

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203756Orig1s000

MEDICAL REVIEW(S)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---------------|---|-----|----|----|---------|
| | Pivotal Study #2 Indication: | | | | |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | | | | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | | | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|--|-----|----|----|---|
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | NA | | | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | ■ | | | |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | NA | | | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | NA | | | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | ■ | | | Exelixis has submitted a form certifying that they have not entered into a financial arrangement any sit investigators or sub-investigators. No disclosure forms signed by the individual investigators have been provided. |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | ■ | | | |

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

RUTHANN M GIUSTI
11/15/2012

SUZANNE G DEMKO
11/15/2012

CLINICAL REVIEW

Application Type NDA
Application Number(s) 203756
Priority or Standard Priority

Submit Date(s) May 21, 2012
Received Date(s) May 29, 2012
PDUFA Goal Date November 29, 2012
Division / Office DOP-2/OHOP

Reviewer Name(s) Ruthann M. Giusti
Review Completion Date November 4, 2012

Established Name Cabozantinib (XL 184)
(Proposed) Trade Name Cometriq
Therapeutic Class Multiple Tyrosine Kinase
Inhibitor
Applicant Exelixis, Inc

Formulation(s) Oral/Capsule
Dosing Regimen 140 mg daily
Indication(s) Advanced medullary thyroid
carcinoma
Intended Population(s) Patients with progressive
metastatic medullary thyroid
cancer

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval

1.2 Risk Benefit Assessment

The recommendation for approval is 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). This trial demonstrated a 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]. These results were robust based on various sensitivity analyses and were consistent across all subgroups (including RET mutation status). The objective response rate in the cabozantinib arm was 27%; all responses were partial responses. No responses were observed in the placebo arm. The interim analysis of overall survival (OS), based on 44% OS events show no difference between study arms (HR=0.997, 95%=0.64, 1.54). Of note, the analysis of PFS by dose intensity suggests no difference in PFS response over the range of exposures administered in this study which may suggest that a dose lower than that proposed for labeling may be equally efficacious.

While the percentage of deaths reported within 30 days of the last study drug administration was similar between study arms, 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%), palmer-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 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 RPLS (<1%). Fatal events of hemorrhage, gastrointestinal and non-GI fistula were also observed. Cabozantinib did not appear to be associated with clinically significant Torsades de Pointes or drug-induced liver disease.

In this patient population with limited therapeutic options, approval of cabozantinib appears warranted based on the robust results demonstrating an improvement in PFS in the absence of evidence of a negative impact on overall survival. The toxicity related to cabozantinib therapy, while substantial, is manageable through monitoring and dose reductions. It is the assessment of this reviewer that the risk/benefit margin is favorable. However, post-marketing studies should be undertaken to determine whether a lower cabozantinib dose is as efficacious and less toxic.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk Evaluation and Mitigation Strategies (REMS) are not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The following clinical post marketing requirement (PMR) is recommended:

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

The following post marketing commitment (PMC) is recommended:

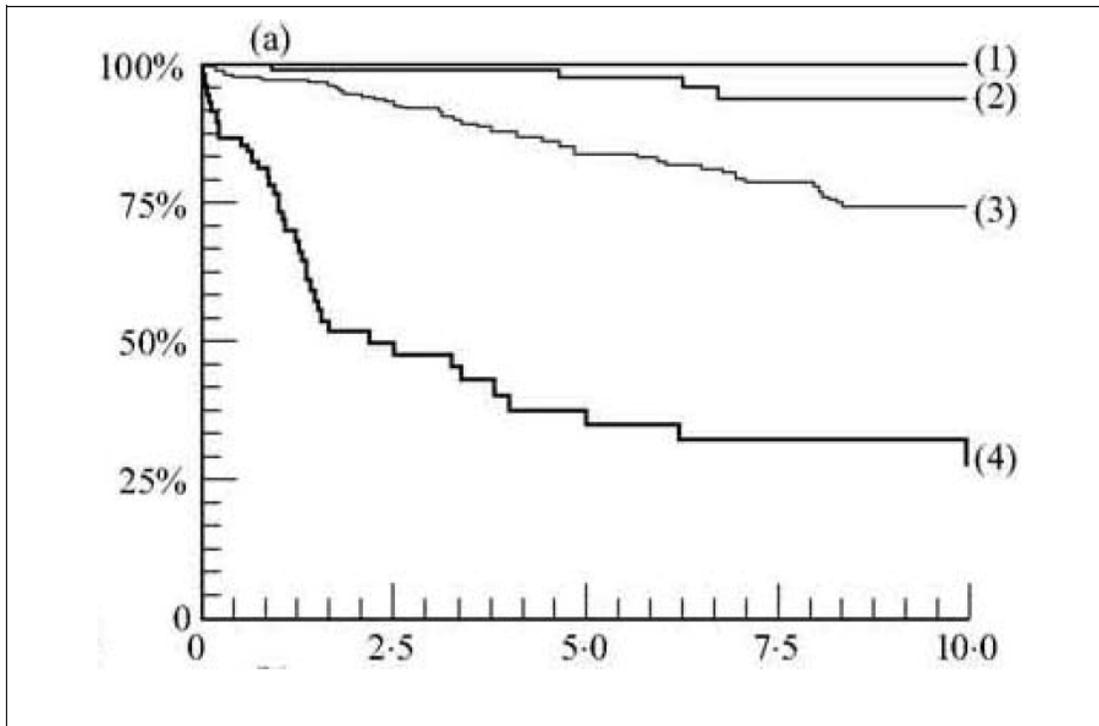
Submit the results of the final analysis of overall survival data from the randomized clinical trial of cabozantinib 175 mg vs. placebo in progressive metastatic medullary thyroid cancer (XL184-301).

2 Introduction and Regulatory Background

Medullary thyroid cancer (MTC), which accounts for 5-8% of all thyroid cancers, is diagnosed in approximately 2000 patients in the United States annually (1). The incidence of MTC peaks in the fifth or sixth decade and there is a slight female preponderance. MTC typically presents as a solitary thyroid nodule, however, most patients have metastatic disease at the time of diagnosis with about 50% having clinically detectable cervical lymph node involvement, 15% having symptoms of upper aerodigestive tract compression or invasion (dysphasia or hoarseness) and 5% having symptomatic distant metastatic disease.

The only curative treatment for MTC is complete surgical resection, and survival is correlated with stage at diagnosis (2-4). Median overall survival (OS) is less than 2 years from the time of initial surgical resection in patients with Stage 4 disease (Figure 1).

Figure 1. Influence of Stage on Survival in MTC Patients



X-axis: years after surgery; Y-axis: survival

1) Stage 1 (n = 143); 2) Stage 2 (n = 146); 3) Stage 3 (n = 320); 4) Stage 4 (n = 79), p-value $<10^{-6}$

Note: this Stage 4 population included patients with stable disease, and therefore is likely to over-estimate the median OS in high-risk patients with evidence of progressive disease.

Taken from: [Modigliani et al 1998](#)

The poor prognosis in patients with MTC can be accounted for in part by the high proportion of patients diagnosed with late-stage diagnoses (3, 5). Survival after the discovery of distant metastases is about 20% at 10 years (2, 6). Distant metastases often affect multiple organs including the lungs, bones, and liver, and more rarely the brain, skin, and breast (1). Disease spread to the trachea and esophagus can also lead to death (7).

Medullary thyroid cancer (MTC) is a neuroendocrine tumor which originates 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 the 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 (8). Some tumors secrete carcinoembryonic antigen (CEA), which like calcitonin is used as a tumor marker (9).

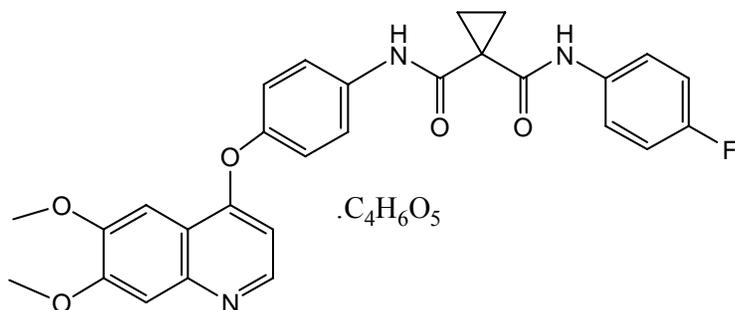
Up to 75% of MTC cases occur sporadically, while the remainder occur with an autosomal dominant inheritance pattern as one of three disorders comprising Multiple Endocrine Neoplasia 2 (MEN 2): MEN 2A, MEN 2B, and familial MTC (10,11).

- **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.

Ninety-eight per-cent of individuals with inherited MTC, germline activating mutations in the gene encoding the RET receptor tyrosine kinase (RTK) have been identified. Activating somatic mutations in RET are also present in tumor tissue of up to 65% of sporadic MTC cases (12). In addition to RET, MET and vascular endothelial growth factor receptor 2 (VEGFR2) are also implicated in the pathogenesis of MTC. The MET RTK has been implicated in multiple pathways promoting tumor progression, metastasis and invasion (13).

Moreover, over expression of the MET RTK and its ligand HGF has been detected in MTC (14), and transduction of normal human thyroid cells with a mutant *RET* gene results in upregulation of MET (15). Vascular endothelial growth factor (VEGF) expression has been shown to be higher in differentiated and medullary thyroid cancers than in normal or benign thyroid tissue (16). Vascular endothelial growth factor stimulates the formation of blood vessels, increases vascular permeability, and is likely involved in progressive disease (17).

2.1 Product Information



Cabozantinib (XL184), a new molecular entity, is a small molecule oral multi-targeted inhibitor of receptor tyrosine kinases (RTK) which are implicated in tumor growth and angiogenesis, pathologic bone remodeling and in the metastatic progression of cancer. Cabozantinib inhibits MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including RET (glial cell derived neurotrophic factor receptor rearranged during transfection), AXL (GAS6 receptor), KIT (stem cell factor receptor), and FLT3 (Fms-like tyrosine kinase-3). Cabozantinib exhibited potent dose-related tumor growth inhibition, tumor regression and, or inhibited metastasis in a broad range of preclinical tumor models. For additional product information, please refer to Dr. Brower's non-Clinical Review and/or Dr. Hsieh's and Dr. Martin's Product Quality Review.

2.2 Tables of Currently Available Treatments for Proposed Indications

| TABLE 1. CURRENTLY APPROVED TREATMENTS FOR MTC | | | |
|--|------------------------------|------------------|-------------------------------|
| Agent | Class | Type of Approval | Basis of approval |
| Doxorubicin | Cytotoxic, monotherapy | Full | RR < 20%; no survival benefit |
| Vandetanib (CAPRELSA®) | Small Molecule TKI Inhibitor | Full | PFS, RR; no survival benefit |

Doxorubicin is the only approved cytotoxic chemotherapy for thyroid cancer; however, the single agent response rate is less than 20% (Table 1). Doxorubicin therapy is often associated with significant cardiac and hematologic toxicity (6, 8,18). Combination chemotherapy regimens explored in the treatment of MTC have demonstrated increased toxicity without improvements in efficacy. A 15% response rate was observed with the combination of doxorubicin, streptozotocin, 5-FU, and dacarbazine (19). Two partial responses (28%) were observed in a small trial of seven advanced MTC subjects treated with cyclophosphamide, vincristine, and dacarbazine (20).

Vandetanib (CAPRELSA®) (21), a tyrosine kinase inhibitor (TKI) which inhibits epidermal growth factor receptor (EGFR), VEGFR2 and RET, was approved by the US FDA in 2011 and by the EU in 2012, for the treatment of patients with symptomatic or progressive unresectable MTC. Progression within 14 months prior to enrollment was documented for 87% of patients on the vandetanib arm and 86% of patients on the placebo arm. The approval of vandetanib was based on the results of a randomized (1:1), double-blinded, placebo-controlled trial of 631 patients (vandetanib: n=331; placebo: 330) (22) which demonstrated a statistically significant improvement in PFS as determined by a blinded central review using RECIST criteria (Hazard Ratio = 0.35; 95% Confidence Interval (CI) = 0.24, 0.53; p <0.0001). The median PFS (95% CI) in the vandetanib arm was not reached (22.6, months, NE); the median PFS (95% CI) in the placebo arm was 16.4 months (8.3, 19.7). At the time of the primary analysis of PFS, only 15% of survival events had occurred. There was no difference in overall survival between study arms. Because of the prolonged half-life of the drug and the risk observed for QT prolongation, Torsades de pointes and sudden death, vandetanib was approved under a REMS program. The rate of other Grade 3-4 adverse events included: Stevens-Johnson syndrome (<1%), interstitial lung disease (<1%), ischemic cerebrovascular events (<1%), hemorrhage (<1%), heart failure (1%), diarrhea (11%), hypertension (9%) and reversible posterior leukoencephalopathy syndrome (RPLS) (<1%).

There remains an unmet medical need for effective therapy for patients with progressive, locally advanced and metastatic MTC who are not candidates for or who have progressed following vandetanib therapy.

2.3 Availability of Proposed Active Ingredient in the United States
Cabozantinib is not currently available for use in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Imatinib (23) was the first approved anticancer drug considered to be a multi-targeted TKI, targeting KIT, PDGFR and BCR-ABL. The following multi-targeted TKI have recently been approved in the U.S.:

- Sorafenib (24), an inhibitor of VEGFR, PDGFR, KIT, Fms-like tyrosine kinase [3 (FLT3)] and p38 α as well as Raf kinase, a downstream effector of Ras
- Sunitinib (25), an inhibitor of KIT, PDGFR, VEGFR, 3 (FLT3), and RET
- Votrient (26), an inhibitor of VEGFR, PDGFR, Kit, interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms)
- Vandetanib (21), an inhibitor of EGFR, VEGFR, protein tyrosine kinase 6 (BRK, TIE2, members of the EPH receptors kinase family and members of the Src family of tyrosine kinases.

As the targets and relative levels of target inhibition for these compounds vary, while some toxicities of these multi-targeted TKIs are overlapping, these compounds retain distinctive toxicity profiles. In addition to other TKIs, the safety experience with selective small molecule tyrosine kinase inhibitors and monoclonal antibodies such as bevacizumab (27) and aflibercept (28), which target VEGFR, are also relevant.

Toxicities reported with these agents in the WARNINGS AND PRECAUTIONS or ADVERSE REACTIONS: Postmarketing Experience sections of the current or proposed US Package Insert (USPI) are listed below in Table 2. Any of these toxicities might be anticipated in post-marketing surveillance of cabozantinib.

| TABLE 2. TOXICITIES REPORTED IN THE WARNINGS AND PRECAUTIONS OR ADVERSE REACTIONS SECTIONS OF THE USPI FOR SMALL MOLECULE MULTI-TARGETED TYROSINE KINASE INHIBITORS AND MONOCLONAL ANTIBODIES TARGETING VEGFR | | | | | | | |
|---|----------|-----------|-----------|----------|------------|-------------|---------|
| | Imatinib | Sorafenib | Sunitinib | Votrient | Vandetanib | Bevacizumab | (b) (4) |
| Hepatic toxicity/hepatic impairment | X | X | X | X | | | |
| Congestive heart failure | X | X | X | X | X | | |
| Hemorrhagic events | X | | X | X | X | X | X |
| Ischemic cerebrovascular events | | X | | | X | | |
| Interstitial lung disease/pulmonary fibrosis | X | | | | X | | |
| QT prolongation | | X | X | X | X | | |
| Dermatologic toxicities/Stevens-Johnson syndrome | X | X | | | X | | |
| Diarrhea | | | | | X | | X |
| Hypothyroidism | X | | X | X | X | | |
| Hypertension | | X | X | X | X | X | X |
| Reversible posterior leukoencephalopathy syndrome (RPLS) | | | | X | X | X | X |
| Arterial thrombotic events | | | | X | | X | X |
| Venous thrombotic events | X | | | X | | | |
| Gastrointestinal and non-gastrointestinal perforations and fistulas | X | | | X | | X | X |
| Impaired wound healing | | | X | X | | X | X |
| Proteinuria/renal failure | X | X | | X | | X | X |
| Infection | | | | X | | | |
| Mucositis/stomatitis | | X | | | | | |
| Osteonecrosis | X | X | | | | X | |
| Fluid retention/edema | X | | | | | | |
| Hematologic toxicity | X | | | | | | X |

*Label currently under review.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission
A summary of the key pre-submission regulatory milestones is provided in Table 3.

| TABLE 3. NDA 2003756 – KEY REGULATORY MILESTONES | | |
|--|--|--|
| Date | Type of submission/meeting | Key comments |
| JUL 2005 | Exelixis opened IND (b) (4) for XL-184 (cabozantinib) | |
| MAR 2008 | MTC EOP-2 Meeting | <ul style="list-style-type: none"> PFS based on blinded IRS review may be an acceptable endpoint in this disease setting, depending on the magnitude of the effect observed and the risk to benefit ratio, OS secondary endpoint. |
| JUN 2008 | SPA agreement for XL184-301 | <ul style="list-style-type: none"> The number of patients without measurable disease was to be limited. Dose modification guidelines were revised such that no more than two dose reductions were allowed. PFS analysis to be based on IRC assessment and to be event driven. The MDASI measure is exploratory (b) (4) |
| NOV 2010 | Orphan Drug Designation Granted | |
| DEC 2010 | Pre-NDA Meeting | <ul style="list-style-type: none"> Format and timelines of the rolling submission agreed upon. |
| MAR 2011 | EOP-2 CMC Meeting | |
| APR 2011 | Fast Track designation granted for unresectable, locally advanced, or metastatic MTC | |
| DEC 2011 | Conditional approval of proposed trade name (Cometriq) | |
| DEC 2011 | Initial component (Non-Clinical) of the rolling NDA submission received. | |
| DEC 2011 | (b) (4) IND 113756) | NDA transferred to DOP-2 |
| DEC 2011 | Pre-IND (113756)/Pre-NDA Meeting | <ul style="list-style-type: none"> High level data and format of the submission discussed with new review team |
| MAY 2012 | Submission of final component (Clinical) of the rolling NDA submission received | |
| JUN 2012 | Applicant orientation meeting | |

2.6 Other Relevant Background Information
None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable as judged by review of case report forms and narratives for all deaths on study and a 10% sample of Grade 3 and 4 adverse events in the cabozantinib study arm of the XL184-301 trial with comparison to the adverse event data set for this trial.

The number of protocol deviations as characterized based on the International Conference on Harmonization (ICH) E3 guidelines was examined (Table 4). The distribution of deviations by category was similar across both study arms. The primary reasons given for deviations potentially affecting patient safety were: minor elevation in screening blood pressure (n=10), screening or pre-cycle pregnancy test not performed (n=3), failure to report SAE within 24hours (n=4), other screening laboratory test not obtained or out of bounds (n=4), prior history of melanoma in situ (n=1), prior history of endobronchial lesion (n=1). Review of these cases did not suggest that patients were harmed as a result of these protocol deviations. A total of 15 patients remained on study after an investigators assessment of radiologic progression by RECIST. In 9 cases, the justification given was that confirmation of results was required or that there was a delay in obtaining radiology results.

| TABLE 4. PROTOCOL DEVIATIONS CATEGORIZED BASED ON INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) E3 GUIDELINES | | | | |
|--|-----------------------|---|------------------|---|
| Protocol Deviation | Cabozantinib N=219 | | Placebo N=111 | |
| | n | % | n | % |
| Inclusion/exclusion criteria or other protocol deviations that may have affected a patient's safety | 17 | 8 | 8 | 7 |
| Protocol deviations of subjects who received study treatment past investigator assessment of disease progression per mRECIST | 11 | 5 | 4 | 4 |
| Incorrect dose of study drug | 4 | 2 | 0 | 0 |
| Prohibited medication | 0 | 0 | 0 | 0 |

In four patients, a cabozantinib dosing error was reported. These four cases are outlined in Table 5 below.

| Patient Number | Protocol Deviation |
|----------------|---|
| 39043002 | Because of a medical history of dysphasia, the subject took study drug for three days dissolved in water. A review of safety and laboratory data during this time frame show no new adverse events or laboratory abnormalities. Study drug was then withheld due to dysphasia and restarted at a lower dose. |
| 44023001 | After a study drug was held due to Grade 2 diarrhea, the subject restarted the study drug at 100 mg instead of the reduced dose of 60 mg for one day. The subject discontinued study treatment due to adverse events of CTCAE Grade 2 diarrhea, Grade 1 vomiting, Grade 2 nausea, and Grade 2 lethargy. |
| 48053007 | Subject had Grade 1 vomiting after study drug administration and took another study drug dose on the same day. A review of safety and laboratory data during this time frame show no new or worsening adverse events or laboratory abnormalities. |
| 97043002 | Subject took 280 mg of cabozantinib for 9 days instead of 140. The study drug was withheld for 4 days due to the adverse events of Grade 3 cognitive disorder, Grade 3 memory impairment, Grade 2 weight decrease, Grade 3 mental status changes, Grade 1 increased free thyroxine and Grade 1 blood urea nitrogen elevation. Study drug was restarted at 100 mg and these events resolved. |

3.2 Compliance with Good Clinical Practices

The protocol and study conduct 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.

Informed consent was obtained prior to the conduct of any study-related procedures. The written informed consent form (ICF) was signed and dated by the patient or by the patient's legally acceptable representative as well as by the person who conducted the informed consent discussion. The IFC used by the Investigator for obtaining the patient's informed consent was reviewed and approved by the Applicant prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The patient informed consent form was modified according the local regulations and requirements and verification of this approval was provided in the NDA.

Three clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811). Three sites were selected for review. These were selected from the highest accruing sites for the

single randomized trial (XL184-301) supporting this application, the 6 sites which accrued 10 (3%) or more study participants to this trial. These three sites were selected because an 1) the PFS estimate for the site fell below the study mean, 2) more than half of study radiographs from these sites required adjudication, or 3) the death rate or rate of Grade 3-4 adverse events appeared high relative to other high accruing sites. The three sites selected included one in the U.S., one in Italy and one in Germany (Table 6).

Table 6. Clinical Site Inspections

| Name of CI, Location | Protocol #/ Site #/ # of Subjects | Inspection Dates | Final Classification |
|--|--|--------------------|------------------------------------|
| Shah, Manisha, MD The Ohio State University James Cancer Hospital 320 West 10th Avenue Columbus, OH 43210 | XL 184-301/ Site 1315/ 10 (randomized) | 30 Jul-15 Aug 2012 | VAI. Pending final classification. |
| Elisei, Rossella, MD U.O.Endocrinologia 1 Univ.- Dipartimento di Endocrinologia e Metabolismo Ortopedia e Traumatologia Medicina del Lavoro Ospedale Cisanello – Azienda Ospedaliero Universitaria Pisana Via Paradisa 2 56124 Pisa, Italy | XL 184-301/ Site 3908/ 20 (randomized) | 7-14 Sep 2012 | NAI. Pending final classification. |
| Bockisch, Andreas, MD Universitätsklinikum Essen Klinik für Nuklearmedizin Hufelandstr. 55 45122 Essen, Germany | XL 184-301/ Site 4902/ 12 (randomized) | 14-21 Sep 2012 | NAI. Pending final classification. |
| Exelixis (sponsor) 210 East Grand Avenue, P.O. Box 511 South San Francisco, CA 94083-0511 | XL 184-301 | 10- 27 Sep 2012 | VAI. Pending final classification. |

NAI – No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending – Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of the EIR is pending.

A Form FDA 483 was issued to Dr. Elisei’s site due to delays in reporting of laboratory adverse events, and lack of oversight which resulted in delayed dose administration errors and drug overdose of one patient. The Applicant, Exelixis, was also issued a Form FDA 483 related to a lack of adequate source and monitoring documentation. However, the Applicant implemented standard operating procedures to address the deficiencies and the conclusion of the inspection was that the studies appear to have been adequately conducted and it is unlikely that the irregularities observed would alter the study findings.

3.3 Financial Disclosures

Disclosure of financial interest (FDA form 3454) was submitted in the NDA for all investigators participating in the randomized trial. The disclosure was certified by Dr. Gisela Schwab, Executive Vice President and Chief Medical Officer for Exelixis. No investigators participating in the XL184-301 trial were reported to have had conflicts of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following information was abstracted from the combined Chemistry Manufacturing and Controls (CMC) review. Please refer to the full report for additional details.

Drug Substance

The proposed commercial manufacturing process is (b) (4)
(b) (4) Manufacture and testing
is at a single site in (b) (4) with contract laboratories in (b) (4). All three sites
have been found to meet cGMP requirements.

The release specification includes testing for appearance, identity, assay ordinary impurities; (b) (4) four GTIs, water content, residual solvents, inorganic impurities, (b) (4), heavy metals and particle size distribution. Methods for impurities are sensitive to appropriate levels. Criteria are justified by batch analysis data and non-clinical studies. Reference standards have been established for drug substance and potential impurities.

Stability information 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 results from the long term studies on commercial lots stored at ICH conditions are sufficient to support storage of bulk drug substance at (b) (4) (b) (4) with a retest period of (b) (4).

Drug Product

Cabozantinib capsules contain drug equivalent to 20 mg or 80 mg freebase and the following inactive ingredients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid.

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. 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.

The following container closure systems will be provided:

1. The blister card packaging system contains 80-mg and/or 20-mg capsules in three card configurations that provide 140-mg (one 80-mg and three 20-mg capsules), 100-mg (one

80-mg and one 20-mg capsules), or 60-mg (three 20-mg capsules) weekly dosage cards. Each row of capsules in the blister card represents the required daily dose. Four cards are packaged into a carton to provide a 28-day supply. (b) (4)

2. The bottle packaging system contains sixty 20-mg capsules and is intended to provide for an alternate packaging presentation of a single capsule strength. (b) (4)

4.2 Clinical Microbiology

Cabozantinib is taken orally and is not sterile.

4.3 Preclinical Pharmacology/Toxicology

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

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

In contrast to other VEGF inhibitors, changes in epiphyseal growth plates were not observed following treatment with cabozantinib, although atrophy of the femur was observed in dogs administered doses ≥ 100 mg/kg/day for 14 days; this finding was not observed following recovery, and was considered to be secondary to the systemic toxicity observed in these animals. It is also of note that distribution studies in rats showed high concentrations of cabozantinib at late time points in the eye and uveal tissue. No associated ocular toxicity has been observed in clinical or non-clinical studies with the exception of ocular keratitis in dogs administered toxic levels of cabozantinib. Ocular toxicities have been reported with other multi-targeted TKIs and may emerge in humans in the post-marketing setting.

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

Reproductive and developmental toxicology studies conducted in rats and rabbits to assess the effects of XL184 on fertility and embryo-fetal development showed effects on male and female reproductive organs as well as fertility. Based on the non-clinical data, cabozantinib has been assigned a Pregnancy Category D.

Four process impurities in the drug substance were identified as genotoxic. At the specification proposed, none of the impurities exceeds an intake of (b) (4)/day. At the recommended dose of cabozantinib this level is considered to represent a low safety risk and are considered

acceptable. The applicant has indicated that with revised purity/impurity methodology, stability specifications of genotoxic and non-genotoxic impurities will equal release specifications. Based on a nonclinical lot tested in the 6-month repeat-dose toxicology study in dogs, the clinical intake of the impurity at this limit is qualified.

Please refer to Dr. Brower's review for additional details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Cabozantinib is a multiple tyrosine kinase inhibitor (TKI) with activity against targets known to play important roles in tumor cell proliferation and/or tumor vascularization: i.e., MET, VEGFR2, and RET. Other recognized targets include AXL, VEGFR1, VEGFR3, KIT and FLT-3. The mode of action for cabozantinib is similar to other TKIs: binding in a reversible manner to a region of the kinase domain which includes the ATP-binding site, thereby inhibiting catalytic activity.

4.4.2 Pharmacodynamics

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.

Please refer to Dr. Brar's review for additional details.

4.4.3 Pharmacokinetics

A population pharmacokinetic analysis of cabozantinib was performed using data collected from 289 patients with solid tumors including MTC following oral administration of 140 mg daily doses. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

Median time to peak cabozantinib plasma concentrations (T_{max}) following cabozantinib administration ranged from 2 to 5 hours post-dose. Repeat daily dosing of COMETRIQ at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma ($\geq 99.7\%$). A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose. Within a 48-day collection period after a single dose of ^{14}C -cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. The effect of mild and moderate renal impairment on clearance of cabozantinib appears to be minimal.

Pharmacokinetics (PK) of cabozantinib in patients with severe renal impairment or in patients with hepatic impairment has not been studied.

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 showed a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Dose modifications for patients concomitantly taking a strong CYP3A4 inhibitor or inducer are recommended.

The solubility of cabozantinib is pH-dependent with the solubility at normal gastric pH the highest and practically insoluble when pH is greater than 4. The effect of gastric pH modifying drugs (proton pump inhibitors, H2 blockers, antacids) on PK of cabozantinib based on a population PK analysis was inconclusive.

A high proportion (86.4%) of cabozantinib-treated patients in XL184-301 required at least one, dose modification (e.g., dose interruption, dose reduction, and dose discontinuation) due to adverse events. Exposure-response analyses for PFS within the exposure range studied in this trial do not show a relationship, suggesting that lower dose intensity may not be associated with reduction of PFS.

Please refer to Dr. Yang's review for additional details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In support of the NDA application for the treatment of MTC, Exelixis has provided full or abbreviated study reports for three clinical trials (Table 7).

Table 7. Clinical Study Reports Included in the NDA Filing

| Study (Phase) | Study Report | Proposed Role of Study in NDA | | Number of Subjects | | |
|-------------------------------|--------------|-------------------------------|--------|---|------------------------------------|--------------------------|
| | | Efficacy | Safety | Cabozantinib 175 mg (138 mg freebase equivalent weight) | Placebo | Cabozantinib Other Doses |
| XL184-301 (Phase 3) | Full | √ | √ | 219 MTC (efficacy) 214 (safety) | 111 MTC (efficacy) 109 (safety) | - |
| XL184-001 (Phase 1) | Full | √ | √ | Efficacy: 25 (MTC) Safety: 35 (MTC/non-MTC) | - | 50 |
| XL184-201 (Group A) (Phase 2) | Abbreviated | | √ | 46 glioblastoma multiforme | - | - |

XL184-301 (see section 5.3.1) is a double-blind, placebo-controlled randomized trial of 330 patients with metastatic progressive MTC conducted at 90 sites in Europe, North America, the Middle East, South America and Asia. Patients were randomized to receive an oral dose of cabozantinib 140 mg daily (n=219) or a matched placebo control capsule (n=111). Patients were required to have radiographically documented progressive disease (PD) within 14 months of study entry. The primary efficacy outcome measure was PFS assessed by a blinded Independent Radiology Review Committee (IRC) using a modified response evaluation criteria in solid tumors (mRECIST) (29). Overall survival (OS) and objective response rate (ORR) were secondary outcome measures. Enrollment is complete and the primary analysis for PFS has been conducted; subjects continue to be followed for safety and OS.

XL184-001(see section 5.3.2) is an open-label Phase 1 dose-escalation trial in patients with advanced malignancies including MTC that was conducted in the US. The study consisted of a conventional “3+3” design for dose escalation to determine the maximum tolerated dose (MTD). Once the MTD of 140 mg daily administered orally as a capsule formulation was defined, dosing in the 140 mg qd dosing cohort was expanded. The expansion cohort primarily enrolled patients with MTC. A total of 85 patients received cabozantinib during the study. Of these, 56 were enrolled in the dose escalation phase of the study (six of whom received the capsule formulation at the MTD dose). Overall, 35 patients were treated with the capsule formulation at the MTD, 25 of whom had MTC. The primary outcome measures for XL184-001 were safety and pharmacokinetics (PK). The ORR by mRECIST (29) as assessed by the investigator was analyzed as a secondary outcome measure.

XL184-201 (see section 5.3.3) is an open-label trial of cabozantinib for the treatment of recurrent and progressive glioblastoma multiforme (GB) that is currently being conducted in the US. Data

from a cohort of 46 patients (Group A) who were treated with cabozantinib 140 mg (capsule formulation) orally qd are included in this filing.

Data in support of clinical efficacy are based on an analysis of the results of a single randomized trial of 330 patients with MTC (XL 184-301); 219 of these received XL184-301. Exelixis proposes to use data collected on a subset of 25 patients treated under an open-label dose escalation trial (XL184-001) who had measurable MTC and received XL-184. To support safety, Exelixis provided a between arm comparison of patients treated with XL184 (n=214) and patients who received a placebo control (n=111), 35 MTC and non-MTC patients who received cabozantinib on XL184-001, and 46 patients with glioblastoma multiforme (GB) who received cabozantinib on XL184-201. All cabozantinib-treated patients received 140 mg of cabozantinib in the capsule formulation until disease progression, intolerable toxicity or until other study withdrawal criteria were met.

The development of cabozantinib is also supported by six clinical pharmacology studies (including two biopharmaceutics studies) performed in 186 evaluable subjects (154 healthy subjects, 32 cancer subjects [Study XL184-008]). XL184-004 assessed the effect of food on cabozantinib bioavailability; XL184-006 and XL184-007 assessed the interaction of cabozantinib with rifampin (cytochrome P450[CYP] 3A4 inducer) and ketoconazole (CYP 3A4 inhibitor), respectively; XL184-008 assessed the effect of cabozantinib on rosiglitazone (CYP2A8 substrate) PK and is supplied as a PK report; XL184-012 was a mass balance study using radioactively labeled cabozantinib. XL184-016 was conducted to evaluate (b) (4)

An exposure-response (E-R) analysis for efficacy and safety was performed based on data from XL184-301 (214 subjects receiving cabozantinib; 109 subjects receiving placebo). A hepatic impairment study has been initiated and is currently ongoing. Please refer to Jun Yang's clinical pharmacology review for details of these studies.

5.2 Review Strategy

The review of clinical efficacy was based on an analysis of trial XL 184-301 and is summarized in section 6, REVIEW OF EFFICACY. Efficacy data from the subset of patients with MTC was not formally reviewed as the primary endpoint for this study, ORR was not independently verified, but is commented upon in section 6.1.6, Other Endpoints. Safety data was reviewed in detail from all three trials (XL 184-301, XL184-001 and, XL184-001) and is summarized in section 7, REVIEW OF SAFETY with data from XL184-001 and, XL184-001 discussed in section 7.7, Additional Submissions / Safety Issues.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study Title: An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 Versus Placebo in Subjects With Unresectable, Locally Advanced, or Metastatic Medullary Thyroid Cancer (XL184-301)

First Patient Enrolled: September 10, 2008

Clinical Review
Ruthann Giusti, M.D.
NDA 203756
Cometriq [Cabozantinib (XL184)]/Exelixis

Last Patient Completed: The study is ongoing.

Children Enrolled: None

Investigators/Study Centers: Ninety-eight principal investigators enrolled subjects at 90 unique sites in 23 countries in Europe, North America, Middle East, South America and Asia.

Data Cutoff Date: June 15, 2011

Objectives:

| TABLE 8. XL184-301: STUDY OBJECTIVES | |
|--------------------------------------|---|
| Primary | <ul style="list-style-type: none"> To evaluate progression-free survival (PFS) with XL184 treatment compared to placebo in patients with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC). |
| Secondary | <ul style="list-style-type: none"> To evaluate overall survival (OS) with LX184 treatment compared with placebo. To evaluate the objective response rate (ORR) and duration of response (durR) in patients with measurable disease treated with XL184 compared with placebo based on the modified Response Evaluation Criteria in Solid Tumors 1.0 (mRECIST), as assessed by a blinded Independent Radiology Review Committee (IRC). To evaluate changes in serum levels of calcitonin (CTN) and carcinoembryonic antigen (CEA) as prognostic biomarkers for XL 184 treatment benefit as compared with placebo. To assess the potential relationship between RET germline and/or tumor DNA sequence alterations and efficacy of XL 184. To assess the pharmacodynamic effects of XL 184. To evaluate the safety and tolerability of XL 184 treatment. To assess the pharmacokinetics (PK) of XL 184. |
| Exploratory | <ul style="list-style-type: none"> To evaluate subject self-assessment parameters and symptom burden with XL 184 treatment as compared with placebo using the MD Anderson Symptom Inventory (MDASI) Thyroid Module. |

Study Design:

This was an international, randomized, double-blinded, multicenter, placebo-controlled trial in which patients were randomized 2:1 to receive either a single oral daily dose of 140 mg cabozantinib (LX184 - 175 mg L-malate salt weight; 138 mg freebase equivalent weight) or a matched placebo capsule in 4-week cycles. Radiographic tumor assessments were performed every 12 weeks (\pm 5 days) from randomization until progressive disease (PD) was determined by the investigator using mRECIST. Tumor assessments were evaluated by a blinded central independent review committee (IRC) to determine response and/or progression. Hematology and serum chemistry laboratory evaluations and vital signs assessments were conducted every two weeks during Cycles 1 and 2 and every four weeks during subsequent cycles according to a pre-defined study calendar (Table 10). Blood and tissue samples for biomarker and blood samples for PK assessments were collected at specific protocol-defined visits. At each study visit, evaluations of adverse events (AEs) and concomitant medication use were performed.

Patients remained on treatment until documented progression using mRECIST as determined by the investigator, unacceptable toxicity or other protocol-specified criteria. If study treatment was discontinued for reasons other than PD, tumor assessments, pharmacodynamic blood sampling,

calcitonin (CTN), CEA, thyroid stimulating hormone (TSH), and free thyroxine (FT4) measurements; and MDASI thyroid module were followed until disease progression.

Number of Subjects:

Assuming exponential distribution of PFS time and proportional hazards, 138 PFS events were required for this study to have 90% power to detect a hazard ratio (HR) of 0.571 based on a log-rank test and a 2-sided 5% significance level. This effect corresponds to a 43% reduction in the PFS risk, or a difference of 8 months versus 14 months in median PFS time.

Assuming one interim analysis of OS at the 31% information level at the time of the primary analysis of PFS and a subsequent primary analysis, 217 deaths were required to have an 80% power to detect a HR of 0.667 using a log-rank test and a 2-sided 4% significance level. This effect corresponds to a 33.3% reduction in the risk of death, or a treatment difference of 22 versus 33 months in median survival time.

A total of 315 eligible patients (210 in XL184 and 105 in placebo) were planned to be randomized and followed to observe the required number of events within the planned study duration (33 months accrual; approximately 66 months total to observe the required deaths for OS). The number of patients enrolled with nonmeasurable disease per mRECIST was capped at 10%. A total of 330 patients (219 cabozantinib; 111 placebo) were randomized to receive treatment [intent-to-treat (ITT) study population], and were analyzed as of the database cut-off date of June 15, 2011. The safety population comprised 323 patients (214 cabozantinib, 109 placebo), and the per protocol (PP) population was comprised of 300 patients (198 cabozantinib, 102 placebo).

Study Population:

Inclusion Criteria:

- Measurable or unmeasurable (mRECIST), histologically confirmed unresectable, locally advanced, or metastatic MTC
- ≥ 18 years of age
- ECOG performance status ≤ 2
- Progressive disease (PD) documented at screening using computerized tomography (CT), magnetic resonance imaging (MRI), bone scan, or X-ray using mRECIST criteria compared with a previous image done within 14 months of screening
- Recovered to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 Grade ≤ 1 from clinically significant AEs due to anti-neoplastic agents, investigational drugs, or other medication administered prior to randomization
- Organ and marrow function as follows:
 - Absolute neutrophil count (ANC) $\geq 1000/\text{mm}^3$
 - Hemoglobin (HBg) ≥ 9

- Bilirubin \leq 1.5 times the upper limit of normal(ULN)(excepting patients with Gilbert's syndrome)
- Serum creatinine \leq 1.5 mg/dL
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) \leq 2.5 times ULN
- Sexually active patients must have agreed to use medically acceptable methods of contraception during the course of the study and for 3 months following discontinuation of study treatments (excluding women not of childbearing potential and sterilized men)
- Women of childbearing potential must have had a negative pregnancy at screening
- No history or evidence of other malignancy (excluding non-melanoma skin cancer, carcinoma in situ of the cervix)

Exclusion Criteria:

- Prior systemic anti-tumor therapy or investigational agents within 4 weeks of randomization (6 weeks for nitrosoureas or mitomycin C)
 - Radiation received to \geq 25% of the bone marrow.
 - Prior treatment with XL 184
 - Brain metastases or spinal cord compression (except in patients who received radiation therapy \geq 4 weeks prior to randomization and are stable without steroids or anticonvulsant treatment for \geq 10 days)
 - History of clinically significant hematemesis or hemoptysis of $>$ 2.5 ml of red blood or other signs indicative of pulmonary hemorrhage or evidence of endobronchial lesion(s)
 - Urine protein/creatinine ratio of \geq 1 (reported in grams of protein divided by grams of creatinine)
 - Serious intercurrent illness such as:
 - Hypertension ($>$ 140mm Hg systolic or $>$ 90 mmHg diastolic measured on two or more blood pressure (BP) readings) despite optimal treatment)
 - Unhealed wounds from recent surgery
 - Cardiac arrhythmias
 - Recent history of congestive heart failure (CHF), unstable angina pectoris within the past 3 months or myocardial infarct, stroke or transient ischemic attack within the past 6 months
 - Pregnant or breast feeding
 - Active infection requiring systemic treatment
- Known allergy or hypersensitivity to the components of the XL 184 or placebo formulations
Incapable of understanding and complying with the protocol; unable to provide informed consent

Study Drug:

Cabozantinib was administered as an oral dose of 140 mg (175 mg L-malate salt weight; 138 mg freebase equivalent weight) once per day. Cabozantinib was supplied as 20-mg and 80-mg capsules using the following lot numbers:

20 mg: 303632, L0205271, L0209383, L0209927, L0209928

80 mg: 303614, L0205272, L0208700, L0301013, L0302163

Placebo was administered as an oral daily dose. Placebo was packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib and was supplied using the following lot numbers:

20 mg: 300201, L0203573, L0203892, L0209418

80 mg: 301079, L0203574, L0203893, L0209419

Dose Reduction or Treatment Delay for Toxicity:

Study treatment (cabozantinib or placebo) was withheld for unacceptable toxicity defined as:

- Intolerable Grade 2 toxicity that could not be adequately managed
- Grade 3 or greater non-hematological toxicity (including nausea, vomiting, or diarrhea despite optimal management)
- Urine protein/creatinine ratio > 2
- Grade 4 hematological toxicity

If the toxicity resolved to \leq Grade 1 or to baseline within 6 weeks of dosing and the toxicity was not deemed to be related to study drug, then the patient could restart treatment with no change in dose. If the toxicity resolved to \leq Grade 1 or to baseline within 6 weeks and the toxicity was deemed related to the study drug, the protocol-defined first dose reduction was to 100 mg, and the protocol-defined second dose reduction was to 60 mg. Patients that received a daily dose of 60 mg could restart at the same dose at the discretion of the investigator and could be re-escalated to the previous dose no sooner than 2 weeks beyond resolution of symptoms. Patients who were unable to tolerate a dose of 60 mg or who had a toxicity which did not resolve within 6 weeks were taken off treatment.

Blinding:

Placebo was administered in the same manner as the active agent and was packaged and matched to the study drug in color size, and shape to be indistinguishable from cabozantinib. Study treatment assignment and identity was unknown to the subject, investigators, study centers, IRC, central laboratory and study personnel. However, unblinding procedures were specified in the event that the treating physician assessed unblinding to be required for patient management.

Reviewer Comment: Even though an attempt was made to double-blind this study, it is most likely, due to the cabozantinib toxicity profile, that patients and providers were able to ascertain the treatment assignment which is a potential source of bias in assessment of the study endpoint.

Study Endpoints:

Evaluation of Efficacy:

A bone scan, liver MRI, and MRI or CT of the head, neck, chest, and abdomen were obtained at screening and were assessed by the IRRC using mRECIST criteria. If MRI of the liver was not available, liver metastases could be assessed by contrast enhanced triple phase CT. If lesions were seen or suspected on bone scan, an X-ray, CT, or MRI of the location of the bone scan lesion was to be done. After randomization, tumors were assessed by liver MRI and MRI or CT scans of the neck, chest, and abdomen every 12 weeks (\pm 5 days) until PD per mRECIST. If there were bone lesions at screening/baseline, an X-ray, CT, or MRI of the bone lesion(s) were to be repeated every 12 weeks (\pm 5 days) until PD was assessed by mRECIST. Bone scans were to be acquired at follow-up visits if only if clinically indicated (i.e., new metastasis suspicion). The same radiologic assessment method was used to assess a lesion at screening and after randomization.

Available clinical information such as history of new fracture/trauma, infection, cytology, and pathology that could have influenced the interpretation of radiographic images was documented at the time of tumor assessments. Tumor response and progression were assessed using mRECIST. Objective overall responses [complete response (CR), partial response (PR)] as determined by the investigator were confirmed with a follow-up tumor assessment at least four weeks after the criteria for the initial response was first met. The decision to discontinue study treatment due to PD was based on the assessment of the investigator. The analysis of the primary radiographic study endpoints was based on the assessment of tumor response and progression as assessed by the blinded IRC.

Evaluation of Safety:

Safety data was collect on the occurrence of adverse events (AE), serious AEs (SAEs), and deaths. Routine laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations (including vital sign measurements), and electrocardiogram (ECG) were obtained according to the monitoring plan described in Table 10. Central laboratories performed laboratory tests. For unscheduled visits that required a sample for a local laboratory, if feasible, a sample for the central laboratory was also collected. If a central laboratory sample was not obtained, the local laboratory results were collected for unscheduled visits that met AE criteria or were used for monitoring AEs. Results for standard laboratory analytes were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0, or for those not falling into a CTCAE descriptive terminology category, grading was based on sponsor-defined criteria.

Scheduled ECGs were digitally analyzed by a validated ECG laboratory. The Fridericia correction of the QT interval values (QTcF) provided by the digital analysis was used for assessment of AE and SAE. All scheduled ECG assessments were performed just prior to the PK sample collection.

Pharmacokinetics:

PK samples for analysis of cabozantinib plasma concentrations were collected up to 6 hours post-dose on Day 1 of Cycles 1 and 2 and at the time of treatment discontinuation.

Clinical Biomarker Measurements:

Blood samples for assessment of calcitonin (CTN) and carcinoembryonic antigen (CEA) were collected at screening and every 12 weeks (± 5 days) from randomization, concurrent with tumor assessments until PD was assessed per mRECIST. Additional assessments were performed at the discretion of the investigator. Blood plasma samples were collected for analysis of cabozantinib mechanism-of-action-based biomarkers and for genotyping/single nucleotide polymorphism analysis and to assess the mutational status of *RET*.

Study Endpoints:

Primary: PFS as assessed by the IRC using mRECIST criteria

Secondary: OS, ORR as assessed by the IRC using mRECIST criteria

Exploratory: To assess change in the M. D. Anderson Symptom Inventory Thyroid Module (MDASI-THY), a multi-system patient reported outcome measure to assess response to treatment.

Statistical Analysis Plan (See also, Dr. Shen's Statistical Review):

Statistical Methods:

For the primary endpoint of PFS, with a 2:1 (cabozantinib:placebo) randomization, 138 events were required to provide 90% power to detect a hazard ratio (HR) of 0.571 using the log-rank test and a 2-sided significance level of 5%. The primary analysis was event-driven, to be conducted after at least 315 subjects were randomized and at least 138 events (non-censored progression events as assessed by the IRC or non-censored deaths) were observed. The data cut-off for the primary PFS analysis was 06 April 2011.

Efficacy:

The primary analysis of PFS was performed on patients in the ITT population. Hypothesis testing to evaluate PFS between the two treatment arms was performed using the stratified log-rank test with a 2-sided 0.05 level of significance. The stratification factors were the same factors used to stratify the randomization: age (≤ 65 years versus > 65 years) and known prior receipt of a tyrosine kinase inhibitor (TKI) (Yes versus No). The median duration of PFS and the associated 95% confidence interval (CI) for each treatment arm was estimated using the Kaplan-Meier method. The HR was estimated using a Cox regression model and included the treatment groups as the main effect and stratified by the factors above.

If the result of the primary endpoint (PFS) was significant, the two key secondary endpoints would be tested in parallel. The ORR and OS would be tested at 2-sided 0.01 and 0.04 levels, respectively. An interim analysis of OS was expected to be performed at the 0.00006 level per a Lan-DeMets O'Brien-Fleming alpha spending function based on an expected 31% information level. The actual alpha level would be based on the actual information fraction at the time of the

analysis. If the result of the interim analysis for OS was not significant, the primary analysis of OS would be performed when the required number of deaths (217) had been observed. The primary analysis was expected to be conducted at the 0.04 significance level per the alpha spending function.

As the null hypothesis for PFS was rejected, the two key secondary endpoints were tested in parallel. The ORR was tested at the 0.01 α level. An interim analysis of OS was performed and a final analysis planned using a Lan-DeMets O'Brien-Fleming alpha-spending function to control the total α for OS at the 0.04 level.

The primary analysis of ORR was performed at the time of the primary analysis of the primary endpoint using patients in the ITT Population with measurable disease at baseline and was based upon response as determined by the IRC. Patients with no post-baseline data were counted as non-responders. A Cochran-Mantel-Haenszel method was used to adjust for randomization stratification factors. Point estimates of ORR, the difference in response rates between the two arms and associated 95% and 99% CIs were calculated.

The primary analysis for OS will be conducted after 217 deaths are observed in the study among subjects in the ITT Population to provide 80% power to detect a HR of 0.667 using the log-rank test and a 2-sided significance level of 4%. This corresponds to a 33.3% reduction in the risk of death, or a 50% increase in median survival from 22 to 33 months. A single planned interim analysis for OS occurred at the time of the primary analysis of PFS at the 44% information fraction (i.e., 96 deaths were observed) using the data base cut-off date of 15 June 2011. Type I error was controlled by implementing a Lan-DeMets O'Brien-Fleming alpha spending function to account for the actual information fraction at the time of the interim analysis (critical value 0.0009). The protocol does not include criteria for early stopping for futility. For patients who were alive at the time of data cut-off or who were lost to follow up, duration of OS was right censored at the date the patient was last known to be alive. Testing between the two treatment arms was performed by the stratified log-rank test with the same stratification factors as for PFS analyses. The median duration of OS was estimated using the Kaplan-Meier method. The HR was estimated using a Cox regression model with treatment group as the main effect and that included the above stratification factors. The influence of baseline and demographic characteristics on the effect of cabozantinib on PFS and ORR were evaluated as exploratory analyses.

Pharmacokinetics:

Cabozantinib plasma concentrations and non-compartmental PK parameters were summarized using descriptive statistics. The relationship between cabozantinib plasma concentrations and QTc effects was examined using a linear mixed effects model (Please refer to Dr. Yang's review for details).

Clinical Biomarkers:

Means values for CTN, CEA, soluble vascular endothelial growth factor receptor (sVEGFR2) and soluble KIT (sKIT) were determined. The differences in the means values between

treatment groups and pre- and post-treatment were assessed using paired and unpaired t-tests. The relationships between XL184 plasma exposure and changes in sVEGFR2 and sKIT, and between tumor marker biochemical response and radiologic response, were evaluated using linear regression. Tumor genotyping results and tumor marker biochemical responses were summarized.

Pharmacogenomics:

DNA samples derived from blood and tumor tissue were analyzed for alterations in the sequence of the gene encoding *RET*; subjects with a documented *RET* mutation were not required to provide a tumor sample for analysis. *RET* mutation status, MTC disease type (sporadic or hereditary), and presence or absence of the *RET* M918T mutation were evaluated in PFS and response rate subgroup analyses.

For blood DNA samples, *RET* exons 5, 8, 10, 11, and 13-16 (which cover the vast majority of the characterized *RET* mutations) were analyzed at a minimum. For tumor DNA samples, *RET* mutational hotspot exons 11 and 16 were analyzed initially, with additional exons analyzed subsequently if no mutations were identified in exons 11 and 16. All blood samples and the majority of tumor samples were sequenced using Sanger technology. Samples with low percentage tumor cell content were evaluated with a highly parallel sequencing method (b) (4) to increase sensitivity down to approximately 5% mutant allele burden. For a sample to be considered negative for *RET* mutation, the complete DNA sequence for exons 10, 11, and 13-16 must have been obtained, and all *RET* sequence analyzed must have been clearly free of alteration, with the exception of the single nucleotide polymorphisms (SNPs) G691S, L56M, or R982C. Blood or tumor samples that showed evidence for a *RET* sequence alteration were considered *RET* mutation positive if the identified mutation is listed as related to MTC or MEN 2 syndromes in the American Thyroid Association Medullary Thyroid Cancer Guideline publication. Note that *RET* sequence alterations not described in this publication were classified in the ‘unknown’ category, even though some of these are likely to be functional mutations. Also described as ‘unknown’ was any sample lacking sufficient sequence coverage of *RET*, and without an identified qualifying *RET* mutation. In addition, a subject is classified as having sporadic MTC if his or her blood or tumor DNA sample qualified as *RET* mutation negative as described.

Safety:

Safety data were summarized descriptively. All treatment emergent adverse events (TEAEs) with onset up to 30 days following the last dose of study drug were included in the analyses. The frequency and percentage of subjects with adverse events (AEs) were tabulated by system organ class and preferred term or only by preferred term. AEs resulting in treatment discontinuation, dose modification (dose reduction or dose interruption), serious adverse events (SAEs), and related SAEs were similarly summarized. For each patient, multiple events with the same preferred terms were counted only once at the respective level of summary.

All deaths occurring within 30 days of the last dose of study drug and those occurring more than 30 days after the last dose were summarized with respect to the cause of death and relationship to

study treatment. Select laboratory values are presented as change from baseline by CTCAE grade (or sponsor-defined) to worst grade after first dose. Change from baseline for selected vital signs (weight, systolic BP, and diastolic BP) and ECG parameters were summarized using descriptive statistics. For change from baseline ECG parameters, the 2-sided 90% confidence interval corresponding to each mean was also calculated. The change from baseline QTc for subjects in the XL184-treated population was done using a placebo-corrected QTc value. These data were analyzed using a linear mixed effects model that included subject as a random effect on intercept and slope of the concentration term. Parameter estimates from the model were used to calculate the upper bound of the 1-sided 95% confidence interval.

Analysis Sets:

Intent-to-Treat Population:

The intent-to-treat (ITT) population consisted of all patients who were randomized and were analyzed by treatment assignment.

Safety Population:

The Safety population consisted of all patients who received any amount of treatment with XL184 or placebo. The Safety population was analyzed according to the actual treatment received.

Per-Protocol Population:

The Per-protocol (PP) population included all patients in the Safety population who met the following criteria:

- Received treatment as randomized
- Had a baseline and at least one adequate post-randomization tumor assessment as scheduled per protocol, obtained at the time of suspected progression, or was determined to have progressive disease by clinical deterioration or death.
- Met all of the following inclusion criteria:
 - Had histologically confirmed, unresectable, locally advanced or metastatic MTC
 - Had an ECOG performance status ≤ 2
 - Had PD documented (CT, MRI, bone scan, or X-ray) at screening compared with images obtained within 14 months prior to screening as determined by the IRC or by the investigator (Protocol Amendment 2.0) using mRECIST criteria
 - Had organ and marrow functions as follows:
 - absolute neutrophil count $\geq 1500/\text{mm}^3$
 - platelets $\geq 100,000/\text{mm}^3$
 - hemoglobin ≥ 9 g/dL
 - bilirubin ≤ 1.5 mg/dL (excluding patients with Gilbert's syndrome)
 - serum creatinine ≤ 1.5 mg/dL (or calculated creatinine clearance ≥ 60 mL/min if the serum creatinine was >1.5 mg/dL),
 - ALT and AST ≤ 2.5 times the upper limit of normal
- Did not meet any of the following Exclusion Criteria:
 - Had previously received treatment with XL184

- Had brain metastases or spinal cord compression, unless completed radiation therapy ≥ 4 weeks prior to randomization and stable without steroid and without anticonvulsant treatment for ≥ 10 days
- Had serious intercurrent illness, such as:
 - hypertension (two or more blood pressure readings performed at screening of >140 mm Hg systolic or >90 mm Hg diastolic),
 - unhealed wounds from recent surgery or
 - cardiac disease (cardiac arrhythmias, symptomatic congestive heart failure or unstable angina pectoris within the past 3 months, or myocardial infarction, stroke, or transient ischemic attack within the past 6 months)

PK Analysis Population:

The PK analysis was performed on the full Safety Population and on the subset of the Safety Population with uninterrupted dosing of study drug (140 mg/day) administered up to and including the day of the PK visit.

ECG Analysis Populations:

The ECG population included all patients who received at least one dose of study drug, had at least one baseline ECG before dosing and at least one on-treatment ECG after dosing, and who met the dosing and ECG collection timing requirements specified in the ECG and Pharmacokinetic-Pharmacodynamic (PK/PD) Statistical Analysis Plan. The PK/PD electrocardiographic population included subjects in the ECG population that received at least 1 dose of cabozantinib, had at least 1 measurable post-dose concentration time matched to an ECG change from baseline, and met the PK collection and timing requirements specified in the ECG and PK/PD Statistical Analysis Plan.

Table 9. XL184-301: Amendments to the Protocol

| PROTOCOL VERSION | VERSION DATE | # ENROLLED | | MAJOR AMENDMENTS |
|-----------------------|----------------|-------------|---------------|--|
| | | XL184 N=219 | Placebo N=111 | |
| Original | April 21, 2008 | 0 | 0 | |
| Amendment Number: 1.0 | June 11, 2008 | 197 | 98 | <p>In response to comments received from the FDA during an SPA:</p> <ul style="list-style-type: none"> • The ECG and PK time points were modified so that all ECG assessments were time matched with PK sampling. • After a dose reduction or delay, subjects could be re-escalated no sooner than two weeks beyond resolution to Grade ≤ 1 or to the baseline value; subjects unable to tolerate doses of cabozantinib below 60 mg once a day were to be withdrawn from study. • Subject stratification categories were modified to: <ul style="list-style-type: none"> ○ Age: ≤ 65 years vs. >65 years ○ Prior receipt of TKI: Yes vs. No • The enrollment of subjects with only nonmeasurable disease was limited to 10% of the total number of subjects to minimize heterogeneity in the assessment of tumor response. • The inclusion criterion regarding an archival, fresh tumor acquisition or <i>RET</i> mutation status report was removed, and the text related to these was included in the required screening procedures. • The inclusion criterion that a subject must have a life expectancy of >3 months was removed. |
| Amendment Number: 2.0 | September 2010 | 22 | 13 | <ul style="list-style-type: none"> • For study eligibility, PD was determined by the investigator at screening instead of requiring confirmation of PD by a blinded radiologist at the IRC. • A local laboratory result was allowed during the Pre-Treatment Period when the result of an individual test performed at the central laboratory was unavailable. |

Table 10. Protocol XL184-301: Study Assessments

| Assessments | Pre-Treatment Period ^a | | Treatment Period ^b | | | | | Post-Treatment Period | | |
|---|--|---------------|---------------------------------|----------------------------------|-------------------|------------------|-------------------|--|--|--|
| | Screening (Within 28 Days of Randomization) | Randomization | Cycles 1 - 2 (± 2 days) | | | | | Day 57 (± 5 days) (C3D1 and beyond) | 30 days (+7) Post Last Dose ^c | Extended Post- Treatment Follow-Up (Every 90 [±15] days) ^d |
| | | | Pre- Dose Day 1 (C1D1) | Post- Dose Day 1 (C1D1) | Day 15 (C1D15) | Day 29 (C2D1) | Day 43 (C2D15) | | | |
| Informed consent | X ^e | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical and cancer history | X | | | | | | | | | |
| Physical examination ^f | X | | X ^a | | | X | | X | X | |
| Vital signs ^g | X | | X | X | X | X | X | X | X | |
| 12-lead ECG ^h | X | | X | X | | X | | | | |
| ECOG performance status ^f | X | | X ^a | | | X | | X | X | |
| Clinical laboratory tests ⁱ | X | | X ^a | | X | X | X | X | X | |
| Urinalysis ^j | X | | X ^a | | | X | | X | X | |
| Pregnancy test ^k | X | | X ^a | | | X | | X | X | |
| PT, INR, PTT ^f | X | | | | | X | | X | X | |
| Calcitonin, CEA, TSH, and FT4 measurements ^l | X | | | | | | | X | X ^m | |

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| Assessments | Pre-Treatment Period ^a | | Treatment Period ^b | | | | | Post-Treatment Period | | |
|---|--|---------------|--|----------------------------------|-------------------|------------------|-------------------|--|--|--|
| | Screening (Within 28 Days of Randomization) | Randomization | Cycles 1 - 2 (± 2 days) | | | | | Day 57 (± 5 days) (C3D1 and beyond) | 30 days (+7) Post Last Dose ^c | Extended Post- Treatment Follow-Up (Every 90 [±15] days) ^d |
| | | | Pre- Dose Day 1 (C1D1) | Post- Dose Day 1 (C1D1) | Day 15 (C1D15) | Day 29 (C2D1) | Day 43 (C2D15) | | | |
| MDASI Thyroid Module ^a | X | | | | | | | X | X ^m | |
| Documentation of progressive disease ^o | X | | | | | | | | | |
| Tumor assessment ^p | X | | | | | | | X | X ^m | |
| Randomization | | X | | | | | | | | |
| Study treatment administration | | | Study treatment will be administered daily | | | | | | | |
| PK blood samples ^q | | | X | X | | X | | | | |
| Pharmacogenomic blood sample ^r | | | X | | | | | | | |
| Pharmacodynamic blood samples ^s | X | | X | X | | X | | X | X ^m | |
| Archival slides or a fresh tumor biopsy | X ^t | | | | | | | | | |
| Concomitant medications | X | | X | X | X | X | X | X | X | |
| Adverse events | X | | X | X | X | X | X | X | X | |
| Study treatment accountability | | | | | X | X | X | X | X | |
| Follow-up contact | | | | | | | | | X ^v | |

- ^a Screening must occur within 28 days of randomization. Only the physical exam at screening includes height. If the screening visit occurred within 7 days of the first dose, the clinical laboratory tests, urinalysis, ECOG performance status, pregnancy tests, and physical examination need not be repeated prior to dosing on C1D1. Results must be reviewed before randomization to confirm that the subject continues to meet eligibility criteria.
- ^b During the Treatment Period, protocol-specified clinic visits should occur within ± 2 days of the nominal visit during the first 2 cycles (except for Days 1 and 2 of Cycle 1) and within ± 5 days of the nominal visit day from Cycle 3 and on, unless otherwise specified. In the absence of unacceptable treatment-related toxicity or PD, subjects may continue with daily dosing.
- ^c Visit will be conducted 30 (+ 7) days after the last dose of study treatment.
- ^d Every 12 weeks (± 15 days) post last dose of study treatment until final survival status is determined.
- ^e Informed consent may be obtained more than 28 days before randomization, and evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies.
- ^f Measurement taken pre-dose. The physical examination should include weight.
- ^g Vital signs consist of 5-minute sitting blood pressure, pulse, respiratory rate, and oral temperature taken within 1 hour prior to dosing, 4 hours after dosing (will not be taken on C1D15 [Day 15] and C2D15 [Day 43]), and at the same timepoints of PK/pharmacodynamic blood draws.
- ^h 12-lead ECG will be recorded in triplicate (recording repeated three times consecutively within 30 minutes with an interval of at least 2 minutes between ECG) at screening, C1D1 pre-dose and 2, 4, and 6 hours post-dose and C2D1 pre-dose and 2, 4, and 6 hours post-dose. All ECG assessments are time matched with pharmacokinetic samples such that the ECG assessments are performed just prior to the blood sample collection.
- ⁱ Clinical laboratory tests consist of hematology, serum chemistry panel, and urine protein/creatinine ratio prior to dosing.
- ^j Urinalysis will be performed on screening, pre-dose C1D1, pre-dose C2D1, pre-dose C3D1 (Day 57) and every 8 weeks (± 5 days) thereafter, and at End-of-Treatment.
- ^k Pregnancy tests will be done on serum samples in women of childbearing potential prior to dosing.
- ^l Calcitonin, CEA, TSH, and FT4 levels will be assessed at screening and every 12 weeks (± 5 days) from randomization until PD per mRECIST, to coincide with tumor assessments: pre-dose.
- ^m If treatment was discontinued for reasons other than PD or withdrawn consent, the following will continue every 12 weeks thereafter (± 5 days), following randomization until documented tumor progression: 1) Tumor assessments per mRECIST; 2) Pharmacodynamic blood sample; 3) Calcitonin, CEA, TSH, and FT4 measurements; and 4) MDASI Thyroid Module.
- ⁿ Clinical symptoms (including pain and diarrhea) will be assessed per the MDASI Thyroid Module at screening and every 12 weeks (± 5 days) from randomization until PD per mRECIST, to coincide with tumor assessments: pre-dose.
- ^o Documentation of progressive disease within 14 months of screening as determined by the investigator per mRECIST (see Section 5.13.1.1).

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- ^p All known lesions will be assessed. All site assessments of radiographic images will be performed by a radiologist. Tumors will be assessed by bone scan (scintigraphy), liver MRI, and MRI or CT of the head, neck, chest, and abdomen at screening, per mRECIST. Liver metastases may be assessed by contrast-enhanced triple phase CT when MRI is not possible. If lesions are seen or suspected on bone scan, an X-ray, CT, or MRI of the location of the bone scan lesion will be done. This assessment may serve as documentation of prior progression within 14 months if an appropriate historical image is available for reference. After screening, tumors will be assessed by liver MRI and MRI or CT scans of the neck, chest, and abdomen every 12 weeks (\pm 5 days) from randomization until PD per mRECIST. If there are bone lesions at baseline, an X-ray, CT, or MRI of the bone lesion(s) will be repeated every 12 weeks (\pm 5 days) until PD per mRECIST. Bone scans will only be acquired at follow up visits if clinically indicated (ie, new metastasis suspicion). If lesions are seen or suspected on the bone scan, an X-ray, CT, or MRI of the location of the bone scan lesion will be acquired. The same assessment method will be used to assess a lesion at screening and after randomization. Confirmation of response or progression should be performed no earlier than 4 weeks after the criteria for the initial response or progression are first met.
- ^q Blood samples for PK analysis will be collected from subjects at the following timepoints: C1D1 (Day 1): pre-dose and 2, 4, and 6 hours post-dose, C2D1 (Day 29): pre-dose and 2, 4, and 6 hours post-dose. PK sample collection is required in all subjects unless otherwise approved by the Sponsor.
- ^r Where not prohibited by local and country regulations, a blood sample will be collected at pre-dose C1D1 from all subjects that may be used for genotyping/single nucleotide polymorphism analysis to correlate subject DNA sequence variation with safety, tolerability, and potential clinical benefit, as well as to assess mutational status of RET. Sites that are unable to perform the pharmacogenomic sample collection as specified will be permitted to participate in the study upon Sponsor approval.
- ^s Where not prohibited by local and country regulations, one blood sample will be collected at screening for a baseline of pharmacodynamic studies (intra-subject variability). Where not prohibited by local and country regulations blood samples for pharmacodynamic analysis will be collected at the following timepoints: C1D1 (Day 1): pre-dose and 4 hours post-dose, C2D1 (Day 29): pre-dose and 4 hours post-dose, and C3D1 (Day 57) and every 12 weeks (\pm 5 days) from randomization to up to 2 years after C1D1, to coincide with tumor assessments: pre-dose. Pharmacodynamic sample collection is required in all subjects unless otherwise approved by the Sponsor.
- ^t The subject has at least 10 unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy will be identified by the investigator for shipment to the central lab. If the site can provide the Sponsor with the subject's documented RET mutation status, the subject may be enrolled without providing slides.
- ^u Follow-up information will include survival status, subsequent cancer treatment, and any SAEs considered to be possibly related to study treatment, evaluated in the context of any new treatments that have been initiated that would confound the ability to assess the event.

5.3.2 Study Title: A phase 1 dose-escalation study of the safety and pharmacokinetics of XL184 administered orally to subjects with advanced malignancies (XL184-001)

Study Period:

First Patient Enrolled: September 30, 2005

Last Patient Completed: The last patient was enrolled in August, 2008. Follow-up is ongoing

Children Enrolled: None

Investigators/Study Centers: Five US Centers:

Site Number 1: Razelle Kurzrock, MD FACP; The University of Texas MD Anderson Cancer Center; Houston, TX

Site Number 2: Ravi Salgia, MD PhD; University of Chicago; Chicago, IL

Site Number 3: Douglas Ball, MD; Johns Hopkins University; Baltimore, MD

Site Number 4: Roger Cohen, MD, replaced by Barbara Burtness, MD; Fox Chase Cancer Center; Philadelphia, PA

Site Number 5: David Pfister, MD; Memorial Sloan-Kettering Cancer Center; New York, NY

Data Cutoff Date: April 19, 2010

Objectives:

| TABLE 11. XL184-001: STUDY OBJECTIVES | |
|---------------------------------------|--|
| Primary | <ul style="list-style-type: none"> To evaluate the safety and tolerability of oral administration of XL184 in patients with advanced malignancies. To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of oral administration of XL184. To evaluate plasma pharmacokinetics (PK) and estimate renal elimination of oral administration of XL184 in patients with advanced malignancies. |
| Secondary | <ul style="list-style-type: none"> To evaluate the long-term safety and tolerability of XL184 after oral administration for up to one year in subjects with advanced malignancies. To evaluate tumor response (preliminary antitumor activity) after repeated administration of XL184. To evaluate the pharmacodynamic correlates of XL184 activity. To assess the progression-free survival (PFS) and duration of response in subjects with advanced or recurrent medullary thyroid cancer (MTC). |
| Exploratory | <ul style="list-style-type: none"> To further characterize the PK and pharmacodynamic parameters of XL184. To correlate the potential pathway dysfunction of thyroid tumor relevant genes such as RET and BRAF and relevant downstream signaling molecules with clinical outcome. To assess the pharmacodynamic effect of XL184 in biological samples |

Study Design:

XL184-001 was a Phase 1, nonrandomized, open-label, dose-escalation, first-in-human study of XL184 in patients with advanced malignancies. Patients were treated either on an intermittent 5&9 (five days on study treatment and nine days no study treatment) schedule or on a once-daily schedule (following Amendment 4) administered in two 2-week cycles. Patients could continue into the Treatment Extension Period if they did not demonstrate progressive disease (PD) or unacceptable XL184-related toxicity. In the Treatment Extension Period, patients received treatment with XL184 in 2-week cycles at the same dose and schedule administered during the Treatment Period. The Treatment Extension Period could last for up to one year at the discretion of the investigator and beyond one year with the agreement of the sponsor. Patients were assessed 30, 90 and 180 days after the final dose of cabozantinib for survival, subsequent treatments and for SAEs deemed to be cabozantinib-associated.

Cabozantinib was administered at doses ranging from 0.08 to 11.52 mg/kg on an intermittent 5&9 schedule using a powder-in-bottle (PIB) formulation, at 175 and 265 mg on a once-daily schedule using a PIB formulation, and at 175 and 250 mg on a once-daily schedule using a capsule formulation. The study used a conventional “3+3” design for dose escalation to determine the MTD which was assessed through Cycle 2 (Days 1-28).

Dose-limiting toxicity was defined as either of the following occurring during the Study

Treatment Period:

- The occurrence of a treatment-related AE that, in the opinion of the CRC, was of potential clinical significance such that further dose escalation would expose subjects in higher dose cohorts to risk of irreversible medical harm or require medical treatment to avoid irreversible medical harm.
- Any cabozantinib-related Grade 3 or Grade 4 non-hematologic toxicity including Grade 3 nausea and/or vomiting and Grade 3 diarrhea despite prophylaxis and/or treatment or the following Grade 4 hematologic toxicities: Grade 4 thrombocytopenia, Grade 4 neutropenia of > 5 days duration, or Grade 4 neutropenia of any duration with fever or documented infection.

Following Cycle 2, patients were allowed to dose-escalate to the highest cohort level for which there was 4 weeks of safety data demonstrating acceptable tolerability for at least three patients. Under Amendment 4 of the protocol, when capsule formulation became available, patients who were receiving the suspension formulation on a once daily schedule were allowed to transition to the capsule formulation on a once daily schedule at a dose agreed upon by the sponsor using available capsule strengths. When the oral suspension supplies were exhausted, all subjects were transitioned to the capsule formulation at a dose at or below the MTD. After determination of the MTD, with the agreement of the CRC, subjects in cohorts at lower dose levels had the option of escalating to the daily dose MTD during the Treatment Extension Period.

Once the daily oral capsule MTD was defined as 140 mg, an expansion cohort was enrolled with at least 20 patients to receive cabozantinib at the MTD.

Patients were followed for up to death or up to 180 days following the last dose of study drug.

Table 12. XL184-001 Dose Escalation Schedule

| Cohort Number | Formulation | Starting XL184 Dose Level | Schedule ^a |
|-----------------|-------------|---------------------------|-----------------------|
| 1 | PIB | 0.08 mg/kg | Intermittent 5&9 |
| 2 | PIB | 0.16 mg/kg | Intermittent 5&9 |
| 3 | PIB | 0.32 mg/kg | Intermittent 5&9 |
| 4 | PIB | 0.64 mg/kg | Intermittent 5&9 |
| 5 | PIB | 1.28 mg/kg | Intermittent 5&9 |
| 6 | PIB | 2.56 mg/kg | Intermittent 5&9 |
| 7 | PIB | 5.12 mg/kg | Intermittent 5&9 |
| 8 | PIB | 7.68 mg/kg | Intermittent 5&9 |
| 9 | PIB | 11.52 mg/kg | Intermittent 5&9 |
| 10 | PIB | 175 mg | Daily |
| 11 | PIB | 265 mg | Daily |
| 12 | Capsule | 175 mg | Daily |
| 13 | Capsule | 250 mg | Daily |
| 99 ^b | Capsule | 175 mg | Daily |

Intermittent 5&9, five days of daily drug administration, followed by a nine-day observation period every two weeks; MTD, maximum tolerated dose; PIB, powder-in-bottle.

^a Subjects in Cohorts 1-5 were given a single dose of XL184 followed by 72 hours of no study drug treatment before starting the Intermittent 5&9 schedule (Section 9.4.4).

^b Cohort 99 was the MTD Expanded Cohort.

*175 mg as malate salt is approximately equivalent to 140 mg cabozantinib free base capsules.

Number of Subjects: Eighty-five subjects were enrolled and analyzed.

Study Population:

Inclusion Criteria:

- Histologically confirmed metastatic or unresectable solid tumor which is refractory to standard therapy or for which no standard is available (Note: Earlier protocol versions also allowed subjects with lymphoma)
- ≥ 18 years of age; life expectancy ≥ 3 months
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
- Organ/marrow function:
 - absolute neutrophil count ≥ 1500/mm³,
 - platelets ≥ 100,000/mm³,

- hemoglobin ≥ 9 g/dL,
- bilirubin ≤ 1.5 mg/dL,
- serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 times the upper limit of normal if no liver involvement or ≤ 5 times the upper limit of normal with liver involvement.

MTD Expanded Cohort (only):

- MTD Expanded Cohort (Cohort 99) was to include at least 20 subjects with metastatic and/or locally advanced or locally recurrent MTC not appropriate for surgical resection
- measurable (by RECIST)

Exclusion Criteria:

- Chemotherapy or immunotherapy within 4 weeks (nitrosoureas or mitomycin C within 6 weeks) before the scheduled first dose of XL184 and had not recovered from toxicity back to baseline or Grade ≤ 1 .
- Radiation within 4 weeks of XL184 treatment.
- Investigational drug within 30 days of the first dose of XL184.
- Not recovered to Grade ≤ 1 from adverse events (AEs) due to investigational drugs or other medications that were administered more than 4 weeks before study enrollment.
- Known brain metastases.
- Uncontrolled intercurrent illness (active infection, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness) or social situations that would limit compliance with study requirements.

Study drug:

Cabozantinib was administered orally as a suspension at the following dose levels: 0.08, 0.16, 0.32, 0.64, 1.28, 2.56, 5.12, 7.68, 11.52 mg/kg and as 25 mg and 100 mg capsules administered at the 175 and 250 mg dose levels.

Study Endpoints

- Best overall response (BOR) and objective response rate (ORR), duration of Treatment (DurT) for patients treated at the MTD as determined by the study investigator.
- Safety
- Pharmacokinetics
- Exploratory: biomarkers (calcitonin, CEA, VEGF, PIGF, EPO, sVEGFR2, sMET)

Analysis:

Efficacy: Frequency count and percentages are presented for the best overall response (BOR) and the objective response rate (ORR). Exact 90% confidence intervals are calculated for ORR

by Clopper-Pearsons method. Descriptive statistics (including number, mean, median, standard deviation, and range) are presented for duration of treatment for those subjects who had an ORR. Best percent change in tumor size since baseline is presented in a waterfall plot.

Safety: Safety results were summarized descriptively. Adverse events and SAEs for subjects who received at least one dose of study drug were tabulated by system organ class and preferred term as defined by the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were summarized by grade using the Common Terminology Criteria for Adverse Events (CTCAE) and relationship to study drug. Results from standard laboratory tests were summarized by change from baseline in CTCAE grade.

Pharmacokinetics: Descriptive statistics (including number, mean, median, standard deviation, and range) for PK parameters were tabulated by dose level and treatment schedule. Estimated renal elimination was tabulated by dose level.

Amendments to the protocol

| TABLE 13. XL184-001: MAJOR AMENDMENTS TO THE CLINICAL PROTOCOL | | |
|--|---------------|---|
| Protocol Version | Version Date | Major Amendments |
| Original | June 7, 2005 | - |
| Amendment Number: 1.0 | July 21, 2005 | <ul style="list-style-type: none"> The decision for dose escalation was changed to be based on safety data from subjects who completed two cycles of study drug treatment instead of one cycle. Subjects who withdrew from the study during the first two cycles for reasons other than safety could be replaced. |
| Amendment Number: 2.0 | July 6, 2006 | <ul style="list-style-type: none"> The treatment schedule was changed to two 14-day treatment cycles for the Treatment Period, with safety data from the 28-day Treatment Period reviewed prior to dose escalation decisions. This schedule change eliminated the 72-hour interval between the first and second dose. With the agreement of the CRC, subjects could continue to receive study drug for more than 1 year. Inclusion criterion #10 (referring to subjects who had more than three prior regimens) was modified: the determination of suitability for enrollment was changed from the CRC to the sponsor. Exclusion criterion #4 was modified: the threshold for recovery was modified to “Grade \leq 1 or to within 10% of baseline values.” |

| | | |
|-----------------------|---------------|---|
| Amendment Number: 3.0 | March 5, 2007 | <ul style="list-style-type: none"> • A new fixed-dose, once daily treatment schedule was introduced for additional cohorts instead of the weight-based dosing on the Intermittent 5&9 schedule used for previous cohorts. • The objectives were modified to reflect daily dosing of cabozantinib instead of the Intermittent 5&9 schedule. • The secondary objective to radiographically evaluate the effects of XL184 on tumors in subjects in the MTD Cohort by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was removed in Amendment 3 because of the lack of a standardized imaging approach across sites and tumor types. • Exclusion criterion #4 was modified: the threshold for recovery was reverted to “Grade ≤ 1.” |
| Amendment Number: 4.0 | July 17, 2007 | <ul style="list-style-type: none"> • A new oral capsule formulation was introduced to replace the liquid suspension formulation to define a daily MTD. • The number and type of subjects enrolled in the MTD Cohort was expanded to consist of 25-28 (instead of 12-15) subjects with refractory solid tumors, at least 20 of whom had a diagnosis of metastatic, locally advanced, or recurrent MTC. • The exploratory objectives from the original protocol were changed to secondary objectives. • Additional secondary objectives were added for subjects in the MTD Expanded Cohort: <ul style="list-style-type: none"> ○ To assess the PFS and duration of response in subjects with advanced or recurrent MTC. ○ To further characterize the PK and pharmacodynamic parameters of XL184. ○ To correlate the potential pathway dysfunction of thyroid tumor relevant genes such as RET and BRAF and relevant downstream signaling molecules with clinical outcome. • An additional exploratory objective was added to assess the pharmacodynamic effect of cabozantinib in biological samples. • Inclusion criterion #1 was reworded to limit subjects to those with solid tumors only: The subject had a histologically confirmed solid tumor that was metastatic or unresectable and is no longer responding to therapies known to prolong survival or to other standard therapies, or had disease for which no |

| | | |
|-----------------------|---------------|---|
| | | <p>standard therapy exists.</p> <ul style="list-style-type: none"> • Inclusion criterion #9 was modified to define females of childbearing potential as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. Amenorrhea for 12 months must be in the absence of chemotherapy, antiestrogens, or ovarian suppression. • Inclusion criterion #10 (referring to subjects who had more than three prior regimens) was removed and a new inclusion criterion was added for subjects in the MTD Expanded Cohort: <ul style="list-style-type: none"> ○ Included at least 20 subjects with metastatic and/or locally advanced or locally recurrent MTC not appropriate for surgical resection. ○ Had measurable disease as defined by RECIST criteria. ○ Provided 15 unstained slides of archival tumor tissue or paraffin block. If 15 unstained slides were not available, the subject may have been enrolled following a discussion with the sponsor. • Exclusion criterion #1 was modified: a clarification was added that subjects would not be eligible if they had not recovered from toxicity (ie, back to baseline or Grade \leq 1). |
| Amendment Number: 5.0 | June 30, 2009 | <ul style="list-style-type: none"> • The frequency of assessments was reduced for subjects who had been on study more than one year. After at least one year on study, the 8-week tumor assessment was changed to a 12-week tumor assessment schedule. • The ACTH stimulation test was not required to be collected after subjects had been on study for greater than one year. • The number of dose reductions allowed was increased from two to three dose reductions. |

Clinical Review
Ruthann Giusti, M.D.
NDA 203756
Cometriq [Cabozantinib (XL184)]/Exelixis

5.3.3 Study Title: A phase 2 study of XL184 in Subjects with Progressive or recurrent Glioblastoma Multiforme in First or Second Relapse (XL184-201)

Study Period:

First Patient Enrolled: June 2, 2008

Last Patient Completed: Ongoing. Closed to enrollment.

Children Enrolled: None

Investigators/Study Centers: Eight US Sites:

- Marc C. Chamberlain, MD Site 1519 University of Washington; Seattle, WA
- Timothy Cloughesy, MD Site 1510 Brain Research Institute, University of California, Los Angeles; Los Angeles, CA
- John F. DeGroot, MD Site 1419 University of Texas MD Anderson Cancer Center; Houston, TX
- Michael D. Prados, MD Site 1513 University of California, San Francisco; San Francisco, CA
- Tom Mikkelsen, MD Site 3120 Henry Ford Hospital; Detroit, MI
- David A. Reardon, MD Site 1231 Duke University Medical Center; Durham, NC
- David Schiff, MD Site 1230 University of Virginia Health System; Charlottesville, VA
- Patrick Y. Wen, MD Site 1110 Dana-Farber Cancer Institute (which includes Dana-Farber Cancer Institute, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, and Brigham and Women's Hospital); Boston, MA

Data cutoff Date: September 1, 2010 (Treatment Group A only)

Objectives:

The study objectives are listed in Table 14 below:

| | |
|-------------|---|
| Primary | <ul style="list-style-type: none"> To evaluate objective response rate (ORR) for subjects with recurrent or progressive glioblastoma multiforme (GBM) following treatment with XL184 To evaluate the safety and tolerability of XL184 in this population |
| Secondary | <ul style="list-style-type: none"> To assess duration of response, 6-month and median PFS, and overall survival To further characterize the pharmacokinetic (PK) and pharmacodynamic parameters of XL184 To correlate the pathway dysfunction of GBM-relevant genes such as MET and of relevant downstream signaling molecules with clinical outcome To correlate changes in serial vascular magnetic resonance imaging (vascular MRI) with clinical outcome To analyze tumor volumetrics based on MRI To evaluate the glucocorticoid-sparing effect of XL184 |
| Exploratory | <ul style="list-style-type: none"> To assess duration of response, 6-month and median PFS, and overall survival To further characterize the pharmacokinetic (PK) and pharmacodynamic parameters of XL184 To correlate the pathway dysfunction of GBM-relevant genes such as MET and of relevant downstream signaling molecules with clinical outcome To correlate changes in serial vascular magnetic resonance imaging (vascular MRI) with clinical outcome To analyze tumor volumetrics based on MRI To evaluate the glucocorticoid-sparing effect of XL184 |

Study Design:

XL184-201 is an ongoing multi-center, open-label, single agent, single-arm trial of patients with recurrent or progressive GBM in first or second relapse. Two dose levels were explored: 140 mg and 100 mg dosed orally once per day (qd). In the initial study design, subjects were to receive cabozantinib at a starting dose of 140 mg taken orally qd (Treatment Group A). The protocol was subsequently amended to explore the tolerability and antitumor activity of XL184 at a lower starting dose of 100 mg qd (Treatment Group B and Treatment Group C). Group B differs from Group C primarily in the criteria for radiological assessment of tumor response: modified Macdonald criteria for Group B and modified Response Assessment in Neuro-Oncology (RANO) criteria for Group C. Exelixis has provided an interim report including safety data for Group A as of 01 September 2010. Subjects in Group A were retrospectively subdivided into Group A1 (anti-angiogenic therapy naïve) or Group A2 (previously treated with anti-angiogenic therapy). For Group A, the study consisted of a Pre-Treatment Period for screening evaluations 14 days before starting study treatment, a Treatment Period consisting of 4-week cycles, and a Post-Treatment Period 30 (+7) days after the final dose of study drug for follow-up assessments.

Follow-up information was collected quarterly after the 30-day Post-Treatment Visit until death or loss to follow-up. Subjects were allowed to remain in the Study Treatment Period until they exhibited disease progression or unacceptable toxicity.

Number of Subjects:

Approximately 225 subjects were planned for enrollment into the three treatment groups: 46 subjects in Group A, 30 subjects in Group B, and 125 subjects in Group C. A total of 222 subjects were enrolled: 46 subjects in Group A (A1: n = 34, A2: n = 12), 59 subjects in Group B, and 117 subjects in Group C.

Study Population:

Inclusion Criteria:

- The subject had radiographic evidence of progressive or recurrent GBM in the first or second relapse. Subjects with an initial diagnosis of Grade 3 glioma that relapsed as GBM were eligible, provided that the Grade 3 glioma was treated with external beam radiation therapy and systemic chemotherapy.
- The subject had a Karnofsky Performance Scale (KPS) of $\geq 60\%$.
- Archival tumor tissue, paraffin block, or frozen tumor tissue was available (where allowed by local regulatory bodies, including IRB policies).

Exclusion Criteria:

- The subject had received any of a variety of treatments within specified time intervals before the first dose of cabozantinib.
- The subject had received more than two prior systemic antitumor therapies, including initial treatment for GBM and treatment for one prior relapse. Surgical resection was not considered a prior systemic antitumor therapy.
- The subject had evidence of acute intracranial or intratumoral hemorrhage either by MRI or computerized tomography (CT) scan.
- The subject had received enzyme-inducing anti-epileptic agents within 14 days before the first dose of XL184 (eg, carbamazepine, phenytoin, phenobarbital, primidone).
- The subject had not recovered to National Cancer Institute CTCAE v3.0 Grade ≤ 1 from adverse events (AEs) due to antineoplastic agents, investigational drugs, or other medications that were administered before study enrollment.
- The subject had serious intercurrent illness, such as uncontrolled hypertension (sustained blood pressure [BP] readings of > 140 mmHg systolic or > 90 mmHg diastolic not controlled with antihypertensive medication), unhealed wounds from recent surgery or clinically significant cardiac arrhythmias or a recent history of significant disease such as either symptomatic congestive heart failure or unstable angina pectoris within 3 months or myocardial infarction within 6 months before the first dose of cabozantinib.

Study drug:

Cabozantinib was administered orally as 20-mg and 80-mg capsules (lot numbers used for subjects in Group A: 20-mg capsules: L0200881, L0205271, L0209383, L0209927; 80-mg capsules: 07-0003, 07-0107, L0201455). The starting dose for Group A was 140 mg administered daily (qd). The starting dose for Groups B and C was 100 mg qd.

Study Endpoints

Evaluation of Efficacy:

For patients in Treatment Group A and Treatment Group B, disease response and progression will be evaluated using the Macdonald criteria. Treatment Group C will be evaluated using the modified RANO criteria. Efficacy assessments will be evaluated by the investigator and by a central independent radiology facility (IRF).

For Treatment Group A, patients will be evaluated using MRI at baseline, at 8 weeks (\pm 4 days) after first dose, 16 weeks (\pm 4 days), 26 weeks (\pm 4 days), 32 weeks (\pm 4 days), and at 8-week (\pm 4 days) intervals thereafter. Response and progression will be determined per Modified A Macdonald.

For Treatment Group B, patients will be evaluated by MRI scan at baseline, at 4 weeks (\pm 4 days) after first dose, at 8 weeks (\pm 4 days), 16 weeks (\pm 4 days), 26 weeks (\pm 4days), 32 weeks (\pm 4 days), and at 8-week (\pm 4 days) intervals thereafter. A daily record of glucocorticoid use will be documented in the CRF starting 30 days before the first dose of study treatment through the later of 30 days after the last dose of study treatment or the date of the subject's last MRI scan. Neurologic status and glucocorticoid use will be assessed at the time of every tumor evaluation. Response and progression will be determined per Modified B Macdonald criteria.

For Treatment Group C, patients will be evaluated by MRI scan at screening, at 4 weeks (+4 days) after first dose, and then every 6 weeks (\pm 7 days) thereafter. A daily record of glucocorticoid use will be documented in the CRF starting 30 days before the first dose of study treatment through the later of 30 days after the last dose of study treatment or the date of the subject's last MRI scan. Neurological and clinical status will be assessed at the time of every tumor evaluation. Glioblastoma symptom inventory will be completed on C1D1 and at the time of every post-baseline tumor assessment. Response and progression for Treatment Group C will be determined by modified Response Assessments for Neuro-Oncology (RANO) criteria.

Safety:

Safety assessments included AEs, serious adverse events (SAEs), deaths, use of concomitant medications, electrocardiogram (ECG), physical examination, symptom-directed examination, neurological assessment, vital signs, and clinical laboratory tests (including analysis of hematology, serum chemistry, and urinalysis). The original verbatim terms used by investigators to identify AEs on CRFs will be translated into lower-level terms and then preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and graded according to the NCI-CTCAE V 3.0. All safety summaries will be based upon the safety population.

Statistical Analysis Plan:

Sample Size:

The sample size of approximately 225 subjects includes:

- 46 subjects in Treatment Group A (140 mg starting dose)
- Up to 15 subjects in Treatment Group B1 (100 mg starting dose and have not received prior therapy with inhibitors of VEGF or VEGFR2)
- Up to 15 subjects in Treatment Group B2 (100 mg starting dose and have received prior therapy with inhibitors of VEGF or VEGFR2)
- At least 80 evaluable subjects in Treatment Group C1 (100 mg starting dose and have not received prior therapy with inhibitors if VEGF or VEGFR2)
- At least 45 evaluable subjects in Treatment Group C2 (100 mg starting dose and have received prior therapy with inhibitors if VEGF or VEGFR2)
- 10-20% of subjects are expected to be not evaluable.

The study was originally designed to test the following hypotheses for the primary efficacy endpoint, PFS at 6 months, in Treatment Group A:

H0: Proportion with PFS at 6 months = 25%

HA: Proportion with PFS at 6 months = 45%

The sample size estimate of 46 subjects was based upon the binomial distribution with a 1-sided nominal alpha of 0.05 and power of 85%. Analyses in the other treatment subgroups were considered exploratory.

Efficacy Analysis:

Under Amendment 3.0 and later, the primary efficacy endpoint is ORR. The primary analysis will be based on ORR as determined by the IRF.

Secondary efficacy variables include duration of response, duration of SD, PFS at 6 months (182 days from first dose; Study Day 183), median PFS, glucocorticoid sparing and median overall survival. Median duration, landmark proportions, and the associated confidence intervals will be calculated using Kaplan-Meier methods as appropriate. Duration of PFS is defined as the time from first dose of study treatment to the earlier of the following events:

- Disease progression per standardized response criteria
- Death due to any cause

The following censoring rules will be applied:

- Subjects who do not have any post-baseline tumor assessments will be right censored on the date of first dose of study treatment.
- Subjects who receive subsequent anti-cancer therapy (including surgical tumor resection) before experiencing an event will be right censored at the date of the last adequate (i.e., evaluable) tumor assessment prior to the date of initiation of subsequent therapy.

- Subjects who have > 1 consecutive missing or inadequate (i.e., not evaluable) scheduled tumor assessments will be censored at the date of the last adequate tumor assessment prior to the first of the missing or inadequate visits.

Safety Analysis:

The incidence of AEs and SAEs for treated subjects will be tabulated by system organ class and preferred term. Summaries of AEs by worst severity grade, SAEs, and AEs that are related to treatment will be provided. Listings of deaths, SAEs, and AEs leading to early termination of study drug will also be provided.

Amendments to the protocol:

Major amendments to the clinical protocol for XL184-201 to date are listed below:

| TABLE 15. XL184-201: MAJOR AMENDMENTS TO THE CLINICAL PROTOCOL | | |
|--|--------------|---|
| Protocol Version | Version Date | Major Amendments |
| Original | | - |
| Amendment Number: 1.0 | | <ul style="list-style-type: none"> • Inclusion Criterion 8 was modified to ensure adequate kidney function for gadolinium-based contrast administration • Exclusion Criterion 10 was modified to exclude subjects with unhealed wounds from recent surgery or a history of bowel perforation. • A one-time Study Safety Monitoring Committee, whose membership included the Exelixis medical monitor, chief medical officer, drug safety physician, and participating principal investigators, was established to review safety data on the first six patients who completed one cycle of study treatment to determine if enrollment should continue beyond six patients. • Guidance for management of hypertension and VEGF pathway inhibitor class effect on gastrointestinal perforation were updated. |
| Amendment Number: 2.0 | | <ul style="list-style-type: none"> • Clarifications were made in the inclusion and exclusion criteria: <ul style="list-style-type: none"> ○ For Group A, subjects with an initial diagnosis of Grade 3 glioma that relapsed as GBM were eligible. ○ Washout periods for anticancer therapies before first dose of cabozantinib were specified. • Lipase and amylase were added to the serum chemistry panel. |
| Amendment Number: 3.0 | | <ul style="list-style-type: none"> • A central imaging review was added to provide independent analysis of tumor response. |
| Amendment Number: 4.0 | | <ul style="list-style-type: none"> • The requirement for PK sampling when a patient experienced a clinically significant toxicity was removed. |
| Amendment Number: 5.0 | | <ul style="list-style-type: none"> • Clarified that patients who progressed during a drug interruption were not allowed to stay on cabozantinib treatment. • Additional guidelines for the management of common toxicities associated with cabozantinib were provided. |

6 Review of Efficacy

EFFICACY SUMMARY

Exelixis has submitted the results of a single randomized, double-blinded clinical trial (XL184-301) to support an efficacy claim for the use of cabozantinib in the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC).

This trial demonstrated a statistically significant 7.2 month improvement in progression-free survival (PFS) among patients receiving cabozantinib compared to patients receiving a matched placebo pill [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 of this study were robust based on various sensitivity analyses and were consistent across all subgroups (including RET mutation status). The objective response rate among cabozantinib treated patients was 27% (95% CI: 20.8, 33.9). All responses were partial responses.

No responses were observed on the placebo arm ($p < 0.0001$, stratified Cochran-Mantel-Haenszel). However, based on 44% OS events, no difference in OS was observed (HR=0.997, 95%=0.64, 1.54). Of note, the analysis of PFS by dose intensity suggests no difference in PFS response over the range of exposures administered in this study which may suggest that a dose lower than that proposed for labeling may be equally efficacious.

6.1 Indication

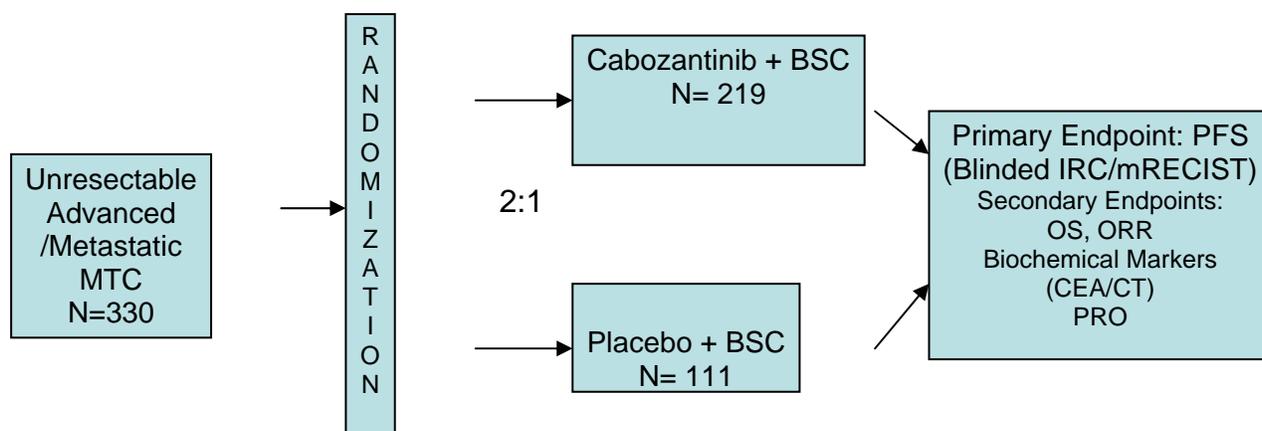
The proposed indication for cabozantinib is for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC).

Review Comment: While the Applicant seeks approval for both Stage III and Stage IV MTC, no evidence is provided to support the efficacy of cabozantinib for use in patients with progressive, locally advanced unresectable MTC (see section 6.1.2). Until such data is provided, it is recommended that the indication be limited to patients with progressive, metastatic MTC.

6.1.1 Methods

The Applicant's claims in support of clinical efficacy are based on the analysis of a single trial (XL 184-301) which is described in detail in Section 5.3.1 and outlined in Figure 2 below. The analysis set used for all efficacy analyses was the Intent-to-Treat (ITT) analysis set, that is, all patients randomized were analyzed by randomized treatment arm.

Figure 2. Trial XL184 – 301: Study Design



- 330 patients randomized; Stratification factors Age (≤ 65 years, > 65 years) and Prior use of TKI (yes, no)
- 323 (cabozantinib – 214; placebo – 109) received ≥ 1 dose
- Cabozantinib orally administered, 140 mg daily

The primary objective of this study was to evaluate progression-free survival (PFS) as assessed by the IRC using modified RECIST criteria. The secondary objectives of this study included the evaluation of:

- Overall survival (OS);
- Objective response rate (ORR) and duration of response (as assessed by the IRC using mRECIST);
- The pharmacodynamic effects of cabozantinib;
- The PK of cabozantinib in a subset of subjects; and
- The safety and tolerability of cabozantinib treatment

Exploratory objectives were to evaluate:

- Changes in serum levels of calcitonin and carcinoembryonic antigen (CEA) from baseline as prognostic biomarkers;
- The treatment effect of cabozantinib in patients with RET germline and/or tumor DNA sequence alteration; and
- Change from baseline in self reported symptom burden as assessed using the MD Anderson Symptom Inventory (MDASI) Thyroid Module (THY);

The reader is referred to section 7.0 of this review for the analysis of safety and tolerability and to Dr. Jun Yang's pharmacology review for details of the pharmacodynamic and pharmacokinetic analysis. The analysis of the primary and secondary endpoints as well as for the subset analyses was provided by Dr. Yuan Li Shen and the reader is referred to her review for additional information concerning these analyses.

6.1.2 Demographics

A total of 330 patients with advanced unresectable or metastatic MTC were randomized (2:1) to receive either cabozantinib or placebo in addition to best supportive care. As shown in Table 16 below, 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.

| | 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) |

| | 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 (%) | 219 | (100) | 110 | (99) |
| 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) |
| Prior TKI, n (%) | 44 | (20) | 24 | (22) |

¹Based on June 15, 2011 data cutoff date.

Review Note: In the randomized trial, only one patient, randomized to the placebo arm had localized disease. The only other data provided in this submission to support the use of cabozantinib in patients with locally advanced MTC comes from the expansion phase of the open label dose-escalation study, XL184-001. In this study, 3 of the 25 patients with MTC had localized disease. Among these 25 patients, a confirmed OR was observed in 7 patients. All 7 patients had metastatic disease. Thus, the sponsor provides no efficacy data to support the use of cabozantinib in patients with localized disease.

Similarly, patients treated on the cabozantinib and control arms were 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 tyrosine kinase inhibitor. However, the median time since initial diagnosis and time since diagnosis of metastatic disease was less in patients randomized to the cabozantinib arm than in the control arm (Table 17).

While screening for *RET* mutation status was not a requirement for enrollment, patients were retrospectively tested (Table 18). Of the 330 subjects enrolled in the study, at least partial *RET* sequence data from one or both sample types was obtained for 319 subjects. The numbers of patients classed as *RET* mutation and as *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 as described in section 5.3.1 and were classed as unknown.

| TABLE 18. XL184-301: <i>RET</i> GENOTYPING RESULTS ¹ | | | | |
|---|-------------------------|------|--------------------|------|
| | Cabozantinib (N=219) | | Placebo (N=111) | |
| | n | % | n | % |
| <i>RET</i> mutation status | | | | |
| Positive | 101 | (46) | 58 | (52) |
| Negative | 87 | (40) | 43 | (39) |
| Unknown | 31 | (14) | 10 | (9) |
| <i>RET</i> 918T mutation status | | | | |
| Positive | 75 | (34) | 43 | (39) |
| Negative | 67 | (31) | 30 | (27) |
| Unknown | 77 | (35) | 38 | (34) |
| MTC disease types: | | | | |
| Sporadic | 191 | (87) | 94 | (85) |
| Hereditary | 12 | (5) | 8 | (7) |
| Unknown | 16 | (7) | 9 | (11) |

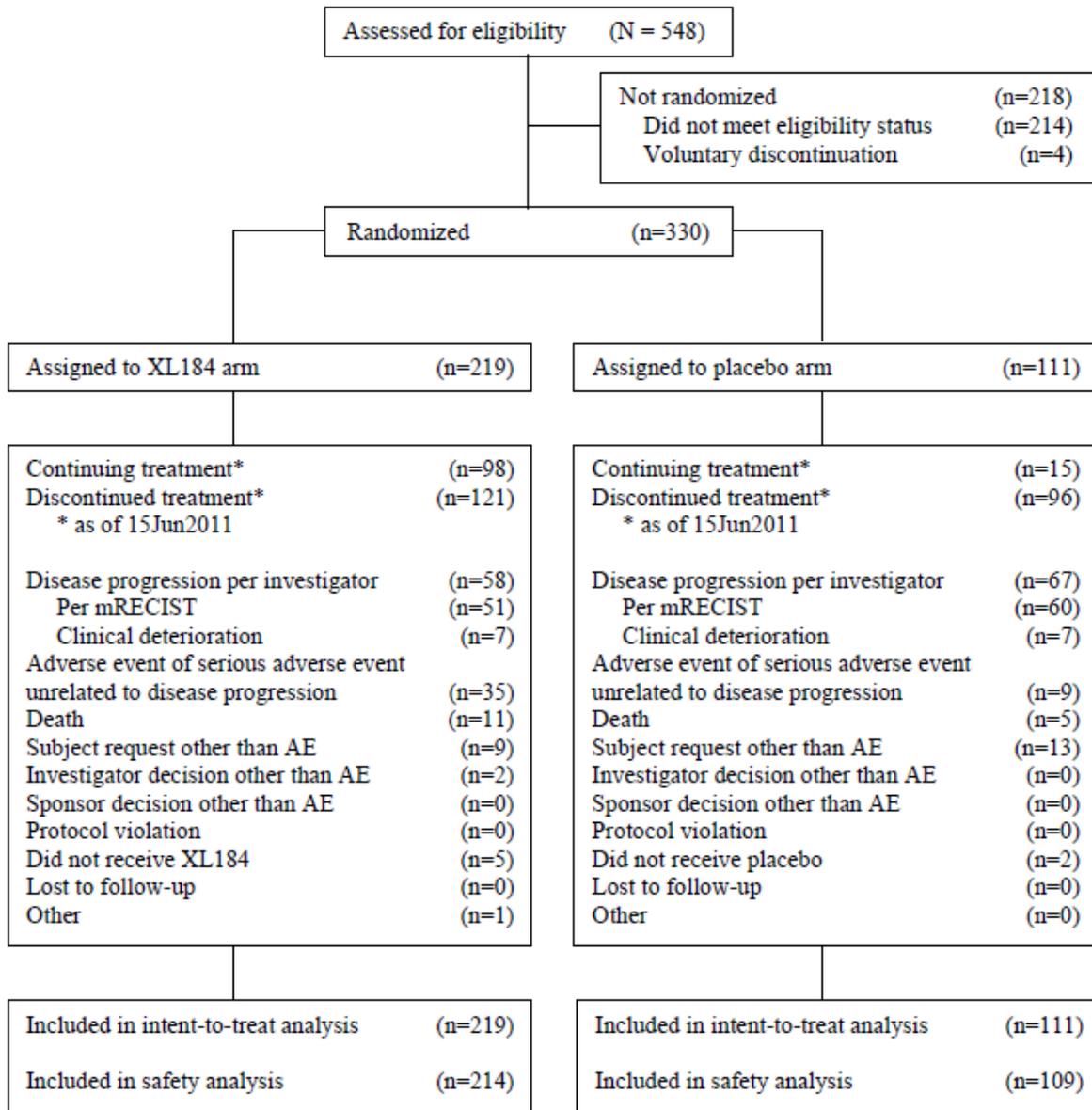
¹Based on June 15, 2011 data cutoff date.

Review comment: Because of the retrospective nature of the RET mutation status, the lack of a validated mutation assay and the high proportion of patients in which the mutation status was undefined, the genotyping analysis should be considered exploratory and does not support a labeling claim.

6.1.3 Subject Disposition

Figure 3 provides an outline of patient disposition for XL184-301. A total of 548 patients were screened to identify 330 patients who were randomized. The primary reason for failure of screened patients to be randomized was that they did not meet study eligibility criteria, a specific breakdown of the reason for exclusion was not provided in the submission.

Figure 3. XL184-301: Patient Disposition



Provided by the Sponsor (XL184-301 Clinical Study Report, May 9, 2012 page 78 of 248

¹Based on June 15, 2011 data cutoff date.

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. In 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 in 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's request not related to AE.

6.1.4 Analysis of Primary Endpoint(s)

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.

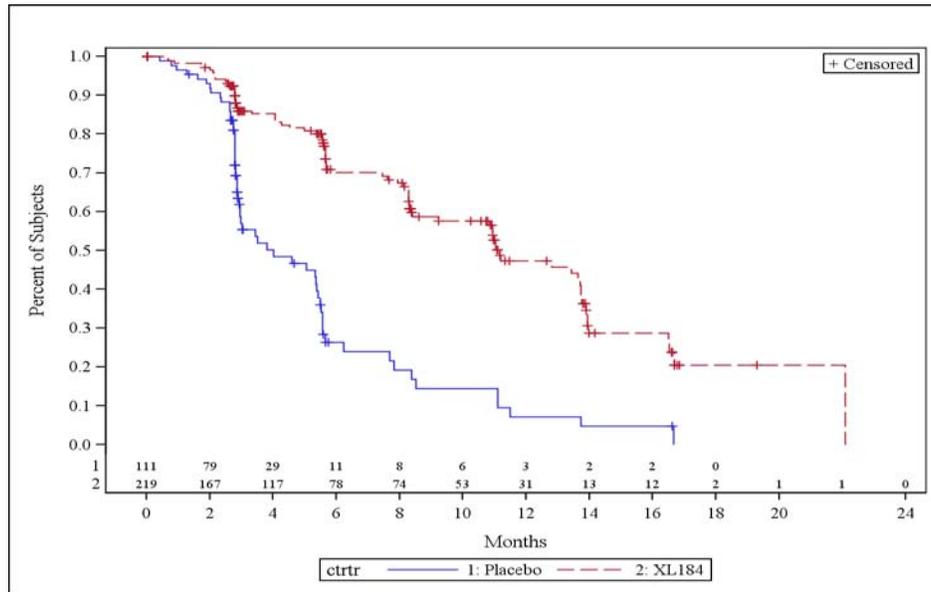
As detailed in the statistical analysis plan, the primary analysis of the primary endpoint was conducted at the time when 138 PFS events had occurred and was based on the April 6, 2011 data cut off date. At the time of the primary PFS analysis 36% of the PFS events had occurred in the cabozantinib arm and 54% PFS events had occurred in the placebo arm. The median survival was 7.2 months longer in the cabozantinib arm than in the placebo arm. The p-value (stratified long-rank test) for the estimated Hazard ratio for this difference was highly statistically significant (Table 19).

| | Cabozantinib N=219 | | Placebo N=111 | |
|---|-----------------------|------|------------------|------|
| | n | % | n | % |
| Number (%) of Subjects | | | | |
| Censored | 140 | (64) | 51 | (46) |
| Event | 79 | (36) | 60 | (54) |
| Death | 21 | (10) | 10 | (9) |
| Progressive disease | 58 | (27) | 50 | (45) |
| Duration of progression free survival (months) | | | | |
| Median | 11.2 | | 4.0 | |
| (95% CI) ^a | (8.4,13.7) | | (3.0, 5.4) | |
| Range | 0.0+ - 22.1 | | 0.0+ - 16.7 | |
| p-value (stratified log-rank test) ^b | <0.0001 | | | |
| Hazard ratio ^c | 0.28 | | | |
| (95% CI; stratified) | (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.

The Kaplan-Meier curves for the primary analysis of PFS by study arm as of the April 6, 2011 data cut off date are shown in Figure 4 below.

Figure 4. Plots of Kaplan-Meier Estimates for PFS (April 6, 2011 Cutoff Date)



To assess the potential for bias in the assessment of PFS, a series of sensitivity analyses were conducted as described in Table 20 below:

| TABLE 20. SUMMARY OF THE SENSITIVITY ANALYSES FOR PROGRESSION FREE SURVIVAL | | |
|--|--|--|
| Sensitivity analyses ^a | Endpoint | Description of the analysis |
| Primary (PFS1) | IRC-assessed PFS | See the description in the texts. |
| PFS2 | IRC-assessed PFS | Events defined based on the date of progression (by IRC) as the scheduled tumor assessment (or the next scheduled tumor assessment date if between assessments) rather than the recorded date of progression, i.e. All PD events were moved to a multiple of 12 weeks. |
| PFS3 | Investigator-assessed PFS (radiological assessment) | Events determined by the investigator assessment of radiographic progression. This analysis did not consider the clinical progression events. |
| PFS4 | Investigator-assessed PFS (include clinical deterioration) | Events defined based on the investigators' claim (i.e. similar to PFS3 except <u>that the clinical deterioration and the initiation of subsequent events were counted as progression events.</u>) |
| PFS5 | IRC-assessed PFS | Censored patients at the last tumor assessment dates prior to data cutoff, i.e. ignore the censoring reasons as indicated for the primary PFS analysis. |
| Per-protocol | IRC-assessed PFS | Similar to the primary PFS analysis except that this analysis is based on per-protocol population |
| ^a PFS2-PFS4 correspond to the applicant's sensitivity analysis plan for PFS described in the SAP. | | |

These sensitivity analyses were conducted both on the ITT data set with events defined by the April 6, 2011 data cut-off date and also based on a data cut-off date set at the time of the 120-day safety update (June 15, 2011) which formed the basis of an additional analysis requested by FDA to assess the trend in overall survival (see section 6.1.5 below). These sensitivity 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 (Table 21).

TABLE 21. STATISTICAL REVIEWER'S SENSITIVITY ANALYSIS FOR PFS FOR BOTH THE APRIL 6, 2011 AND JUNE 15, 2012 DATA CUT OFF DATES

| Cut-off Date | Sensitivity # ^a | #event/total Cabozantinib : Placebo | Hazard Ratio (95% CI) | Median PFS (months) (95% CI) | | Difference (Cab-Placebo) |
|--------------|--------------------------------------|---|-----------------------------|------------------------------------|------------------|-----------------------------|
| | | | | Cabozantinib | Placebo | |
| 4/6/2011 | Primary (IRC) | 79/219:60/111 | 0.27 (0.19,0.40) | 11.2 (8.4,13.7) | 4.0 (3.0,5.4) | 7.2 |
| | PFS2 (IRC) | 79/219:60/111 | 0.28 (0.20,0.41) | 11.1 (10.9,13.7) | 5.4 (2.9,5.6) | 5.7 |
| | PFS3 (INV) | 70/219:66/111 | 0.29 (0.20,0.42) | 13.8 (10.7,16.3) | 3.1 (2.9,5.4) | 10.7 |
| | PFS4 (INV)- w/ clinical events | 84/219:80/111 | 0.31 (0.23,0.43) | 11.2 (8.3,13.9) | 3.0 (2.8,4.3) | 8.2 |
| | PFS5 (IRC) | 93/219:66/111 | 0.29 (0.20,0.41) | 12.8 (10.8,13.9) | 5.3 (3.0,5.6) | 7.5 |
| | Per-protocol | 76/198:59/101 | 0.26 (0.18,0.38) | 11.2 (9.2,13.7) | 3.8 (2.9,5.4) | 7.4 |
| 6/15/2012 | Primary (IRC) | 92/219:67/111 | 0.27 (0.19,0.39) | 12.4 (10.8,13.7) | 4.0 (3.0,5.5) | 8.4 |
| | PFS2 (IRC) | 92/219:67/111 | 0.28 (0.20,0.40) | 12.4 (11.0,13.8) | 5.4 (3.0,5.6) | 7.0 |
| | PFS3 (INV) | 84/219:75/111 | 0.28 (0.20,0.39) | 13.8 (11.0,14.9) | 3.0 (2.9,5.4) | 10.8 |
| | PFS4 (INV)- w/ clinical events | 100/219:91/111 | 0.29 (0.22,0.40) | 12.4 (8.9,13.9) | 3.0 (2.8,3.5) | 9.5 |
| | PFS5 (IRC) | 109/219:75/111 | 0.29 | 11.2 | 5.1 | 6.1 |

| | | | | | | |
|---|--------------|---------------|---------------------|---------------------|------------------|-----|
| | | | (0.21,0.41) | (8.9,13.7) | (3.0,5.5) | |
| | Per-protocol | 88/198:66/101 | 0.26 (0.19,0.38) | 12.8 (10.9,13.8) | 4.0 (2.9,5.4) | 8.8 |
| ^a PFS2-PFS4 correspond to the applicant's sensitivity analysis plan for PFS described in the SAP | | | | | | |

6.1.5 Analysis of Secondary Endpoints(s)

Overall survival (OS) and best overall response rate (ORR) were key secondary endpoints for XL184-301. Analyses of biomarker data and patient reported outcomes were exploratory endpoints and are discussed in sections 6.1.6 and 6.1.10 respectively. Analyses of outcomes by *RET* mutation status are discussed in section 6.1.10 and data concerning outcomes in subpopulations of interest are discussed in 6.1.7.

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 time or was lost to follow-up. ORR was based on the assessment of the 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 cutoff 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. As specified in the statistical analysis plan (SAP), if 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.

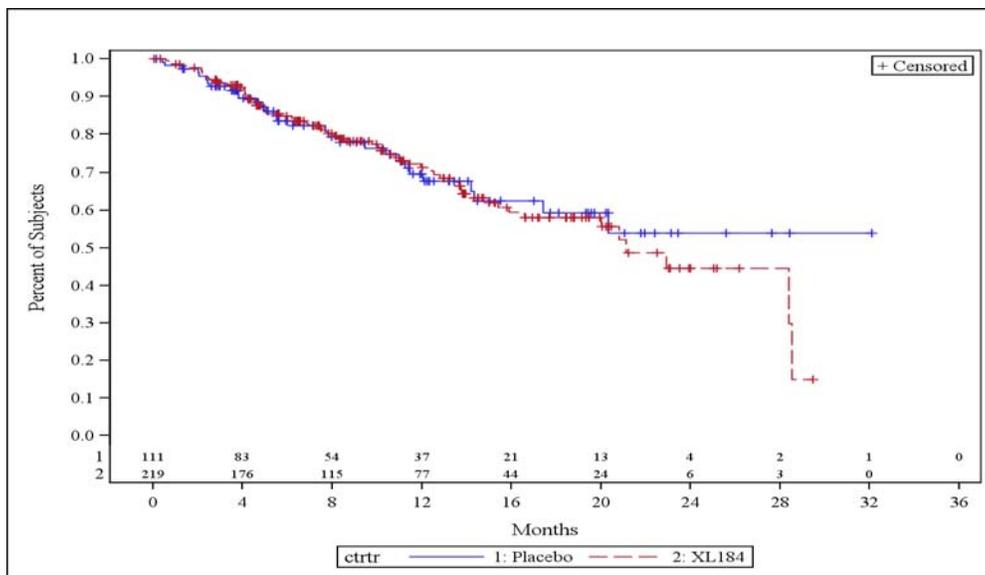
6.1.5.1 Analysis of Overall Survival (OS)

An interim analysis of OS was expected to be performed at the 0.00006 level per a Lan-DeMets O'Brien-Fleming alpha spending function based on an expected 31% information level. The actual alpha level was based on the actual information fraction at the time of the analysis. If the result of the interim analysis for OS was not significant, the primary analysis of OS would be performed when the required number of deaths (217) had been observed. The primary analysis was expected to be conducted at the 0.04 significance level per the alpha spending function.

The pre-specified interim analysis of OS was performed at the time of the primary analysis of PFS and included 217 (44%) deaths required for the final analysis of this endpoint. The criterion for stopping early due to rejection of the null hypothesis at the interim analysis [based upon a significance level (0.0009)] was not met. No difference between study arms in the estimate of overall survival was observed (**Error! Reference source not found.**). The Kaplan-Meier plot of OS for this pre-specified analysis is shown below in Figure 5.

| TABLE 22. STATISTICAL REVIEWER'S ASSESSMENT OF OVERALL SURVIVAL | | | | |
|---|-----------------------|------|------------------|------|
| | Cabozantinib N=219 | | Placebo N=111 | |
| Number of Subjects | n | % | n | % |
| Censored | 153 | (70) | 81 | (73) |
| Death | 66 | (30) | 30 | (27) |
| Duration of overall survival (months) | | | | |
| Median | 21.1 | | NA | |
| (95% CI) ^a | (16.59, 28.52) | | (14.32, NA) | |
| Min- Max | 0.0+ - 29.5+ | | 0.1+-32.1+ | |
| Hazard ratio (95% CI; stratified) ^c | 0.997 (0.644, 1.542) | | | |
| p-value (stratified log-rank test) ^b | 0.989 | | | |
| <p>+ 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.</p> | | | | |

Figure 5. Plots of Kaplan-Meier Estimates for OS



Because of safety concerns detailed in section 7 below, 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 the OS remained insignificant and without suggestion of a trend towards decrement in OS (Table 23).

| TABLE 23. STATISTICAL REVIEWER'S SUMMARY OF OVERALL SURVIVAL (BASED ON 120-DAY UPDATED DATA WITH 6/15/2012 CUTOFF DATE) | | | | |
|---|-------------------------|------|-------------------------|------|
| | XL184 N=219 | | Placebo N=111 | |
| Number (%) of Subjects | | | | |
| Death | 103 | (47) | 59 | (53) |
| Duration of overall survival (months) | | | | |
| Median (95% CI) ^a | 26.02 (22.90, 30.72) | | 20.34 (16.39, 26.68) | |
| p-value (stratified log-rank test) ^b | 0.2432 | | | |
| Hazard ratio (95% CI; stratified) ^c | 0.825 (0.598, 1.14) | | | |
| <small>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 proporti</small> | | | | |

6.1.5.2 Analysis of Objective Response Rate (ORR)

The number of patients assessed by the IRC 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 (Table 24).

| TABLE 24. STATISTICAL REVIEWER'S SUMMARY OF OBJECTIVE RESPONSE RATE | | | | |
|---|------------------------|---|------------------|---|
| Subjects in ITT Population | Cabozantinib N= 219 | | Placebo N=111 | |
| | n | % | n | % |
| Best Overall Response ^a | | | | |

| | | | | |
|---|--------------|------|----|------|
| Confirmed complete response (CR) | 0 | 0 | 0 | 0 |
| Confirmed partial response (PR) | 58 | (27) | 0 | 0 |
| Stable disease (SD) | 100 | (46) | 52 | (47) |
| Progressive disease | 18 | (8) | 35 | (32) |
| Unable to evaluate | 5 | (2) | 1 | (1) |
| Missing ^d | 38 | (17) | 23 | (21) |
| Objective Response Rate (ORR=CR+PR) | 58 | (27) | 0 | 0 |
| 95% confidence level | 20.8, 32.9 | | NA | |
| 99% confidence level | 19.2, 34.9 | | NA | |
| p-value (stratified Cochran-Mantel-Haenszel) | <0.0001 | | | |
| Duration of Response (month) | 14.7 | | NA | |
| Range | (11.1, 19.3) | | NA | |
| IRC=Independent Radiology Review Committee; NA=not available a Best overall response determined by IRC using mRECIST criteria. b Missing=no qualifying post-baseline assessment for overall response. c Stratification factors : age and prior tyrosine kinase inhibitor status. | | | | |

6.1.6 Other Endpoints

6.1.6.1 Tumor Marker Data

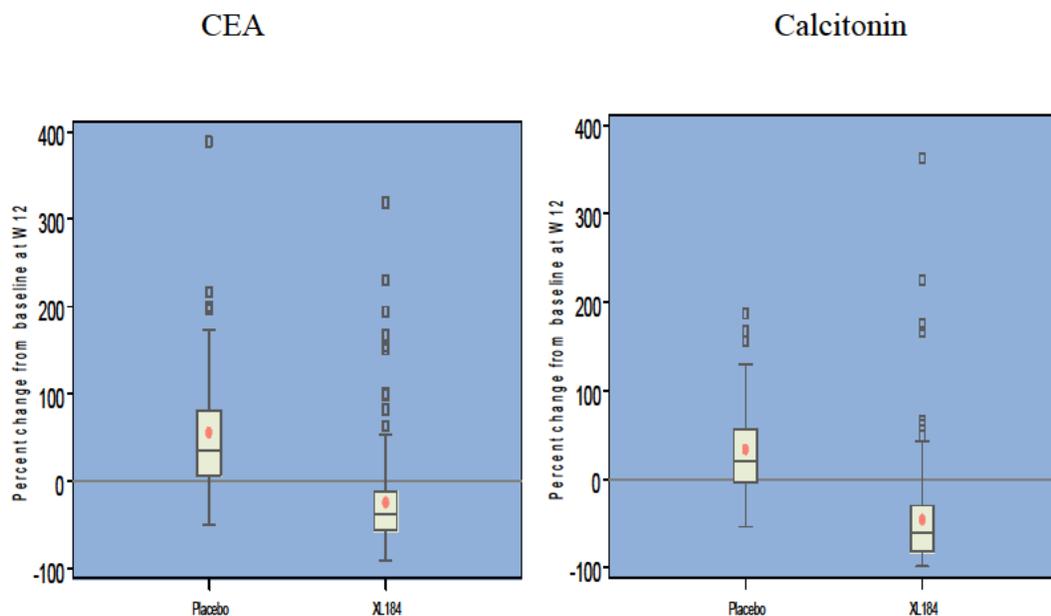
The change in the levels of the tumor markers CEA and calcitonin at week 12 compared to the baseline level was calculated. Both CEA and calcitonin levels declined at week 12 compared to baseline levels in the treatment arm. In the placebo arm, both CEA and calcitonin levels were increased at week 12 compared to baseline (Table 25). The change in these markers is shown in Figure 6.

| TABLE 25. REVIEWER'S SUMMARY OF TUMOR MARKER DATA, CHANGE FROM BASELINE AT WEEK 12 | | |
|--|--|-------------------------------------|
| Marker | Cabozantinib N=219 Median (q1, q3) | Placebo N=111 Median (q1, q3) |

| | | |
|------------------------------|------------------------|-------------------------|
| CEA µg/L[n (%)] | 170 (78%) | 71 (64%) |
| Baseline | 120.7 (33.5,422.7) | 153.1 (32.3,478.2) |
| W12 | 56.4 (21.4, 260.9) | 221.8 (69.5, 962.7) |
| Change from baseline | -23.7 (-143.1, -3.2) | 35.6 (4.1, 269.6) |
| Percent Change from baseline | -38.0 (-56.1, -11.5) | 38.0 (8.9, 104.0) |
| p-value ^a | <0.0001 | |
| Calcitonin pmol/L[n (%)] | 140 (64%) | 61 (55%) |
| Baseline | 2298.1 (544.5,5754.0) | 3886.0(792.0,9237.4) |
| W12 | 584.8 (177.3, 2671.5) | 4968.0 (1219.0,11716.0) |
| Change from baseline | -1188 (-3071.0,-135.4) | 322 (-0.5, 3941.3) |
| Percent Change from baseline | -60.2 (-81.7, -29.5) | 22.7 (-2.3, 67.3) |
| p-value ^a | <0.0001 | |

^aBased on Wilcoxon Rank Sum Test ; nominal p-value from exploratory subgroup analyses.

Figure 6. Percent Change from Baseline in CEA and Calcitonin Level at Week 12



6.1.6.2 MD Anderson Symptom Inventory Thyroid Module (MDASI – THY)

The MD Anderson Symptom Inventory Thyroid Module (MDASI – THY) is a multi-symptom patient reported outcome (PRO) measure validated for use in this patient population, which core assessment items correlate to the most frequently reported and most serious symptoms in thyroid cancer patients. Part 1 (Questions 1-19): covers 13 core cancer and treatment related symptoms and 6 additional symptoms of persons with thyroid cancer. Responses are scored on a scale from 0 (symptoms not present) to 10 (as bad as you can imagine it could be). Part 2 (Questions 20 – 25) summarizes how symptoms have interfered with the subject's life in the preceding 24 hours and is scored on a scale which ranges from 0 (did not interfere) to 10 (interfered completely).

Mean scores and change from baseline are obtained for:

- Primary Symptom Severity Score – based on 5 symptoms: diarrhea, fatigue, sleep disturbance, distress and difficulty remembering
- Overall Mean Symptom Severity Score: based on 13 core and 6 thyroid specific symptoms

The Mean Symptom Interference subscale is defined as the average of a subject's six interference items. Mean scores were calculated for all composite scores when subjects answered more than half of the items for that score. A high score means more symptoms/more interference. The results of these analyses are shown below in Figure 7, Figure 8, and Figure 9.

Figure 7. MDASI- THY: Primary Severity Score Change in Mean Score from Baseline

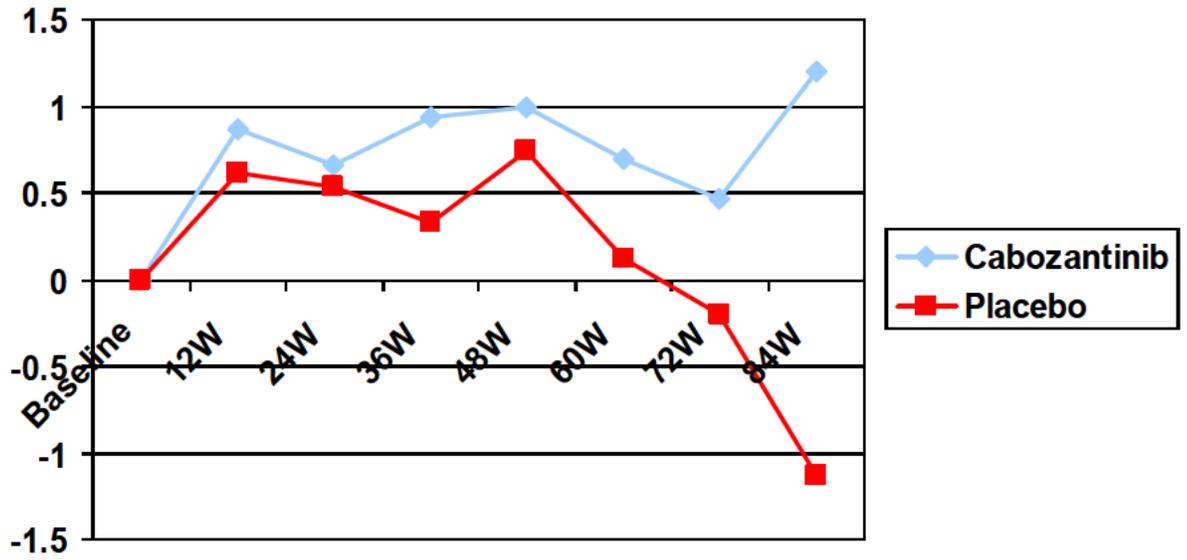


Figure 8. MDASI-THY: Overall Mean Symptom Severity Score Change in Mean Score from Baseline

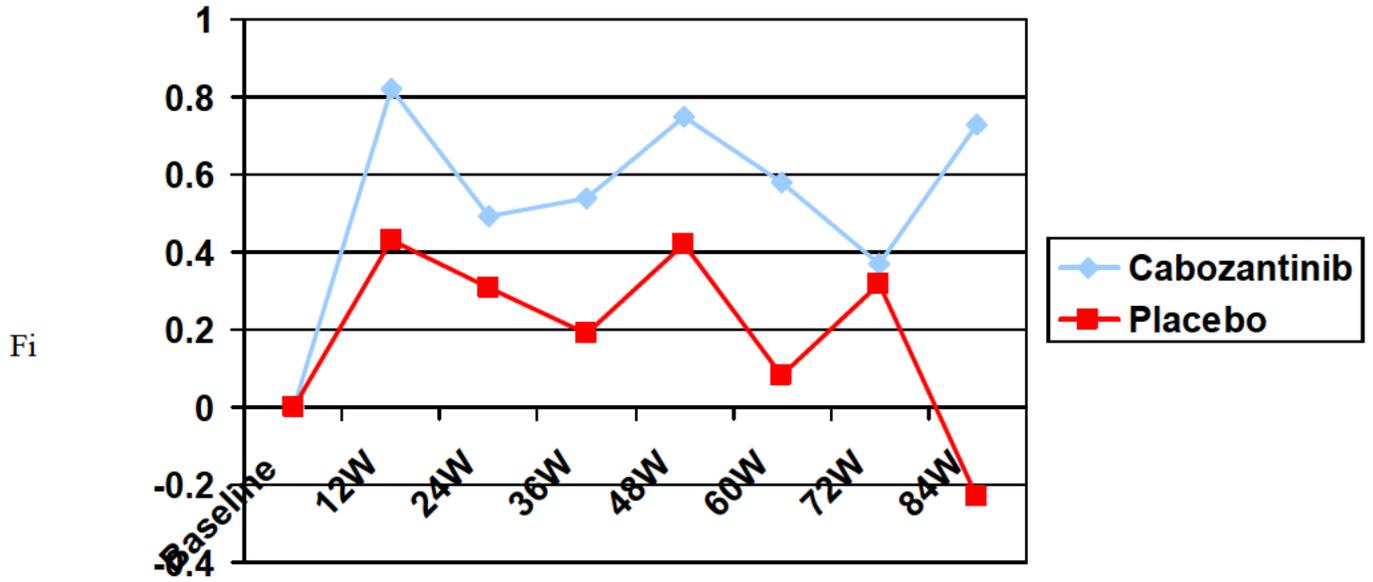
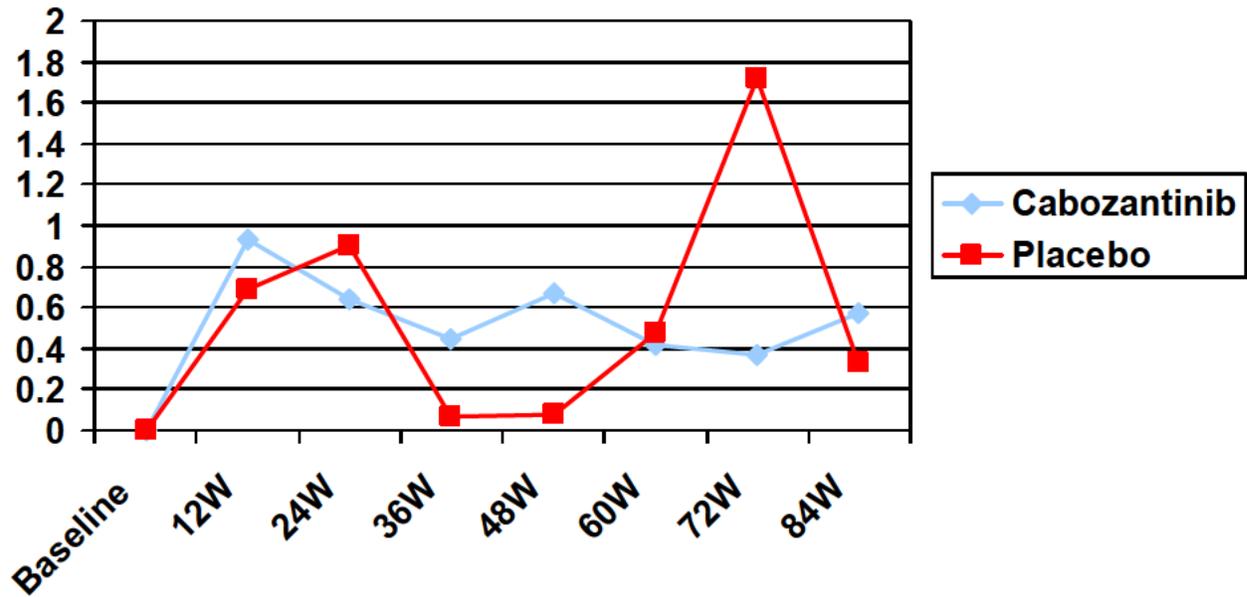


Figure 9. MDASI-THY: Mean Symptom Severity Score Change in Mean Score from Baseline



Review Comment: With only 71% of cabozantinib-treated patients and 76% of placebo-treated patients responding at week 12 and marked fall-off thereafter, these data must be considered exploratory in nature. However, these PROs do not suggest benefit in terms of quality of life or symptom control. If anything, they suggest that cabozantinib treatment results in an increased symptom burden and decrement in quality of life.

6.1.7 Subpopulations

Subgroup analyses for PFS by major demographic and baseline disease characteristics as provided by the applicant and confirmed by the statistical reviewer are shown below in Figure 10 and Figure 11. These analyses demonstrate a consistent improvement in PFS associated with cabozantinib treatment across all major demographic and baseline disease subgroups. In almost all analyses, the 95% confidence levels for the estimate of the hazard ratio did not overlap 1.0. In those analyses in which the estimate of the hazard ratio did overlap 1.0 (best response to prior therapy of progressive disease, non-Whites, region of accrual other than Europe or North America, and RET mutation negative), the estimate of the hazard ration was above 1.0 and the 95% confidence level for the estimate was unstable due to small numbers of patients.

Figure 10. Forest Plots Based on Hazard Ratio Estimates for PFS by Demographic Information

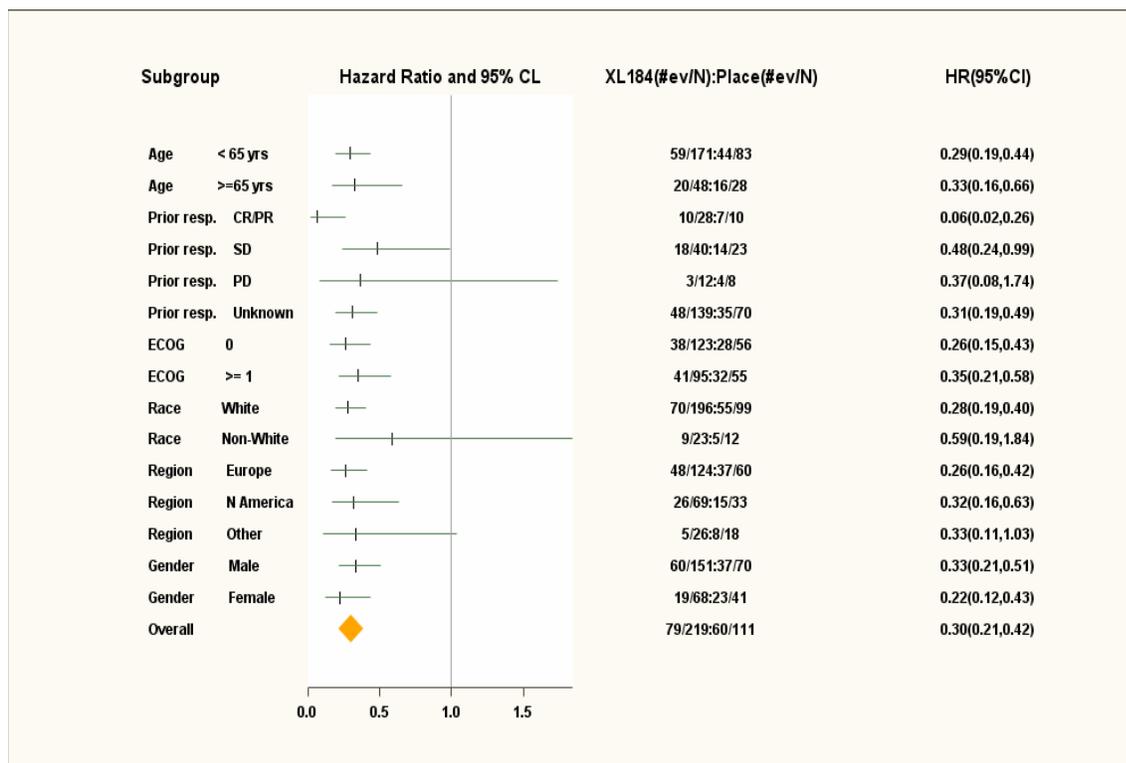


Figure 11. Forest Plots Based on Hazard Ratio Estimates for PFS by Baseline Characteristics

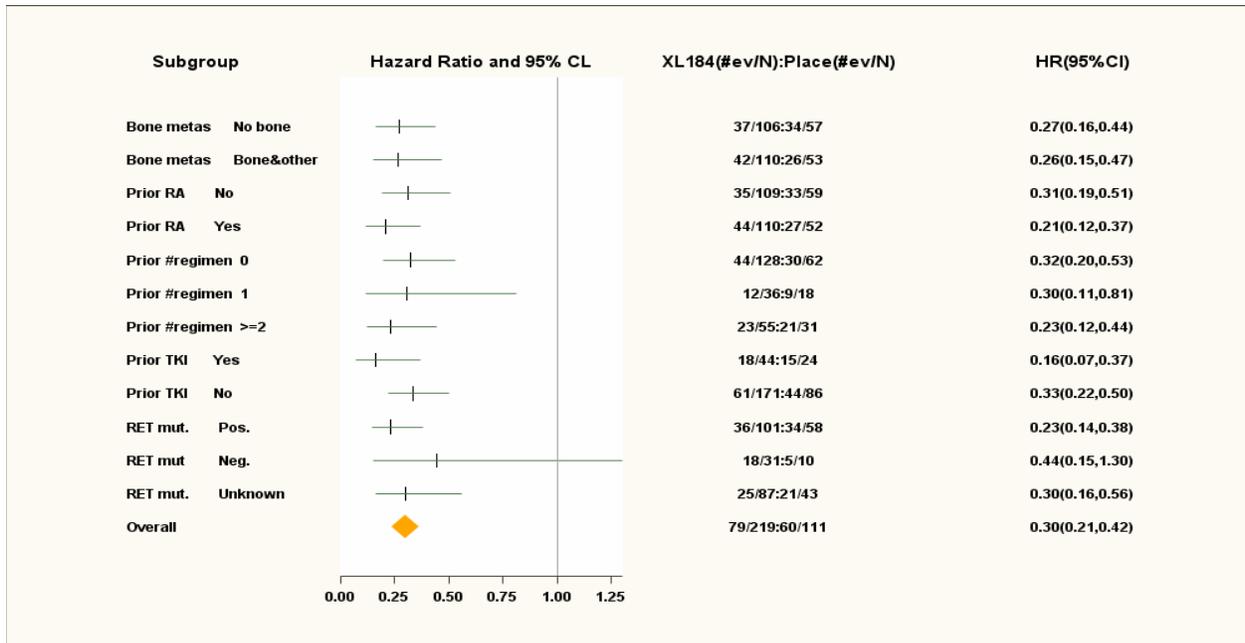
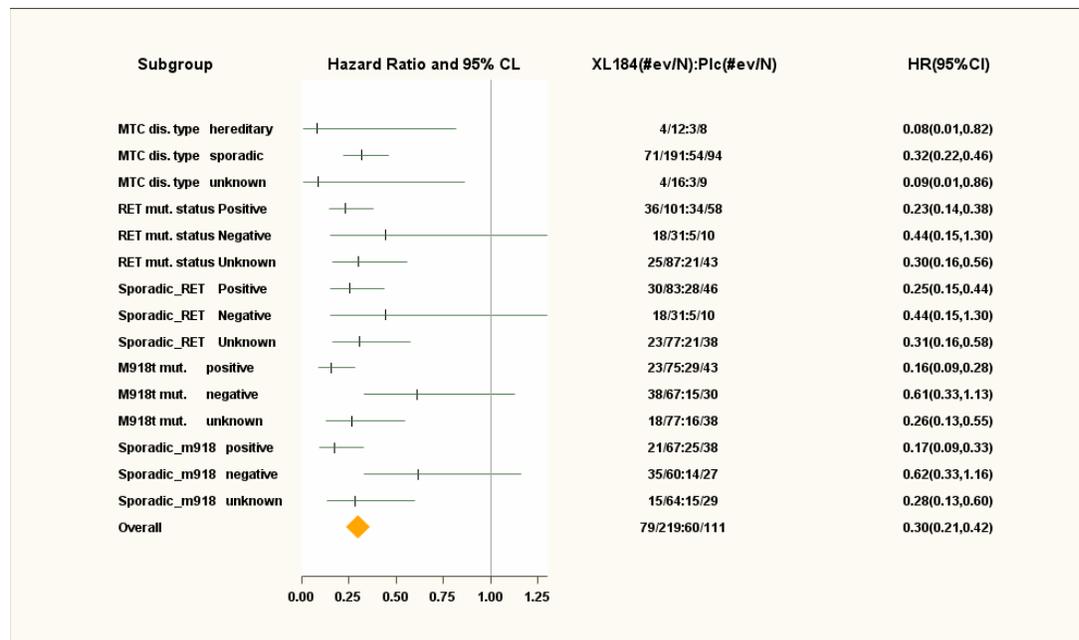


Figure 12 demonstrates the subgroup analyses by RET mutation status or type of MTC (hereditary, sporadic or unknown). Based on these analyses treatment there appears to be a benefit to cabozantinib treatment irrespective of RET mutation status or type of MTC. However as testing was done retrospectively and a large subset of patients had unknown status, these analyses must be considered exploratory and will not support a labeling claim.

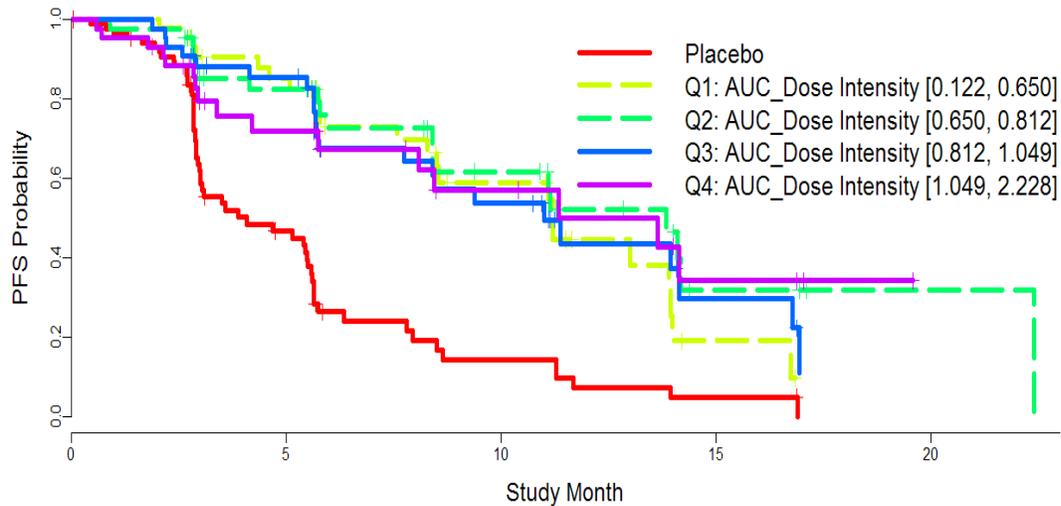
Figure 12. XL184-301: Forest Plots Based on Hazard Ratio Estimates for PFS by *RET* Mutation Subgroup



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

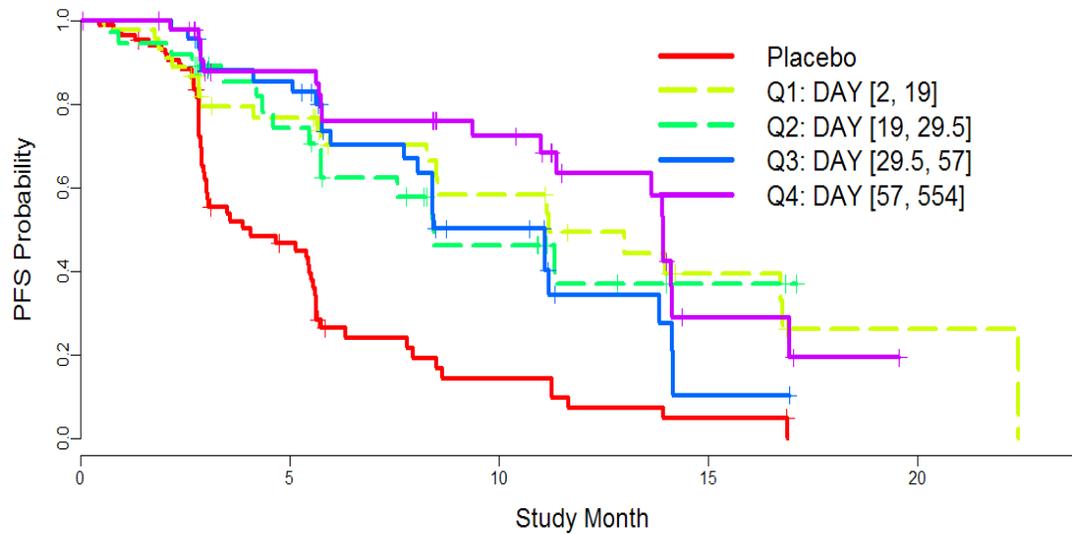
As further discussed in section 7 below, the mean dose intensity defined as the per-cent of the total planned dose was only 70% and 86 % of patients enrolled in XL184-301 required a dose reduction or delay with 79% of patients requiring at least a 1-level dose reduction and 41% of patients requiring 2 dose-level reductions. Patients requiring more than 2 dose-level reductions were taken off 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 (Figure 13) or with the time to the first cabozantinib dose reduction (Figure 14).

Figure 13. XL184-301: PFS by Dose Intensity Level



AUC Dose Intensity, mg*day/L = Dose intensity x AUC_{ss} = Dose intensity x 140 mg/Individual CL
 Dose intensity= accumulated actual dose/total planned dose

Figure 14. XL184-301: PFS by Day of First Cabozantinib Dose Reduction



Time to 1st dose modification: first occurrence of a dose that was not equal to the starting dose.
 • 2 - 554 days with median 29.5 days

- An indicator of both exposure (earlier dose modification, the less exposure) and safety (earlier dose modification, the earlier AEs occurred)

These findings bring into question whether the dosing of cabozantinib was optimized in clinical development and specifically whether a lower dose may be equally efficacious as the proposed dose.

The reader is referred to Dr. Yang's review for additional details of this analysis.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

The applicant provides the results of a single randomized clinical trial (XL184-301) to support the efficacy of cabozantinib used for the treatment of patients with progressive locally advanced or metastatic MTC. By all measures, the design and conduct of this clinical trial appear to be acceptable and to demonstrate a significant prolongation of PFS in cabozantinib-treated patients that is consistent across relevant subpopulations and supported by secondary endpoints. There are, however, several issues of concern. First, it is unlikely given the potentially identifying adverse event profile of cabozantinib that XL184-301 could be truly blinded to patients or to physicians. An assessment of the number of patients censored for reasons other than adverse events did not suggest a large difference between study arms. Moreover, a series of pre-planned sensitivity analyses consistently demonstrated a PFS benefit with cabozantinib treatment. Second, it is of concern that despite a highly statistically significant 7.2 month difference in PFS with and without 75% of OS events reported, no trend toward increased OS among cabozantinib-treated patients has been observed. Third, in light of the high rate of Grade 3-4 toxicities described in section 7 below and the evidence from clinical pharmacology studies that the doses lower than the currently proposed cabozantinib dose may be equally efficacious, OS may be a reflection of safety as well as efficacy.

7 Review of Safety

SAFETY SUMMARY

The safety of cabozantinib was assessed in an international, double-blinded study of 323 patients randomized 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 was 230 days (SD:180) on the cabozantinib arm and 140 days (SD: 122) on the placebo arm. However, the relative dose intensity (the per cent of the maximum dose delivered) was 63% (SD: 18.9) compared to 83% (SD: 16.7) in the placebo arm. Fully 79% 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 reduction were, in decreasing

order: palmar-plantar erythrodysesthesia syndrome, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

While the percentage of deaths reported within 30 days of the last study drug administration was similar between study arms, 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%), palmer-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 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 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.

Based on the information provided in this submission, A REMS is not warranted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials included in the cabozantinib safety analysis set (SAS) in support of NDA 203756 are listed below in Table 26. The SAS included:

- Subjects who received at least one dose of study treatment (cabozantinib or placebo) in Study XL184-301 (N = 214 and 109, respectively)
- Subjects treated at the 140-mg dose level in Study XL184-001 (N = 35)
- Subjects treated at the 140-mg dose level in Study XL184-201 (Group A) (N = 46)

| |
|---|
| TABLE 26. NDA 203756 CABOZANTINIB SAFETY ANALYSIS SET |
|---|

| Total | | Number of Patients Treated | | | |
|-------------------------|---------|-------------------------------|-----------------------|---------|-----------|
| Study | Phase | Cabozantinib 140 mg, PO QD | | Placebo | |
| XL 184-301 | Phase 3 | 214 | (MTC) | 109 | (MTC) |
| XL 184-001 | Phase 1 | 35 | (25 MTC, 10 non-MTC) | - | - |
| XL 184-201 (Group A) | Phase 2 | 46 | (GB) | - | - |
| Total | | 295 | (239 MTC, 56 non-MTC) | 109 | (109 MTC) |

The following data cut-off dates for the clinical database were used: 19 April 2010 (XL184-001), 01 September 2010 (XL184-201), and 15 June 2011 (XL184-301).

7.1.2 Categorization of Adverse Events

At each study visit, evaluations of AEs were performed. Clinical laboratory test results or ECGs that were considered clinically significant were to be reported as an AE. An event deemed serious was also reported as an SAE. For every AE, the verbatim term was recorded and the event was coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. Events were categorized and the level of severity coded according to NCI CTCAE v. 3.0. The action taken, if any, with study drug was also recorded.

The relationship of the AE to the study treatment was assessed by the investigator as:

- Not Related - The AE was assessed as not related to study treatment by the investigator, as the AE was attributed to an alternate cause or causes.
- Related/Possibly Related - The AE was assessed as possibly related to study treatment by the investigator, as the AE was temporally related to the administration of study treatment and there was clinical evidence to support a causal relationship between the AE and study treatment.

An AE was considered to be an SAE if the following criteria were met:

- Resulted in death
- Was immediately life threatening (i.e., in the opinion of the investigator, the AE placed the subject at immediate risk of death; it did not include a reaction that, had it occurred in a more severe form, might have caused death)
- Required inpatient hospitalization or resulted in prolongation of an existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect
- Was an important medical event jeopardized the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence
Because of the small numbers of patients enrolled in XL184-001 and XL184-201 and the lack of a comparator arm in these trials, data from these trials were not pooled with data from XL184-301. However, safety data from these trials were reviewed for safety signals. No new or unexpected safety events were identified from these trials and the presentation of safety data in section 7.0 is limited to data derived from XL184-301.

7.2 Adequacy of Safety Assessments

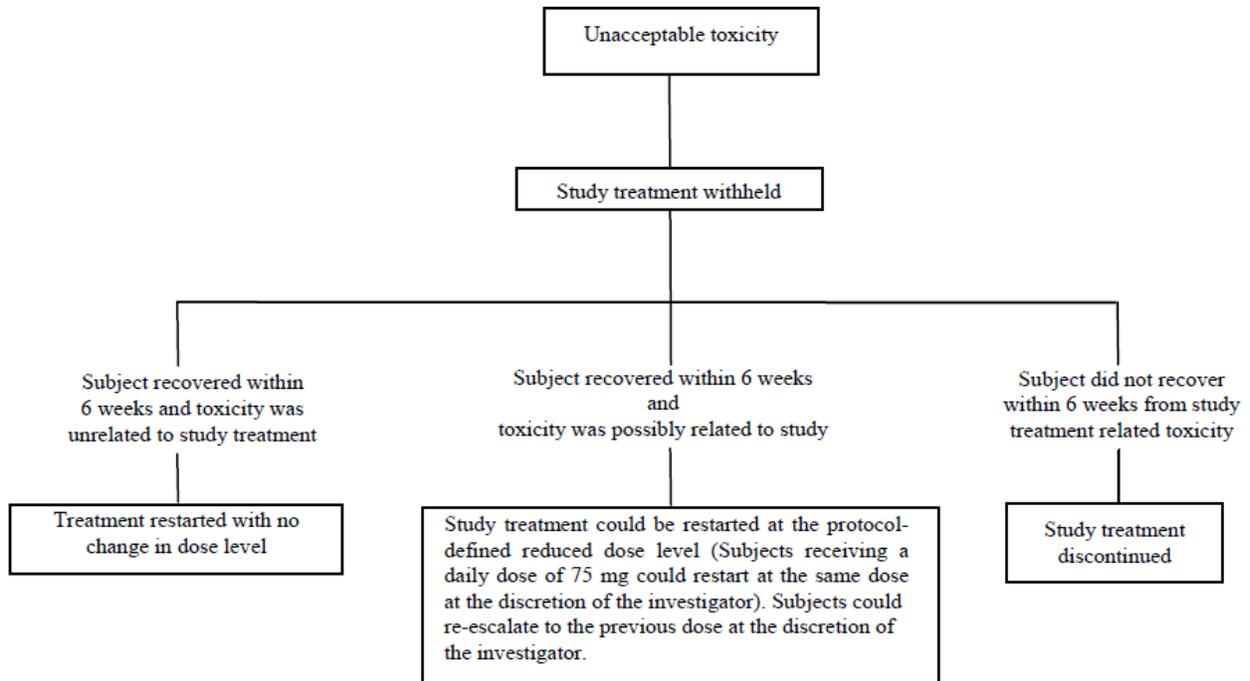
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In XL184-301, 7 patients randomized to receive treatment, 5 in the cabozantinib arm and 2 in the placebo arm, did not do so. While the number of patients who dropped out prior to treatment is similar between arms and thus not likely to bias the interpretation of the study findings, the reason for drop out is not provided by the applicant. All other patients randomized to receive treatment were treated as randomized.

The demographics of the SAS for XL184 was not substantially changed by the drop out of these patients and the reader is referred to Table 16- 18 in section 6.1.2 for a comparison of the demographic and tumor characteristics in the ITT study population. The demographics of patients included in the cabozantinib development program are generally similar to the target population in the United States; exceptions include patients over the age of 65 and non-White patients who were both underrepresented.

The dose reduction schema for XL184-301 is shown below in Figure 15. The cabozantinib dose was held in patients who developed unacceptable toxicity. Patients who recovered from the toxicity within six weeks could be re-treated at a reduced level but could be re-escalated to the previous dose at the discretion of the investigator. Patients who had toxicities and did not recover within a six-week time frame or who required more than two dose-level reductions were discontinued from study.

Figure 15. XL184-301 Dosing Algorithm



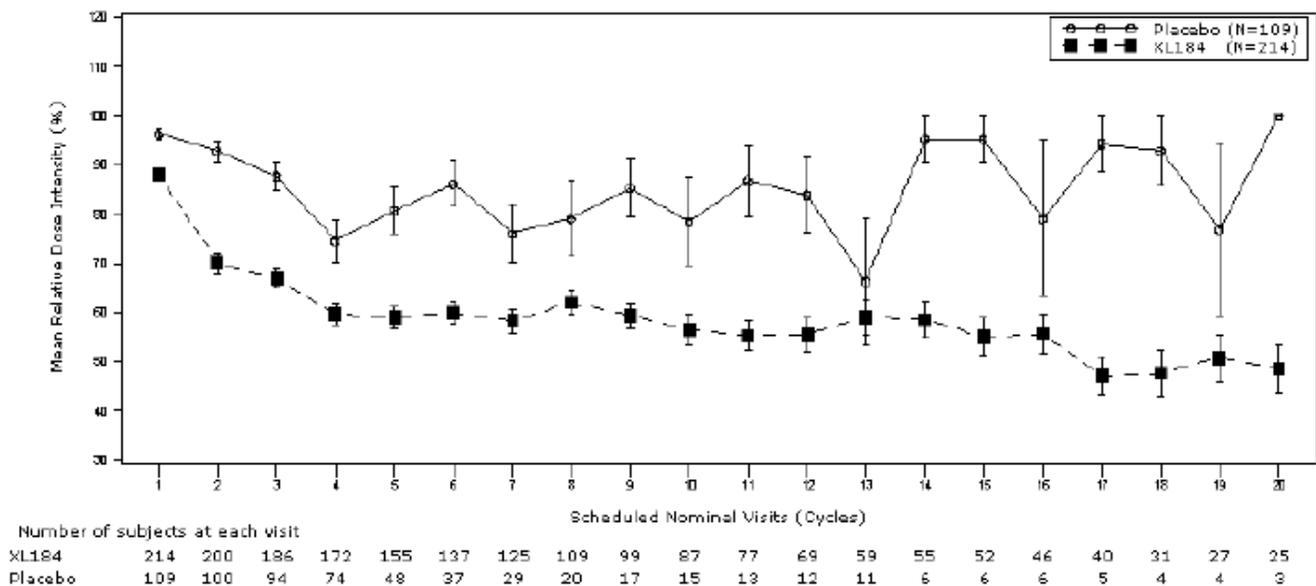
The median duration of study treatment in the cabozantinib and placebo treatment arms was 188 and 104 days, respectively. It is of note that almost 79% of patients on the cabozantinib arm required one level dose reduction and 41% required a two level dose reduction. Adverse events which led to cabozantinib dose reduction in $\geq 5\%$ of patients treated on the cabozantinib arm in XL184-301 included: palmar-plantar erythrodysesthesia syndrome, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

| TABLE 27. XL184-301: EXPOSURE TO STUDY DRUG, SAS POPULATION | | | | |
|---|-----------------------|----------|------------------|-----------|
| | Cabozantinib N=214 | | Placebo N=109 | |
| Duration of treatment (days) | | | | |
| Mean (SD) | 230 | (180.0) | 140 | (122.2) |
| Median (min, max) | 188 | (8, 818) | 104 | (11, 624) |
| Number of dose reductions per subject | | | | |
| Mean (SD) | 1.8 | (0.8) | 1.2 | (0.6) |
| Median (min, max) | 2 | (1,4) | 1 | (1,3) |
| Subjects with at least one: | | | | |
| 1- level dose reduction – n (%) | 169 | (79) | 10 | (9) |
| 2- level dose reduction – n (%) | 88 | (41) | 1 | (1) |
| Time to first dose delay (days) | | | | |
| Mean (SD) | 67 | (95.3) | 104 | (98.3) |
| Median (min, max) | 33 | (2, 554) | 73 | (10, 506) |
| Number of dose delays per subject | | | | |
| Mean (SD) | 2.5 | (5.2) | 0.5 | (1.1) |
| Median (min, max) | 1 | (0, 61) | 0 | (0, 9) |
| Relative dose intensity – Overall (%) | | | | |
| Mean (SD) | 63 | (18.9) | 83 | (16.7) |
| Median | 64.7 | | 86.6 | |

Moreover, the overall dose intensity, the per-cent of the planned cabozantinib dose actually delivered was only 65% (Table 27) and the relative dose intensity by treatment cycle appeared to continue to decline far into the treatment course (Figure 16).

Review Comment: Only 14% of cabozantinib-treated patients were able to continue treatment at the starting dose. Factors which may alter pharmacokinetics in these patients (e.g., concomitant medications which may decrease the effective dose) or other identifying characteristics have not been fully explored.

Figure 16. XL184-301: Relative Dose Intensity by Treatment Cycle, SAS Population



Note: Error bars represent the standard error of mean.

Source: Figure 14.3.1.17

7.2.2 Explorations for Dose Response

Little dose exploration was attempted during cabozantinib clinical development. The high number of patients who received dose reductions and the low overall dose intensity described in section 7.2.1 coupled with evidence that there does not appear to be a strong correlation between dose intensity and PFS as summarized in section 6.1.8 and as detailed in Dr. Yang’s clinical pharmacology review suggest that dosing for cabozantinib has not been optimized and that a lower administered dose may be as efficacious and potentially less toxic.

7.2.3 Special Animal and/or In Vitro Testing

The non-clinical development of cabozantinib appears to be acceptable to anticipate clinical toxicities. Please see Dr. Brower’s review for additional details concerning non-clinical studies.

Reviewer Comment: It is noted that distribution studies in rats showed high concentrations of cabozantinib at late time points in the eye and uveal tissue. No associated ocular toxicity has been observed in clinical or non-clinical studies with the exception of ocular keratitis in dogs administered toxic levels of cabozantinib. Ocular toxicities have been reported with other multi-targeted TKIs and may emerge in humans in the post-marketing setting.

7.2.4 Routine Clinical Testing

The plan for routine clinical testing for XL184-301 is detailed in Table 10 in section 5.3.1 and is adequate in methodology and frequency to assess laboratory adverse events related to cabozantinib.

7.2.5 Metabolic, Clearance, and Interaction Workup

Except as noted in Dr. Yang's review, the submission was adequate to assess the metabolism and clearance of cabozantinib and to assess potential drug-drug interactions. The reader is referred to Dr. Yang's review for additional details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Evaluations for adverse events related to drugs similar to cabozantinib were adequate (see section 2.4).

7.3 Major Safety Results

Review Comment: The results of the 120 day safety update did not materially change the safety findings presented below and these data were not included in the safety analysis.

Adverse events were reported in all patients receiving cabozantinib and in 95% of patients receiving placebo. The rates of Grade 3 or 4 adverse events, serious adverse events, and adverse events leading to study discontinuation were nearly twice as high in the cabozantinib arm as in the placebo arm. However, the number of adverse events leading to death and the number of deaths within 30 days of the last study drug were comparable in the two study arms (Table 28).

| TABLE 28. 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) |
| 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) |

7.3.1 Deaths

Fewer deaths on the cabozantinib than on the placebo arm were judged by the FDA reviewer to be due to progressive disease (Table 29). The occurrence of sepsis/septic shock and aspiration pneumonia were similar in both study arms. The narratives of the remaining cabozantinib deaths are provided in Table 30 below. In three patients, the cause of death was listed as sudden death, death, cause not otherwise specified (NOS), cardiopulmonary failure, or myocardial infarction (multiple causes specified for one case). These were reviewed to assess whether the death could be attributed to Torsades de Pointes. However, review of the case report form and case narrative suggested other underlying conditions or predisposing factors in these cases. No deaths in the two other single arm supporting studies were judged to be related to cardiac arrhythmia or conduction abnormalities. One death in the cabozantinib arm was attributed to hemorrhage, in two cases the cause of death was attributed to fistula (tracheo-esophageal or esophageal-cutaneous) and one case was attributed to pulmonary failure related to pulmonary hemorrhage with tracheal-bronchial fistula.

| Cause of Death | Cabozantinib (n=22) | Placebo (n=8) |
|--|---------------------|---------------|
| Deaths Consistent with Disease Progression | 10 (45%) | 5 (63%) |
| Sudden Death, Death (NOS), Cardiopulmonary failure, MI | 3 | 0 |
| Hemorrhage | 1 | 0 |
| Fistula formation | 2 | 0 |
| Esophageal/Cutaneous | 1 | 0 |
| Tracheal/Esophageal | 1 | 0 |
| Sepsis/Septic Shock | 2 | 1 |
| Respiratory failure | 4 | 2 |
| Aspiration pneumonia | 3 | 2 |
| Respiratory failure complicated by hemorrhage and/or fistula formation | 1 | 0 |

| Patient ID | Cause of Death | Narrative |
|------------|----------------|---|
| 49073003 | Sudden Death | 67 year old white male with baseline dyspnea, high blood pressure, peripheral edema metastatic disease to the lung and hilum. On Study Day 13, hepatic enzyme levels were increase from a normal baseline level, considered possibly related to study treatment [alanine aminotransferase (ALT) 108 U/L (6-43 U/L) (Grade 1) and aspartate aminotransferase (AST) 164 U/L (11-36 U/L) (Grade 2)]. On the same day, one out of three electrocardiograms (ECG) showed APCs with QTcF intervals of 406, 396, and 392 milliseconds (ms) compared to QTcF intervals at screening of 411, 406, and 415 ms. Laboratory analysis revealed (normal ranges in parentheses) decreased levels of calcium [2.02 mmol/L (2.07-2.64 mmol/L)] and sodium [132 mmol/L (135-145 mmol/L)], with potassium and chloride levels within normal limits On Study Day 17, the subject's wife reported that he had collapsed suddenly. Emergency medical services arrived to find the subject unconscious, not breathing, without blood pressure or pulse, and with dilated pupils. Resuscitation measures unsuccessful and the |

| | | |
|----------|-------------------------|--|
| | | subject was pronounced dead. The cause of death was reported as sudden death. An autopsy was not performed. |
| 14213002 | Sudden Death | <p>58 year old white male diagnosed Oct 1996 who underwent total thyroidectomy in 1996 and a neck dissection and resection of liver mets in 1998. Prior treatment included cyclophosphamide, vincristine, dacarbazine and radiation to the neck and whole brain and treatment with sunitinib. At the time of enrollment, sites of metastatic disease included bone, lymph nodes (cervical mediastinal), liver, brain, and lung. The patient developed nausea (Grade 1) and vomiting (Grade 2) following the first dose of study drug which transiently improved with reglan. ECG results obtained on C2D2 in triplicate were interpreted as normal and pre-dose QTcF intervals were 427, 417 and 407 msec.</p> <p>On study day 100, the patient was hospitalized for hemorrhoidal bleeding (Grade 3 with ongoing nausea (Grade 2 and vomiting (Grade 2). An EGD with biopsy and colonoscopy performed the following day showed esophagitis (Grade 2) Gastritis (Grade 2) and internal hemorrhoids, a small amount of oozing at the suture site of a prior surgical anastomosis related to a previously resected diverticular rupture and colevescicular fistula with inflammation and ulceration which was clipped.</p> <p>On study day 312 (Cycle 12 Day 1), the PT, aPTT and INR were found to be elevated [41.2(9.7-12.3), 36.5 (22.8 – 31.0), 4.1 (0.8-1.2)]. The AST 56U/L (11-36, ALT 57 (6-43, total bilirubin 0.4 and vitamin K was administered. The patient continued to have persistent nausea (Grade 2), vomiting (Grade 2) and diarrhea (Grade 2) and when seen on study day 452, continued to have elevated PT, aPTT, and INR (Grade 1), as well as hypocalcemia and head and neck edema (Grade 2). No ECG was obtained. The patient was found dead 16 days after the last dose of study drug.</p> |
| 49053001 | Cardiopulmonary Failure | <p>42 year old white male who was diagnosed with MTC in October, 2001 with a diagnosis of metastatic disease in Nov., 2008 with a history of thyroidectomy and lymph node dissection and internal jugular vein resection at the time of diagnosis and resection of tumor recurrence and right lymph node resection in 2009. Medical history was significant for palsy of the recurrent laryngeal nerve, hypoparathyroidism and dysphagia. The patient had a history of smoking. The screening electrocardiogram was normal</p> <p>On study day 19, while taking his study drug, the patient turned blue and collapsed. The patient was resuscitated at home and transported to the emergency room where he was found to have sinus rhythm and incomplete right bundle branch block with S waves. On exam he was found to have marked myoclonus, adequate respirations, atonic tetraparesis and a positive Babinski sign bilaterally and it was concluded that the patient had</p> |

| | | |
|----------|--------------------------------|--|
| | | <p>experienced hypoxic brain damage with partially intact brain stem function. The patient subsequently developed aspiration pneumonia and sepsis.</p> <p>The investigator assessed the event of cardiac arrest to be possibly related to study treatment. The sponsor postulated that the cardiac arrest was due to aspiration of the study drug capsule and attributed the event to a vagal reaction and aspiration pneumonia due to aspiration of the study drug (given the subject's medical history of dysphagia and recurrent nerve palsy).</p> |
| 44033003 | Hemorrhage | <p>42 year old white male with a history of thyroidectomy and bilateral neck dissections (b) (6) pharyngo-laryngo-esophagectomy/level 6 clearance/manubriectomy and superior mediastinal dissection/gastric transposition (b) (6) and radiation to mandible, cervical vertebrae, bilateral clavicle (b) (6). The study drug was first administered on (b) (6). AE include grade 4 hypocalcemia, an abscess at the gastrectomy site (Grade 3) (study day 160). New J-tube inserted. Bleeding/oozing at J-tube insertion site (day 175). Hospitalization/replacement of J-tube (day-176). Fatal Hemorrhage (study day 184). Autopsy performed which suggested fatal laryngeal bleeding.</p> |
| 11243001 | Esophageal - cutaneous fistula | <p>47 year old Asian woman diagnosed in Feb. 2008, with diagnosis of metastatic disease May, 2008 with radical neck dissection, central compartment exploration, repair of esophagotomy and sternocleidomastoid muscle flap (Mar 2010) and radiation to the neck was hospitalized for mucositis and esophageal cutaneous fistula (study day 45). She underwent an anterior arteriogram with right subclavian and innominate artery stent to control bleeding from her right neck. On study day 47, she developed a gastric perforation and underwent a gastrostomy and Wietzel jejeunostomy. A head CT performed the same day revealed a large right middle cerebral artery infarct and findings concerning for a posterior cerebral artery infarct. She died on study day 50, 14 days after the last study drug administration.</p> |
| 32013009 | Tracheoesophageal fistula | <p>44 year old white female with parathyroid and pre-tracheal lymph nodes and metastatic disease to the bronchus and right and left lung. The patient had received prior radiation therapy to the mediastinum completed approximately 16 days prior the first dose of study drug. The patient's medical history included placement of a left main bronchus stent, achalasia of the esophagus and radiation esophagitis. She was assessed to have had a partial response by mRECIST. On study day 119 she presented with difficulty swallowing. An esophagogastroduodenoscopy revealed esophageal ulceration. She died 5 days after the last study drug. An autopsy demonstrated a massive peripheral pulmonary embolism with a 1cm tracheo-esophageal fistula.</p> |

| | | |
|----------|--|--|
| 34143001 | Acute respiratory Failure – Pulmonary hemorrhage- Tracheobronchial fistula | 47 year old male, had surgery for local excision of tracheal lesion about 2 months prior to initiating study treatment. Tumor invasion of the tracheal wall and mucosa from its upper third to the main bronchus was noted. Two right lateral neoplastic masses coming from the tracheal cartilage were removed by laser excision and were photocoagulated. On study day 30 the patient developed a DVT. On study day 56 the patient presented with hemoptysis and was hospitalized for pulmonary, tracheal, bronchial and upper respiratory hemorrhage (grade 2). The hemoptysis did not recur and the patient remained hemodynamically stable. On study day 59, the patient developed a pulmonary embolism, new bilateral pulmonary effusions. He was noted to have significant reduction in mediastinal and pulmonary hilar lymphadenopathy with the development of a necrotic mass and the appearance of a tracheobronchial fistula in the same area. The patient’s dyspnea worsened and he died of acute respiratory failure on study day 65. |
|----------|--|--|

Review Comment: While the number of deaths within the safety database is limited and most appear to be confounded by underlying disease factors reports to date suggest an emerging pattern of toxicity consistent with other strong VEGF inhibitors. No deaths from XL184-001 or XL184-201 were attributed to causes other than progressive disease.

7.3.2 Nonfatal Serious Adverse Events

The most frequently reported serious adverse events are listed by preferred term (PT) and system-organ-class (SOC) in Table 32 below. The most commonly reported PTs reported as SAEs in decreasing order of the between arm difference were: mucosal inflammation, hypertension and pulmonary embolism. Grade 3 and 4 adverse events coded according to CTCAE version 3.0 are delineated in Table 33 in section 7.3.1 below.

| | Cabozantinib N=214 | | Placebo N=109 | |
|---|-----------------------|-------------|------------------|------------|
| | n | (%) | 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 DISORDERS | 5 | (2) | 1 | (1) |
| THROMBOCYTOPENIA | 3 | (1) | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 4 | (2) | 0 | 0 |
| PPE SYNDROME | 3 | (1) | 0 | 0 |

Source: Cabozantinib Clinical Study Report, Table 57 page 163.; SAEs coded based on MedDRA version 14.0.

7.3.3 Dropouts and/or Discontinuations

Adverse events unrelated to disease progression led to study discontinuation in 35 (16%) of patients treated on the cabozantinib arm and in 9 (8%) of patients treated on the placebo arm. Adverse events leading to study discontinuation in 2 or more patients are listing below in Table 32. The most frequent reasons for study discontinuation were by decreasing order of between arm differences: gastrointestinal disorders, PPE and hypocalcemia.

| Adverse Event | Cabozantinib (N=214) | | Placebo (N=109) | |
|--|-------------------------|------|--------------------|------|
| | n | (%) | n | (%) |
| All Events | 35 | (16) | 9 | (8) |
| Gastrointestinal disorders | 8 | (4) | 0 | 0 |
| Diarrhea | 2 | (1) | 0 | 0 |
| Nausea | 2 | (1) | 0 | 0 |
| Vomiting | 2 | (1) | 0 | 0 |
| Pancreatitis | 2 | (1) | 0 | 0 |
| Investigations | 7 | (3) | 5 | (5) |
| Lipase increased | 3 | (1) | 3 | (3) |
| General disorders and administration site conditions | 5 | (2) | 1 | (<1) |
| Fatigue | 2 | (1) | 0 | 0 |
| Metabolism and nutrition disorders | 5 | (2) | 1 | (<1) |
| Hypocalcemia | 3 | (1) | 0 | 0 |
| Decreased appetite | 2 | (1) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 3 | (1) | 0 | 0 |
| PPE | 3 | (1) | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 2 | (1) | 0 | 0 |
| Tracheal fistula | 2 | (1) | 0 | 0 |
| Vascular disorders | 2 | (1) | 0 | 0 |
| Hypertension | 2 | (1) | 0 | 0 |

7.3.4 Significant Adverse Events

Significant adverse events are discussed under section 7.3.5 below.

7.3.5 Submission Specific Primary Safety Concerns

Based on the mechanism of action of cabozantinib and the safety profile which emerged in early clinical development, concern was raised that while cabozantinib was a multi-kinase inhibitor, toxicities commonly seen with VEGF inhibitors such as bevacizumab appeared prominent. In the safety assessment of cabozantinib, special concern was focused on an assessment of the following adverse events, which are known to be associated with VEGF inhibition: hypertension/hypertensive crisis, hemorrhage, gastrointestinal and other viscus perforations and fistula and abscess formation, wound complications, arterial and venous thromboses, proteinuria, osteonecrosis and reversible posterior leukoencephalopathy syndrome (RPLS). The frequency of these events by grade and study arm for XL184-301 is shown below in Table 33.

TABLE 33. XL184-301: INCIDENCE OF TOXICITIES ASSOCIATED WITH VEGF INHIBITION

| Adverse Event Category | Cabozantinib (N=214) n (%) | | | | Placebo (N=109) n (%) | | | |
|------------------------------|-------------------------------|--------|--------|--------|--------------------------|--------|--------|---|
| | CTCAE Grade | | | | CTCAE Grade | | | |
| | All | 3 | 4 | 5 | All | 3 | 4 | 5 |
| Hypertension | 70 (33) | 18 (8) | 0 | 0 | 5 (5) | 1 (<1) | 0 | 0 |
| Hemorrhage | 54 (25) | 4 (2) | 1 (<1) | 2 (1) | 17 (16) | 0 | 1 (<1) | 0 |
| Venous Thrombosis | 12 (6) | 3 (1) | 5 (2) | 0 | 3 (3) | 1 (<1) | 1 (<1) | 0 |
| Gastrointestinal perforation | 7 (3) | 3 (1) | 4 (2) | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal fistula | 2 (1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Abdominal/pelvic abscess | 5 (3) | 2 (1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-GI fistula | 8 (4) | 2 (1) | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |
| Arterial thrombosis | 5 (2) | 2 (1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Proteinuria | 4 (2) | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| Wound complications | 2 (2) | 2 (1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Osteonecrosis | 3 (1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| RPLS | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 |

Thirty-three per-cent of caboxantinib treated patients and 5% of placebo treated patients developed hypertension. Most events were Grade 1-2. Eight per-cent of patients in the cabozantinib arm and < 1% of patients in the placebo arm developed Grade 4 hypertension. Two patients in the cabozantinib arm were removed from study treatment due to an adverse event of hypertension, which was uncontrolled despite cabozantinib dose reductions and medical management.

Hemorrhage was reported in 25% of patients on the cabozantinib arm and 16% of patients on the placebo arm. Most reports on both study arms were Grade 1-2. In the cabozantinib arm, 47

patients experienced Grade 1-2 hemorrhagic events including pulmonary, respiratory, bronchial, tracheal hemorrhage, and hemoptysis (n=10), epistaxis (n=21), hematochezia (n=5), hematuria (n=5), rectal (n=4) and vaginal hemorrhage (n=2). Grade 3 hemorrhagic events occurred in 4 patients and included hemorrhoidal hemorrhage, colonic hematoma, duodenal ulcer hemorrhage and intestinal hemorrhage. One Grade 4 event of hemoptysis was reported in a patient with a previous history of hemoptysis with bronchus arterial embolization prior to enrollment. This patient was reported to have subsequently died of respiratory failure. Two patients on the cabozantinib arm were reported to have fatal hemorrhage. The first (4433003) (Table 30), had a cause of death reported as hemorrhage with autopsy findings of asphyxia, tracheostomy injury, hemorrhage and widespread cancer. The second (39043005) was assessed at the 12-week tumor assessment to have PD by mRECIST and was discontinued from study due to tumor progression with “tracheal and esophageal invasion by cancer”. Ten days after the last dose of study drug, the patient experienced fatal hemoptysis. The cause of this death was attributed to progressive disease (the reviewer concurs with this assessment). One patient on the placebo arm had a Grade 4 event of epistaxis. Other events of Grade 1-2 on the placebo arm included: hemorrhoidal hemorrhage (n=2), hematuria (n=2), hemoptysis (n=1), hemorrhagic diathesis (n=1) and epistaxis (n=10). Gastrointestinal perforations, fistulas and abdominal/pelvic abscesses as well as non-gastrointestinal fistulas were observed in the cabozantinib arm and not in the placebo arm. Fatal adverse events of gastrointestinal and tracheo-esophageal fistula were reported. Adverse events of arterial and venous thrombosis as well as proteinuria and wound complications were also reported in excess in the treatment arm. Osteonecrosis of the jaw was reported in three patients treated on the cabozantinib and dental events (dental pain and abscess) were also frequently reported in the treatment arm. RPLS was reported in one patient on the cabozantinib arm.

The incidence of renal failure was further explored using the preferred terms listed in Table 34 below. While there did appear to be an increase in renal events among patients treated on the cabozantinib arm, review of the narratives for these cases suggested that most were confounded by underlying risk factors (for example, prior history of hypertension or concurrent treatment with zoledronic acid for bone metastasis) and the review was considered inconclusive. The risk of renal toxicity should be prospectively assessed in post-marketing reports.

| Preferred Term | Cabozantinib N=214 | | Placebo N=109 | |
|--|-----------------------|---------------------|---------------------|---------------------|
| | All Grades n (%) | Grades 3-4 n (%) | All Grades n (%) | Grades 3-4 n (%) |
| Acute prerenal failure, Renal failure, Acute renal failure | 6 (3) | 3 (1) | 1 (1) | 0 |
| Nephrotic syndrome | 1 (<1) | 1(<1) | 0 | 0 |
| Hemolytic uremic syndrome | 1(<1) | 1(<1) | 0 | 0 |

7.4 Supportive Safety Results

The risk of hepatotoxicity was assessed by screening for potential cases which met the Hy’s Law criteria (Table 35). The incidence of these events was comparable on both study arms suggesting no marked increase in the risk of hepatotoxicity associated the use of cabozantinib.

| Potential Hy’s Law Case | Cabozantinib (N=214) n (%) | | Placebo (N=109) n (%) | |
|--|----------------------------------|-------|-----------------------------|-----|
| > 3 x ULN (ALT or AST), > 2 x ULN Total Bilirubin, and < 2 x ULN ALP | 1 | (< 1) | 1 | (1) |
| > 3 x ULN (ALT or AST), > 2 x ULN Total Bilirubin, and ≥ 2 x ULN ALP | 3 | (1) | 2 | (2) |

7.4.1 Common Adverse Events

Adverse events occurring in at least 5% of patients on the cabozantinib arm with a between arm difference of ≥ 5% for all grades combined or ≥ 2% for Grade 3 or 4 adverse events are listed below in Table 36. Adverse reactions which occurred in ≥ 20% of cabozantinib treated patients and which occurred more frequently in the cabozantinib arm (between-arm difference ≥ 5%) in order of decreasing frequency were: oral pain, diarrhea, stomatitis, palmar-plantar erythrodysesthesia (PPE) syndrome, weight decreased, nausea, hair color changes (hypopigmentation), dysgeusia, hypertension/hypertensive crisis, and constipation. Grade 3-4 adverse reactions which occurred in ≥ 5% of cabozantinib treated patients and which occurred more frequently in the cabozantinib arm (between-arm difference ≥ 2%) in order of decreasing frequency were: PPE, diarrhea, fatigue, asthenia, weight decrease, oral pain, stomatitis and decreased appetite.

TABLE 36. XL184-301: PERCENT OF ADVERSE EVENTS OCCURRING IN ≥ 5% OF

| CABOZANTINIB TREATED PATIENTS WITH A BETWEEN ARM DIFFERENCE OF $\geq 5\%$ (ALL GRADES) OR $\geq 2\%$ (GRADES 3-4) BY MEDDRA SYSTEM ORGAN CLASS (SOC) AND PRIMARY TERM (PT) | | | | |
|--|--------------------------------------|------------|--------------------|------------|
| SOC/PT ³ | Cabozantinib ² (n=214) | | Placebo (n=109) | |
| | All Grades ¹ | Grades 3-4 | All Grades | Grades 3-4 |
| GASTROINTESTINAL DISORDERS | | | | |
| ORAL PAIN (ORAL PAIN, OROPHARYNGEAL PAIN, GLOSSITIS, BURNING MOUTH SYNDROME, GLOSSODYNIA) | 72 | 5 | 6 | 0 |
| STOMATITIS (STOMATITIS, APTHOUS STOMATITIS, MOUTH ULCERATION, MUCOSAL INFLAMMATION) | 51 | 5 | 6 | 0 |
| DIARRHEA | 64 | 16 | 34 | 2 |
| NAUSEA | 44 | 1 | 23 | 0 |
| CONSTIPATION | 27 | 0 | 6 | 0 |
| VOMITING | 24 | 2 | 4 | 2 |
| ABDOMINAL PAIN, ABDOMINAL PAIN LOWER, ABDOMINAL PAIN UPPER, ABDOMINAL REGIDITY, ABDOMINAL TENDERNESS, ESOPHAGEAL PAIN | 27 | 3 | 13 | 1 |
| DYSPEPSIA | 11 | 0 | 0 | 0 |
| DYSPHAGIA | 13 | 4 | 6 | 0 |
| DRY MOUTH | 14 | 0 | 8 | 0 |
| HEMORRHOIDS | 9 | 0 | 3 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| FATIGUE | 41 | 9 | 30 | 3 |
| ASTHENIA | 22 | 6 | 14 | 1 |
| INVESTIGATIONS | | | | |
| WEIGHT DECREASED | 49 | 5 | 11 | 0 |
| METABOLISM AND NUTRITION DISORDERS | | | | |
| DECREASED APPETITE | 46 | 5 | 18 | 2 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | | |
| MUSCLE SPASMS | 12 | 0 | 5 | 0 |
| ARTHRALGIA | 14 | 1 | 8 | 0 |
| MUSCULOSKELETAL CHEST PAIN | 9 | 1 | 4 | 0 |
| NERVOUS SYSTEM DISORDERS | | | | |
| DYSGEUSIA | 34 | 0 | 6 | 0 |

| | | | | |
|---|----|----|----|---|
| HEADACHE | 18 | 0 | 8 | 0 |
| DIZZINESS | 14 | 0 | 7 | 0 |
| PERIPHERAL SENSORY NEUROPATHY/PERIPHERAL NEUROPATHY | 12 | 0 | 0 | 0 |
| PARAESTHESIA | 7 | 0 | 2 | 0 |
| PSYCHIATRIC DISORDERS | | | | |
| ANXIETY | 9 | 0 | 2 | 0 |
| INSOMNIA | 12 | 0 | 6 | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | | |
| DYSPHONIA | 21 | 0 | 9 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | | |
| PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME | 50 | 13 | 2 | 0 |
| HAIR COLOR CHANGES (DEPIGMENTATION) | 34 | 0 | 1 | 0 |
| DRY SKIN | 20 | 0 | 3 | 0 |
| ALOPECIA | 17 | 0 | 2 | 0 |
| ERYTHEMA | 11 | 1 | 3 | 0 |
| HYPERKERATOSIS | 7 | 0 | 0 | 0 |
| RASH | 19 | 1 | 13 | 0 |
| VASCULAR DISORDERS | | | | |
| HYPERTENSION, HYPERTENSIVE CRISIS | 31 | 8 | 5 | 1 |
| HYPOTENSION | 7 | 1 | 0 | 0 |

¹National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0; does not include laboratory abnormalities reported as adverse events

²Includes patients who received study medication.

³Ordered within SOC by decreasing between arm differences (All Grades)

Review Comments: A number of adverse events associated with cabozantinib treatment such as depigmentation of the hair and skin and dysphonia were distinctive and would have made blinding of the study difficult, if not impossible.

7.4.2 Laboratory Findings

Laboratory adverse events reported with a between arm difference for all Grades of $\geq 5\%$ or a between arm difference for Grades 3-4 toxicities $\geq 2\%$ are shown below in Table 37. Laboratory adverse events were primarily low grade. Of note is the increase in blood thyroid stimulating

hormone (TSH) in this population of post-thyroidectomy patients. While the significance of this finding is not clear, it was also seen with the TKI, vandetanib, in a similar population of patients.

| TABLE 37. XL184-301: PERCENT OF LABORATORY ADVERSE EVENTS ¹ (MEDDRA) OCCURRING WITH A BETWEEN ARM DIFFERENCE OF $\geq 5\%$ (ALL GRADES) OR $\geq 2\%$ (GRADES 3-4) BY MEDDRA SYSTEM ORGAN CLASS (SOC) AND PRIMARY TERM (PT) | | | | |
|--|---------------------|-----------|--------------------|-----------|
| PT | COMETRIQ (n=214) | | Placebo (n=109) | |
| | All Grades | Grade 3-4 | All Grades | Grade 3-4 |
| ↑ ALANINE AMINOTRANSFERASE (ALT) | 21 | 3 | 6 | 2 |
| ↑ ASPARTATE AMINOTRANSFERASE (AST) | 21 | 1 | 7 | 1 |
| ↑ BLOOD LACTATE DEHYDROGENASE (LDH) | 19 | 2 | 3 | 1 |
| ↑ BLOOD THYROID STIMULATING HORMONE (THS) | 14 | 0 | 3 | 0 |
| HYPOCALCEMIA | 22 | 9 | 7 | 1 |
| HYPOKALEMIA | 11 | 5 | 5 | 4 |
| THROMBOCYTOPENIA | 6 | 1 | 1 | 1 |

¹Some values that fall within normal range may also meet CTCAE criteria as being Grade ≥ 1 ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase

7.4.3 Vital Signs

Hypertension and weight loss were reported more frequently in the treatment arm than in the placebo arm (Table 36). A graph of temporal trends in blood pressure and weight are provided below in section 7.5.2.

7.4.4 Electrocardiograms (ECGs)

No large changes in mean QT interval (>20 ms) was detected in XL184-301 following the treatment of cabozantinib 140 mg once daily. The largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 13.95 ms, observed at 0 hours (pre-dose) on Day 1 of Cycle 2, following continuous dosing of 28 days. no XL184-treated subject was identified with a new QTcF >500 ms on Day 1 or on Day 29, though there were single reports of new QTcF >480 ms on Days 1 and 29; and one subject was identified with a change from baseline QTcF >60 ms on Day 29 which resulted in an average maximum QTcF value of 442 ms. There was one placebo subject that was identified with a new QTcF >500 ms on Day 1 and on Day 29, though no other QTcF abnormalities were observed in the placebo group.

Please refer to Dr. Brar's review for additional details.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

An analysis of anaphylactic/anaphylactoid shock conditions using Standard MedDRA Queries terminology (SMQ/Narrow) revealed no cabozantinib-treated patients who met the criteria for this SMQ. Review of clinical safety does not raise concerns of immunogenicity with this small molecule. No formal immunogenicity studies were required or were done.

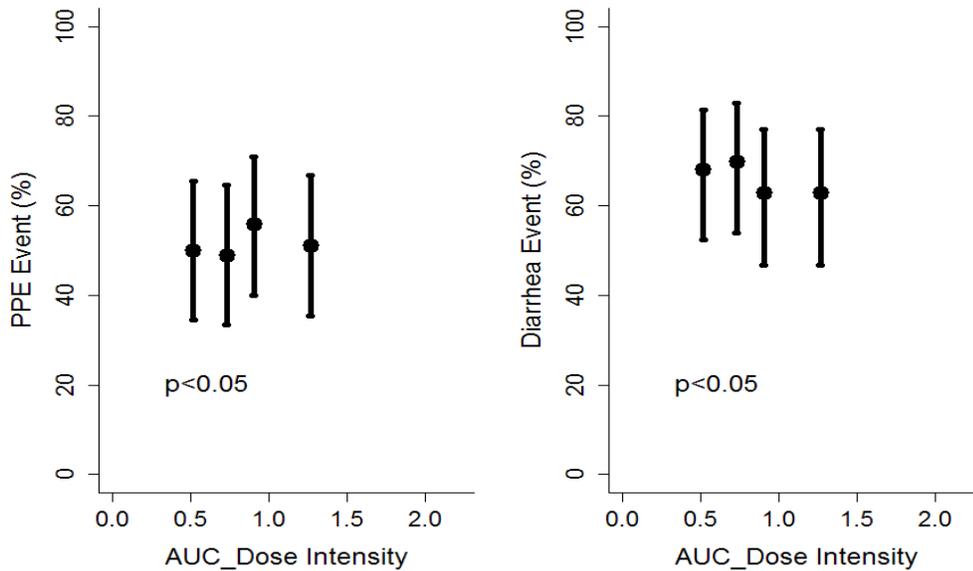
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose exploration was conducted over a very limited range in the clinical development program for cabozantinib. The safety data set is limited to less than 300 patients; few of these were treated at doses below 60 mg. However, within the range of exposures studied in the XL184-301, there was no clear trend in the relationship between toxicity and overall dose intensity (

Figure 17). This does not rule out an association between toxicity and peak exposure levels.

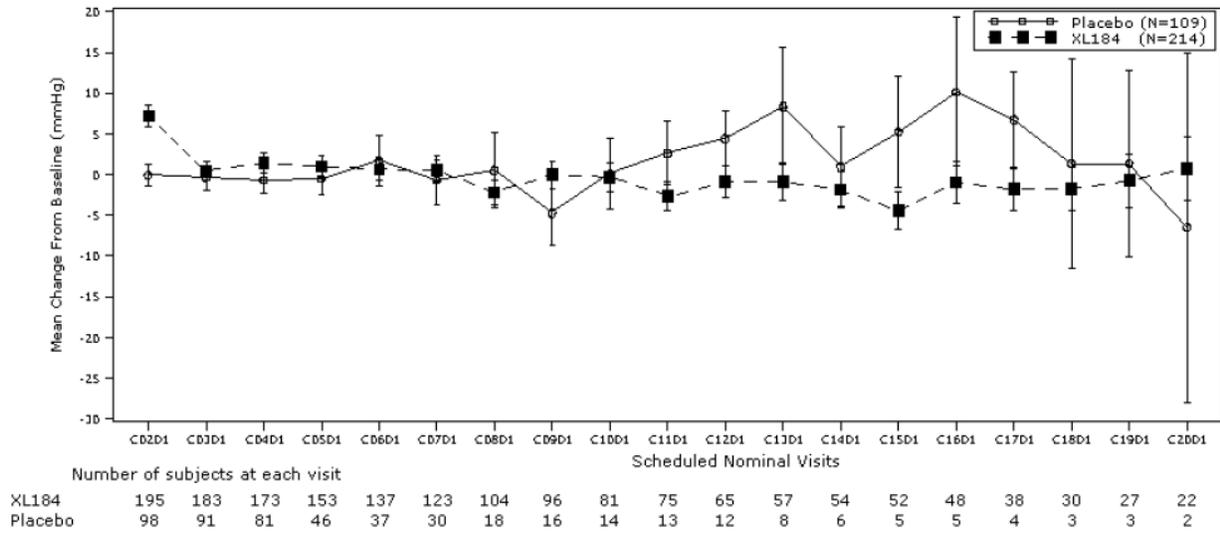
Figure 17. Cabozantinib Dose Intensity and Incidence of PPE and Diarrhea, XL184-301



7.5.2 Time Dependency for Adverse Events

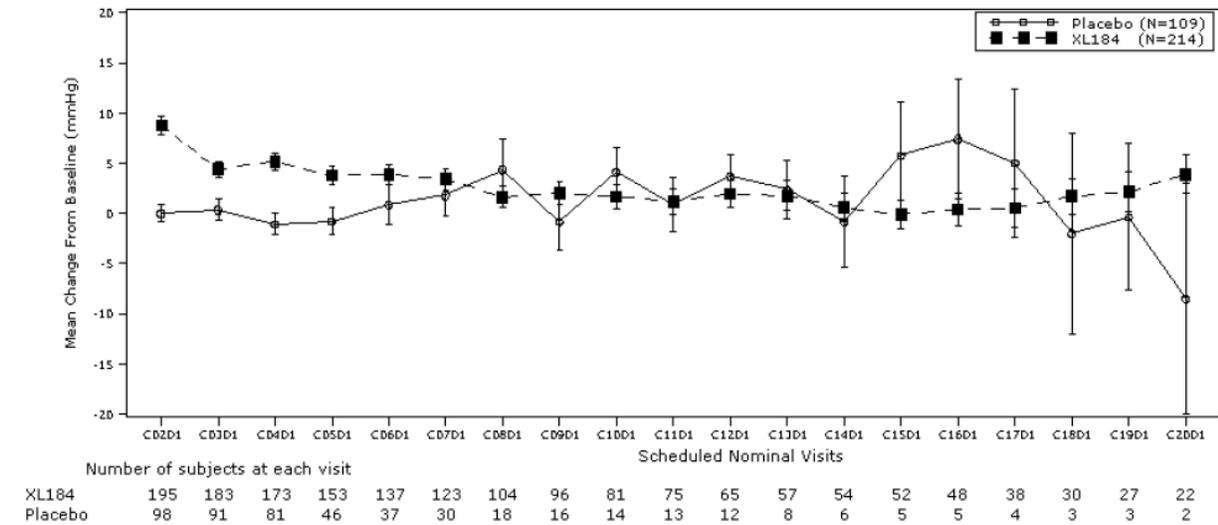
An increase was observed in both systolic and diastolic blood pressure in the cabozantinib arm which appeared to normalize by the second treatment cycle for systolic blood pressure and by the fifth treatment cycle for diastolic blood pressure (Figure 18 and Figure 19). This trend was due to a combination of dose reduction and medical treatment.

Figure 18. XL184-301. Change from Baseline by Visit for Systolic Blood Pressure, SAS



*NDA 203765 XL184-301 Final Study Report page 385

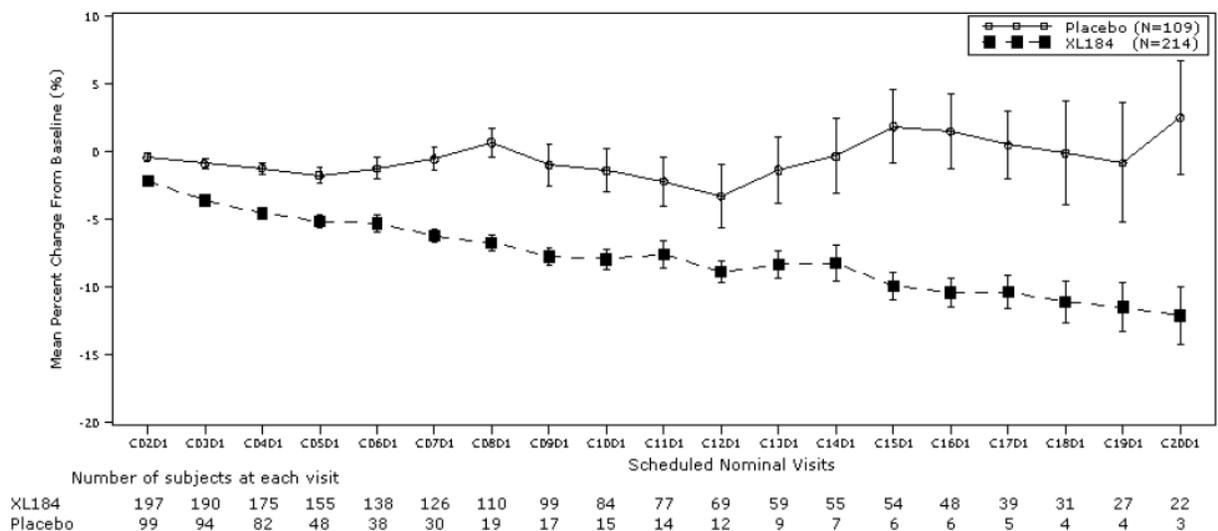
Figure 19. XL184-301. Change from Baseline by Visit for Diastolic Blood Pressure, SAS



*NDA 203765 XL184-301 Final Study Report page 386

Patients on the cabozantinib arm continued to lose weight over the entire course of cabozantinib treatment (Figure 20).

Figure 20. XL184-301. Change from Baseline by Visit for Weight, SAS



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7.5.3 Drug-Demographic Interactions

A higher rate of Grade 3-4 adverse events, serious adverse events and events leading to study discontinuation were observed among females (Table 38).

Review Comment: This increase in toxicity may be related to decreased cabozantinib clearance in females which was found to be 22% lower in females than in males.

| Number of Patients with: | Male (n=149) n (%) | | Female (n=65) n (%) | |
|--|--------------------------|------|---------------------------|-------|
| Any Adverse Event | 146 | (98) | 65 | (100) |
| Any Grade 3 or 4 Adverse Event | 88 | (59) | 49 | (75) |
| Any Serious Adverse Event | 44 | (30) | 27 | (42) |
| Any Adverse Event leading to study discontinuation | 21 | (14) | 14 | (22) |
| AE Leading to Deaths | 6 | (4) | 3 | (5) |

No obvious trends in toxicity were observed by age- or race- group (Table 39 and Table 40). However, the number of patients 65 years of age and older and the number of non-White patients was small.

| Number of Patients with: | Age < 65 N=166 n (%) | | 65 ≤ Age < 75 N=35 n (%) | | Age ≥ 75 N=13 n = (%) | |
|--|----------------------------|------|--------------------------------|-------|-----------------------------|------|
| Any Adverse Event | 164 | (99) | 35 | (100) | 12 | (92) |
| Any Grade 3 or 4 Adverse Event | 18 | (64) | 4 | (57) | 0 | 0 |
| Any Serious Adverse Event | 54 | (33) | 13 | (37) | 4 | (31) |
| Any Adverse Event leading to study discontinuation | 27 | (16) | 4 | (11) | 4 | (31) |
| AE Leading to Deaths | 8 | (5) | 1 | (3) | 0 | 0 |

| TABLE 40. XL184-301: ADVERSE EVENTS AMONG CABOZANTINIB TREATED PATIENTS BY RACE* | | | | |
|--|-------------------------|------|-----------------------------|------|
| Number of Patients with: | White N=194 n (%) | | Non-White N=15* n (%) | |
| Any Adverse Event | 190 | (99) | 14 | (93) |
| Any Grade 3 or 4 Adverse Event | 122 | (64) | 10 | (67) |
| Any Serious Adverse Event | 65 | (34) | 4 | (27) |
| Any Adverse Event leading to study discontinuation | 31 | (16) | 2 | (13) |
| AE Leading to Deaths | 7 | (4) | 2 | (13) |

*7 Not Reported

7.5.4 Drug-Disease Interactions

Patients with predisposing conditions were excluded from XL184-301. There are no data on which to base an assessment of drug-disease interactions. Studies in patients with impaired renal and hepatic function will be post-marketing requirements.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Yang's review for details concerning drug-drug interaction studies.

CYP Enzyme Inhibition and Induction: Cabozantinib is a noncompetitive inhibitor of CYP2C8 ($K_{iapp} = 4.6 \mu\text{M}$), a mixed-type inhibitor of both CYP2C9 ($K_{iapp} = 10.4 \mu\text{M}$) and CYP2C19 ($K_{iapp} = 28.8 \mu\text{M}$), and a weak competitive inhibitor of CYP3A4 (estimated $K_{iapp} = 282 \mu\text{M}$) in human liver microsomal (HLM) preparations. IC_{50} values $>20 \mu\text{M}$ were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control β -naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations ($\geq 100 \text{ mg/day}$ daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) in patients with solid tumors.

P-glycoprotein Inhibition: Cabozantinib is an inhibitor ($IC_{50} = 7.0 \mu\text{M}$), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Studies examining the carcinogenic potential of cabozantinib have not been conducted.

7.6.2 Human Reproduction and Pregnancy Data

In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately equal to the clinical plasma exposure at the recommended human dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (approximately 50% of the clinical plasma exposure at the recommended clinical dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

There were similar findings in male and female dogs in a 6-month repeat dose study at exposures equal to 6% and 3%, respectively, the clinical plasma exposure at the recommended human dose, and female rats administered 1.5 mg/kg/day for 14 days (approximately 0.1 times the recommended human dose, based on body surface area), as well as male rats administered a single dose of cabozantinib.

Please refer to Dr. Brower's review for details.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cabozantinib has not been studied in a pediatric population. A pediatric waiver was granted by the Pediatric Review Committee based on cabozantinib's orphan drug status.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A small number of patients have been treated at doses above the 140 mg dose proposed by the Applicant for labeling. One patient on XL184 took 280 mg of cabozantinib for 9 days instead of 140. The study drug was withheld for 4 days due to the adverse events of Grade 3 cognitive disorder, Grade 3 memory impairment, Grade 2 weight decrease, Grade 3 mental status changes, Grade 1 increased free thyroxine and Grade 1 blood urea nitrogen. The study drug was restarted at 100 mg and these events resolved.

There is no specific treatment recommendation for cabozantinib overdose. Drug abuse potential, withdrawal and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

While patients were not prospectively screened for study entry based on *RET* mutation status, patients were retrospectively classified. An exploratory analysis provided by the sponsor and confirmed by FDA indicates that cabozantinib is effective in patients who carry a germline *RET* mutation and in those who do not. An additional analysis was performed to determine whether

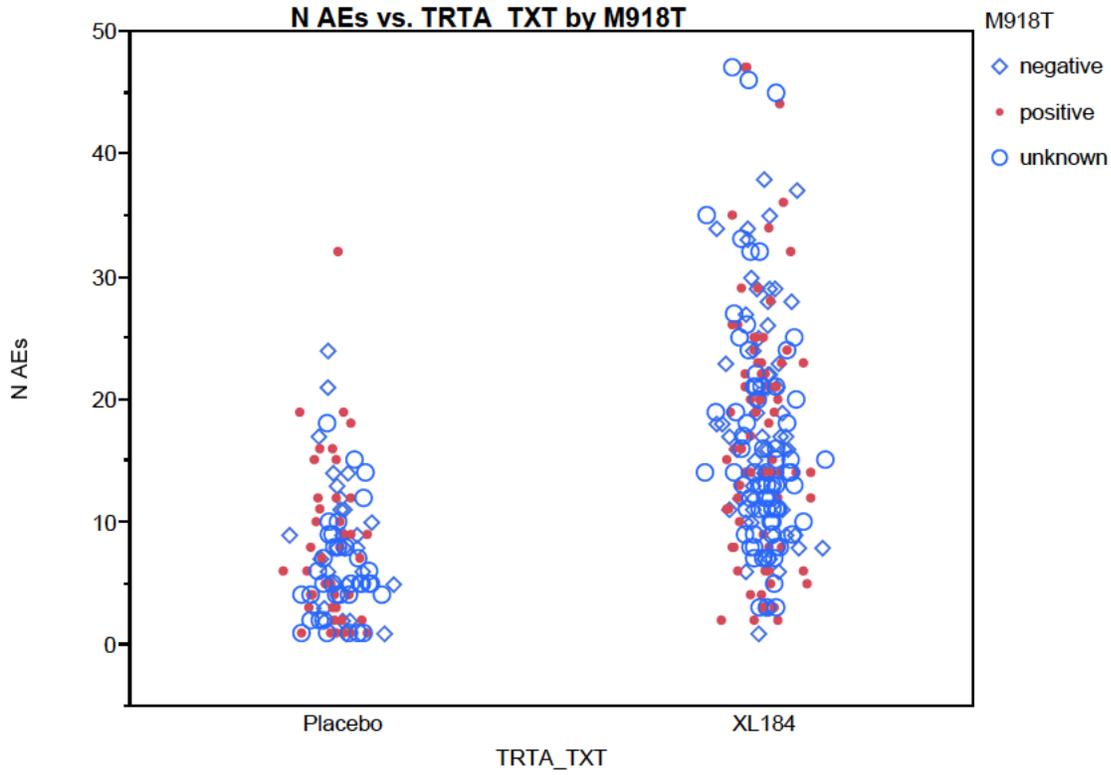
the safety profile of cabozantinib in patients with a germline *RET* mutation differs from other patients (Table 41).

| Number of Cabozantinib-Treated Patients with: | Cabozantinib N=214 n(%) | | Placebo N=109 n(%) | |
|--|-------------------------------|---------------|--------------------------|---------------|
| | RET M918T Positive | | RET M918T Positive | |
| | No/Unknown (n=140) | Yes (n=74) | No/Unknown (n=66) | Yes (n=43) |
| Any Adverse Event | 140 (100) | 74 (100) | 64 (97) | 39 (91) |
| Any Grade 3 or 4 Adverse Event | 103 (74) | 60 (81) | 22 (33) | 19 (44) |
| Any Serious Adverse Event | 58 (41) | 32 (43) | 12 (18) | 13 (30) |
| Any Adverse Event leading to study discontinuation | 19 (14) | 14 (19) | 4 (6) | 5 (12) |
| AE Leading to Deaths | 49 (35) | 16 (22) | 16 (24) | 14 (33) |
| Deaths within 30 days of last study drug | 28 (20) | 15 (20) | 12 (18) | 10 (23) |
| Deaths within 30 days due to causes other than PD | 17 (12) | 5 (7) | 4 (6) | 4 (9) |

There does not seem to be a consistent pattern of increased Grade 3 or 4 adverse events, serious adverse events, adverse events leading to study discontinuation or death between mutation carriers and non-carriers on the cabozantinib arm. Patients on the placebo arm with a germline mutation in the *RET* gene, seemed to fare poorly by these indicators compared to patients without a known mutation, however these findings may be unreliable based on the small number of patients in the placebo arms.

Similarly, the number of adverse events per patient was plotted by study arm and mutation status (Figure 21). No clear pattern was observed in the number of adverse events by mutation status among patients in either arm.

Figure 21. XL184-301. Distribution of Adverse Events per Patient by Treatment Arm and *RET* Mutation Status



8 Postmarket Experience

Cabozantinib is a new molecular entity with no prior approval history.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

As of the date of this review, labeling negotiations with the Applicant are ongoing. The final red-lined version of the label, including label recommendations made by all FDA scientific disciplines, which was sent to the Applicant on October XX, 2012 is included here for reference.

Clinical Review
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NDA 203756
Cometriq [Cabozantinib (XL184)]/Exelixis

9.3 Advisory Committee Meeting

This application was not brought to the Oncology Drug Advisor Committee (ODAC).

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/s/

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11/06/2012

SUZANNE G DEMKO
11/06/2012