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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208692
Supporting document/s:	1
Applicant's letter date:	12 October 2015
CDER stamp date:	
Product:	Cabometyx (cabozantinib) tablets
Indication:	For the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy
Applicant:	Exelixis, Inc
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
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1 Executive Summary

1.1 Introduction

Exelixis, Inc. (the Applicant) has submitted New Drug Application (NDA) on December 22, 2015 for Cabometyx (cabozantinib) tablets for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. Cabozantinib will be given to patients once daily orally (tablet) at 60 mg. Cabozantinib is a kinase inhibitor with activity against multiple kinases. Cometriq (cabozantinib) capsules is an FDA approved drug since 2012 (140 mg orally [capsules], once daily) for the treatment of patients with progressive, metastatic medullary thyroid cancer (NDA # 203756; Applicant owned). The change in formulation from capsules to tablets for the advanced RCC indication required this submission to be a new NDA rather than a supplemental NDA. For pharmacology and toxicology data in support of the current indication, the Applicant cross-referenced NDA # 203756. Furthermore, the Applicant submitted a 26-week mouse carcinogenicity study final report to the current application, which was also previously submitted to NDA 203756 to fulfill a post marketing requirement (PMR). This report was not previously reviewed. The report for that study was reviewed under the current NDA, and the results were included in the product label for Cabometyx. Additional nonclinical study reports submitted under the current NDA in support of the proposed indication are discussed in this review.

1.2 Brief Discussion of Nonclinical Findings

Cabozantinib (XL184) is a kinase inhibitor with activity against MER, TYRO3 [RSE], ROS1, Aurora-B and RON in addition to other known kinases listed in the FDA approved label for Cometriq (MET, VEGFR-1, -2 and -3, AXL, RET, KIT, TRKB, FLT-3, and TIE-2). Administration of an anti-VEGF antibody or kinase inhibitor in a pancreatic acinar tumor cell xenograft model resulted in reduced tumor burden, but increased tumor hypoxia, HIF-1α levels, c-Met activation, invasion and metastasis. Administration of an anti-VEGF antibody or kinase inhibitor and PF-04217903 (c-Met inhibitor) concurrently or cabozantinib (VEGFR and c-MET inhibitor) resulted in tumor inhibition with reduced invasion and metastasis and increased survival. This suggests that inhibition of VEGF alone may increase the aggressiveness of tumors as demonstrated by increased invasiveness and/or metastasis, while simultaneous inhibition of VEGF and c-Met signaling may aid in circumventing tumor resistance as indicated by decreased invasiveness and metastasis.

Four major metabolites of XL184 were identified (EXEL-1644, EXEL-1646, EXEL-5162, and EXEL-5366), three of which were quantified (EXEL-1644 was not quantifiable) in plasma of healthy human subjects subsequent to the initial approval of Cometriq. The levels of these human metabolites exceeded those found in nonclinical species in repeat-dose studies of up to 6 months duration. Based on data submitted to NDA 203756, metabolites EXEL-5162 and EXEL-5366 were not pharmacologically active, while EXEL-1644 and EXEL-1646 were not tested for activity (per Dr. Margaret Brower's review for NDA# 203756). In the current submission, reports from studies testing the inhibitory activity of these four metabolites in biochemical assay against a

panel of kinases were submitted. Metabolite EXEL-1646 showed reduced potency relative to cabozantinib (i.e. for MET, RET and VEGFR2), but exhibited higher inhibitory potency than EXEL-1644 (i.e. >90% inhibition of MET, RET, AXL and FLT4) at a single concentration. EXEL-5162 and EXEL-5366 showed minimal inhibitory activity against the primary target (RET).

The four major metabolites were also identified and quantified in plasma from patients with RCC. Metabolite EXEL-1644 was the predominant cabozantinib metabolite present in human plasma. Metabolite EXEL-1644 was quantified at AUC levels of 35.8% of the total drug-related exposure, which exceeded the level of the same metabolite in plasma samples of nonclinical species. As such, the toxicity of this major metabolite was characterized in a 2-week subcutaneous toxicology study in rats. No adverse findings were associated with the highest EXEL-1644 dose tested (13.6-fold the EXEL-1644 human AUC at 175 mg/day of cabozantinib). EXEL-1644 was not mutagenic in an in vitro reverse mutation assay in bacterial cells (Ames), (per Dr. Margaret Brower's review NDA # 203756).

To fulfill a PMR for NDA 203756, the Applicant evaluated the carcinogenicity potential of cabozantinib in a 26-week Tg.rasH2 mouse study. No cabozantinib-related increases in the incidence of neoplastic lesions were reported in this model at doses ≤ 15 mg/kg/day (1.2-fold, the nominal maximum recommended human dose of 60 mg/day of cabozantinib). Based on reports from studies submitted to NDA 203756, cabozantinib was not mutagenic or clastogenic (per Dr. Margaret Brower's review NDA# 203756).

1.3 Recommendations

1.3.1 Approvability

There are no nonclinical findings that would preclude the approval of cabozantinib (S)-malate (cabozantinib or XL184) for the proposed indication.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling Recommendations

In section 12.1, the **bolded** phrases in the following excerpts were added in the label for Cabometyx, which did not previously appear in the approved label for Cometriq.

"cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, **ROS1**, **TYRO3**, **MER**, KIT, TRKB, FLT-3, and TIE-2. "

- The kinases ROS1, TYRO3 and MER were inhibited with lower or similar IC_{50} values compared to the other kinases included in this sentence (study # (b) (4)-EXL085).

"These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, **drug resistance**"

- This addition was supported by data in study # XL184-TM-001.

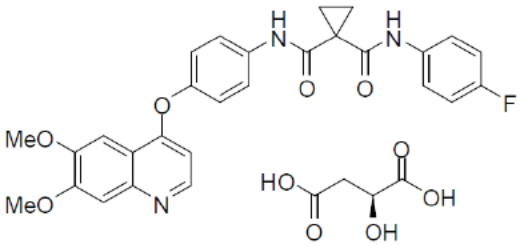
In section 13.1 the following statement was added in the label for Cabometyx, which did not previously appear in the approved label for Cometriq

"Cabozantinib was not carcinogenic in [redacted] rasH2 mouse [redacted]."

- This addition was supported by the data in study # XL184-NC-042.

2 Drug Information

2.1 Drug

Name:	Cabozantinib (S)-malate
Drug Code Name:	XL184, EXEL-7184, EXEL-02977184
CAS Registry Number:	1140909-48-3
Molecular Formula:	$C_{28}H_{24}FN_3O_5.C_4H_6O_5$
Molecular Weight:	635.6 Daltons (L-malate salt) 501.5 Daltons (freebase)
Structure or Biochemical Description:	 (excerpted from Applicant's submission)
Pharmacologic Class:	Kinase inhibitor

2.2 Relevant INDs, NDAs and DMFs

NDA 203756 (Cometriq®) Applicant owned, DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted]

2.3 Drug Formulation

The Cabometyx drug product formulation is an immediate release tablet (20-mg, 40-mg, and 60-mg) for oral administration.

Table 1: Composition of Cabometyx Tablets

Table 2: Composition of Proposed Commercial Cabozantinib Tablets

Ingredient	Function	Compendial Code	Theoretical Quantity (mg/unit dose)		
			20-mg	40-mg	60-mg
(b) (4)					
Cabozantinib (*S*)-malate	Active ingredient	N/A	25.34	50.69	76.03
Microcrystalline Cellulose, (b) (4)	(b) (4)	USP, NF, EP, JP			(b) (4)
Lactose Anhydrous, (b) (4)		USP, NF, EP, JP			
Hydroxypropyl Cellulose, (b) (4)		USP, NF, EP, JP			
Croscarmellose Sodium		USP, NF, EP, JP			
					(b) (4)
Colloidal Silicon Dioxide	(b) (4)	USP, NF, EP, JP			(b) (4)
Magnesium Stearate (b) (4)	(b) (4)	USP, NF, EP, JP			
FILM COATING MATERIALS					
(b) (4) Yellow (b) (4)	Film Coating Material	(USP, NF, EP, JP)[a]	3.200	6.400	9.600
Theoretical tablet weight					(b) (4)

EP, European Pharmacopoeia; JP, Japanese Pharmacopoeia; N/A, not applicable; NF, National Formulary; USP, United States Pharmacopeia

[a] Components of (b) (4) Yellow (b) (4) comply with compendial or regulatory standards. For details, please refer to (b) (4) DMF No. (b) (4) letter of authorization to DMF No. (b) (4) is provided in Section 1.4.1.

(excerpted from Applicant's submissio)

2.4 Comments on Novel Excipients

There were no novel excipients used in the Cabometyx final drug product.

2.5 Comments on Impurities/Degradants of Concern

No new impurities were identified in the formulation components that required qualification.

2.6 Metabolites

Summary of previous findings (nonclinical review for NDA 203756, Margaret Brower, *PhD*):
"Metabolic profiling evaluations of clinical plasma samples (Clinical studies XL184-008 PK002 and XL184-012) 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 or of total drug-related exposure. These XL184 metabolites include an N-oxide (EXEL-5162), a monohydroxy sulfate (EXEL 1646), a half dimer (EXEL-5366), and a mono-demethyl half dimer (EXEL 1644). The EXEL-5162 and EXEL-5366 were not considered to be pharmacologically active and other metabolites were not tested for activity. The XL184 N-oxide and EXEL-5366 metabolites were tested for mutagenicity, and found to be negative. Metabolites were not tested for clastogenicity."

To fulfill a PMR for NDA 203756, the Applicant conducted an In Vitro Reverse Mutation Assay in Bacterial Cells (Ames) with EXEL-1646 (M4) and EXEL-1644 (M9). M4 and M9 were not found to be mutagenic at doses up to 5000 µg/plate in the presence or absence of metabolic activation (as reviewed by Dr. Margaret Brower under NDA 203756).

Metabolite EXEL-1644 (M9) was identified in plasma of healthy subjects (clinical study XL184-012; oral solution) at the time of the Cometriq (NDA 203756) approval in 2012, but was not quantified. Subsequently, EXEL-1644 was quantified in RCC patients under NDA 208692 (clinical study XL184-008.PK.002; capsule) and was considered to be the predominant cabozantinib metabolite present in human plasma (35.8% of the total drug-related exposure). Table 2 below shows the levels of the 4 major metabolites in study XL184-008.PK.002. Metabolite 1644 has a half-life of approximately 500 hours in humans. Due to its long half-life, EXEL-1644 accumulates with repeated administration of cabozantinib, which may explain why the exposure to this metabolite and it's percentage of total cabozantinib plus metabolites increases over time compared to a single administration in humans. EXEL-1644 toxicity was characterized in an in vitro study (negative in Ames test) and in vivo studies, including two subcutaneous repeat-dose toxicology studies in rats and mice. EXEL-1644 administration resulted in no adverse toxicological findings (see section 6 under General Toxicology of this review). The Applicant's rationale for using the subcutaneous route of administration was that EXEL-1644 has poor oral, but good subcutaneous bioavailability. The submitted data supported this rationale.

No additional nonclinical systemic toxicology or carcinogenicity studies are required to characterize metabolite EXEL-1644 under the current NDA based on the ICH S9 guidance recommendations, given the intended indication (advance RCC). Pharmacology studies demonstrated that cabozantinib had higher potency in vitro in a panel of tyrosine kinase receptors than its metabolites. The need for additional studies to support other indications should be determined based on the indication and patient population.

Table 2: Cabozantinib Major Metabolites

Metabolite	% AUC of metabolite to AUC of cabozantinib (AUC/cabozantinib + total metabolites)			
	NDA203756	NDA203756 (Cometriq)	NDA208692 (Cabometyx)	
	Rat/dog 6 month	Clinical study XL184-012; oral solution[1]	Clinical study XL184-008PK002; capsule[2]	Toxicology testing
M1 (EXEL 5162, XL184 N-oxide)	2-4	15 (8.8%)	15.4 (5.5%)	Not mutagenic *(not pharmacologically active)*
M8 (EXEL-5366, amide cleavage product/half-dimer)	0.5-2	10 (6%)	17 (5.9%)	Not mutagenic *(not pharmacologically active)*
M4 (EXEL 1646, mono hydroxy sulfate)	0.24-7	42.9 (25%)	38.9 (13%)	Not mutagenic
M9 (EXEL 1644, 6DACPS, dimethyl half-dimer sulfate)	<0.1-0.8	NC[3]	99.7 (35.8%)	▪ Not mutagenic ▪ 4-Week SC mice study

				(XL184-NC-037) ▪ 2-week SC rat study *(EXEL1644-NC-004)*
p-FA (Para-fluoroaniline)	<1	<LOQ	<LOQ	--

[1]Health volunteers administered ≥175mg/kg/day, single dose; (X%) = AUC metabolite/AUC total (XL184+3 metabolites)
[2]Subjects with solid tumors administered ≥100mg/kg/day, 21 days dosing; (X%)= AUC metabolite/AUC total (XL184+4 metabolites)
Light gray font: not considered pharmacologically active (pharmacology studyXL184-Disc-002) based on in vitro biochemical and cellular assays
[3]metabolite identified in human plasma but not quantified (NA=not available)

2.7 Proposed Clinical Population and Dosing Regimen

The proposed Cabometyx regimen for the treatment of subjects with advanced renal cell carcinoma who have received (b) (4) prior therapy will be 60 mg administered orally once daily.

2.8 Regulatory Background

Cabozantinib was granted fast track designation (on 4/8/2015) and breakthrough therapy designation (on 8/21/2015) for the treatment of advanced renal cell carcinoma in patients who have received one prior therapy indication. Cometriq (cabozantinib) is an FDA approved drug since 2012 (140 mg orally [capsules], once daily) for the treatment of patients with progressive, metastatic medullary thyroid cancer. Cometriq (NDA 203756) is owned by the Applicant of the current NDA (Exelixis, Inc.).

At the time of NDA 203756 approval, the Applicant was required to conduct additional studies as post marketing requirement (PMR) due to the expected extended survival of the patient population (≥5 years):

- Carcinogenicity studies in two species (a 26-week mouse study and a 2-year rat study) with orally administered cabozantinib. On 4 December 2013, the executive CAC approved the study design and doses for the 26-week mouse study and the final report was submitted on 7/6/2015 under NDA 203756/Supp. # 115 (applicant-owned) and the current NDA on 12 October 2015. The report from the 2-year rat carcinogenicity study is scheduled to be submitted on October 15, 2016.

- *In vitro* mutagenicity assay of the EXEL-1646, monohydroxy sulfate metabolite. The Applicant conducted an In Vitro Reverse Mutation Assay in Bacterial Cells (Ames) with M4 (EXEL-1646, monohydroxy sulfate) and M9 (EXEL-1644, 6DACPS). The final report was submitted to the FDA on 3/7/2013 and reviewed by Margaret Brower, PhD under NDA 203756.

3 Studies Submitted

Study #	Study Name	Reviewed/ Summarized
XL184-NC-033	5-Day oral gavage repeat-dose study with XL184 in 001178-W (rasH2 wild type) mice, CD-1 mice, and Sprague Dawley rats (no-GLP)	Yes
XL184-NC-042	26-Week oral gavage carcinogenicity study with cabozantinib S-Malate in 001178 T (Hemizygous) RasH2 mice (GLP)	Yes
XL184-NC-037	4-Week exploratory toxicity and toxicokinetic study in 001178-W (wild type) mice administered cabozantinib S-Malate by oral gavage and EXEL-1644 by subcutaneous injection with a 4-week recovery phase (non-GLP)	Summarized
EXEL1644-NC-004	2-Week toxicity and toxicokinetic subcutaneous injection study with EXEL-1644 in rats with a 4-week recovery phase (GLP)	Yes
(b) (4) EXL085	Profiling services project report (non-GLP)	Yes
(b) (4) EXL084	Profiling services project report (non-GLP)	Yes
(b) (4) EXL087	Profiling services project report (non-GLP)	Yes
(b) (4) 100007795	In vitro pharmacology study of EXEL-1644 and EXEL-1646 (non-GLP)	Yes
XL184-TM-001	Combined inhibition of c-Met and VEGF signaling suppresses tumor invasion and metastasis and prolongs survival (no-GLP, peer reviewed publication)	Summarized
XL184-TM-002	Targeting MET with XL184 to Reverse EGFR Tyrosine Kinase Inhibitor (TKI) Resistance in NSCLC: Impact of Preclinical Studies on Clinical Trial Design (non-GLP, poster presentation)	No
XL184-Disc-016	In vivo acute time course study with EXEL-02977184 in MDA-MB-231 xenograft tumors (non-GLP)	No
XL184 (b) (4) -receptorbd	In vitro pharmacology study of EXEL-7184 (non-GLP)	No
(b) (4) -Ex-01	Testing of an Exelixis compound (G1208) in both osteoclast and osteoblast differentiation and activity assays *in vitro.* (non-GLP)	No
(b) (4) -Ex-03	Effects of cabozantinib in a syngeneic 5TGM1 multiple myeloma mouse model in prevention setting (non-GLP)	No
(b) (4) -6920	Inhibitory impact of 1 compound (G1208, staurosporine, sunitinib, crizotinib and dasatinib) on the cellular kinase activity of Aurora-B, AXL, RON, SRC and VEGFR-2 (non-GLP)	No

4 Pharmacology

Study Title: Profiling Services Project Report	
Study No:	(b) (4) -EXL085
Conducting laboratory and location:	(b) (4)
Date of study:	July 31, 2013
Compliant:	Non-GLP

Objective: To determine the inhibition of enzymatic activity of purified protein kinase domains by XL184 and metabolite EXEL-1646

Results:
In order to determine kinase specificity, XL-184 was tested against a panel of 47 tyrosine kinase receptors (see table).

- XL184 was found to inhibit MER, TYRO3 (RSE), ROS1, Aurora-B and RON with IC_{50} values of 0.3, 12, 24, 23 and 46 nM, respectively, in addition to other known kinases (MET, VEGFR-1, -2 and -3, AXL, RET, KIT, TRKB, FLT-3, and TIE-2) that were identified in Dr. Margaret Brower's review of NDA # 203756.

- Metabolite EXEL-1646 showed reduced potency relative to XL184, against the panel of kinases tested (i.e. MER, TYRO3 (RSE), ROS1, Aurora-B and RON with IC_{50} values of 104, 309, >1000, 52 and >1000 nM, respectively), except for Aurora-A.

Table 3: Estimated IC_{50} (nM) Values For XL184 and EXEL-1646

Kinase	XL184 malate salt	EXEL-1646
Abl(h)	597	>1000
ALK(h)	>1000	>1000
Aurora-A(h)	381	152
Aurora-B(h)	23	52
Axl(h)	8	87
Blk(h)	103	>1000
BTK(h)	443	>1000
cKit (h)	752	>1000
cSRC(h)	559	>1000
DDR2(h)	54	221
EGFR(h)	>1000	>1000
FGFR1, 2, 3, 4(h)	>1000	>1000
Flt1(h)	13	>1000
Flt3(h)	21	155
Flt4(h)	3	175
Fms(h)	9	647
Fyn(h)	389	>1000
IGF-1R(h)	>1000	>1000

IR(h)	492	>1000
JAK2(h)	>1000	>1000
JAK3(h)	>1000	>1000
KDR(h)	14	308
Lck(h)	209	1035
Lyn(h)	135	>1000
MEK1(h)	886	>1000
Mer(h)	0.3	104
Met (h)	2	199
Met(D1246H)(h)	4	261
Met(D1246N)(h)	5	709
Met(M1268T)(h)	10	>1000
Met(Y1248C)(h)	4	100
Met(Y1248D)(h)	5	50
Met(Y1248H)(h)	4	230
PDGFRα(h)	512	>1000
PDGFRβ(h)	575	>1000
Ret (h)	8	234
Ret (V804L) (h)	23	>1000
Ret (V804M)(h)	276	>1000
Ron(h)	46	>1000
Ros(h)	24	>1000
Rse(h)	12	309
Tie2 (h)	13	60
TrkA(h)	64	>1000
TrkB(h)	27	>1000

(excerpted from Applicant's submission)

In conclusion, XL184 was more potent than its metabolite (EXEL-1646) against the panel of kinase receptors tested (with exception of Aurora-A)

Study Title: Profiling Services Project Report	
Study No:	(b) (4)-EXL084
Conducting laboratory and location:	(b) (4)
Date of study:	February 13, 2013
Compliant:	Non-GLP

Objective: To determine the inhibition of enzymatic activity of purified protein kinase domains by XL184 metabolites EXEL-1644 and EXEL-1646 at a single concentration.

Results:

At a concentration of 1 µM, metabolite EXEL-1644 caused > 50% inhibition of 2 of 42 kinases tested (MET and RON at 68% and 75%, respectively), while EXEL-1646 caused > 50% inhibition of 21 of 42 kinases tested (Abl, Aurora-A and B, AXl, BLK, Kit, FLT1, FLT4, Fms, IGF, Lck, Lyn, Mer, Met, Ret, Ron, Ros, Rse, Tie2, TrkA and TrkB). As such, EXEL-1644 showed considerably less inhibitory potency than EXEL-1646.

Table 4: Percent Activity (%) of EXEL-1644 and EXEL-1646

Data: Summary Sheet, Activity %

	EXEL1644 / A11209018 @ 1 µM	EXEL1646 / 3638-64-1 @ 1 µM
Abl(h)	88	43
ALK(h)	96	97
Aurora-A(h)	50	15
Aurora-B(h)	75	10
Axl(h)	84	4
Blk(h)	96	39
BTK(h)	90	78
cKit(h)	94	41
cSRC(h)	103	75
EGFR(h)	116	112
FGFR1(h)	112	104
FGFR2(h)	90	85
FGFR3(h)	88	94
FGFR4(h)	105	108
Flt1(h)	95	31
Flt3(h)	96	50
Flt4(h)	66	7
Fms(h)	99	42
Fyn(h)	100	76
IGF-1R(h)	98	29
IR(h)	98	103
JAK2(h)	103	107
JAK3(h)	76	107
KDR(h)	99	88
Lck(h)	87	38
Lyn(h)	104	32
MEK1(h)	128	79
Mer(h)	95	-1
Met(h)	32	5
mTOR(h)	80	111
MuSK(h)	98	76
PDGFRα(h)	87	58
PDGFRβ(h)	102	92
Ret(h)	98	3
Ron(h)	25	40
Ros(h)	95	47
Rse(h)	90	10
SAPK4(h)	103	105
Tie2 (h)	65	46
TrkA(h)	102	5
TrkB(h)	95	6
Yes(h)	99	98

(excerpted from Applicant's submission)

In conclusion, EXEL-1644 exhibited less inhibitory activity than EXEL-1646 against the panel of receptor kinases tested.

Study Title: Profiling Services Project Report	
Study No:	(b) (4)-EXL087
Conducting laboratory and location:	(b) (4)
Date of study:	February 13, 2013
Compliant:	Non-GLP
Objective: To determine the inhibition of enzymatic activity of purified protein kinase domains by XL184 metabolites EXEL-1644, EXEL-5162, and EXEL-5366.	
Results: No significant inhibitory activity of EXEL-1644 against MET, or of EXEL-5162 or EXEL-5366 against RET. **Table 5: Estimated IC_{50} Values Against MET and RET** Estimated IC_{50} values are as follows:-	

Compound	Kinase	IC50 (nM)
EXEL-5366 / 3237-205-2	Ret(h)	>1,000
EXEL-1644 / A11209018	Met(h)	3044
EXEL-5162 / 3466-004-1	Ret(h)	>1,000

(excerpted from Applicant's submission)

Reviewer comment
In this study only two kinases were tested (Ret and Met).

Study Title: In vitro pharmacology study of EXEL-1644 and EXEL-1646	
Study No:	(b) (4)-100007795
Conducting laboratory and location:	(b) (4)
Date of study:	March 6, 2013
Compliant:	Non-GLP
Objective: to evaluate the specificity of EXEL-1644 and EXEL-1646 against a panel of 75 pharmacological targets (receptors, transporters, enzymes) at a single concentration of 1 µM.	
Results: EXEL-1646 and EXEL-1644 showed no targets at > 50% inhibition in a panel of 75 pharmacological targets: A_{2a}, A_3, α_1, α_2, β_1, β_2, AT_1, AT_2, BZD, BB, B_2, CGRP, CB_1, CCK_1, CCK_2, D_1, D_{2s}, D_3, D_4,	

D_5, ET_A, ETB, GABA, $GAL_{1,2}$, PDGF, $CXCR_2$, CCR_1, TNF-α, $H_{1,2}$, MC_4, MT_1, $M_{1,2,3,4,5}$, $NK_{1,2,3}$, $Y_{1,2}$, NTS_1, DOP, KOP, NOP, PAC_1, PPARγ, PCP, $EP_{2,4}$, IP, P_{2X}, P_{2Y}, 5-$HT_{1A,1B,2A,\ 2B,\ 2C,\ 3,\ 5a,\ 6,\ 7}$, sigma, sst, GR, $VPAC_1$, V_1, Ca, K_v, SK_{ca}, Na, Cl, norepinephrine transporter, dopamine transporter, 5-HT transporter.

In conclusion, both metabolites showed no activity against the above panel of pharmacological targets.

Study Title: Combined inhibition of c-Met and VEGF signaling suppresses tumor invasion and metastasis and prolongs survival

Study #: XL184-TM-001

Reviewer comment:

- This study was published in 2012 in a peer reviewed journal under modified title: "Suppression of tumor invasion and metastasis by concurrent inhibition of c-Met and VEGF signaling in pancreatic neuroendocrine tumors". Sennino B, Ishiguro-Oonuma T, Wei Y, Naylor RM, Williamson CW, Bhagwandin V, Tabruyn SP, You WK, Chapman HA, Christensen JG, Aftab DT, McDonald DM. Cancer Discov. 2012 Mar; 2(3):270-87. doi: 10.1158/2159-8290.CD-11-0240. Epub 2012 Feb 24

- Only relevant selected data from this publication are discussed in this review.

Background and Objective:

The authors stated that tumors can develop resistance to antiangiogenic therapies through adaptive mechanisms such as upregulation of alternative proangiogenic signaling pathways and enhancement of metastasis. For example, tumor cell evasion of VEGF pathway inhibition may occur as a response to hypoxia. Under hypoxic conditions, HIF-1α is upregulated, resulting in increased expression of both VEGF and MET in tumor cells. These responses may allow tumor cells to compensate for the hypoxic environment through stimulation of angiogenesis or migration away from the hypoxic zone. Additionally, it was reported that the MET pathway played an important role in the development of resistance to VEGF pathway-inhibition in murine tumor models, and VEGF-inhibitors such as sunitinib, sorafenib, cediranib, a VEGFR2-targeting antibody, or a neutralizing anti-murine VEGF antibody were observed to increase the aggressiveness of tumors, with increased invasiveness and/or metastasis. In the current study the authors examined the involvement of hypoxia, c-Met, and epithelialmesenchymal transition (EMT) in the promotion of tumor invasion and metastasis after inhibition of VEGF signaling and whether selective c-Met inhibition was sufficient to block this effect.

Methods:

Transgenic mice (RIP-Tag2)

- Treated with XL184 (c-Met and VEGFR inhibitor), vehicle (saline), anti-VEGF antibody, sunitinib (VEGF inhibitor), PF-04217903 (c-Met inhibitor), anti-VEGF antibody plus PF-04217903 or sunitinib plus PF-04217903.
- At 10 weeks of age, mice were treated for 4 weeks; and at 14 weeks of age mice

were treated for 3 days or 1, 3, or 6 weeks.

Nude mice implanted with MDA-MB- 231 tumor cells

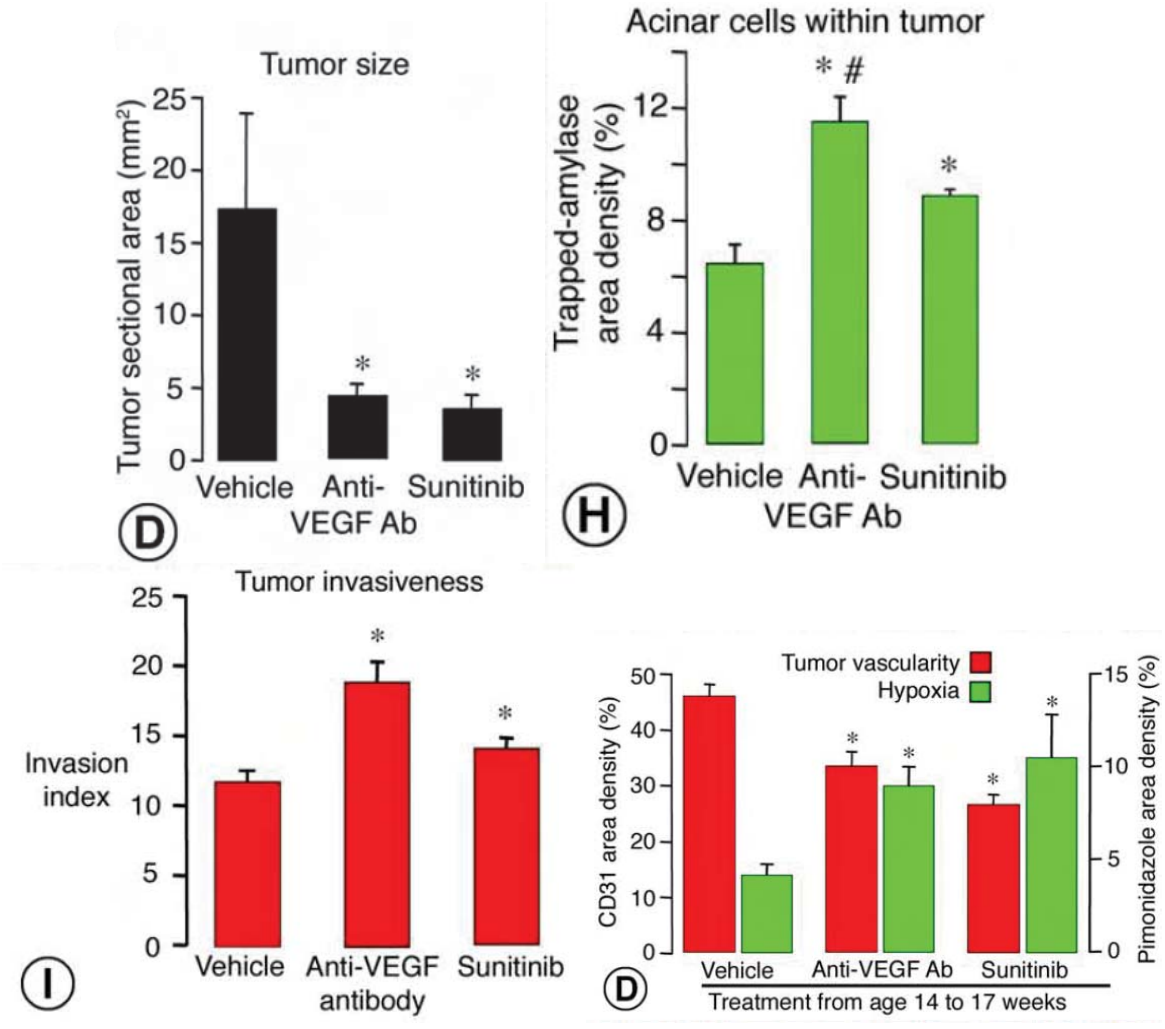
- Treated with vehicle (saline) or XL184 (10 or 60 mg/kg) daily by gavage for 2 weeks.

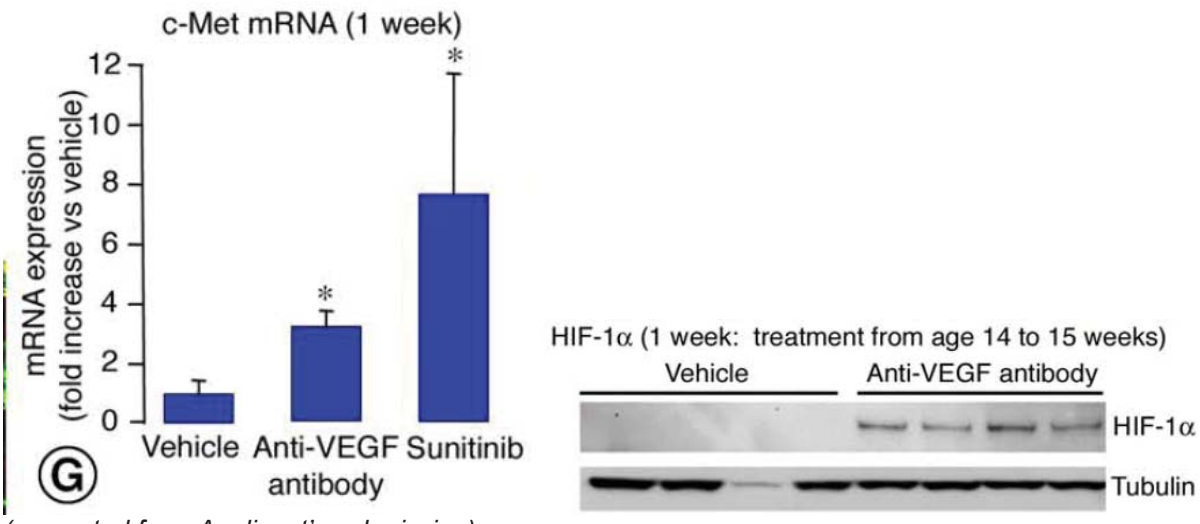
Endpoints assessed: Tumor size, tumor vascularity, abundance of amylase-positive acinar cells trapped and the amount of intratumoral hypoxia.

Results:

- Treatment of pancreatic acinar tumor cells in RIP-Tag2 mice with anti-VEGF antibody reduced tumor burden, but increased tumor hypoxia, HIF-1α, and c-Met activation, and ultimately increased invasion and metastasis**.**

Figure 1: Effects on Tumor size, Acinar Cells, Tumor Invasiveness, Vascularity, Hypoxia, c-Met mRNA and HIF-1α



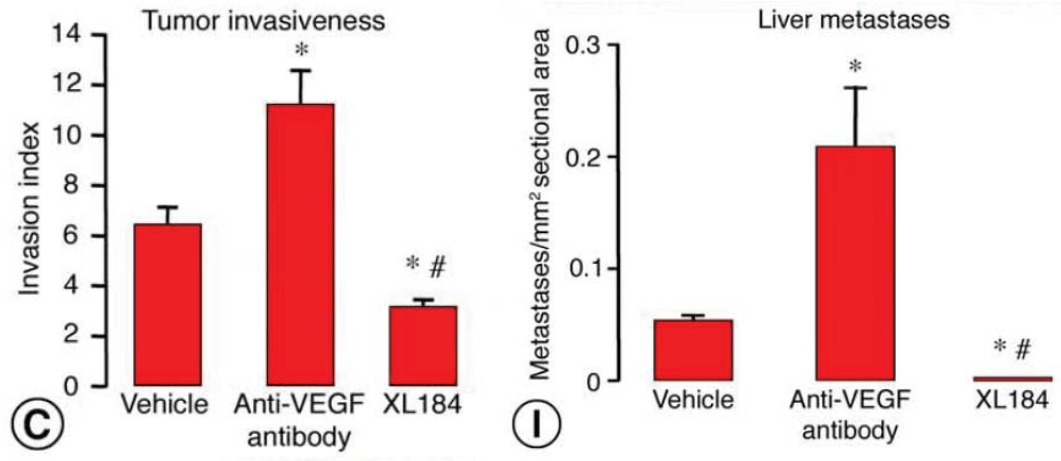


(excerpted from Applicant's submission)

- Administration of anti-VEGF and PF-04217903 (c-Met inhibitor) concurrently, reduced the invasion and metastasis.

- Similarly, administration of XL184 (c-Met and VEGFR inhibitor) resulted in greater tumor inhibition, decreased tumor invasiveness and metastasis, as compared to treatment with vehicle, or with anti-VEGF antibody.

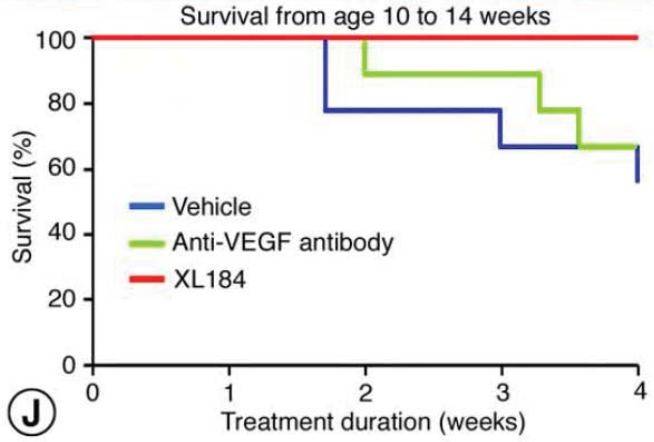
Figure 2: Effects on Tumor Invasiveness and Liver Metastases



(excerpted from Applicant's submission)

- All mice administered XL184 survived until scheduled termination (20 weeks), while none of the vehicle- or anti-VEGF antibody-receiving mice survived to scheduled termination.

Figure 3: Effects on Survival



(excerpted from Applicant's submission)

The authors concluded that the reported tumor invasion and metastasis following an inhibition of VEGF signaling was accompanied by intratumoral hypoxia, activation of HIF-1α, c- Met, EMT, invasiveness, and metastasis. These effects were blocked by c-Met inhibitors. Furthermore, a combined treatment of c-Met and VEGFR inhibitors or by XL-184 (c-Met and VEGFR inhibitor) resulted in tumor inhibition, decreased tumor invasiveness and metastasis. As such, inhibition of c-Met and VEGF together demonstrated synergistic effects on tumor growth, angiogenesis, invasiveness, and metastasis.

5 Pharmacokinetics/ADME/Toxicokinetics

Study Title: 5-Day Oral Gavage Repeat-Dose Study with XL184 in 001178-W (rasH2 wild type) Mice, CD-1 Mice, and Sprague Dawley Rats	
Study No:	XL184-NC-033
Conducting laboratory and location:	(b) (4)
Date of study:	December 20, 2012
Compliant:	Non-GLP
Objective: to characterize the toxicity and determine the toxicokinetics of XL184 and selected metabolites when XL184 was administered daily by oral gavage to wild type, RasH2 mice for 5 days; to compare the toxicokinetics of XL184 and metabolites among wild type RasH2 mice, CD-1 mice, and Sprague Dawley rats; and to determine dose levels for a 1-month dose range-finding (for a 26-week carcinogenicity study in transgenic mice) study in 001178-W (wild type) mice.	

Table 6: Study Design of 5-Day Oral Repeat-Dose Study with XL184

Study Design

Group/Subgroup[a]	No. of Animals[b] Male	Female	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)
1/1 (RasH2 mice - low)	8	8	10	1
2/1 (RasH2 mice - mid)	8	8	30	3
3/1 (RasH2 mice - high)	8	8	100	10
4/2 (CD-1 mice)	8	8	30	3
5 (SD rat)	9	9	10	1

a Due to a system limitation, subgroups were assigned by strain to mouse groups (Groups 1 through 4); there was not more than one subgroup/group. Because rats were in a separate account (due to system limitation), no subgroup was assigned to Group 5.

b An additional two RasH2 mice/sex not assigned to groups were used for blood collection during the predose phase for baseline metabolic profile.

(excerpted from Applicant's submission)

- XL184 was administered daily by oral gavage for 5 days.
- XL184 and primary metabolites exposure were assessed on Day 5.

Results:

No adverse XL184-related clinical observations, body weight or food consumption were reported.

In wild type RasH2 mice (only selected data presented):

- Half-life was determined to be: XL184 (5.1- 8.7 hr), EXEL-1646 (4.7-7.0 hr), EXEL-5162 (3.7-6.1 hr) and EXEL-5366 (5.3-11.5 hr). EXEL-1644 was not estimated by the Applicant.
- $AUC_{0\text{-last}}$ (ng.h/mL): XL184 (25900-292000), EXEL-1646 (114-3030), and EXEL-1644 (155-339).

SD Rats (only selected data presented):

- Half-life was not estimated by the Applicant for the parent compound and its metabolites.
- $AUC_{0\text{-last}}$ (ng.h/mL): XL184 (314000), EXEL-1646 (14500), and EXEL-1644 (122).

The data suggested that in mice and rats, the parent compound (XL184) undergoes relatively little metabolic conversion (0.04 to 5%). In contrast, human XL184 undergoes much higher metabolic conversion (i.e. 5% to 36% of total drug exposure in plasma).

Table 7: Toxicokinetics of XL184 in Mice (Oral Route)

Table 3-1-1: Summary of Toxicokinetics Parameters of XL184 in Mice

Dose (mg/kg)	Gender	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (hr*ng/mL)	AUC_{last}/D (kg*hr*ng/mL/mg)	AUC_{INF_obs} (hr*ng/mL)	total AUC (ng*hr/mL)	% (AUC XL184/AUCtotal)
10	F	3.39	8.00	1780	178	20800	2080	21100	22673	91.7
RasH2	M	8.25	8.00	2680	268	31000	3100	37800	32934	94.1
	N	2	2	2	2	2	2	2	2	2
	Mean	5.82	8.00	2230	223	25900	2590	29400	27803	92.9
30	F	3.82	8.00	6200	207	73100	2437	75000	79889	91.5
RasH2	M	6.37	8.00	8720	291	120000	4000	135000	130326	92.1
	N	2	2	2	2	2	2	2	2	2
	Mean	5.10	8.00	7460	249	96600	3218	105000	105107	91.8
100	F	6.44	12.0	16700	167	265000	2650	294000	308881	85.8
RasH2	M	10.9	8.00	18500	185	320000	3200	427000	361635	88.5
	N	2	2	2	2	2	2	2	2	2
	Mean	8.69	10.0	17600	176	292000	2925	361000	335258	87.1
30	F	3.17	2.00	4420	147	36500	1217	36800	42208	86.5
CD-1	M	2.12	4.00	4600	153	39400	1313	39400	44598	88.3
	N	2	2	2	2	2	2	2	2	2
	Mean	2.64	3.00	4510	150	37900	1265	38100	43403	87.4

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D; dose-normalized C_{max}; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time 0.5hr to infinity; total AUC, sum of $AUC_{0.5\text{-last}}$ of XL184 and 5 metabolites; % (AUC_{XL184}/AUC_{total}), (ratio of $AUC_{0.5\text{-last}}$ of XL184 to $AUC_{0.5\text{-last}}$ of total)×100; F, female; M, male

Table 8: Toxicokinetics of XL184 in SD Rats (Oral Route)

Table 3-1-2: Summary of Toxicokinetics Parameters of XL184 in SD Rats

Dose (mg/kg)	Gender	$t_{1/2}$,hr	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (ng*hr/mL)	AUC_{last}/D (kg*ng*hr/mL/mg)	%(AUC/AUC_{XL184})	%(AUC_{XL184}/AUC_{total})
10	F	NR	12.0	20500	2050	396000	39600	.	96.8
	M	NR	4.00	13400	1340	232000	23200	.	88.7
	n	.	2	2	2	2	2	.	2
		NR	8.00	17000	1700	314000	31400	.	92.8

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D; dose-normalized C_{max}; AUC_{last}, area under the plasma concentration-time curve from time 0.5 to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; total AUC, sum of $AUC_{0.5\text{-last}}$ of XL184 and 5 metabolites; % (AUC_{XL184}/AUC_{total}), (ratio $AUC_{0.5\text{-last}}$ of XL184 to $AUC_{0.5\text{-last}}$ of total)×100; F, female; M, male; NR, not reportable; ".", not applicable

(excerpted from Applicant's submission)

Table 9: Toxicokinetics of EXEL-1646 in Mice (Oral Route)

Table 3-3-1: Summary of Toxicokinetics Parameters of Sulfate Metabolite (EXEL-1646) in Mice

Dose (mg/kg)	Gender	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (hr*ng/mL)	AUC_{last}/D (hr*ng*kg/mL/mg)	AUC_{INF_obs} (hr*ng/mL)	XL184 AUC_{last} (hr*ng/mL)	total AUC (hr*ng/mL)	%($AUC_{Sulfate}$/AUC_{XL184})	%($AUC_{Sulfate}$/Total AUC)
10	F	5.97	4.00	25.40	2.54	181.0	18.10	258	20800	22673	0.87	0.80
RasH2	M	3.48	2.00	10.60	1.06	47.3	4.73	61	31000	32934	0.15	0.14
	N	2	2	2	2	2	2	2	2	2	2	2
	Mean	4.73	3.00	18.00	1.80	114.0	11.42	160	25900	27803	0.51	0.47
30	F	10.50	2.00	87.70	2.92	638.0	21.27	1060	73100	79889	0.87	0.80
RasH2	M	3.51	2.00	56.80	1.89	337.0	11.23	378	120000	130326	0.28	0.26
	N	2	2	2	2	2	2	2	2	2	2	2
	Mean	6.99	2.00	72.30	2.41	488.0	16.25	720.00	96550	105107	0.58	0.53
100	F	7.22	12.00	584.00	5.84	7090.0	70.90	7720	265000	308881	2.68	2.30
RasH2	M	6.02	2.00	330.00	3.30	3030.0	30.30	3260	320000	361635	0.95	0.84
	N	2	2	2	2	2	2	2	2	2	2	2
	Mean	6.62	7.00	457.00	4.57	5060.0	50.60	5490	292000	335258	1.81	1.57
30	F	14.70	0.50	106.00	3.53	526.0	17.53	1330	36500	42208	1.44	1.25
CD-1	M	NR	2.00	55.20	1.84	178.0	5.93	NR	39400	44598	0.45	0.40
	N	1	2	2	2	2	2	1	2	2	2	2
	Mean	14.70	1.25	80.60	2.69	352.0	11.73	1330	37900	43403	0.95	0.82

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D; dose-normalized C_{max}; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time 0.5 hr to infinity; XL184AUC_{last}, $AUC_{0.5\text{-last}}$ of XL184; total AUC, sum of $AUC_{0.5\text{-last}}$ of XL184 and 5 metabolites; % ($AUC_{Sulfate}/AUC_{XL184}$), (ratio of $AUC_{0.5\text{-last}}$ of sulfate metabolite to $AUC_{0.5\text{-last}}$ of XL184)×100; % ($AUC_{Sulfate}/AUC_{total}$), (ratio of $AUC_{0.5\text{-last}}$ of sulfate metabolite to $AUC_{0.5\text{-last}}$ of total)×100; F, female; M, male; NR, not reportable

Table 10: Toxicokinetics of EXEL-1646 in SD Rats (Oral Route)

Table 3-3-2: Summary of Toxicokinetics Parameters of Sulfate Metabolite (EXEL-1646) in SD Rats

Dose (mg/kg)	Gender	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (ng*hr/mL)	AUC_{last}/D (kg*ng*hr/mL/mg)	%($AUC_{sulfate}$/AUC_{XL184})	%($AUC_{sulfate}$/AUC_{total})
10	F	NR	6.00	359	35.9	7340	734	1.9	1.8
	M	NR	8.00	1140	114	21700	2170	9.4	8.3
	N	.	2	2	2	2	2	2	2
	Mean	NR	7.00	748	74.8	14500	1452	5.6	5.0

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D, dose-normalized C_{max}; AUC_{last}, area under the plasma concentration-time curve from time 0.5 to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; ; % ($AUC_{sulfate}$/AUC_{XL184}), (ratio $AUC_{0.5\text{-}last}$ of sulfate metabolite to $AUC_{0.5\text{-}last}$ of XL184)×100%; ($AUC_{sulfate}$/AUC_{total}), (ratio of $AUC_{0.5\text{-}last}$ of sulfate to $AUC_{0.5\text{-}last}$ of total)×100; F, female; M, male; NR, not reportable

(excerpted from Applicant's submission)

Table 11: Toxicokinetics of EXEL-1644 in Mice (Oral Route)

Table 3-5-1: Summary of Toxicokinetics Parameters of Desmethyl-Sulfate Metabolite (EXEL-1644) in Mice

Dose (mg/kg)	Gender	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (hr*ng/mL)	AUC_{last}/D (hr*ng*kg/mL/mg)	XL184 AUC_{last} (hr*ng/mL)	total AUC (ng*hr/mL)	%($AUC_{Desmethyl\ sulfate}$/AUC_{XL184})	%($AUC_{Desmethyl\ Sulfate}$/Total AUC)
10	F	NR	4.00	6.03	0.603	49.5	5.0	20800	22673	0.24	0.22
RasH2	M	NR	8.00	17.1	1.71	254	25.4	31000	32934	0.82	0.77
	N	NR	2	2	2	2	2	2	2	2	2
	Mean	NR	6.00	11.6	1.16	152	15	25900	27803	0.53	0.49
30	F	NR	0.500	25.9	0.863	367	12.2	73100	79889	0.50	0.46
RasH2	M	NR	8.00	61.0	2.03	994	33.1	120000	130326	0.83	0.76
	N	NR	2	2	2	2	2	2	2	2	2
	Mean	NR	4.25	43.5	1.45	680	23	96600	105107	0.67	0.61
100	F	NR	12.0	132	1.32	1530	15.3	265000	308881	0.58	0.50
RasH2	M	NR	12.0	318	3.18	5250	52.5	320000	361635	1.64	1.45
	N	NR	2	2	2	2	2	2	2	2	2
	Mean	NR	12.0	225	2.25	3390	9880	292000	335258	1.11	0.97
30	F	NR	6.00	18.1	0.603	146	4.9	36500	42208	0.40	0.35
CD-1	M	NR	6.00	41.9	1.40	560	18.7	39400	44598	1.42	1.26
	N	NR	2	2	2	2	2	2	2	2	2
	Mean	NR	6.00	30.0	1.00	353	12	37900	43403	0.91	0.80

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D; dose-normalized Cmax; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; XL184AUC_{last}, $AUC_{0.5\text{-}last}$ of XL184; total AUC, sum of $AUC_{0.5\text{-}last}$ of XL184 and 5 metabolites; % ($AUC_{desmethyl\ sulfate}$/AUC_{XL184}), (ratio of $AUC_{0.5\text{-}last}$ of desmethyl sulfate metatabolite to $AUC_{0.5\text{-}last}$ of XL184)×100; % ($AUC_{Sulfate}$/AUC_{total}), (ratio $AUC_{0.5\text{-}last}$ of desmethyl sulfate metabolite to $AUC_{0.5\text{-}last}$ of total)×100; F, female; M, male; NR, not reportable

Table 12: Toxicokinetics of EXEL-1644 in SD Rats (Oral Route)

Table 3-5-2: Summary of Toxicokinetics Parameters of Desmethyl Sulfate Metabolite (EXEL-1644) in SD Rats

Dose (mg/kg)	Gender	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	AUC_{last} (ng*hr/mL)	AUC_{last}/D (kg*ng*hr/mL/mg)	%($AUC_{desmethyl\ sulfate}$/AUC_{XL184})	%($AUC_{desmethyl\ sulfate}$/AUCtotal)
10	F	NR	12.0	5.15	0.515	88.7	8.9	0.02	0.02
	M	NR	8.00	9.16	0.916	155	15.5	0.07	0.06
	N	.	2	2	2	2	2	2	2
	Mean	NR	10.0	7.16	0.716	122	12.2	0.04	0.04

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; C_{max}/D; dose-normalized C_{max}; AUC_{last}, area under the plasma concentration-time curve from time 0.5hr to the last observable concentration above the limit of quantitation; AUC_{last}/D, dose normalized AUC_{last}; , % ($AUC_{desmethyl\ sulfate}$/AUC_{XL184}), (ratio $AUC_{0.5\text{-}last}$ of desmethyl sulfate metabolite to $AUC_{0.5\text{-}last}$ of XL184)×100%; ($AUC_{desmethyl\ sulfate}$/AUC_{total}), (ratio of $AUC_{0.5\text{-}last}$ of desmethyl sulfate to $AUC_{0.5\text{-}last}$ of total)×100; F, female; M, male; NR, not reportable; ". " not applicable

(excerpted from Applicant's submission)

The following data was used as a reference to estimate the safety margins based on the systemic exposure levels of the XL184 metabolite (EXEL-1644) in RCC patients (XL184-008.PK.002):

Study # XL184-008.PK.002: A phase 1 drug-drug interaction study of the effects of XL184 on the pharmacokinetics of a single oral dose of rosiglitazone in subjects with solid tumors

Table 13: Toxicokinetics of EXEL-1644 in Patients (Oral Route)

Table 3-1: Summary of PK Parameters of XL184 and Selected Metabolites on Day 22 Subjects with Solid Tumors after Daily Administration of XL184 at ≥100 mg/day (Continued)

Analyte	Statistics	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (hr*ng/mL)	AUC_{total} (ng*hr/mL)	%($AUC_{desmethyl\ sulfate}/AUC_{XL184}$)	%($AUC_{desmethyl\ sulfate}/AUC_{total}$)
Desmethyl sulfate	N	6	6	6	6	6	6
EXEL-1644	Mean	2.63	1960	42400	107457	99.7	35.8
	SD	1.41	1592	33319	62599	42.7	8.5
	Min	0.00	745	16200	55930	49.7	28.5
	Median	3.00	1140	26000	79495	96.6	33.0
	Max	4.25	4090	85200	197730	160.2	48.6
	CV%	53.8	81.1	78.6	58	42.9	23.7
	GeoMean	NA	1500	33000	94051	91.7	35.0

T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time zero to the last observable concentration above the limit of quantitation; AUC_{last}, $AUC_{0\text{-last}}$ of XL184 or metabolites; AUC_{total}, sum of $AUC_{0\text{-last}}$ of XL184 and 4 metabolites; % ($AUC_{analyte}/AUC_{XL184}$), (ratio of $AUC_{0\text{-last}}$ of each analyte to $AUC_{0\text{-last}}$ of XL184)×100; % ($AUC_{analyte}/AUC_{total}$), (ratio of $AUC_{0\text{-last}}$ of analyte to $AUC_{0\text{-last}}$ of total)×100; GeoMean, geometric mean

(excerpted from Applicant's submission)

6 General Toxicology

Study title: 2-Week toxicity and toxicokinetic subcutaneous injection study with EXEL-1644 in rats with a 4-week recovery phase (GLP)	
Study no.:	XL1644-NC-004
Conducting laboratory and location:	(b) (4)
Date of study initiation:	29 May, 2013
GLP Compliant:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	EXEL-1644, #3697-67 and 96.9% purity
Certificate of Analysis:	Yes

Key Study Findings:

- Target organs of toxicity were reported at the highest dose tested (30 mg/kg/day), which included skeletal muscle (chronic inflammation of the perimuscular fascia, minimal to slight) and heart (cardiomyopathy, minimal). No findings were reported at the end of the recovery period.
- Procedure/vehicle-related findings included clinical observations and macro and microscopic findings at the injection site in the control and all dosing groups.

Methods:

Doses (Group #):

Table 14: Study Design For 2-Week SC Rat Toxicity Study With EXEL-1644

Group	Subgroup[a,b]	No. of Animals Male	No. of Animals Female	Dose Level (mg/kg/day)[c]	Dose Concentration (mg/mL)
1 (Control)[d]	1 (Toxicity)	15	15	0	0
	2 (Toxicokinetic)	3	3	0	0
2 (Low)	1 (Toxicity)	10	10	3	0.3/0.6
	2 (Toxicokinetic)	9	9	3	0.3/0.6
3 (Mid)	1 (Toxicity)	10	10	10	1/2
	2 (Toxicokinetic)	9	9	10	1/2
4 (High)	1 (Toxicity)	15	15	30	3/6
	2 (Toxicokinetic)	9	9	30	3/6

a Toxicokinetic animals were included solely for the purpose of blood sample collections.
b Toxicity animals designated for the recovery sacrifice (five animals/sex in Groups 1 and 4) underwent at least 4 weeks of recovery following the terminal sacrifice.
c The dose volume was 10 mL/kg for Days 1 through 7 of the dosing phase. Starting on Day 9 through Day 15 of the dosing phase, the dose volume was 5 mL/kg.
d Group 1 received the vehicle control article only.

(excerpted from Applicant's report)

Route/Frequency of dosing/ Dose volume:

Subcutaneous (SC) injection (total of 4 sites, two scapular and two lumbar). The rationale provided for the SC route was that EXEL-1644 has poor oral, but good subcutaneous (SC) bioavailability.

Rats were dosed on Days 1 to 7 and then Days 9 to 15.

The Applicant stated that due to clinical observations of skin sores at the scapular sites precluded further dosing on Day 8, in all animals. Dose volume was reduced from 10 mL/kg to 5 mL/kg and dosing was then resumed on Day 9.

Reviewer comment:
The dosing volume used is significantly higher than the recommended SC volume in the scientific literature. The ideal SC dosing volume is typically listed as 1 ml/kg.

The Sponsor did not provide a rationale for the high dose volume used in this study. High volume of SC injection with test article formulated in vehicle containing ethanol may result in irritation to the tissue, muscle damage, and animal stress that may mask any effects that may result from the test article administration.

Formulation/Vehicle: Ethanol (200 proof): polyethylene glycol 400:reverse osmosis water, 5:45:50 (v:v:v).

Species/Strain: Male and female Sprague-Dawley®SD rats

Age at initiation of dosing: 7 to 8 weeks

Weight: 158 to 200g for females and 235 to 273 g for males

Observations and Results

Cageside observations:	Daily during the dosing and recovery phases.
Body weights:	Once predose on Day 1, and weekly thereafter during the dosing phase. During recovery: Days 1 and 7, and weekly thereafter.
Food consumption:	Quantitative measurement. Weekly during the dosing and recovery phases.
Ophthalmoscopy:	Predose and on Day 10.
Irritation scoring (erythema and edema):	Days 1 through 7 of dosing phase (prior and postdose)
Clinical pathology:	Day 16 of the dosing phase and Day 30 of the recovery phase.
Toxicokinetics:	**Table 15: Blood Collection Times For EXEL-1644 Toxicokinetics Evaluation** Group / Subgroup / Set / Dosing Phase Day / Time Points[a] 1 / 2 / 1st three/sex/group / 1, 14 / 2 hours postdose 2, 3, 4 / 2 / 1st three/sex/group / 1, 14 / Predose and 4 hours postdose 2, 3, 4 / 2 / 2nd three/sex/group / 1, 14 / 1, 6, and 12 hours postdose 2, 3, 4 / 2 / 3rd three/sex/group / 1, 14 / 2, 8 and 24 hours postdose a Blood collection times were approximate. *(excerpted from Applicant's report)*
Necropsy/Gross pathology:	Animals were necropsied on Day 16 of the dosing phase (10/sex/group) and on Day 30 of the recovery phase (5/sex/groups 1 and 4).
Histopathology:	Control, high dose group and from animals that died during the study. Target organs were evaluated at lower dose groups.
Pathology peer review:	No

Mortality

At 30 mg/kg/day, two female rats were reported dead. The Applicant stated that both rats died after blood collection on the day of terminal sacrifice and the cause of death was undetermined.

Table 16: Unscheduled Deaths

Dose (mg/kg/day)	Day of death	Sex (animal #)	Prior to Death and Necropsy Findings
30	16	F (B68925)	Clinical observations: Scab and overlying skin at dosing site. No body weight changes.
			Macroscopic findings: Injection site: sore, overlying skin, red Microscopic findings: - Liver-minimal chronic inflammation

			- Mandibular lymph node- slight to severe hyperplasia lymphoid - Spleen-slight hematopoiesis - Thymus- minimal hemorrhage - Injection site, epidermis-moderate exudate, slight hyperplasia, minimal hemorrhage, slight fibrosis, minimal chronic inflammation, slight necrosis.
30	16	F (B68929)	Clinical observations: Scab and overlying skin at dosing site. No body weight changes.
			Macroscopic findings: Injection site: sore, overlying skin, red Microscopic findings: - Mandibular lymph node- minimal hyperplasia lymphoid - Spleen-slight hematopoiesis - Injection site, epidermis-moderate exudate, slight hyperplasia, minimal hemorrhage, minimal ulceration, slight fibrosis, minimal chronic inflammation, slight necrosis.

Clinical Signs

Table 17: EXEL-1644 Clinical Observations (# of affected animals)

Clinical Sign	Sex	0 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Number Examined		**15**	**10**	**10**	**15**
Dosing phase					
Skin and pelage- scab dose site	M/F	11/14	10/10	9/10	15/15
Recovery phase					
Skin and pelage- scab dose site	M/F	4/5	--	--	5/7

-- = no data available

Body Weights and Food Consumption
There were no test article-related effects reported.

Ophthalmoscopy:
There were no test article-related effects reported.

Clinical Pathology (hematology, clinical chemistry, coagulation and urine analysis)
There were no adverse test article-related changes reported.

Table 18: EXEL-1644 Hematology and Coagulation (% change from control)

Day 16 and recovery				
Dose Group	**Sex**	**3 mg/kg**	**10 mg/kg**	**30 mg/kg**
Triglycerides	M	-21	-33*	-33*(-24)
	F	--	--	--

**p≤0.05*
-- = no change;
( ) = recovery group value

Organ Weights
There were no test article-related changes reported.

Gross Pathology
Procedural/vehicle-related findings were reported at the injection site in the control and all dosing groups. The findings may be attributed to the high dose volume administered (10/5 mL/kg) and to the vehicle control that contained ethanol. The findings were correlated with microscopic findings.

Table 19: EXEL-1644 Gross Pathology Findings

Test Article	(dosage)	1	2	3	4
EXEL-1644	mg/kg/day	0	3	10	30

Tissue/ Observation	Group/Subgroup/Sex: Number of Animals:	1/1/M 10	2/1/M 10	3/1/M 10	4/1/M 10	1/1/F 10	2/1/F 10	3/1/F 10	4/1/F 8
Subcutaneous Injection Site, A	Number Examined:	10	10	10	10	10	10	10	8
	Unremarkable:	5	3	4	4	3	5	3	3
Discolored		1	1	1	1	0	0	0	0
Scab		4	7	6	6	7	5	7	5
Thickened		0	2	2	2	0	0	1	0
Subcutaneous Injection Site, B	Number Examined:	10	10	10	10	10	10	10	8
	Unremarkable:	6	5	7	4	5	2	5	3
Discolored		0	1	0	1	0	1	0	0
Scab		4	3	3	5	5	7	5	5
Thickened		0	3	0	1	0	1	0	0
Subcutaneous Injection Site, C	Number Examined:	10	10	10	10	10	10	10	8
	Unremarkable:	4	2	2	3	5	4	3	4
Discolored		3	4	2	4	1	2	5	0
Scab		3	2	4	3	2	5	4	4
Thickened		2	7	6	4	2	3	5	0
Subcutaneous Injection Site, D	Number Examined:	10	10	10	10	10	10	10	8
	Unremarkable:	5	1	3	3	4	3	2	5
Discolored		3	4	3	4	1	3	4	0
Scab		0	1	4	3	5	5	6	2
Thickened		4	7	4	5	4	2	6	2

(excerpted from Applicant's report)

Histopathology
Adequate Battery – Yes
Signed Pathology Report – Yes
Peer Reviewed- No

Histological Findings: The predominant target organs of toxicity were: Skeletal muscle (minimal to slight) and heart (minimal).

Procedural/vehicle related findings were reported at the injection site in the control and all dosing groups. Findings were evident at the end of the recovery period.

Table 20: EXEL-1644 Microscopic Findings (dosing phase)

Tissue/ Observation	Group/Subgroup/Sex: Number of Animals:	1/1/M 10	2/1/M 10	3/1/M 10	4/1/M 10	1/1/F 10	2/1/F 10	3/1/F 10	4/1/F 8
Heart	Number Examined:	10	0	0	10	10	0	0	8
	Unremarkable:	9	0	0	7	10	0	0	8
Cardiomyopathy		1	0	0	3	0	0	0	0
Lymph Node, Mandibular	Number Examined:	10	0	0	10	10	0	0	8
	Unremarkable:	6	0	0	2	3	0	0	1
Lymphoid hyperplasia		4	0	0	8	7	0	0	7
Lymph Node, Mesenteric	Number Examined:	10	0	0	10	10	0	0	8
	Unremarkable:	3	0	0	1	2	0	0	0
Lymphoid hyperplasia		7	0	0	9	8	0	0	8
Muscle, Biceps Femoris	Number Examined:	10	0	0	10	10	0	0	8
	Unremarkable:	9	0	0	4	10	0	0	4
Perimuscular fascia, inflammation, chronic		1	0	0	6	0	0	0	4
Subcutaneous Injection Site, A	Number Examined:	10	7	6	10	10	5	7	8
	Unremarkable:	0	0	0	2	0	0	0	0
Adnexa, atrophy		0	1	0	1	1	0	0	1
Dermis, fibrosis		7	6	5	6	8	5	7	5
Epidermis, exudate		5	7	5	5	5	5	5	6
Epidermis, hyperplasia		9	7	6	7	10	5	7	7
Epidermis, ulceration		2	1	1	1	3	3	2	0
Subcutis, hemorrhage		1	2	4	3	0	1	0	1
Subcutis, fibrosis		6	6	6	6	7	5	5	4
Subcutis, inflammation, chronic		7	6	6	7	6	5	6	3
Subcutis, necrosis		1	2	1	1	0	0	0	0
Subcutaneous Injection Site, B	Number Examined:	10	5	3	10	10	8	5	8
	Unremarkable:	1	0	0	0	1	0	0	0
Adnexa, atrophy		1	1	0	1	0	0	0	1
Dermis, fibrosis		6	3	3	5	5	6	5	3
Epidermis, exudate		6	5	3	4	7	7	4	5
Epidermis, hyperplasia		8	5	3	6	9	6	5	7
Epidermis, ulceration		2	2	1	0	3	1	0	2
Subcutis, fibrosis		6	5	3	8	6	6	1	4
Subcutis, hemorrhage		2	3	0	3	2	2	0	4
Subcutis, inflammation, chronic		9	5	2	9	8	7	2	6
Subcutis, necrosis		0	2	0	0	0	1	0	3
Subcutaneous Injection Site, C	Number Examined:	10	8	8	10	10	6	7	8
	Unremarkable:	0	0	0	0	0	0	0	0
Adnexa, atrophy		2	3	1	3	1	0	2	0
Dermis, fibrosis		3	3	3	4	2	4	2	4
Epidermis, exudate		4	2	4	4	3	5	2	3
Epidermis, hyperplasia		10	8	6	9	9	5	7	8
Epidermis, ulceration		1	0	3	3	1	2	2	1
Subcutis fibrosis		10	7	7	9	8	6	6	7
Subcutis, hemorrhage		10	7	8	8	8	6	7	7
Subcutis, inflammation, chronic		10	8	8	9	9	6	7	8
Subcutis, necrosis		10	7	6	8	7	6	6	7

Subcutaneous Injection Site, D	Number Examined:	10	9	7	10	10	7	8	8
	Unremarkable:	0	0	0	0	0	0	0	0
Adnexa, atrophy		3	5	1	3	2	0	2	2
Dermis, fibrosis		0	2	4	2	3	5	8	1
Epidermis, exudate		1	1	2	2	3	4	7	1
Epidermis, hyperplasia		10	5	6	8	9	6	8	4
Epidermis, ulceration		1	2	1	1	2	1	4	1
Subcutis, fibrosis		8	7	7	8	9	7	7	5
Subcutis, hemorrhage		10	7	6	10	10	7	8	7
Subcutis, inflammation, chronic		10	9	7	10	10	7	8	7
Subcutis, necrosis		10	7	6	10	10	7	3	6

(excerpted from Applicant's report)

Table 21: EXEL-1644 Microscopic Findings (recovery phase)

Tissue/ Observation	Group/Subgroup/Sex: Number of Animals:	1/1/M 5	4/1/M 5	1/1/F 5	4/1/F 5
Lymph Node, Mandibular	Number Examined:	5	5	5	5
	Unremarkable:	0	0	0	1
Lymphoid hyperplasia		5	5	5	4
Lymph Node, Mesenteric	Number Examined:	5	5	5	5
	Unremarkable:	1	4	1	0
Lymphoid hyperplasia		4	1	4	5
Subcutaneous Injection Site, A	Number Examined:	5	5	5	5
	Unremarkable:	0	0	0	0
Adnexa, atrophy		5	5	5	4
Dermis, fibrosis		2	0	1	1
Epidermis, exudate		1	0	0	1
Epidermis, hyperplasia		5	5	2	3
Epidermis, ulceration		1	0	0	0
Subcutis, fibrosis		2	2	0	1
Subcutaneous Injection Site, B	Number Examined:	5	5	5	5
	Unremarkable:	0	0	0	0
Adnexa, atrophy		4	5	5	4
Dermis, fibrosis		0	1	0	0
Epidermis, hyperplasia		5	4	0	2
Subcutis, fibrosis		3	1	0	1
Subcutis, inflammation, chronic		2	0	0	0
Subcutaneous Injection Site, C	Number Examined:	5	5	5	5
	Unremarkable:	0	0	0	0
Adnexa, atrophy		5	5	5	5
Dermis, fibrosis		0	1	0	0
Epidermis, exudate		0	0	0	1
Epidermis, hyperplasia		3	5	0	1
Subcutis fibrosis		0	3	0	0
Subcutaneous Injection Site, D	Number Examined:	5	5	5	5
	Unremarkable:	0	1	1	0
Adnexa, atrophy		3	2	4	5
Dermis, fibrosis		1	2	1	0
Epidermis, exudate		0	0	0	1
Epidermis, hyperplasia		3	4	0	2
Subcutis, fibrosis		1	2	1	0

(excerpted from Applicant's report)

Toxicokinetics

Table 22: EXEL-1644 Toxicokinetic Parameters Following SC Administration

Text Table 4.1: Summary of Toxicokinetic Parameters of EXEL-1644 in Rats on Days 1 and 15 after Daily SC Administration of EXEL-1644 at 3, 10 and 30 mg/kg Dose

Dose (mg/kg)	Nominal Day	Gender	$t_{1/2,z}$	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (kg*ng/mL/mg)	$AUC_{0\text{-last}}$ (hr*ng/mL)	$AUC_{0\text{-last}}$/D (hr*ng/mL/mg/kg)	$AUC_{0\text{-inf}}$ (hr*ng/mL)	ARAUC	AUC%_Extrap (%)
3	1	Female	NC	2.00	4690	1560	67800	22600	352000	.	79.5
		Male	NC	4.00	4820	1610	72000	24000	363000	.	79.0
		N	.	2	2	2	2	2	2	.	2
		Mean	.	3.00	4760	1590	69900	23300	357000	.	79.3
	15	Female	NC	2.00	10600	3530	95300	31767	145000	1.41	34.0
		Male	NC	2.00	8290	2760	104000	34667	276000	1.44	60.1
		N	.	2	2	2	2	2	2	2	2
		Mean	NC	2.00	9450	3150	99600	33217	210000	1.43	47.1
10	1	Female	13.9	2.00	35000	3500	248000	24800	352000	.	26.9
		Male	9.73	4.00	34900	3490	323000	32300	408000	.	19.2
		N	2	2	2	2	2	2	2	.	2
		Mean	11.8	3.00	35000	3500	285000	28550	380000	.	23.1
	15	Female	7.51	2.00	38600	3860	214000	21400	242000	0.86	9.14
		Male	9.72	2.00	50500	5050	323000	32300	396000	1.00	16.1
		N	2	2	2	2	2	2	2	2	2
		Mean	8.62	2.00	44600	4460	269000	26850	319000	0.93	12.6
30	1	Female	9.21	2.00	112000	3730	585000	19500	682000	.	12.4
		Male	8.87	2.00	101000	3370	759000	25300	898000	.	14.1
		N	2	2	2	2	2	2	2	.	2
		Mean	9.04	2.00	107000	3550	672000	22400	790000	.	13.3
	15	Female	8.17	2.00	99300	3310	460000	15333	507000	0.79	8.74
		Male	8.79	2.00	104000	3470	692000	23067	789000	0.91	11.9
		N	2	2	2	2	2	2	2	2	2
		Mean	8.48	2.00	102000	3390	576000	19200	648000	0.85	10.3

$AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to the time of last quantification concentration or 24 hours dosing interval; $AUC_{0\text{-last}}$/D, dose normalized $AUC_{0\text{-last}}$; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, observed maximum plasma concentration; C_{max}/D, dose-normalized C_{max}; t_{max}, time to reach the maximum plasma concentration; ARAUC, accumulation ratio on Day 15 based on AUC; $t_{1/2,z}$, terminal half-life; AUC%extrap, % of $AUC_{0\text{-inf}}$ that was extrapolated; NC, not calculated due to AUC%extrap>30%; ".", not applicable.

(excerpted from Applicant's report)

- Plasma exposure ($AUC_{0\text{-last}}$) increased in a dose-proportional manner after a single dose, and in less than dose-proportional manner after repeat dosing.
- C_{max} increased in a greater than dose-proportional manner after a single dose and repeat dosing.
- No accumulation was reported after repeat dosing.
- Slightly higher systemic exposure was reported in males relative to females (1.5 X fold).
- T_{max} ranged between 2 to 4 hours.
- $T_{1/2}$ (half-life) ranged between 8.5 to 11.8 hours.

Stability and Formulation Analysis

- Samples obtained for homogeneity and concentration verification analysis were within the acceptable limits of ±10% error.

- Stability was evaluated under (b) (4) Study No. 8283797. The Applicant stated that the formulations (0.1 and 100 mg/mL) were stable for 24 hours at room temperature and for 15 days at 2 to 8°C.

Study Title: 4-Week Exploratory Toxicity and Toxicokinetic Study in 001178-W (Wild Type) Mice Administered Cabozantinib S-Malate by Oral Gavage and EXEL-1644 by Subcutaneous Injection with a 4-Week Recovery Phase	
Study No:	XL184-NC-037
Conducting laboratory and location:	(b) (4)
Study initiation:	April 22, 2013

Compliant:	Non-GLP

Objective: to determine the toxicity and toxicokinetics profile of the test articles, cabozantinib S-malate and EXEL-1644, when administered daily by oral gavage and subcutaneous injection, respectively, to wild type CByB6F1-Tg(HRas) 2Jic mice for at least 28 days and to assess the reversibility, following a 4-week recovery.

Route:

- Cabozantinib, oral.
- EXEL-1644 subcutaneous (SC)

Animals: wild type litter mate CByB6F1-Tg(HRas) 2Jic mice

Dosing duration and frequency: Daily for 28 days. Each animal received Cabozantinib (orally) and EXEL-1644 (SC)

Study design:

Table 23: Study Design For 4-Week Toxicity Study with XL184 (orally) and EXEL-1644 (SC) in Mice

3.1.5 Study Design

		No. of Animals[a,b]		Test Article No. 1 (cabozantinib S-malate)[c]		Test Article No. 2 (EXEL-1644)[c]	
Group	Subgroup	Male	Female	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)
1	1 (Toxicity)	12	12	5	1	20	4
	2 (Toxicokinetic)	24	24				

a Six toxicity animals/sex were designated as recovery animals and were dosed with test articles for at least 28 days, after which dosing was discontinued, and animals were observed for reversibility, persistence, or delayed occurrence of toxic effects for at least 4 weeks after dosing.
b Subgroup 2 included six animals/sex for possible use as replacements if needed.
c Test Article No. 1 was administered by oral gavage at a dose volume of 5 mL/kg. Test Article No. 2 was administered by subcutaneous injection at a dose volume of 5 mL/kg.

(excerpted from Applicant's report)

Reviewer comment:
No concurrent control group was used in this study.

End points: clinical observations, body weights, food consumption, clinical pathology, toxicokinetic, organ weights, macroscopic and microscopic evaluation.

Results:

Clinical Observations
Injection site observations (red skin and sores/scabs). Erythema was reported in 9/12 males and 5/12 females.

Macroscopic findings
One female was reported to have discoloration at the injection site and one male had a scab at the injection site.

Microscopic findings
Microscopic findings were reported at the injection site by the end of dosing and

recovery phases (foreign material surrounded by mixed cell inflammation). Findings occurred at a lower incidence and severity in recovery animals.

The injection site findings may be attributed to the high dose volume administered (5 mL/kg) and/or to the vehicle control that contained ethanol.

Table 24: EXEL-1644 Microscopic findings (dosing and recovery phases)

Text Table 3.1: Incidence and Severity of Test Article-Related Microscopic Findings in Dosing Phase Animals

		Cabozantinib S-malate and EXEL-1644	
	Sex	Males	Females
Dose Level cabozantinib S-malate/EXEL-1644 (mg/kg/day)		5/20	5/20
Subcutaneous Injection Site, A			
	Number Examined	6	6
Foreign material			
	Present	2	1
Inflammation, mixed cell			
	Minimal	1	1
	Slight	1	1
	Total Incidence	2	2
Subcutaneous Injection Site, B			
	Number Examined	6	6
Foreign material			
	Present	3	1
Inflammation, mixed cell			
	Slight	2	1
	Moderate	1	0
	Total Incidence	3	1

Text Table 3.2: Incidence and Severity of Test Article-Related Microscopic Findings in Recovery Phase Animals

		Cabozantinib S-malate and EXEL-1644	
	Sex	Males	Females
Dose Level cabozantinib S-malate/EXEL-1644 (mg/kg/day)		5/20	5/20
Subcutaneous Injection Site, A			
	Number Examined	6	6
Foreign material			
	Present	2	0
Inflammation, mixed cell			
	Minimal	1	0
	Total Incidence	1	0
Subcutaneous Injection Site, B			
	Number Examined	6	6
Foreign material			
	Present	0	0
Inflammation, mixed cell			
	Total Incidence	0	0

(excerpted from Applicant's submission)

Toxicokinetics

Table 25: Toxicokinetics of XL184 Following Oral Administration

Table 3-1: Summary of Toxicokinetics Parameters of Cabozantinib after 5 mg/kg/day Daily Oral Administration of Cabozantinib S-Malate and after Daily SC Administration of 20 mg/kg of EXEL-1644 to RasH2 Wild Type Mice for 28 Days

Day	Sex	$t_{1/2,z}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (hr*ng/mL)	AUC_{0-inf_obs} (hr*ng/mL)	Cl/F_{obs} (mL/hr/kg)	ARAUC
1	F	5.90	2.00	2170	17800	19000	263	
	M	4.84	2.00	1550	15500	16200	309	
	N	2	2	2	2	2	2	
	Mean	5.37	2.00	1860	16700	17600	286	
14	F	4.32	2.00	1850	18500	.	270	1.04
	M	5.68	4.00	2390	22000	.	227	1.42
	N	2	2	2	2	.	2	2
	Mean	5.00	3.00	2120	20300	.	249	1.23
28	F	4.21	4.00	1510	14900	.	336	0.81
	M	5.74	4.00	1870	21200	.	236	0.96
	N	2	2	2	2	.	2	2
	Mean	4.98	4.00	1690	18000	.	286	0.88

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hrs postdose; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; CL/F, apparent oral administration; ARAUC, accumulation ratio on Days 14 and 28 based on AUC; F, female; M, male; ".", not applicable or not reported.

Table 26: Toxicokinetics of EXEL-1644 Following SC Administration

Table 3-2: Summary of Toxicokinetics Parameters of EXEL-1644 after 20 mg/kg/day Daily SC Administration of EXEL-1644 and 5 mg/kg/day Daily Oral Administration of Cabozantinib S-Malate to RasH2 Wild Type Mice for 28 Days

Day	Sex	$t_{1/2,z}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (hr*ng/mL)	AUC_{0-inf_obs} (hr*ng/mL)	Cl/F_{obs} (mL/hr/kg)	ARAUC
1	F	6.26	1.00	56100	277000	295000	67.7	
	M	7.02	1.00	98400	276000	293000	68.1	
	N	2	2	2	2	2	2	
	Mean	6.64	1.00	77300	277000	294000	67.9	
14	F	3.87	1.00	43400	337000	.	59.3	1.22
	M	5.02	1.00	61200	248000	.	80.6	0.90
	N	2	2	2	2	.	2	2
	Mean	4.44	1.00	52300	292000	.	70.0	1.06
28	F	4.64	2.00	45900	233000	.	85.8	0.84
	M	3.75	1.00	44300	229000	.	87.3	0.83
	N	2	2	2	2	.	2	2
	Mean	4.20	1.50	45100	231000	.	86.6	0.84

$T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}; C_{max}, observed maximum concentration; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hrs postdose; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; CL/F, apparent SC administration; ARAUC, accumulation ratio on Days 14 and 28 based on AUC; F, female; M, male; ".", not applicable or not reported.

(excerpted from Applicant's submission)

- Cabozantinib and EXEL-1644: No accumulation after repeat dosing and no

significant differences between sexes.
- Systemic exposure (C_{max} and AUC) for EXEL-1644 were higher than XL184.
- Half-life for XL184 were approximately similar on Days 1, 14 and 28 with mean values ranging from 4 to 5.9 hours.
- Half-life for EXEL-1644 was approximately similar on Days 1, 14 and 28 with mean values ranging from 4 to 7 hours.

7 Genetic Toxicology

No new studies were submitted.

8 Carcinogenicity

CARCINOGENICITY
STUDY REPORT DATE: 30 June 2015

THERAPEUTIC CATEGORY: Advanced renal cell carcinoma (RCC); progressive, metastatic medullary thyroid cancer (MTC)

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Kinase inhibitor

MUTAGENIC/GENOTOXIC: 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.

BACKGROUND: The Applicant submitted a New Drug Application (NDA) on December 22, 2015 for Cabozantinib (S)-malate (cabozantinib) for the treatment of advanced renal cell carcinoma (RCC). Cabozantinib 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).
Cometriq (cabozantinib) is an FDA approved drug since 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (NDA# 203756). This patient population is expected to have an extended survival of 5 years or longer. At the time of approval, the Applicant was required to conduct carcinogenicity studies in two species with orally administered cabozantinib as a post marketing requirement (PMR). The Applicant proposed a 26-week mouse study and a 2-year rat study. The final 26-week mouse carcinogenicity report was submitted on 7/6/2015 under NDA 203756/Supp. # 115 (Applicant owned) and the current NDA on October 12, 2015. The 2-year rat carcinogenicity study report is scheduled to be submitted on October 15, 2016.

MOUSE CARCINOGENICITY STUDY:

MOUSE STUDY DURATION: 26 weeks
STUDY STARTING DATE: 15 October 2013
STUDY ENDING DATE: 30 June 2015
MOUSE STRAIN: Tg.rasH2 mice (CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)
ROUTE: Oral gavage

DOSING COMMENTS:

The eCAC recommended the inclusion of a second control group (water or saline), in addition to the vehicle control group (vehicle), to help interpret any findings due to the vehicle. Moreover, the committee noted that if the vehicle affects the study or study interpretation adversely, the study may not be acceptable.
Statistical analysis of the submitted data indicated that there were no statistically significant differences between the vehicle control group (group 1) and the water control group (group 2). The vehicle control group showed no adverse effects that impacted the interpretation of the study data.

Study Groups and Dose levels:

	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg/kg/day)	(mg/mL)
1 (Control)[a]	25	25	0	0
2 (Water Control)[b]	25	25	0	0
3 (Low)	25	25	2.0	0.4
4 (Mid)	25	25	5.0	1.0
5 (High)	25	25	15.0	3.0
6 (Positive Control)[c]	20	20	75	7.5

a Group 1 received vehicle control article only.
b Group 2 received RO water only
c Group 6 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately express oncogenes and responded to carcinogenic insult.

(excerpted from Applicant's submission)

BASIS FOR DOSES SELECTED: MTD; 4-week dose range finding toxicity study in wild type, CByB6F1-Tg(HRAS) 2Jic mice.

PRIOR FDA DOSE CONCURRENCE: Yes, per eCAC recommendation on December, 3, 2013

MOUSE CARCINOGENICITY: Negative

MOUSE STUDY COMMENTS:

No test article-related neoplastic lesions were reported. Non-neoplastic microscopic findings (slight to moderate) were reported at 15 mg/kg/day in the spleen (lymphocyte depletion), glandular stomach (hyperplasia of the epithelium), duodenum (hyperplasia of the epithelium) and pancreas (zymogen depletion).

Survival analysis showed that at 15 mg/kg/day, males had a statistically significant increase in mortality when compared to the vehicle control (p=0.0031) and water control (p=0.0031) groups. No statistically significant increase in mortality was reported in females.

Despite the high mortality rate in males (36%), dosing was not ceased for the remaining surviving mice. All surviving mice were euthanized on Day 184, necropsied and evaluated microscopically.

The positive control, MNU, showed a clear carcinogenic response (increase in mortality, clinical observations and tumor formation), and as such, the data provided validity to the test assay.

Executive CAC Recommendations and Conclusions

Tg.rasH2 mouse:

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Study title: 26-Week Oral Gavage Carcinogenicity Study with Cabozantinib S-Malate in 001178 T (Hemizygous) RasH2 Mice	
Study no.:	8290001 (XL184-NC-042)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15 October 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Cabozantinib S-Malate, batch# 1305366, 99.9%
CAC concurrence:	Yes, design and dose selection

Key Study Findings

Adequacy of Carcinogenicity Study

Study design and dose selection were approved by the executive CAC. Doses were determined to be adequate based on maximum tolerated dose. A positive carcinogenic response was reported using MNU as a positive control.

Appropriateness of Test Models

The Tg.rasH2 mouse model used is recommended for genotoxic and non-genotoxic carcinogen identification. A short-term (26-week) carcinogenicity assay is generally considered an acceptable alternative to the traditional two-year mouse carcinogenicity assay. The oral route of administration reflects the intended clinical route.

Neoplastic Findings

- No test article-related increases in the incidence of neoplastic lesions were reported at any dose tested.
- The positive control, MNU, showed a clear carcinogenic response, and as such the data provided validity to the test assay.

Clinical Signs and Non-neoplastic Findings

- There were no differences between the vehicle control (Group 1) and water control (Group 2) based on the survival analysis and tumor analysis.
- Statistically significant test article-related increases in mortalities were reported in males at 15 mg/kg/day due to general debilitation of the animals.
- At 15 mg/kg/day, non-neoplastic microscopic findings (slight to moderate) were reported in the spleen (lymphocyte depletion), glandular stomach (hyperplasia of the epithelium), duodenum (hyperplasia of the epithelium) and pancreas (zymogen depletion).

Methods

Doses:

Table 27: XL184-Carcinogenicity Study Design

	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg/kg/day)	(mg/mL)
1 (Control)[a]	25	25	0	0
2 (Water Control)[b]	25	25	0	0
3 (Low)	25	25	2.0	0.4
4 (Mid)	25	25	5.0	1.0
5 (High)	25	25	15.0	3.0
6 (Positive Control)[c]	20	20	75	7.5

a Group 1 received vehicle control article only.
b Group 2 received RO water only
c Group 6 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately express oncogenes and responded to carcinogenic insult.

(excerpted from Applicant's submission)

Frequency of dosing:	Daily (Groups 1-5); Once (Positive Control-Group 6)
Dose volume:	5 ml/kg (Groups 1-5); 10 ml/kg (Group 6)
Route of administration:	Oral gavage (Groups 1-5); Intraperitoneal injection (Group 6)
Formulation/Vehicle (Group 1):	Ethanol [EtOH, 200 proof]:polyethylene glycol [PEG] 400:reverse osmosis [RO] water, 5:45:50 [v:v:v]
Control (Group 2):	Water
Basis of dose selection:	4-Week study in the non-transgenic littermates, CByB6F1 animals, (b) (4) study # 8280818; Applicant # XL184-NC-037)
Species/Strain:	Tg.rasH2 mice (CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras, referred to as Tg.rasH2).
Age at initiation of dosing:	10 to 11 weeks
Animal housing:	Males: Individual Females: 3 mice/cage
Positive control:	N-methyl-N-nitrosourea (MNU)
Satellite groups:	no
Clinical observations:	Daily for cageside observations and weekly for detailed observations
Body weight:	Prior to dosing, Day 1, and weekly thereafter
Food consumption:	Prior to dosing, Day 1, twice weekly for 4 weeks, and weekly thereafter
Hematology:	Blood samples were collected from all surviving mice (Groups 1-5)
Termination, necropsy and macroscopic observations:	After at least 26 weeks of dosing, on Day 184 all surviving mice were euthanized and necropsied
Microscopic evaluation:	All groups and macroscopic lesions

Historical Control Data:	Laboratory specific historical background values for control and MNU treated rasH2 mice were not provided.
Statistical analysis (FDA):	The tumor data were analyzed for dose-response relationships and pairwise comparisons of control groups with each of the treated groups. The dose-response relationship tests and pairwise comparisons were performed using the Poly-k method. For the adjustment of multiple testing of dose-response relationships, the FDA statistician stated in his review that he followed FDA guidance for statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals, which recommends to use for the 26-week transgenic mouse study data analyses test at α=0.05 significance level for both the trend tests and the pairwise comparisons, regardless of tumor type (i.e. common or rare).

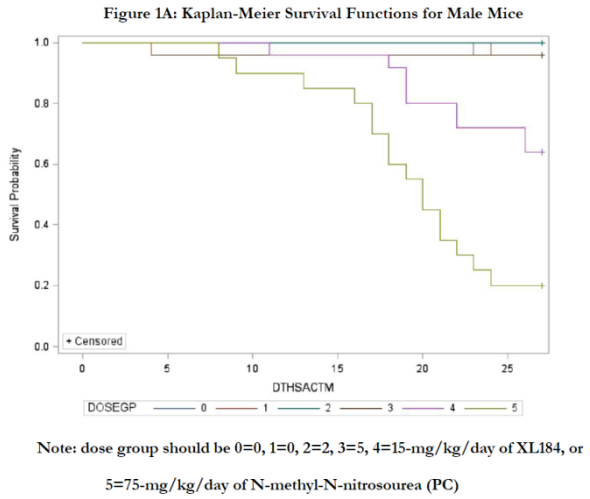
Results

Mortality

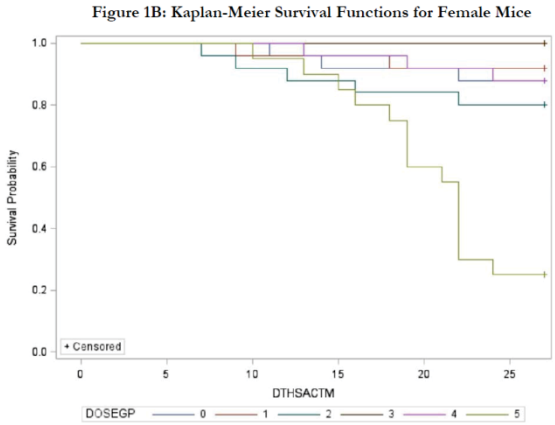
Test article-related mortalities were reported at 15 mg/kg/day. Survival analysis showed that at 15 mg/kg/day, males had a statistically significant increase in mortality when compared to the vehicle control (p=0.0031) and water control group (p=0.0031). No statistically significant increase in mortality was reported in females. The survival rates in the vehicle control, water control, 2, 5 and 15 mg/kg/day at termination were 96%, 96%, 100%, 96% and 64% in males and 88%, 92%, 80%, 100% and 88% in females, respectively.

The positive control group in both sexes showed statistically significant increases in mortality when compared with the individual control groups ($p < 0.001$). The mortality rate in male and female mice was 80% (16/20) and 75% (15/20), respectively, which was an expected findings based on MNU toxicity (Long et al. 2010). Most of the MNU deaths were associated with malignant neoplasms, including malignant lymphoma, squamous cell carcinoma (non-glandular stomach), and hemangiosarcoma. These findings were consistent with those reported in the published literature for MNU in the RasH2 mouse model (Long *et al.* 2010).

Figure 4: Survival Data



Note: dose group should be 0=0, 1=0, 2=2, 3=5, 4=15-mg/kg/day of XL184, or 5=75-mg/kg/day of N-methyl-N-nitrosourea (PC)



(excerpted from FDA statistician's review)

Table 28: Unscheduled Deaths

Animal #	Sex	Dose (mg/kg)	Day of Death (in weeks)	Observations/Cause of death[3]
A04991	M	Water	155 (23)[2]	General debilitation (hunched, rough haircoat), Neoplasm, Carcinoma
A05028	M	Water	165 (24)[2]	General debilitation (hypoactivity, cold to touch, pale), Neoplasm, Vascular
A05066	M	5	27 (4)[1]	Neoplasm, Vascular
A05082	M	15	128 (19)[2]	General debilitation (discolored haircoat), Undetermined
A05087	M	15	180 (26)[2]	General debilitation (hunched, malocclusion, discolored haircoat, hind feet sore), Undetermined
A05089	M	15	128 (19)[2]	General debilitation (hunched, malocclusion, discolored haircoat), Undetermined
A05090	M	15	176 (26)[2]	General debilitation (hunched, discolored haircoat), Undetermined
A05091	M	15	120 (18)[2]	General debilitation (discolored haircoat), Undetermined
A05093	M	15	128 (19)[2]	General debilitation (hunched, discolored haircoat), Undetermined
A05094	M	15	154 (22)[2]	General debilitation (hunched, malocclusion, discolored and rough haircoat), Undetermined
A05095	M	15	77 (11)[2]	General debilitation (hunched, malocclusion, irregular respiration, discolored haircoat), Undetermined
A05101	M	15	154 (22)[2]	General debilitation (hunched, malocclusion, missing teeth, discolored and rough haircoat), Degeneration, enamel organ

A05126	F	Vehicle	95 (14)[1]	Undetermined
A05143	F	Vehicle	148 (22)[1]	Neoplasm, Vascular
A05148	F	Vehicle	72 (11)[1]	Undetermined
A05156	F	Water	126 (18)[1]	Neoplasm, Vascular
A05157	F	Water	57 (9)[2]	General debilitation (hunched), Undetermined
A05177	F	2	46 (7)[1]	Urinary bladder, infiltration, neutrophils
A05182	F	2	60 (9)[2]	General debilitation (hunched, thin, ataxic, hypoactive, irregular respiration, labored, cold to touch), Neoplasm, Vascular
A05185	F	2	111 (16)[2]	General debilitation (hunched, thin, irregular respiration, labored), Neoplasm, Hematopoietic
A05187	F	2	81 (12)[2]	General debilitation (hunched, thin, irregular respiration, labored), Neoplasm, Carcinoma
A05198	F	2	151 (22)[1]	Undetermined
A05228	F	15	89 (13)[2]	General debilitation (malocclusion, discolored hair), Undetermined
A05230	F	15	127 (19)[1]	General debilitation (discolored hair), Neoplasm, Carcinoma
A05233	F	15	162 (24)[2]	General debilitation (hunched, thin, nonformed feces, discolored hair), Undetermined

Positive control (MNU)	M	75	• 12/22 on days 61-168 (9-24)[2] • 4/22 on days 56-147 (8-21)[1]	Malignant neoplasms, including malignant lymphoma, squamous cell carcinoma (non-glandular stomach), and hemangiosarcoma.
	F	75	• 11/22 on days 85-164 (13-24)[2] • 4/22 on days 68-153 (10-21)[1]	

[1]*Found dead*
[2] *Moribund terminations*
[3] *Cause of death as determined by the Applicant*

Clinical Observations

Test article-related observations were reported at 15mg/kg/day.

Table 29: Predominant Clinical Signs in Unscheduled Deaths and Surviving Animals

Clinical Sign	Sex	Vehicle	Water	2 (mg/kg/day)	5 (mg/kg/day)	15 (mg/kg/day)

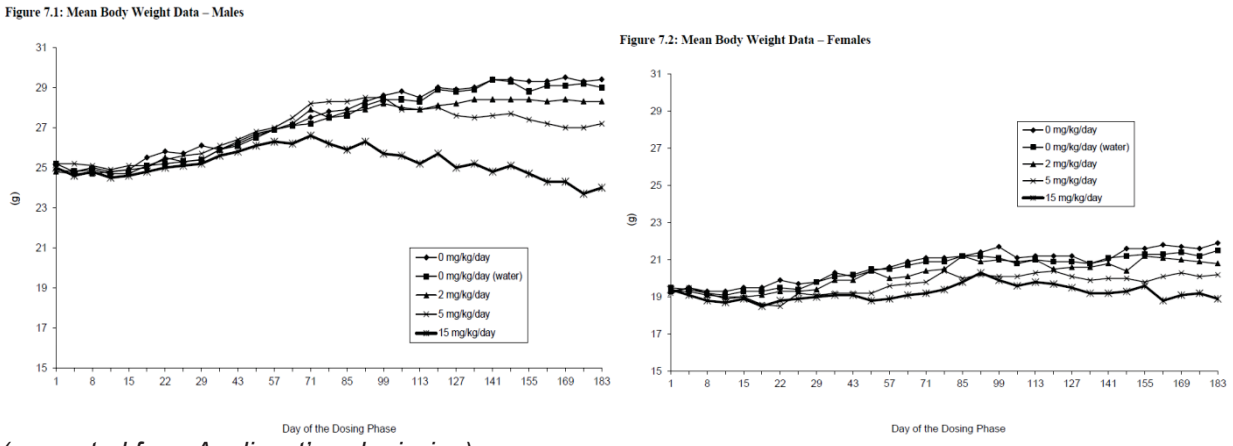
Number of Animals Affected; 25/sex/group						
Hunched	M	1	0	0	3	11
	F	3	2	5	0	4
Malocclusion	M	0	0	0	0	14
	F	0	0	0	0	10
Missing teeth	M	0	0	0	0	3
	F	0	0	0	0	0
Discharge (nasal, red)	M	0	0	0	0	3
	F	0	0	0	0	5
Discolored haircoat at various body regions (white)	M	0	0	0	0	23
	F	0	0	0	0	23

Administration of MNU (positive control) to males and females resulted in irregular/labored respiration in 8/20 mice/sex possibly due to lung toxicity. This was expected based on MNU toxicity (Long *et al.* 2010).

Body Weights

Test article-related decreases in mean body weights were reported at 5 mg/kg/day (up to -8%) and 15 mg/kg/day (up to -19%).

Figure 5: Mean Body Weight



(excerpted from Applicant's submission)

Food consumption

Statistically significant reduction in mean food consumption was reported at 15 mg/kg/day. The decline was partially attributed to the observation of malocclusion and other teeth findings, which necessitated the transition of some mice to crushed feed.

Table 30: Significant Food Consumption Changes (% change from control)

Week	Sex[1]	2 mg/kg/day	5 mg/kg/day	15 mg/kg/day
6 - 7	M	--	--	--
	F	--	--	-23
8 - 9	M	--	--	-12
	F	--	--	--
10-11	M	--	--	-12
	F	--	--	--
11-12	M	--	--	-14
	F	--	--	-17
12-13	M	--	--	-17
	F	--	--	--
13-14	M	--	--	--
	F	--	--	-17
14-15	M	--	--	-15
	F	--	--	--
16-17	M	--	--	--
	F	--	--	-19
21-22	M	--	--	--
	F	--	--	-26

** p≤0.05*

[1]= Females were group housed and males were individually housed

Hematology

Test article-related changes in hematological parameters were reported at 15mg/kg/day. These changes were not considered to be adverse because they were small in magnitude and had no microscopic correlates.

Table 31: Significant Hematological Changes on Day 184 (% change from control)

	Sex	2 mg/kg/day	5 mg/kg/day	15 mg/kg/day
RBC	M	--	-7	-24
	F	--	--	-22
HGB	M	--	--	-7
	F	--	--	--

HCT	M	--	--	-6
	F	--	--	--
MCV	M	--	--	24
	F	--	--	23
MCH	M	--	--	24
	F	--	--	23
PLT	M	--	--	-21
	F	--	--	--

** p≤0.05*

Gross Pathology

The reported increase in the incidence of raised area in the glandular stomach at 15 mg/kg/day correlated to epithelial hyperplasia of the glandular stomach and was considered treatment-related. No other findings were considered treatment-related.

Table 32: Incidence of Macroscopic Findings (all animals*)

	Sex	5 mg/kg/day	15 (mg/kg/day)
		25/sex	25/sex
Duodenum, large	M	0	2
	F	0	0
Jejunum, large	M	0	1
	F	0	0
Ovary, cyst	F	0	1
Spleen, small	M	0	1
	F	0	1
Stomach, glandular, raised area	M	0	0
	F	1	2
Stomach, non-glandular, raised area	M	0	1
	F	2	2
Thymus, large	M	0	1
	F	0	0
Lung, discolored	M	0	0
	F	1	2

**Scheduled and unscheduled termination*

The findings in the positive control group were consistent with those in the published literature for MNU toxicity (Long *et al.* 2010).

Table 33: Incidence of Macroscopic Findings (positive control -MNU)

	Sex	75 (mg/kg)
		20/sex

Liver, large	M	1
	F	3
Lymph node, mandibular, large	M	1
	F	4
Lymph node, mesenteric, large	M	0
	F	4
Lymph node, other, large	M	5
	F	6
Skin/subcutis, raised area	M	9
	F	4
Spleen, large	M	5
	F	10
Stomach, raised area	M	13
	F	13
Thymus, large	M	2
	F	3
Uterus, large	F	2

Histopathology

Adequate Battery- Yes
Signed Pathology Report – Yes
Peer Review- No

Histological Findings:
Benign and malignant neoplasms

Tumor analysis showed no statistically significant dose-response in tumor incidence or pairwise difference in tumor incidence in any organs between the individual controls and XL184 treated groups in male and female mice (Table 8).

All reported neoplastic lesions (Table 7) either fell within the published background spontaneous tumor ranges, or were not statistically different between treated groups and control groups.

Table 34: Incidence of Benign and Malignant Neoplasms in Mice

Text Table 4.2: Incidence of Benign and Malignant Neoplasms

	Cabozantinib S-malate									
Sex	Males					Females				
Dose Level (mg/kg/day)	0[a]	0[b]	2	5	15	0[a]	0[b]	2	5	15
Number Examined[c]	25	25	25	25	25	25	25	25	25	25
Tongue										
M-Carcinoma, squamous cell	0	0	0	0	0	0	0	1	0	0
Liver										
B-Adenoma, hepatocellular	0	1	0	0	0	0	0	0	0	0
Lung										
B-Adenoma, bronchiolo-alveolar	1	2	2	1	0	2	1	0	0	0
M-Carcinoma, Bronchiolo-alveolar	2	0	1	0	0	0	0	0	0	2
Kidney										
B-Adenoma, tubule cell	0	0	0	0	0	0	1	0	0	0
M-Carcinoma, tubule cell	0	0	0	0	0	0	1	0	0	0
Stomach, Nonglandular										
M-Carcinoma, squamous cell	1	0	0	0	0	0	0	0	0	0
Harderian Gland										
Number Examined	25	24	25	25	25	25	25	25	25	25
B-Adenoma	0	0	0	0	0	0	1	0	0	0
Body, Whole/Cavity										
M-Hemangiosarcoma	2	2	3	1	4	2	4	3	2	2
M-Lymphoma, Malignant	0	0	0	0	1	0	0	1	0	0
Muscle, Skeletal Other										
Number Examined	0	2	1	0	1	0	0	2	0	0
M-Sarcoma	NA	0	1	NA	0	NA	NA	0	NA	NA

NA = Not applicable.
a Vehicle control article.
b Water control.
c Number examined for each tissue unless otherwise noted.
M = Primary, malignant neoplasm
(excerpted from Applicant's submission)

Table 35: Tumor Rates in Male Mice - Vehicle Control vs. XL184 Groups

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Male Mice

Organ Name	Tumor Name	0 mkd VC N=25	2 mkd LD N=25	5 mkd MD N=25	15 mkd HD N=25	P-Value			
						Dose Response	VC vs. LD	VC vs. MD	VC vs. HD
Body, Whole/Cav	M-Hemangiosarcoma	2	3	1	4	0.1161	0.5000	0.5000	0 2308
	M-Lymphoma, malignant	0	0	0	1	0.2128	.	.	0.4444
Lung	B-Adenoma, bronchiole	1	2	1	0	0.7883	0.5000	0.7449	0.4444
	M-Carcinoma, bronchie	2	1	0	0	0.9269	0.5000	0.7449	0 6970
Muscle, Skeleta	M-Sarcoma	0	1	0	0	0.4681	0.5000	.	.
Stomach, Nongla	M-Carcinoma, squamous	1	0	0	0	0.7340	0.5000	0.4898	0.4444

Table 36: Tumor Rates in Male Mice - Vehicle Control vs. XL184 Groups

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Water Control – Male Mice

Organ Name	Tumor Name	0 mkd WC	2 mkd LD	5 mkd MD	15 mkd HD	P-Value

		N=25	N=25	N=25	N=25	Dose Response	VC vs. LD	VC vs. MD	VC vs. HD
Body, Whole/Cav	M-Hemangiosarcoma	2	3	1	4	0.1161	0 5000	0 5000	0.2308
	M-Lymphoma, malignant	0	0	0	1	0 2128	.	.	0.4444
Liver	B-Adenoma, hepatocelllular	1	0	0	0	0.7340	0 5000	0.4898	0.4444
Lung	B-Adenoma, bronchiole	2	2	1	0	0 8923	0 6954	0.4844	0.6970
	M-Carcinoma, bronchi	0	1	0	0	0.4681	0 5000	.	.
Muscle, Skeleta	M-Sarcoma	0	1	0	0	0.4681	0 5000	.	.

Table 37: Tumor Rates in Female Mice - Vehicle Control vs. XL184 Groups

Table 4A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Female Mice

Organ Name	Tumor Name	0 mkd VC N=25	2 mkd LD N=25	5 mkd MD N=25	15 mkd HD N=25	P-Value			
						Dose Response	VC vs. LD	VC vs. MD	VC vs. HD
Body, Whole/Cav	M-Hemangiosarcoma	2	3	2	2	0.5587	0.4782	0.3369	0 6961
	M-Lymphoma, malignant	0	1	0	0	0.5161	0.4889	.	.
Lung	B-Adenoma, bronchiole	2	0	0	0	0.9396	0.7326	0.7757	0.7556
	M-Carcinoma, bronchi	0	0	0	2	0.0645	.	.	0 2553
Tongue	M-Carcinoma, squamous	0	1	0	0	0.5161	0.4889	.	.

Table 38: Tumor Rates in Female Mice - Water Control vs. XL184 Groups

Table 4B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Water Control – Female Mice

Organ Name	Tumor Name	0 mkd WC N=25	2 mkd LD N=25	5 mkd MD N=25	15 mkd HD N=25	P-Value			
						Dose Response	VC vs. LD	VC vs. MD	VC vs. HD
Body, Whole/Cav	M-Hemangiosarcoma	4	3	2	2	0.7656	0.4490	0.6864	0 6460
	M-Lymphoma, malignant	0	1	0	0	0.5161	0.4889	.	.
Harderian Gland	B-Adenoma	1	0	0	0	0.7500	0.4773	0.5208	0 5000
Kidney	B-Adenoma, tubule cell	1	0	0	0	0.7500	0.4773	0.5208	0 5000
	M-Carcinoma, tubule	1	0	0	0	0.7500	0.4773	0.5208	0 5000
Lung	B-Adenoma, bronchiole	1	0	0	0	0.7500	0.4773	0.5208	0 5000
	M-Carcinoma, bronchi	0	0	0	2	0.0645	.	.	0 2553
Tongue	M-Carcinoma, squamous	0	1	0	0	0.5161	0.4889	.	.

Table 39: Tumor Rates in Male Mice - Water Control, Vehicle Control vs. Positive Control

Table 5A: Tumor Rates and P-Values for Comparisons between WC, VC, and PC – Male Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	0 mg/kg/day WC (N=25)	75 mg/kg/day PC (N=20)	P-Value VC vs. WC	P-Value VC vs. PC	P-Value WC vs. PC
Body, Whole/Cav	M-Hemangiosarcoma	2	2	2	0.6954	0 3191	0.3191
	M-Lymphoma, malignant	0	0	7	.	<0.001*	<0.001*
Liver	B-Adenoma, hepatocellular	0	1	0	0.5000	.	0.2647
Lung	B-Adenoma, bronchiole	1	2	0	0.5000	0 2647	0.4652
	M-Carcinoma, bronchi	2	0	0	0.7551	0.4652	.
Skin/Subcutis	B-Papilloma, squamous	0	0	16	.	<0.001*	<0.001*
	M-Carcinoma, squamous	0	0	1	.	0 2857	0.2857

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	0 mg/kg/day WC (N=25)	75 mg/kg/day PC (N=20)	P-Value VC vs. WC	P-Value VC vs. PC	P-Value WC vs. PC
Stomach, Nongla	B-Papilloma, squamous	0	0	10	.	<0.001*	<0.001*
	M-Carcinoma, squamous	1	0	6	0.5000	0.0035*	<0.001*

*Indicted the significant at 0.05 alpha levels.

VC=Vehicle control
WC= Water control
LD= low dose (2mg/kg/day)
MD= Middle dose (5mg/kg/day)
HD= High dose (15mg/kg/day)

(excerpted from FDA statistician's review)

Non-neoplastic findings

At 15 mg/kg/day, non-neoplastic microscopic findings were reported in the spleen, glandular stomach, duodenum and pancreas. The microscopic findings in the spleen (lymphocyte depletion) and glandular stomach (hyperplasia of the epithelium) were similar to those reported previously in the dose range finding study using the non-transgenic wild type litter mate CByB6F1-Tg(HRAS) 2Jic mice (4-week study # XL184-NC-035).

Table 40: Non-neoplastic Microscopic Findings (incidence and severity) in Mice

Text Table 4.3: Incidence and Severity of Cabozantinib S-Malate-Related Microscopic Findings

	Cabozantinib S-malate									
Sex	Males					Females				
Dose Level (mg/kg/day)	0[a]	0[b]	2	5	15	0[a]	0[b]	2	5	15
Number Examined	25	25	25	25	25	25	25	25	25	25
Spleen										
Depletion, lymphocytes, marginal zone, diffuse										
Not Present	25	25	25	25	9	25	25	25	25	12
Slight	0	0	0	0	4	0	0	0	0	3
Moderate	0	0	0	0	12	0	0	0	0	10
Stomach, glandular										
Hyperplasia, epithelium, multifocal										
Not Present	25	25	25	25	21	25	25	25	25	18
Slight	0	0	0	0	4	0	0	0	0	5
Moderate	0	0	0	0	0	0	0	0	0	2
Duodenum										
Number Examined	25	25	25	24	25	24	25	23	25	24
Hyperplasia, epithelium, diffuse										
Not Present	25	25	25	24	23	24	25	23	25	24
Moderate	0	0	0	0	2	0	0	0	0	0
Pancreas										
Depletion, zymogen, multifocal										
Not Present	25	25	25	25	20	25	25	25	25	25
Minimal	0	0	0	0	4	0	0	0	0	0
Slight	0	0	0	0	1	0	0	0	0	0

NA = Not applicable.
a Vehicle control article.
b Water control.
c Number examined for each tissue unless otherwise noted.

(excerpted from Applicant's submission)

Positive control (MNU)

The positive control group showed statistically significant increases in the incidence of a number of tumors in both males and females ($p<0.05$), as compared to the individual control groups, including malignant M-Lymphoma in the whole body, squamous B-papilloma in skin, and squamous B-papilloma and M-papilloma in stomach. The reported increases in incidence were consistent with those reported in the published literature for MNU treated rasH2 mice. As such, the data provided validity to the test assay.

Table 41: Predominant Microscopic Findings in All MNU Animals

	No. of animals affected	
Gender	**Males**	**Females**
Dose (mg/kg)	75	75
Total No. examined	20	20
Treatment-related Findings:		
Body, whole/cavity		
M- Lymphoma, malignant	7	8
M-Hemangiosarcoma	2	0
Neoplasma (carcinoma, hematopoietic, vascular)	12	12
Papilloma	4	1
Lung		
M-carcinoma, bronchiolo-alveolar	0	1
Stomach, non-glandular (forestomach)		
Papilloma, squamous cell	10	12
Carcinoma, squamous cell	6	1
Thymus		
C-hematopoietic neoplasm	7	8
Lymph Node, mandibular		
C-hematopoietic neoplasm	1	5
Lymph Node, mesenteric		
C-hematopoietic neoplasm	0	4
Lymph Node, other		
C-hematopoietic neoplasm	5	6
Skin/subcutis		
Papilloma, squamous cell	16	8
Carcinoma, squamous cell	1	2

C = Multicentric neoplasm
M = Primary, malignant neoplasm

Table 42: Tumor Rate in Male Mice (Water Vehicle, Vehicle Control vs. Positive Control)

Table 5A: Tumor Rates and P-Values for Comparisons between WC, VC, and PC – Male Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	0 mg/kg/day WC (N=25)	75 mg/kg/day PC (N=20)	P-Value VC vs. WC	P-Value VC vs. PC	P-Value WC vs. PC
Lung	B-Adenoma, bronchiole	1	2	0	0.5000	0 2647	0.4652
	M-Carcinoma, bronchi	2	0	0	0.7551	0.4652	.
Skin/Subcutis	B-Papilloma, squamous	0	0	16	.	<0.001*	<0.001*
	M-Carcinoma, squamous	0	0	1	.	0 2857	0.2857
Stomach, Nongla	B-Papilloma, squamous	0	0	10	.	<0.001*	<0.001*
	M-Carcinoma, squamou	1	0	6	0.5000	0.0035*	<0.001*

*Indicted the significant at 0.05 alpha levels.

Table 43: Tumor Rate in Female Mice (Water Vehicle, Vehicle Control vs. Positive Control)

Table 5B: Tumor Rates and P-Values for Comparisons between WC, VC, and PC – Female Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	0 mg/kg/day W(N=25)	75 mg/kg/day PC (N=20)	P-Value VC vs. WC	P-Value VC vs. PC	P-Value WC vs. PC
Body, Whole/Cav	M-Hemangiosarcoma	2	4	0	0.3540	0 5490	0.7971
	M-Lymphoma, malignant	0	0	8	.	<0.001*	<0 001*
Harderian Gland	B-Adenoma	0	1	0	0.5000	.	0.3235
Kidney	B-Adenoma, tubule cell	0	1	0	0.5000	.	0.3235
	M-Carcinoma, tubule	0	1	0	0.5000	.	0.3235
Lung	B-Adenoma, bronchiole	2	1	0	0.5000	0 5490	0.3235
	M-Carcinoma, bronchi	0	0	1	.	0 3429	0.3429
Mammary Gland,	M-Carcinoma	0	0	1	.	0 3429	0.3429
Ovary	M-Malignant granulos	0	0	1	.	0 3235	0.3235
Skin/Subcutis	B-Papilloma, squamous	0	0	8	.	<0.001*	<0 001*
	M-Carcinoma, squamous	0	0	2	.	0 0980	0.0980
Stomach, Nongla	B-Papilloma, squamous	0	0	12	.	<0.001*	<0 001*
	M-Carcinoma, squamous	0	0	1	.	0 3235	0.3235

*Indicted the significant at 0.05 alpha levels.

**Indicated significant at ≥0.05 alpha levels.*
VC= vehicle control
PC= positive control
(excerpted from FDA statistician's review)

Stability and Dosing Suspension Analysis

Groups 1-5:

- Samples obtained for homogeneity and concentration verification analysis were within the acceptable limits of ±10% error.

- Stability was evaluated under [redacted] (b) (4) Study No. 7359211. Formulations (0.1 and 100 mg/mL) were stable for up to 13 days at 2 to 8°C, and for 30 days at -60 to -80°C.

- The Applicant did perform homogeneity analysis for the middle dose group (1mg/mL).

Group 6:

- The stability of the positive control MNU (Group 6) was confirmed under [redacted] (b) (4) Study No. 8227315 which bracketed conditions of use for this study.

(b) (4)

9. Integrated Summary and Safety Evaluation

For pharmacology and toxicology data to support the current indication of cabozantinib (XL184), advanced RCC, the Applicant cross-referenced cabozantinib NDA # 203756 (Cometriq™, Applicant-owned). Additional studies were submitted under the current NDA to fulfill a post marketing requirement (PMR) for NDA 203756 (26-week mouse carcinogenicity study), to support additional pharmacological activity and to further characterize the pharmacokinetics/toxicity of the major XL184 metabolite, EXEL1644.

Pharmacology:

Cometriq (cabozantinib) capsules is an FDA approved drug since 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer. In the approved label it was stated that cabozantinib is a tyrosine kinase inhibitor with activity at multiple kinases, including, MET, VEGFR2/KDR, VEGFR1, VEGFR3, RET, FLT3, TIE2, AXL, TRKB, and KIT. Dr. Margaret Brower stated in her review of NDA # 203756 (Cometriq™) under study # XL184-Disc-001, that the IC_{50} values for the above kinases were 1.8, 0.035, 12.2, 6.0, 9.8,14.4, 14.3, 7.7, and 4.6nM, respectively. Under the current NDA, the Applicant submitted data for additional kinase receptor targets for XL184 which included MER, TYRO3 (RSE), ROS1, Aurora-B and RON with IC_{50} values of 0.3, 12, 24, 23 and 46 nM, respectively, supporting a new label claim.

Furthermore, in the approved Cometriq (cabozantinib) label it was stated that the tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment. In the proposed label for the advanced RCC indication, the Applicant added that the kinases *are additionally involved in drug resistance*. In support of this statement the Applicant submitted study data (published in a peer reviewed journal) suggesting that MET and VEGF are involved in pathologic processes such as metastasis and tumor invasion which leads to drug resistance. In this submitted study, pancreatic acinar tumor cells xenografted in RIP-Tag2 mice were treated with anti-VEGF antibody. The treatment with an anti-VEGF antibody or kinase inhibitor resulted in reduced tumor burden, but increased tumor hypoxia, HIF-1α, c-Met activation, invasion and metastasis. Administration of an anti-VEGF antibody or kinase inhibitor and PF-04217903 (c-Met inhibitor), concurrently, reduced the invasion and metastasis. Similarly, administration of cabozantinib alone (VEGF and Met inhibitor) resulted in greater tumor inhibition, decreased tumor invasiveness, metastasis and increased survival in comparison to treatment with vehicle or anti-VEGF antibody. These data suggest that while VEGF inhibitors increase the aggressiveness of tumors, as demonstrated by increased invasiveness and/or metastasis, simultaneous inhibition of

VEGF and c-Met signaling may prevent tumor resistance as indicated by decreased invasiveness and metastasis. and that these effects can be blocked by a combined treatment of c-Met and VEGFR inhibitors.

Pharmacology of the major metabolites:
Four major metabolites of XL184 were identified in human plasma of health subjects (EXEL-1644, EXEL-1646, EXEL-5162, and EXEL-5366), which exceeded levels of the same metabolites in plasma samples of nonclinical species in repeat-dose studies up to 6 months in duration. Metabolite EXEL-1644 was not quantifiable in healthy subjects. The EXEL-5162 and EXEL-5366 were not considered to be pharmacologically active. The metabolites were tested for their inhibitory activity in biochemical assay against selected kinases. EXEL-1644 showed less inhibitory activity than EXEL-1646 at a single concentration (1μM). EXEL-1644 caused > 50% inhibition of 2 of 42 kinases tested (MET and RON), while, EXEL-1646 inhibited (>50%) 21 of 42 kinases tested (Abl, Aurora-A and B, AXl, BLK, Kit, FLT1, FLT4, Fms, IGF, Lck, Lyn, Mer, Met, Ret, Ron, Ros, Rse, Tie2, TrkA and TrkB). Furthermore, cabozantinib showed higher potency (IC_{50} ranged between 0.3 to 46 nM) relative to metabolite EXEL-1646 (IC_{50} ranged between 104 to >1000 nM) against targets such as MER, TYRO3 (RSE), ROS1, RON and other selected kinase targets (with exception of Aurora-A).

The pharmacological specificity of EXEL-1644 and EXEL-1646 was assessed against a panel of 75 pharmacological targets, including receptors, transporters and enzymes. No target was reported to have > 50% inhibition at a single concentration of 1 μM. These data suggest that cabozantinib metabolites do not have non-target pharmacologic specificity.

Toxicity of the major metabolite EXEL-1644
Metabolite EXEL1644 was identified and quantified in RCC patient plasma at AUC levels of 35.8% of the total drug-related exposure, which exceeded levels of the same metabolite in plasma samples of nonclinical species. To characterize the toxicity of this major metabolite, the Applicant conducted a GLP complaint 2-week subcutaneous (SC) toxicology study in rats, and a non-GLP 4-week toxicity study in wild type RasH2 mice; Cabozantinib was administered orally and EXEL-1644 by SC route.
A rationale was provided by the Applicant for the use of the SC route, EXEL-1644 has poor oral but good subcutaneous (SC) bioavailability. The Applicant's statement was verified, and this reviewer agrees that the SC route of administration for EXEL1644 provided higher bioavailability.

In the 2-week SC toxicology study in rats, administration of EXEL1644 resulted in no adverse findings at the highest dose tested of 30 mg/kg/day (13.6-fold higher than the AUC of EXEXL1644 at clinical dose of 175 mg/day of cabozantinib). Procedural/vehicle related findings included pathology (non-recoverable) at the injection site skin/dermis.

In the 4-week exploratory toxicity and toxicokinetic study in wild type RasH2 Mice (no-GLP), the parent compound (cabozantinib) was administered by the oral route at 5 mg/kg/day and EXEL-1644 by SC injection at 20 mg/kg/day (5.4-fold higher than the

AUC of EXEX-1644 at 175 mg/day of cabozantinib). Injection site observations (red skin and sores/scabs) and erythema were reported at the end of dosing and recovery phases.
These findings were correlated with microscopic findings at the injection site of foreign material surrounded by mixed cell inflammation. This study did not include a control group for comparison.

The injection site findings reported in both studies, might be attributed to the high dose volume administered (10/5 mL/kg) used in this study and/or the ethanol-containing vehicle.

(b) (4), the Applicant conducted an In Vitro Reverse Mutation Assay in Bacterial Cells (Ames); EXEL-1644 was not found to be mutagenic (Dr. Margaret Brower review NDA# 203756).

Carcinogenicity:
To fulfill a PMR for NDA 203756, the Applicant evaluated the carcinogenicity potential of cabozantinib in a 26-week Tg.rasH2 mouse study. Cabozantinib did not resulted in test article-related increases in the incidence of neoplastic lesions in this model at doses up to 15 mg/kg/day, the highest doses tested (1.2 fold the nominal MRHD of 60 mg/day of Cabozantinib). At 15 mg/kg/day, non-neoplastic microscopic findings were reported in the spleen (lymphocyte depletion), glandular stomach (hyperplasia of the epithelium), duodenum (hyperplasia of the epithelium) and pancreas (zymogen depletion). Test article-related mortalities were reported at 15 mg/kg/day due to general debilitation of the animals. Cabozantinib was not mutagenic or clastogenic.

Pharmacokinetics of the major metabolites:
In rats (XL1644-NC-004), systemic exposure (AUC and C_{max}) following SC repeat-dose administration of the metabolite EXEL-1644 (10 mg/kg) was higher than that following oral repeat-dose administration (XL184-NC-033) of the metabolite at 10 mg/kg ($AUC_{0\text{-last}}$ was 269,000 vs 122 ng.h/mL, respectively). The half-life following the SC was reported to range between 9 to 12 hours, while the half-life following the oral administration was not reported. Similarly, in the non-transgenic RasH2 wild type mice, the systemic exposure (AUC and C_{max}) following the SC repeat dose (20 mg/kg) administration of the metabolite EXEL-1644 was higher than following the oral repeat dose administration (XL184-NC-033) of the metabolite at 10 mg/kg ($AUC_{0\text{-last}}$ was 292,000 vs 152 ng.h/mL, respectively). The half- life following the SC administration ranged between 9 to 12 hours, while the half-life following the oral administration was not reported. These systemic exposure data suggest that the SC route of administration for EXEL1644 will provide better bioavailability than the oral route, supporting the Applicant's justification for use of the SC route to characterize the toxicity profile of the major metabolite EXEL-1644.

The systemic exposure (AUC and C_{max}) levels in mice and rats administered the parent compound (cabozantinib) were significantly higher than the levels reported for the major 4 metabolite, suggesting that the cabozantinib undergoes relatively little metabolic

conversion (0.04 to 5%) in these species. In contrast, cabozantinib undergoes much higher metabolic conversion in humans (i.e. 5% to 36% of total drug exposure in plasma).

Conclusion: major metabolites

Given the intended indication (advance RCC), no additional nonclinical systemic toxicology or carcinogenicity studies are required to characterize metabolite EXEL-1644 under the current NDA, based on ICHS9 guidance recommendations. In addition, pharmacology studies demonstrated that cabozantinib had higher activity in the panel of tyrosine kinase receptors tested compared to its metabolites. As such, the data suggested that the activity and toxicity of the metabolites was covered by the parent drug in the reported toxicity and carcinogenicity studies. Nevertheless, the need for additional studies to support other indications should be determined on a case-by-case basis, taking into account the indication and patient population.

Table 44: Exposure Margins for EXEL-1644

Species	Route	Dose (mg/kg/day)	Dose (mg/m^2)	$AUC_{0\text{-last}}$ (ng.h/mL)	Human $AUC_{0\text{-last}}$ (at clinical oral dose of 175 mg/day)	Ratio (animal AUC/Human AUC)
Rat	oral	10	60	122	42400	0.0029
Rat	SC	30	180	576000	42400	13.6
RasH2 wild type mice	oral	100	300	3390	42400	0.08
RasH2 wild type mice	SC	20	60	231000	42400	5.4

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/s/

EIAS A ZAHALKA
04/15/2016

TODD R PALMBY
04/17/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208692 **Applicant: Exelixis, Inc** **Stamp Date: 12/22/2015**

Drug Name: Cabozantinib (S)-malate **NDA Type: 505(b)(1)**

On **initial** overview of the NDA 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		
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		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	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, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		This reviewer is not aware of any pending impurity issues. We defer to CMC for the identification of impurities that may require qualification. Ultimately, this will be determined during the review.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A		
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	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.

N/A

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

None

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

EIAS A ZAHALKA
01/19/2016

TODD R PALMBY
01/21/2016