mediated nephrotoxicity though renal degeneration was observed in a single male at the high dose level of 5 mg/kg in a 6-month study and kidney mineralization was observed in females at the 20 mg/kg dose level. Proteinuria has been observed clinically.

Dedicated studies to examine the effects of cabozantinib on fertility and embryofetal development were included to support the use of cabozantinib in the proposed patient population. In general toxicology studies in both rats and dogs there were effects on male and female reproductive organs including hypospermatogenesis and the absence of corpora lutea in dogs. In the fertility study, there was total loss of fertility at cabozantinib doses ≥ 2.5 mg/kg in rats (approximately 1.5 times the human exposure by AUC). As animals of both genders were administered cabozantinib prior to mating, loss of fertility cannot be fully attributed to either gender. At the 2.5 mg/kg dose level male rats exhibited dose related reductions in reproductive organ weights with correlative reductions in sperm counts and concentration; at the same dose level female rats exhibited prolongation of diestrus. Increased pre- and post-implantation loss and reduction in the number of viable fetuses was also observed in females administered cabozantinib at the 1 mg/kg/day dose level. Embryofetal development studies were conducted in 2 species—Sprague Dawley rats and New Zealand White rabbits. In rats, administration of cabozantinib at doses ≥ 0.03 mg/kg (< 1% of the human exposure at the recommended dose of 140 mg measured by AUC) resulted in increases in post-implantation loss compared to controls. In addition there were limited findings of cardiac anomalies at doses as low as 0.01 mg/kg/day in the same study along with dose dependent increases in skeletal variations, all in the absence of

maternal toxicity. In rabbits there was a small increase post-implantation loss at the high dose of 3 mg/kg (approximately 9-11% of the human exposure at the recommended dose) administered daily during organogenesis as well as a mild dose-dependent decrease in fetal body weight. In the same study fetuses from dams administered cabozantinib at the 3 mg/kg dose level displayed increases in the incidence of visceral variations and malformations including reduced spleen size and missing lung lobes. Exposures at all doses in both studies (rats and rabbits) were significantly lower than the human exposure at the recommended dose. Overall, the reproductive toxicity findings suggest that male and female fertility can be impaired by treatment with cabozantinib and that there is a significant risk of loss of pregnancy or teratogenic effects in a fetus following exposure to cabozantinib. Pregnancy Category D is recommended.

Cabozantinib was negative for genotoxic potential in both *in vitro* and *in vivo* assays; however, 4 process impurities were identified over the course of drug development that were determined to be mutagenic in the bacterial reverse mutation assay: (b) (4) and (b) (4) (b) (4) and (b) (4) (b) (4) and (b) (4) are also degradants and (b) (4) (b) (4). Driven in part by the presence of these genotoxic impurities at unacceptable levels, the Applicant made multiple changes to the manufacturing process of cabozantinib over the course of development. These changes included changes in the analytical methods used to detect impurities and led to uncertainty about the comparative levels of the genotoxic impurities present in previous batches and the final requested specifications for the genotoxic impurities. In a teleconference between the FDA and the Applicant held late in the review process the Applicant confirmed that the final requested specifications for (b) (4) (b) (4) + (b) (4) and (b) (4) in the drug substance are (b) (4), respectively. After this teleconference it was discovered that the requested specifications for the drug product are higher at (b) (4) (b) (4) for (b) (4) (b) (4) + (b) (4) and (b) (4) respectively. At the highest proposed specifications the maximum daily levels of the impurities delivered as a result of administration of the cabozantinib drug prodcut at the recommended daily dose of 140 mg are (b) (4) µg, respectively with a total exposure to all genotoxic impurities of (b) (4) µg. Although these impurities exceed the theoretical threshold of toxicological concern of 1.5 µg/day for individual genotoxic impurities, this threshold is based on a lifetime risk of carcinogenic potential for a compound and, thus, as discussed in the ICH S9 guidance, does not adequately reflect the risk/benefit consideration for a patient population with advanced cancer. With the risk/benefit consideration of patients with progressive metastatic thyroid cancer in mind, the proposed specifications are considered acceptable from a safety standpoint. A single non-genotoxic impurity was identified during the course of the review as being above the level for qualification. The specification for this impurity is (b) (4) and it was qualified in the 6-month long dog study.

Recommendations: I concur with the conclusion of Dr. Brower that the pharmacology and toxicology data provided are sufficient support the approval of NDA 203756 for COMETRIQ for the treatment of patients with medullary thyroid cancer at the stage studied in the pivotal clinical trial supporting the safety and efficacy of this drug. Due to the potentially large variability in the natural progression of this disease, however, there will be postmarketing requirements for studying the carcinogenicity of the cabozantinib in two species (i.e. rat and mouse), for further studying the effects of cabozantinib on reproductive toxicology in a pre-and post-natal study, and for conducting a bacterial reverse mutation assay for the M4 metabolite.

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/s/

WHITNEY S HELMS
11/06/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203,756 **Applicant: Exelixis, Inc.** **Stamp Date: May 29, 2012**

Drug Name: Cometriq (cabozantinib) **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The need for carcinogenicity studies is dependent upon OS results from Ph3 study XL184-301. In December, 2011, Exelixis was advised to submit plans to conduct carcinogenicity studies as PMR. These PMR have not been submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		See comment for question 4.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Pending further review and discussions with other disciplines.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Margaret Brower, Ph.D. June 29, 2012
Reviewing Pharmacologist Date

Whitney Helms, Ph.D. June 29, 2012
Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARET E BROWER
06/28/2012

WHITNEY S HELMS
06/28/2012