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APPLICATION NUMBER:

203756Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 8, 2012
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
NDA/Supplement#	203756/0
Applicant	Exelixis, Inc.
Date of Submission	May 29, 2012
PDUFA Goal Date	November 29, 2012
Proprietary Name / Established (USAN) name	Cometriq™/cabozantinib
Dosage forms / Strength	20 mg, 80 mg capsules
Proposed Indication	For the treatment of progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC).
Recommended:	Approval

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Abbreviations

%CV	inter-subject variability
ACTH	adrenocorticotrophic hormone
AE	adverse event
CEA	carcinoembryonic antigen
CMC	Chemistry, Manufacturing and Controls
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
CTN	calcitonin
DSI	Division of Scientific Investigations
ECOG	Eastern Cooperative Oncology Group

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EOP2	end of phase 2
E-R	exposure-response
GCP	Good Clinical Practices
GTI	genotoxic impurities
IRC	independent review committee
MDASI	MD Anderson Symptom Inventory
MEN 2	Multiple Endocrine Neoplasia 2
MTC	medullary thyroid cancer
MET	mesenchymal epithelial transition factor
ORR	objective response rate
OS	overall survival
PDUFA	Prescription Drug User Fee Act
PIB	powder-in-bottle
PFS	progression-free survival
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PPE	palmer-plantar dysesthesia
PS	Performance Status
RET	glial cell derived neurotrophic factor receptor rearranged during transfection
RTK	receptor tyrosine kinase
RPLS	reversible posterior leukoencephalopathy syndrome
SPA	Special Protocol Assessment
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
VEGFR2	vascular endothelial cell growth factor receptor 2

NDA 203756 Cabozantinib (Cometriq™) Cross Discipline Team Leader Review

1. Introduction

The final clinical component of a rolling application for NDA 203756 was submitted to FDA by Exelixis, Inc. for cabozantinib (XL184/Cometriq™) on May 29, 2012. This submission initiated the Prescription Drug User Fee Act (PDUFA) clock for review purposes.

Cabozantinib is a new molecular entity and small molecule oral multi-targeted inhibitor of receptor tyrosine kinase (RTK). The initial non-clinical component of the NDA was submitted to FDA in December, 2011. The application was submitted for regular approval and a priority review was assigned with a PDUFA goal date of November 29, 2012. The indication sought by the applicant is "... for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC)".

As noted in the clinical review of Dr. Giusti, MTC is diagnosed in approximately 2000 patients in the United States annually and this histology accounts for 5% to 8% of all thyroid cancers. The peak incidence of MTC occurs in the fifth or sixth decade of life and there is a slight female preponderance. The typical presentation is a solitary thyroid nodule; however, the majority of patients have metastatic disease at the time of diagnosis with approximately 50% having clinically detectable cervical lymph node involvement, 15% having symptoms of upper aero-digestive tract compression or invasion (dysphasia or hoarseness) and 5% having symptomatic distant metastatic disease.

Complete surgical resection is the only curative treatment for MTC, and survival is correlated with stage at diagnosis. Median overall survival (OS) is less than 2 years from the time of initial surgical resection in patients with Stage 4 disease. This poor prognosis in patients with MTC is accounted for, in part, by the high proportion of patients diagnosed with late-stage disease. Survival after the discovery of distant metastases, which can involve multiple organs including the lungs, bones, and liver, and more rarely the brain, skin, and breast, is approximately 20% at 10 years. Disease spread to the trachea and esophagus is often fatal.

Currently, there are only two FDA-approved chemotherapeutic agents for MTC, doxorubicin, a cytotoxic, and vandetanib, a small molecule tyrosine kinase inhibitor (TKI). Neither of these drugs has demonstrated, in controlled clinical trials, a survival benefit for patients.

A number of multidisciplinary issues arose during the review of this application. Specific issues to be discussed in greater detail in this review are:

- Incomplete development for the drug's dissolution method
- Genotoxic impurities observed in the drug substance (DS)
- The appropriate pregnancy category for labeling
- The exposure-response relationship, toxicity and treatment dose
- (b) (4)

- A lack of a correlation observed between the statistically significant improvement in progression-free survival (PFS) for patients treated with cabozantinib, and the effect observed for overall survival (OS)
- OS as safety issue

2. Background

IND (b) (4) for XL184 (cabozantinib) was submitted initially in July, 2005. In March of 2008 an end of phase 2 (EOP2) meeting was held with the drug's sponsor during which the trial, XL184-301, submitted to support the current NDA, was discussed. A key agreement made during the meeting involved the proposed progression-free survival (PFS) endpoint. FDA agreed that PFS in MTC is an acceptable endpoint for a trial to support a regulatory filing provided that the magnitude and duration of the effect observed and the benefit: risk ratio were also acceptable. In addition, overall survival (OS) was agreed upon as a secondary endpoint. A Special Protocol Assessment (SPA) agreement was reached for trial XL184-301 in June, 2008. Key points of agreement for the SPA included:

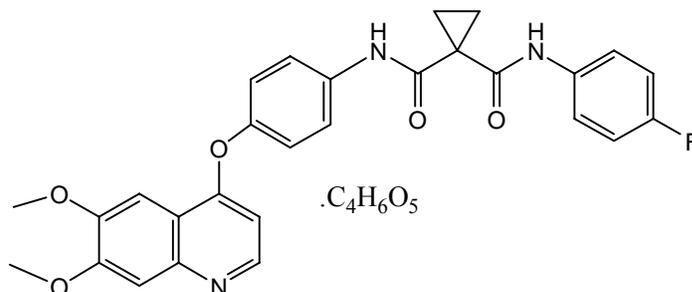
- The number of patients without measurable disease was to be limited.
- Dose modification guidelines were revised to allow no more than two dose reductions.
- Analysis of PFS was to be based on independent review committee (IRC) assessment and to be event driven.
- The MD Anderson Symptom Inventory (MDASI) Thyroid Module (THY) analysis was deemed exploratory (b) (4)

Orphan drug designation was granted for cabozantinib in November, 2010, and a pre-NDA meeting was held in December of the same year during which the format and timelines for the rolling submission were agreed upon. An EOP2 Chemistry, Manufacturing and Controls (CMC) meeting was held in March, 2011, and a Fast Track Designation was granted for the development of cabozantinib for unresectable, locally advanced, or metastatic MTC in April, 2011. Conditional approval of the proposed trade name, Cometriq, was granted in December, 2011. Around the same time, (b) (4)

A pre-IND/pre-NDA meeting was held with the newly assigned review division to discuss the high level results from the supporting trial and the format for the NDA submission.

Cabozantinib primarily targets the proto-oncoproteins glial cell derived neurotrophic factor receptor rearranged during transfection (RET) and mesenchymal epithelial transition factor (MET), and the vascular endothelial cell growth factor receptor 2 (VEGFR2). Additional targets include the tyrosine kinases FLT3, TIE2, AXL, TRKB, and KIT as well as VEGFR1 and VEGFR3. In addition to biochemical inhibition, cabozantinib inhibits *in vitro* proliferation of a variety of tumor cell lines including some with mutations leading to MET over-expression.

The molecular formula of the drug is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$. The figure immediately below, copied from the primary clinical review of Dr. Giusti, represents the chemical structure of this molecule.



Medullary thyroid cancer (MTC) is a neuroendocrine tumor originating from the parafollicular or C cells of the thyroid gland. The C cells originate from the embryonic neural crest and, as a result, MTC has clinical and histologic features in common with other neuroendocrine tumors such as carcinoid and islet-cell tumors. The parafollicular cells secrete calcitonin (CTN) and are distinct from the follicular cells, which synthesize thyroid hormones T3 and T4. As a consequence, these tumors are not responsive to treatment with radioactive iodine. Medullary thyroid cancer progression and recurrent disease are often associated with debilitating diarrhea due to tumor secretion of calcitonin, calcitonin-gene related peptide or other substances, as well as weight loss, fatigue, and bone pain. In some cases, Cushing's syndrome may develop as a result of ectopic adrenocorticotrophic hormone (ACTH) secretion from the tumor. Management of metastatic disease is primarily oriented towards the relief of symptoms. Some tumors secrete carcinoembryonic antigen (CEA), which, like calcitonin, is used as a tumor marker.

Up to 75% of MTC cases occur sporadically, while the remainder occur with an autosomal dominant inheritance pattern as one of three disorders comprising Multiple Endocrine Neoplasia 2 (MEN 2): MEN 2A, MEN 2B, and familial MTC.

- **MEN2A** is associated with MTC, pheochromocytoma, and primary parathyroid hyperplasia. The penetrance of MTC is nearly 100%; however the pattern of the other disease manifestations varies within and between families.
- **Familial MTC (FMTC)** is considered a variant of MEN2A in which there is a strong predisposition to MTC, but not of the other disease manifestations.
- **MEN2B**, like MEN2A, has high penetrance of MTC and pheochromocytoma but this subtype does not include hyperparathyroidism. In MEN2B, MTC occurs at an earlier age and may be more aggressive than in MEN2A. Patients will typically have marfanoid features, mucosal neuromas and intestinal ganglioneuromatosis.

Germ line activating mutations in the gene encoding the RET receptor tyrosine kinase (RTK) have been identified in 98% of individuals with inherited MTC. Activating somatic mutations in RET are also present in tumor tissue of up to 65% of sporadic MTC cases. MET and VEGFR2 are also implicated in the pathogenesis of MTC. The MET RTK has been implicated in multiple pathways promoting tumor progression, metastasis and invasion. Over-expression of the MET RTK and its ligand HGF has been detected in MTC, and transduction of normal

human thyroid cells with a mutant *RET* gene results in upregulation of MET. Vascular endothelial growth factor (VEGF) expression is higher in differentiated and medullary thyroid cancers than in normal or benign thyroid tissue. VEGF stimulates the formation of blood vessels, increases vascular permeability, and is likely involved in progressive disease.

The table below lists the current FDA-approved treatments for MTC.

FDA-Approved Treatments for MTC

Agent	Class	Approval Type	Basis of approval
Doxorubicin	Cytotoxic, monotherapy	Full	RR < 20%; no survival benefit
Vandetanib (CAPRELSA®)	Small Molecule TKI Inhibitor	Full	PFS, RR; no survival benefit

Copied from the clinical review of Ruthann Giusti, M.D.

3. CMC/Device

This section was derived from the primary reviews of William Adams, Ph.D., Li-Shan Hsieh, Ph.D., and Minerva Hughes, Ph.D., Office of New Drug Quality Assessment and Denise Miller, Microbiologist, Office of Pharmaceutical Science

There are no unresolved CMC issues for this NDA and approval is recommended by the CMC review team. I concur with this recommendation. The key issue identified during the conduct of the review relates to the proposed dissolution method for the product for which a discussion follows.

Biopharmaceutics: Cabozantinib is classified as a BCS Class (b) (4) compound. For such compounds, drug dissolution can be rate limiting for absorption. Dr. Hughes' biopharmaceutics review notes that an appropriate dissolution method provides the greatest assurance of product quality for this class of compounds, and the proposed dissolution method was deemed "reasonable" upon initial review. There were a number of issues, however, that the biopharmaceutics reviewer asked the Applicant to address. Specifically, the proposed dissolution method was judged to be incomplete, as was the validation test data; in addition, there was a perception of "testing to pass" for one of the pre-specified acceptance limits for the dissolution validation method. The specific issues (copied from Dr. Hughes' review) conveyed were as follows:

"1. Your dissolution method development summary is incomplete. Provide the following additional information to support your position that the proposed method (USP 2, 0.01N HCl with 0.5% Triton X-100 at 75 rpm) is discriminating and the acceptance criterion ($Q =$ (b) (4) is meaningful for product quality assurance.

a. Rationale for using two different approaches for determining saturation solubility (b) (4).

b. Complete dissolution profile data (individuals, mean, RSD, and plots) for each surfactant type and amount ((b) (4) tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to

surfactant selection; other factors such as micelle structure, excipient interactions, etc., should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.

c. Complete dissolution profile data (individuals, mean, and RSDs) supporting the evaluation and selection of the proposed testing apparatus and paddle speed.

d. A summary of the meaningful process or product variations that could impact in vivo performance for which the proposed method and acceptance criterion are adequate to detect and reject, as per USP <1092>, for optimal quality assurance.

e. A science and data-based justification for the proposed acceptance criterion of $Q = (b) (4)$ when your dissolution data could support a criterion of $Q = (b) (4)$ at 15 minutes using the proposed method. Include in your response descriptive statistics (mean, min, max, RSDs) for pooled dissolution data from the bio-batches and primary registration stability batches at 15 and 30 minutes by dosage strength and testing time (T0, 3, 6 months, etc.), and an estimation of the dissolution pass rate for lots at stage 1, stage 2, and stage 3 applying your proposed acceptance criterion as well as a criterion of $Q = (b) (4)$ at 15 minutes.

2. Dissolution method validation studies should address the variation associated with different profile time points. As per your protocol, QM4334.01, dissolution profile sampling is performed at 15, 30, 45, and 60 minutes. In addition, your proposed sampling specification time point is $(b) (4)$. Thus, the robustness and intermediate precision attributes of the method should address performance at the 15 and 30 minute sampling time points. Provide the validation test data on the variation associated with the 15 and 30 minute sampling time points.

3. It is noted in the dissolution method validation report, KCM-2011-0543-ANA, that the mean percent recovery for the low concentration accuracy standard was below the pre-specified 97% acceptance limit for one analyst. It appears that re-sampling was performed two additional times until one of the three samples prepared met the 97% passing threshold. The perception of “testing to pass” is concerning. Provide a copy of the investigation report INV2009-0060-L and your scientific rationale why the method should be considered valid for its intended use, despite the findings.

4. Provide copies of the HPLC chromatograms supporting your conclusions on the specificity of the dissolution test method, as noted in validation report KCM-2011-0543-ANA.”

The Applicant responded to the issues raised by FDA in an NDA amendment dated August 1, 2012; however, the initial response was inadequate. Further information from the Applicant was sought in an FDA Information Request letter dated August 30, 2012. Based on additional data submitted in two separate responses, Dr. Hughes’ judged the proposed dissolution method and acceptance criterion to be adequate and recommended approval for this NDA.

Drug Substance: Cabozantinib (S)-malate

$(b) (4)$
 $(b) (4)$ Structure elucidation studies were submitted and, according to the CMC reviewer, were sufficient to have established the molecular structure. $(b) (4)$

The release specification includes testing for appearance, identity, assay/ordinary impurities, (b) (4) four known genotoxic impurities (GTI), water content, residual solvents, inorganic impurities, (b) (4), heavy metals and particle size distribution. Each method is described in sufficient detail in the submission, validated for its intended use and confirmed by the CMC reviewers. Methods for impurities are deemed sensitive to appropriate levels. The criteria are justified by batch analysis data and non-clinical studies. Reference standards have been established for drug substance and potential impurities.

Stability information submitted includes forced degradation, heat stress, light stress and long term studies. These studies indicate sensitivity to acid hydrolysis (formation of ordinary impurities) and high heat (formation of GTIs). The proposed post approval stability protocol and commitment are acceptable to the CMC reviewer. The results from the long term studies on commercial lots stored at ICH conditions are deemed sufficient to support storage of bulk drug substance at (b) (4) with a retest period of (b) (4).

Drug Product: Cometriq (cabozantinib) capsules contain drug equivalent to 20 mg or 80 mg freebase and inactive ingredients including silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid.

The drug product is described by the CMC reviewer as being manufactured by (b) (4). The CMC reviewer also regards the manufacturing procedure and process controls submitted to have been described in sufficient detail. The cabozantinib 20-mg capsule is a gray, opaque, (b) (4), two-piece hard gelatin capsule imprinted with “XL184 20 mg” on the capsule body. Capsule fill contains a (b) (4). The cabozantinib 80-mg capsule is a Swedish orange, opaque, (b) (4) two-piece hard gelatin capsule imprinted with “XL184 80 mg” on the capsule body. Capsule fill contains a (b) (4). Capsule shell and imprinting ink components are described in sufficient detail.

Cometriq capsules will be marketed as a blister card or a high density polyethylene bottle with child resistant closure. For the blister cards, each row of capsules represents a daily dose of 60 mg, 100 mg or 140 mg and each card provides a 7-day drug supply. Four cards are packaged into a carton to provide a 28-day supply. The bottle contains sixty 20 mg capsules as a 28-day drug supply.

The quality of Cometriq capsules was assessed by the CMC reviewer based on its manufacturing process and process controls; the analytical procedures for identification, purity, strength, and sterility; and stability. Based on the submitted stability data, a 24 months expiry period was granted by FDA with storage at controlled room temperature.

Microbiology: Cometriq is a non-sterile, solid, oral product. The formulated powder is filled into capsules and packaged into blister packages or child resistant bottles. There were no microbiology deficiencies noted in the NDA submission and approval was recommended by the product quality microbiology reviewer.

Facilities inspection: All facilities inspections have been completed and are deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

This section was derived from the primary review of Margaret Brower, Ph.D., and the secondary review of Whitney S. Helms, Ph.D., Division of Hematology and Oncology Toxicology

All review issues identified by the nonclinical team during the review of this NDA have been resolved and the application is recommended for approval. The review team has also recommended postmarketing requirements for studying the carcinogenicity of cabozantinib in two species (i.e. rat and mouse), for further assessment of the effects of cabozantinib on reproductive toxicology in a pre-and post-natal study, and for conducting a bacterial reverse mutation assay for the M4 metabolite. I concur with these recommendations.

The key issue identified during the nonclinical review relates to 4 process impurities identified that were determined to be mutagenic in the bacterial reverse mutation (Ames) assay: (b) (4)

(b) (4)
Over the course of drug development, the presence of these genotoxic impurities was identified at unacceptable levels. To address this finding, a number of changes were made to the manufacturing process. The changes included revisions of the analytical methods used to detect impurities. These changes led to uncertainty on the part of the nonclinical review team regarding comparative levels of the genotoxic impurities present in previous batches and the final requested specifications for the genotoxic impurities. In a teleconference between the review team and the Applicant held late in the review process, the Applicant confirmed that the final requested specifications for (b) (4) in the drug substance are (b) (4), respectively. It was noted thereafter by the review team that the requested specifications for the drug product are higher at (b) (4) for (b) (4) respectively. At the highest proposed specifications the maximum daily levels of the impurities delivered as a result of administration of the cabozantinib drug product at the recommended daily dose of 140 mg are (b) (4) µg, respectively with a total exposure to all genotoxic impurities of (b) (4) µg. In the opinion of the review team, although these impurities exceed the theoretical threshold of toxicological concern of 1.5 µg/day for individual genotoxic impurities, this threshold is based on a lifetime risk of carcinogenic potential for a compound. As discussed in ICH S9 guidance, this does not adequately reflect the risk/benefit consideration for a patient population with advanced cancer. As a result, the proposed specifications are deemed acceptable from a safety standpoint by the nonclinical review team.

Also notable during the nonclinical review were the identification of 4 major metabolites of cabozantinib present at levels $\geq 10\%$ of total exposure of the parent drug. Three of these, M1, M4, and M8, had greater exposure in humans compared to animals. The M1 and M8 metabolites were examined to assess their contribution to the activity of cabozantinib. Neither metabolite had significant activity in biochemical inhibition studies. The M1 metabolite was also negative in a bacterial reverse mutation assay. As the tested metabolites had no significant

pharmacologic activity *in vitro*, no further testing was conducted. The third metabolite, M4, showed the biggest difference between animal and human exposure with levels in humans of up to 43% of the total cabozantinib exposure while the highest exposure in animals was only up to 7%. Because this metabolite was present at high levels in humans, the Applicant will conduct, as a postmarketing requirement, an *in vitro* mutagenicity assay with M4, as noted previously.

A single non-genotoxic impurity was identified during the course of the primary review as being above the level for qualification. Based on Dr. Helms secondary review, the specification for this impurity is (b) (4) and it was qualified in the 6-month long dog study.

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

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

In an effort to identify a recommendation for the Pregnancy category for this molecule, dedicated studies to examine the effects of cabozantinib on fertility and embryofetal development were reviewed. Overall, the reproductive toxicity findings suggest that male and female fertility can be impaired by treatment with cabozantinib and that there is a significant risk of loss of pregnancy or teratogenic effects in a fetus following exposure to cabozantinib. (For a complete discussion of the findings, please refer to the primary review of Dr. Brower.)

The Pregnancy Category proposed by the Applicant for this drug is (b) (4) however, based on their interpretation of the animal study findings, Pregnancy Category D is recommended by the nonclinical review team. I also concur with this recommendation.

5. Clinical Pharmacology/Biopharmaceutics

This section was derived from the primary reviews of Jun Yang, Ph.D., Kevin Krudys, Ph.D., and Nitin Mehrotra, Ph.D., Division of Clinical Pharmacology V and Division of Pharmacometrics

It is the recommendation of the primary review team that the application be approved once a mutually satisfactory agreement is reached regarding labeling language and postmarketing requirements. I concur with this recommendation.

The primary issue raised by the clinical pharmacology and biopharmaceutics review team relates to the exposure-response relationship and the toxicities observed for this drug. In the registration trial, 86.4% of patients treated with cabozantinib at the recommended dose of 140 mg experienced at least one dose modification due to adverse events (AEs) during the conduct of the trial. This made the results of the exposure-response (E-R) analyses difficult for the reviewers to interpret. To account for different exposure levels as a result of dose modification, the reviewers performed Kaplan-Meier analyses of PFS stratified by quartiles based on the average exposure. The results of these analyses suggested that lower exposure may not reduce PFS.

Patients required dose reduction as early as 2 days after the start of treatment and as late as 554 days, with median reduction within 29 days. The Kaplan-Meier analyses for PFS and time to the first dose modification indicate that early dose modification for toxicity did not reduce efficacy. Further analyses by the reviewers also indicated that patients with higher exposures required dose modification earlier than patients with lower exposures. A Cox proportional hazard model identified AUC_{SS} as the only significant covariate for prediction of time to the first dose modification (hazard ratio [HR]=1.95; 95% CI [1.47-2.59]) with age, sex, body size, smoking status, ECOG status, and race not identified as significant covariates. Based on these observations and analyses, the review team has concluded that the E-R relationships observed for efficacy and safety suggest that a lower dose of cabozantinib could be effective and result in an improvement in tolerability.

The clinical pharmacology review team has recommended that the label include a starting dose of 100 mg with a provision to increase the dose to 140 mg or decreased to a dose of 60 mg as tolerated. As an alternative approach, the review team has recommended that a clinical trial be conducted as a PMR to identify a lower equally effective and better tolerated cabozantinib dose for patients with MTC. I concur with the review team that the optimal dose of cabozantinib for this patient population was not identified during the drug's development. While labeling a lower dose of 100 mg makes sense based on the team's observations and analyses of the trial data, a prospective, appropriately designed, clinical trial may be able to answer the question of optimal dose with greater accuracy. As of this review, a multidisciplinary team is engaged in designing a trial, which will be a postmarketing requirement, to answer this question.

General clinical pharmacology/biopharmaceutics considerations: The half-life of cabozantinib at steady state is approximately 55 hours, the oral volume of distribution is approximately 349 L, and the clearance (CL/F) at steady-state was estimated to be 4.4 L/hr. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in an approximately 4- to 5-fold accumulation of AUC compared to a single dose administration with the ratio of minimum to maximum plasma concentration (C_{min} to C_{max}) of 0.64. Inter-subject variability (%CV) in exposure for cabozantinib following single dose administration in healthy subjects was 38-61% for C_{max} and 27-55% for AUC, and in cancer patients after repeat-dosing was 37-43% for C_{max} and 38-43% for AUC. Single dose intra-subject variability estimate (%CV) in healthy subjects was 34% for C_{max} and 25% for AUC.

Dose proportionality of the cabozantinib capsules has not been evaluated. The cabozantinib exposure (AUC and C_{max}) were increased approximately dose proportional after 5 daily oral doses of a powder-in-bottle (PIB) formulation (range: 4.8 mg/day – 1,382 mg/day). A cross-study comparison for the capsule formulation identified that a single 80 mg dose yielded comparable dose-normalized AUC₀₋₂₄ and C_{max} values with the dose of 140 mg, suggesting that cabozantinib exposure increases approximately in proportion to dose over the dose range of 80 to 140 mg for capsules administered as a single dose.

Absorption and Distribution: PK parameters for cabozantinib were comparable in cancer patients and healthy subjects following a single oral dose. The median T_{max} was approximately 2-4 hours in cancer patients and 4-5 hours in healthy subjects. The plasma PK profile of cabozantinib following a single oral dose in healthy subjects is characterized by a terminal phase half-life of approximately 120 hours with multiple peaks suggesting that cabozantinib is either enterohepatically recirculated or absorbed at different rates or both. Absolute oral bioavailability of cabozantinib in capsule form has not been determined. Mean AUC_{0-inf} values for cabozantinib from healthy subject studies using capsules were 74 to 93% of the corresponding value in the mass balance study where cabozantinib was administered as a solution.

When cabozantinib was administered with a high-fat, high calorie meal in healthy subjects, the C_{max} and AUC values were increased by 41% and 57%, respectively. Cabozantinib is highly protein bound ($\geq 99.7\%$) *in vitro* in human plasma.

Metabolism and Elimination: Cabozantinib is a noncompetitive inhibitor of CYP2C8, a mixed-type inhibitor of both CYP2C9 and CYP2C19, and a weak competitive inhibitor of CYP3A4 in human liver microsomal preparations. Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations, but is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib is a CYP3A4 substrate. Administration of a strong CYP3A4 inhibitor, ketoconazole to healthy subjects increased single-dose plasma cabozantinib exposure by 38%. Administration of a strong CYP3A4 inducer, rifampin to healthy subjects decreased single-dose plasma cabozantinib exposure by 77%. Cabozantinib at steady-state plasma concentrations has no effect on single-dose plasma exposure of rosiglitazone, a CYP2C8 substrate in patients with solid tumors. Cabozantinib is an inhibitor, but not a substrate, of P-

gp transport activities. Evaluation of cabozantinib to breast cancer resistance protein has not been conducted. Following a single oral dose of cabozantinib 140 mg in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Specific Populations: No formal PK studies have been conducted in patients with hepatic or renal impairment, or in pediatric patient populations. Results of a population PK analyses suggest that clearances of cabozantinib in patients with mild or moderate renal impairment are comparable to that of a normal patient population. No correlation was identified between creatinine clearance and cabozantinib clearance. A total of 27% of administered radioactivity was recovered from human urine. No dose adjustment is necessary for patients with renal impairment. A dedicated study using the Child- Pugh criteria evaluating hepatic impairment on PK of cabozantinib is ongoing and will be requested by the clinical pharmacology review team as a PMR.

A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between whites (89%) and non-whites (11%). In addition, cabozantinib PK was not affected by age (20-86 years).

QT Assessment: The effect of orally administered cabozantinib 140 mg on QTc interval was evaluated in the randomized, double-blinded, placebo-controlled study in patients with MTC submitted as the supporting study for this application. Cabozantinib treatment resulted in an increase in QTcF of 10-15 ms over baseline levels within the first 4 weeks of treatment. A pharmacokinetic/pharmacodynamic analysis demonstrated a concentration-dependent QTc interval prolongation. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects had a QTcF >500 ms.

6. Clinical Microbiology

Not applicable to this application.

7. Clinical/Statistical- Efficacy

This section was derived from the primary reviews of Yuan-Li Shen, Ph.D., Office of Biometrics V and Ruthann Giusti, M.D., Division of Oncology Products 2.

Both Drs. Shen and Giusti have concluded that the data submitted in support of this application demonstrated a statistically significant and clinically meaningful 7.2 month improvement in progression-free survival (PFS) for patients who received cabozantinib [median PFS (months)/95% CI: Cabozantinib - 11.2 months/8.4, 13.7 vs. Placebo: 4.0/3.0, 5.4; HR: 0.28, 95% CI=0.19, 0.40; p <0.0001]. The favorable results from the cabozantinib arm were also deemed robust based on various sensitivity analyses performed by each reviewer and the results were consistent across subgroups, including RET mutation status. The increase in objective response rate (ORR) was also statistically significant in favor of the cabozantinib arm (ORR cabozantinib: 27% vs. placebo: 0%) with an observed response duration of 14.7 months (11.1, 19.3). However, based on the 44% overall survival (OS) events submitted with the application, no difference in OS was observed (HR=0.997, 95%=0.64, 1.54). Of note as well, the analysis of PFS by dose intensity suggests that a dose lower than that proposed may

be equally efficacious. Based on these findings, as well as the additional data analyses to be discussed below, it is recommended that this application be approved.

The data submitted to support this application are the results from a single international, randomized, double-blind trial, XL184-301, which was conducted under a Special Protocol Assessment (SPA). Patients enrolled in the trial had unresectable, locally advanced, or metastatic medullary thyroid cancer. The primary objective of the trial was to evaluate progression-free survival (PFS) as assessed by an independent review committee for patients treated with cabozantinib (XL184) as compared to those treated with placebo. The key secondary objectives were to evaluate OS and ORR. The first patient was enrolled on September 10, 2008 and the study was on-going at the time of this submission. There were 98 principal investigators who enrolled patients at 90 sites in 23 countries in Europe, North America, Middle East, South America, and Asia.

A total of 330 patients with advanced unresectable or metastatic MTC were randomized (2:1) to receive either oral cabozantinib 175 mg (138 mg freebase equivalent weight or 140 mg based on available capsules) or matching placebo (in addition to best supportive care) administered daily in 4-week cycles. Patients were stratified by age and by prior tyrosine kinase inhibitor (TKI) use and had a histologically confirmed diagnosis of MTC. The treatment and control arms were comparable with respect to age, sex, race, baseline weight, baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and region of study accrual as demonstrated in the table below, which was copied from Dr. Giusti's review.

XL184 – 301: Demographic Characteristics, ITT study population¹

	Cabozantinib (N=219)		Placebo (N=111)	
	n	%	n	%
Age (years)				
Mean (SD)	55	(13.3)	54	(13.4)
Med (min, max)	55	(20, 86)	55	(21, 79)
> 65 years, n (%)	47	(22)	25	(23)
Sex - Male, n (%)	151	(69)	70	(63)
Race - White, n (%)	196	(89)	99	(89)
Weight (kg)				
Mean (SD)	72	(17.9)	73	(19.7)
Median (min, max)	71	(30, 138)	73	(41, 136)
Region – n (%)				
Europe	124	(57)	60	(54)
North America	69	(32)	33	(30)
Rest of World	26	(12)	18	(16)
ECOG PS				
0	123	(56)	56	(50)
1	86	(39)	44	(40)
2	9	(4)	11	(10)

¹Based on June 15, 2011 data cutoff date.

Patients treated were also comparable with respect to most baseline tumor characteristics and prior therapy for the treatment of metastatic MTC, including the number of patients with prior treatment with a TKI. This is noted in the table below copied from Dr. Giusti's review. Also notable are the median time since initial diagnosis and time since diagnosis of metastatic disease were less in patients randomized to the cabozantinib arm versus the control arm.

XL184 – 301: baseline tumor Characteristics and prior therapy for MTC, ITT study population

	Cabozantinib (N=219)		Placebo (N=111)	
	n	%	n	%
Measurable Disease, n (%)				
Per IRC/mRECIST	208	(95)	104	(94)
Baseline SLD (IRC) (mm)				
Mean (SD)	104	(68)	116	(74)
Median (min/max)	89	(11, 330)	106	(11,420)
25 th , 75 th Percentile	12, 147		63, 148	
Years since initial diagnosis of MTC - N	219		111	
Mean (SD)	5.9	(6.4)	7.3	(7.9)
Median (min,max)	3.4	(0.1, 33.7)	7.4	(0.2, 48.4)
25%, 75%	1.5, 7.6		1.7, 10.1	
Years since diagnosis of mMTC – N	218		110	
Mean (SD)	3.6	(4.7)	4.6	(5.9)
Median (min,max)	1.9	(0.1, 33.7)	2.0	(0.04, 29.2)
(25%, 75%)	0.8, 4.7		0.9, 5.9	
AJCC Stage at enrollment – n (%)				
III	0	0	1	(<1)
IVa	4	(2)	1	(<1)
IVb	2	(<1)	1	(<1)
IVc	210	(96)	105	(95)
Unknown	3	(1)	3	(3)
Extent of metastatic disease at enrollment – n (%)				
Bone	112	(51)	56	(51)
Lymph nodes	175	(80)	86	(78)
Liver	152	(69)	67	(60)
Brain	5	(2)	2	(2)
Lung	116	(53)	64	(58)
Other	24	(11)	20	(18)
Prior thyroidectomy	201	(92)	104	(94)
Prior radiation n (%)	110	(50)	52	(47)
Number of prior regimens for mMTC				
0	128	(58)	62	(56)
1	36	(16)	18	(16)
≤ 2	55	(25)	31	(28)

XL184 – 301: baseline tumor Characteristics and prior therapy for MTC, ITT study population

	Cabozantinib (N=219)		Placebo (N=111)	
	n	%	n	%
Prior TKI, n (%)	44	(20)	24	(22)

While screening for *RET* mutation status was not a requirement for enrollment in the trial, patients were tested retrospectively. Of the 330 patients enrolled in the trial, at least partial *RET* sequence data from one or both sample types (blood and tissue) were obtained for 319 patients. The numbers of patients classed as *RET* mutation and *RET* 918T mutation positive and negative and the number categorized as sporadic and hereditary MTC were comparable in both study arms. However, a substantial number of patients failed to meet the criteria for classification as *RET* mutation, *RET* 918T mutation or MTC hereditary disease negative and were classed as unknown.

After screening, tumors were assessed by MRI or CT scans of the neck, chest, and abdomen every 12 weeks from randomization until progressive disease based on modified RECIST. Bone lesions detected at baseline were followed on study by CT, X-rays or MRI. Responses were confirmed with a follow-up tumor assessment at least 4 weeks after the criteria for the initial response were first met. The same assessment method was used to assess a lesion at baseline and after randomization. Blood and tissue samples for pharmacodynamic analysis, blood samples for PK assessments, and patient-reported outcome assessments were also collected at protocol-defined visits.

Of the 330 patients randomized, 219 were assigned to the treatment arm and 111 to the placebo arm. As of the June 15, 2011 data cut off date, 98 (45%) patients on the cabozantinib arm and 15 (14%) patients on the placebo arm remained on treatment. On the cabozantinib arm, 26% of patients had progressed compared to 60% of patients on the placebo arm. Among patients who had discontinued treatment, 5% of patients on both study arms had died, 6% of patients on the treatment arm and 8% of patients on the placebo arm had discontinued treatment due to a serious adverse event unrelated to disease progression, and 4% of patients on the cabozantinib arm and 12% on the placebo arm discontinued at subject request not related to an AE.

The primary study endpoint for XL184-301 was progression-free survival (PFS) defined as the time from randomization to the earlier of the following events:

- Documented disease progression (IRC determined per mRECIST)
- Death due to any cause.

The statistical analysis method for PFS was based on the stratified log rank test at a 2-sided 0.05 α level using the stratification factors documented. This was based on an April 6, 2011 data cut-off date. At the time of the primary PFS analysis, 36% of the PFS events had occurred on the cabozantinib arm and 54% PFS events had occurred on the placebo arm. The

median PFS was 7.2 months longer for cabozantinib than for placebo treated patients (11.2 months vs. 4 months, respectively). The p-value for the estimated Hazard ratio for the PFS difference was highly statistically significant ($p < 0.0001$). The estimated hazard ratio for PFS was 0.28 (95% CI=0.19, 0.40) in favor of the cabozantinib arm.

A number of sensitivity analyses were also performed by the reviewers to assess the robustness of the primary analyses. These analyses demonstrated consistent improvement in median PFS in favor of the treatment arm with a between arm difference in PFS ranging from 6.1 to 10.8 months and confirmed the results of the primary analysis. A summary of the primary endpoint analyses and the Kaplan-Meier estimates are below in tables copied from Dr. Shen's review.

Summary of Progression Free Survival (based on the 139th event; 4/6/2011 cutoff date)	XL184 N=219	Placebo N=111
Number (%) of Subjects		
Censored	140 (63.9)	51 (46.0)
Event	79 (36.1)	60 (54.1)
Death	21 (9.6)	10 (9.0)
Progressive disease	58 (26.5)	50 (45.0)
Duration of progression free survival (mon.)		
Median (95% CI) a	11.2 (8.4,13.7)	4.0 (3.0, 5.4)
Range	0.0+ - 22.1	0.0+ - 16.7
p-value (stratified log-rank test)b	<0.0001	
Hazard ratio (95% CI; stratified)c	0.28(0.19, 0.40)	

Note: 139 events occurred by the date of the 138th event.

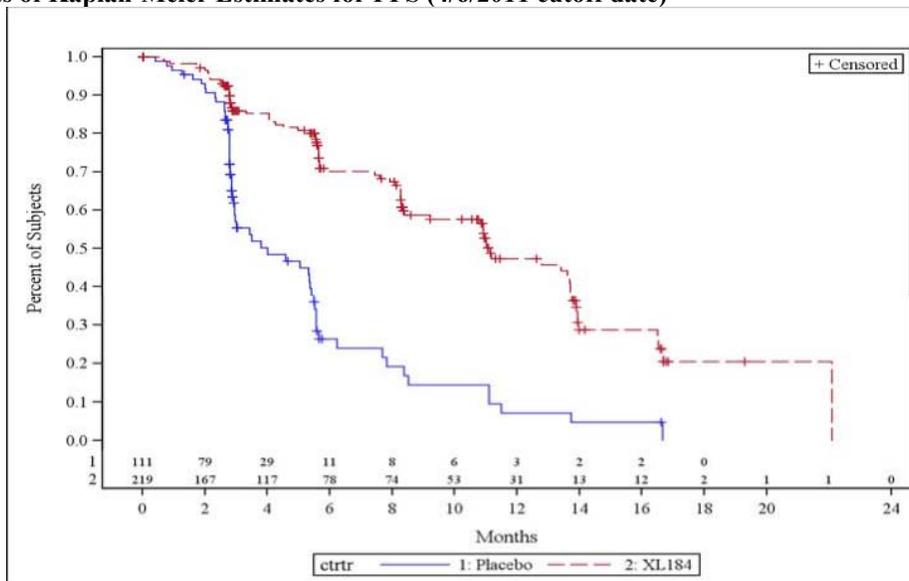
+ indicates a censored observation; CI=confidence interval; IRC=Independent Radiology Review Committee.

a Median and percentiles are based on Kaplan-Meier survival estimates.

b Stratification factors include age at randomization (≤ 65 , >65) and prior tyrosine kinase inhibitor status (yes, no).

c Estimated using the Cox proportional hazard model adjusted for stratification factors.

Plots of Kaplan-Meier Estimates for PFS (4/6/2011 cutoff date)



Since the result of the primary analysis of PFS was significant, the two key secondary endpoints, OS and ORR were tested in parallel using a 2-sided significance level of 0.01 and 0.04, respectively.

OS was defined as the time from randomization to death due to any cause. OS was censored at the last date the patient was known to be alive, if a patient was alive at the cut-off date or was lost to follow-up. ORR was based on the assessment of an independent radiology review (IRR) and was defined as the proportion of patients with measurable disease at baseline who had the best overall response (BOR) of CR or PR at the time of data cut-off which was confirmed by a subsequent visit ≥ 28 days later. If multiple assessments were performed and an overall response of CR or PR was observed, the latest assessment date within the set was chosen as the response date.

There were 96 deaths (at an information level of 44%) at the data cutoff date (6/15/2011) for the PFS analysis. The median follow-up time for the intent-to-treat population was 8.4 and 7.8 months for the cabozantinib and placebo arm respectively. At the cutoff date, the hazard ratio was close to 1 (HR=0.997, 95% CI=0.64, 1.54) which indicates that the overall survival times were similar between treatment arms. The median survival time was 21 months (95% CI=16.6, 28.5) for the cabozantinib arm while the median survival time for the placebo arm had not yet been reached. Based on the Lan-DeMets O'Brien-Fleming alpha spending function, the significance level for the interim analysis for OS was 0.0009. The OS result did not cross the boundary for claiming an overall survival benefit.

Because of safety concerns detailed later in this review, and to assess the potential for a negative impact on OS related to treatment with cabozantinib, FDA instructed Exelixis to conduct an administrative (unplanned) analysis of OS at the time of the 120-day safety update (June 15, 2012 data cutoff date).

Based on the 120-day updated data (66 additional deaths; 75% of OS events), the hazard ratio estimate for OS remained insignificant and without suggestion of a trend towards a decrement in OS for patients treated with cabozantinib.

Summary of Overall Survival (based on 6/15/2011 cutoff date)	XL184 N=219	Placebo N=111
Number (%) of Subjects		
Censored	153 (69.9)	81 (73.0)
Death	66 (30.1)	30 (27.0)
Duration of overall survival (months)		
Median (95% CI) ^a	21.1 (16.59, 28.52)	NA (14 32, NA)
Min- Max	0.0+ - 29.5+	0.1+ - 32.1+
p-value (stratified log-rank test) ^b	0.989	
Hazard ratio (95% CI; stratified) ^c	0.997 (0.644, 1.542)	

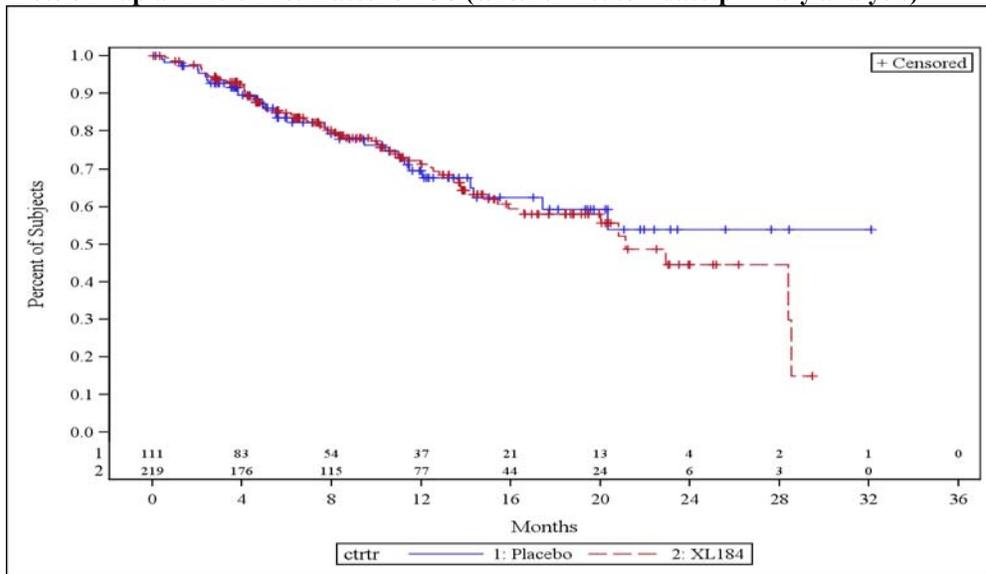
+ indicates a censored observation; CI=confidence interval;

a Median and percentiles are based on Kaplan-Meier survival estimates.

b Stratification factors include age at randomization (≤ 65 , >65) and prior tyrosine kinase inhibitor status (yes, no).

c Estimated using the Cox proportional hazard model adjusted for stratification factors.

Plots of Kaplan-Meier Estimates for OS (6/15/2011 cutoff date-primary analysis)

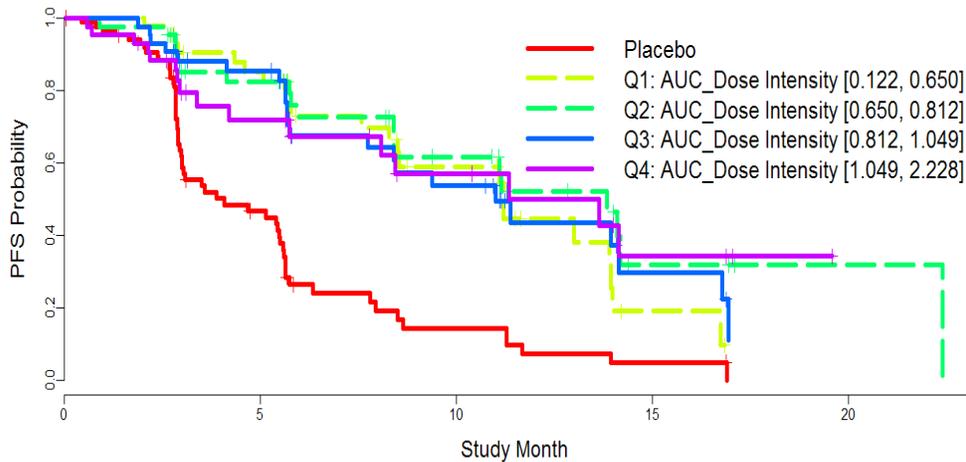


The number of patients assessed by the IRR to have progressive disease was higher in the placebo arm (32%) than in the cabozantinib arm (8%). The ORR in the cabozantinib arm was 27%. The median duration of response was 14.7 months in the treatment arm. No objective responses were observed in the placebo arm.

The mean dose intensity, defined as the per-cent of the total planned dose, was only 70% and 86 % of patients enrolled in XL184-301 required a dose reduction or delay with 79% of patients requiring at least a 1-level dose reduction and 41% of patients requiring 2 dose-level

reductions. Patients requiring more than 2 dose-level reductions were removed from the study. As described by Dr. Yang in his Clinical Pharmacology Review, there did not appear to be a significant trend in PFS with increasing dose-intensity. See table below, copied from Dr. Yang's review.

XL184-301: PFS by Dose Intensity Level



AUC Dose Intensity, $\text{mg} \cdot \text{day/L} = \text{Dose intensity} \times \text{AUC}_{\text{ss}} = \text{Dose intensity} \times 140 \text{ mg/Individual CL}$
Dose intensity = accumulated actual dose/total planned dose

In summary, based on the results of study XL184-301, there was a statistically significant improvement in progression free survival for cabozantinib-treated patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer. The results are robust based on sensitivity analyses performed by the primary reviewers and they are consistent across many subgroups, including RET mutation status. The result for the objective response rate also demonstrated beneficial effect in favor of cabozantinib. The overall survival result does not demonstrate a treatment benefit for cabozantinib-treated patients based on 44% or 75% information levels; however the updated 75% results suggest a positive trend in favor of cabozantinib.

8. Safety

This section was derived from the primary review of Ruthann Giusti, M.D., Division of Oncology Products 2.

The safety review for this application supports the recommendation for approval made by Dr. Giusti, with which I concur.

The safety database for this application consists of 295 patients with MTC, non-MTC and glioblastoma who received at least one dose of cabozantinib in phase 1, 2 and 3 trials. While this database is limited, it is satisfactory for identification of the major safety issues associated with this drug given the rare disease indication sought by this application.

Patients enrolled in the single trial submitted to support this application were randomized (2:1) to receive 140 mg cabozantinib (n=214) or a matched placebo capsule (n=109) orally each day until intolerable toxicity despite dose delay and/or dose reduction or disease progression as assessed by an independent radiology review committee. The mean duration of treatment was 230 days (standard deviation: 180) for patients on the cabozantinib arm and 140 days (standard deviation: 122) for patients on the placebo arm. The relative dose intensity was 63% (SD: 18.9) compared to 83% (SD: 16.7) in the placebo arm. As noted in the clinical pharmacology primary review, 84% of cabozantinib-treated patients required at least one decrease in the cabozantinib dose due to toxicity and 41% required two dose reductions. The main adverse events leading to dose reductions were palmar-plantar erythrodysesthesia syndrome, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

The incidence of deaths reported within 30 days of study drug administration was balanced between the treatment arms; however, NCI CTCAE Grade 3-4 adverse events, serious adverse events, and adverse events leading to study discontinuation were twice as frequent in the cabozantinib arm as in the placebo arm. The most common adverse events included diarrhea (64%), stomatitis (51%), palmar-plantar dysesthesia (PPE) syndrome (50%), weight decrease (49%), decreased appetite (46%), nausea (44%) and musculoskeletal and connective tissue pain (43%). The most common Grade 3-4 adverse events included diarrhea (16%), PPE syndrome (13%), fatigue (9%), and hypertension (8%).

Toxicities associated with VEGF inhibition were also observed in patients treated with cabozantinib, including hypertension (33%) hemorrhage (25%), venous and arterial thrombosis (6% and 2%), GI and non-GI fistulas and GI perforations (8%), proteinuria (2%), wound complications (2%), osteonecrosis (1%) and reversible posterior leukoencephalopathy syndrome [RPLS] (<1%). Fatal events of hemorrhage, gastrointestinal and non-GI fistula were observed.

Cabozantinib did not appear to be associated with clinically significant Torsades de Pointes or drug-induced liver disease.

The table below, copied from Dr. Giusti's review, summarizes the adverse event profile observed in the randomized trial, XL184-301.

XL184-301 ADVERSE EVENTS				
NUMBER OF PATIENTS WITH:	CABOZANTINIB N =214 N (%)		PLACEBO N =109 N (%)	
Any Adverse Event	214	(100)	103	(95)
Any Grade 3 or 4 Adverse Event	163	(76)	41	(38)
Any Serious Adverse Event	90	(42)	25	(23)
Any Adverse Event leading to study discontinuation	33	(15)	9	(8)
AE Leading to Deaths	65	(30)	30	(28)

XL184-301 ADVERSE EVENTS				
NUMBER OF PATIENTS WITH:	CABOZANTINIB		PLACEBO	
	N =214	N (%)	N =109	N (%)
Deaths within 30 days of last study drug	43	(20)	22	(20)
Deaths within 30 days due to causes other than PD	22	(10)	8	(7)

The following table, copied from Dr. Giusti’s review summarizes serious adverse events observed in the randomized trial, XL184-301.

XL184-301: PERCENT OF SERIOUS ADVERSE EVENTS (SAE) OCCURRING IN ≥ 1% OF CABOZANTINIB-TREATED PATIENTS BY MEDDRA SYSTEM ORGAN CLASS (SOC) AND PRIMARY TERM (PT)				
	CABOZANTINIB		PLACEBO	
	N =214	N (%)	N =109	N (%)
NUMBER OF PATIENTS WITH AT LEAST ONE SAE	90	(42)	25	(23)
GASTROINTESTINAL DISORDERS	30	(14)	4	(4)
DYSPHAGIA	5	(2)	2	(2)
VOMITING	4	(2)	1	(1)
DIARRHEA	3	(1)	1	(1)
ABDOMINAL PAIN	3	(1)	0	0
PANCREATITIS	3	(1)	0	0
INFECTIONS AND INFESTATIONS	29	(14)	6	(6)
PNEUMONIA	7	(3)	3	(3)
LUNG ABCESS	3	(1)	0	0
SEPSIS	3	(1)	0	0
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	24	(11)	7	(6)
PULMONARY EMBOLISM	5	(2)	0	0
ACQUIRED TRACHEO-ESOPHAGEAL FISTULA	3	(1)	0	0
ASPIRATION PNEUMONIA	4	(2)	1	(1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	22	(10)	6	(6)
MUCOSAL INFLAMMATION	6	(3)	0	0
FATIGUE	4	(2)	1	(1)
MULTI-ORGAN FAILURE	3	(1)	0	0
VASCULAR DISORDERS	11	(5)	1	(1)
HYPERTENSION	5	(2)	0	0
HYPOTENSION	3	(1)	0	0
INVESTIGATIONS	9	(4)	2	(2)
LIPASE INCREASED	3	(1)	1	(1)
BLOOD AND LYMPHATIC SYSTEM	5	(2)	1	(1)

XL184-301: PERCENT OF SERIOUS ADVERSE EVENTS (SAE) OCCURRING IN ≥ 1% OF CABOZANTINIB-TREATED PATIENTS BY MEDDRA SYSTEM ORGAN CLASS (SOC) AND PRIMARY TERM (PT)				
	CABOZANTINIB N=214		PLACEBO N=109	
	N	(%)	N	(%)
DISORDERS				
THROMBOCYTOPENIA	3	(1)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4	(2)	0	0
PPE SYNDROME	3	(1)	0	0

The majority of laboratory adverse events were low grade. Noted by the safety reviewer is the increase in thyroid stimulating hormone (TSH) in this population of post-thyroidectomy patients. While the significance of this observation is not clear, this finding was also noted in a similar population of patients with the TKI vandetanib.

The safety reviewer also conducted an analysis of anaphylactic/anaphylactoid shock conditions using Standard MedDRA Queries (SMQ) terminology. The results of this analysis, as expected, do not support a finding of immunogenicity associated with this small molecule. No formal immunogenicity studies were required of the applicant nor were such studies conducted.

9. Advisory Committee Meeting

No issues were identified in the review of this NDA which required the advice of the Oncologic Drugs Advisory Committee, and no Advisory Committee meeting was planned or held for this application.

10. Pediatrics

A request for waiver of pediatric studies was submitted by the Applicant on May 25, 2012. Cabozantinib was granted orphan drug status for treatment of follicular, medullary and anaplastic carcinoma and metastatic or locally advanced papillary thyroid cancer on November 29, 2012. In accordance with the Pediatric Research Equity Act, pediatric studies are waived.

11. Other Relevant Regulatory Issues

Financial disclosures: Financial Disclosure forms were submitted to the NDA for all participating investigators for the randomized trial on June 29, 2012. The disclosures were certified by Dr. Gisela Schwab, Executive Vice President and Chief Medical Officer for Exelixis. No investigators participating in the trial were reported to have had conflicts of interest.

GCP issues: The Applicant avers that the protocol and study conduct for the randomized trial complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments approved by the World Medical Assemblies, and the International Conference for Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The

protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the studies were conducted.

DSI audits: Three clinical investigator sites and the Applicant were inspected by FDA staff in the Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, Office of Scientific Investigations in support of this NDA. One site, in Ohio, was issued a FDA Form 483 based on delayed reporting of SAEs. The Applicant was also issued a FDA Form 483, for observations regarding a lack of adequate source and monitoring documentation and delayed SAE reporting. The Applicant's written response noting that case report forms were sometimes used as source documentation was deemed adequate if not optimal. The Applicant's Standard Operating Procedures related to source documentation needs and expediting SAE reporting were revised. Overall, the data generated by the clinical sites and submitted by the Applicant were deemed adequate to support the NDA.

OSI suggested that DOP2 might wish to consider excluding data from certain patients because of study drug administration irregularities; however, neither the clinical nor statistical reviewer believed this was necessary because the small number of patients involved would not change the outcome of the trial significantly. I concur.

Discipline consults: No consults unrelated to other sections of this review were obtained for this application.

Outstanding regulatory issues: There are no outstanding regulatory issues.

12. Labeling

At the date of this review, labeling negotiations are ongoing and the final labeling language is as yet to be agreed upon. The most recent red-lined version of the label was received from the sponsor on November 5, 2012. The language in section 1, Indications and Usage, will require further negotiation. While the Applicant would like to include in their indication statement patients with MTC that are "unresectable and locally advanced", very few patients meeting this criterion were enrolled in the clinical trial. Therefore, the indication for cabozantinib should not include these patients. Additionally, language and stylistic considerations described in the Code of Federal Regulations and FDA labeling guidance require further changes to many sections of the label for which the Applicant reverted to their original proposed language after reviewing FDA's proposals.

Proprietary name: The proposed proprietary name, Cometriq™, was granted on August 22, 2012.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment

Cometriq (cabozantinib) is recommended for approval as a new molecular entity and small molecule oral inhibitor of receptor tyrosine kinases for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC).

MTC is a rare disease diagnosed in approximately 2000 patients in the United States annually and this histology accounts for 5% to 8% of all thyroid cancers. Complete surgical resection is the only curative treatment for MTC, and survival is correlated with stage at diagnosis. Median overall survival (OS) is less than 2 years from the time of initial surgical resection in patients with Stage 4 disease. This poor prognosis in patients with MTC is accounted for, in part, by the high proportion of patients diagnosed with late-stage disease. Survival after the discovery of distant metastases, which can involve multiple organs including the lungs, bones, and liver, and more rarely the brain, skin, and breast, is about 20% at 10 years. Disease spreading to the trachea and esophagus is often fatal.

Currently, there are only two FDA-approved chemotherapeutic agents for MTC, doxorubicin, a cytotoxic, and vandetanib, a small molecule tyrosine kinase inhibitor. Neither of these drugs has demonstrated a survival benefit in randomized controlled clinical trials for patients.

Approval for cabozantinib is recommended based on the results of a single, international, double-blind clinical trial of 330 patients with progressive, metastatic medullary thyroid carcinoma (MTC) randomized to receive 140 mg cabozantinib (n = 219) or a matched placebo capsule (n = 111). The trial demonstrated a highly statistically significant 7 month improvement in progression free survival as determined by a blinded independent radiology review which favored the cabozantinib arm [median PFS (months)/95% CI: Cabozantinib - 11.2 months/8.4, 13.7 vs. Placebo: 4.0/3.0, 5.4; HR: 0.28, 95% CI=0.19, 0.40; p <0.0001]. The results were robust as demonstrated by multiple sensitivity analyses and were consistent across all subgroups, including RET mutation status. The objective response rate in the cabozantinib arm (all responses were partial responses) was 27% with an observed response duration of 14.7 months (11.1, 19.3). There were no responses observed in the placebo arm. The interim analysis of overall survival (OS), based on 44% OS events (at the time of the primary PFS analysis) demonstrates no difference between study arms (HR=0.997, 95% CI: 0.64, 1.54). Analysis of PFS by dose intensity suggests no difference in PFS response over the range of exposures administered in this study. This finding, in light of an overall 84% dose modification rate for the trial, suggests that a tolerable optimal treatment dose has not been identified during the development program and a dose lower than that proposed for labeling could be equally safe and effective.

The primary and most common safety risks associated with the primary mechanism of action of cabozantinib include diarrhea (64%), stomatitis (51%), palmer-plantar dysesthesia (PPE) syndrome (50%), weight decrease (49%), decreased appetite (46%), nausea (44%), and musculoskeletal and connective tissue pain (43%). Other safety risks identified associated with the VEGF inhibition properties of cabozantinib, including fatalities, were hypertension (33%) hemorrhage (25%), venous and arterial thrombosis (6% and 2%), GI and non-GI fistulas and GI perforations (8%), proteinuria (2%), wound complications (2%), osteonecrosis (1%) and RPLS (<1%). It is notable that the toxicities associated with cabozantinib were

largely manageable, as demonstrated by the low drop-out rate for treated patients in the clinical trial.

In spite of the considerable toxicities associated with cabozantinib, for patients with MTC, who have a rare disease with a poor prognosis, the benefit: risk assessment for cabozantinib favors benefit. It is important to again note that optimal dose exploration for this drug was not undertaken by the Applicant during development. It is expected that, as a result of the postmarketing requirements being imposed by FDA, a more tolerable, but equally effective dose, will be identified. If this expectation is borne out, the benefit: risk profile for cabozantinib for the treatment of patients with MTC will be even more favorable for this group of patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No REMS is required for cabozantinib.

Recommendation for other Postmarketing Requirements and Commitments

The following PMRs and PMCs have been proposed by the review teams and were sent to the Applicant for comment:

PMR

Nonclinical

1. There is a concern that chronic exposure to cabozantinib could cause additional cancers in patients with medullary thyroid cancer administered cabozantinib, based on the expected extended survival (5 years or longer after first exposure to cabozantinib), and extended dosing duration of this patient population. Based on this consideration, two rodent carcinogenicity studies, a long-term (2-year) rat study and a mouse study need to be conducted to assess the potential for cabozantinib to cause carcinogenicity.

2. Based on the expected extended survival, and extended dosing duration of this patient population, as well as the pharmacological mechanism of action (e.g. inhibition of MET and VEGF pathways which may result in altered bone development in neonates), pre- and post-natal reproduction studies will be needed.

Clinical

3. Conduct a randomized dose-comparison, non-inferiority trial in which patients with progressive metastatic medullary thyroid cancer will be randomized to receive oral cabozantinib 140 mg or 80 mg daily. A primary endpoint will be progression-free survival with overall response rate as a secondary endpoint. The trial will be designed to retain 50% of the effect size determined in trial XL184-301 as the non-inferiority margin. The study will also assess between arm differences in the incidence of a composite safety endpoint incorporating adverse events which led to cabozantinib dose reduction in $\geq 5\%$ of patients treated on the cabozantinib arm in XL184-301, that is: palmar-plantar erythrodysesthesia syndrome, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea. The study arms will be also be compared with respect to differences in the number of dose reductions and delayed doses and the incidence of a composite index of toxicities associated with VEGF inhibition, including: hemorrhage, gastrointestinal and non-gastrointestinal perforation, fistula

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and abscess formation, hypertension/hypertensive crisis, arterial and venous thrombosis, proteinuria, wound complications, osteonecrosis and RPLS.

Clinical Pharmacology

4. Conduct a clinical trial to determine the appropriate dose of cabozantinib in patients with hepatic impairment. Submit the final protocol for FDA review before conducting the trial.

5. Conduct a clinical trial to evaluate if proton pump inhibitors, H2 antagonists and antacids alter the bioavailability of cabozantinib. You may study the worst case scenario first, and then determine if further studies on other drugs are necessary. The study results should allow for a determination on how to dose cabozantinib with regard to these gastric pH elevating agents. Submit the final protocol for FDA review before conducting the trial.

PMC

Clinical

6. Submit the results of the final analysis of overall survival data from the randomized clinical trial of cabozantinib 175 mg vs. placebo in progressive metastatic medullary thyroid cancer (XL184-301).

Recommended Comments to Applicant

None.

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/s/

SUZANNE G DEMKO
11/08/2012