CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	203756
Submission Date	May 29, 2012
Submission Type; Code	Original NDA; 505 (b)(1); New Molecular Entity
Brand Name	COMETRIQ®
Generic Name	Cabozantinib
Dosage Form / Strength	Oral Capsules (20 mg and 80 mg)
Dosing Regimen	140 mg Orally Daily
Indication	Progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC)
Related IND	113446
Applicant	Exelixis, Inc.
Clinical Pharmacology Reviewer	Jun Yang, Ph.D.
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1. EXECUTIVE SUMMARY

The safety and efficacy of cabozantinib were assessed in a randomized (2:1), double-blind placebo-controlled registrational trial (XL184-301) in patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC). Progression free survival (PFS), the primary endpoint for the cabozantinib treatment arm (N = 219) was 11.2 months (median) compared to 4.0 months for the placebo arm (N = 111). The proposed dosing regimen for cabozantinib is 140 mg (capsules) administered orally once daily, taken at least 1 hour before or 2 hours after a meal. In this trial, a high proportion (86.4%) of patients in the cabozantinib arm experienced at least one dose modification (e.g., dose interruption, dose reduction, and dose discontinuation) due to adverse events. Exposure-response analyses for efficacy indicated that lower dose intensity may not be associated with reduction of PFS; further exposure-response analyses indicated that early dose modifications due to adverse events are associated with higher exposures, indicating that a lower dose might be effective with improved tolerability. Therefore, label should include a starting dose of 100 mg with a provision to increase the dose to 140 mg or decreased to 60 mg as tolerated. If the starting dose of 100 mg is not acceptable, conducting a clinical trial as a PMR to identify a lower effective cabozantinib dose in patients with MTC is recommended.

Mass balance study identified that approximately 54% and 27% of radioactivities were recovered in feces and urine, respectively. Results of population pharmacokinetics (population PK) analyses suggest that the effect of mild and moderate renal impairment on clearance of cabozantinib is minimal. Pharmacokinetics (PK) of cabozantinib in patients with severe renal impairment or in patients with hepatic impairment has not been studied. A PMR for conducting a hepatic impairment study is recommended.

Cabozantinib is a CYP3A4 substrate. Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose cabozantinib exposure by 38%. Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose cabozantinib exposure by 77%. 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 PMR for conducting a dedicated pH effect study is recommended.

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.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language and the post-marketing requirements (PMRs). See Section 3 for detailed labeling recommendations.

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

Clinical Pharmacology recommends a starting dose of 100 mg capsule in the COMETRIQ$^®$ label, and the dose may be increased to 140 mg or decreased to 60 mg as tolerated based on the exposure-response analyses and the observed clinical results (See Clinical Pharmacology Review Section 2.2.4). If this is not an acceptable option, then Clinical Pharmacology supports a randomized dose-comparison trial testing 140 mg dose and a biologically active lower dose in patients with progressive metastatic medullary thyroid cancer. The details regarding the study design will be discussed further (See Clinical Review).

The following two PMRs are requested:

PMR#1. Conduct a clinical trial to determine the appropriate dose of cabozantinib in patients with hepatic impairment. Submit the final protocol for FDA review before conducting the trial.

PMR#2. Conduct a clinical trial to evaluate if proton pump inhibitors, H_2 antagonists and antacids alter the bioavailability of cabozantinib. You may study the worst case scenario first, and then determine if further studies of other drugs are necessary. The study results should allow for a determination on how to dose cabozantinib with regard to these gastric pH elevating agents. Submit the final protocol for FDA review before conducting the trial.

Address the following issue and submit the results to the IND:
Conduct a pharmacokinetic drug interaction trial in subjects administered an oral P-glycoprotein probe substrate with and without cabozantinib in accordance with the FDA draft Guidance for Industry: "*Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing, and Labeling Recommendations*." Submit the final protocol for FDA review before conducting the trial.

Signatures:

Jun Yang, Ph.D. Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5
Jun Yang, Ph.D. Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D. Pharmacometrics Team Leader (Acting)
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Cc: DDOP2: MO - Ruthann Giusti; MTL - Suzanne Demko; RPM - Gina Davis DCP-5: DDD –Brian Booth;	

A Required OCP Office Level Briefing was held on October 24, 2012 attended by:

Issam Zineh, Atiqur Rahman, John Lazor, Mehul Mehta, Lei Zhang, Mike Pacanowski, Ruby Leong, Stacy Shord, Runyan Jin, Bei Yu, Jack Wang, Gene Williams, Sarah Schrieber and others.

1.3 CLINICAL PHARMACOLOGY SUMMARY

Cabozantinib (COMETRIQ®), a new molecular entity, is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs). Cabozantinib is granted an orphan drug status for the treatment of follicular, medullary and anaplastic carcinoma and metastatic or locally advanced papillary thyroid cancer. The applicant seeks an approval of COMETRIQ® (cabozantinib) for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC). The proposed dosing regimen for cabozantinib is 140 mg (capsules) administered orally once daily (QD), taken at least 1 hour before or 2 hours after a meal. The 140 mg daily dose can be reduced to 100 mg and then to 60 mg for management of intolerable toxicities. The safety and efficacy of cabozantinib were assessed in a multi-center, randomized (2:1) double-blind registrational trial (XL184-301) in MTC patients who received best supportive care (BSC) with either cabozantinib (N = 219) or placebo (N = 111) administered daily. The trial results demonstrated a statistically significant improvement on the primary endpoint, progression-free survival (PFS): 11.2 months versus 4.0 months for patients in the cabozantinib arm and placebo arm, respectively (Hazard Ratio (HR) = 0.27; 95% CI: 0.19, 0.40; p<0.0001). The secondary endpoint, objective response rate (ORR), was 27.9% for patients in the cabozantinib arm and 0% for patients in the placebo arm (p<0.0001). There was no statistically significant improvement in overall survival (OS) in the treatment arm based on the OS data including 75% of the total required deaths.

The most commonly reported adverse events (AEs) (>20%) are diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair color changes (depigmentation), hypertension, stomatitis, constipation, vomiting, mucosal inflammation, asthenia, and dysphonia. The most frequent AEs that led to dose modifications were PPE syndrome, diarrhea, fatigue, weight decreased, and decreased appetite.

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

Dose proportionality of the cabozantinib capsules has not been formally evaluated. The cabozantinib exposure (AUC and C_{max}) were increased approximately dose proportional after 5 daily oral doses of a powder-in-bottle (PIB) formulation (range: 4.8 mg/day – 1,382 mg/day). A cross-study comparison for the capsule formulation identified that a single 80 mg dose yielded comparable dose-normalized AUC_{0-24} and C_{max} values with the dose of 140 mg, suggesting that

cabozantinib exposure increases approximately in proportion to dose over the dose range of 80 to 140 mg for capsules administered as a single dose.

Absorption and Distribution: PK parameters for cabozantinib were comparable in cancer patients and healthy subjects following a single oral dose. The median T_{max} was approximately 2-4 hours in cancer patients and 4-5 hours in healthy subjects. The plasma PK profile of cabozantinib following a single oral dose in healthy subjects is characterized by a terminal phase half-life of approximately 120 hours with multiple peaks suggesting that cabozantinib is either enterohepatically recirculated or absorbed at different rates or both. Absolute oral bioavailability of cabozantinib capsule has not been determined. Mean AUC_{0-inf} values for cabozantinib from these healthy subjects studies using capsules (XL184-004, XL184-006, and XL184-007) were 74 to 93% of the corresponding value in the mass balance study where cabozantinib was administered as a solution.

When cabozantinib was administered with a high-fat, high calorie meal in healthy subjects, the C_{max} and AUC values (AUC_{0-t} and AUC_{0-inf}) were increased by 41% and 57%, respectively. Cabozantinib is highly protein bound ($\geq 99.7\%$) *in vitro* in human plasma.

Metabolism and Elimination: Cabozantinib is a noncompetitive inhibitor of CYP2C8 ($Ki_{app} = 4.6 \ \mu M$), a mixed-type inhibitor of both CYP2C9 ($Ki_{app} = 10.4 \ \mu M$) and CYP2C19 ($Ki_{app} = 28.8 \ \mu M$), and a weak competitive inhibitor of CYP3A4 (estimated $Ki_{app} = 282 \ \mu M$) in human liver microsomal (HLM) preparations. IC_{50} values $>20 \ \mu M$ 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 is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Cabozantinib is a CYP3A4 substrate. Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 38%. Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 77%. Cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) has no effect on single-dose plasma exposure (C_{max} and AUC) of rosiglitazone (a CYP2C8 substrate) in patients with solid tumors.

Cabozantinib is an inhibitor ($IC50 = 7.0 \ \mu M$), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Evaluation of cabozantinib to breast cancer resistance protein (BCRP) has not been conducted.

Following a single oral dose of ^{14}C-cabozantinib (140 mg) in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Pharmacokinetics in Specific Populations: No formal PK studies have been conducted in patients with hepatic or renal impairment, or in pediatric patient populations. Results of a

population PK analysis suggest that clearances of cabozantinib in patients with mild or moderate renal impairment are comparable to that of normal patient population. No correlation was identified between creatinine clearance and cabozantinib clearance. A total of 27% (metabolites and parent drug) of administered radioactivity was recovered from human urine. No dose adjustment is necessary for patients with renal impairment. A dedicated study using the Child-Pugh criteria evaluating hepatic impairment on PK of cabozantinib is undergoing and will be requested as a PMR.

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

Exposure-Response (E-R) Relationship: In the registrational trial, 86.4% of patients in the cabozantinib arm experienced at least one dose modification (e.g., dose reduction, dose interruption, and dose discontinuation) due to adverse events (AEs), which made the results of the E-R analyses difficult to interpret. To account for different exposure levels due to dose modification, Kaplan-Meier analyses of PFS stratified by quartiles of the average exposure, $AUC_{Dose\ Intensity}$ ($AUC_{Dose\ Intensity}$ =Starting Dose*Dose intensity/individual CL/F) suggest that lower exposure may not reduce PFS. Patients required dose reduction as early as after 2 days and as late as 554 days with median reduction needed within 29 days. Kaplan-Meier analyses for PFS and time to the first dose modification indicate that early dose modification in patients due to toxicity does not reduce efficacy. Further analyses indicated that patients with higher exposures required dose modification earlier than patients with lower exposures. The Cox proportional hazard model identified AUC_{ss} (ranging from 0.51 to 3.53 mg*day/L) as the only significant covariate for prediction of time to the first dose modification (hazard ratio [HR]=1.95; 95% CI [1.47-2.59]) with age, sex, body size, smoke status, AUC_{ss}, ECOG status, race not identified as significant covariates. These E-R relationships for efficacy and safety suggest that a lower dose might be effective with improved tolerability; therefore, label should include a starting dose of 100 mg with a provision to increase the dose to 140 mg or decreased to 60 mg as tolerated. If the starting dose of 100 mg is not acceptable, conducting a clinical trial as a PMR to identify a lower effective cabozantinib dose in patients with MTC is recommended.

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.

Conclusion: Overall, the review team accepts the Clinical Pharmacology information presented in this application.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The drug substance (DS), cabozantinib (S)-malate salt, is insoluble in aqueous solution. Cabozantinib has   (b) (4)
   The commercial capsules contain   (b) (4)

. A two-period, two-sequence crossover bioequivalence (BE) study demonstrated that the capsule formulation containing an approximate   (b) (4) is comparable to capsules containing primarily the   (b) (4) (Study XL184-016, see Section 2.5.2).

The capsule dosage form used in clinical trials was expressed as salt-based weight (25 mg and 100 mg) corresponding to 19.7 mg and 78.9 mg freebase, respectively. The commercial strengths of cabozantinib capsules are expressed as 20 mg and 80 mg freebase. The reviewer agrees with the applicant's point that the difference between the clinical and proposed commercial dosage strengths (i.e., 19.7 vs. 20 mg or 78.9 vs. 80 mg) is not considered clinically meaningful given to the relative large PK variability of cabozantinib (See PK section). The *in vitro* dissolution profiles for the 20 mg and 80 mg capsule strengths were comparable. A summary of the structural information for cabozantinib is presented in Table 1.

Table 1: Structure Information for Cabozantinib (*S*)-Malate (XL184)

Structural Formula (L-malate salt)	
Molecular Formula	$C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$
Relative Molecular Mass	635.6 Daltons (L-malate salt) 501.5 Daltons (freebase)
Chirality/Stereochemistry	(b) (4)
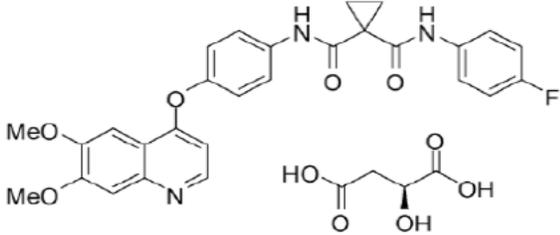
2.1.2   What are the proposed mechanisms of action and therapeutic indications?

Cabozantinib is an inhibitor of multiple intracellular kinases involved in a range of pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor environment. *In vitro* biochemical or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of RET, mesenchymal epithelial transition factor (MET), vascular endothelial cell growth factor (VEGFR) receptors, KIT, TRKB, FLT-3, AXL, and TIE-2 receptors.

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

2.1.3   What are the proposed dosage and route of administration?
The proposed dosing regimen for cabozantinib is 140 mg (capsule) administered orally once daily (QD), taken at least 1 hour before or 2 hours after a meal. The 140 mg daily dose can be reduced to 100 mg and then to 60 mg for management of intolerable toxicities.

2.2   GENERAL CLINICAL PHARMACOLOGY

2.2.1   What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
The clinical pharmacology studies of cabozantinib (XL184) included three Pharmacokinetic (PK) studies of cabozantinib capsule (XL184-001, XL184-201, and XL184-301), one food effect study (Study XL184-004), three drug-drug interaction (DDI) studies (XL184-006, XL184-007, XL184-008), one mass balance study (XL184-012) using a formulated cabozantinib solution, and one bioequivalent (BE) study (XL184-016) testing BE between   (b) (4) (Table 2).

A population PK (PopPK) analysis was performed using data collected from 289 evaluable patients across the three clinical studies (XL184-001, XL184-201, and XL184-301). PK/

pharmacodynamic (PD) analyses evaluated correlative relationships of plasma XL184 concentration and serum biomarkers associated with VEGFR2, MET, EPO and KIT pathways (Studies XL184-001 and XL184-301).

Table 2. Summary of Clinical Pharmacology Studies of Cabozantinib

Study Report	Study Objective	Study Design	Treatments	Study Population
XL184-001	Safety, tolerability, MTD, and PK	Phase 1 dose escalation, dense PK sampling	138 mg capsule (free base)	Cancer patients (n=40)
XL184-201	Objective response rate, safety, and tolerability	Phase 2, sparse PK sampling	138 mg capsule (free base)	GB Cancer patients (n=40)
XL184-301	PFS	Phase 3 pivotal trial	138 mg capsule (free base)	MTC Cancer patients (n=219)
XL184-012	Metabolism, excretion, and PK	Phase 1, Mass balance	138 mg formulated solution	Healthy males (n=8)
XL184-016	BE for ___(b) (4)___	Phase 1, BE	78.9 mg capsule (free base)	Healthy subjects (n=43)
XL184-004	BA under fasted and fed condition	Randomized, single-dose, two-sequence cross-over	138 mg capsule (free base)	Healthy subjects (n=56)
XL184-006	DDI (3A4 inducer): Effect of rifampin on cabozantinib PK	Randomized, single dose two period, two-sequence, cross-over	138 mg capsule (free base)	Healthy subjects (n=28)
XL184-007	DDI (3A4 inhibitor): Effect of ketoconazole on cabozantinib PK	Single sequence, cross-over	138 mg capsule (free base)	Healthy subjects (n=28)
XL184-008. PK001	Effect on PK of 2C8 substrate (rosiglitazone)	Single sequence cross-over	138 mg capsule (free base)	Cancer patients (n=40)

GB=glioblastoma multiforme; MTD=maximum tolerated dose; DDI=drug-drug interaction

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

At the time of study initiation, there were no effective, approved treatments for patients with locally advanced or metastatic MTC. The registrational trial XL184-301 compared the efficacy and safety of cabozantinib with that of placebo. According to the applicant, the expected overall survival (OS) in this patient population is relatively long in duration, a large number of patients or a long duration study would be required to demonstrate an OS benefit in this rare indication. Because only patients with documented tumor progression were enrolled into the study, a compelling improvement in progression-free survival (PFS) represents a benefit for this patient population. As agreed with the FDA, PFS was selected as the primary endpoint for this trial and objective response rate (ORR) and OS were included as the secondary endpoints.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In Study XL184-012, eight metabolites of cabozantinib in human plasma of male healthy subjects (N=8) have been identified following a single oral administration of $[^{14}C]$-XL184 (100 µCi and 138 mg) and they are summarized together with their activity in Table 3 below.

Table 3. Percentage of Parent Drug and Its Metabolites of Total Radioactivity

Parent drug and metabolites	Percentage/AUC_{0-168}	IC50 VEGFR2 (KDR)	IC50 (MET)	IC50 phosphorylation
XL184	27.2%	0.035 nM	1.8 nM	7.8 nM
XL184 *N*-oxide	6.5%	40 nM	187 nM	2.0 µM
half-dimer (including demethyl XL184 glucuronide B)	8.7%	>20 µM	5 µM	Inactive
XL184 monohydroxy sulfate	25.2%			
demethyl half-dimer sulfates	35.3%			
half-dimer methyl ester				

Metabolite para-fluoroaniline concentrations were below quantifiable limits (< 2 ng/mL) in plasma using a validated LC-MS/MS assay. For metabolites XL184-half-dimer, XL184-*N*-oxide and XL184-monohydroxy sulfate, the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) were 9.9%, 15.0% and 42.9%, respectively. Two non-conjugated metabolites (cabozantinib *N*-oxide and cabozantinib half-dimer) possess <1% of the on-target kinase inhibition potency of parent cabozantinib (Table 3), suggesting that these metabolites do not contribute significantly to the overall pharmacologic activity of cabozantinib. A full characterization of XL184 metabolites in plasma, feces and urine is ongoing.

2.2.4 Exposure-response

2.2.4.1 Is there an exposure-response relationship for progression free survival (PFS), the primary efficacy endpoint?

No, the proposed dosing regimen is not supported by the E-R relationship of efficacy and the analysis suggests that a lower dose may provide similar benefit in terms of the primary endpoint, PFS. E-R relationship between PFS and dose intensity or $AUC_{Dose\ Intensity}$ could not be identified in patients treated with cabozantinib in the registrational trial (XL184-301), indicating that lower dose may not be associated with reduction of the PFS. Because majority of patients (86.4%) in the cabozantinib arm experienced a dose modification (e.g., dose interruption, dose reduction, and discontinuation) at some time during the pivotal trial, it is difficult to interpret the efficacy results based on E-R analysis. To account for different exposure levels due to dose modification, a Kaplan-Meier analysis of PFS stratified by quartiles of dose intensity was conducted to evaluate the E-R relationship for patients treated with cabozantinib. Dose intensity was defined as the actual administered dose to the time of the event divided by the planned dose to the same time. No E-R relationship between the PFS and dose intensity could be identified in patients treated with cabozantinib (Figure 2, Left), while all quartiles in the treatment arm had significant PFS improvement compared to placebo. The covariates such as body size, age, gender, smoking status, ECOG status were equally distributed within each quartile of dose intensity (See section

of reviewer's analysis).

To further account for inter-individual variability in clearance, the quartile of average exposure ($AUC_{Dose\ Intensity}$) was used in the Kaplan-Meier analysis for PFS. $AUC_{Dose\ Intensity}$ was defined as the average dose (Starting Dose * Dose Intensity) divided by posthoc estimates on individual CL/F. Similar to the results obtained from dose intensity, no E-R relationship between the PFS and $AUC_{Dose\ Intensity}$ could be identified in the cabozantinib arm (Figure 2, Right). These results indicated that decreases of average exposure may not be associated with reduction of PFS.

Figure 2: E-R Relationship for PFS Stratified by Quartiles of Dose Intensity (Left) and by $AUC_{Dose\ Intensity}$ (Right) in Cabozantinib Arm.
Dose Intensity=Actual dose/Planned dose (%);
$AUC_{Dose\ Intensity}$(mg*day/L)=Starting dose*Dose Intensity/(individual CL/F)
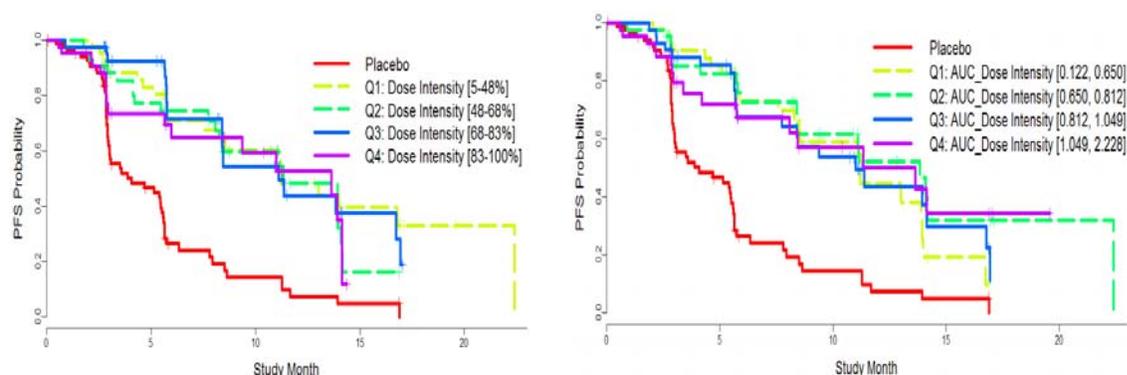
Similar to the results obtained from the E-R analysis for PFS and dose intensity, there was no E-R relationship identified between PFS and the time to the first dose modification (Figure 3), indicating that the early dose modification may not be associated with the reduction of PFS. Time to the first dose modification (defined as the first occurrence of a dose that was not equal to 138 mg freebase) is an indicator of a total dose that a patient received prior to a dose modification due to toxicity since each patient received the same dose (138 mg freebase) initially in the cabozantinib arm. The value of time to the first dose modification was ranged from 2 to 554 days, with a median of ~30 days, indicating that approximately 50 % of patients experienced dose modifications within the first month of treatment. Patients in the treatment arm, regardless the time to first dose modification, all had significant improvement in PFS compared to the placebo group. The high incidence of early dose modification (e.g., 50% patients had dose modification within a month) and the lack of relationship between dose intensity and PFS, suggest that the tested cabozantinib dose (138 mg freebase) could be too high and such high dose could mask the E-R relationship for efficacy (PFS).

Figure 3: ER Relationship for PFS Stratified by Time to the First Dose Modification Quartiles in

Cabozantinib Arm in Trial XL184-301.
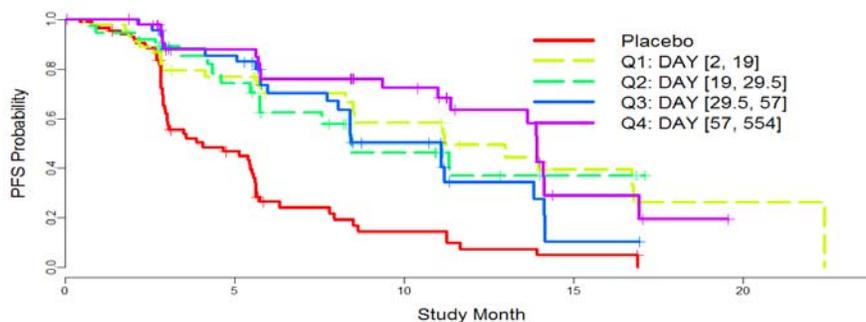
### 2.2.4.2 Is there evidence of exposure-response for safety?

An E-R relationship for time to the first dose modification and model-predicted steady-state exposure ($AUC_{ss, pred}$) quartiles was identified indicating that patients with higher $AUC_{ss, pred}$ tends to have earlier time to the first dose modification. However, no E-R relationship was identified between incidences of PPE and $AUC_{Dose\ Intensity}$, or between incidences of diarrhea event and $AUC_{Dose\ Intensity}$.

Frequent adverse events (AEs) observed in Trial XL184-301 were diarrhea, palmar-plantar erythrodysaesthesia (PPE) syndrome, weight decrease, decreased appetite, nausea, fatigue, dysgeusia, hair color changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, ALT increased, AST increased, asthenia, hypocalcemia, and dysphonia. The most frequent AEs that led to dose modifications were PPE syndrome, diarrhea, fatigue, weight decreased, decreased appetite, etc. The sponsor's ER analyses for safety included ALT, weight loss, PPE, fatigue, diarrhea, and mucositis (see Section of sponsor's analyses).

To evaluate whether early dose modification is associated with high individual exposure (noted that everyone received the same dose before a dose modification), a Kaplan-Meier analysis was conducted to evaluation the relationship between $AUC_{ss, pred}$ and the time to the first dose modification. A significant E-R relationship between the time to the first dose modification and $AUC_{ss, pred}$ quartiles (Figure 4) was identified (P<0.001, Log-rank test). The difference in median dose modification free time for patients within the highest and the lowest $AUC_{ss, pred}$ quartiles is 0.8 month. The sponsor has conducted a similar survival analysis stratified by $AUC_{ss, pred}$ tertiles (see sponsor's analysis) and reached to a similar conclusion. A stepwise Cox proportional hazard model consisting age, sex, body size, smoke status, $AUC_{ss, pred}$, ECOG status, race as covariates was further conducted. Only $AUC_{ss, pred}$ (ranging from 0.51 to 3.53 mg*day/L) was identified as a significant covariate (p<0.0001) for prediction of time to the first dose modification (hazard ratio (HR) of 1.95 (95% CI [1.47-2.59]), while the other covariates were not significant (p>0.05). The hazad ratio of 1.95 implies that with every unit increase of cabozantinib exposure, the hazard of experiencing a dose modification increases by 95%.

Figure 4: ER Relationship for Time to First Dose Modification Stratified by $AUC_{ss, pred}$ (mg*day/L)

A logistic regression was further conducted to evaluate the relationship between the most important AEs that led to dose modification (PPE and diarrhea) and $AUC_{Dose\ Intensity}$. No E-R relationship was identified between incidences of PPE and $AUC_{Dose\ Intensity}$, or between incidences of diarrhea event and $AUC_{Dose\ Intensity}$ ($P>0.05$). The incidences of PPE and diarrhea events and $AUC_{Dose\ Intensity}$ are shown in Figure 5.

Figure 5. ER Relationship between AEs (PPE and Diarrhea) and Dose Intensity.


2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of orally administered cabozantinib 138 mg freebase on QTc interval was evaluated in the registrational Trial XL184-301. An increase in QTcF of 10 - 15 ms was observed within the first 4 weeks of initiating treatment. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated patients had a QTcF >500 ms.

A PK/PD analysis demonstrated a concentration-dependent QTc interval prolongation. Data obtained for the Days 1 and 29 visits were combined in this analysis. Data from patients with and without dose modifications prior to ECG collection were also combined. Baseline-adjusted change from placebo QTcF vs. matched plasma concentrations are shown in Figure 6. Based on graphical analysis and mixed effects linear modeling, a linear model with log-transformed concentrations was chosen to describe the relationship. A positive and significant relationship between log XL184 plasma concentrations and $\Delta\Delta$QTcF with a positive slope of 7.54 ms per log ng/mL (95%CI: 6.13 – 8.96, p-value = <0.0001) was observed.

Figure 6. QTcF Change from Baseline vs. Cabozantinib Plasma Concentrations

Figure: Scatter plot of QTcF change from placebo and baseline adjusted (ms) vs. XL184 concentration (ng/mL), with XL184 data points (open circles) and Mean predicted (red line).
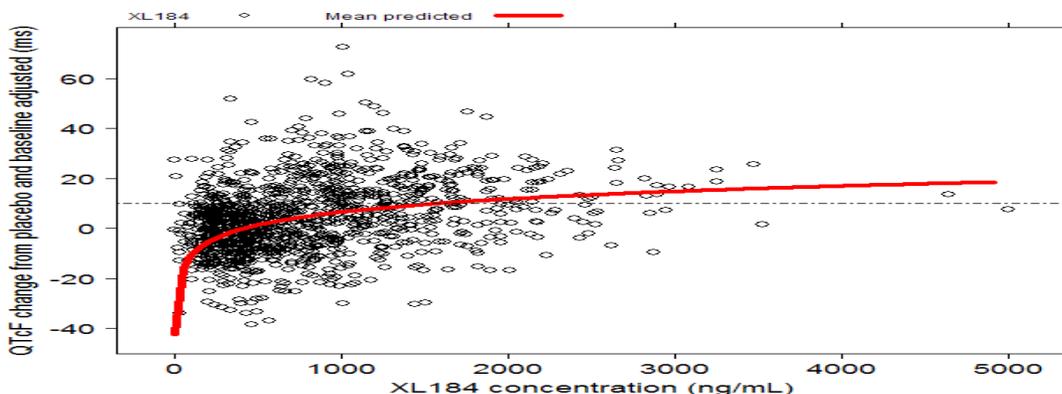
2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

No, the proposed dose of 140 mg is not supported by the E-R of efficacy and safety and the observed clinical data for the following reasons:

- In a Phase 1 dose escalation trial in patients with advanced solid tumors (refer to trial XL184-001), the maximum tolerated dose (MTD) for cabozantinib was determined to be 138 mg freebase (equivalent to 175 mg L-malate salt) QD using traditional '3+3' rule. After the MTD was determined, 25 MTC patients were treated at the MTD and 80% patients suffered grade 3 or 4 toxicities and 83% patients required dose reduction. A total of 25 MTC patients were treated at the MTD and 80% patients required dose reduction. Note that the sponsor proposed a dose of 140 mg instead of 138 mg because commercial strengths of 20 mg and 80 mg freebase will be used. The difference between the clinical and proposed commercial dose (138 mg vs. 140 mg) is small and will not be considered to be clinically relevant given to the relative large PK variability of cabozantinib.

- The MTD dose (138 mg) was further tested in a Phase 2 trial (XL184-201) in Glioblastoma (GB) patients. A total 46 patients received the MTD dose daily and 85% of patients suffered grade 3 or 4 toxicities and 80% patients required dose modification.

- The safety and efficacy of the MTD dose were evaluated in the pivotal trial (XL184-301). A total of 69% patients experienced grade 3 or 4 toxicities and 86% patients experienced dose modification in the cabozantinib arm. Approximately 80% of patients had dose reduced to 100 mg during the treatment, and 40% patient had dose further reduced to 60 mg.

- Our E-R analyses of efficacy showed high exposure associated with early time of dose modification due to adverse events and lower dose intensity may not result in reduction in PFS.

As such, Clinical Pharmacology recommends a starting dose of 100 mg capsule in the COMETRIQ® label, and the dose may be increased to 140 mg or decreased to 60 mg as tolerated. If this is not an acceptable option, then Clinical Pharmacology supports a randomized dose-comparison trial testing 140 mg dose and a biologically active lower dose in patients with progressive metastatic MTC. The details regarding the study design will be discussed further (refer to clinical review by Dr. Ruthann Giusti).

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single-dose and multiple dose pharmacokinetic parameters?

The single and multiple dose PK data for cabozantinib in cancer patients were assessed in Studies XL184-00l, XL184-201, XL184-301, and XL184-008 (Tables 4&5). Major metabolites of cabozantinib do not contribute significantly to the overall pharmacologic activity of cabozantinib (see Table 3), and therefore their PK were not characterized.

Following a single oral dose capsule containing 138 mg free base (Table 4), the median T_{max} occurred at 2 to 4 hours post-dose on Day 1 (ranged from 2-24 h). Multiple peaks in the plasma concentration-time profiles after a single oral dose suggest that cabozantinib is either entero-hepatically recirculated or absorbed at different rates or both.

Repeated dose PK parameters in cancer patients after daily 138 mg capsule dose of cabozantinib (taken at least 1 hour before or 2 hours after a meal) were shown in Table 5. The cohort mean accumulation ratio (AR) (day 19 vs. day 1) based on AUC and C_{max} were 5.4 and 3.6, respectively.

Table 4. Single Dose Mean (%CV) PK Parameters of Cabozantinib across Studies in Cancer Patients Dosed with Capsules Containing 138 mg Freebase

Study	XL184-001 (Phase 1)	XL184-201 (Phase 2)	XL184-301 (Phase 3)
Patient Population	Solid Tumors	GB	MTC
PK Sampling	Dense	Sparse	Sparse
N	34-35	40	200
C_{max}, ng/mL, mean (%CV)	570 (43)	566 (47)[a]	541 (42)
T_{max}, h, median (range)	2 (2-23.9)	NC	2.37 (1-6.617)
AUC_{0-24}, h*ng/mL, mean (%CV)	8228 (34)	NC	NC

NC=not calculated; [a] =data reported at 4 h post-dose.

Table 5. Steady-state PK Parameter (Mean (%CV)) of Cabozantinib across Studies in Cancer Patients after 138 mg Freebase QD Dosing

Study	XL184-001 (Phase 1)	XL184-201 (Phase 2)	XL184-301 (Phase 3)	XL184-008 (Phase 1 DDI)
Patient Population	Solid Tumors	GB	MTC	Solid Tumors
PK Sampling	Dense	Sparse	Sparse	Dense
N	34-35	40	200	30-32
C_{max}, ng/mL	2220 (37)	1660 (39.5)[a]	1640 (43.2)	1970 (39)
C_{trough}, ng/mL	1710 (44)	1690 (53)	1380 (53)	1484 (48)
T_{max}, h, median (range)	2 (0-24.7)	NC	2 (0-6.667)	2.21 (0-25.4)
AUC_{0-24}, h*ng/mL	37850 (43)	NC	NC	29700 (38)
Accumulation Ratio	5.4 (64)[b]	NC	3.6 (66.2)[c]	NC

NC=not calculated; [a] =data reported at 4 h post-dose. [b] =AUC ratio, [c] = C_{max} ratio.

2.2.5.2 How dose the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The mean (%CV) of cabozantinib PK parameters following a single 138 mg (Study Reports XL184-004, XL184-006, XL184-007) or 78.9 mg (Study Report XL184-016) freebase dose in the healthy volunteers and cancer patients (XL184-001) are summarized in Table 6. Note that the table listed dose, 175 mg and 100 mg, are salt-based weight, which are equivalent to 138 mg and 78.9 mg freebase. Mean C_{max} and AUC_{0-24h} values after a single dose of 138 mg on Day 1 in healthy volunteers (combined the data from studies XL184-004, XL184-006 and XL184-007) were consistent with the data observed in cancer patients (Table 6).

Table 6. Single Dose PK Parameters in Healthy Volunteers and Cancer Patients

Study	Study XL184-004[b] Food Effect	Study XL184-006[b] DDI with Rifampin	Study XL184-007[b] DDI with Ketoconazole	Study XL184-016[b] BE	Study XL184-001 Dose-Escalating	Combined[c] 004, 006 and 007
Population	HV	HV	HV	HV	Cancer patients	HV
Formulation	Capsule	Capsule	Capsule	Capsule (b) (4)	Capsule	Capsule
Dose (mg)	175	175	175	100	175	175
Food intake	Fast 10 hr before and 4 hr after dose	Fast 10 hr before and 4 hr after dose	Fast 10 hr before and 4 hr after dose	Fast 10 hr before and 4 hr after dose	Fast 2 hr before and 1 hr after dose	Fast 10 hr before and 4 hr after dose
N	47	28	28	43	34-35	100-103
C_{max}, ng/mL	536 (38)	582 (45)	488 (41)	294 (61)	570 (43)	536 (41)
T_{max}, h[a]	4 (2-24.03)	4 (1.98-24.08)	4 (1.13-24.05)	5 (2-24.02)	2 (2-23.9)	4 (1.1-24.1)
AUC_{0-t}, h·ng/mL	59200 (27)	55500 (27)	47600 (29)	29600 (38)	NC	55051 (29)
AUC_{0-24}, h·ng/mL	7420 (33)	7860 (38)	6220 (36)	3980 (55)	8228 (34)	7211 (36)
AUC_{0-inf}, h·ng/mL	63200 (28)	58800 (28)	50400 (32)	31300 (39)	NC	58607 (30)
$t_{1/2}$, h	124 (24)	111 (27)	122 (33)	111 (30)	NC	120 (28)

C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; $t_{1/2}$, apparent terminal elimination half-life; BE, bioequivalence; DDI, drug-drug interaction; HV, healthy volunteer; NC, not reported
[a] median and range were reported for T_{max}; [b] data displayed are for the reference (no interacting treatment) group; [c] summary was pooled from individual subjects data from these studies
Sources: XL184-004, XL184-006, XL184-007, XL184-016, and XL184-001.PK.001

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 h post-dose across studies (Table 5 and Table 6). Multiple peaks in the plasma concentration-time profiles after a single oral dose suggest that cabozantinib is either entero-hepatically recirculated or absorbed at different rates or both.

The absolute bioavailability of cabozantinib has not been determined. In a phase 1 dose escalation study (XL184-001), the capsule formulation yielded approximately 2-fold higher dose-normalized AUC_{0-24h} after a single dose compared to the powder-in-bottle (PIB) suspension. A true solution formulation was used for the mass balance study (XL184-012) and yielded an earlier T_{max}, higher C_{max} and AUC_{0-inf}, and less inter-subject variability compared to the capsule formulation used in other healthy subject studies at the same cabozantinib dose level (138 mg freebase) (Table 7). Mean AUC_{0-inf} values for cabozantinib from these healthy subject studies using capsules (XL184-004, XL184-006, and XL184-007) were 74 to 93% of the corresponding values in the mass balance study where cabozantinib was formulated as a solution.

Table 7: Comparison of Single Dose XL184 Plasma Exposure Parameters between the Mass Balance Solution Formulation and Capsules in Healthy Subjects

Study	Formulation	C_{max} (ng/mL) Mean	CV%	AUC_{0-inf} (hr*ng/mL) Mean	CV%	T_{max} (hr)
XL184-012 (Mass Balance, N=8)	Solution	1250	19.0	68000	10	1.5
XL184-006 (DDI, rifampin, N=28)	Capsules	582	45.0	58800	28	4
XL184-007 (DDI, ketoconazole, N=28)	Capsules	488	41.0	50400	32	4
XL184-004 (Food Effect, N=47)	Capsules	536	38.0	63200	28	4

C_{max}, maximum concentration, AUC_{0-inf}, area under the curve from time zero to infinity; T_{max}, time to maximum concentration, reported as median
Sources: XL184-012, XL184-006, XL184-007, and XL184-004.

2.2.5.4 What are the characteristics of drug distribution?

Plasma protein binding: In vitro plasma protein binding study (XL184-Disc-035, equilibrium dialysis) showed that cabozantinib was highly plasma protein bound at all concentration levels tested (0.2, 1.0, and 10.0 µM). The percentage bound was > 99.9% at 0.2 and 1.0 µM, and > 99.7% at 10 µM level. For comparison, daily dosing with the 138 mg/day freebase of cabozantinib yields steady state C_{max} values of approximately 4 µM in patients with solid tumors. *Ex-vivo* plasma protein binding in human blood samples was not evaluated.

Blood to plasma ratio: The concentrations of total radioactivity in the plasma and in the blood were measured in the mass balance study (Study XL184-012). The mean values of systemic exposures (AUC_{0-24h} and AUC_{0-72h}) in plasma were around 1.6 times higher than those in whole blood. The mean percent total radioactivity/concentration present in erythrocytes relative to whole blood were ranged from 0.174 to 12.3 % within 72 h after a single dose, suggesting that radioactivity was present primarily in plasma and not markedly associated with red blood cells.

2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The human mass balance study (XL184-012) suggested that both urinary and fecal excretions are main routes of elimination of cabozantinib. Within a 48-day collection period after a single dose of 100 µCi ^{14}C-cabozantinib (138 mg) in healthy subjects, 81.1±1. 6 % (range: 78.1% to 83.4%) of the total administered radioactivity was recovered with 53.8±4.5 % in feces and 27.3±4.6 % in urine. Approximately 1% of total mean radioactivity was recovered in feces and urine after Day 28 post-dose.

2.2.5.6 What are the characteristics of drug metabolism?

Cabozantinib is a substrate of CYP3A4. Metabolism of cabozantinib catalyzed upon addition of NADPH to incubations containing human liver microsomal protein and 5 µM cabozantinib (~0.3 µCi/mL [14]C- cabozantinib) yielded a single XL184 *N*-oxide metabolite as determined by LC-MS/MS (Study XL184-NC-030). A neutralizing antibody to CYP3A4 inhibited formation of XL184 *N*-oxide metabolite by >80%; A neutralizing antibody to CYP2C9 showed a minimal effect on XL184 metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

Metabolites of cabozantinib in human plasma of male healthy subjects following a single oral administration of [^{14}C]-XL184 (100 μCi and 138 mg) have been identified using LC-MS/MS (Study XL184-012). Quantitation of cabozantinib and its metabolites based on the radio-chromatograms indicated that cabozantinib accounted for 27.2% of total radioactivity (AUC$_{0-168}$). The eight identified metabolites in plasma are: XL184 *N*-oxide, XL184 monohydroxy sulfate, half-dimer, 6- and 7- demethyl half-dimer sulfate, half-dimer methyl ester, and demethyl XL184 glucuronide A and B. These metabolites do not contribute significantly to the overall pharmacologic activity of cabozantinib (See Table 3). A full characterization of cabozantinib metabolites in plasma, feces and urine is ongoing.

2.2.5.7 What are the characteristics of drug elimination and excretion?
The human mass balance study (XL184-012) suggested that both urinary and fecal excretions are main routes of elimination of cabozantinib. A population PK analysis was conducted with data collected from 289 patients with solid tumors including MTC following oral administration of 138 mg daily doses. The estimated mean clearance (CL/F) at steady-state is 4.4 L/h; the population predicted effective t$_{1/2}$ in plasma is approximately 55 hours, and the oral volume of distribution (V/F) is approximately 349 L (SE ±2.73%). The plasma terminal t$_{1/2}$ of cabozantinib in single dose studies is approximately 120 hours in healthy subjects.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?
Dose proportionality was assessed for the powder-in-bottle (PIB) formulation administered to cancer subjects (Study XL184-001). The cabozantinib exposure (AUC and C$_{max}$) were increased approximately dose proportional after 5 daily oral doses of a powder-in-bottle (PIB) formulation (range: 4.8 mg/day – 1,382 mg/day) (Figure 7). Dose-normalized plasma exposures (AUC) were approximately 2-fold higher for cabozantinib capsule formulation relative to cabozantinib PIB formulation.

Figure 7: Dose Proportionality Assessment of the Cabozantinib Powder-In-Bottle (PIB) Formulation after 5 Daily Doses (Cohorts 1 – 9: 4.8 – 1,352 mg/day).
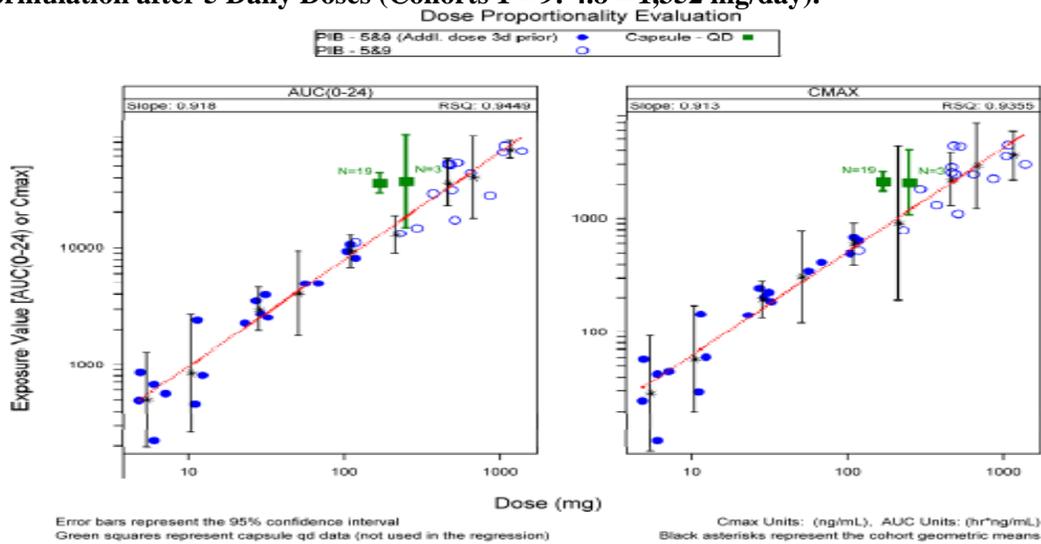
Dose proportionality of the cabozantinib capsules has not been formally evaluated. However, a cross-study comparison suggested that a single 78.9 mg dose yielded comparable dose-normalized AUC_{0-24} and C_{max} values with the dose of 138 mg (Study XL184-006, XL184-007, and XL184-004, see Table 8).

Table 8. Comparison of Mean Single Dose XL184 Plasma Exposure Parameter Values across Studies in Healthy Subjects.

Study	XL184 L-Malate Dose (mg)	N	C_{max} (ng/mL)	C_{max}/Dose (ng/mL)/mg	AUC_{0-inf} (hr*ng/mL)	AUC_{0-inf}/Dose (hr*ng/mL)/mg
XL184-016 (BE)	100	43	294	2.94	31300	313
XL184-006 (DDI, rifampin)	175	28	582	3.33	58800	336
XL184-007 (DDI, ketoconazole)	175	28	488	2.79	50400	288
XL184-004 (Food Effect)	175	47	536	3.06	63200	361

C_{max} = maximum concentration; AUC_{0-inf} = area under the curve from time zero to infinity
Sources: XL184-016, , XL184-006, XL184-007, and XL184-004.

2.2.5.9   How do the PK parameters change with time following chronic dosing?

After multiple daily doses, the mean accumulation ratio (AR) based on AUC and C_{max} were 5.4 and 3.6, respectively at 138 mg capsule dose (Study XL184-001.PK.001). Steady state was achieved by approximately Day 15. See Section 2.2.5.1 for more information on the PK of cabozantinib following multiple doses.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy subjects following a single dose, the inter-subject variability (%CV) ranged from 27 to 55% for AUC values and from 38 to 61% for C_{max} across the studies. The within-subject variability (%CV) was 34% for C_{max} and 25% for AUC values; these values were estimated in Study XL184-016.

The inter-subject variability in cancer subjects (%CV) was 43% for C_{max} and 34% for AUC after a single dose, and 37-43% for C_{max} and 38-43% for AUC at steady state (Study XL184-001.PK.001, XL184-301 and XL184-008.PK.001).

2.3   INTRINSIC FACTORS

2.3.1   What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

A PopPK analysis was performed on pooled data for cabozantinib-treated cancer patients receiving daily doses of the capsule formulation (Study XL184-301.PopPK.001). Patients were enrolled across 3 studies (Studies XL184-301, N=214; XL184-201, N=40, and XL184-001, N=40). The dose for patients in the PopPK analysis population was 138 mg/day of cabozantinib, except for 5 patients in study XL184-001 who were dosed at 197 mg/day. Patients were fasted 2 h before and 1 h after each cabozantinib dose.

The final model was based on 2,079 records from 289 patients. The data were described by a 1-compartment model with first-order absorption and first-order elimination with a small lag time. The mean oral clearance (CL/F) and central volume (V/F) were estimated to be 4.4 L/h and 349 L, respectively. The predicted elimination half-life is 55 h. Inter-individual variability was modest (CV approximately 35%). The applicant's PopPK analysis included both gender and body mass index (BMI) on oral clearance in the final model. The results of this PopPK analysis were used to assess the effects of intrinsic factors on the PK of cabozantinib.

2.3.1.1   Body size and Gender

Based on the criteria used for covariate selection, weight and body surface area (BSA) were not retained in the final model. Explorations of the CL/F relationship between gender and CL/F, between BMI and CL/F are provided in Figure 8. The median clearance was approximately 20% lower in females than in males. However, this effect is not considered clinically important. Neither body size nor gender contributed to clinically relevant changes in PK of cabozantinib.

**Figure 8. Inter-individual Variability for the Base Model and Final Model**
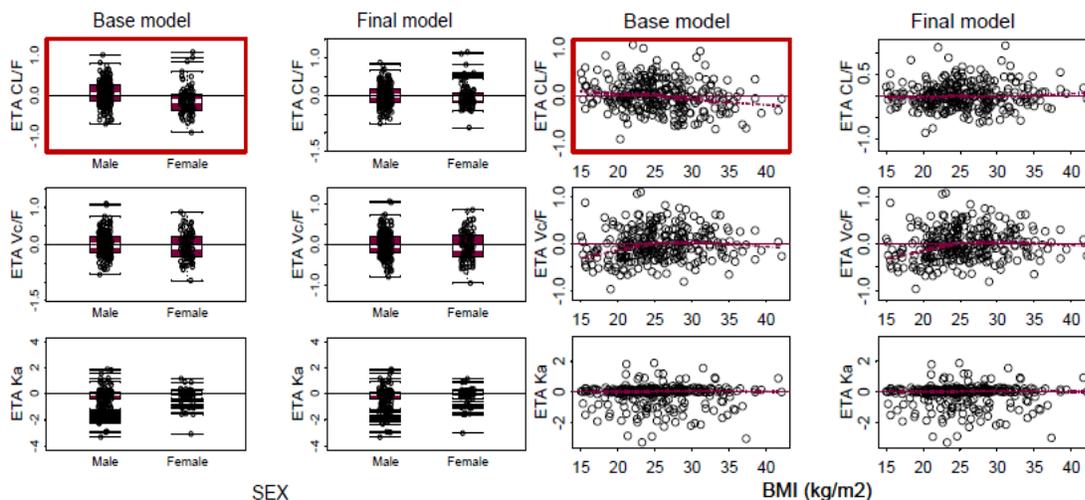
2.3.1.2   Race

The effect of race on clearance or volume did not enter the final PopPK model based on

covariate selection criteria. The impact of race (other, Asian, Black, White and Unknown) on inter-individual variability (ETA for CL/F) was shown in Figure 9. No clinically relevant difference between White (89%) and Non-White (11%) was identified (Figure 9).

Figure 9. Impact of Race on CL/F of Cabozantinib.
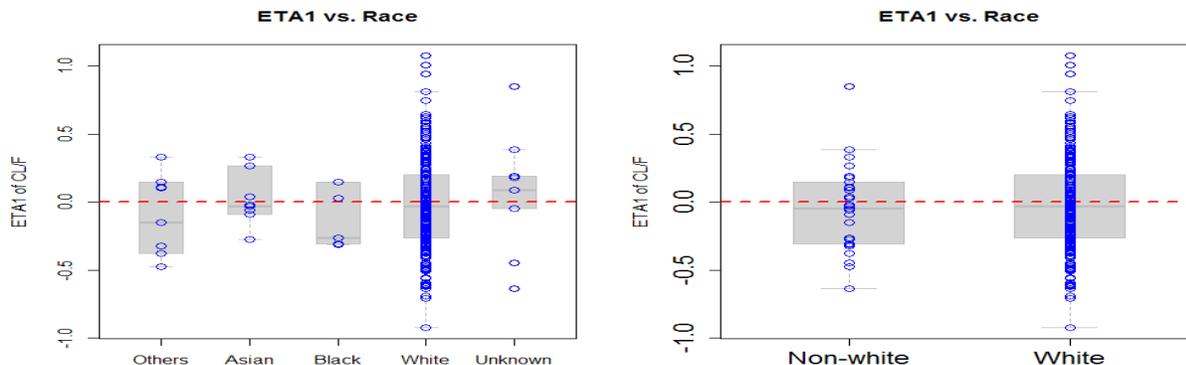
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients
Safety and effectiveness of cabozantinib have not been established in pediatric patients. A full pediatric waiver has been granted by the FDA on May 11, 2011, as cabozantinib has been designated as an orphan drug for the treatment of MTC. (b) (4)

2.3.2.2 Renal impairment
No formal PK trial has been conducted in patients with renal impairement. Results of the PopPK analysis suggested that the impact of renal impairment (mild: CrCL = 50-80 mL/min; moderate: CrCL = 30-50 mL/min) on CL/F of cabozantinib is minimal (Figure 10, Left). Evaluation of PK of cabozantinib in patients with severe renal impairment (CrCL <30 mL/min) is not possible due to limited sample size (N=1). Dose adjustment for patients with renal impairment is not recommended for the following reasons:
- The continuous plot between ETA of CL/F and CrCL (Figure 10, Right) did not reveal a trend or a correlation.
- *In vitro* study indicated that cabozantinib is a high plasma protein binding drug (>99.7%).
- Only 27% of total radioactivity (including 8 metabolites) was recovered in human urine.
- Large PK variability and frequent dose modification.
- Extremely low solubility of the drug under urine pH (normal range >pH 4) (refer to Figure 1).

2.3.2.3 Hepatic impairment
No formal PK trial has been conducted in patients with hepatic impairment. Results of the

PopPK analysis suggested that the impact of hepatic function impairment (total bililubin ≥1.5 xULN) on cabozantinib CL/F is minimal (Figure 10, Middle). A conclusion can not be drawn due to limited number of patients (N=4) with total bililubin ≥1.5 xULN. A dedicated study using the Child-Pugh criteria evaluating hepatic impairment on PK of cabozantinib is undergoing and will be requested as a PMR.

**Figure 10. Plot of ETA of CL/F versus Renal and Hepatic Impairments**
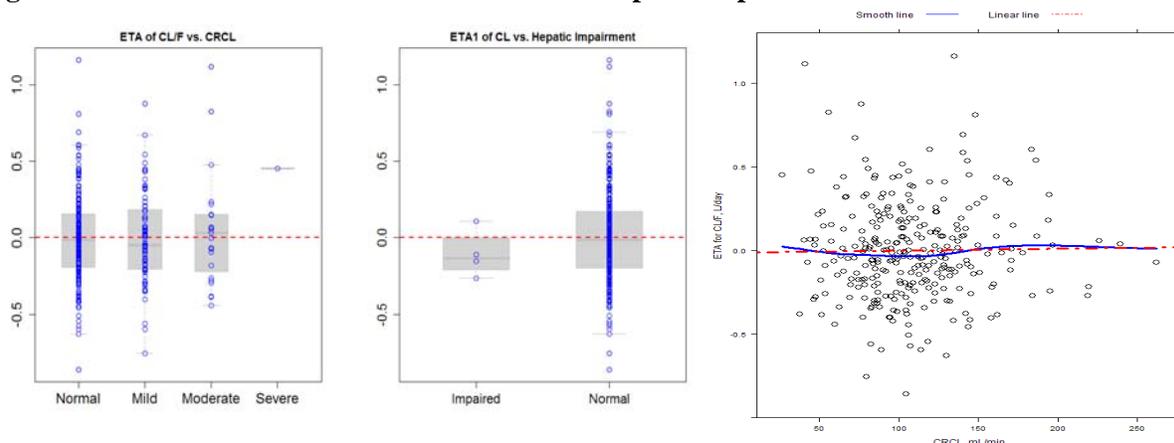
2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, alcohol use on the PK of cabozantinib.

The effect of smoking status (Figure 11a) on CL of cabozantinib is not clinical relevant and was not included in the final PopPK model based on the covariate selection criteria.

**Figure 11a. Plot of ETA of CL/F versus Smoking Status**
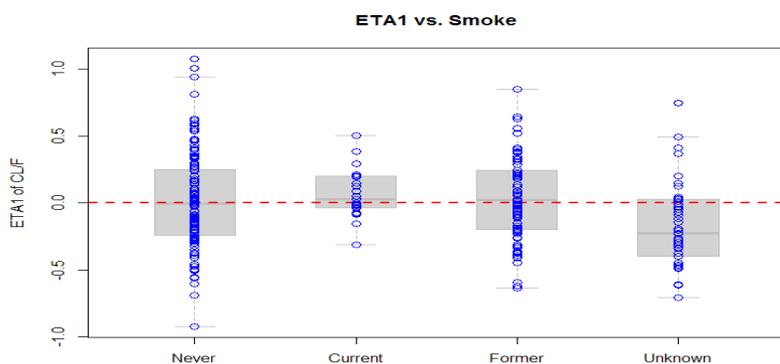
The effect of co-medication of gastric pH modifying drugs (proton pump inhibitors [PPIs] and/or H2 blockers) has been evaluated in the PopPK analysis (Figure 11b). The effect of use of PPIs or H2 blockers on CL of cabozantinib was not included in the final PopPK model as a covariate.

However, a conclusion can not be drawn based on the PopPK model derived from sparse PK samples. A PMR will be requested based on the following reasons:

- 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 (Figure 1).
- The gastric pH modifying drugs (proton pump inhibitors, H2 blockers, antacids) can elevate the stomach pH at levels close to 6 or 7, therefore, co-medication may greatly decrease the solubility of cabozantinib.

Figure 11b. Plot of ETA (CL/F) versus Co-medication with gastric pH modifying drugs
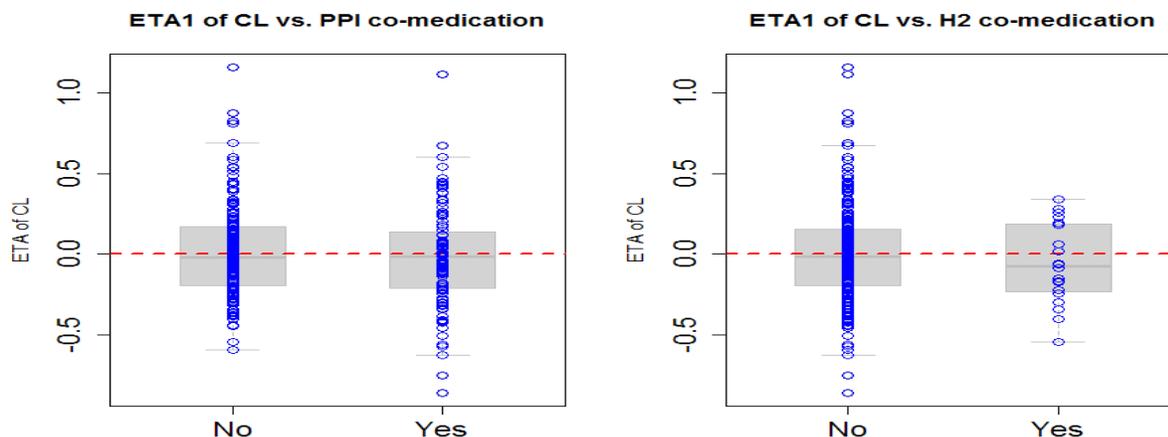
2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?
Yes. Cabozantinib is a substrate for CYP3A4. It inhibits CYP2C8, CYP2C9, and CYP2C19 with Ki values = 4.6 μM, 10.4 μM, and 28.8 μM, respectively.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
Cabozantinib is a substrate for CYP3A4, as a neutralizing antibody to CYP3A4 inhibited formation of a XL184-derived metabolite (XL184 *N*-oxide) by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation (Study XL184-NC-030); a neutralizing antibody to CYP2C9 showed a minimal effect on XL184 metabolite formation (i.e., a <20% reduction). Neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on XL184 metabolite formation.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
In vitro inhibition
Cabozantinib inhibited recombinant CYP2C8 and CYP2C19 isozymes with IC$_{50}$ values of 5.0 μM and 8.3 μM, respectively (Study Report XL184-Disc-037); this inhibition was reversible. Using human liver microsomal (HLM) preparations, XL184 also inhibited isozyme-associated enzyme activities for CYP2C8 and CYP2C19, as well as CYP2C9, with IC$_{50}$ values of 6.4, 6.2, and 6.1 μM, respectively; inhibition of CYP2C8 and CYP2C19 was also shown to be reversible.

Inhibition of CYP1A2, CYP2D6, and CYP3A4 isozymes by XL184 exhibited IC_{50} values >20 µM in both recombinantand HLM assay systems.

In a separate HLM study (Study Report 7359-420), cabozantinib was shown to be a noncompetitive inhibitor of CYP2C8-associated amodiaquine N-deethylase (Kiapp = 4.6 µM), and a mixed-type inhibitor of CYP2C9-associated diclofenac 4′-hydroxylase (Kiapp = 10.4 µM) and CYP2C19-associated S-mephenytoin 4′-hydroxylase (Kiapp = 28.8 µM). In addition, cabozantinib was a competitive inhibitor of CYP3A4-associated midazolam 1′-hydroxylase (estimated Kiapp = 282 µM).

***In vitro* Induction**
In vitro study data indicate that XL184 is an inducer of CYP1A1, but is not a potent inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 (Study XL184-Disc-037). IC_{50} values >20 µM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems.

Because of the low number of concomitant medications metabolized by the CYP1A1 pathway, no clinical pharmacology study was conducted to evaluate the potential induction effect of cabozantinib on PK of CYP1A1 substrates.

2.4.2.4   Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
Cabozantinib was an inhibitor (IC50 = 7.0 µM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells (Study Report XL184-Disc-037). In a separate study, cabozantinib was observed to be a more potent P-gp inhibitor (IC_{50} = 0.5 ± 0.2 µM) in a Caco-2 cell monolayer assay system (Study Report BMS-PGP). The lower IC_{50} value may reflect measurement of the actual cabozantinib concentration in the incubation well in the Caco-2 study (rather than the final administered concentration as reported in the MDCK-MDR1 study), and may also reflect possible cabozantinib absorption to cell culture contents thereby reducing free drug concentration in the incubation media. The applicant states in the label that patients should be cautioned regarding taking a P-gp substrate. (b) (4)

2.4.2.5   Are there other metabolic/transporter pathways that may be important?
Cabozantinib has not been evaluated for possible interactions with other metabolic/transporter pathways.

2.4.2.6   Does the label specify co-administration of another drug and, if so, has the
              interaction potential between these drugs been evaluated?
No co-administration of other drugs is specified in the label since cabozantinib is used as monotherapy in the proposed indication.

2.4.2.7 Are there any _in-vivo_ drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. Cabozantinib is a substrate of CYP3A4. Cabozantinib has the highest _in vitro_ inhibition potency (I/Ki ~1.0) to CYP2C8. Cabozantinib at clinically-relevant steady-state plasma concentrations (≥125 mg/day daily for a minimum of 21 days) showed no statistically significant effect on single-dose plasma PK exposure values (C_{max} and AUC) for CYP2C8 substrate rosiglitazone in 40 patients with solid tumors (Study XL184-008) (Table 9). Thus cabozantinib is not considered to be a potential inhibitor of metabolism _in vivo_ for substrates of CYP2C8 and other CYP isozymes with lower _in vitro_ I/Ki values.

Administration of strong CYP3A4 inducer rifampin (600 mg daily for 31 days) to 28 healthy subjects (cross-over study) increased cabozantinib clearance and decreased single-dose plasma cabozantinib exposure (AUC range: 76-77% lower) (Study XL184-007) (Table 9).

Administration of strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to 28 healthy subjects (cross-over study) decreased cabozantinib clearance and increased single-dose plasma cabozantinib exposure (AUC range: 34-38% higher) (Study XL184-007) (Table 9) with no change in C_{max}.

Based on the low number of concomitant medications metabolized by the CYP1A1 pathway, no clinical pharmacology study has been conducted to evaluate cabozantinib CYP1A1 induction potential.

Table 9: Results of Drug-Drug Interaction Studies

Study	CYP450	Population	Results
XL184-006, rifampin	CYP3A4 induction by rifampin on XL184 PK	Healthy volunteers	XL184: AUC ↓ 76-77%; C_{max} ↔ (not markedly changed)
XL184-007, ketoconazole	CYP3A4 inhibition by ketoconazole on XL184 PK	Healthy volunteers	XL184: AUC ↑ 34-38%; C_{max} ↔
XL184-008, rosiglitazone	XL184 effect on CYP2C8	Cancer subjects	Rosiglitazone: AUC and C_{max} ↔ n-desmethyl metabolite: AUC and C_{max} ↔

The results from clinical pharmacology studies evaluating extrinsic factors (food and concomitant medications) are shown in Figure 12.

Figure 12: The Effect of CYP Interactions and Food on Study Drug Pharmacokinetics.

Change Due To	PK Parameter		Conclusion

XL184 effect on CYP2C8[a] — AUC (0-inf) 1.07 / Cmax 1.04 — XL184 does not inhibit CYP2C8

CYP3A4 Induction by Rifampin on XL184 PK[b] — AUC (0-inf) 0.23 / Cmax 1.08 — Avoid chronic use of strong CYP3A4 inducers with XL184.

CYP3A4 Inhibition by Ketoconazole on XL184 PK[c] — AUC (0-inf) 1.34 / Cmax 0.97 — No dose adjustment recommended

Food Effect on XL184 PK[d] — AUC (0-inf) 1.57 / Cmax 1.41 — Fast 2 hours before and 1 hour after each dose

Test Relative to Reference (reference = no interacting treatment): 0.2 0.5 0.8 1 1.25 1.6 2

[a] This study tested for an XL184 effect on the PK of rosiglitazone, a CYP2C8 substrate (XL184-008). Note: This study does not test an extrinsic factor on XL184 PK, but was included in this plot for comparison.
[b] This study tested for a rifampin CYP3A4 induction effect on XL184 PK (XL184-006).
[c] This study tested for a ketoconazole CYP3A4 inhibition effect on XL184 PK (XL184-007).
[d] This study tested for a food effect on XL184 PK (XL184-004).
Note: Plotted symbols represent the geometric mean test:reference ratio and error bars represent the 90% confidence interval. This figure is for illustration purposes only and assumes that only the tested interaction is operative.

Sources: XL184-008.PK.001, XL184-006, XL184-007, and XL184-004.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Cabozantinib is considered a   (b) (4)
                                                          However, it has not received official BCS classification/designation from the FDA.

2.5.2 What moieties should be assessed in bioequivalence studies?

Cabozantinib, the active ingredient of drug product, should be assessed in BE studies. The to-be-marketed formulation is the same as the clinical tested formulation, therefore, no BE test is required for the to-be-marketed product.

                                                                              (b) (4)

                    A two-period, two-sequence crossover BE study demonstrated that the capsule formulation containing   (b) (4)
                          is comparable to capsules containing primarily   (b) (4) based on AUC_{0-t} or AUC_{0-inf} (Table 10). The upper bound of the 90% CI for C_{max} (128.3%) slightly exceeded the protocol-defined BE acceptance limit.

Table 10. Bioequivalence Study Results for   (b) (4)

	LSM Treatment A (n=43)	LSM Treatment B (n=43)	LSM Ratio (%) (Treatment A / Treatment B)	90% CI of the Ratio	Within-Subject Variability (CV%)
C_{max}	282	248	113.71	100.77 - 128.30	34.12
AUC_{0-t}	29700	27700	107.36	98.40 - 117.14	24.30
AUC_{0-inf}	31600	29200	108.09	98.94 - 118.09	24.68

2.5.3   What is the composition of the to-be-marketed formulation?

The formulation is supplied as printed hard gelatin capsules containing cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg cabozantinib free base and the following inactive ingredients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid.

The grey gelatin capsule shells contain black iron oxide and titanium dioxide and the Swedish orange gelatin capsule shells contain red iron oxide, and titanium dioxide. The printing ink contains shellac glaze, black iron oxide, *N*-butyl alcohol, isopropyl alcohol, propylene glycol, and ammonium hydroxide.

2.5.4   What is the absolute bioavailability of cabozantinib?

Absolute oral bioavailability of cabozantinib capsule has not been determined. Dose-normalized plasma exposures (AUC) were approximately 2-fold higher for the capsule formulation relative to the PIB solution formulation. Mean AUC_{0-inf} values for cabozantinib from healthy subject studies using capsules (XL184-004, XL184-006, and XL184-007) were 74 to 93% of the corresponding values in the mass balance study where cabozantinib was administered as a solution.

2.5.5   What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed capsule formulation is identical to the formulation used in the registration trial.

2.5.6   What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the PK of a single dose of cabozantinib-malate salt containing 138 mg free base) was evaluated in a randomized, single-dose, two-treatment, two-sequence cross-over study of 47 evaluable healthy subjects (Study Report XL184-004). The C_{max} and AUC values (AUC_{0-t} and AUC_{0-inf}) were moderately increased by 41% and 57%, respectively, when cabozantinib was administered with a high-fat, high calorie meal (Figure 13). Subjects in the clinical trials have been instructed to take cabozantinib at least 1 hour before or 2 hours after a meal to avoid possible food effects on cabozantinib exposure. There were no other specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, or alcohol use on the PK of cabozantinib.

Figure 13: Plasma Concentrations (Mean±SD) Following Administration of Treatments A (fed) and B (fasted) in Healthy Adults

0-504 hours
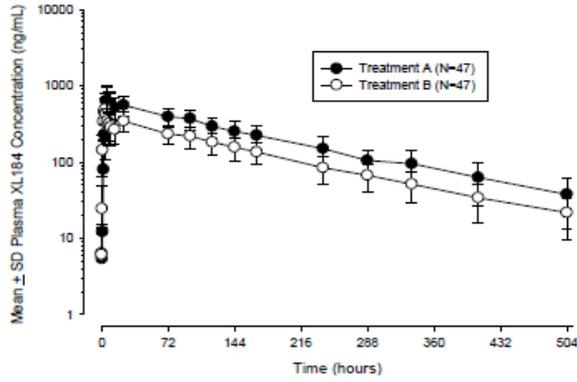
0-24 hours
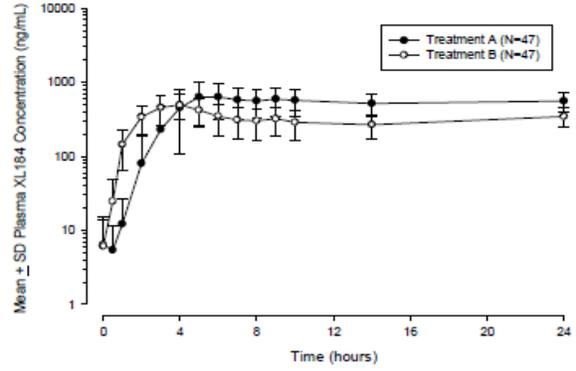
2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

A bioanalytical method (BA-M-084.00) using ~~(b) (4)~~ as the internal standard has been validated for the quantitation of cabozantinib and its four metabolites (hydroxylsulfonic acid, XL184 N-oxide, XL184 half-dimer, XL184 para-fluoroaniline) containing K_2EDTA as an anticoagulant. An LC-MS/MS method (~~(b) (4)~~ 351-1101) has been validated for the quantitation of cabozantinib/XL184 N-oxide/XL184 half-dimer/XL184 sulfate in K_2EDTA human plasma from 1/1/1/4 to 500/500/500/400 ng/mL, respectively. A bioanalytical method (BA-M-077.00) has been developed and validated for the determination of 4-fluoroaniline in human plasma containing K_2EDTA.

Eight metabolites of cabozantinib in human plasma of male healthy subjects following a single oral administration of [14C]-XL184 (100 μCi and 138 mg freebase) have been identified (Study XL184-012) as the follows: XL184 *N*-oxide, XL184 monohydroxy sulfate, half-dimer, 6- and 7-demethyl half-dimer sulfate, half-dimer methyl ester, and 2 demethyl XL184 glucuronides (Table 3). Among these metabolites, XL184 *N*-oxide and XL184 half-dimer were identified to be active targets of MET and VEGFR2 (KDR) kinases. However, XL184 *N*-oxide and XL184 half-dimer are at least 100-fold less potent than that of the parent drug, cabozantinib.

2.6.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma crizotinib was measured for cabozantinib. The total drug instead of free drug concentration measurement appears acceptable as cabozantinib was highly bound (>99.7 %) to human plasma proteins at all concentration levels tested (0.2, 1.0, and 10.0 μM).

2.6.3 Were the analytical procedures used to determine drug concentrations in the NDA acceptable?

The analytical procedures appear to be acceptable from a clinical pharmacology perspective. A bioanalytical method (BA-M-003.00) has been developed for the determination of cabozantinib in human plasma. Samples were prepared using methanol/acetronitrile (20/80) protein precipitation. The supernatant was taken and mixed with equal amount of 0.1% formic acid/water and analyzed by LC-MS/MS. The extraction recoveries (mean and RSD%) for quality control (QC) samples at 1.5, 80, and 800 ng/mL were determined to be 110.4 (5.6%), 100 (1.3%), and 96.9 (4.8%).

The method demonstrates a linearity (r>0.99) over the concentration range of 0.5 to 1000 ng/mL for determination of cabozantinib in human plasma. A weighing factor of $1/concentration^2$ was applied to the least square regression. This linear range of the standard curve adequately meets the needs for clinical studies. The lower limit of quantification (LLOQ) for cabozantinib was 0.5 ng/mL in 50 μL of human plasma. The inter-assay precision and accuracy based on percent relative standard deviation (%RSD) and percent deviation of mean from theoretical (%DMT) of the calibration standards are summarized in Table 11.

Table 11. Inter-assay Precision and Accuracy and Percent Deviation of the Calibration Standards

	Calibration Level (ng/mL)										
	0.50	1.00	2.50	5.00	10.0	25.0	50.0	100	250	500	1000
XL184											
n	8	8	8	8	8	8	8	8	8	8	8
Mean (ng/mL)	0.498	0.996	2.55	5.00	10.22	24.7	50.0	96.7	247.8	528.9	958.9
Precision (%RSD)	5.4	4.4	3.5	1.4	1.8	3.8	2.9	3.1	1.9	4.7	2.7
Accuracy (%)	99.7	99.6	102.2	100.1	102.2	98.8	100.1	96.7	99.1	105.8	95.9

The intra-assay precision and accuracy data of quality control (QC) samples are summarized in Table 12.

Table 12. Intra-assay Precision and Accuracy of the Quality Control Samples

	LLOQ QC 0.50 ng/mL	Low QC 1.50 ng/mL	Medium QC 80.0 ng/mL	High QC 800 ng/mL	Dilution QC* 2500 ng/mL
XL184					
n	6	6	6	6	6
Mean (ng/mL)	0.495	1.51	77.9	781	2533.3
Precision (%RSD)	8.8	7.4	3.7	4.6	1.0
Accuracy (%)	99.0	100.6	97.3	97.6	101.3

* 20-fold dilution

The inter-assay precision and accuracy data of QC samples are summarized in Table 13.

Table 13. Inter-assay Precision and Accuracy of the Quality Control Samples

	Low QC 1.50 ng/mL	Medium QC 80.0 ng/mL	High QC 800 ng/mL
XL184			
n	18	18	18
Mean (ng/mL)	1.47	76.3	762
Precision (%RSD)	6.1	4.0	3.7
Accuracy (%)	97.7	95.4	95.2

Stability of cabozantinib under a variety of conditions is summarized in Table 14.

Table 14. Stability of Cabozantinib Under a Variety of Conditions

Test	Conditions	Minimum Stability
Standard stock solution of XL184	Room Temperature	6 hours
Internal Standard stock solution, (b) (4)	Room Temperature	6 hours
Standard stock solution of XL184	-20°C	145 days
Short-term in matrix	Freeze-thaw	Three cycles
Short-term in matrix	Room Temperature	25.6 hours
Long-term frozen in matrix of XL184	-80°C	145 days
Processed-samples in auto-sampler	5°C	48 hours

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

FDA recommended label:
2.   Dosage and administration
The recommended daily dose of COMETRIQ is 140 mg (one 80-mg and three 20-mg capsules) taken at least 1 hour before or 2 hours after a meal.

Continue treatment until disease progression or unacceptable toxicity occurs.
Do not take a missed dose within 12 hours of the next dose.
Swallow COMETRIQ capsules whole. Do not open COMETRIQ capsules.

2.1   Dosage Adjustment
Withhold COMETRIQ capsules for severe or intolerable toxicity. When toxicity has resolved, resume treatment at a daily dose of 100 mg (one 80-mg and one 20-mg capsule) orally.

Withhold COMETRIQ for second occurrence of severe or intolerable toxicity. When toxicity has resolved, resume treatment at a daily dose of 60 mg (three 20-mg capsules) orally.

Permanently discontinue COMETRIQ:
In patients unable to tolerate a daily dose of 60 mg orally.
For development of gastro-intestinal or other fistula, viscous perforations, or life-threatening hemorrhage

Hepatic Impairment
COMETRIQ is not recommended for use in patients with moderate and severe hepatic impairment [see Warnings and Precautions (5.11) and Use in Specific Populations (8.6)]

CYP3A4 Inhibitors
Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving COMETRIQ [see Warnings and Precautions (5.10) and Drug Interactions (7.1)]. For patients who require treatment with a strong CYP3A4 inhibitor:
Reduce COMETRIQ dose by approximately 40%

Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of a strong inhibitor.
Do not ingest foods or nutritional supplements (e.g., grapefruit, grapefruit juice) that are known to inhibit cytochrome P450.

Strong CYP3A4 Inducers
Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available [see Warnings and Precautions (5.10?) and Drug Interactions (7.2)]. For patients who require treatment with a strong CYP3A4 inducer:
Increase the dose of COMETRIQ in increments of 40 mg by only two weeks as tolerated.
Return the dose of COMETRIQ to that used prior to initiating the strong CYP3A4 inducer when the strong inducer is discontinued..

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity.

5. Warnings and Precautions
5.10 Drug Interactions
The administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors should be avoided [see Dosage and Administration (2.1) and Drug Interactions (7.1, 7.2)]

5.11 Hepatic Impairment
COMETRIQ is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established [see Use in Specific Populations (8.6)].

7. Drug Interactions
7.1 Effect of CYP3A4 Inhibitors
Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC0-inf) by 38%.
For patients who require treatment with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconizole), reduce the COMETRIQ dose [see Dosage and Administration (2.1) and Warnings and Precautions (5.10)].

7.2 Effect of CYP3A4 Inducers
Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC0-inf) by 77%. Co-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) with COMETRIQ can decrease cabozantinib exposure and should be avoided. Consider a dose increase of COMETRIQ when co-administered with a strong CYP3A4 inducer if alternative treatment cannot be administered [see Dosage and Administration (2.1) and Warnings and Precautions (5.10)].

8. Use in Specific Populations

8.6 Hepatic Impairment

Cabozantinib pharmacokinetics has not been studied in patients with hepatic impairment. There are limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). COMETRIQ is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established. [see Dosage and Administration (2.1) and Warnings and Precautions (5.11)].

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is no experience with COMETRIQ in patients with severe renal impairment.

12.3 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.

Absorption and Distribution
Following oral administration of COMETRIQ, median time to peak cabozantinib plasma concentrations (Tmax) 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 Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral COMETRIQ dose.

Metabolism and Elimination
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.

Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Specific Populations
Renal Impairment: No formal pharmacokinetic study of cabozantinib has been conducted in patients with renal impairment. The results of a population pharmacokinetic analysis suggested that mild to moderate renal impairment (creatinine clearance value >30 mL/min) does not have clinically relevant effect on the clearance of cabozantinib.

Hepatic Impairment: The pharmacokinetics of cabozantinib has not been studied in patients with

hepatic impairment [see Dosage and Administration (2.1), Warnings and Precautions (5.11) and Use in Specific Populations (8.6)].

Pediatric Population: The pharmacokinetics of cabozantinib has not been studied in pediatric population [see Use in Specific Populations (8.3)].

Effects of Age, Gender and Race: A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11%). Cabozantinib pharmacokinetics was not affected by age (20-86 years).

Drug Interactions
CYP Enzyme Inhibition and Induction: Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 µM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 µM) and CYP2C19 (Kiapp = 28.8 µM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 µM) in human liver microsomal (HLM) preparations. IC50 values >20 µM 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 (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in patients with solid tumors.

P-glycoprotein Inhibition: Cabozantinib is an inhibitor (IC50 = 7.0 µM), 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.

12.3   Cardiac Electrophysiology
The effect of orally administered COMETRIQ 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC. An increase in QTcF of 10 - 15 ms was observed within the first 4 weeks of initiating COMETRIQ. A pharmacokinetic/pharmacodynamic analysis demonstrated a concentration-dependent QTc interval prolongation. Changes in cardiac wave form morphology or new rhythms were not observed. No COMETRIQ-treated patients had a QTcF >500 ms.[see Clinical Studies:(14)]

4 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRICS REVIEW

NDA Number	203,756 (submitted on May 29, 2012)
Brand Name	COMETRIQ®
Generic Name	Cabozantinib
PM Reviewer	Jun Yang, Ph.D.
PM Secondary Reviewer and Team Leader (Acting)	Nitin Mehrotra, Ph.D.
Division	Clinical Pharmacology V
Clinical Division	Division of Drug Oncology Product II
Sponsor	Exelixis
Submission Type; Code	NDA (NME)
Proposed Indication	Progressive metastatic medullary thyroid cancer (MTC)

1. SUMMARY OF FINDINGS

1.1. KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

1.1.1. Is the proposed dosing regimen supported by the exposure-response (ER) relationship for efficacy?

No, the proposed dosing regimen is not supported by the E-R relationship of efficacy and the analysis suggests that a lower dose may provide similar benefit in terms of the primary endpoint, progression-free survival (PFS). E-R relationship between PFS and dose intensity or $AUC_{Dose\ Intensity}$ could not be identified in patients treated with cabozantinib in the pivotal trial (XL184-301), indicating that lower dose may not be associated with reduction of the PFS. Because majority of patients (86.4%) in the cabozantinib arm experienced a dose modification (e.g., dose interruption, dose reduction, and discontinuation) at some time during the pivotal trial, it is difficult to interpret the efficacy results based on E-R analysis. To account for different exposure levels due to dose modification, a Kaplan-Meier analysis of PFS stratified by quartiles of dose intensity was conducted to evaluate the E-R relationship for patients treated with cabozantinib. The dose intensity was defined as the actual administered dose to the time of the event divided by the planned dose to the same time. No E-R relationship between the PFS and dose intensity could be identified in patients treated with cabozantinib (Figure 1, Left), while all quartiles in the treatment arm had significant PFS improvement compared to placebo. The covariates such as

body size, age, gender, smoking status, ECOG status were equally distributed within each quartile of dose intensity (See section of reviewer's analysis).

To further account for inter-individual variability in clearance, the quartile of average exposure ($AUC_{Dose\ Intensity}$) was used in the Kaplan-Meier analysis for PFS. $AUC_{Dose\ Intensity}$ was defined as the average dose (Starting Dose * Dose Intensity) divided by posthoc estimates on individual CL/F. Similar to the results obtained from dose intensity, no E-R relationship between the PFS and $AUC_{Dose\ Intensity}$ could be identified in the cabozantinib arm (Figure 2, Right). These results indicated that decreases of average exposure may not be associated with reduction of PFS.

Figure 1: E-R Relationship for PFS Stratified by Quartiles of Dose Intensity (Left) and by $AUC_{Dose\ Intensity}$ (Right) in Cabozantinib Arm.
Dose Intensity=Actual dose/Planned dose (%);
$AUC_{Dose\ Intensity}$(mg*day/L)=Starting dose*Dose Intensity/(individual CL/F)
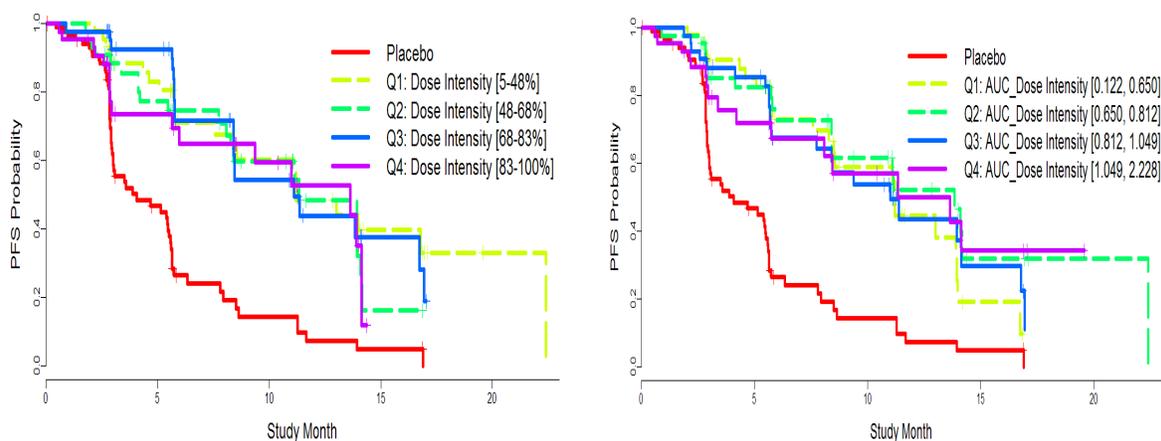
Similar to the results obtained from the E-R analysis for PFS and dose intensity, there was no E-R relationship identified for PFS and the time to the first dose modification (Figure 2), indicating that the early dose modification may not be associated with the reduction of PFS. Time to the first dose modification (defined as the first occurrence of a dose that was not equal to 138 mg freebase) is an indicator of a total dose that a patient received prior to a dose modification due to toxicity since each patient received the same dose (138 mg freebase) initially in the cabozantinib arm. The value of time to the first dose modification was ranged from 2 to 554 days, with a median of ~30 days, indicating that approximately 50 % of patients experienced dose modifications within the first month of treatment. Patients in the treatment arm, regardless the time to first dose modification, all had significant improvement in PFS compared to the placebo group. The high incidence of early dose modification (e.g., 50% patients had dose modification within a month) and the lack of relationship between dose intensity and PFS, suggest that the tested cabozantinib dose (138 mg freebase) could be too high and such high dose could mask the E-R relationship for efficacy (PFS).

Figure 2: E-R Relationship for PFS Stratified by Time to the First Dose Modification Quartiles in

Cabozantinib Arm in Trial XL184-301.
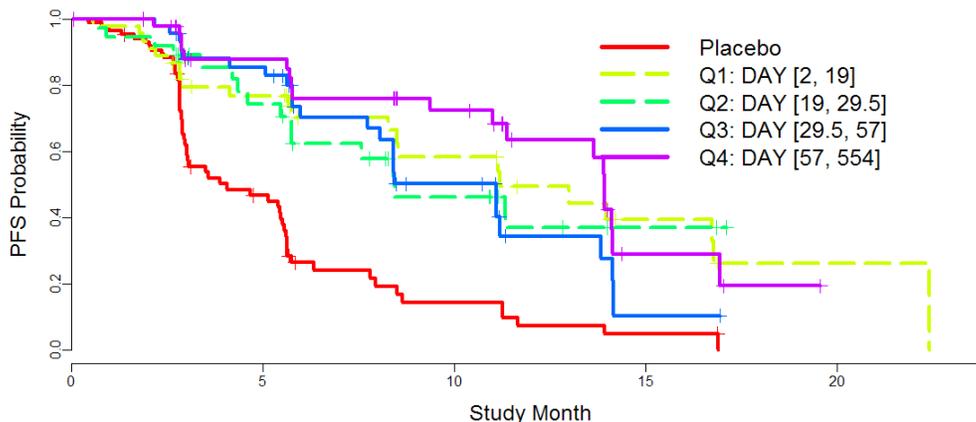
1.1.2. What are the characteristics of the exposure-response relationships for safety?

An E-R relationship for time to the first dose modification and model-predicted steady-state exposure ($AUC_{ss, pred}$) quartiles was identified indicating that patients with higher $AUC_{ss, pred}$ tends to have earlier time to the first dose modification. However, no E-R relationship was identified between incidences of PPE and $AUC_{Dose\ Intensity}$, or between incidences of diarrhea event and $AUC_{Dose\ Intensity}$.

Frequent adverse events (AEs) observed in Trial XL184-301 were diarrhoea, palmar-plantar erythrodysaesthesia (PPE) syndrome, weight decrease, decreased appetite, nausea, fatigue, dysgeusia, hair color changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, ALT increased, AST increased, asthenia, hypocalcemia, and dysphonia. The most frequent AEs that led to dose modifications were PPE syndrome, diarrhoea, fatigue, weight decreased, decreased appetite, etc. The sponsor's ER analyses for safety included ALT, weight loss, PPE, fatigue, diarrhea, and mucositis (see Section of sponsor's analyses).

To evaluate whether early dose modification is associated with high individual exposure (noted that everyone received the same dose before a dose modification), a Kaplan-Meier analysis was conducted to evaluation the relationship between $AUC_{ss, pred}$ and the time to the first dose modification. A significant E-R relationship between the time to the first dose modification and $AUC_{ss, pred}$ quartiles (Figure 3) was identified (P<0.001, Log-rank test). The difference in median dose modification free time for patients within the highest and the lowest $AUC_{ss, pred}$ quartiles is 0.8 month. The sponsor has conducted a similar survival analysis stratified by $AUC_{ss, pred}$ tertiles (see sponsor's analysis) and reached to a similar conclusion. A stepwise Cox proportional hazard model consisting age, sex, body size, smoke status, $AUC_{ss, pred}$, ECOG status, race as covariates was further conducted. Only $AUC_{ss, pred}$ (ranging from 0.51 to 3.53 mg*day/L) was identified as a significant covariate (p<0.0001) for prediction of time to the first dose modification (hazard ratio (HR) of 1.95 (95% CI [1.47-2.59]), while the other covariates were not significant (p>0.05). The hazad ratio of 1.95 implies that with every unit increase of cabozantinib exposure, the hazard of experiencing a dose modification increases by 95%.

Figure 3: ER Relationship for Time to First Dose Modification Stratified by $AUC_{ss, pred}$ (mg*day/L) quartiles for Cabozantinib Treated Patients (Trial XL184-301).
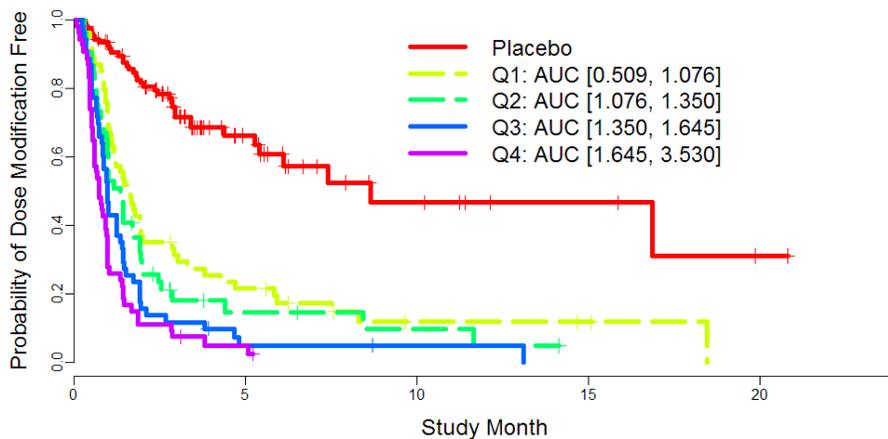
A logistic regression was further conducted to evaluate the relationship between the most important AEs that led to dose modification (PPE and diarrhea) and $AUC_{Dose\ Intensity}$. No E-R relationship was identified between incidences of PPE and $AUC_{Dose\ Intensity}$, or between incidences of diarrhea event and $AUC_{Dose\ Intensity}$ (P>0.05). The incidences of PPE and diarrhea events and $AUC_{Dose\ Intensity}$ are shown in Figure 4.

Figure 4. ER relationship between AEs (PPE and Diarrhea) and Dose Intensity.
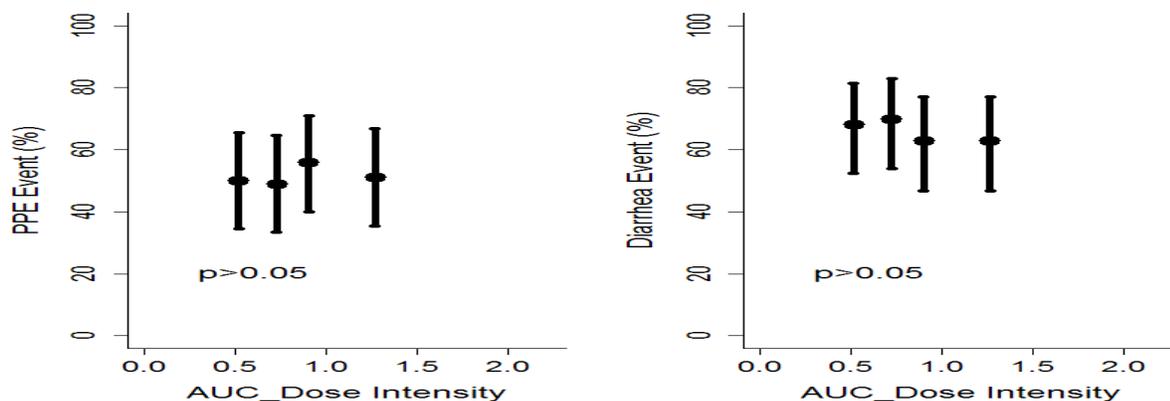
1.1.3. Does the E-R for efficacy and safety along with observed clinical data support the proposed dose of 140 mg?

No, the proposed dose of 140 mg is not supported by the E-R of efficacy and safety and the observed clinical data for the following reasons:

- In a Phase 1 dose escalation trial in patients with advanced solid tumors (refer to trial XL184-001), the maximum tolerated dose (MTD) for cabozantinib was determined to be 138 mg freebase (equivalent to 175 mg L-malate salt) QD using traditional '3+3' rule. After the MTD was determined, 25 MTC patients were treated at the MTD and 80%

patients suffered grade 3 or 4 toxicities and 83% patients required dose reduction. A total of 25 MTC patients were treated at the MTD and 80% patients required dose reduction. Note that the sponsor proposed a dose of 140 mg instead of 138 mg because commercial strengths of 20 mg and 80 mg freebase will be used. The difference between the clinical and proposed commercial dose (138 mg vs. 140 mg) is small and will not be considered to be clinically relevant given to the relative large PK variability of cabozantinib.

- The MTD dose (138 mg) was further tested in a Phase 2 trial (XL184-201) in Glioblastoma (GB) patients. A total 46 patients received the MTD dose daily and 85% of patients suffered grade 3 or 4 toxicities and 80% patients required dose modification.

- The safety and efficacy of the MTD dose were evaluated in the pivotal trial (XL184-301). A total of 69% patients experienced grade 3 or 4 toxicities and 86% patients experienced dose modification in the cabozantinib arm. Approximately 80% of patients had dose reduced to 100 mg during the treatment, and 40% patient had dose further reduced to 60 mg.

- Our E-R analyses of efficacy showed high exposure associated with early time of dose modification due to adverse events and lower dose intensity may not result in reduction in PFS.

As such, labeling a starting dose of 100 mg (can be increased to 140 mg or decreased to 60 mg as tolerated) or conducting a clinical trial as a PMR to identify a lower effective cabozantinib dose in patients with MTC is recommended.

1.2. RECOMMENDATIONS

Based on the E-R analysis of efficacy and safety and the clinical observation that over 86% of patients experienced dose modifications in the pivotal trial, Clinical Pharmacology recommends a starting dose of 100 mg capsule in the COMETRIQ® label, and the dose may be increased to 140 mg or decreased to 60 mg as tolerated. If this is not an acceptable option, then Clinical Pharmacology supports a randomized dose-comparison trial testing 140 mg dose and a biologically active lower dose in patients with progressive metastatic MTC (refer to clinical review by Dr. Ruthann Giusti for more details).

1.3. LABEL STATEMENTS

The ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

(b) (4)

FDA recommended label:

Special Populations

8.3   Pediatric Use

The safety and effectiveness of COMETRIQ in pediatric patients have not been studied.

8.6   Hepatic Impairment

Cabozantinib pharmacokinetics has not been studied in patients with hepatic impairment. There are limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). COMETRIQ is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established. *[see Dosage and Administration (2.1) and Warnings and Precautions (5.11)]*.

8.7   Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is no experience with COMETRIQ in patients with severe renal impairment.

12.3   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.

Specific Populations

Renal Impairment: No formal pharmacokinetic study of cabozantinib has been conducted in patients with renal impairment. The results of a population pharmacokinetic analysis suggested that mild to moderate renal impairment (creatinine clearance value >30 mL/min) does not have clinically relevant effect on the clearance of cabozantinib.

Hepatic Impairment: The pharmacokinetics of cabozantinib has not been studied in patients with

hepatic impairment [*see Dosage and Administration (2.1), Warnings and Precautions (5.11) and Use in Specific Populations (8.6)*].

Pediatric Population: The pharmacokinetics of cabozantinib has not been studied in pediatric population *[see Use in Specific Populations (8.3)]*.

Effects of Age, Gender and Race: A population PK analysis did not identify any clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11%). Cabozantinib pharmacokinetics was not affected by age (20-86 years).

12.6   Cardiac Electrophysiology
The effect of orally administered COMETRIQ 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC. An increase in QTcF of 10 - 15 ms was observed within the first 4 weeks of initiating COMETRIQ. A pharmacokinetic/pharmacodynamic analysis demonstrated a concentration-dependent QTc interval prolongation. Changes in cardiac wave form morphology or new rhythms were not observed. No COMETRIQ-treated patients had a QTcF >500 ms.[*see Clinical Studies:(14)]*

2.   PERTINENT REGULATORY BACKGROUND
Cabozantinib, a new molecular entity, is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs). The applicant seeks an approval of cabozantinib for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC). The proposed dosage of Cabozantinib is 140 mg administered orally once daily (QD), taken at least 1 hour before or 2 hours after a meal. The 140-mg daily dose can be reduced to 100 mg and then to 60 mg for management of intolerable toxicities.

3.   RESULTS OF SPONSOR'S ANALYSIS

3.1.   PIVOTAL TRIAL (XL184-301)

A multi-center, randomized (2:1) double-blind trial comparing cabozantinib (N = 219) with placebo (N = 111) was conducted in patients with unresectable locally advanced or metastatic MTC who had documented radiographic disease progression prior to study entry. The primary objective was to compare progression-free survival (PFS) in patients receiving cabozantinib versus patients receiving placebo. The secondary objective was to compare overall response rate (ORR) and overall survival (OS). The result of the PFS analysis demonstrated a statistically significant difference in the duration of PFS with cabozantinib versus placebo: the median duration was 11.2 months for patients in the treatment arm versus 4.0 months for patients in the placebo arm (Hazard Ratio (HR) = 0.28; 95% CI: 0.19, 0.40; p<0.0001). The PFS results were consistent across all baseline and demographic subgroups evaluated, including prior TKI therapy (which may have consisted of agents targeting pathways associated with anti-angiogenesis), *RET* mutational status, prior anticancer or radiotherapy status, or the presence of bone metastases at baseline. The ORR was 27.9% and 0% for patients in the cabozantinib arm and placebo arm,

respectively (p<0.0001). The median duration of objective responses was 14.6 months (95% CI: 11.1, 17.5) for patients in the cabozantinib arm. A total of 86.4% of patients in the cabozantinib arm had an AE that led to a drug dose modification (e.g., dose reduction, dose interruption).

3.2. POPULATION PHARMACOKINETIC (POPPK) ANALYSIS

4.1 Studies Included in the Analysis

This analysis includes the data from Phase 1 Trial XL184-001, Phase 2 Trial XL184-201, and Phase 3 Trial XL184-301. A summary of these studies is provided Table 1. For all three studies, only patients receiving capsules were included in the PopPK analysis. All study doses were expressed in terms of the L-malate salt form of cabozantinib. However, these doses were converted to the equivalent XL184 freebase dose prior to formal PopPK modeling. The objectives of the PopPK analysis are as follows:

- Characterize the disposition and concentration-time profile of cabozantinib
- Determine the extent of between individual variability in the PK of cabozantinib
- Quantify the amount of cabozantinib PK variability explained by patient covariates
- Use final PopPK model to provide cabozantinib exposures/PK parameters to drive drug-effect input for ER analyses reported separately.

Table 1. Summary of studies included in the population PK analysis

Protocol	Study Design	En-rolled	N*	Population	Treatment
XL184-001	Phase 1 Open-label	85	40/40	Patients with advanced malignancies (MTD and MAD capsule cohorts)	175 or 250 mg XL184 L-malate salt (equivalent to 138 mg or 197 mg XL184 freebase, respectively) (qd)
XL184-201	Phase 2 Open-label	196 (46 in Group A, 175 mg qd)	39/40	Progressive or recurrent Glioblastoma Multiforme (GB)	175 mg XL184 L-malate salt (equivalent to 138 mg XL184 freebase) qd
XL184-301	Phase 3 Randomized, double blinded, placebo controlled	330	210/214	Unresectable, locally advanced or metastatic MTC	175 mg XL184 L-malate salt (equivalent to 138 mg XL184 freebase) qd

* Number of patients eventually included in the PopPK analysis/number of patients with PK samples collected or planned to be collected.

Source: XL184-301-popPK Report, Page 18. Table 1.

The PopPK of XL184 in plasma was evaluated in 289 patients with 2079 samples from three trials (Table 2). The software package NONMEM 7, version 7.1.2 was used for the population PK (PopPK) analysis. The first-order conditional estimation method with interaction (FOCEI) was used. The impact of age, body weight, BMI, sex, race, BSA, calculated CRCL, hepatic function (ALT, AST, ALB, and TBIL), protein binding (ALB), smoking status (former, current, never, and ever, never), and use of co-medication (CYP3A4 inhibitors/inducers and gastric pH modifiers) on the PK of XL184 were investigated. The original dataset contained 2,680 concentration-time data points from subjects. Out of these data, 601 plasma XL184 concentration data points were excluded in the PopPK analysis with reasons detailed in Table 3.

Table 2. Summary of XL184 data in the PopPK datasets

Study	N	Nobs	Sex (M/F)	Age (range), yr	Weight (range), kg	Race *(NA/A/B/W/O)	Smoking #(N/C/F/U)
XL184-001	40	569	31/9	60 (20 to 70)	83 (53 to 120)	2/1/2/35/0	0/0/0/40
XL184-201	39	206	26/13	50 (20 to 70)	79 (52 to 130)	1/1/3/33/1	28/3/8/0
XL184-301	210	1304	146/64	60 (20 to 90)	71 (40 to 140)	5/8/1/189/7	108/21/81/0
Total	289	2079	203/86	55 (20 to 86)	74.7 (40 to 137.9)	8/10/6/257/8	136/24/89/40

* A=Asian, B=black or African American, W=white, NA=unknown, O=other race. #N=never, C=current, F=former, U=unknown, Nobs=number of observations.

Source: XL184-301-popPK Report, Page 23. Table 2.

Table 3. Exclusion of data points in the PopPK model evaluation dataset

Label	Exclusion criteria	XL184-001	XL184-201	XL184-301	Total
C0	zero concentration	37	39	209	285
C1	non-zero concentration before 1st dose	1	0	2	3
C2	observations that were not associated with a dosing event	4	3	32	39
C3	missing sample time	13	29	18	60
C4	incorrect sample time	36	0	6	42
C5	subject did not have the 1st dose time	0	0	13	13
C6	sample time>=58 days in study XL184-301	0	0	149	149
C100/C101	concentration records with |CWRES| > 6 or subject was identified as an outlier	1	0	9	10
Total	**All**	**92**	**71**	**438**	**601**
*C99	Dose records with dose=0, i.e., dose holds	26	34	84	144

*Dose holds not counted in total number of exclusions as they did not have any PK concentration information

Source: XL184-301-popPK Report, Page 26. Table 3.

The PK of cabozantinib was described by a one-compartment model with first order absorption and elimination. When adding the BMI covariate to clearance term, the likelihood function decreased from -1285.75 (base model) to -1303.55 (a change of 17.8 in likelihood function), while adding BSA or gender to the clearance term resulted in a likelihood function decrease of 1.23 and 14.82 from the base model, respectively. After adding BMI to the clearance term, including sex or BSA can further result in a likelihood function decrease of 18.91 and 6.67, respectively. Covariates (BWI and SEX) in final model were identified by forward addition (p < 0.05) and backward elimination steps (p<0.001, likelihood ratio changes >10.28) and included the following parameter-covariate relationships:

$$CLBMI = \exp[\theta_6 \cdot (BMI - 24.76)]$$
$$CLSEX = 1, SEX = M; \quad CLSEX = 1 + \theta_7, SEX = F$$
$$CL_i = \theta_1 \cdot CLBMI \cdot CLSEX \cdot \exp[\eta_{CL_i}]$$

The population PK parameter estimates for both base model and final model were shown in Table 5. The clearance (CL/F) and volume (Vc/F) in final model were estimated to be 106 (±2.98%) L/day and 349 (±2.73%) L, respectively, resulting in an estimated elimination half-life of 55 hours. Although covariates such as BWI and SEX were identified by the model building criteria, the addition of both covariates did not result in a reasonable decrease in between subject variability (BSV). The PK parameter estimates between base and final model are similar (Table 4).

Table 4. Population PK parameters from Base (Top) and Final model (Bottom).

Base Model:

Parameter	Parameter Description	Population Estimated (% CV)	Inter-Individual variability (%CV)
θ_1	Apparent clearance, CL/F (L/day)	97.4 (2.60%)	38.3 (11.1%)
θ_2	Volume of central compartment, Vc (L)	349 (2.73%)	39.5 (11.3%)
θ_3	Absorption rate constant, KA (L/day)	62.5 (13.0%)	131 (18.1%)
θ_4	Lag absorption time, ALAG1 (hrs)	0.471 (0.826%)	
δ	Intra-individual variability	0.347 (1.88%)	

Final Model:

Parameter	Parameter Description	Population Estimated (% SE)	Inter-Individual variability (%SE)
θ_1	Apparent clearance, CL/F (L/day)	106 (2.98%)	35.4 (11.4%)
θ_6	Influence of BMI on CL/F	-0.0244 (20.3%)	
θ_7	Influence of SEX on CL/F	-0.219 (19.5%)	
θ_2	Volume of central compartment, Vc/F (L)	349 (2.73%)	39.5 (11.3%)
θ_3	Absorption rate constant, Ka (1/day)	62.8 (13.3%)	131 (18.0%)
θ_4	Lag absorption time, ALAG1 (hrs)	0.471 (0.83%)	
σ	Intra-individual variability	0.347 (1.88%)	

Note: Off-diagonal covariance terms are $\Omega_{CL/F,V1} = 0.0419$ (28.9%)
Inter-individual variability=ω x 100, %SE=standard error/absolute value (estimate) x 100%
Source: XL184-301-popPK Report, Page 43 & 97. Table 8 & 18.

Sensitivity analyses were conducted to evaluate the impact of covariates on the PK of cabozantinib. The impacts of gender and BMI on CL/F are listed in Table 5.

**Table 5: Predicted XL184 PK parameters across the BMI range**

CL/F, population estimate	Covariate			Covariate impact on CL/F	
	Covariate, Median value	Percentile	Value	CL/F, value at covariate percentile	Change from population estimate[a] (%)
CL/F, 106 L/day	BMI (M) 25.2 kg/m²	5th	18.6 kg/m²	123	16
		95th	34.2 kg/m²	84.3	−20.5
	BMI (F) 24.0 kg/m²	5th	16.8 kg/m²	101	−4.72
		95th	36.3 kg/m²	62.5	−41

[a] Population estimate of CL/F (ie, 106 L/day) is engendered by males because 70% of the 289 subjects in the final model were males.
Source: XL184-301-popPK Report, Page 57. Table 12.

The shrinkage of these model parameters such as inter-individual variability on CL/F, Vc/F and residual error were 16.4 %, 15.0 %, and 12.7 %, respectively. The estimated Ka had a shrinkage value of 44.3%, which could be due to insufficient PK sampling at the absorption phase for most patients. The standard goodness of fit plots for the final model are shown in Figure 5.

Figure 5: Goodness of fit plot of the final model
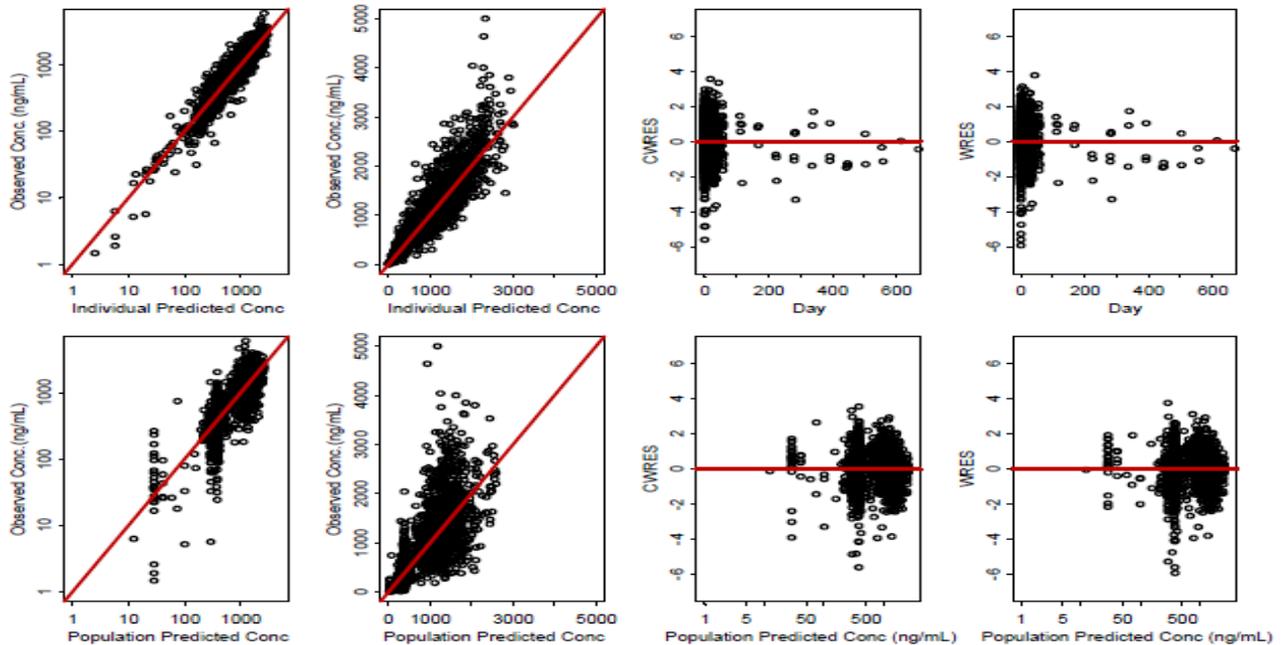
*Source: XL184-301-popPK Report, Page 46. Figure 4.*

Reviewer's Comments: The sponsor included BMI instead of BSA or body weight in the final model because the addition of BMI resulted in the lowest objective function value compared to BSA or body weight. Gender can further reduce the objective function value after adding BMI to the base model. However, both BMI and gender could account for less than 10% between subjective variability in clearance which is not considered to be clinically relevant. Similarly, neither BSA nor body weight could explain the between subjective variability in clearance. The major PK parameters were similar between the base and final model. Neither of BMI nor gender appeared to have clinically relevant impact on cabozantinib PK given the large PK variability

and frequent dose modification on cabozantinib arm. The diagnostic plots and shrinkage of model parameters appear reasonable. Overall, the applicant's population PK model reasonably describes the data and the AUCss based on post hoc estimates of individual clearances can be used for E-R analysis.

3.2.2. Body Size and Gender

Explorations of the CL/F relationship with BMI and CL/F with Gender are provided in Figure 6. The median of clearance was approximately 20% lower in females than in males. However, this effect is not considered clinically relevant. Body size does not contribute to clinically relevant changes in PK of cabozantinib.

Figure 6. Distribution of Inter-individual Variability (ETA) for the Base Model and Final Model against covariates
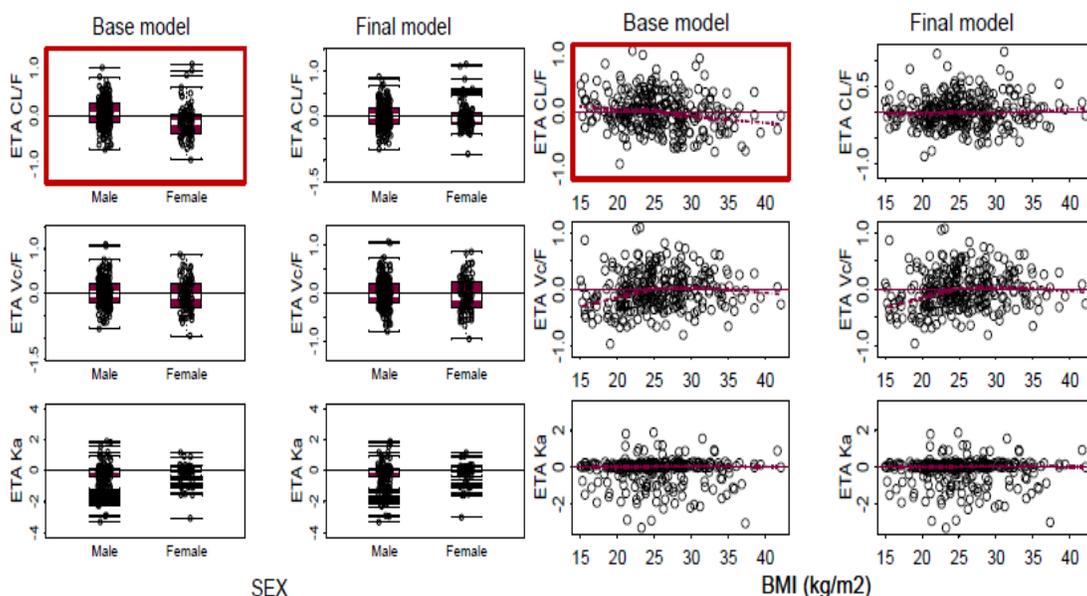
Source: XL184-301-popPK Report, Page 108. Figure 30 & 31.

3.2.3. Renal Impairment

See Reviewer's Analysis (Section 4.3.5.) and Clinical Pharmacology Review Section 2.3.2.2.

3.2.4. Hepatic Impairment

See Clinical Pharmacology Review Section 2.3.2.3.

3.2.5. Age, Race, and Smoking Status

In a population PK analysis, age did not significantly influence cabozantinib PK in patients ranging from 20 to 86 years of age (Figure 7). No PK data are available in pediatric patients. The population PK analysis did not identify clinically relevant differences in clearance of cabozantinib among different races (N: others=8, Asian=10, Black=6, White=257, Unknown=8). There was no clinically relevant difference between white (89%) and non-white (11%) (Figure 8). The smoke status (N: Never=136, Current=24, Former=89, Unknown=40) did not appear to

affect PK of cabozantinib (Figure 8).

**Figure 7. ETA (Between subject variability) of CL vs. Age**
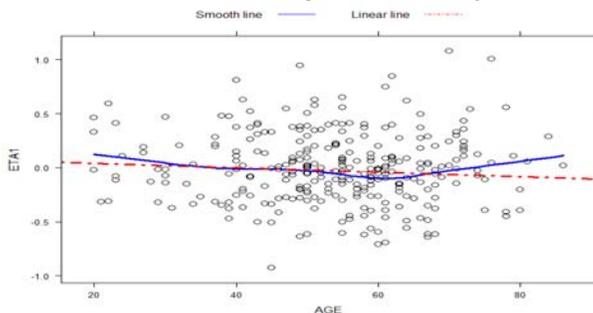
Figure 8. ETA of CL/F vs. Race and vs. Smoking Status
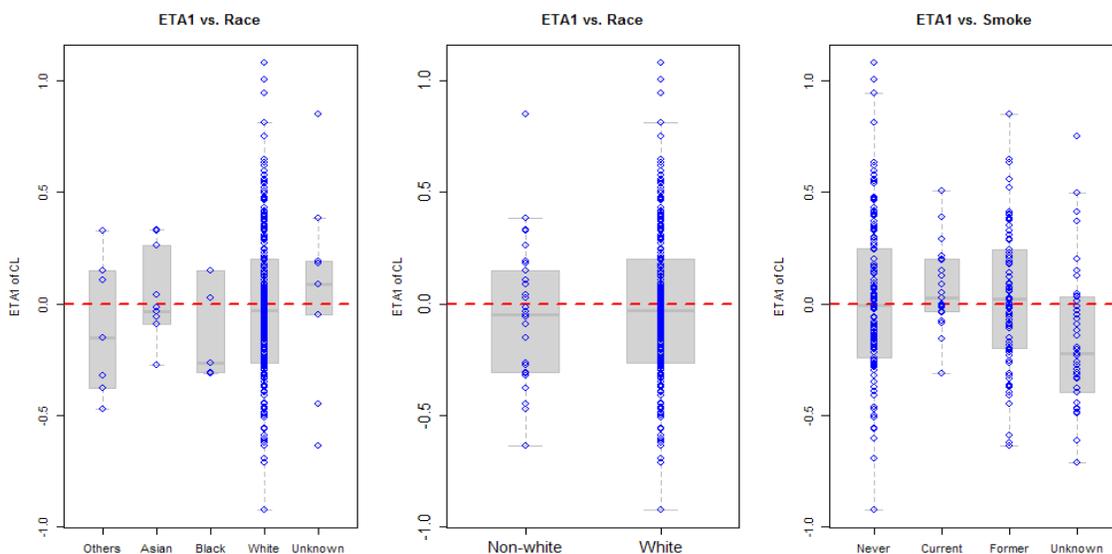
3.3. EXPOSURE-RESPONSE (ER) ANALYSIS

The Applicant performed several E-R analyses to explore the relationship between PK parameters and safety and efficacy endpoints in the pivotal trial XL184-301. The following model- parameters were used in the analyses:

- Predicted steady-state AUC ($AUC_{ss, pred}$): derived from posthoc CL divided by the dose expressed as 138 mg freebase

- Time to the first dose modification

3.3.2. Exposure-Efficacy Analysis

The PFS was explored in a Kaplan-Meier analysis stratified by $AUC_{ss, pred}$ tertiles (Figure 9). The influence of sex and BMI, covariates on CL in the sponsor's final PopPK model, was not identified as important covariates for PFS using Kaplan-Meier analysis (Figure 10).

Figure 9. ER Analysis for PFS stratified by tertiles of $AUC_{ss, predv.}$ Dotted lines represent 95% CI.
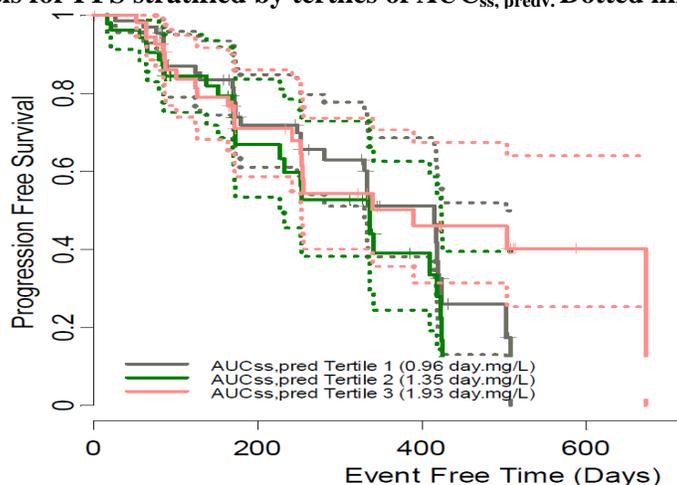
*Source: XL184 -301.ER.001- Clinical Exposure-Response Report, page 38, Figure 6.*

Figure 10. ER Analysis for PFS stratified by BMI and Gender. Dotted lines represent 95% CI.
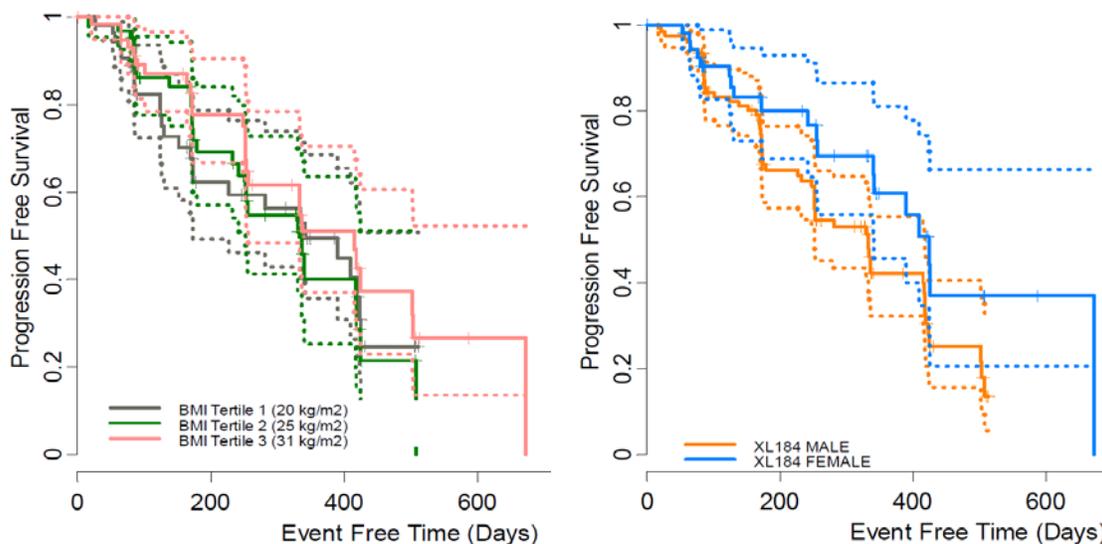
Source: XL184 -301.ER.001- Clinical Exposure-Response Report, page 41&43, Figures 8&10.

The time to first dose modification (FMOD) has also been included in the Kaplan-Meier analysis to evaluate whether dose modification is associated with PFS. The result suggested that early time to first dose modification is not associated with the reduction of PFS (Figure 11).

Figure 11: ER Analysis for PFS stratified by tertiles of time to FMOD. Dotted lines represent 95% CI.
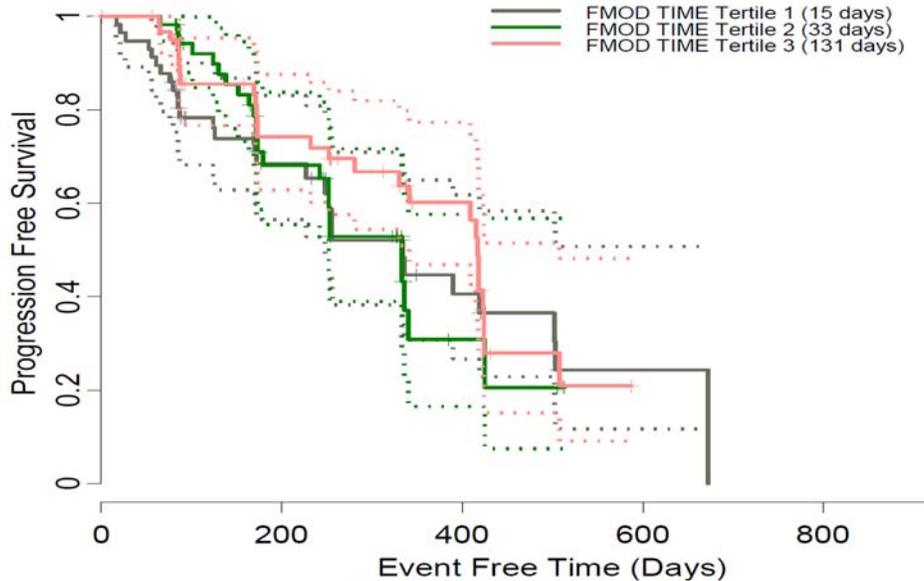
Source: XL184 -301.ER.001- Clinical Exposure-Response Report, page 47, Figure 15.

3.3.3. Exposure-Safety Analysis

The safety endpoints evaluation included (PPE, Grade 1+), fatigue category (Grade 1+ that led to a dose reduction or dose hold, and includes the preferred terms fatigue and asthenia), diarrhea (Grade 2+), mucositis category (Grade 1+), ALT (Grade 3+ and at least one grade increase from baseline) and weight loss (more than 10% decrease from baseline). Kaplan-Meier curves were generated for each safety endpoint stratified by $AUC_{ss, pred}$ tertiles in the cabozantinib treatment group (Figure 12). Similar to the ER analysis results for efficacy, the interpretation of ER for safety is difficult as majority of patients (86.4 %) experienced either dose reduction or interruption and many patients experienced dose reductions or interruptions prior to experiencing an AE. The risk of ALT appeared to be associated with increased $AUC_{ss, pred.}$ However, the number of patients with ALT events (N=13) as defined in this analysis was too small to draw a conclusion. Kaplan-Meier analysis performed for each safety endpoint after stratification by sex or BMI suggested that no clinical relevant relationship identified for each safety endpoint after stratified by sex or BMI.
.

Figure 12: Kaplan-Meier Curves for Safety stratified by AUCss, pred. Dotted lines represent 95% CI.
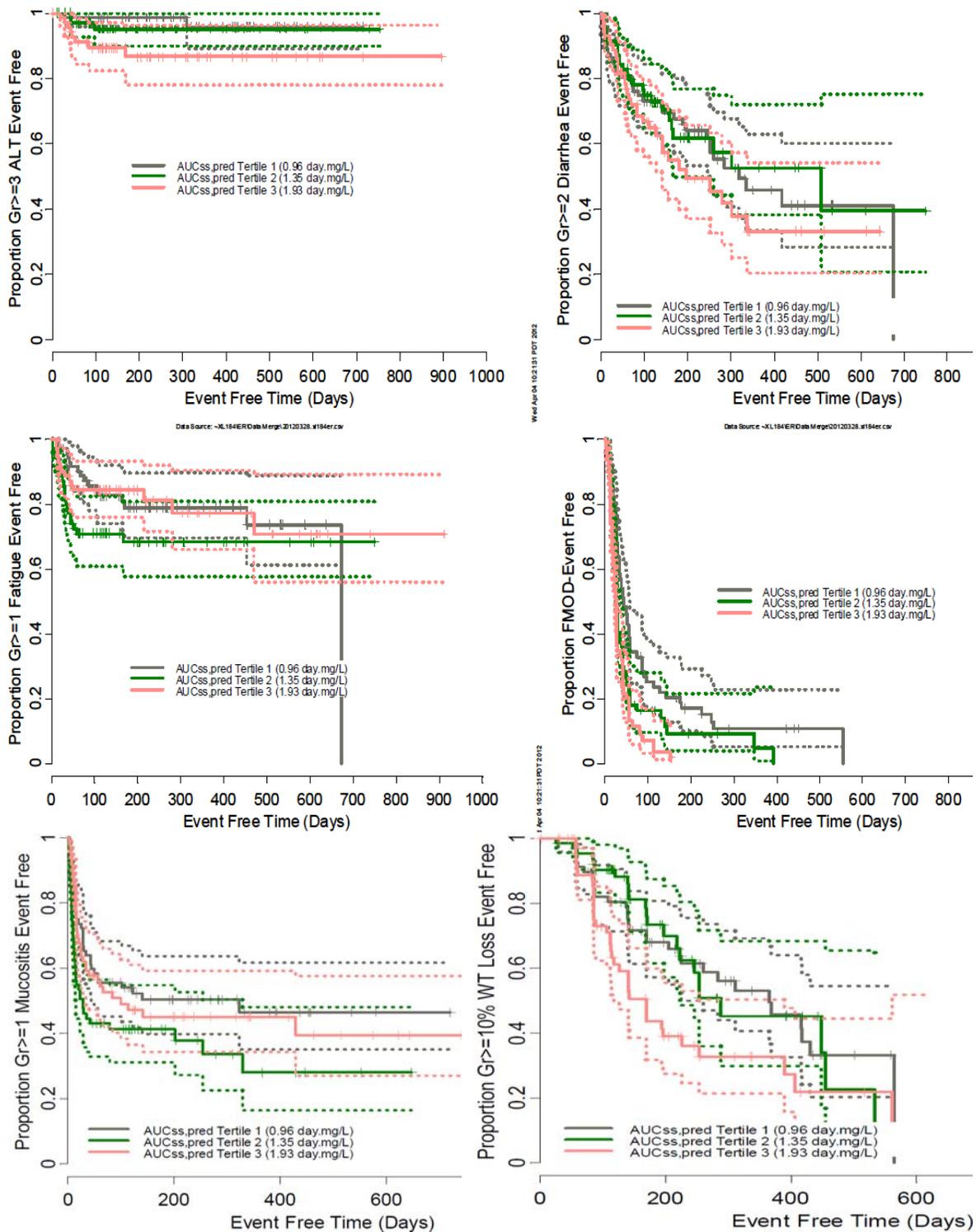
*Source: XL184 -301.ER.001- Clinical Exposure-Response Report, page 37-38, Figures 5&6.*

The sponsor choose PPE for further analysis because PPE was almost entirely confined to the cabozantinib treatment group, was most frequently associated with dose modification, and was not a feature of the underlying disease. It appears that PPE is not associated to $AUC_{ss, pred}$ (Figure

13) and the influence of sex and BMI, were not identified to impact this ER relationship for PPE (Figure 14).

Figure 13: Kaplan-Meier Curves for PPE stratified by AUC$_{ss, pred}$. Dotted lines represent 95% CI.
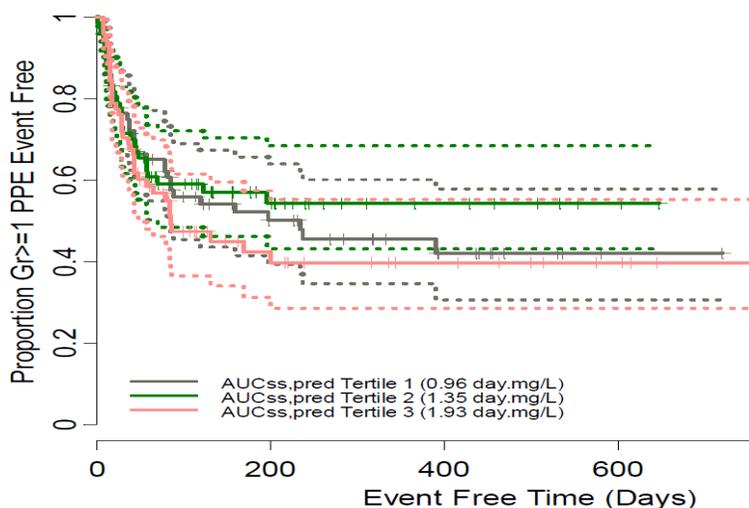
Source: XL184 -301.ER.001- Clinical Exposure-Response Report, page 38, Figure 6.

Figure 14: Kaplan-Meier Curves for PPE stratified by BMI and SEX. Dotted lines represent 95% CI.
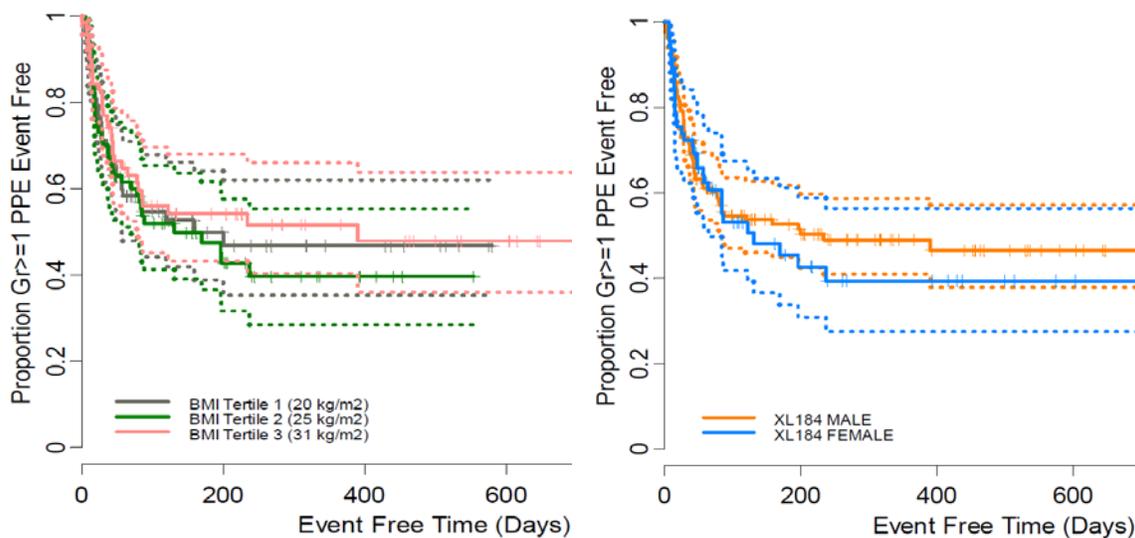
Source: XL184 -301.ER.001- Clinical Exposure-Response Report, pages 41& 43, Figures 8&10.

The applicant conducted a Cox regression and a logistic regression analysis using AUC$_{ss,pred}$ as a predictor of PPE and PFS. AUC$_{ss,pred}$ was not identified as a predictor of PPE or PFS in both Cox and logistic regression results (results not shown). However, both the Cox and logistic regression results were difficult to interpret because many subjects experienced dose reductions

or interruptions prior to experiencing a PPE event, progression, or censoring.

The sponsor conducted a Kaplan-Meier analysis on time to the first dose modification (FMOD) vs. $AUC_{ss,pred}$ tertiles. The correlation between $AUC_{ss,pred}$ and time to the first dose modification was identified (Figure 15, Left) with $p<0.05$ in the logrank test. This relationship was further confirmed in a logistic regression analysis (Figure 15, Right).

Figure 15. ER for time to first dose modification (FMOD) and $AUC_{ss,\ pred.}$ Dotted lines represent 95% CI.
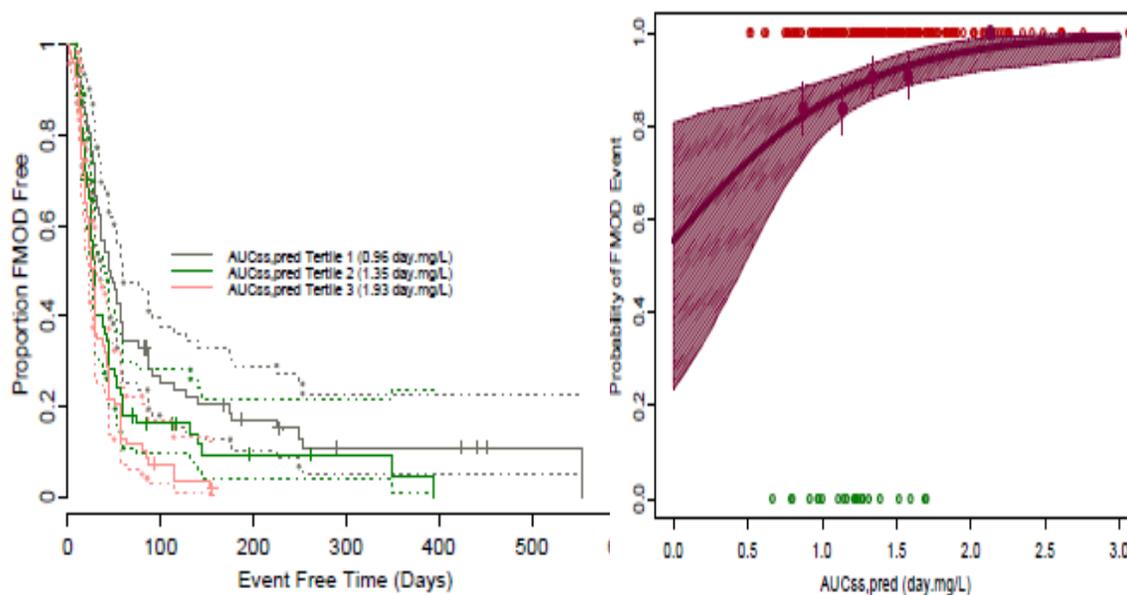
Source: XL184 -301.ER.001- Clinical Exposure-Response Report, pages 45-46, Figures 12&14.

4. REVIEWER'S ANALYSIS

4.1. INTRODUCTION

Majority of patients (86.4%) in the cabozantinib arm had a dose modification (e.g., dose reduction, dose interruption) at some time during the study. Such high incidence of dose modification makes the exposure-response (ER) analyses for efficacy difficult to interpret. The dose intensity and $AUC_{Dose\ Intensity}$ were included in the ER analysis to account for different exposure levels due to dose reduction and interruptions.

4.2. OBJECTIVES

This analysis objective is to evaluate the ER relationship for efficacy.

4.3. METHODS

4.3.2. Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
XL184-301	20120315-xl184poppk-v1.xpt	\\Cdsesub1\evsprod\NDA203756\0002\m5\datasets\xl184-301-poppk-001\analysis\legacy\datasets
XL184-301	km.xpt	\\Cdsesub1\evsprod\NDA203756\0002\m5\datasets\xl184-301\analysis\legacy\datasets
XL184-301	lab.xpt	\\Cdsesub1\evsprod\NDA203756\0002\m5\datasets\xl184-301\tabulations\legacy\raw
XL184-301	dolv.xpt	\\Cdsesub1\evsprod\NDA203756\0002\m5\datasets\xl184-301\analysis\legacy\datasets
XL184-301	20120326-xl184er.xpt	\\Cdsesub1\evsprod\NDA203756\0002\m5\datasets\xl184-301-er-001\analysis\legacy\datasets

4.3.3. Software

R Version 2.14.0 and NONMEM 7.2 were used for the analyses.

4.3.4. Exposure-Response Relationship for PFS Stratified by $AUC_{ss, pred}$ Quartiles

In the pivotal trial (XL184-301), the primary endpoint, progression-free survival (PFS) was tested as stratified by model-predicted steady state exposure ($AUC_{ss, pred}$) using Kaplan-Meier analysis. There was no ER relationship between the $AUC_{ss, pred}$ and the PFS in the pivotal trial XL184-301 as the quartile's survival curves are overlapping (logrank test p-value > 0.05). The covariates such as body size, age, gender, smoking status, ECOG status (0, 1, and 2) were equally distributed within each quartile of dose intensity (Figure 16) except males represent higher portion in the high dose intensity quartiles. However, the ER analysis suggested that gender does not contribute to the PFS difference (Section 3. Sponsor's Analysis). Similarly, the covariates such as body size, age, gender, smoking status, ECOG status (0, 1, and 2) were equally distributed within each quartile of $AUC_{Dose\ Intensity}$.

A Cox proportional hazard model was run to evaluate the role of several covariates for PFS. Age, gender, body size, smoke status, $AUC_{ss, pred}$, race, time to the first dose modification were not identified to be significant predictors of PFS (p>0.05).

Figure 16: Covariates distribution within each dose intensity quartile.
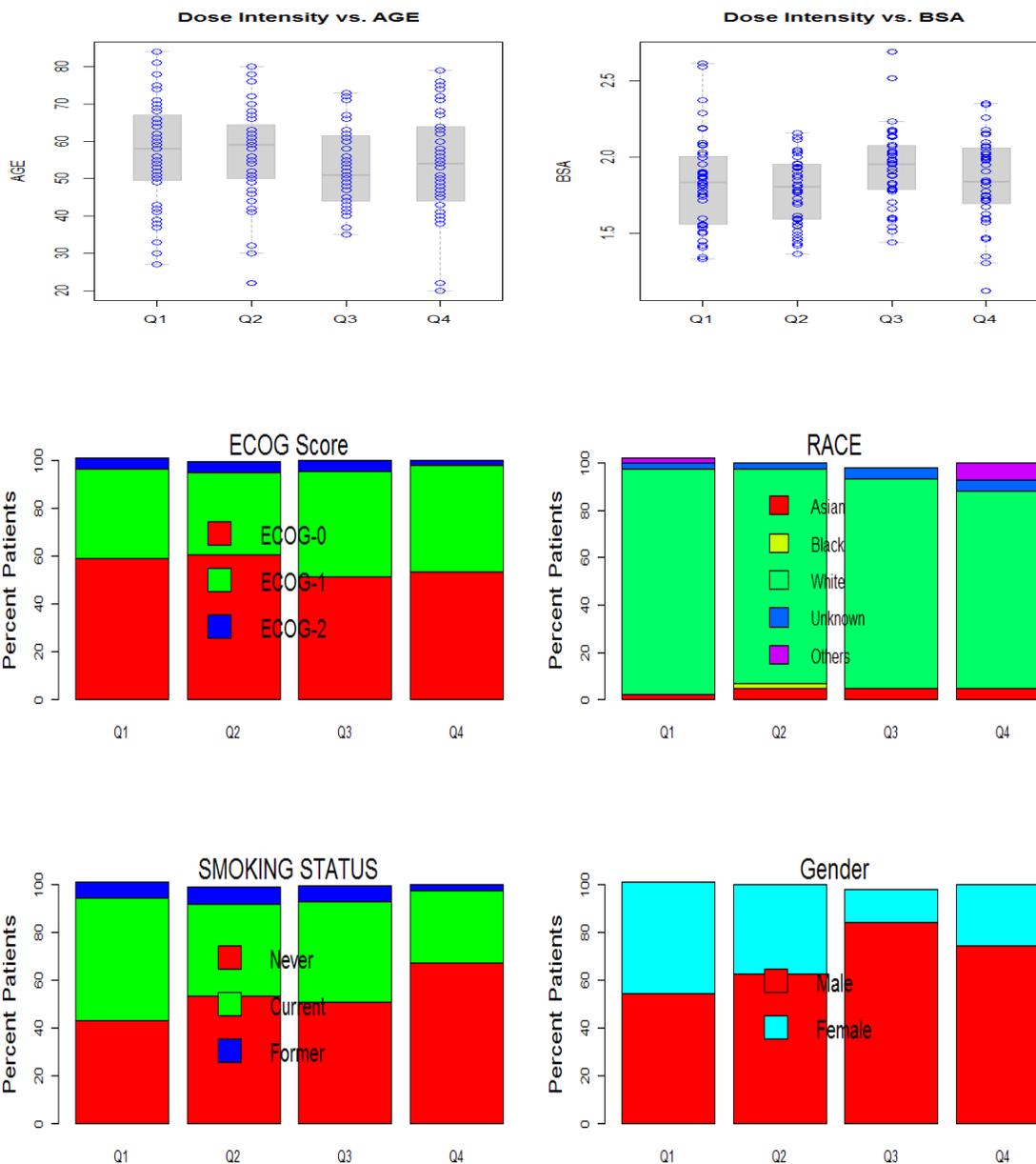
4.3.5. Impact of renal impairment on PK of Cabozantinib

No formal PK trial has been conducted in patients with renal impairement. Results of the PopPK analysis suggested that the impact of renal impairment (mild: CrCL = 50-80 mL/min; moderate: CrCL = 30-50 mL/min) on CL/F of cabozantinib is minimal (Figure 17, Left). Evaluation of PK of cabozantinib in patients with severe renal impairment (CrCL <30 mL/min) is not possible due to limited sample size (N=1). Dose adjustment for patients with renal impairment is not recommended for the following reasons:

- The continuous plot between ETA of CL/F and CrCL (Figure 17, Right) did not reveal a trend or a correlation.

- *In vitro* study indicated that cabozantinib is a high plasma protein binding drug (>99.7%).
- Only 27% of total radioactivity (including 8 metabolites) was recovered in human urine.
- Large PK variability and frequent dose modification.
- 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. Therefore, the solubility of cabozantinib under normal urine pH (>pH 4) is very limited.

Figure 17. Plot of ETA of CL/F versus Renal Impairments
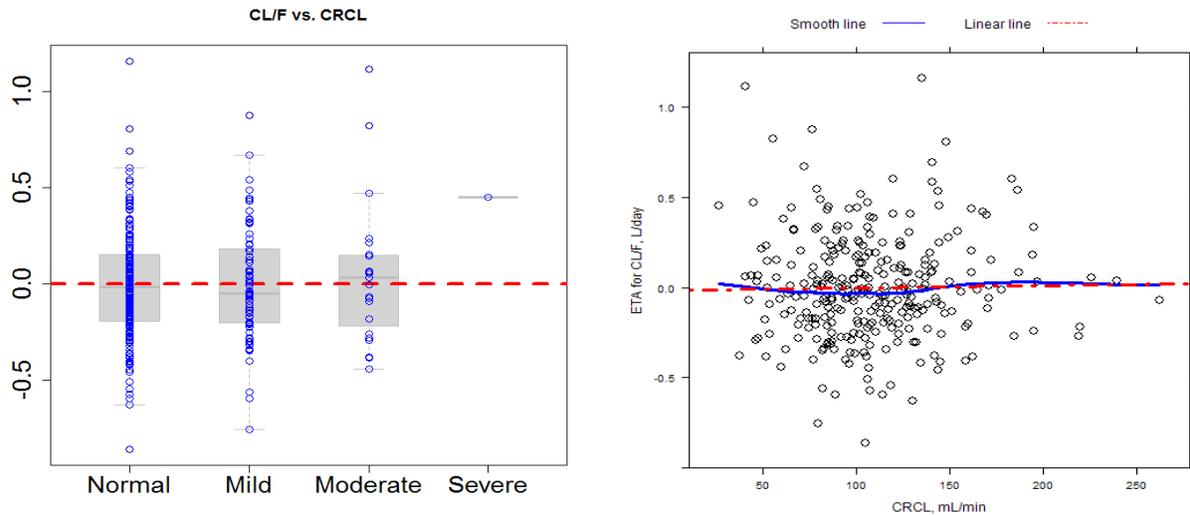
LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER1.R	ER Analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Cabozantinib_NDA203756_JY

5. NDA FILLING FORM

<table>
<tr><td colspan="4" align="center"># Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM</td></tr>
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Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA/BLA Number	**203756/0**	**Brand Name**	COMETRIQ
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	Cabozantinib
Medical Division	**DDOP2**	**Drug Class**	**Small Molecular Drug**
OCP Reviewer	**Jun Yang, Ph.D.**	**Indication(s)**	Progressive, unresectable locally advanced or metastatic medullary thyroid cancer
OCP Team Leader	**Hong Zhao, Ph.D.**	**Dosage Form**	Oral Capsules (20 mg and 80 mg capsules)
Pharmacometrics Reviewer	**Jun Yang, Ph.D.**	**Dosing Regimen**	140 mg Orally Daily
Date of Submission	**5/29/12**	**Route of Administration**	Oral
Estimated Due Date of OCP Review	**11/10/12**	**Sponsor**	Exelixis
Medical Division Due Date	**11/5/12**	**Priority Classification**	**Priority**
PDUFA Due Date	**11/29/12**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology	x			
Mass balance:	x	1		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -	x	3		
HEALTHY VOLUNTEERS-				
single dose:	x	5		
multiple dose:	x	4		
Patients-				
single dose:				
multiple dose:	x	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	3		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	3		
In-vitro:	x	12		
Subpopulation studies -				

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ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**x**	**1**		
Phase 3:	x	2		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		
Phase 3 clinical trial:	x	1		
Population Analyses -				
Data rich:	**X**	**2**		
Data sparse:	x	1		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class	(b) (4)			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**19**		

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

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			XL184-016 (b) (4), See comments below
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		Relative F to solution deter. by cross study compa. (XL184-012 vs. 006, 007, 004)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?		x		Need do further analysis
6	Is the clinical pharmacology and biopharmaceutics section	x			

#				
	of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		**Waiver requested for orphan drug.** (b) (4)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

Reviewer's Comments
-Absolution BA has not determined yet. However, cross-study comparison for relative BA regarding capsule vs. oral solution and capsule vs. powder in bottle (PIB) have been evaluated.
-PK trials for hepatic impairment pts are ongoing
-Effect of gastric pH elevating agents on PK of cabozantinib has to be evaluated.
-Need to consult QT-IRT review team.
-Clinical review team requested the sponsor to clarify the marketed dose (140mg) vs. the pivotal trial

dose (138 mg free base). Clin Pharm will address this in review.
-Further flat dose vs. weight based dose and ER for efficacy and safety may be evaluated during the
review.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology 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 Clinical Pharmacologist   Date

_____
Team Leader/Supervisor   Date

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

/s/

JUN YANG
11/02/2012

NITIN MEHROTRA
11/02/2012

NAM ATIQUR RAHMAN
11/02/2012

<table>
<tr><td colspan="5" align="center">**BIOPHARMACEUTICS REVIEW**
Office of New Drug Quality Assessment</td></tr>
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Application No.:	NDA 203-756			
Submission Date:	29 May 2012		**Reviewer:** Minerva Hughes, Ph.D.	
Division:	Division of Oncology Products 2		**Team Leader (Acting):** Sandra Suarez-Sharp, Ph.D	
			Supervisor (Acting): Richard Lostritto, Ph.D.	
Applicant:	Exelixis			
Trade Name:	Cometriq	**Date Assigned:**	19 March 2012	
		GRMP Date: **PDUFA Date:**	1 November 2012 29 November 2012	
Generic Name:	Cabozantinib	**Date of Review:**	**(Review #2)** 29 October 2012	
Indication:	Progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC)	**Type of Submission:** Original NDA (NME), Priority Review		
Formulation/strengths	Capsule, 20 mg and 80 mg			
Route of Administration	Oral			

Biopharmaceutics Review Focus: Dissolution Method

SUMMARY

Cabozantinib, a new molecular entity, is a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) implicated in tumor growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. NDA 203-756 requests approval to use cabozantinib (140 mg daily) for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). The proposed drug product is a hard gelatin capsule formulation containing cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg cabozantinib and the following excipients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid. ▮▮▮▮▮▮▮▮▮▮▮▮▮▮ (b) (4) ▮▮▮▮▮▮▮▮ (see Biopharmaceutics Review #1 dated 29 June 2012 for general background and initial review notes).

This Review #2 continues evaluates the Applicant's responses to two Biopharmaceutics Information Requests submitted during the review cycle (9 July 2012 and 30 August 2012). Overall, the Applicant satisfactorily addressed the review deficiencies.

RECOMMENDATION

(1) The following dissolution method and acceptance criteria are recommended for approval.

1

Dissolution Method QM4334	
Apparatus	USP Apparatus 2 (with sinker)
Medium	0.01N HCl with 0.5% Triton X-100, 900 mL
Paddle Speed	75 rpm
Temperature	$37 \pm 0.5\ °C$
Sampling Times	15, 30, 45, 60, and 90 minutes
Quantitation	HPLC
Acceptance Criterion	Q = (b) (4) in 15 min, USP <711>

(2) The requested shelf-life of 24 months is acceptable from a dissolution stability perspective.

(3) There are no Biopharmaceutics PMCs.

From the perspective of Biopharmaceutics, the NDA is recommended for approval.

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.
(Acting) Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

2

BIOPHARMACEUTICS REVIEW NOTES

1.0 GENERAL INFORMATION

General background for this NDA and initial Biopharmaceutics review conclusions are located in Biopharmaceutics Filing/Initial Review dated 29 June 2012.

Cabozantinib is classified as a BCS Class ⬛⬛⬛⬛⬛⬛⬛ (b) (4)) compound by the Applicant. ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)

⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛

The 29 June 2012 Biopharmaceutics review noted that the proposed dissolution method seemed reasonable. However, there were a few issues the Applicant needed to address. The following comments were conveyed to the Applicant in the FDA Information Request letter dated 9 July 2012.

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

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

   b. Complete dissolution profile data (individuals, mean, RSD, and plots) for each surfactant type and amount ⬛⬛⬛⬛⬛⬛⬛ (b) (4) tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to surfactant selection; other factors such as micelle structure, excipient interactions, etc., should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.

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

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

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

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

3

precision attributes of the method should address performance at the 15 and 30 minute sampling time points. Provide the validation test data on the variation associated with the 15 and 30 minute sampling time points.

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

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

After reviewing the Applicant's response to comments 1-4 above, NDA amendment dated 1 August 2012, Biopharmaceutics conveyed the following comment in the FDA Information Request letter dated 30 August 2012.

1. Your proposed dissolution acceptance criterion of Q= ___(b) (4)___ is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of Q= (b) (4) at 15 minutes for your cabozantinib 20 mg and 80 mg capsule products. Provide a revised drug product regulatory specification table, revised stability protocol, and revised method protocols with the aforementioned dissolution acceptance criterion change.

This Biopharmaceutics Review #2 evaluates the Applicant's responses submitted in NDA amendments dated 1 August 2012 and 13 September 2012 and provides a final assessment on the proposed dissolution method.

2.0 BIOPHARMACEUTICS REVIEW

2.1   Dissolution method

The proposed dissolution method and acceptance criterion are as follows.

Dissolution Method QM4334	
Apparatus	USP Apparatus 2 (with sinker)
Medium	0.01N HCl with 0.5% Triton X-100, 900 mL
Paddle Speed	75 rpm
Temperature	$37 \pm 0.5 \,°C$
Sampling Times	15, 30, 45, 60, and 90 minutes
Quantitation	HPLC
Acceptance Criterion	Q = _____(b) (4)_____ USP <711>

Additional dissolution method development information was provided in the NDA amendment dated 1 August 2012, in response to FDA's comments on the amount of surfactant, the method's discriminating ability, and the proposed acceptance criterion.

Responses to the 9 July 2012 Information Request:

- **FDA Comment:** Provide a rationale for using two different approaches for determining saturation solubility [(b) (4)   ]).

  o **Applicant's Response:** (b) (4)

Table 1: Solubility of Cabozantinib (*S*)-Malate in Aqueous HCl Solutions (Lot 0904813)

Media	Time Point (hr)	Solubility (mg/mL)
		(b) (4)

Table 2: Solubility of Cabozantinib (*S*)-Malate in Aqueous HCl Solution in the Presence of Surfactants (Lot 0904813)

Media	Time Point (hr)	Solubility (mg/mL)
		(b) (4)

<u>Reviewer's Assessment:</u> *The Applicant's response satisfactorily addressed the review issue. The complete solubility profile data support the claim that 0.5% triton improves the drug's solubility in the medium, and salt disassociation is still an issue when using a surfactant.*

- **FDA Comment:** Provide the complete dissolution profile data (individuals, mean, RSD, and plots) for each surfactant type and amount [(b) (4)   ] tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to surfactant selection; other factors such as micelle structure, excipient interactions, etc., should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.

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o **_Applicant's Response:_**

(b) (4)

Table 3: Comparison of Cabozantinib (*S*)-Malate Solubility in Different Surfactants at 0.5% in 0.01 N HCl

Surfactant	CMC (%w/v)ᵃ	HLBᵃ	Measured Solubility of Cabozantinib (*S*)-Malate (mg/mL) at 2 hours
			(b) (4)

(b) (4) Triton X-100 was selected because of preference.

The Triton X-100 concentration was optimized by further testing using (b) (4) Triton X-100. The drug substance solubility by surfactant concentration is summarized below.
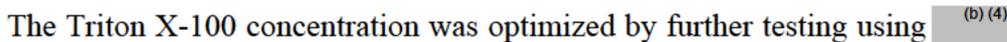
Cabozantinib (*S*)-Malate Solubility Data at Different Triton X-100 Concentrations in 0.01 N HCl (Lot 0904813)

Triton X-100 Level (%)	Measured Solubility (mg/mL) at 2 hours
	(b) (4)
0.5	0.65

(b) (4)

The figure below summarizes the mean dissolution profile at (b) (4) 0.5% Triton X-100.

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**Dissolution Profiles of 80-mg Capsules (Lot# A11807-54)
in 0.01 N HCl with** (b) (4) **and 0.5% Triton X-100 (n = 6)**
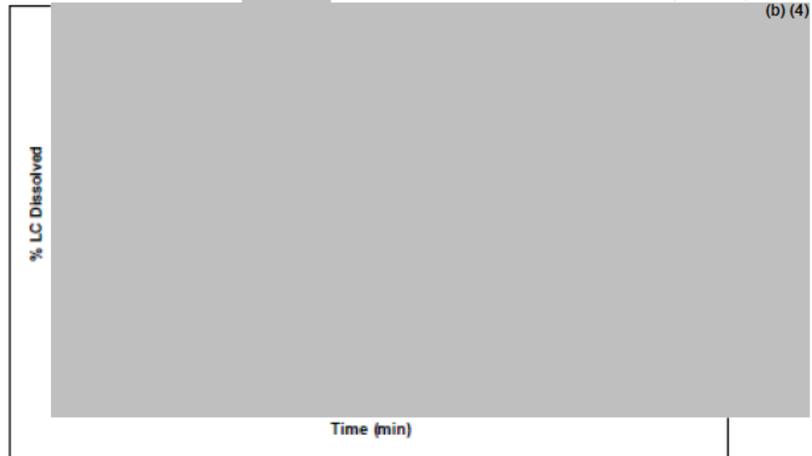
The Applicant selected 0.5% Triton X-100 (b) (4)

Reviewer's Assessment: _The Applicant's response provides an acceptable rationale for selecting 0.5% Triton X-100._ (b) (4)

- _**FDA Comment:**_ Provide the complete dissolution profile data (individuals, mean, and RSDs) supporting the evaluation and selection of the proposed testing apparatus and paddle speed.

   o _**Applicant's Response:**_ (b) (4) The complete dissolution profile data are tabulated below.

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Dissolution Data (% Dissolved) of 80-mg Capsules Lot L0301013, Method Condition: (b) (4) **0.01 N HCl with 0.5% Triton X-100**

Time (minutes)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	RSD%
15								
30								
45								
60								
90 *								

* Infinity, agitation speed at 250 rpm.

Dissolution Data (% Dissolved) of 80-mg Capsules Lot L0301013, Method Condition: Apparatus 2 (b) (4) **0.01 N HCl with 0.5% Triton X-100**

Time (minutes)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	RSD%
15								
30								
45								
60								
90*								

* Infinity, agitation speed at (b) (4)

Dissolution Data (% Dissolved) of 80-mg Capsules Lot L0301013, Method Condition: Apparatus 2 (b) (4) **0.01 N HCl with 0.5% Triton X-100**

Time (minutes)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	RSD%
15								
30								
45								
60								
90*								

(b) (4)

Reviewer's Assessment: The Applicant's rationale for paddle speed selection is acceptable.

(b) (4)

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(b) (4)

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

  o **Applicant's Response:**

(b) (4)

(b) (4)

The mean dissolution profiles are illustrated below.

Dissolution Profiles of 80-mg Capsules with (b) (4) **without** (b) (4)
and Drug Substance in Capsule, in 0.01 N HCl with 0.5% Triton X-100 (n = 6)

(b) (4)

% LC Dissolved

9
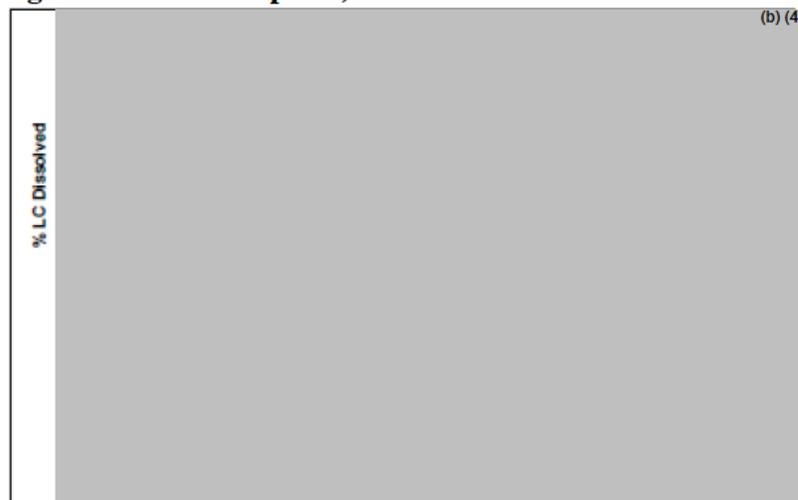
The observed differences in dissolution profiles are used to show the discriminating potential of the method.

Reviewer's Assessment: *The dissolution method's ability to detect meaningful manufacturing changes was not illustrated by the data* (b) (4) (b) (4) *, is not a meaningful manufacturing change. Meaningful changes typically refer to changes that are likely to occur during processing (e.g., 20-30% shift from target values). From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before in vivo performance is affected. (see FDA Guidance on Dissolution Testing of IR Products)*

As discussed in NDA Section 3.2.P.2.2, and noted in the initial Biopharmaceutics Review, a Phase 1 study was conducted using a powder-in-a bottle (PIB) formulation during early development. The PIB formulation consisted of drug substance and vehicle (PEG/Ethanol/Water), which is most similar to the drug substance in capsule formulation illustrated above. The drug exposure (AUC) using the PIB formulation was at least 2-fold lower when compared to the proposed capsule blend, which parallels the observed dissolution relationship between the proposed formulation and drug substance only. Thus, it seems reasonable to expect that the slower dissolution rate for the drug substance only formulation would correlate to lower drug exposures for patients, and the proposed method could observe this effect.

However, although the proposed method can detect major formulation changes that are likely to impact absorption, its utility to detect meaningful process or formulation changes was not established. Since it is known that a slow dissolution rate can affect the PK for this drug, it is prudent to define an acceptance criterion that mitigates the risk of suboptimal PK and, based on the available dissolution data, a Q of (b) (4) *at 15 minutes is better suited to achieve this goal.*

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

  - o ***Applicant's Response:*** The results of statistics on the pooled dissolution release and stability data from 7 lots of 20-mg and 5 lots of 80 mg capsules were:

    - ▪ (b) (4)

-   (b) (4)

-   (b) (4)

Data tables were submitted in the response submission to support the statistics.

Reviewer's Assessment: _The dissolution method's effectiveness in a QC setting is a function of both the selected parameters and the tolerance limits. It is not appropriate to set limits such that any lot would pass testing, but rather, define limits to assure that product meets the quality design targets. Using the proposed method, the clinical material rapidly dissolves in vitro. To assure that future batches maintain the same performance characteristic, the acceptance criterion should also be consistent with a rapidly dissolving product. The mean drug dissolution at 15 minutes was generally_ (b) (4) _at each time point for both strengths. In addition, the dissolution data on extreme formulation changes show that the 15 minute time point was most sensitive to detect quality differences. Therefore, quality assurance is most controlled for at a 15 minute specification-time._

The Applicant was requested on 30 August 2012 to change the dissolution acceptance criterion from Q = (b) (4) _to Q =_ (b) (4) _at 15 minutes._

Response to 30 August 2012 Information Request:

- **_FDA Comment:_** Your proposed dissolution acceptance criterion of Q= (b) (4) is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of Q (b) (4) at 15 minutes for your cabozantinib 20 mg and 80 mg capsule products. Provide a revised drug product regulatory specification table, revised stability protocol, and revised method protocols with the aforementioned dissolution acceptance criterion change.

    - **_Applicant's Response:_** The Applicant accepts FDA's revised acceptance criterion of Q = (b) (4) in 15 minutes. A revised specification table was submitted for the 20 mg and 80 mg capsules. The dissolution method QM4334 does not specify the specification and was not revised. Similarly the post-approval stability commitment does not list the specification and was not revised.

Reviewer's Assessment: _The Applicant's response is satisfactory._

Final Conclusion: _The following dissolution method and acceptance criteria are recommended for approval._

Dissolution Method QM4334	
Apparatus	USP Apparatus 2 (with sinker)
Medium	0.01N HCl with 0.5% Triton X-100, 900 mL
Paddle Speed	75 rpm
Temperature	37 ± 0.5 °C

Dissolution Method QM4334	
Sampling Times	15, 30, 45, 60, and 90 minutes
Quantitation	HPLC
Acceptance Criterion	Q = (b) (4) in 15 min USP <711>

The revised dissolution acceptance criterion is supported by the batch release and stability test data.

2.2 Dissolution HPLC Method

The dissolution HPLC method parameters are as follows.

- HPLC - (b) (4)
- Colum – (b) (4)
- Colum Temp. – (b) (4)
- Flow rate – (b) (4)
- Injection vol. – (b) (4)
- Mobile phase – (b) (4)
- Detection – (b) (4)

The dissolution HPLC method validation data were provided in report KCM-2011-0543-ANA-Disso. This report referenced validation for method QM 4028; however, it is noted that method QM4028 is the same as QM4334. The only difference is the way in with the dosage strength is expressed. The method validation parameters included specificity, linearity, accuracy, repeatability, intermediate precision, instrument precision, solution stability, filter evaluation, dissolution robustness, and HPLC robustness.

A tabular summary of the validation results is presented below.

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Validation Parameter	Acceptance Criteria	Results
Specificity	The chromatograms of mobile phase, dissolution medium, capsule shells and excipient blend do not contain any peaks with the same retention time as cabozantinib (XL184), with an area ≥1% of the average area for cabozantinib in the working standard injections.	(b) (4)
Linearity	Coefficient of determination (r): ≥0.997	
Accuracy/ range	97% to 103%	
Precision	Repeatability: RSD: ≤3.0%	
	Intermediate precision: RSD: ≤10%, difference between two analysts: ≤10%	
Sample and standard solution stability	Sample solution: recovery of %LC within 98% to 102% when compared to the initial data.	
	Standard solution: recovery of %LC within 98% to 102% when compared to the initial data.	
Filter compatibility study	Recovery agreement: The percent recovery of the filtered and unfiltered samples must be within 97% to 103%	

Validation Parameter	Acceptance Criteria	Results
Robustness	HPLC parameters variations: 1) System suitability requirements should be met for each variable range assessed 2) Report mean percent recoveries (the result from each solution is compared to the result obtained using the original HPLC parameters in the method) 3) Identify critical parameters	(b) (4)

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Validation Parameter	Acceptance Criteria	Results
Robustness (continued)	Dissolution parameters variations: 1) Report the percent absolute differences (the result from each parameter is compared to the result obtained using the original dissolution parameters in the method) 2) Identify critical parameters	(b) (4)

ACN, acetonitrile; HPLC, high-performance liquid chromatography; LC, label claim; RSD, relative standard deviation; TFA, trifluoroacetic acid.

Reviewer's Assessment (Initial): At the request of the assigned CMC Review Chemist, Dr. Li Shan Hsieh, the dissolution HPLC method is covered in this review.

The HPLC method validation parameters were generally consistent with the recommendations in ICH Q2(R1) and USP <1092>. The pre-specified SOP validation criteria and results met acceptable levels of performance; however, the robustness information was not provided for the complete dissolution profile, HPLC chromatograms were missing for specificity testing and sample recovery issues were unclear. An information request was submitted on 9 July 2012 for additional information and responses were received on 1 August 2012.

Responses to 9 July 2012 Information Request:

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

  - *Applicant's Response:* Method validation included dissolution sampling at 15, 30, 45 and 60 minutes; however only the 45 and 60 minute sampling times were included in the initial report because the proposed specification-sampling time was ___(b) (4)___ The NDA was amended to include the complete dissolution profile data for robustness and intermediate precision; the data are reproduced in the following tables.

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Robustness: Dissolution Parameters 25-mg Capsule (20mg capsule)

Parameter	Mean % Dissolved				Absolute Difference (%)	
	Adulterated		Unadulterated			
	15min	30min	15min	30min	15min	30min
Surfactant Concentration						(b) (4)
Medium Temperature						
Paddle Speed						
Paddle Height						

Note: Adulterated and unadulterated relate to intentional changes in the HPLC parameters to challenge the system.

Robustness: Dissolution Parameters 100-mg Capsule (80mg capsule)

Parameter	Mean % Dissolved				Absolute Difference (%)	
	Adulterated		Unadulterated			
	15min	30min	15min	30min	15min	30min
Surfactant Concentration						(b) (4)
Medium Temperature						
Paddle Speed						
Paddle Height						

Robustness Reference A11655:10-14, 20 and A11655:15-19, 21

Note: Adulterated and unadulterated relate to intentional changes in the HPLC parameters to challenge the system.

25 mg (20mg) Intermediate Precision – Analyst 1

	%LC				
	15 min	30 min	45 min	60 min	90 min
1					(b) (4)
2					
3					
4					
5					
6					
Mean					
Low					
High					
SD					
RSD					

Reference A11655:1-6

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25 mg (20 mg) Intermediate Precision – Analyst 2

	%LC				
	15 min	30 min	45 min	60 min	90 min
1					(b) (4)
2					
3					
4					
5					
6					
Mean					
Low					
High					
SD					
RSD					

Reference A11197:32-38

100 mg (80 mg) Intermediate Precision – Analyst 1

	%LC				
	15 min	30 min	45 min	60 min	90 min
1					(b) (4)
2					
3					
4					
5					
6					
Mean					
Low					
High					
SD					
RSD					

Reference A11655:1-6

100 mg (80 mg) Intermediate Precision – Analyst 2

	%LC				
	15 min	30 min	45 min	60 min	90 min
1					(b) (4)
2					
3					
4					
5					
6					
Mean					
Low					
High					
SD					
RSD					

Reference A11197:32-38

Reviewer's Assessment: *The amended validation data support acceptable method robustness and precision at the 15 minute sampling time, which is the proposed specification time for the method. Of note, the validation data are consistent with the dissolution method development data, which show* (b) (4) *dissolution at 15 minutes with acceptable RSDs. The*

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(b) (4)

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

    o **Applicant's Response**:

(b) (4)

The recovery data by analyst and preparation are summarized in the following table.

Percent Recovery by Analyst 1 and Analyst 2

Low Concentration (L1) Preparations	% Recovery	Average % Recovery
Analyst 1, Original Preparation		(b) (4)
Analyst 2, Preparation 1		
Analyst 1, Original Preparation, Reinjected		
Analyst 1, Re-preparation 1		
Analyst 1, Re-preparation 2		

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Reviewer's Assessment: *The laboratory investigation was executed in a reasonable manner to identify the possible root cause of the low recovery and alleviates this reviewer's concerns about data quality. The Applicant's justification for pooling the data is acceptable.*

- ▪ *FDA Comment*: Provide copies of the HPLC chromatograms supporting your conclusions on the specificity of the dissolution test method, as noted in validation report KCM-2011-0543-ANA.

  - o *Applicant's Response*: The representative chromatograms were provided to support the conclusions on method specificity. A copy of the working standard and the placebo matrix for the 80 mg capsule are illustrated below.

(b) (4)

Reviewer's Assessment: *The representative chromatograms clearly show that there are no interfering peaks from the excipients using the proposed HPLC method. Thus, the method was appropriately validated for specificity.*

Final Conclusion: *Acceptable.*

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2.3   Dissolution Stability

A shelf life of 24 months is requested for the 20 mg and 80 mg capsules, when stored at controlled room temperature. ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)
⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛
⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛.

The submission included at least 18 months of stability data at 25°C/60% RH and 6 months data at 40°C/75% RH for product packages in bottles and blister cards. Stability data at 24 months was submitted for the 20 mg capsule.

The dissolution stability data at 25°C/60% RH are summarized in the following table.

Pooled Data from Registration and Clinical Lots (25°C/60% RH)			
Stability Pull	Statistic	20 mg – Capsule 15 minutes	80 mg – Capsule 15 minutes
T = 0	Mean (n=6)	96	94
	%RSD	2.9	3.7
T = 18	Mean (n=6)	93	92
	%RSD	3.3	4.0
T = 24	Mean (n=6)	92	TBD
	%RSD	2.7	TBD

All tested conditions and packaging configurations passed the revised acceptance criterion of Q ⬛⬛ (b) (4) at 15 minutes, with a 24 month shelf life.

Reviewer's Assessment: With respect to dissolution stability, a shelf-life of 24 months can be granted.   However, dissolution is only one of the many quality attributes evaluated on stability. Therefore, refer to the CMC Quality review by Dr. Li Shan Hsieh, which evaluates all other CMC stability attributes, for the final decision on the product's shelf life.

Conclusion: 24 months is acceptable for dissolution.

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

/s/

MINERVA HUGHES
10/29/2012

SANDRA SUAREZ
10/29/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW AND INITIAL ASSESSMENT

NDA Number	203-756
Submission Date	29 May 2012
Product name, generic name of the active	Cabozantinib (S)-malate
Dosage form and strength	20 and 80 mg Hard Gelatin Capsules
Applicant	Exelixis 210 East Grand Ave. South San Francisco, CA 94083
Clinical Division	Division of Oncology Products 2
Type of Submission	Original NDA (rolling submission) - **NME**
Biopharmaceutics Reviewer	Minerva Hughes, Ph.D.
Biopharmaceutics Lead	Angelica Dorantes, Ph.D.
Review Date	6/29/2012

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<table>
<tr><td colspan="5">ONDQA-BIOPHARMACEUTICS
A. <u>INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</td></tr>
<tr><td colspan="2">PARAMETER</td><td>YES</td><td>NO</td><td>COMMENT</td></tr>
<tr><td>1.</td><td>Does the application contain dissolution data?</td><td>x</td><td></td><td></td></tr>
<tr><td rowspan="2">2.</td><td rowspan="2">Is the dissolution test part of the DP specifications?</td><td rowspan="2">x</td><td rowspan="2"></td><td>

Dissolution Method QM4334	
Apparatus	USP Apparatus 2 (with sinker)
Medium	0.01N HCl with 0.5% Triton X-100, 900 mL
Paddle Speed	75 rpm
Temperature	37 ± 0.5 °C
Sampling Times	15, 30, 45, 60, and 90 minutes
Quantitation	*HPLC*
Acceptance Criterion	Q = (b) (4) USP <711>

</td></tr>
<tr></tr>
<tr><td>3.</td><td>Does the application contain the dissolution method development report?</td><td>x</td><td></td><td>A method development summary was provided in Section 3.2.P.5.2; however, the information is incomplete.</td></tr>
<tr><td>4.</td><td>Is there a validation package for the analytical method and dissolution methodology?</td><td>x</td><td></td><td></td></tr>
<tr><td>5.</td><td>Does the application include a biowaiver request?</td><td></td><td>x</td><td></td></tr>
<tr><td>6.</td><td>Does the application include an IVIVC model?</td><td></td><td>x</td><td></td></tr>
</table>

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW AND INITIAL ASSESSMENT

	ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING			
	PARAMETER	**YES**	**NO**	**COMMENT**
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	A BCS Class (b)(4) is claimed but the supportive data are incomplete. This is not a review issue; however, (b)(4) .
8.	Is information on mixing the product with foods or liquids included?		x	This issue was raised under the IND, but the proposed labeling states " (b)(4)
9.	Is there any in *vivo* BA or BE information in the submission?	x		Study XL184-004 (Food Effect) Study 184-016 (BE study (b)(4) 7 other Clinical PK and Pharmacology studies were submitted.

10.	Is there a modified-release claim? If yes, address the following:
	    a.) Is there information submitted to support the claim in accordance with 320.25(f)?
	
	    b.) Is there information on the potential for alcohol-induced dose dumping?
			x	The drug product is an immediate release formulation.

	B. FILING CONCLUSION			
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			No applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		*__See Comments for Applicant Below.__*

Comments to be conveyed to the Applicant:

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

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

   b. Complete dissolution profile data (individuals, mean, RSD, and plots) for each surfactant type and amount (▮ (b) (4)) tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to surfactant selection; other factors such as micelle structure, excipient interactions, etc., should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.

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

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

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

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

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

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

Administrative Block:

{See appended electronic signature page}
Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW AND INITIAL ASSESSMENT

INITIAL BIOPHARMACEUTICS ASSESSMENT

1.0 GENERAL INFORMATION

1.1 Relevant Regulatory History

Cabozantinib, a new molecular entity, is a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) implicated in tumor growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. NDA 203-756 requests approval to use cabozantinib (140 mg daily) for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). An Orphan drug designation was granted for the use of carbozantinib to treat MTC on 29 Nov 2010, and the product development program was granted Fast-Track on 8 April 2011 under IND 113,446.

Several meetings were held with the Applicant to support the clinical development program. Relevant biopharmaceutics comments communicated to the Applicant prior to the NDA submission were as follows.

- 6 Mar 2008 – End-of-Phase 2 Meeting

  - According to 21 CFR 320.25, the bioavailability (i.e., absolute and relative) of KL184 should be assessed.

- 4 Mar 2011 – pre NDA CMC-Only Meeting

  - Applicant proposed a commercial high strength capsule of 80 mg drug instead of 79 mg, which was used in the Phase 3 clinical study. This change was considered not clinically relevant by the Applicant given the variance in mean exposures in subjects administered the recommended daily dose (40% CV). FDA concluded that the Applicant's approach was reasonable, and a determination on acceptability will be made in the NDA

  - FDA noted differences in the dissolution profiles between the ⁽ᵇ⁾⁽⁴⁾ ⁽ᵇ⁾⁽⁴⁾ The Applicant was advised that as long as the to-be-marketed formulation was sufficiently similar to the clinical trial formulation, in terms of ⁽ᵇ⁾⁽⁴⁾ and proper controls were applied, a bioequivalence (BE) study would not be needed. Alternatively, the sponsor may choose to conduct a BE study.

  - To support the Applicant's proposal ⁽ᵇ⁾⁽⁴⁾

- 20 Dec 2011 – pre NDA Meeting

  - FDA recommended including a complete dissolution method development report in Module 3 that includes the data justifying the selected method and instrumental parameters (equipment, dissolution media, agitation speed, pH,

assay, sink conditions, etc.) and demonstrating the discriminating capabilities of the selected method. Validation data should also be submitted. (The Applicant agreed with the approach)

- o FDA recommended that the Applicant collect and include complete dissolution profile data from the biobatches (PK and clinical) and registration stability batches in the NDA. The Applicant acknowledged that dissolution data will be presented in tabular format for the PK, clinical, and registration stability batches.

- o FDA requested supporting biowaiver information as per 21 CFR 320.22 for the lower strength if a waiver was planned. The Applicant commented that a biowaiver was not planned for the lower capsule strength since the same capsule formulation, strengths, and dosing configurations used in the clinical studies will be used commercially.

NDA 203-756 was submitted for filing in a rolling format. The CMC Module was submitted on 9 March 2012 and the final review Module was submitted on 29 May 2012, which initiated the review clock.

1.2 Drug Substance Summary

The drug substance, cabozantinib (S)-malate, is the malic acid salt of the active moiety cabozantinib. The chemical structure is illustrated below.
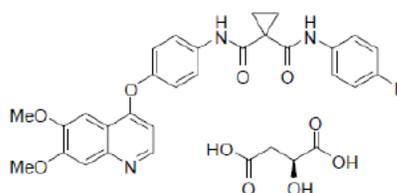
Structure of cabozantinib (S)-malate; MW 635.6; MF = $C_{28}H_{24}FN_3O_5 * C_4H_6O_5$.

The manufacturing process is ███████████████ (b) (4)
███████████████ Relevant process parameters were established using a combination of systematic experimentation, design of experiments, statistical process analysis, and process scale-up experience. A risk assessment was performed to identify process-critical parameters, appropriate process controls, as well as appropriate courses of action to mitigate risks.

(b) (4)

(b) (4)

Other general drug substance physico-chemical attributes are as follows.

(b) (4)

Since clinical trials were conducted using capsule formulations with drug substance batches containing either a mixture of _____ (b) (4), a bioequivalence (BE) study (XL184-016-CSR) was conducted. The two capsule formulations containing either (b) (4) _____ (Lot L0301013) _____ (b) (4) (L0208700) appeared to be bioequivalent based on AUC parameters (i.e., 90% confidence [CI] ratio is within 80-125%). However, the 90% CI of the Cmax ratio (101-128%) was outside of the 80-125% acceptable range, which was thought to be due to the smaller number of evaluable subjects than anticipated (n = 43) based on the subject sample size initially dosed in this study (n = 53).   A tabular summary of the BE assessment is provided below.

	LSM Treatment A (n=43)	LSM Treatment B (n=43)	LSM Ratio (%) (Treatment A / Treatment B)	90% CI of the Ratio	Within-Subject Variability (CV%)
C_{max}	282	248	113.71	100.77 - 128.30	34.12
AUC_{0-t}	29700	27700	107.36	98.40 - 117.14	24.30
AUC_{0-inf}	31600	29200	108.09	98.94 - 118.09	24.68

Treatment A (Test): 100 mg XL184 capsule _____ (b) (4)
Treatment B (Reference): 100 mg XL184 capsule _____ (b) (4)

LSM, least square mean; C_{max}, maximum observed concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity.

Within-Subject Variability $\%CV = \sqrt{\exp(\sigma_w^2) - 1}$, where σ_w^2 is the within–subject variance from the mixed model on log transformed value, using PROC MIXED SAS procedure.

A retest period of _____ (b) (4) is proposed for the drug substance.

Reviewer's Comments:

- *With respect to physico-chemical properties such as solubility, melting point,* (b) (4) *and intrinsic dissolution rates,* (b) (4) *However, dissolution profiles were not submitted to the NDA for Lots L0301013 and L0208700 to better understand the effects of* (b) (4) *on in vitro dissolution performance. Previous interactions with the Applicant suggest that the profiles were not comparable, which seems to indicate formulation effects beyond the obvious solubility consideration. IND 113,446 is not available electronically for ease of reference.*

  Batch analyses data for Lots 0208700 and L0301013 were included in NDA Section 3.2.P.5.5. The mean dissolution using a USP 2 apparatus with 0.01N HCl in 0.5% Triton X-100, 75 rpm, was (b) (4) *at 15 minutes for both lots. Thus, no difference in the in vitro performance was observed using the currently proposed method.*

- *The Applicant's position that the BE study XL184-016 was underpowered due to the higher than expected intra-subject variability is acknowledged. This BE study failed to show bioequivalence with respect to the rate of drug exposure (Cmax), upper CI limit of 128.3, but met the 80-125% criteria for the extent of exposure (AUC). Although 53 subjects were enrolled, only 43 subjects met the statistical analysis population criteria. Indeed, additional exploratory analyses including all subjects who completed at least 1 period of the study (n = 53) had 90% CIs within the 80 – 125% BE limit.*

- *The drug substance has a long half-life, >100 hours and an observed mean Tmax of 5 hours. Per labeling, patients are to receive daily doses of treatment for an extended period. Given the high inter- and intra- subject variability, repeated dosing protocol, and limitations of the* (b) (4) *detection analytical method* (b) (4)*), a* (b) (4) *limit for* (b) (4) *appears reasonable. This drug substance control parameter should also be evaluated by the Review Chemist for acceptability.*

1.3   Drug Product Summary

A 20 mg and 80 mg immediate-release capsule formulation, based on free base weight, are proposed for commercialization. The 20 mg capsules are gray opaque (b) (4) two-piece hard gelatin capsules with "XL184 20 mg" printed on the body of the capsule shell. On the other hand, the 80 mg capsules are Swedish orange opaque (b) (4) two-piece hard gelatin capsules with "XL184 80 mg" printed on the capsule shell's body. The formulation composition information is summarized in the following tables.

Composition of 20 mg Cabozantinib Capsules (Clinical vs. Commercial)

Ingredient	Theoretical Quantity			
	Initial[a]		Proposed Commercial	
	(wt %)	(mg)	(wt %)	(mg)
Cabozantinib (S)-malate				(b) (4)
(b) (4) (silicified microcrystalline cellulose)				
(b) (4) (croscarmellose sodium)				
(b) (4) (sodium starch glycolate)				
(b) (4) (fumed silica)				
Stearic acid				
Total fill weight				

[a] Used with Lots 07-0002, 07-0106, L0205271, 303632, L0209383, L0209927, L0209928, L0209971, L0303838, L0303840, and L0304238.

Composition of 80 mg Cabozantinib Capsules (Clinical vs. Commercial)

Ingredient	Theoretical Quantity					
	Initial[a]		Optimized[b]		Proposed Commercial	
	(wt %)	(mg)	(wt %)	(mg)	(wt %)	(mg)
Cabozantinib (S)-malate						(b) (4)
(b) (4) (silicified microcrystalline cellulose)						
(b) (4) (croscarmellose sodium)						
(b) (4) (sodium starch glycolate)						
(b) (4) (fumed silica)						
Stearic acid						
Total fill weight						

[a] Used with Lots 07-0003, 07-0107, L0205272, and 303614.
[b] Used with Lots L0208700, L0301013, L0302163, L0304187, L0304188, and L0304189.

The drug product was initially developed as a powder-in-bottle (PIB) oral suspension formulation for initiation of the Phase 1 XL184-001 study. Capsules were developed to accommodate flexible dosing in the Phase 1 study, for patient convenience, and for ease of dosage manufacture and subsequent commercialization. The capsule formulations were introduced in the Phase 1 study and were used to determine the maximum tolerated dose. Following the Phase 1 study, a Phase 3 study in MTC was initiated using the same capsule formulations used in the Phase 1 study. Of note, clinical Lots L0200881 (20 mg) and L0201455 (80 mg) were slightly different (b) (4)
The dissolution profiles for these two lots compared with the optimized formulation were assessed using (b) (4)

Mean Dissolution Profiles L-R 20 mg and 80 mg Capsules, Initial and w/ (b) (4)
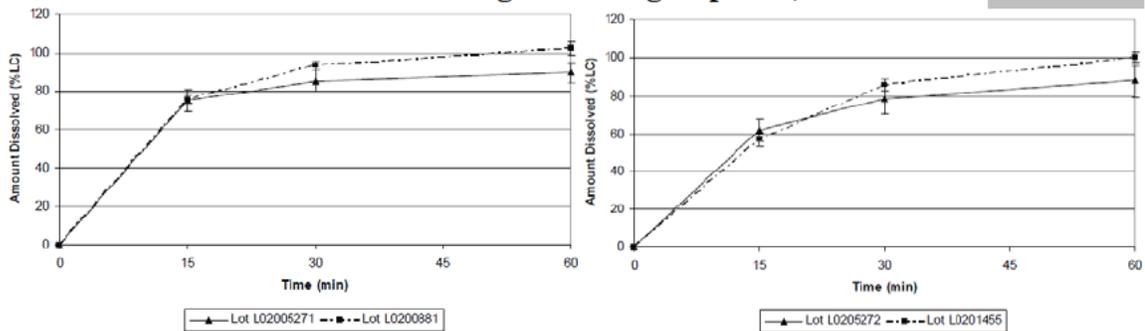
The capsule strengths used in clinical studies were expressed as the salt-based weight (25 mg and 100 mg). These strengths correspond to 19.7 mg and 78.9 mg (expressed as freebase), respectively. The difference between the clinical and proposed commercial dosage strengths is small (i.e., 19.7 vs. 20 mg or 78.9 vs. 80 mg). In Clinical Study XL184-001, the C_{max} and AUC for cabozantinib capsules at steady state had a mean CV of 37% and 43%, respectively, for the highest dose (175 mg malate salt, which is equivalent to 138 mg freebase). Given the inter-subject variability, the small difference (i.e., 19.7 vs. 20 mg or 78.9 vs. 80 mg) is not considered clinically relevant by the Applicant. In addition to the differences in drug load, minor differences in the 80 mg capsule formulation were noted in the Pharmaceutical Development section. The clinical trial material formulation comprised (b) (4)

respectively, in the commercial formulation.

(b) (4)

Finished product will be packaged in either blister packaging or high-density polyethylene (HDPE) bottle packaging.

Reviewer's Comments:

- *Incomplete drug dissolution is noted for the early dissolution test method. The Applicant did not provide any information on mass balance to explain the observation; however, it was noted elsewhere that precipitation was occurring in the dissolution vessel. Given that the* (b) (4) *method is not the final method proposed for quality control, additional information may not be needed. It will be important, however, to have sufficient information to permit FDA to understand the rationale for selecting the optimized method proposed for final release and stability testing.*

- *Based on the observed drug PK and inter/intra subject variability, this reviewer agrees with the Applicant's assertion that the minor difference in drug load between the clinical and to-be-marketed product should not translate into any observable differences in bioavailability for the dosage strengths. In addition, it should be noted that the proposed potency specification allows for +/- 10% variability. Thus, minor shifts about the nominal dose are generally allowed from a quality control perspective.*

- *The Applicant did not submit any data on manufactured lots using the final proposed commercial formulation; however, the modifications made to the nominal amount of each component in the drug product was minor and did not affect the overall % (w/w) for each component in the finished capsule.* (b) (4) *as noted previously. Additionally, the data summarized in Section 2.3.1 of this review show now effect of larger changes in excipient concentration on dissolution. Thus, no additional information is necessary from the Biopharmaceutics perspective to support this change.*

1.4 Biopharmaceutics Classification System

Cabozantinib was classified as a BSC Class ⬜(b) (4)⬜ compound by the Applicant.

Reviewer's Comments: ⬜(b) (4)⬜

⬜(b) (4)⬜.

There were no in vitro permeability data in the NDA. An absolute bioavailability study was not completed; however, elimination studies using ^{14}C labeled compound accounted for 81% of total administered radioactivity in the urine and feces. It is noted that the observed Tmax is prolonged at 5 hours and the rate and extent of drug exposure is increased by ~50% when taken with food.

1.5   Biopharmaceutics Review Focus

The drug product regulatory specification includes test methods and acceptance criteria for the following: appearance, identification, potency, impurities, content uniformity, ▨ (b) (4) ▨ dissolution, and microbial purity.   The dissolution test method and acceptance criteria are evaluated by the Biopharmaceutics review discipline.

In addition, relevant pharmacokinetic studies, in collaboration with the Office of Clinical Pharmacology, are evaluated in support of defining appropriate controls to assure the consistency of drug dissolution/release kinetics, and thereby bioavailability, of commercial product.

2.0   BIOPHARMACEUTICS – PRODUCT QUALITY

2.1   Dissolution Test Method

2.1.1   Method Parameters

The proposed dissolution test method and acceptance criteria for both the 20 mg and 80 mg capsule are as follows.

Proposed Dissolution Method QM4334	
Apparatus	USP Apparatus 2 (with sinker)
Medium	0.01N HCl with 0.5% Triton X100, 900 mL
Paddle Rotation Speed	75 rpm
Vessel Temperature	37 ± 0.5 °C
Sampling Times	15, 30, 45, 60, and 90 minutes
Quantitation	*HPLC* - ▨(b) (4)▨ Colum – ▨ ▨(b) (4) ▨) Colum Temp. – ▨(b) (4) Flow rate – ▨(b) (4) Injection vol. – ▨(b) (4) Mobile phase – ▨(b) (4) Detection – ▨(b) (4)
Proposed Acceptance Criterion	Q = ▨(b) (4) USP <711>

The development and justification for the proposed method and acceptance criteria are evaluated in the following sections.

2.1.2   Method Development/Justification Information

Two early stage dissolution methods were used for quality control prior to final optimization. The initial method used ▨(b) (4)▨ (1036 TM-011). It was later discovered that the pH of the medium after dissolution was approximately ▨(b)(4)▨, so the Applicant switched to ▨(b) (4)▨ (QM3653). During the course of development, it was discovered that ▨(b) (4)▨

(NDA 203756)

(b) (4)

A summary of the early dissolution methods is illustrated in the following table.

Dissolution Parameter	1036-TM-011	QM3653
Apparatus	USP Apparatus 2 (with sinker)	USP Apparatus 2 (with sinker)
Medium		(b) (4)
Paddle Speed	75 rpm	75 rpm
Temperature	$37 \pm 0.5\ °C$	$37 \pm 0.5\ °C$

Building upon their experience with the early dissolution methods, the Applicant developed the proposed final dissolution method as follows.

<u>Medium</u>

In consideration of the pH solubility and sink conditions, a dissolution medium at lower pHs was considered optimal. The final media, 0.01N HCl was selected since it had the highest observed solubility. The solubility of the drug substance, Lot 0904813, at various pHs is summarized in the following table.

pH Medium	Measured Solubility (mg/mL)
	(b) (4)

ND, not detected.

Note: *Solubility at 24 hours, 37°C.*

To increase drug solubility, four non-ionic surfactants (⁽ᵇ⁾ ⁽⁴⁾
Triton X-100) were evaluated. ⁽ᵇ⁾ ⁽⁴⁾
. Triton X-100 in 0.01 N HCl provided the highest solubility
(0.65 mg/mL), ⁽ᵇ⁾ ⁽⁴⁾

The drug solubility data in different surfactants are summarized in the following table.

Drug Substance Lot	Surfactant	Surfactant Concentration (%)	Solubility (mg/mL)
0904773			(b) (4)
0904813			

Note: Solubility determined at 2 hours, 37°C.

Reviewer's Comments:

- *Dissolution profile data were not provided to justify the medium selection as requested during IND meetings with the Applicant. Although solubility considerations are important, the optimal medium should also use the minimum amount of surfactant necessary to achieve robust dissolution performance of the drug product. For Triton X-100, a concentration of* (b) (4) *was sufficient to meet the sink condition requirement (i.e., 3X saturation concentration), which was calculated by this reviewer as* (b) (4).

- *The rationale for selecting a non-ionic surfactant and identifying a low pH dissolution medium for use is acceptable. However, comparative dissolution profiles with and without surfactant should be provided* (b) (4)

Apparatus/Agitation

The dissolution apparatus type and paddle agitation speed were evaluated by using 80 mg capsules (Lot L0301013) with 0.01N HCl with 0.5% Trition X-100. The (b) (4) were screened. The resulting dissolution profiles are illustrated in the following figures.

Mean Dissolution Profiles, 80 mg Capsule Lot L0301013 in 0.01N HCl with 0.5% Triton X-100 Using Different Apparatus
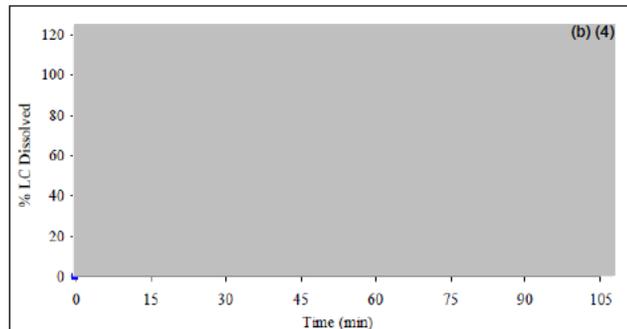
Mean Dissolution Profiles, 80 mg Capsule Lot L0301013 in 0.01N HCl with 0.5% Triton X-100, USP Apparatus 2, Different Paddle Speed
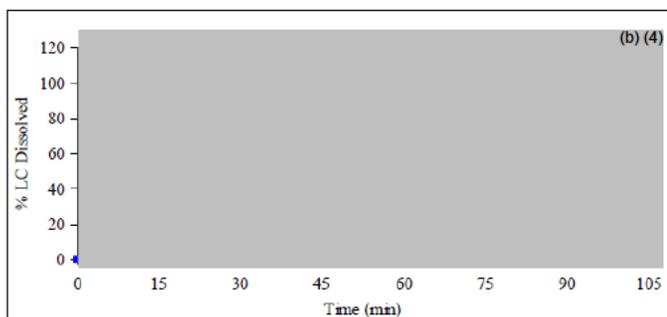
Reviewer's Comments:

- *Complete dissolution data (individuals, mean, RSDs) were not provided as requested for review. Based on the plots, the dissolution rate was rapid* (b) (4) *within 15 minutes) using the* (b) (4) *Also, the error bars were noticeably higher when operating at* (b) (4) *compared with* (b) (4) *and dissolution was incomplete when using a* (b) (4) *paddle speed. Although incomplete, the dissolution plots support the selection of 75 rpm as optimal for paddle rotation.*

- *There was no appreciable difference between the* (b) (4)*. The Applicant stated that USP 2 was selected due to lower data variability; however, the complete dissolution data are needed to verify this conclusion.*

2.2 Dissolution Acceptance Limits

The proposed dissolution tolerance limit is $Q =$ (b) (4). The proposed acceptance criterion was based on lot release and stability testing and registration lots and is claimed to be consistent with the requirements of USP <1092>. For the 20-mg capsules, the mean dissolution profiles for seven lots were summarized graphically. In addition, the mean dissolution profiles for one lot on stability (up to 12 months at long-term and accelerated storage conditions) were plotted. For the 80 mg capsules, the mean dissolution profiles from five lots at release were plotted. In addition, the mean dissolution profiles for one lot on stability (up to 9 months at long-term and accelerated conditions) were plotted.

These lots were manufactured at the intended commercial scale and at the commercial manufacturing site.

The dissolution plots for the 20 mg and 80 mg capsules are illustrated in the following figures.

Mean Dissolution Profiles at Release, 20 mg Capsules
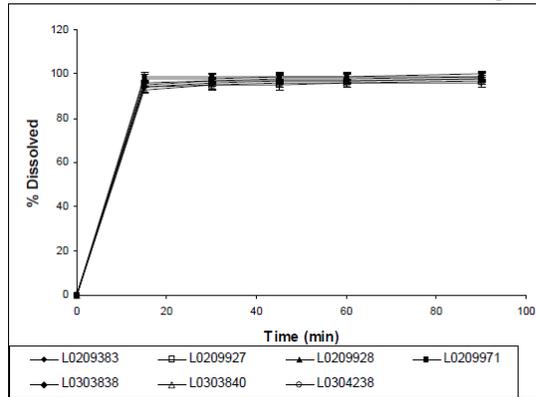
Mean Dissolution Profiles on Stability, 20 mg Capsules
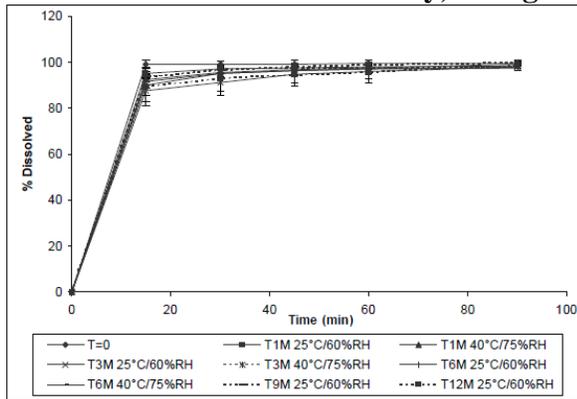
Mean Dissolution Profiles at Release, 80 mg Capsules
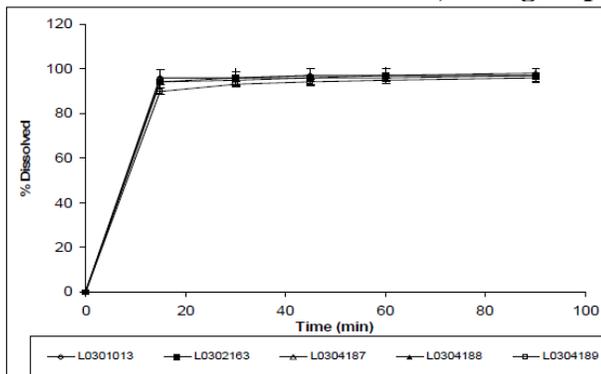
Mean Dissolution Profiles on Stability, 80 mg Capsules
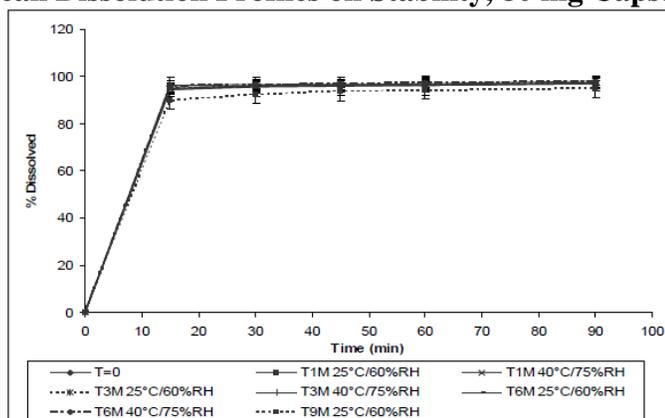
A tabular summary of product dissolution data was also submitted in the batch analysis section (3.2.P.5.4), 12 lots of 20 mg capsules and 11 lots of 80 mg capsules.

Reviewer's Comments:

- *It is acknowledged that the dissolution method changed throughout the clinical development program. However, only the lots using the proposed regulatory method are relevant for setting an acceptance criterion. The seven 20 mg and five 80 mg lots placed on stability were tested using the proposed dissolution method. However, 23 lots of capsules were manufactured, placed on stability, and used in clinical studies. Product release and stability data for all lots were not submitted to the NDA. Multipoint dissolution data (15, 30, 45, 60, and 90 min) were included in the stability summary tables to permit a more comprehensive review of the dissolution performance through the product's proposed shelf life.*

- *A statistical summary of the overall mean drug dissolution at the various sampling time points would be helpful to better understand both the variability and process capability with respect to drug dissolution testing. As presented, the proposed dissolution method clearly supports* (b) (4) *dissolution with 15 minutes. Therefore, the proposed limit of Q=* (b) (4) *does not provide an acceptable level of product quality assurance. This issue will be reviewed further during the NDA review period.*

2.3 Dissolution Method Validation

2.3.1 Method Discriminating Studies

Studies evaluating the discriminating ability of the proposed dissolution method and acceptance criterion were not summarized in the dissolution method development summary section of the NDA (3.2.P.5.2.4.1). These method evaluation studies are required as part of dissolution method development under USP<1092> and relevant FDA guidance documents. In addition, the Applicant was advised during pre-NDA meeting discussions to include the data assessing the discriminating ability of the dissolution method in the NDA.

Referencing the product and process development NDA sections (3.2.P.2.2 and 3.2.P.2.3), dissolution (*USP 2, 0.01N HCl with 0.5% TritonX-100, 75 rpm*) was used as the output measure for evaluating the impact of certain manufacturing and formulation changes during optimization work. These data are summarized in the subsequent paragraphs as a measure of the proposed method's discriminating ability.

Drug Substance (b) (4)

1. 20 mg Capsules

(b) (4)

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

2.3.2   Analytical Method Validation

Analytical method validation was completed, as reported in method validation report KCM-2011-0543-ANA-Disso. The report references validation for method QM 4028; however, it is noted that method QM4028 is the same as QM4334. The only difference is the way in with the dosage strength is expressed.

Method validation parameters included specificity, linearity, accuracy, repeatability, intermediate precision, instrument precision, solution stability, filter evaluation, dissolution robustness, and HPLC robustness.

Reviewer's Comments: The review of the analytical method validation report has not been assigned to ONDQA-Biopharmaceutics to address; however, sample solution stability was reviewed to verify acceptable stability for the selected method parameters.   The sample solution stability was acceptable, with >99% recovery through 6 days.

(NDA 203756)

It was noted in the validation report that method robustness was not evaluated for sampling at 15 and 30 minutes, which is necessary to evaluate the method's performance for both profile and single point analysis. Comments are outlined at the end of this initial assessment for the Applicant to address. This issue will be evaluated further during the review cycle.

Reference is also made to the assigned CMC Reviewer's review for additional comments.

2.4   Product Dissolution Stability

Twelve lots (seven lots of 20-mg capsules and five lots of 80-mg capsules) of cabozantinib drug product have been placed on the long-term storage condition of 25 °C/60% RH, and accelerated condition of 40 °C/75% RH in accordance with ICH guidelines. These drug-product lots were manufactured with a process representative of the final manufacturing process and from representative batches of drug substance. All these lots were manufactured at the intended commercial scale (one lot of 80 mg capsules was manufactured at two-fold the intended commercial scale) and at the commercial manufacturing site (b) (4)

A tabular summary of the stability lots is provided below.

Stability Lots Testing for the 20 mg Capsules

Capsule Lot No./ Study Type[a]	DS Batch No.	Date of Mfg	Lot Size (Capsules)	Container/ Closure	Initial Date of Stability	Stability at Time of Initial Submission
			(b) (4)			
L0209383 (REP)	0904750	27-Aug-2009		Bottle (b) (4)	20-Nov-2009	24 months
L0209927 (REP)	0904750	12-Nov-2009		Bottle (b) (4)	5-Feb-2010	24 months
L0209928 (REP)	0904773	13-Nov-2009		Bottle (b) (4)	5-Feb-2010	24 months
L0209971 (REP)	0904774	2-Dec-2009		Bottle (b) (4)	5-Feb-2010	24 months
				Blister Card[b]	5-May-2010	21 months
L0303838 (RSL)	0904773	2-Dec-2010		Blister Card	23-Feb-2011	9 months
L0304238 (RSL)	0904813	17-Dec-2010		Blister Card	23-Feb-2011	9 months
L0303840 (RSL)	1004899	7-Dec-2010		Blister Card	23-Feb-2011	9 months

ct, count; DS, Drug Substance; Mfg, manufacturing; REP, representative lot; RSL, registration lot.
[a] The only difference between the REP and RSL lots is the designation of RSL lots as registration lots.
[b] A portion of the samples in bottles stored at controlled room temperature for 3 months was repackaged into the blister packages.

Stability Lots Testing for the 80 mg Capsules

Capsule Lot No./ Study Type[a]	DS Batch No.	Date of Mfg	Lot Size (Capsules)	Container/ Closure	Initial Date of Stability	Stability at Time of Initial Submission
L0301013 (REP)	0904773	18-Feb-2010	(b) (4)	Bottle (b) (4)	28-Apr-2010	18 months
				Blister Card	5-May-2010	18 months
L0302163 (REP)	0904774 0904813	21-Jun-2010		Bottle (b) (4)	27-Aug-2010	12 months
L0304187 (RSL)	0904773	6-Jan-2011		Blister Card	23-Feb-2011	9 months
L0304188 (RSL)	0904813	7-Jan-2011		Blister Card	23-Feb-2011	9 months
L0304189 (RSL)	1004899	10-Jan-2011		Blister Card	23-Feb-2011	9 months

ct, count; DS, Drug Substance; Mfg, manufacturing; REP, representative lot; RSL, registration lot.
[a] The only difference between the REP and RSL lots is the designation of RSL lots as registration lots.

Reviewer's Comments: *As noted previously, dissolution profile data (mean, min, and max) were provided for stability lots, but RSDs were not specified and some data had wide min- max ranges. The Applicant used a stability dissolution specification of Q=* (b) (4) *for stability testing. On the basis of these dissolution data, a tighter criterion is proposed for commercial product. All stability lots complied with the Q=* (b) (4) *criterion; however, this limit is not the most optimal for product quality assurance. Mean dissolution was* (b) (4) *at 15 minutes across all samples and tested conditions.*

3.0 INITIAL ASSESMENT CONCLUSIONS AND RECOMMENDATIONS

From ONDQA-Biopharmaceutics perspective, the NDA is considered fileable. However, several review issues have been identified and additional information is requested from the Applicant as follows.

Please convey the following comments to the Applicant.

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

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

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

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

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

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

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

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

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

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