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APPLICATION NUMBER:

208692Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	208692
Submission Date	December 22, 2015
Submission Type; Code	Original NDA; Type 3- New Dosage Form
Brand Name	CABOMETYX™
Generic Name	Cabozantinib
Dosage Form / Strength	Oral Tablets (20 mg, 40 mg, and 60 mg)
Dosing Regimen	60 mg Orally Daily
Indication	Advanced renal cell carcinoma (RCC)
Related IND	72596
Applicant	Exelixis, Inc.
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1. EXECUTIVE SUMMARY

Cabozantinib is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs) that was approved for the treatment of medullary thyroid cancer (MTC) in 2012 (as COMETRIQ™) under NDA203756. The approved dosing regimen for COMETRIQ was 140 mg (capsules) administered orally once daily, taken at least 1 hour before or 2 hours after a meal. A post-marketing requirement (PMR) was issued to evaluate a lower dose ((b) (4) (b) (4) .

In the current submission for a new dosage form and a new indication, the Applicant seeks the approval of cabozantinib tablet (CABOMETYX™) for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy. The proposed dosing regimen for CABOMETYX was 60 mg tablet administered orally once daily, taken at least 1 hour before or 2 hours after a meal.

In a randomized Phase 3 trial (Study XL184-308), CABOMETYX treatment (60 mg tablet QD) significantly improved progression-free survival (7.4 months vs 3.8 month) with a hazard ratio of 0.58 (95% confidence interval [CI]: 0.45, 0.74; P < 0.001), and overall survival (21.4 months vs 16.5 months) with a hazard ratio of 0.66 (95% CI: 0.53, 0.83, p=0.0003), as well as objective response rate (17% vs 3%, P < 0.0001) over everolimus treatment. The dose was reduced in 60% of patients, with 20% of patients received 20 mg CABOMETYX as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), fatigue, and hypertension.

CABOMETYX dose selection of 60 mg QD for the RCC indication is acceptable from a clinical pharmacology perspective. A dose higher than 60 mg QD is not considered appropriate, given dose reductions occurred in 60% patients at 60 mg QD. Modeling and simulations indicated that lower starting doses such as 40 mg or 20 mg QD likely compromises efficacy though the incidences of dose reductions may be lower than 60 mg QD dose. Taking the cabozantinib concentration of 1125 ng/mL (median concentration at 60 mg QD dose) as the reference, the hazard ratio would be 1.1 and 1.39 if the exposure was reduced to 67% and 33% of the reference concentration, respectively. Reduction in tumor size in the 20 mg QD (median percent change from baseline = -4.45%) and 40 mg QD (-9.1%) starting dose groups were predicted to be smaller than that in the 60 mg QD dose group (-11.9%). Objective response rates (ORR) in the 40 mg QD (15.6%) and 20 mg QD (8.70%) starting dose groups were predicted lower than that in the 60 mg QD (19.1%) dose groups.

Cross-study PK analysis indicated similar steady-state exposures ($C_{trough,ss}$) at different doses across patient populations of medullary thyroid cancer (MTC, 140 mg capsules), advanced renal cell carcinoma (RCC, 60 mg tablet), and castration-resistant prostate cancer (CRPC, 60 mg tablet). Correspondingly, the apparent oral clearance predicted by population PK model was estimated as 4.4 L/hr in MTC and 2.2 L/hr in RCC. This result is unexpected, as C_{max} and AUC of the tablet formulation (CABOMETYX) and the capsule formulation (COMETRIQ) were similar following a single 140 mg dose. Therefore, a post-marketing commitment (PMC) will be requested to evaluate the potential impact of (b) (4) on the PK of cabozantinib (b) (4) PK data from different patient populations and healthy subjects in an integrated population PK model.

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 and a post-marketing commitment (PMC). See Section 3 for detailed labeling recommendations.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Dose selection	☒ Yes ☐ No Refer to **Section 2.2.3**	The proposed dosing regimen of 60 mg cabozantinib oral tablet QD is acceptable from a clinical pharmacology perspective. Cabozantinib treatment with 60 mg QD oral tablet significantly improved progression-free survival (7.4 months vs 3.8 month) and overall survival (21.4 months vs 16.5 months), as well as objective response rate (17% vs 3%) over everolimus control arm in a randomized Phase 3 trial (Study XL184-308). Exposure-response analyses support the dose selection of 60 mg QD. Doses higher than 60 mg QD are not considered, given that dose reductions are needed in 60% patients at 60 mg QD. Simulation suggested that lower starting doses such as 40 mg or 20 mg QD likely compromise efficacy though the incidence of dose reductions may be lower than 60 mg QD dose.
Formulation comparison and systemic exposure at steady-state	☐ Yes ☒ No Refer to **Sections 2.2.4.3, 2.2.4.4, 2.5.4**	Following a single 140 mg dose administration of cabozantinib tablet and capsule formulations, the extent of exposure (AUC_{0-t} and AUC_{0-inf}) was similar for both formulations, with the 90% CIs of the geometric least square mean ratio within 80.00% - 125.00% criteria. However, for C_{max}, the upper limit of the 90% CI around the ratio of LS means (131.65%) was outside the 80.00% -125.00% criteria. Therefore, the systemic exposure following cabozantinib capsule and tablet formulations are similar, though bioequivalence could not be concluded due to small excursion of C_{max} beyond 125% criterion. Similar steady-state exposures ($C_{trough,ss}$) were observed at different doses across patient populations of medullary thyroid cancer (MTC, 140 mg capsules), advanced renal cell carcinoma (RCC, 60 mg tablet), and castration-resistant prostate cancer (CRPC, 60 mg tablet). Correspondingly, the apparent oral clearance predicted by population PK model is 4.4 L/hr in MTC and 2.2 L/hr in RCC. This result is unexpected, as $C_{trough,ss}$ in MTC patients with 140 mg dose is expected to be higher than in RCC patients with 60 mg dose, given similar exposure (C_{max} and AUC) of capsule and tablet formulations after a single dose of 140 mg. PMC: A PMC will be requested to evaluate the potential impact of (b) (4) (b) (4) on the PK of cabozantinib (b) (4) (b) (4) PK data from different patient populations and healthy subjects in an integrated population PK model.
Dose adjustment in patients with hepatic impairment	☒ Yes ☐ No Refer to **Section 2.3.2.3**	The results of hepatic impairment trial (Study XL184-003) suggested after a single oral administration of a 60 mg cabozantinib in capsule form, the geometric LSM ratios for exposure (AUC_{0-inf}) were increased by approximately 81% and 63% in subjects with mild and moderate hepatic impairment, respectively, relative to matched controls. C_{max} values were not markedly different in mild and moderate hepatic impairment relative to matched controls (119% and 103%, respectively).

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
		PMR fulfillment: The fulfillment of this PMR trial has been concluded under NDA203756. Labeling recommendation: To recommend 40 mg QD as the starting dose in patients with mild or moderate hepatic impairment.
Dose adjustment in patients with renal impairment	☒ Yes ☐ No Refer to **Section 2.3.2.2**	The Labeling language for MTC indication stated that no dose adjustment is recommended in patients with mild to moderate renal impairment based on population PK analysis. In the current submission for RCC, results of a dedicated renal impairment study suggested that C_{max} and AUC values were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. However, both C_{max} and AUC values were similar between the moderate impairment and control cohorts, with a less than 7% difference in exposure parameters. Labeling recommendation: No dose adjustment is needed for patients with mild to moderate renal impairment.
Gastric pH elevating agents	☒ Yes ☐ No Refer to **Sections 2.1.1; 2.4.1.2**	Co-administration of multiple doses of esomeprazole (40 mg QD) with a single 100 mg dose of cabozantinib did not decrease cabozantinib plasma exposure. The 90% CIs for the ln-transformed ratio of the test to reference treatment for both AUC_{0-t} and AUC_{0-inf} were within the limits of 80% - 125%. PMR fulfillment: The PMR issued under NDA203756 has been fulfilled (as documented under NDA203756). Labeling recommendation: To describe the results in 12.3 Pharmacokinetics section.

Signatures:

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1.2 CLINICAL PHARMACOLOGY SUMMARY

Cabozantinib is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs) that was approved for the treatment of medullary thyroid cancer (MTC) in 2012 (as COMETRIQ™) under NDA203756. The approved dosing regimen for COMETRIQ was 140 mg (capsules) administered orally once daily (QD), taken at least 1 hour before or 2 hours after a meal. A post-marketing requirement (PMR) was issued to evaluate a lower efficacious dose (b) (4) (b) (4)

In the current submission of a new dosage form for a new indication, the Applicant seeks the approval of Cabozantinib tablet (CABOMETYX™) for the treatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy. The proposed dosing regimen for CABOMETYX is 60 mg (tablet) QD, taken at least 1 hour before or 2 hours after a meal.

The pivotal Phase 3 trial (Study XL184-308) was a randomized (1:1), open-label, multicenter study of CABOMETYX (administered orally at 60 mg daily) versus everolimus conducted in patients (N=658) with advanced RCC who had received at least 1 prior anti-angiogenic therapy. Cabozantinib treatment with 60 mg oral tablet significantly improved progression-free survival (7.4 months vs 3.8 month) with a hazard ratio of 0.58 (95% CI: 0.45, 0.74; P < 0.001), and overall survival (21.4 months vs 16.5 months) with a hazard ratio of 0.66 (95% CI: 0.53, 0.83, p=0.0003), as well as objective response rate (17% vs 3%, P < 0.0001) over everolimus treatment in a randomized Phase 3 trial (Study XL184-308).

Formulation comparison: Following a single 140 mg dose administration of cabozantinib tablet and capsule formulations, the extent of exposure (AUC_{0-t} and AUC_{0-inf}) was similar for both formulations, with the 90% CIs of the geometric least square mean ratio within the recommended bioequivalence criteria of 80.00% - 125.00%. However, for C_{max}, the upper limit of the 90% CI (131.65%) was outside upper limit of 125.00%. Therefore, the systemic exposure following cabozantinib capsule and tablet formulations are similar, though bioequivalence could not be concluded due to small excursion of C_{max} beyond 125% criterion.

Population PK: A population PK analysis of cabozantinib was performed using data from 318 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 60 mg, 40 mg, and 20 mg. The predicted terminal half-life is approximately 99 hours, the oral volume of distribution (Vz/F) is approximately 319 L, and the apparent clearance (CL/F) at steady-state is estimated to be 2.2 L/hr. It is noted that the estimated PK parameters are different from MTC population, where 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. Steady-state exposure ($C_{min,ss}$) were similar in RCC (1260 ng/mL, 44.4% CV) and in MTC (1380 ng/mL, 53% CV) following different formulations at different doses of cabozantinib in RCC (60 mg once daily tablet) and MTC (140 mg once daily capsule) patient populations.

Absorption:

Food effect: The food effect on the PK of cabozantinib with the tablet formulation is unknown. When cabozantinib capsule 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. The tablet will be administered on an empty stomach.

Impact of gastric pH elevating agents: The results of a PMR trial suggested that co-administration of multiple doses of esomeprazole (40 mg QD) with a single 100 mg dose of cabozantinib did not decrease cabozantinib plasma exposure. The PMR issued under NDA203756 has been fulfilled (as documented under NDA203756).

Specific Populations:

Hepatic impairment: The results of a PMR hepatic impairment trial (Study XL184-003) suggested after a single oral administration of a 60 mg cabozantinib in capsule form, the geometric LSM ratios for exposure ($AUC_{0\text{-}inf}$) were increased by approximately 81% and 63% in subjects with mild and moderate hepatic impairment, respectively, relative to matched controls. C_{max} values were not markedly different in mild and moderate hepatic impairment relative to matched controls (119% and 103%, respectively). The fulfillment of this PMR trial has been concluded under NDA203756.

Renal impairment: The Labeling language for MTC indication stated that no dose adjustment is recommended in patients with mild to moderate renal impairment based on population PK analysis. In the current submission for RCC, the results of a dedicated renal impairment study suggested that C_{max} and AUC values were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. However, both C_{max} and AUC values were similar between the moderate impairment and control cohorts, with a less than 7% difference in exposure parameters. Therefore, the impact of renal impairment on the PK of cabozantinib is considered low.

Exposure-Response (E-R) Relationship: Dose selection of 60 mg QD is acceptable from a clinical pharmacology perspective. A dose higher than 60 mg QD is not considered appropriate, given dose reductions occurred in 60% patients at 60 mg QD. Modeling and simulations indicated that lower starting doses such as 40 mg or 20 mg QD likely compromises efficacy though the incidences of dose reductions may be lower than 60 mg QD dose. Taking the cabozantinib concentration of 1125 ng/mL (60 mg) as the reference, the hazard ratio would be 1.1 and 1.39 if the exposure was reduced to 67% and 33% of the reference concentration, respectively. Reduction in tumor size in the 20 mg QD (median percent change from baseline = -4.45%) and 40 mg QD (-9.1%) starting dose groups were predicted to be smaller than that in the 60 mg QD dose group (-11.9%). Objective response rates (ORR) in the 40 mg QD (15.6%) and 20 mg QD (8.70%) starting dose groups were predicted lower than that in the 60 mg QD (19.1%) dose groups.

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?

As the drug substance (DS), cabozantinib (*S*)-malate salt, demonstrate a pH- dependant solubility profile (b) (4) In order to determine the impact of gastric pH elevating agent on the PK of cabozantinib, a post-marketing requirement (PMR) was issued when cabozantinib was approved for COMETRIQ™ under original NDA203756 (PMR1970-7), as below:

> "A drug-drug interaction clinical trial to evaluate if gastric pH elevating agents alter the bioavailability of cabozantinib. The trial may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitor (PPI) on the single-dose exposure of cabozantinib. In the event that concomitant administration of a PPI has a large effect on cabozantinib exposure following single-dose administration, H_2 antagonist and an antacid will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect exposure differences. The trial results should allow for a determination on how to dose cabozantinib with regard to concomitant gastric pH elevating agents.

The trial has been completed and submitted to FDA for review. The study results suggested that esomeprazole administration had no clinically-relevant effect on cabozantinib PK (See Section 2.4.1.2): It was concluded that this PMR has been fulfilled under NDA203756 (see Clinical Pharmacology review by Dr. Jun Yang dated October 1, 2014 in DARRTs).

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. I*n 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 advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosing regimen for cabozantinib is CABOMETYX 60 mg (tablet) administered orally once daily (QD), taken at least 1 hour before (b) (4) 2 hours after a meal. The 60 mg daily dose can be reduced to 40 mg and then to 20 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 majority of the clinical pharmacology content of cabozantinib has been reviewed under NDA203756 for the treatment of medullary thyroid cancer (MTC) in 2012 (as COMETRIQ). In this submission, the Applicant intends to update the label with the new clinical pharmacology related information obtained from a Phase 1 PK study (XL184-020) of three tablet strengths (20, 40, and 60 mg FBE) in healthy adult subjects in which dose proportionality was demonstrated; a hepatic impairment study (XL184-003) and a renal impairment (XL184-017), and a drug-drug interaction study evaluating the effect of gastric pH modification (XL184-018). The results of PMR trials XL184-003 and 184-018 have been reviewed by FDA and concluded the PMRs have been fulfilled under NDA203756 for MTC.

A population pharmacokinetic analysis of cabozantinib was performed using data collected from 282 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 20 mg, 40 mg, and 60 mg. Population exposure-response models were also developed to characterize the relationship between cabozantinib exposure and various efficacy and safety endpoints in subjects with renal cell carcinoma (RCC).

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?

Progression-free survival (PFS) was selected as the primary endpoint for this trial and objective response rate (ORR) and OS were included as the secondary endpoints. PFS is considered an acceptable endpoint for oncology studies and has been used as the primary efficacy endpoint for several agents approved for RCC including sorafenib, sunitinib, everolimus, bevacizumab, pazopanib, and axitinib.

2.2.3 Exposure-response Analyses

Exposure-response analyses base on the pivotal Trial XL184-308 indicated that a saturable exposure-efficacy relationship for PFS and anti-tumor activity, and positive exposure-safety relationships across the exposure range under 60 mg QD.

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

Yes, the proposed dosing regimen is supported by the ER relationship of efficacy. A lower dose may result in compromised benefit in terms of the primary endpoint, progression-free survival (PFS), as well as the drug anti-tumor activity in terms of tumor size and Objective Response Rate (ORR).

Exposure-PFS analysis

On the basis of ER analysis, there appears to a positive and saturable exposure-efficacy relationship between cabozantinib exposure and PFS or anti-tumor activity under the exposure range of 60 mg QD and lower dose levels for the proposed indication.

In the exposure-PFS relationship analysis, the relationship was explored by Cox regression model where the drug exposure effect on hazard was an E_{max} function of the PPK model-

predicted cabozantinib exposure. On each day, the average cabozantinib concentration over its prior three weeks was calculated, and employed as the exposure metrics (CAVG3W).

The model indicted that exposure under lower dose levels (eg. 40 mg or 20 mg) may result in an inferior PFS compared with 60 mg QD. Taking the cabozantinib concentration of 1125 ng/mL (60 mg) as the reference, the hazard ratio would be 1.1 and 1.39 if the exposure was reduced to 67% and 33% of the reference concentration, respectively (Table 1). The potential loss of efficacy at lower dose levels suggest that the proposed cabozantinib dose (60 mg QD) is reasonable based on this exposure-PFS analysis.

Table 1: E_{max} Model Hazard Ratios for Progression Free Survival

CAVG3W[a]	HR Relative to CAVG3W = 1125 mg/mL (60 mg QD)
375 ng/mL (20 mg QD)	1.39
750 ng/mL (40 mg QD)	1.10

HR = hazard ratio

[a]Cabozantinib concentrations correspond to model predicted typical individual steady-state average concentrations for the 20 mg and 40 mg once daily dosing regimens.

Source: Adapted from the SSynopsis of Exposure-Response Report, Study No. XL184-308.ER.001, Table 14

HR = hazard ratio; LL = lower confidence limit; UL = upper confidence limit

[a]Cabozantinib concentrations correspond to model predicted typical individual steady-state average concentrations for the 20 mg, 40 mg, and 60 mg once daily dosing regimens.

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001, Table 14

Exposure-tumor size analysis

An exposure-tumor size model was developed by the Applicant per the pharmacometrics reviewer's request to predict the tumor dynamics at different lower dose levels (40 mg and 20 mg) with dose interruption/reduction taken into account. The model is composed of a first-order growth rate, nonlinear cabozantinib drug effect, and a resistance component. The drug effect on tumor suppression was described as an E_{max} function with EC_{50} as 251 ng/mL. The virtual dosing history was simulated using Applicant's exposure-dose-altering model. Based on the simulated dosing history, the tumor dynamics was simulated to evaluate the potential loss of efficacy at different starting dose levels.

For starting dose levels at 20 mg, 40 mg, and 60 mg, the median percent change from baseline tumor size is shown in Figure 1. Subjects in the 60 mg QD dose group are predicted to have greater reduction in tumor size (median percent change from baseline = -11.9%) relative to the 40 mg and 20 mg QD dose groups. Subjects in the 40 mg QD dose group are predicted to have a lower median percent reduction from baseline (-9.1% for 40 mg and -4.45% for 20 mg) tumor sizes relative to the case in the 60 mg starting dose group.

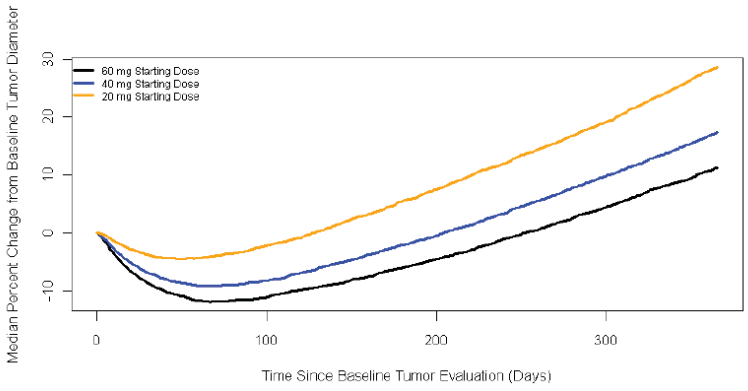


Figure 1: Comparison of Predicted Median Percent Change from Baseline Tumor Diameter for 20 mg, 40 mg, and 60 mg Cabozantinib Starting Doses

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

Based on the simulated tumor size, best overall response (BOR) was computed for each subject. The predicted percentage of subjects with different BOR for a 20 mg, 40 mg, and 60 mg starting dose treatment regimen are shown in Table 2. Objective response rates (ORR) in the 40 mg QD (15.6%) and 20 mg QD (8.70%) starting dose groups were predicted lower than that in the 60 mg QD (19.1%) dose groups.

Table 2: Simulated ORR based on model predicted tumor dynamics

Best Overall Response (BOR)	20 mg Starting Dose (%)	40 mg Starting Dose (%)	60 mg Starting Dose (%)
Complete Response (CR)	0.10	0.00	0.00
Partial Response (PR)	8.60	15.6	19.10
Stable Disease (SD)	81.1	76.3	73.40
Progressive Disease (PD)	10.2	8.10	7.50

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

2.2.3.2 What are the characteristics of the exposure-response relationships for safety?

Exposure safety analysis indicates that patients with higher drug exposure tend to experience adverse reactions and dose modifications earlier.

The exploratory KM plot for time to first incidence of different AE types shows the following results (Figure 2):

- Fatigue/Asthenia: The result shows an increased fraction of subjects with fatigue or asthenia in the highest exposure tertile.
- Nausea/Vomiting: The relatively small fraction of subjects that experienced nausea or vomiting was observed.
- PPES: The fraction of subjects with PPE increases with higher exposure tertiles.
- Diarrhea: The fraction of subjects with diarrhea increases with higher exposure tertiles.

- Stomatitis: The plot highlights the relatively small fraction of subjects that experienced stomatitis.
- Hypertension: The fraction of subjects with hypertension is increased in the two larger exposure tertiles relative to the lowest exposure tertile. The fractions of subjects with hypertension are similar for the two largest exposure tertiles.

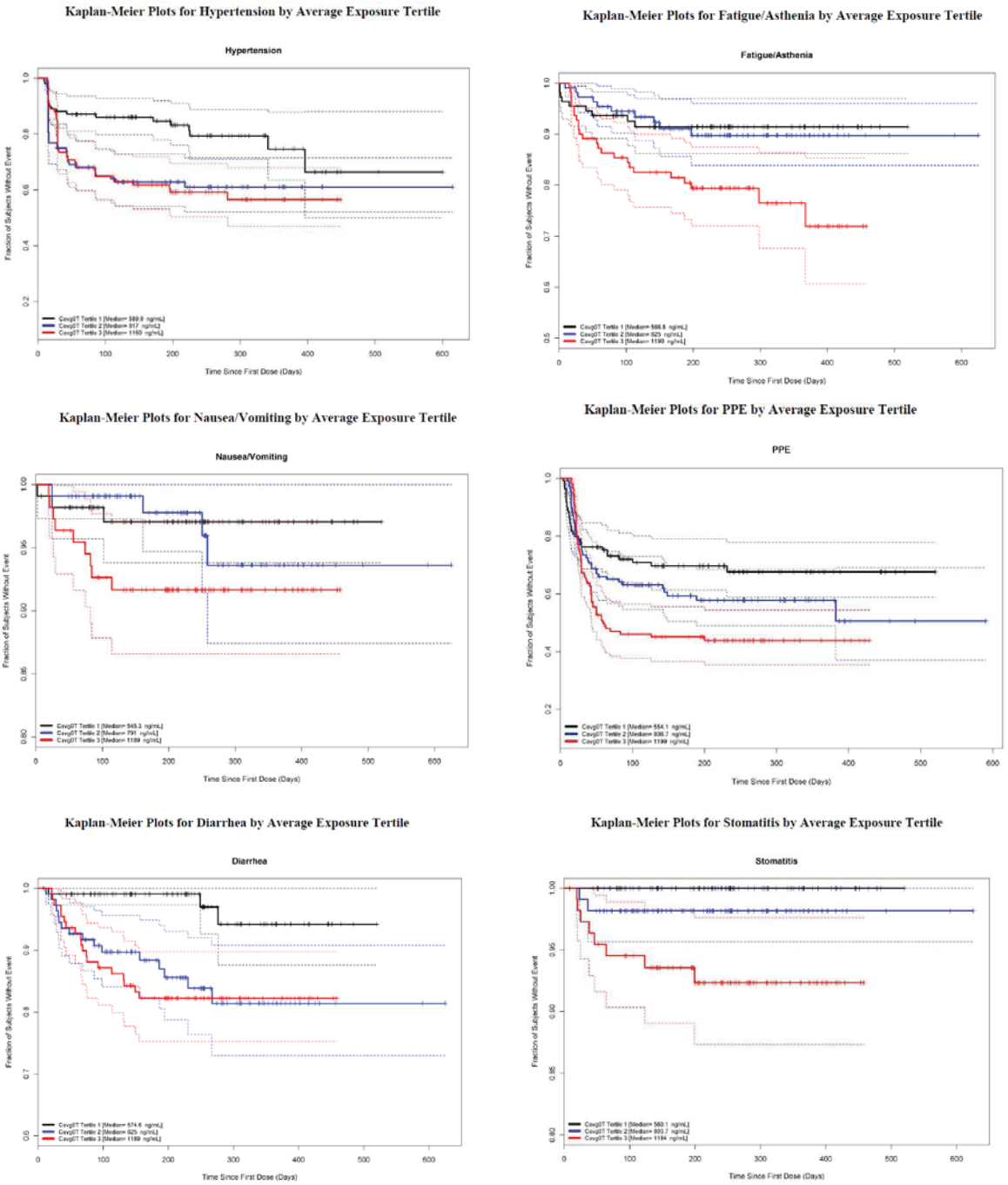


Figure 2: Kaplan-Meier Plots for Adverse Reactions by Average Exposure Tertile

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

To evaluate the association between dose modification and individual exposure, a longitudinal exposure dose-altering AE model was developed. The survival model for repeated events showed a significant relationship between the time to dose modifications and individual-predicted cabozantinib concentration over the 24 hours prior to time equal t (CAVG1D). Using this model, the virtual dosing history was simulated at different starting dose levels (20 mg and 40 mg), to evaluate the potential improvement in reducing the incidence of dose interruption/reduction (Table 3).

Table 3: Simulation of Dosing History: Percentage of Subjects on 20 mg, 40 mg, or 60 mg Once Daily Treatment Regimens at Month 6 and Month 12

Time Point	Dose (mg)	Observed (%)	Simulated 20 mg Starting Dose (%)	Simulated 40 mg Starting Dose (%)	Simulated 60 mg Starting Dose (%)
6 Months	20	15.81	100	24.10	9.80
6 Months	40	35.87	NA	75.90	35.10
6 Months	60	48.02	NA	NA	55.10
12 Months	20	17.02	100	36.70	20.80
12 Months	40	39.82	NA	63.30	43.30
12 Months	60	42.86	NA	NA	35.90

NA = not applicable

Numbers in the table are the percentage of subjects that stay on 20 mg, 40 mg, and 60 mg (excluding dose interruptions) at 6 months and 12 months in Study 308, the simulated 20 mg starting dose scenario, the simulated 40 mg starting dose scenario, and the simulated 60 mg starting dose scenario.

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

2.2.3.3 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?

Yes. Exposure-response analyses support the dose selection of 60 mg QD. Doses higher than 60 mg QD is not considered, given a dose reduction in 60% patients are needed at 60 mg QD. Modeling and simulations indicated that lower starting doses such as 40 mg or 20 mg QD likely compromises efficacy though the incidences of dose reductions may be lower than 60 mg QD dose.

There is no unresolved dosing or administration issue in the RCC indication.

2.2.4 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.4.1 What are the single-dose and multiple-dose pharmacokinetics?

Single-dose PK

The PK parameters of cabozantinib in healthy subjects following a single 20 mg, 40 mg (Study Report XL184-020), 60 mg (Study Reports XL184-003, XL184-017, and XL184-020), 80 mg (Study XL184-018), or 140 mg (Study XL184-010) tablet formulation dose are displayed in Table 13.

After a single dose of cabozantinib, absorption had a median T_{max} of 3 to 5 hours (range: 1-120). Across these studies, some individual subjects had a prolonged absorption phase with C_{max} occurring as late as 120 hours after dosing. Following the absorption peak, plasma concentrations declined slowly with a mean terminal $t_{1/2}$ of 111 to 131 hours across the studies.

Table 4: Single Dose Mean (%CV) PK Parameters of Cabozantinib After a Tablet Dose of 20, 40, 60, 80 or 140 mg FBE in Healthy Subjects

Study	Study XL184-010 BE	Study XL184-018[b] Gastric pH Effect	Study XL184-003[b] Hepatic Impaired	Study XL184-017[b] Renal Impaired	Study XL184-020 Dose-Linearity		
Population	HS	HS	HS	HS	HS	HS	HS
Formulation	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Dose (mg)	140	80	60	60	60	40	20
Food intake	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose		
N	72	21	10	10	21	21	21
C_{max}, ng/mL	702 (54)	647 (30)	353 (21)	341 (28)	343 (41)	239 (56)	117 (72)
T_{max}, h[a]	3 (2, 24)	3 (2, 5)	4 (2, 5)	4 (3.00, 4.03)	4 (2, 8)	3 (2, 48)	3 (1, 120)
AUC_{0-t}, h·ng/mL	61900 (44)	55800 (25)	31100 (27)	29720 (26)	29800 (38)	19800 (42)	9290 (50)
AUC_{0-24}, h·ng/mL	8140 (47)	7580 (31)	NR	3915 (20)	3880 (33)	2620 (53)	1280 (59)
AUC_{0-inf}, h·ng/mL	65800 (46)	58900 (25)	32700 (29)	32030 (27)	32100 (39)	21100 (42)	10400 (48)
$t_{½}$, h	115 (31)	117 (25)	108 (26)	126 (22)	111 (18)	122 (22)	131 (25)

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; C_{max}, maximum observed concentration; CV, coefficient of variation; FBE, freebase equivalent; T_{max}, time of the maximum concentration; $t_{1/2}$, apparent terminal elimination half-life; BE, bioequivalence; HS, healthy subject; NR, not reported

[a] Median (range) were reported for T_{max};

[b] Data are for the Reference (no interacting treatment) group or the matched healthy subject cohort

Source: Study Reports XL184-003, XL184-010, XL184-017, XL184-018, and XL184-020

Multiple Dose PK

Intensive PK is not available for tablet formulation. In the pivotal Phase 3 study XL184-308 in subjects with RCC, mean steady-state plasma concentrations for cabozantinib for subjects receiving at least 14 of 15 60 mg/day doses over the 15 days prior to PK sampling for males and females combined were 1260 ng/mL (±559) (n=211) at Week 5 Day 1, and 1050 ng/mL (±504) at Week 9 Day 1. PK samples were taken approximately 8 hours or more after the previous dose of cabozantinib for the Week 5 Day 1 and Week 9 Day 1 visits. Accurate timing of the plasma PK sample collection was not deemed critical to the steady-state PK evaluation given the long half-life and low fluctuation of steady-state cabozantinib concentrations.

2.2.4.2 What are the characteristics of drug absorption?

Following a single oral tablet dose, cabozantinib was absorbed with maximum plasma concentrations of XL184 achieved at median time of 3 to 4 hours post-dose across studies (Table 4). Multiple peaks in the plasma concentration–time profile following a single oral dose, suggesting that XL184 is enterohepatically recirculated or has delayed or multiple sites of absorption, may relate to the substantially delayed maximum concentrations observed for some subjects.

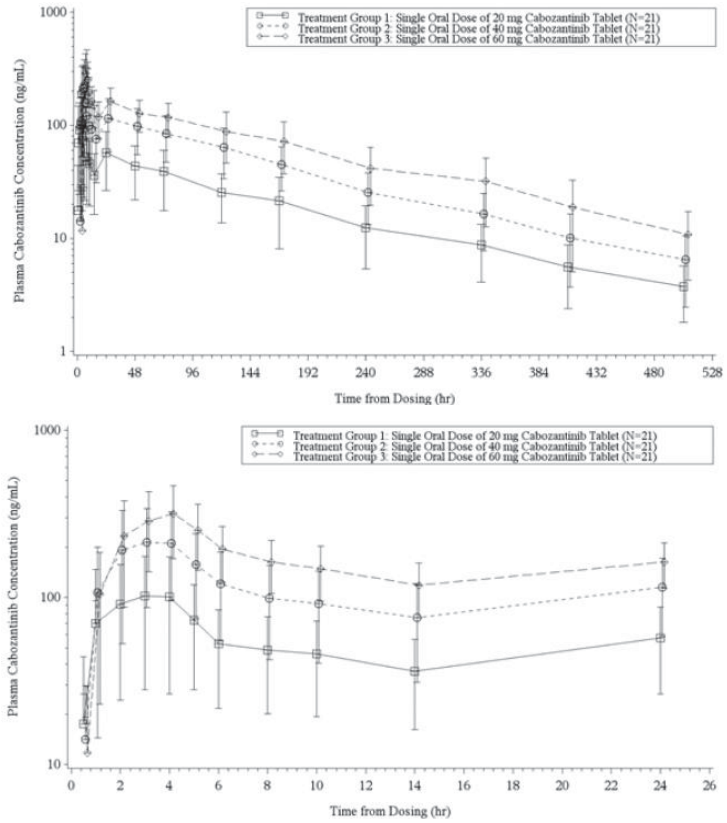


Figure 3: Mean (± SD) Cabozantinib Plasma Concentrations Over Time Plots Following a Single Oral Dose of a 20, 40, or 60 mg Cabozantinib Tablet in Healthy Subjects (n=21) (Upper Panel: 0-504 Hours Post-dose; Lower Panel: B. 0-24 Hours Post-dose)

2.2.4.3 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?

The cabozantinib PK of tablet formulation is linear in terms of dose proportionality and time-independence.

Dose proportionality:

Dose proportionality analyses were performed on the ln-transformed cabozantinib PK parameters C_{max}, AUC_{last} and AUC_{inf}. The slope and 95% CIs for the slope of each ln-transformed PK

parameter were calculated from the regression analyses. The 95% CIs for the slopes of the ln-transformed C_{max}, AUC_{last}, and AUC_{inf} versus ln-transformed cabozantinib for tablet formulation included the value of 1; therefore, dose proportionality was concluded for tablet in the dose range of 20 to 140 mg.

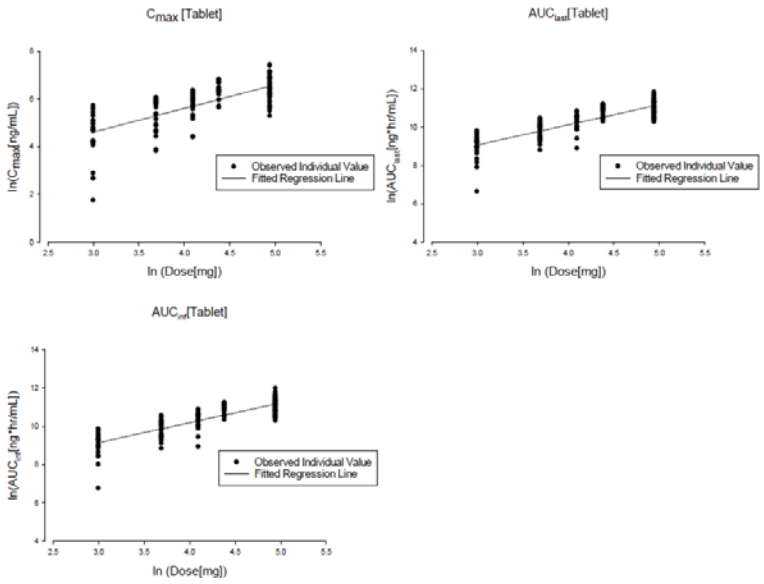


Figure 4:. Linear Dose-Proportional Regression for Plasma Cabozantinib C_{max}, AUC_{last} and AUC_{inf} Following a Single Oral Dose of Tablet

Table 5. Dose Proportionality Analysis Results

Parameter	Slope	Standard error	95% Confidence Intervals (CIs) for Slopes
		Tablet	
C_{max} (ng/mL)	0.991	0.0897	0.814-1.169
AUClast (ng*hr/mL)	1.052	0.0635	0.927-1.178
AUCinf (ng*hr/mL)	1.039	0.0628	0.915-1.163

PK time-independence:

Cabozantinib tablet formulation demonstrated a time-independent PK as single dose PK can predict multiple dose PK of cabozantinib.

The mean single dose PK data of 60 mg tablet was well described by 1-compartmental model with the estimated Ka = 0.5/hr, V/F=295 L and CL/F= 1.8 L/hr. These parameters were used to simulate the concentration-time profiles for 60 mg tablet daily for 28 days. The predicted $C_{min,ss}$ on Day 29 (W5D1, 672 hrs postdose) was 1284 ng/mL; the observed $C_{min,ss}$ at W5D1 at 60 mg daily tablet in Study XL184-308 was 1250 ng/mL (Figure X); these data suggest that the single-dose PK data of 60 mg tablet well-predicted the multiple PK of cabozantinib.

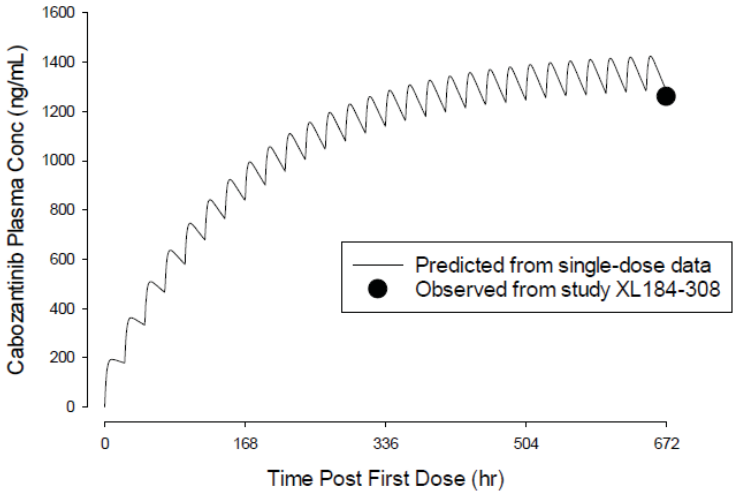


Figure 5: Simulations of Steady-state Trough Concentration of Cabozantinib in Randomized Phase 3 Trial XL 184-308 Based on Single-dose PK of Cabozantinib in Healthy Subjects.

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

After multiple daily doses of capsule formulation, 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.

2.2.4.5 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 subject subjects following a single capsule (Table 12) or tablet (Table 13) dose, the inter-subject variability (%CV) ranged from 20 to 59% for AUC values and from 28 to 72% for C_{max} across the studies. The within-subject variability (%CV) was 39% for C_{max} and 28% for AUC values (Study Report XL184-010).

The inter-subject variability in cancer subjects (%CV; see Table 11) was 43% for Cmax and 34% for AUC after a single dose (Study Report XL184-001.PK.001), and 39% for C_{max} and 38% for AUC at steady state (Study Report XL184-008.PK.001). Exposure variability in cancer subjects and healthy subjects was similar.

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 population PK analysis was performed on pooled data from Study XL184-020 in healthy subjects and sparse PK data from Study XL184-308 in patients with RCC. A two-compartment disposition model with dual (fast and slow) lagged first-order absorption processes adequately characterized the concentration-time profile of cabozantinib in healthy subjects and patients with RCC.

The predicted PK parameter values for a typical White male subject were: approximately 99 hours for terminal plasma half-life, approximately 319 L for terminal phase volume of distribution (Vz), and approximately 2.23 L/hr for steady state oral clearance (CL/F). Inter-individual variability (IIV) in clearance (%CV for CL/F) was estimated to be 46%.

Gender and race were significant covariates on CL/F, where female subjects had 21% lower CL/F compared with male subjects and Asian subjects had 27% lower CL/F compared with White subjects. However, this effect is not considered clinically important.

Covariates determined to have a non-significant effect on CL/F were age, baseline body mass index, baseline hemoglobin, baseline total bilirubin, baseline alanine aminotransferase, baseline serum albumin, baseline calculated creatinine clearance and population (healthy subjects or patients with RCC).

Reviewer's note: It is noted that the apparent oral clearance estimate for cabozantinib of 4.4 L/hr determined in the MTC PopPK analysis is two-fold higher than the apparent oral clearance estimate for cabozantinib determined in the RCC PopPK analysis (2.2 L/hr) (Table X).

Table 6: PK Parameter Estimates from the MTC and RCC PopPK Analyses

PK Parameter	MTC PopPK[1]	RCC PopPK[2]
CL/F	4.4 L/hr	2.2 L/hr
V_c/F	349 L	-
V_z/F	-	319 L
$t_{1/2}$	55	99
CL/F Inter-subject Variability (CV%)	35%	46%

CL/F, apparent plasma clearance at steady-state; V_c/F, apparent volume of distribution (central compartment, 1-compartment model); V_z/F, apparent terminal volume of distribution (2-compartment model); $t_{1/2}$, terminal elimination half-life.

[1]Study Report XL184-301.PopPK.001: Clinical Population Pharmacokinetics Report for Pooled Data from XL184-001, XL184-201 and XL184-301 (20 April 2012), submitted in NDA 203,756.

Similar exposure: Similar steady-state exposures ($C_{trough,ss}$) were observed at different doses across patient populations of medullary thyroid cancer (MTC, 140 mg capsules), advanced renal cell carcinoma (RCC, 60 mg tablets), and castration-resistant prostate cancer (CRPC, 60 mg tablets). This result is unexpected as the exposure (C_{max} and AUC) of capsule and tablet formulations after a single dose of 140 mg. A post-marketing comitmment (PMC) will be issued to evaluate the potential impact of [redacted] (b) (4) on the PK of

cabozantinib [redacted] (b) (4) PK data from different patient populations and healthy subjects in an integrated population PK model.

Per FDA's request, the applicant provided a scatter plot to visualize $C_{min,ss}$ over time among groups of MTC, RCC, and castration-resistant prostate cancer (CPRC) at different doses and different formulations. These plasma concentration data are from analysis of eligible subjects who received before plasma PK sampling at least 14 of the 15 prior scheduled doses of cabozantinib at:

- 140 mg in MTC subjects in study XL184-301 with PK sampling on Day 29 [n=96]
- 60 mg in CRPC subjects in study XL184-306 with PK sampling on Week 3 Day 7 [n=42], Week 6 Day 7 [n=31], and Week 12 Day 7 [n=8];
- 60 mg in CRPC subjects in study XL184-307 with PK sampling on Week4 Day1 [n=503] and Week 13 Day 1 [n=114];
- 60 mg in RCC subjects in study XL184-308 with PK sampling on Week 5 Day 1 [n=211] and Week 9 Day 1 [n=148].

Data from subjects that dose reduced were not included in the scatter plots due to the very low number of these subjects that achieved steady-state plasma concentrations at a reduced dose. Repeat-daily dosing of cabozantinib in healthy subjects has not been performed.

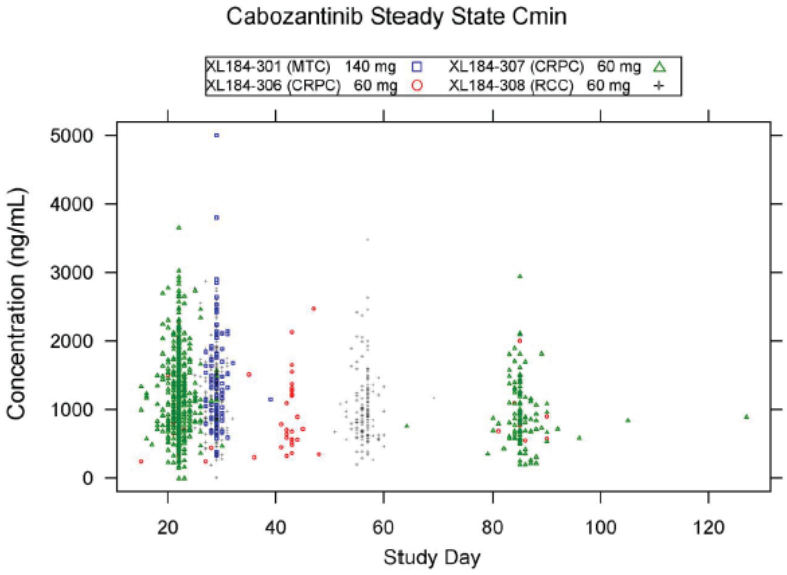


Figure 6: Steady-state Trough Concentrations in Different Patient Populations (MTC, RCC, CRPC) with Different Doses (140 mg vs 60 mg) and Formulations (Capsules and Tablets).

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.

2.3.2.2 Renal impairment

In a dedicated renal impairment trial (XL184-017), a total of 32 subjects were enrolled: 12 subjects into the matched normal group, and 10 subjects each into the mild and moderate renal impairment groups. No subjects were enrolled in the severe impairment group.

The geometric LSM of C_{max} and AUC values were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. Both C_{max} and AUC values were similar between the moderate impairment and control cohorts, with a less than 7% difference in exposure parameters. Mean fraction cabozantinib unbound to plasma proteins (%fu) was also comparable for the control and the mild impairment cohorts, and higher %fu was observed in the moderate impairment cohort (approximately 0.28%, 0.24%, and 0.36%, respectively). There was no statistically significant relationship between the measures of renal function (creatinine clearance; CLcr) at screening and the plasma cabozantinib $AUC_{0\text{-}inf}$.

Table 7: Statistical Comparison of Pharmacokinetic Parameters of Cabozantinib in Subjects with Hepatic Impairment versus Normal Hepatic Function

Parameter	Mild Hepatic Impairment versus Normal			Moderate Hepatic Impairment versus Normal		
	GLS Mean		%GLS Mean Ratio [90%CI]	GLS Mean		%GLS Mean Ratio [90%CI]
	Normal (n=10)	Mild Impairment (n=8)	(Mild/Normal)	Normal (n=9)	Moderate Impairment (n=8)	(Moderate/Normal)
C_{max}, ng/mL	347.20	383.32	110.40 [82.37-147.97]	330.94	234.66	70.91 [52.71-95.38]
$AUC_{0\text{-}t}$, h*ng/mL	30059.75	47369.66	157.58 [109.60-226.58]	28952.01	41127.90	142.06 [97.56-206.85]
$AUC_{0\text{-}inf}$, hr*ng/mL	31492.49	57061.22	181.19 [121.44-270.34]	30426.49	49517.19	162.74 [107.37-246.67]

$AUC_{0\text{-}t}$, area under the plasma concentration –time curve from time 0 to the last quantifiable concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, observed maximum plasma concentration; CI, confidence interval; GLS, geometric least square.

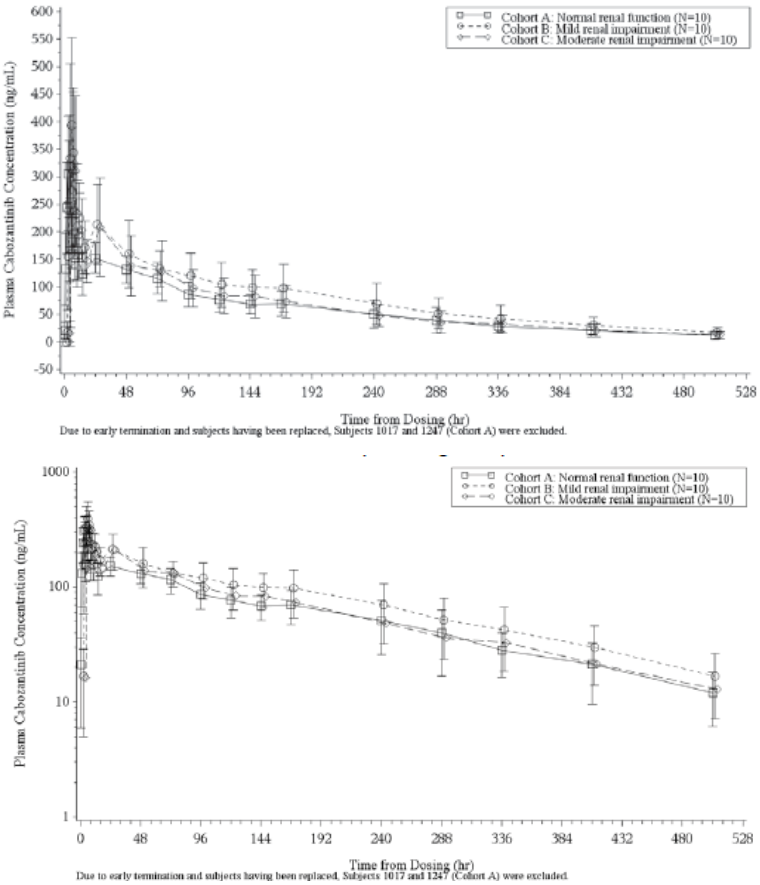


Table 8. Mean (SD) Plasma Cabozantinib Concentrations Versus Time Following Oral Administration of Single 60 mg Dose of Cabozantinib in Patients with Normal Renal Function, Mild and Moderate Renal Impairment (Linear Scale in Upper Panel and Semi-Log Scale in Lower Panel)

2.3.2.3 Hepatic impairment

In a dedicated hepatic impairment trial (XL184-003) the applicant conducted to fulfil the PMR under original NDA203756, a total of 26 subjects were enrolled and completed the study: 10 subjects into the matched normal group, and 8 subjects each into the CP-A and CP-B groups; no subjects were enrolled in the CP-C group.

After a single oral administration of a 60 mg cabozantinib in capsule form, $AUC_{0\text{-}inf}$ was increased by approximately 81% and 63% in subjects with mild and moderate hepatic impairment, respectively, relative to matched controls. C_{max} were not markedly different in mild and moderate hepatic impairment relative to matched controls.

In the 4-hour post-dose samples, the mean unbound plasma protein binding of cabozantinib (%fu) in mild hepatic impaired and healthy control groups was comparable (approximately 0.34% and 0.35%, respectively) and was slightly higher for moderate hepatic impaired group (approximately 0.57%).

Table 9: Statistical Comparison of Pharmacokinetic Parameters of Cabozantinib in Subjects with Hepatic Impairment versus Normal Hepatic Function

Parameter	Mild Hepatic Impairment versus Normal			Moderate Hepatic Impairment versus Normal		
	GLS Mean		%GLS Mean Ratio [90%CI]	GLS Mean		%GLS Mean Ratio [90%CI]
	Normal (n=10)	Mild Impairment (n=8)	(Mild/Normal)	Normal (n=9)	Moderate Impairment (n=8)	(Moderate/Normal)
C_{max}, ng/mL	347.20	383.32	110.40 [82.37-147.97]	330.94	234.66	70.91 [52.71-95.38]
AUC_{0-t}, h*ng/mL	30059.75	47369.66	157.58 [109.60-226.58]	28952.01	41127.90	142.06 [97.56-206.85]
AUC_{0-inf}, hr*ng/mL	31492.49	57061.22	181.19 [121.44-270.34]	30426.49	49517.19	162.74 [107.37-246.67]

AUC_{0-t}, area under the plasma concentration –time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, observed maximum plasma concentration; CI, confidence interval; GLS, geometric least square.

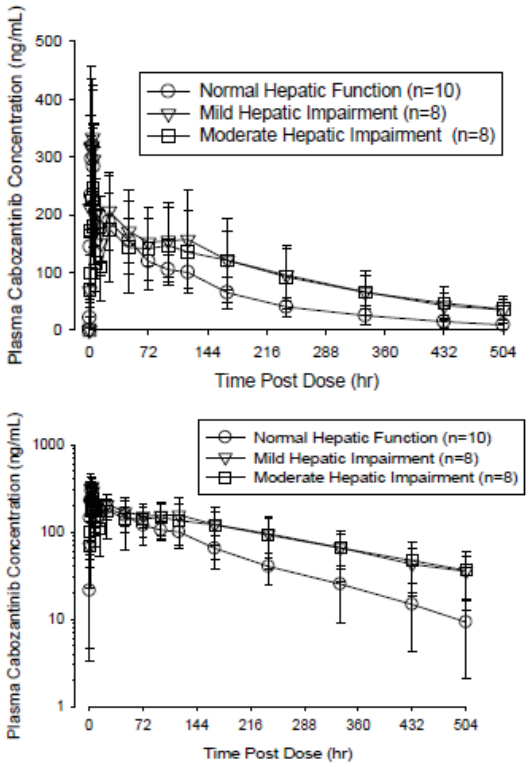


Figure 7: Mean (± SD) Plasma Cabozantinib Concentration-time Profiles After a Single Oral 60 mg FBE Weight Dose to Subjects with Normal Hepatic Function, Subjects with Mild Hepatic Impairment (CP-A), and Subjects with Moderate Hepatic Impairment (CP-B); Top Panel, Linear Scale; Bottom Panel, Log Scale

2.4 EXTRINSIC FACTORS

2.4.1 Drug-drug interactions

The drug-drug interaction regarding induction and inhibition of CYP enzymes, P-gp has been evaluated under NDA203756. In the current submission, additional *in vitro* study results suggested that cabozantinib is a substrate of MRP2.

2.4.1.1 Are there other metabolic/transporter pathways that may be important?

In vitro study suggested that cabozantinib is likely a substrate of MRP2, but not of the other transporters evaluated including OAT1, OCT1, OATP1B1, and OATP1B3.

In vitro study suggested that cabozantinib demonstrated inhibition of on MATE1 and MATE2-K (estimated IC_{50} values of 5.94 and 3.12 μM, respectively), but no marked inhibition on BCRP, BSEP, MRP2, P-gp, OAT1, OAT3, OCT1, OATP1B1, and OATP1B3.

2.4.1.2 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?

Co-administration of multiple doses of esomeprazole (40 mg once daily) with a single 100 mg dose of cabozantinib did not decrease cabozantinib plasma exposure.

In Study XL184-018, cabozantinib was administered in 22 healthy subjects as a single 100 mg dose in Period 1 (Reference) followed by a 31 day washout period. Daily esomeprazole administration was initiated 6 days prior to administration of a second 100 mg dose of cabozantinib in Period 2 (Test). On Day 6, esomeprazole was administered 1 hour before the cabozantinib dose. PK samples were obtained over a 504 hour timeframe post dose in each period.

The 90% CIs for the ln-transformed ratio of the test to reference treatment for both AUC_{0-t} and AUC_{0-inf} were within the limits of 80% - 125%, although the upper 90% CI for C_{max} was determined to be 125.1%.

Esomeprazole administration did not result in any statistically significant decrease in cabozantinib plasma PK parameters; therefore, no clinically significant drug-drug interaction in subjects taking both cabozantinib and a proton pump inhibitor is considered likely. Based on this result, the effect of weaker gastric pH modifying agent, famotidine, on PK of cabozantinib was not evaluated.

Table 10: Statistical Comparisons of Plasma Cabozantinib Pharmacokinetic Parameters Following Oral Administration of Cabozantinib + Esomeprazole (Treatment B, Test) Versus Cabozantinib Alone (Treatment A, Reference)

Pharmacokinetic Parameter	Geometric LS Means		Geometric Mean Ratio (%)	90% Confidence Intervals	p-Value	Intra-Subject CV%
	Test (Treatment B) (N=21)	Reference (Treatment A) (N=21)				
C_{max} (ng/mL)	678.861	614.328	110.50	97.61 – 125.10	0.1720	23.62
AUC_{0-t} (ng*hr/mL)	58087.89	53961.52	107.65	96.92 – 119.57	0.2357	19.92
AUC_{0-inf} (ng*hr/mL)	62032.71	56883.39	109.05	97.96 – 121.40	0.1732	20.35

Parameters were ln-transformed prior to analysis.
Geometric least-squares (LS) means were calculated by exponentiating the LS means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference).
Treatment A: Oral Administration of Cabozantinib Alone (Reference)
Treatment B: Oral Administration of Cabozantinib + Esomeprazole (Test)

2.5 GENERAL BIOPHARMACEUTICS

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

CABOMETYX tablets are supplied as 20, 40 and 60 mg tablets with the composition as shown in Table X.

Table 11. Composition of Clinical and To-be-marketed CABOMETYX tablets

Ingredient	Function	Reference to Quality Standard	Theoretical Quantity (mg/unit dose)		
			20-mg Tablet	40-mg Tablet	60-mg Tablet
Cabozantinib (S)-malate	Active ingredient	N/A	25.34	50.69	76.03
Microcrystalline Cellulose, (b) (4)	(b) (4)	USP, NF, EP, JP	(b) (4)		
Lactose Anhydrous, (b) (4)		USP, NF, EP, JP			
Hydroxypropyl Cellulose, (b) (4)		USP, NF, EP, JP			
Croscarmellose Sodium		USP, NF, EP, JP			
Colloidal Silicon Dioxide		USP, NF, EP, JP			
Magnesium Stearate (b) (4) (b) (4)		USP, NF, EP, JP			
(b) (4) Yellow (b) (4)	Film coating material	(USP, NF, EP, JP)[a]			
Total tablet weight			83.20	166.4	249.6

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

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

2.5.2 What is the absolute bioavailability of cabozantinib?

The absolute bioavailability of cabozantinib tablet or capsule formulations has not been determined. In a Phase 1 dose escalation study in subjects with solid tumors (XL184-001), the capsule formulation yielded approximately 2-fold higher dose-normalized $AUC_{0\text{-}24hr}$ after a single dose compared to an oral liquid formulation (PIB suspension), as shown in Figure 3. The formulation that was used for the mass balance study (XL184-012) was a true solution, and was different from the liquid suspension formulation studied in XL184-001. Although the number of subjects was small (N=8), a single 140 mg FBE oral XL184 dose formulated as a solution yielded an earlier T_{max}, higher C_{max} and $AUC_{0\text{-}inf}$, and less inter-subject variability compared to the capsule or tablet formulation used in healthy subjects at the same cabozantinib (XL184) dose level (see Table X). Mean $AUC_{0\text{-}inf}$ values for XL184 in healthy subjects using tablets (XL184-010) were 97% of the corresponding value in the mass balance study where XL184 was formulated as a solution. This suggests that the relative bioavailability of the tablet formulation was high.

Table 12: Comparison of Single Dose XL184 Plasma Exposure Parameters for the Mass Balance Solution Formulation Versus Capsules and Tablets in Healthy Subjects (Dose: 140 mg Cabozantinib FBE)

Study	Formulation	C_{max} (ng/mL)		AUC_{0-inf} (h*ng/mL)		T_{max} (h)
		Mean	CV%	Mean	CV%	
XL184-012 (Mass Balance, N=8)	Solution	1250	19.0	68000	10	1.5
XL184-010 (BE, N=72)	Capsules	554	43	58300	39	3.95
XL184-010 (BE, N=72)	Tablets	702	54	65800	46	3.75

AUC_{0-inf}, area under the curve from time zero to infinity; BE, bioequivalence; C_{max}, maximum concentration; FBE, freebase equivalent; T_{max}, time to maximum concentration, reported as median;
Source: Study Reports XL184-012 and XL184-010.

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

The to-be-marketed tablet formulation is identical to the formulation used in the registration Phase 3 trial (Study XL184-308).

2.5.4 Are the tablet formulation and capsule formulation bioequivalent?

Following a single 140 mg dose administration of cabozantinib tablet formulation (for RCC indication) and capsule formulation (for MTC indication), the extent of exposure (AUC_{0-t} and AUC_{0-inf}) was similar for both formulations, with the 90% CIs around the ratio Tablet/Capsule of LS means for AUC_{0-t} and AUC_{0-inf} within the recommended bioequivalence limits of 80.00% - 125.00%. However, for C_{max}, the upper limit of the 90% CI around the ratio of LS means (131.65%) was outside the 80.00% -125.00% criteria.

Mean PK parameters were highly variable with %CVs for the main parameters ranging from 44 - 47% (AUC) to 54% (C_{max}) for cabozantinib tablets (Test: Treatment A) and from 35% to 39% (AUC) and 43% (Cmax) for cabozantinib capsules (Reference: Treatment B). The median Tmax was 3.5 hours for the tablet formulation and 4.0 hours for the capsule formulation, while the terminal t1/2 of cabozantinib appeared to be similar for both tablet and capsule formulations, with mean values of 112 - 115 hours. CL/F and VZ/F were comparable between the tablet and capsule formulations.

Table 13. Statistical Comparisons of Plasma Cabozantinib Pharmacokinetic Parameters Following Oral Administration of Cabozantinib 140 mg Tablet Formulation (Treatment A, Test) Versus Cabozantinib 140 mg Capsule Formulation (Treatment B, Reference)

	Geometric LS Means					
	Treatment A	Treatment B	Geometric Mean Ratio (%)	Confidence Intervals		Intra-subject
Parameter	(N=72)	(N=72)	(Test/Reference)	(90% Confidence)	P-Values	%CV
AUC0-inf (ng*hr/mL)	59437.04	54913.22	108.24	100.38 - 116.71	0.0842	27.57
AUC0-t (ng*hr/mL)	56271.18	51980.35	108.25	100.40 - 116.73	0.0837	27.58
Cmax (ng/mL)	601.580	506.817	118.70	107.02 - 131.65	0.0074	38.54

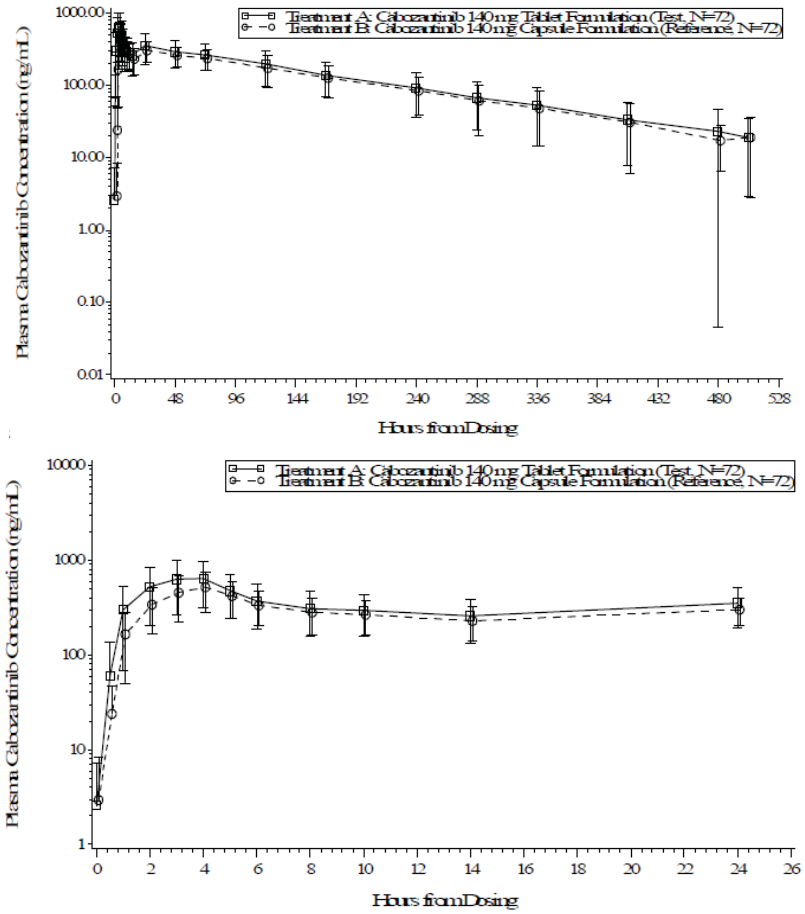


Figure 8: Mean (SD) Cabozantinib Plasma Concentrations Over Time Plots Following a Single Oral 140 mg Dose of Cabozantinib Capsule or Tablet Formulations in Healthy Subjects (N=72) (A. 0-504 hours post-dose; B. 0-24 hours postdose)

2.5.5 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 tablet formulation is not available. For the clinical pharmacology food effect study, where the results may be formulation-dependent, a standard conservative dosing guidance is proposed (ie, cabozantinib administration only in the fasted state) for both capsule and tablet formulations in order to eliminate the risk of any clinically-meaningful effects of food intake on plasma exposure.

The following results of food effect study were excerpted from the original NDA203756 for MTC:

> The effect of food on the PK of a single dose of cabozantinib capsule formulation (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.

3 DETAILED LABELING RECOMMENDATIONS

The proposed labeling language of CABOMETYX™ (oral tablets) for RCC was based on the FDA approved label of COMTRIQ™ (oral capsules) for the treatment of medullary thyroid cancer (MTC) under NDA203756. Three columns were generated for the approved COMTRIQ™ (oral capsules), proposed CABOMETYX (oral tablets), and FDA's counterproposal for CABOMETYXTM in order to effectively keep consistency and compare the differences due to changes in formulations, doses, and indications, and new information of cabozantinib.

Only clinical pharmacology relevant sections are included. Double underlines indicate the content that was added by the Applicant to the originally approved label or by the Agency to the applicant's proposed label, and ~~strikethroughs~~ indicate contents taken out by the applicant from the originally approved label or by the Agency from the applicant's proposed label.

Approved COMTRIQ™ (Capsules for MTC, Dose 140 mg Once Daily)	Proposed CABOMETYX™ (Tablets for RCC, Dose 60 mg Once Daily)	FDA's Counterproposal to CABOMETYX™
Highlights **DOSAGE AND ADMINISTRATION** • Recommended Dose: 140 mg orally, once daily. (2.1) • Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. (2.1). **DOSAGE FORMS AND STRENGTHS** • 20 mg and 80 mg capsules. (3) **DRUG INTERACTIONS** Cabozantinib is a CYP3A4 substrate (5.10, 7.1, 7.2). Coadministration of strong CYP3A4 inhibitors can increase cabozantinib exposure (2.1, 5.10, 7.1). Chronic co-administration of strong CYP3A4 inducers can reduce cabozantinib exposure. (2.1, 5.10, 7.2)	**Highlights** **DOSAGE AND ADMINISTRATION** • Recommended Dose: 60 mg orally, once daily. (2.1) • Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. (2.1). **DOSAGE FORMS AND STRENGTHS** • 20 mg, 40 mg, and 60 mg tablets. (3) **DRUG INTERACTIONS** (b) (4)	Acceptable **DRUG INTERACTIONS** • Strong CYP3A4 inhibitors: Reduce the CABOMETYX dosage. (2.2, 7) • Strong CYP3A4 inducers: Increase the CABOMETYX dosage. (2.2, 7)
2. DOSAGE AND ADMINISTRATION **1.1. Recommended Dose** The recommended daily dose of COMETRIQ is 140 mg (one 80-mg and three 20-mg capsules). Do not administer COMETRIQ with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. Continue treatment until disease progression or unacceptable toxicity occurs. Swallow COMETRIQ capsules whole. Do not open COMETRIQ capsules. Do not take a missed dose within 12 hours of the next dose. Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during COMETRIQ. **2.2 Dosage Adjustments** For Adverse Reactions	**2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dose** The recommended daily dose of CABOMETYX is 60 mg. Do not administer CABOMETYX with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Continue treatment until patient no longer experiences clinical benefit or experiences unacceptable toxicity. Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets. Do not take a missed dose within 12 hours of the next dose. Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during CABOMETYX treatment. **2.2 Dosage Adjustments** For Adverse Reactions	

	(b) (4)	
Withhold COMETRIQ for NCI CTCAE Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions or intolerable Grade 2 adverse reactions. Upon resolution/improvement of the adverse reaction (i.e., return to baseline or resolution to Grade 1), reduce the dose as follows: • If previously receiving 140 mg daily dose, resume treatment at 100 mg daily (one 80-mg and one 20-mg capsule) • If previously receiving 100 mg daily dose, resume treatment at 60 mg daily (three 20-mg capsules) • If previously receiving 60 mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue COMETRIQ Permanently discontinue COMETRIQ for any of the following: • development of visceral perforation or fistula formation • severe hemorrhage • serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction) • nephrotic syndrome • malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management • osteonecrosis of the jaw • reversible posterior leukoencephalopathy syndrome In Patients with 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)]. In Patients Taking 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	Withhold CABOMETYX for NCI CTCAE Grade 4 adverse reactions, Grade 3 adverse reactions that cannot be managed with a dose reduction or supportive care, or intolerable Grade 2 adverse reactions that cannot be (b) (4) managed. Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction (b) (4) reduce the dose as follows: • If previously receiving 60 mg daily dose, resume treatment at 40 mg daily • If previously receiving 40 mg daily dose, resume treatment at 20 mg daily • If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue CABOMETYX Permanently discontinue CABOMETYX for any of the following: • development of unmanageable fistula or GI perforation • severe hemorrhage • (b) (4) arterial thromboembolic event (e.g., myocardial infraction) • severe hypertension despite optimal medical management • nephrotic syndrome • reversible posterior leukoencephalopathy syndrome In Patients with Hepatic Impairment CABOMETYX is not recommended for use in patients with severe hepatic impairment [see (b) (4) Use in Specific Populations (8.6)].	*In Patients Concurrently Taking a Strong CYP3A4 Inhibitor* Reduce the daily CABOMETYX dose by 20 mg (for example from 60 mg to 40 mg daily or from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)].* *In Patients Concurrently Taking a Strong CYP3A4 Inducer*

Interactions (7.1)]. For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily COMETRIQ dose by 40 mg (for example, from 140 mg to 100 mg daily or from 100 mg to 60 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor. In Patients Taking Strong CYP3A4 Inducers Avoid the chronic 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)]. Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity. For patients who require treatment with a strong CYP3A4 inducer, increase the daily COMETRIQ dose by 40 mg (for example, from 140 mg to 180 mg daily or from 100 mg to 140 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of COMETRIQ should not exceed 180 mg.		Increase the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of CABOMETYX should not exceed 80 mg *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. *In Patients with Hepatic Impairment* Reduce the starting dose of CABOMETYX to 40 mg once daily in patients with mild or moderate hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.
5 WARNINGS AND PRECAUTIONS 5.10 Drug Interactions Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors [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 or severe hepatic impairment [see Use in Specific Populations (8.6)].	**5 WARNINGS AND PRECAUTIONS** (b) (4)	~~**5 WARNINGS AND PRECAUTIONS**~~ (b) (4)
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%. Avoid taking a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) when taking COMETRIQ *[see Dosage and Administration (2.1) and Warnings and Precautions (5.10)]*. **7.2 Effect of CYP3A4 Inducers** Administration of a strong CYP3A4	**7 DRUG INTERACTIONS** (b) (4)	**7 DRUG INTERACTIONS** **Table 3 Clinically Significant Drug Interactions Involving Drugs that Affect abozantinib**

inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC0-inf) by 77%. Avoid chronic co-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) with COMETRIQ *[see Dosage and Administration (2.1) and Warnings and Precautions (5.10)]*.	(b) (4)	**Strong CYP3A4 Inhibitors** *Clinical Implications:* • Concomitant use of CABOMETYX with a strong CYP3A4 inhibitor increased the exposure of cabozantinib compared to the use of CABOMETYX alone *[see Clinical Pharmacology (12.3)]*. • Increased cabozantinib exposure may increase the risk of exposure-related toxicity. *Prevention or Management:* Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided *[see Dosage and Administration (2.2)]*. *Examples:* Boceprevir, clarithromycin, conivaptan, grapefruit juice[a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole **Strong CYP3A4 Inducers** *Clinical Implications:* • Concomitant use of CABOMETYX with a strong CYP3A4 inducer decreased the exposure of cabozantinib compared to the use of CABOMETYX alone *[see Clinical Pharmacology (12.3)]*. • Decreased cabozantinib exposure may lead to reduced efficacy. *Prevention or Management:* Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided *[see Dosage and Administration (2.2)]*. *Examples:* Rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John's Wort[b] [a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength). [b] The effect of St. John's Wort varies widely and is preparation-dependent (b) (4)
8 USE IN SPECIFIC POPULATIONS **8.3 Pediatric Use** The safety and effectiveness of COMETRIQ in pediatric patients have not been studied. **8.4 Geriatric Use** Clinical studies of COMETRIQ did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients	**8 USE IN SPECIFIC POPULATIONS** **8.3 Pediatric Use** The safety and effectiveness of CABOMETYX in pediatric patients have not been studied. **8.4 Geriatric Use** In the Phase 3 study, 41% of RCC patients treated with CABOMETYX were age 65 years and older, and 8% were age 75 and older. No differences in safety or efficacy were observed between older and younger patients.	Acceptable Acceptable
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 or severe hepatic impairment, as safety and efficacy have not been established [*see Dosage and Administration (2.1) and Warnings and Precautions (5.11)]*.	**8.6 Hepatic Impairment** CABOMETYX (b) (4), (b) (4) (b) (4) with mild or moderate hepatic impairment (b) (4) (b) (4) CABOMETYX is not recommended for use in patients with severe hepatic impairment, (b) (4) (b) (4) [see Dosage and Administration (2.2), (b) (4) and (b) (4) (12.3)].	**8.6 Hepatic Impairment** Increased exposure to cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the CABOMETYX dose in patients with mild (Child-Pugh score (C-P) A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment [see Dosage and Administration (2.2), and Clinical Pharmacology (12.3)].
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.	**8.7 Renal Impairment** (b) (4) in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment [see (b) (4) (12.3)].	**8 7 Renal Impairment** Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment [see Clinical Pharmacology (12.3)].
12 CLINICAL PHARMACOLOGY	**12 CLINICAL PHARMACOLOGY**	**12 CLINICAL PHARMACOLOGY**

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 (≥ 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 had 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 a clinically relevant effect on the clearance of cabozantinib.

12.3 Pharmacokinetics

(b) (4)

Absorption (b) (4) Distribution

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 3 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean abozantinib 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 (≥ 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 dose of cabozantinib capsules.

Metabolism (b) (4) Elimination

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the (b) (4) metabolite by >80%. Inhibition of CYP2C9 had 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 (b) (4) a single dose of 14C-cabozantinib in healthy subjects, approximately (b) (4)% of the total (b) (4) radioactivi was recovered with 54% in feces and 27% in urine.

Specific Populations

(b) (4)

12 3 Pharmacokinetics

Repeat daily dosing of cabozantinib 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.

Absorption

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 3 hours post dose.

A 19% increase in the Cmax of the tablet formulation (CABOMETYX) compared to the capsule formulation (COMETRIQ®) was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations [see Dosage and Administration (2.1)].

Cabozantinib Cmax and AUC values increased by 41% and 57%, respectively, following a high-fat meal relative to fasted conditions in healthy subjects administered a single 140 mg oral dose of an investigational cabozantinib capsule formulation.

Distribution

The oral volume of distribution (Vz/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination

The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady-state is estimated to be 2.2 L/hr.

Metabolism

Cabozantinib is a substrate of CYP3A4 in vitro.

Excretion

Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational 14C-cabozantinib formulation in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72 hour collection.

Specific Populations

The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (32-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with

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 the pediatric population [see Use in Specific Populations (8.3)].	(b) (4) Hepatic Impairment (b) (4) patients (b) (4) (b) (4) exposure (AUC0-inf) increased by 81% and 63% in (b) (4) with mild (b) (4) and moderate (b) (4) hepatic impairment (b) (4) (b) (4) respectively. Patients with severe hepatic impairment have not been studied [see Dosage and Administration (b) (4) (b) (4) Use in Specific Populations (8.6)]. Pediatric Population: The pharmacokinetics of cabozantinib has not been studied in the pediatric population [see Use in Specific Populations (b) (4).	worse than moderate renal impairment (eGFR less than 29 mL/min/1.73m2) as estimated by MDRD equation or renal impairment requiring dialysis Hepatic Impairment Cabozantinib exposure (AUC0-inf) increased by 81% and 63%, respectively, in patients with mild (C-P A) and moderate (C-P B) hepatic impairment. Patients with severe hepatic impairment have not been studied [see Dosage and Administration (2.2), Use in Specific Populations (8.6)]. Pediatric Population The pharmacokinetics of cabozantinib has not been studied in the pediatric population [see Use in Specific Populations (8.4)].
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	(b) (4) did not clinically relevant cabozantinib (b) (4) Whites and non-Whites. (b) (4) (b) (4) age (32-86 years). Drug Interactions (b) (4)	CYP3A4 Inhibition on Cabozantinib 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%. CYP3A4 Induction on Cabozantinib 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%. Cabozantinib on CYP2C8 substrates No clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) was observed when co-administered with cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) in patients with solid tumors. Gastric pH modifying agents on Cabozantinib No clinically-significant effect on plasma cabozantinib exposure (AUC) was observed following co-administration of the proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers. In vitro Studies Metabolic Pathways Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by > 80%. Inhibition of CYP2C9 had 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. Although cabozantinib is an inhibitor of CYP2C8 in vitro, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this

concentrations of co-administered substrates of P-gp.	(b) (4) (b) (4) (b) (4): Cabozantinib is a substrate of MRP2 *in vitro*. (b) (4) (b) (4) inhibitors (b) (4) MRP2 have the potential to increase plasma concentrations of cabozantinib. (b) (4) (b) (4) (b) (4) Gastric pH (b) (4) ~~modifying~~ agents: Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically-significant effect on plasma cabozantinib exposure (AUC).	finding, other less sensitive substrates of pathways affected by cabozantinib in vitro (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes in vitro. Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4. Drug Transporter Systems Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase plasma concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown. Cabozantinib is a substrate of MRP2 in vitro and MRP2 inhibitors have the potential to increase plasma concentrations of cabozantinib. The clinical relevance of this finding is unknown.
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. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating COMETRIQ. A concentration-QTc relationship could not be definitively established. 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)].	(b) (4) **Cardiac Electrophysiology** The effect of orally administered cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with medullary thyroid cancer administered a dose of 140 mg. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated patients in this study had a confirmed QTcF > 500 ms nor did any cabozantinib-treated patients in the RCC study (at a dose of 60 mg).	Acceptable

4 PHARMACOMETRIC REVIEW

APPEARS THIS WAY ON ORIGINAL

`OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA208692
Submission Date	2/21/2016
Compound	Cabozantinib
Dosing regimen (route of administration)	60 mg daily (oral)
Indication	Advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy.
Clinical Division	Division of Oncology Products 1 (DOP1)
Primary PM Reviewer	Chao Liu, Ph.D.
PM Team Leader	Jingyu Yu, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

Table of Contents

1 SUMMARY OF FINDINGS

The cabozantinib dose of 60 mg QD appears reasonable for proposed indication based on exposure-response (ER) relationship for efficacy and safety. A PMC study is recommended to evaluate the effect of cancer disease type on PK of Cabozantinib as the apparent clearance of Cabozantinib is two-fold higher in MTC patients than RCC patients based on population PK analysis.

1.1 Key Review Questions

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

1.1.1 Is the starting dose of 60 mg QD supported by the ER relationship for safety and efficacy?

Yes.

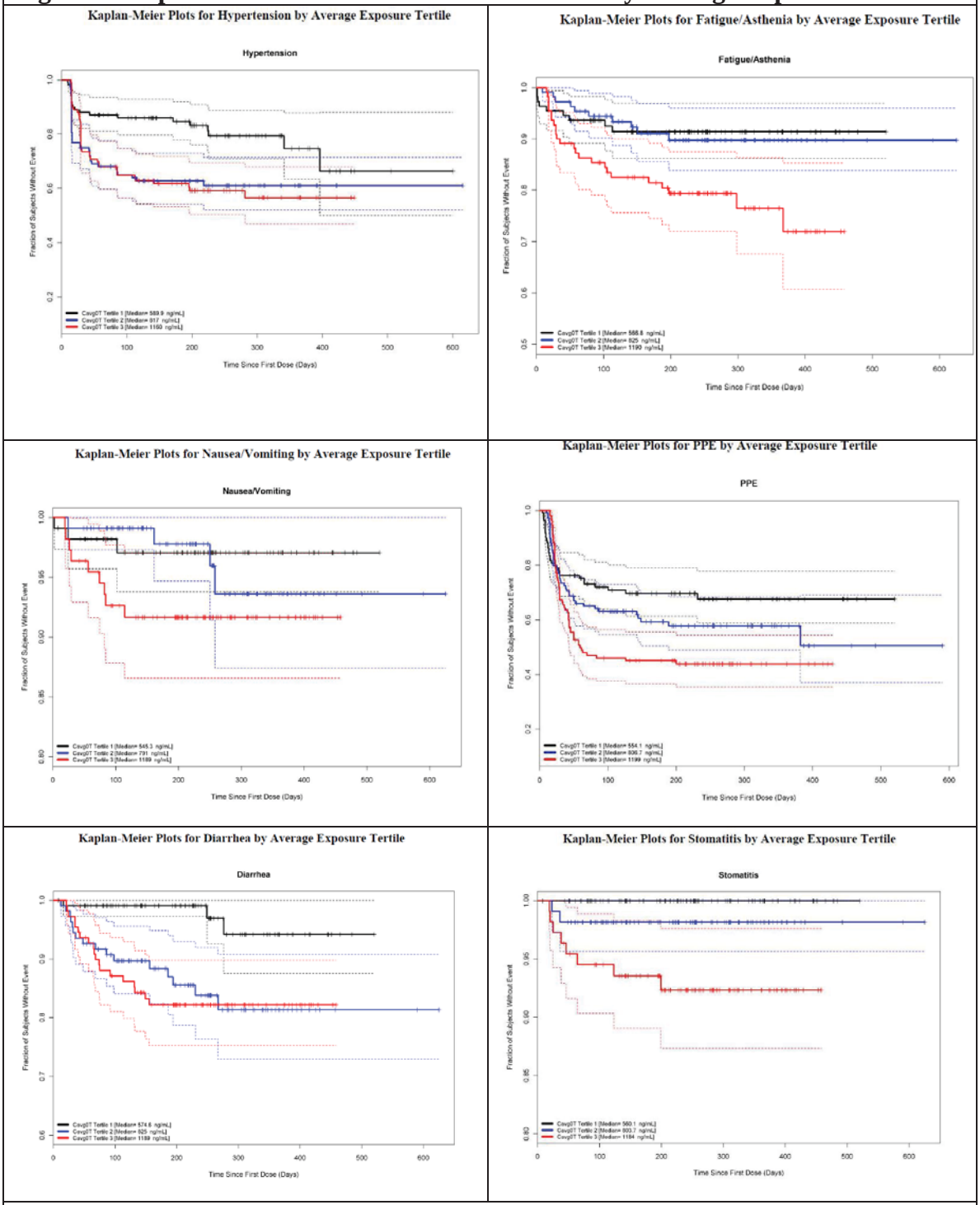
ER Relationship for Safety:

Exposure safety analysis indicates that patients with higher drug exposure tended to experience adverse reactions and dose modifications earlier.

The exploratory KM plot for time to first incidence of different AE types shows the following results (**Figure 1**):

- Fatigue/Asthenia: The result shows an increased fraction of subjects with fatigue or asthenia in the highest exposure tertile.
- Nausea/Vomiting: The relatively small fraction of subjects that experienced nausea or vomiting was observed.
- PPES: The fraction of subjects with PPE increases with higher exposure tertiles.
- Diarrhea: The fraction of subjects with diarrhea increases with higher exposure tertiles.
- Stomatitis: The plot highlights the relatively small fraction of subjects that experienced stomatitis.
- Hypertension: The fraction of subjects with hypertension is increased in the two larger exposure tertiles relative to the lowest exposure tertile. The fractions of subjects with hypertension are similar for the two largest exposure tertiles.

Figure 1: Kaplan-Meier Plots for Adverse Reactions by Average Exposure Tertile



Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

To evaluate the association between dose-altering AE and individual exposure, a longitudinal exposure-dose-altering AE model was developed. The survival model for repeated events showed a significant relationship between the time to dose modifications and individual-predicted cabozantinib concentration over the 24 hours prior to the

observed AEs (CAVG1D). Using this model, the virtual dosing history was simulated at different starting dose levels (20 mg and 40 mg) to evaluate the potential reduction in the incidence of dose interruption/reduction (**Table 1**).

Table 1: Simulation of Dosing History: Percentage of Subjects on 20 mg, 40 mg, or 60 mg Once Daily Treatment Regimens at Month 6 and Month 12

Time Point	Dose (mg)	Observed %	Simulated 20 mg Starting Dose (%)	Simulated 40 mg Starting Dose (%)	Simulated 60 mg Starting Dose (%)
6 Month	20	15.8	100	24.1	9.8
	40	35.9	N/A	75.9	35.1
	60	48.0	N/A	N/A	55.1
12 Month	20	17.0	100	36.7	20.8
	40	39.8	N/A	63.3	43.3
	60	42.9	N/A	N/A	35.9

Numbers in the table are the percentage of subjects that stay on 20 mg, 40 mg, and 60 mg (excluding dose interruptions) at 6 months and 12 months for Study 308, the simulated 20 mg starting dose scenario, the simulated 40 mg starting dose scenario, and the simulated 60 mg starting dose scenario.

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

These results suggest that decreasing starting dose levels could potentially reduce the incidence of dose altering AE.

ER Relationship for Efficacy:

The proposed dosing regimen is supported by the ER relationship of efficacy as the analysis suggests that a lower dose level may result in compromised benefit in terms of the primary endpoint, progression-free survival (PFS), as well as the drug anti-tumor activity. Based on ER analysis, there appears to a positive and saturable exposure-efficacy relationship between cabozantinib exposure and PFS or anti-tumor activity under the exposure range of 60 mg QD and the subsequent lower dose levels (40 mg QD and 20 mg QD) for the proposed indication.

In the exposure-PFS relationship analysis, the relationship was explored by Cox regression model where the drug exposure effect on hazard was an Emax function of the PPK model-predicted cabozantinib exposure based on dosing records. On each day, the average cabozantinib concentration over its prior three weeks was calculated, and employed as the exposure metrics (CAVG3W). The EC50 was estimated as 100 ng/mL, which is less than one tenth of the cabozantinib steady-state average concentrations in a typical individual with 60 mg QD. As there had been a 60% dose reduction rate in the 60 mg treatment group in study 308, higher dose would not be further discussed for dose optimization due to safety concerns.

This model suggests exposure under lower dose levels (*e.g.*, 40 mg and 20 mg) may result in a shorter PFS compared with 60 mg QD (**Table 2**). The potential loss of efficacy at lower dose levels suggests that the proposed cabozantinib dose (60 mg QD) seems reasonable based on this exposure-PFS analysis.

Table 2: Emax Model Hazard Ratios for Progression Free Survival

CAVG3W[a]	HR Relative to CAVG3W = 1125 mg/mL (60 mg QD)
375 ng/mL (20 mg QD)	1.39
750 ng/mL (40 mg QD)	1.10

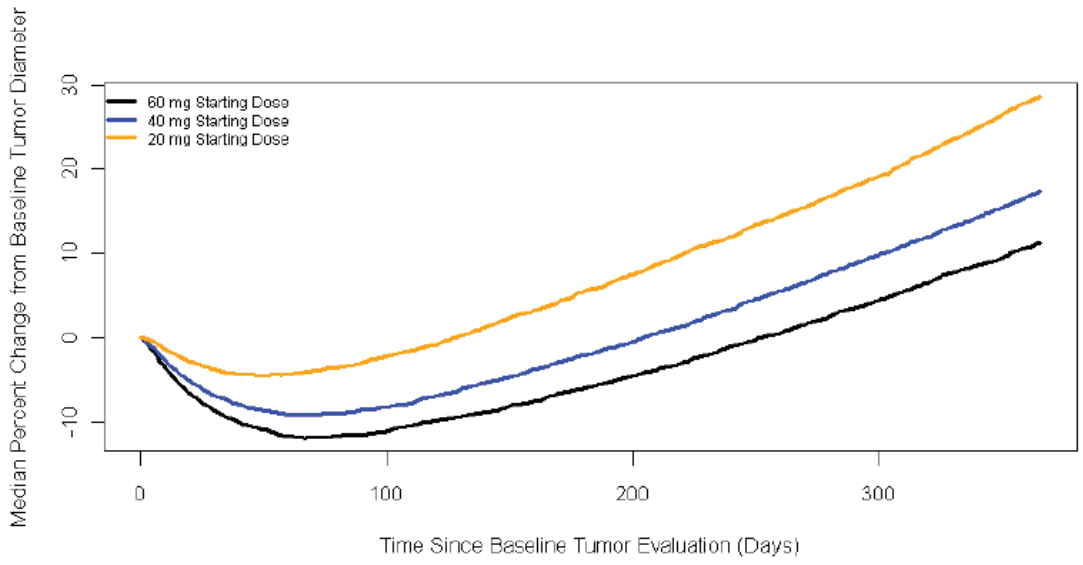
HR = hazard ratio

[a]Cabozantinib concentrations correspond to model predicted typical individual steady-state average concentrations for the 20 mg and 40 mg once daily dosing regimens.

Source: Adapted from the SSynopsis of Exposure-Response Report, Study No. XL184-308.ER.001, Table 14

In addition, an exposure-tumor size model was developed. The model is composed of a first-order growth rate, nonlinear cabozantinib drug effect, and a resistance component. The drug effect on tumor suppression was described as an Emax function with EC50 as 251 ng/mL. This tumor model was used to predict the tumor dynamics at different lower dose levels (40 mg and 20 mg) with dose interruption/reduction taken into account. The virtual dosing history was simulated using sponsor's exposure-dose-altering model (DMPK model, see Section 3 for details). Based on the simulated dosing history, the tumor dynamics was simulated to evaluate the potential loss of efficacy at lower starting dose levels. For starting dose levels at 20 mg, 40 mg, and 60 mg, the median percent change from baseline tumor size is shown in **Figure 2**. Subjects in the 60 mg QD dose group are predicted to have greater reduction in tumor size (median percent change from baseline = -11.9%) relative to the 40 mg and 20 mg QD dose groups. Subjects in the 40 mg QD dose group are predicted to have a lower median percent reduction from baseline (-9.1% for 40 mg and -4.45% for 20 mg) tumor sizes relative to the case in the 60 mg starting dose group.

Figure 2: Comparison of Predicted Median Percent Change from Baseline Tumor Diameter for 20 mg, 40 mg, and 60 mg Cabozantinib Starting Doses



Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

Based on the simulated tumor size, best overall response (BOR) was computed for each subject. The predicted percentage of subjects with different BOR for a 20 mg, 40 mg, and 60 mg starting dose treatment regimen are shown in **Table 3**. A lower objective response rate (ORR) in the 40 and 20 mg starting dose t groups was predicted relative to the 60 dose treatment groups.

Table 3: Simulated ORR based on model predicted tumor dynamics

Best Overall Response (BOR)	20 mg Starting Dose (%)	40 mg Starting Dose (%)	60 mg Starting Dose (%)
Complete Response (CR)	0.10	0.00	0.00
Partial Response (PR)	8.60	15.6	19.10
Stable Disease (SD)	81.1	76.3	73.40
Progressive Disease (PD)	10.2	8.10	7.50

Source: Adapted from Study No. XL184-308.ER.002 – Memorandum

Overall, the proposed 60 mg QD starting dose is acceptable given the overall favorable benefit/risk profile at 60 mg QD dose and potential loss of efficacy at lower starting dose.

1.1.2 Is the relevant labeling regarding intrinsic factors (Age, Gender and Race) adequately supported by population PK analysis?

Yes, female gender and Asian race were identified as statistically significant covariate on apparent clearance in the PPK analysis. According to the PPK model, female subjects had

21% lower apparent clearance compared with a male subjects, and an Asian subjects would have 27% lower apparent clearance compared with a Caucasian subject. The impact of gender and race look mild upon clearance and they explained a small proportion of drug variability. The inter-subject variability was 21.3% when gender and race were adjusted, as compared with 22.7% without these two covariates included in this PPK model. Age was not identified as a statistically significant covariate.
In addition, the apparent clearance for a typical RCC patient is 2.2L/Hr based on the PPK model. However, the apparent clearance in a typical MTC patient is about 4.4 L/Hr according to the FDA pharmacometrics review on NDA203756. Therefore, further investigation is recommended to address such discrepancy in PK between two patient populations.

1.2 Recommendations

Division of Pharmacometrics finds NDA 208692 acceptable from a clinical pharmacology perspective. A PMC study is recommended to evaluate the effect of cancer disease type on PK of Cabozantinib as the apparent clearance of Cabozantinib is two-fold higher in MTC patients than RCC patients based on population PK analysis.

1.3 Label Statements

See section 3 of the Clinical Pharmacology Review.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

The primary objectives of this analysis were to:

- Develop a population pharmacokinetic (PopPK) model to characterize the cabozantinib concentration-time profile in healthy subjects and patients with renal cell carcinoma (RCC);
- Investigate the effects of selected covariates on cabozantinib PK parameters to derive a final parsimonious model;
- Generate individual predicted cabozantinib exposure measures for exploratory graphical assessment of the relationship between pertinent efficacy and safety endpoints and drug exposure in patients with RCC.

2.1.1 Data

The population PK analysis for cabozantinib was based on pooled data collected from Study XL184-020 in healthy subjects, and then updated when data were available from Study XL184-308 in patients with RCC. The summary of demographics is presented in **Table 4** and **Table 5**

Table 4: Summary of Studies included in Population PK Analysis

Study Number	Phase	Design	Cabozantinib Treatment[a]	Dosage Form & Meal Status	Population	PK Samples
XL184-020	1	A Phase 1, Open-Label, Randomized, Single-Dose, Three-Treatment, Parallel Pharmacokinetic Study of Cabozantinib (XL184) Tablet Formulation Administered as a Single Oral Dose in Healthy Adult Subjects	Open label, randomized, single dose, 3-treatment parallel study to assess 3 different cabozantinib tablet dose strengths (20, 40 and 60 mg) and their respective PK parameters in healthy subjects	Tablets Fast overnight for at least 10 hours before dosing and for at least 4 hours after dosing	Healthy subjects (Approximately 63 subjects)	Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120, 168, 240, 288, 336, 408, and 504 hours post-dose
XL184-308	3	A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy	60 mg cabozantinib tablets po QD	Tablets Fast 2 hours before, 1 hour after dosing	Patients with RCC (Approximately 325 cabozantinib arm subjects with on-treatment PK samples)	~8 or more hours after the prior evening dose on the W5D1 (Day 29) and W9D1 (Day 57) visits.

PK = pharmacokinetic; VEGFR = vascular endothelial growth factor receptor; po=oral; QD = once daily; RCC = renal cell carcinoma
[a] Doses in free base equivalents

Source: Synopsis of sponsor's population PK report, XL184-308.PopPK.001

Table 5: Summary of Demographics and Covariates information

Covariate	Statistics	Study		
		XL184-020	XL184-308	Pooled
Age (years)	N	63	318	381
	Mean (SD)	36.9 (8.6)	61.7 (9.6)	57.6 (13.2)
	Median	38	62.5	60
	Range (Min-Max)	(19 – 54)	(32 – 86)	(19 – 86)
Baseline BMI (kg/m^2)[a]	N	63	300	363
	Mean (SD)	27.7 (3.1)	27.3 (5.3)	27.4 (5)
	Median	27.7	26.5	26.7
	Range (Min-Max)	(20.6 – 32.9)	(17.1 – 57.7)	(17.1 – 57.7)
Baseline Albumin (g/L)	N	63	318	381
	Mean (SD)	46.4 (2.5)	37.5 (5.3)	39 (6)
	Median	47	38	39
	Range (Min-Max)	(41 – 53)	(17 – 48)	(17 – 53)
Baseline ALT (U/L)	N	63	318	381
	Mean (SD)	23.3 (10.6)	21.3 (15.5)	21.6 (14.8)
Baseline Hemoglobin (g/L)	N	63	318	381
	Mean (SD)	145.5 (14.8)	123.3 (17.1)	127 (18.6)
	Median	149	122.5	127
	Range (Min-Max)	(119 – 174)	(84 – 181)	(84 – 181)
Baseline Creatinine Clearance (mL/min)	N	63	318	381
	Mean (SD)	137.5 (26.5)	76.4 (28.3)	86.5 (36.1)
	Median	135.5	72.6	78.3
	Range (Min-Max)	(86.4 – 246.7)	(20.8 – 183.6)	(20.8 – 246.7)
Baseline Total Bilirubin (µmol/L)[b]	N	63	304	367
	Mean (SD)	10.2 (5.1)	7.6 (3.2)	8.1 (3.7)
	Median	10.3	7	7
	Range (Min-Max)	(3.4 – 30.8)	(3 – 21)	(3 – 30.8)
Sex	No. Male (%)	33 (52.4)	247 (77.7)	280 (73.5)
	No. Female (%)	30 (47.6)	71 (22.3)	101 (26.5)
Race	No. White (%)	62 (98.4)	257 (80.8)	319 (83.7)
	No. Black (%)	1 (1.6)	6 (1.9)	7 (1.8)
	No. Asian (%)	0 (0)	21 (6.6)	21 (5.5)
	No. Other (%)	0 (0)	19 (6.0)	19 (5.0)
	No. Unknown (%)	0 (0)	15 (4.7)	15 (3.9)

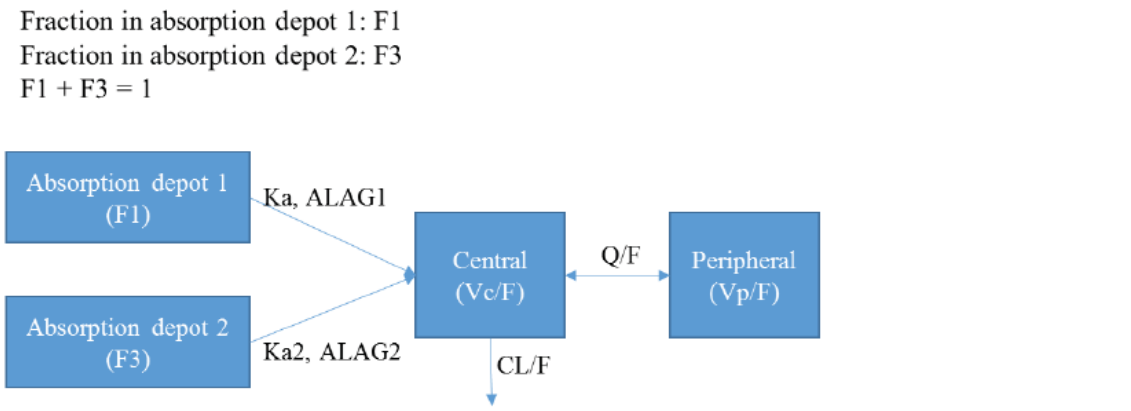
a: 18 subjects from Study XL184-308 had missing baseline BMI
b: 14 subjects from Study XL184-308 had missing baseline total bilirubin
N = number of subjects; SD = standard deviation; BMI = body mass index; ALT = alanine aminotransferase

Source: Synopsis of sponsor's population PK report, XL184-308.PopPK.001

2.1.2 Results

- A two-compartment disposition model with dual (fast and slow) lagged first-order absorption processes adequately characterized the concentration-time profile of cabozantinib in healthy subjects and patients with RCC (**Figure 3**).

Figure 3: Diagram of Cabozantinib Model Structure



F1 = fraction of dose in the first depot; F3 = fraction of dose in the second depot; Ka = depot 1 absorption rate constant; Ka2 = depot 2 absorption rate constant; ALAG1 = depot 1 absorption lag time; ALAG2 = depot 2 absorption lag time; Vc/F = apparent volume of distribution (central compartment); Vp/F = apparent volume of distribution (peripheral compartment); Q/F = apparent flow between plasma (central) and peripheral compartments; CL/F = apparent plasma clearance.

Source: Sponsor's population PK report, XL184-308.PopPK.001

- The predicted PK parameter values for a typical White male subject were: approximately 99 hours for terminal plasma half-life, approximately 319 L for terminal phase volume of distribution (Vz), and approximately 2.23 L/hr for steady state oral clearance (CL/F). Inter-individual variability (IIV) in clearance (%CV for CL/F) was estimated to be 46%.
- Female gender and Asian race were significant covariates on CL/F, where female subjects had 21% lower CL/F compared with male subjects and Asian subjects had 27% lower CL/F compared with White subjects.
- Covariates determined to have a non-significant effect on CL/F were age, baseline body mass index, baseline hemoglobin, baseline total bilirubin, baseline alanine aminotransferase, baseline serum albumin, baseline calculated creatinine clearance and population (healthy subjects or patients with RCC).

Parameter estimates and corresponding 90% CI for the preliminary final covariate model are summarized in **Table 6**.

Table 6: Parameter Estimates (90% CI) for Cabozantinib Final PK Model

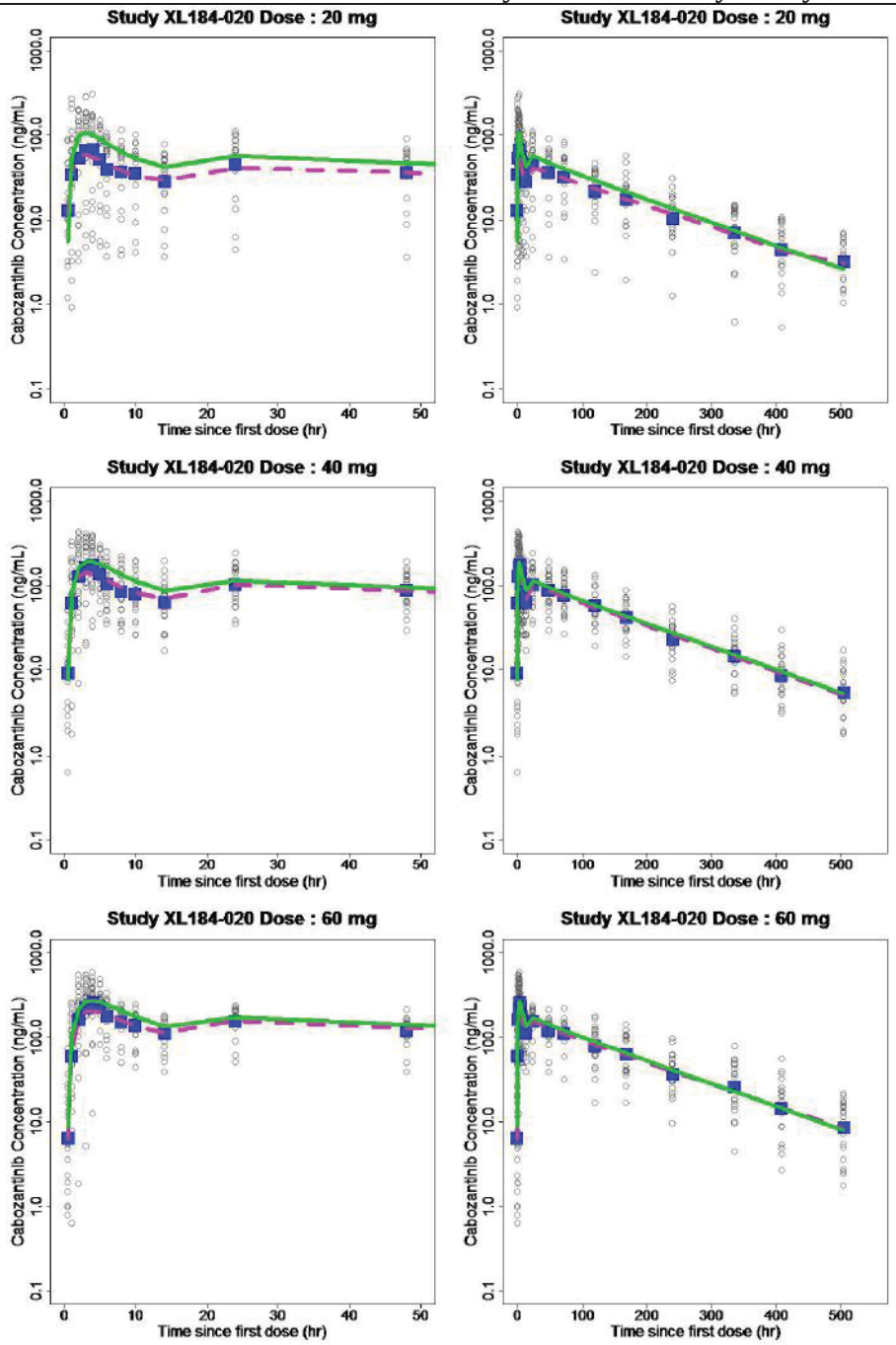
Parameter	Estimate (90% CI)[a]	Transformed Estimate (90% CI)
Ka (hr^{-1})	-0.566 (-0.752, -0.380)	0.568 (0.471, 0.684)
Ka2 (hr^{-1})	-2.28 (-2.69, -1.87)	0.102 (0.068, 0.154)
CL/F (L/hr)	0.80 (0.75, 0.85)	2.23 (2.12, 2.34)
Vc/F (L)	4.40 (4.19, 4.61)	81.5 (66.0, 101)
Q/F (L/hr)	2.65 (2.51, 2.79)	14.2 (12.4, 16.2)
Vp/F (L)	5.36 (5.30, 5.42)	213 (200, 226)
ALAG1 (hr)	-0.78 (-0.81, -0.74)	0.459 (0.443, 0.476)
ALAG2 (hr)	2.82 (2.73, 2.91)	16.8 (15.3, 18.4)
Fraction of dose for the fast absorption process F1[b]	0.73 (0.46, 1.00)	0.675 (0.613, 0.731)
Dose exponent for Ka	-0.5 (-0.85, -0.15)	-
ω2_Ka	0.437 (0.29, 0.58)	-
ω2_CL/F	0.213 (0.181, 0.245)	-
ω2_Vc/F	1.06 (0.82, 1.30)	-
ω2_F1	0.358 (0.151, 0.565)	-
ω2_CL/F:Vc/F	0.44 (0.36, 0.52)	-
Gender on CL/F	-0.23 (-0.31, -0.16)	-
Asian on CL/F	-0.32 (-0.51, -0.12)	-
Residual error	-1.37 (-1.41, -1.33)	0.254 (0.245, 0.264)
Objective Function Value	-1518.6	

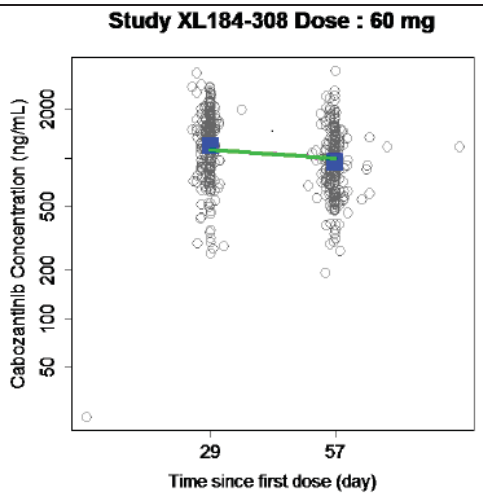
a: Logarithms of base PK parameters were estimated for MU referencing required for using the SAEM estimation method.
b: Logit of F1 was estimated.
Ka = absorption rate constant from first depot; Ka2 = absorption rate constant from second depot; CL/F = apparent plasma clearance; Vc/F = apparent volume of distribution (central compartment); Q/F = apparent flow between compartments; Vp/F = apparent volume of distribution (peripheral compartment); ALAG = absorption lag time; F1 = fraction of dose in the first absorption depot; ω2 = variance of population parameter; BMI = body mass index; HGB = hemoglobin; ALB = albumin; BILI = bilirubin ALT = alanine aminotransferase; CRCL = creatinine clearance; POP = population (healthy subjects or patients with renal cell carcinoma [RCC])

Source: Synopsis of sponsor's population PK report, XL184-308.PopPK.001

The overall goodness-of-fit plots for the preliminary final PK model are shown in **Figure 4**. Goodness-of-fit plots for the preliminary final PK model generally indicated an acceptable model fit based on similarity of geometric mean PREDs and IPREDs to the geometric mean observed data. The NONMEM control stream and output along with the diagnostic plots for the preliminary final PK model are located in Appendix 3. The residuals were generally centered around zero with homogeneous variation across the range of predicted concentrations. No appreciable covariate trends in the ETAs were observed for the preliminary final covariate model, suggesting that the preliminary final model adequately described the covariate effects.

Figure 4: Goodness-of-Fit Plots for Preliminary Final Model by Study and Dose





Black open circles correspond to individual PK observations; blue solid squares, pink dashed lines and green solid lines represent geometric means of observations, individual predictions (IPRED) and typical individual predictions (PRED), respectively.

Source: Sponsor's population PK report, XL184-308.PopPK.001

Reviewer's comments:

- *Sponsor population PK model is reasonable.*
- *From the population PK perspective, the reviewer agrees with sponsor's conclusion that no significant effect on PK was identified for age, baseline body mass index, baseline hemoglobin, baseline total bilirubin, baseline alanine aminotransferase, baseline serum albumin, baseline calculated creatinine clearance and population (healthy subjects or patients with RCC).*
- *Based on the PPK analysis, the estimated apparent clearance is 2.23L/hr. While in MTC patient (refer FDA pharmacometrics review for NDA203756), the estimated apparent clearance for a typical individual is 4.42L/hr, which is about 2-fold higher than apparent clearance estimated in RCC patients. Population PK analysis by pooling the data from MTC and RCC patients is needed to explore the effect of cancer disease type on PK of cabozantinib.*

2.2 Exposure-Response Analysis

In the XL184-308.ER.001, sponsor conducted exposure response analysis to:

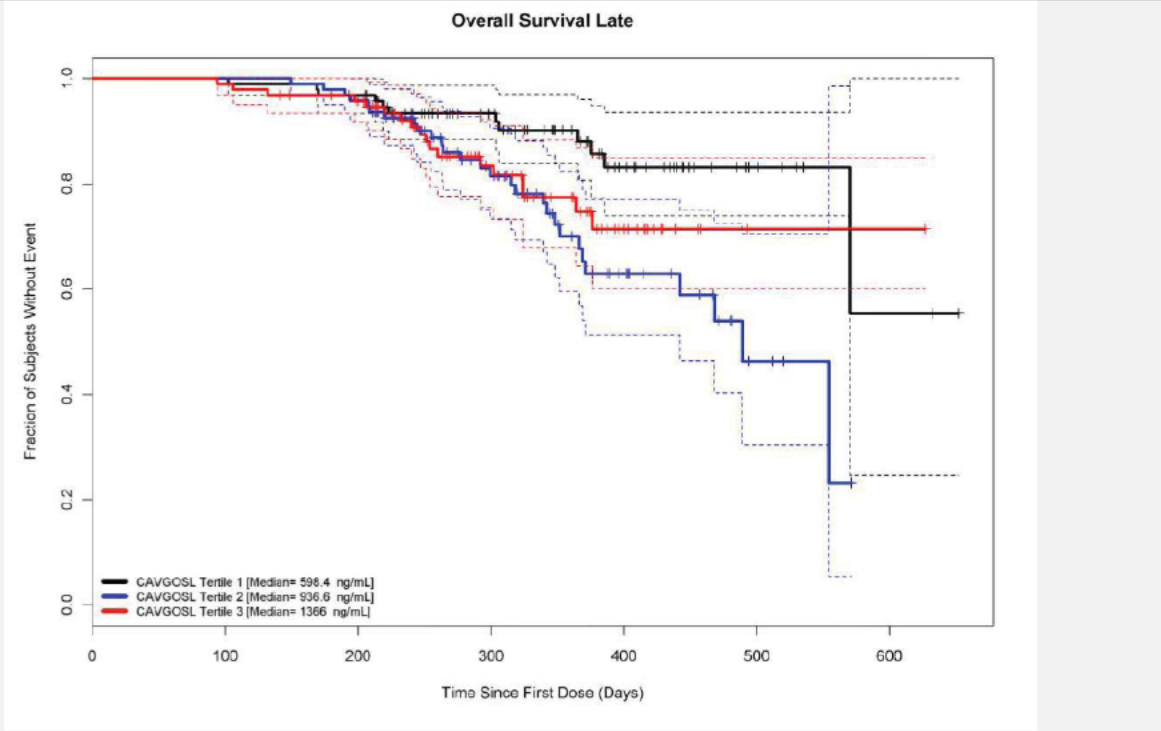
- Develop population exposure-response models to characterize the relationship between cabozantinib exposure and various efficacy and safety endpoints in subjects with renal cell carcinoma (RCC);
- Investigate the effects of selected covariates on the cabozantinib exposure-response relationships for efficacy and perform covariate selections to derive final parsimonious models;
- Generate model predictions to illustrate the relationships between cabozantinib exposure and the clinical endpoints and support dosage recommendations.

2.2.1 Exposure-OS analysis

Sponsor explored exposure-OS relationship by adapting two OS cutoffs. As at the early cut-off, there were only four events observed, this review will be focusing on the OS analysis based on late cutoff. The exposure metrics of cabozantinib was the average cabozantinib concentration over the 4 weeks prior to the Week 12 landmark (CAVGOSL). Exploratory Kaplan-Meier (KM) plots for different tertiles of cabozantinib exposure, as well as Cox model were developed to evaluate the ER relationship.

In the KM plots, sponsor's results show no clear relationship between the different tertiles of CAVGOSL and death for those subjects that received cabozantinib treatment for at least 12 weeks. (**Figure 5**)

Figure 5: Kaplan-Meier Plots for Overall Survival by Average Exposure Tertile



Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

In the Cox model analysis, the relationship between death and average cabozantinib concentration for OSL (CAVGOSL) was assessed using the linear (**Equation 1**) and the nonlinear PH model (**Equation 2**):

$$h\left(t, X_{ex}(t)\right) = h_o(t) \cdot exp\left(\beta_{ex1} \cdot X_{ex}(t)\right) \qquad \text{Eq. 1}$$

$$h\left(t, X'_{ex}(t)\right) = h_o(t) \cdot exp\left(\beta_{ex2} \cdot X'_{ex}(t)\right); X'_{ex}(t) = \frac{X_{ex}(t)}{X_{ex}(t) + EC_{50}} \qquad \text{Eq. 2}$$

where $X_{ex}(t)$ is the cabozantinib exposure measure which may vary with t, β_{ex1} represents the slope in the log-linear model, β_{ex2} represents the maximum drug effect in the E_{max} model, and EC_{50} represents a range of fixed values for the exposure at which half of the maximal effect is achieved.

According to sponsor's results, the linear and nonlinear models did not result in statistically significant reductions in OBV compared to the model without cabozantinib exposure. A parameter summary for the final linear OSL model with covariates is provided as follows

Table 7: Parameter Estimates for Final Overall Survival-Late Model

Parameter	Estimate	Standard Error	χ^2	p-value
$\beta_{CAVGOSL}$	-0.0000651	0.0003390	0.0369	0.8478
$\beta_{ECOG\ Score\ (\geq 1)}$	0.95389	0.28524	11.1834	0.0008
$\beta_{NEPHRECTOMY\ (No)}$	0.53209	0.31672	2.8224	0.0930
$\beta_{CAVGOSL*LIVER\ METASTASIS\ (Yes)}$	0.0007185	0.0002505	8.2244	0.0041

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

The final OSL model included the following covariates: average cabozantinib concentration (CAVGOSL), ECOG (Score ≥1), no prior nephrectomy surgery, and the interaction between CAVGOSL and the presence of liver metastases. CAVGOSL was included in the model as a structural covariate, regardless of the statistical significance.

After incorporating covariate effects, there was no statistically significant relationship identified between the CAVGOSL parameter and the rate of death using Wald-based statistics. However, the interaction between CAVGOSL and the presence of liver metastases was identified as a statistically significant effect based on the score test used in the all subsets selection procedure. This finding is difficult to interpret because CAVGOSL by itself was not an important predictor.

Reviewer's comment: The exposure metrics (CAVGOSL) in sponsor's exposure-OS analysis was the average cabozantinib concentration over the 4 weeks prior to the Week 12 landmark. This could introduce bias as CAVGOS only carries the exposure information between Day 14 to Week 12. The post-week-12 exposure that may drive hazard of OS was not captured in this metrics if dose reduction occurred post week 12. In addition, the Cox model assumed a constant relationship between drug exposure and hazard, thus ignored the potential drug resistance that may impair the patient sensitivity to the drug.

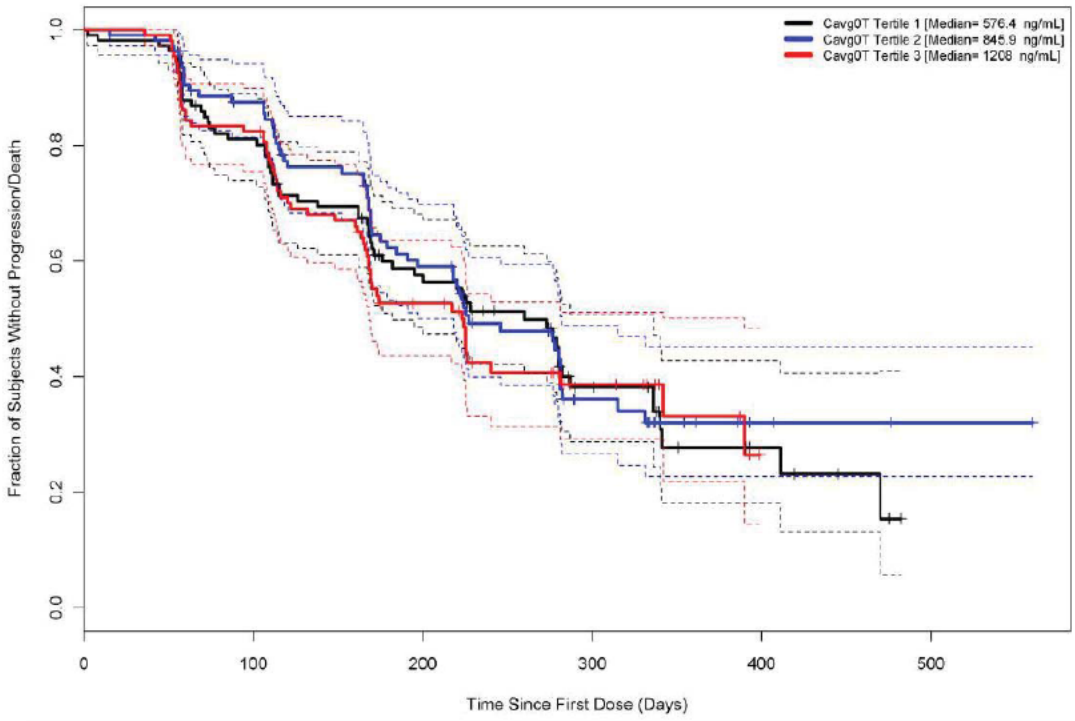
2.2.2 Exposure-PFS analysis

Similar to exposure-OS analysis, sponsor explored exposure-PFS relationship by generating exploratory Kaplan-Meier (KM) plots for different tertiles of cabozantinib exposure and developing PH survival models.

The exploratory KM plot for PFS is shown in **Figure 6**. The plot shows no clear difference between the different tertiles of cabozantinib exposure and the fraction of

subjects without progressive disease or death. Time-varying Cavg calculated from "Time 0" to t (CAVG0T) was used as the individual exposure metrics.

Figure 6: Kaplan-Meier Plots for PFS by Average Exposure Tertile



Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

Sponsor developed Cox models to evaluation relationship between cabozantinib exposure and PFS. Based on the initial assessment of the various cabozantinib exposure measures, the average cabozantinib concentration over its prior three weeks was calculated, and employed as the exposure metrics (CAVG3W) to access the.ER relationship. Nonlinear model(s) was adopted as described as Equation 2. After screening over a grid of fixed EC50 values for CAVG3W ranging from 50 to 3000 ng/mL, the best value of EC50 was fixed as 100 ng/L. A parameter summary for the best nonlinear model (EC50 = 100 ng/mL) is provided in **Table 8**.

Table 8: Emax Model Parameter Summary for Progression Free Survival

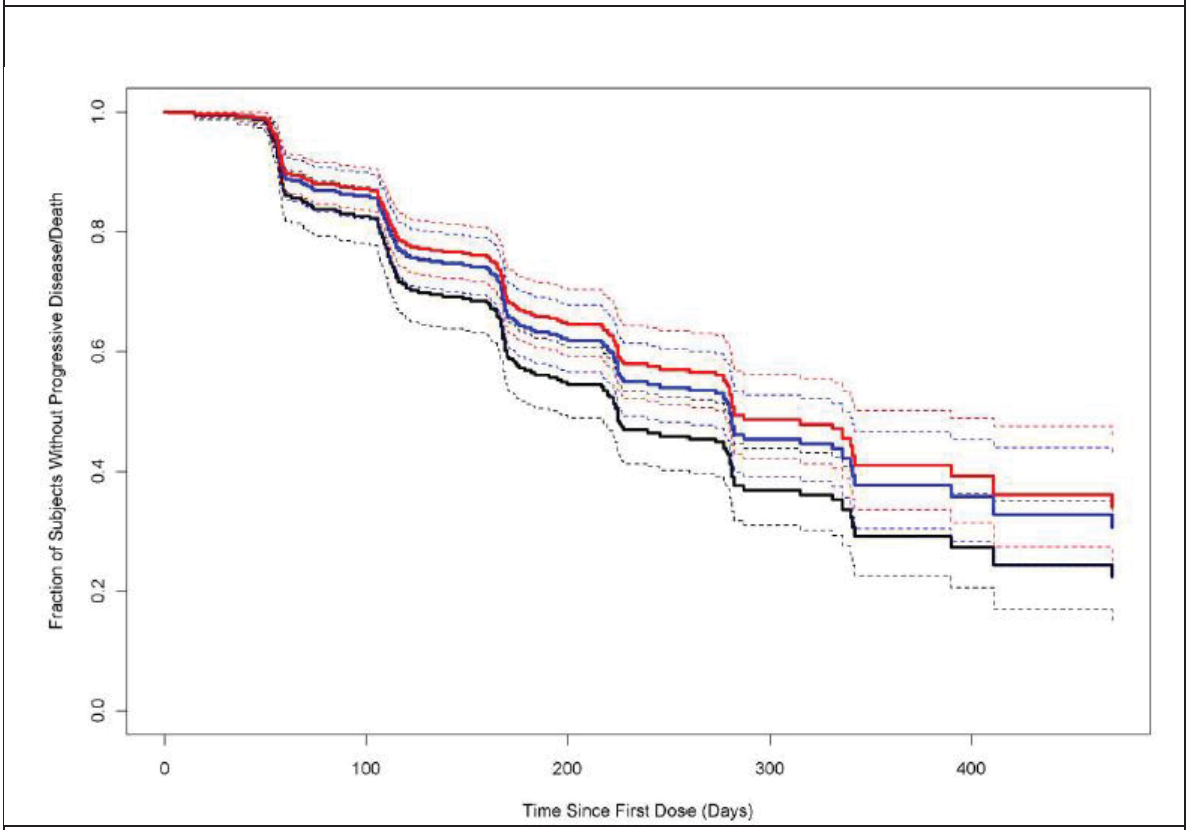
Parameter	Estimate	Standard Error	Likelihood Ratio[a] (χ^2)	p-value
$\beta_{TR\text{-}CAVG3W}$	-2.54432	0.27585	58.4044	< 0.0001

[a] Difference in -2LL between model without covariates and model including cabozantinib exposure
$\beta_{TR\text{-}CAVG3W}$ is the maximum log hazard ratio when average cabozantinib concentration is infinite

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

Figure 7 illustrates the impact of selected cabozantinib exposure values on the predicted survival curves. These curves show the predicted fraction of subjects without disease progression or death. The typical individual predicted average steady-state cabozantinib concentration for 20 mg (375 ng/mL), 40 mg (750 ng/mL), and 60 mg (1125 ng/mL) QD doses was used for exposure in the predictions. The exposures are based on cabozantinib concentrations that are constant over the course of the study. These curves do not reflect the time required to reach steady-state or any observed dosing irregularities which would be expected in observed data. These plots illustrate the relative effect of different cabozantinib concentrations on PFS in an ideal sense.

Figure 7: Predicted Survival Curves for Progression Free Survival for Selected Values of Average Cabozantinib Concentration at Reference Conditions for Other Covariates



Caption: Typical individual predicted steady-state average cabozantinib concentration for the 20 mg (black), 40 mg (blue), and 60 mg (red) doses are 375, 750, and 1125 ng/mL, respectively. The solid line represents the fraction of subjects at each dose level without progress disease or death over time. The dashed lines represent 95% confidence intervals.

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

Other covariates were further evaluated by the sponsor. Besides CAVG3W, baseline ECOG score ≥1, baseline sum of tumor diameter greater than median, liver metastasis, high MET IHC status, and elapsed time less than 3 months before progressive disease on prior TKI therapy. Parameter estimates for the final model are provided in **Table 9**.

Table 9: Parameter Estimates for Final Progression Free Survival Model

Parameter	Estimate	Standard Error	χ^2	p-value
$\beta_{TR\text{-}CAVG3W}$	-1.25581	0.63139	3.9559	0.0467
$\beta_{ECOG\ Score\ (\geq 1)}$	0.85058	0.50374	2.8512	0.0913
$\beta_{TR\text{-}CAVG3W*\ ECOG\ Score\ (\geq 1)}$	-0.31399	0.61166	0.2635	0.6077
$\beta_{SOD(>Median)}$	0.84555	0.49149	2.9597	0.0854
$\beta_{TR\text{-}CAVG3W*\ SOD(>Median)}$	-1.25269	0.59989	4.3606	0.0368
$\beta_{LIVER\ METS(Yes)}$	1.32190	0.50495	6.8534	0.0088
$\beta_{TR\text{-}CAVG3W*\ LIVER\ METS(Yes)}$	-1.26391	0.62994	4.0256	0.0448
$\beta_{IHC\ METS(High)}$	1.18288	0.59877	3.9027	0.0482
$\beta_{TR\text{-}CAVG3W*\ IHC\ METS(High)}$	-1.63127	0.76851	4.5056	0.0338
$\beta_{TR\text{-}CAVG3W*\ Prior\ TKI\ PD(< 3\ Mo.)}$	0.81809	0.24775	10.9041	0.0010
$\beta_{TR\text{-}CAVG3W}$ is the maximum log hazard ratio when average cabozantinib concentration is infinite				

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

Reviewer's comment: The results from exploratory KM plot for exposure-PFS analysis could be biased. Due to the high dose reduction/interruption rate in the trial, the exposure showed a downward trend in a general manner and subjects who had longer time to progressive disease or death could have higher chance to experience dose interruption/reduction. Thus, the CAVG0T might tend to be lower in the patients with longer PFS, which made the exposure-PFS relationship look flat.

In sponsor's Cox model analysis, the model assumed a constant relationship between drug exposure and hazard, thus ignored the potential drug resistance that may impair the patient sensitivity to the drug. In addition, as sponsor mentioned, the dose interruption/reduction was not consider in the comparison of hazard/survival curves among different doses.

Longitudinal Exposure-tumor size model

FDA issued an IR to sponsor with detailed instructions about the tumor model development (see Appendix A). In the sponsor's IR response, a longitudinal exposure-tumor size model was developed.

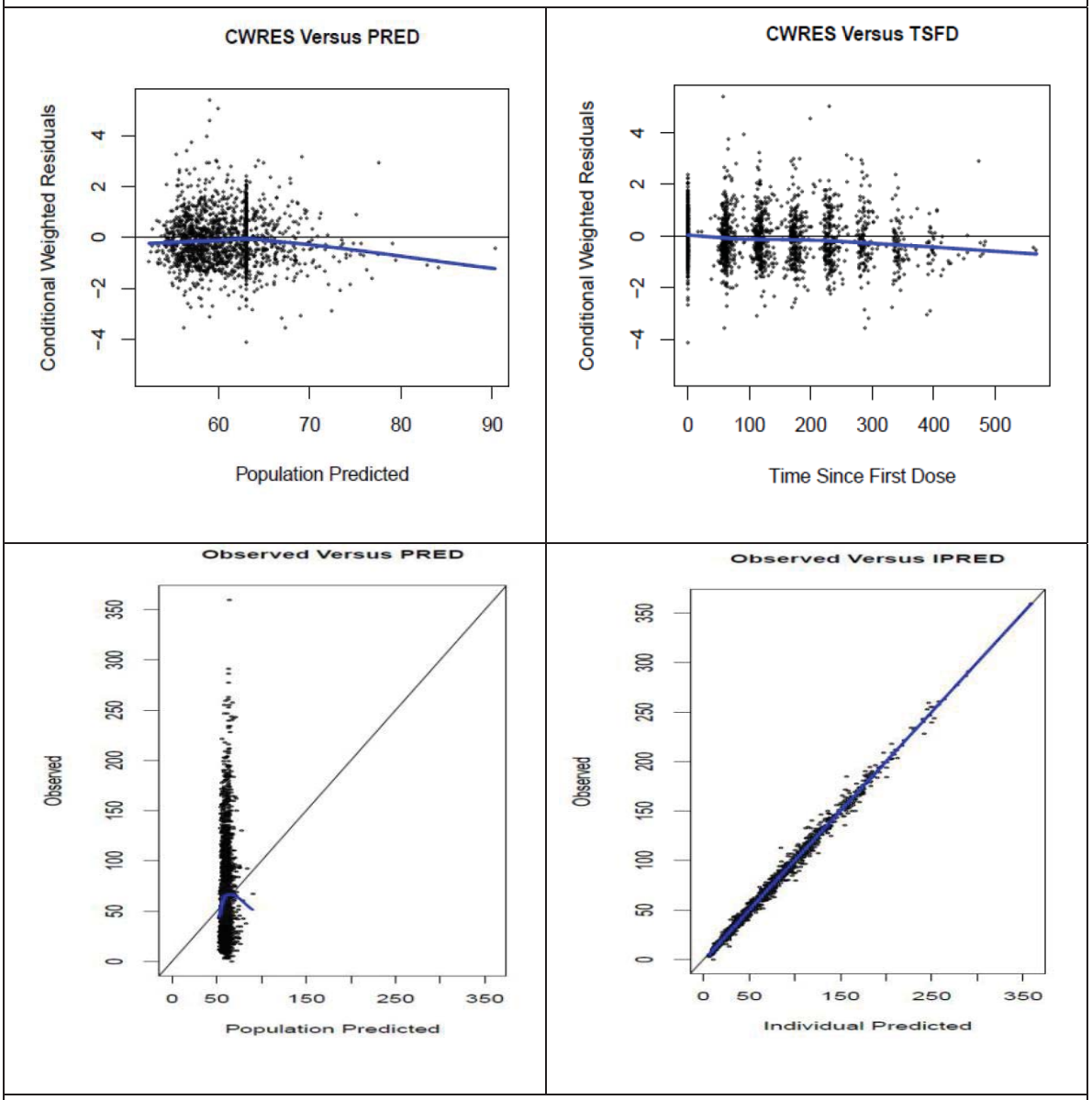
The exposure tumor model based on had a first-order growth rate, nonlinear cabozantinib drug effect, and a resistance component. The change in tumor diameter over time for the best fitting model among those tested is defined in the following equation:

$$\frac{dY}{dt} = k_{grow} \cdot Y - \frac{\left(k_{dmax} + k_{dmax_{tol}} \cdot e^{-k_{tol} \cdot t}\right) \cdot Cavg}{(EC_{50} + Cavg)} \cdot Y$$

where dY/dt is the change in tumor diameter per unit time, k_{grow} is the first-order growth rate constant, k_{dmax} is the maximum non-attenuating drug induced tumor decay rate, k_{dmax_tol} governs the maximum loss in the decay rate due to resistance, k_{tol} is the rate

constant which governs the rate of attenuation, *EC50* is the cabozantinib concentration yielding one-half of the current tumor decay rate, and C_{avg} is the individual predicted daily average cabozantinib concentration. The parameter estimates for the exposure-response tumor model are provided in **Table 10.** The goodness of fit plots are shown in **Figure 8**

Figure 8: Goodness of Fit for Exposure- Tumor Model



Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.001

Table 10: Parameter Estimates for Exposure-Response Model for Sum of Tumor Diameter

Transformed Parameter Description[a]	Estimate	Standard Error	Transformed Estimate	Transformed 90% Confidence Interval
Baseline Tumor Size (mm)	4.14	0.041	63.1	(58.9,67.5)
Tumor Growth Rate (1/day) [k_{grow}]	-6.47	0.0923	0.00155	(0.00133,0.0018)
Maximum (Non-Attenuating) Tumor Decay Rate (1/day) [k_{dmax}]	-6.69	0.143	0.00125	(0.000984,0.00158)
Maximum (Attenuating) Tumor Decay Rate (1/day) [k_{dmax_tol}]	-4.79	0.117	0.00835	(0.00689,0.0101)
Concentration Achieving 1/2 of Maximal Effect (ng/mL) [EC_{50}]	5.53	0.243	251	(169,375)
Attenuation Rate Constant (1/day) [k_{tol}]	-3.61	0.0781	0.0271	(0.0238,0.0308)
Residual Variability (Standard Deviation) (mm)	1.75	0.0253	5.75	(5.52,6)
IIV Base (ω^2)	0.522	0.0438	0.522	(0.45,0.594)
IIV k_{grow} (ω^2)	0.313	0.0578	0.313	(0.218,0.408)
IIV k_{dmax} (ω^2)	0.353	0.0781	0.353	(0.224,0.482)
IIV k_{dmax_tol} (ω^2)	0.641	0.105	0.641	(0.469,0.814)
IIV EC_{50} (ω^2)	0.02 FIX	0	0.02 FIX	(0.02,0.02)
IIV k_{tol} (ω^2)	0.02 FIX	0	0.02 FIX	(0.02,0.02)

[a] Units reflect values for transformed parameters
IIV = interindividual variability

Source: Synopsis of Exposure-Response Report, Study No. XL184-308.ER.002

Reviewer's comment: The sponsor's exposure-tumor size model seems reasonable. The drug resistance was incorporated as an empirical manner by adding a time term onto the maximal effect of the drug.

2.3 Exposure-Safety Analysis

In order to directly evaluate the effects of exposure on dose reduction/interruption, FDA issued an IR to sponsor with detailed instruction to model the relationship between cabozantinib exposure and dose-altering AEs. The following review will be focusing on this part.

Repeated Time-to-Event All Dose Modification Model

A repeated time-to-event model was constructed incorporating all dose changes, including dose increases (DMPK model). The hazard for the all dose modification model is defined by the following equation, where the hazard is dependent on whether a subject is currently on a dose interruption.

$$\lambda = \exp\left(\theta_{base} + \theta_{drug} \cdot C_{avg}\right) \qquad \{if\ Dose > 0\}$$

$$\lambda = \exp\left(\theta_{base} - hold\right) \qquad \{if\ Dose = 0\}$$

The parameter estimates for the final model are provided in **Table 11**. When subjects are not on a dose interruption, increases in cabozantinib concentration increase the instantaneous risk for a dose modification.

Table 11: Parameter Estimates for All Dose Modification Repeated Time-to-Event Model

Transformed Parameter Description	Estimate	Standard Error	Transformed Estimate	Transformed 90% Confidence Interval
Baseline Log Hazard [θ_{base}]	-5.4	0.121	-5.4	(-5.6,-5.2)
Change in Log Hazard Per Unit Cabozantinib Concentration [θ_{drug}]	0.000807	0.0000989	0.000807	(0.000644,0.000969)
Baseline Log Hazard (Dose Hold) [θ_{base}-hold]	-2.7	0.0747	-2.7	(-2.82,-2.57)
IIV Baseline	0.655	0.0899	0.655	(0.507,0.803)

IIV = interindividual variability

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

Reviewer's comment: The exposure-dose altering AE model relies on the assumption that the exposure has instantaneous effects upon the hazard. This assumption may not be valid if drug exposure had an indirect impact on the likelihood to have AEs, through some latent variables. In addition, the probability of dose reduction may be dependent on how many dose interruptions a subject has experienced previously, but this scenario was not described in this model.

2.4 Simulations

Simulation of dose reduction/interruption with varying dosing regimens.

Simulations were performed to compare the effects of cabozantinib on longitudinal tumor size for a starting dose of 60 mg versus a starting dose of 40 mg and 20 mg. The DMAK model was used to simulate longitudinal Cavg for 1000 subjects over 12 months based on the changing dosing events. To mimic dose change scenarios noted in the observed dataset, at the time of each simulated event, the observed probability of having a dose reduction, interruption, or dose escalation based on the current dose was used. Furthermore, if the current dose was 0, representing an interruption, the observed probability of escalating to 20, 40, or 60 given the dose prior to the interruption was used. The simulation results are shown in **Table 1**

Time course of tumor size was simulated with the exposure-tumor size model for different starting dose based on the simulated dosing history (**Figure 2Error! Reference source not found.**). Subjects in the 20mg QD starting dose treatment group showed significant loss of efficacy in terms of the tumor size reduction, relative to the 60 mg QD starting dose treatment group. In addition, tumor suppression is also compromised in the 40 mg QD starting dose treatment group.

Based on the simulated tumor dynamics, the sponsor computed the tumor response at baseline and every 8 weeks for 1 year using the longitudinal sum of tumor diameter predictions.

The response value was computed in accordance with the response criteria specified for Study XL184-308. From the longitudinal response data, the BOR was computed for each subject. The predicted percentage of subjects with CR, PR, SD, or PD for a 20 mg, 40 mg, and 60 mg starting dose treatment regimen are provided in **Table 2**. A higher percentage of subjects achieve the Objective Response Rate (ORR – based on CR plus PR), and a lower percentage of subjects have PD in the 60 mg starting dose treatment group relative to the 20 mg and 40 mg starting dose treatment groups (**Table 12**).

Table 12: Percentage of Simulated Subjects (N=1000) Achieving Each Best Overall Response Category

Best Overall Response (BOR)	20 mg Starting Dose (%)	40 mg Starting Dose (%)	60 mg Starting Dose (%)
Complete Response (CR)	0.10	0.00	0.00
Partial Response (PR)	8.60	15.6	19.10
Stable Disease (SD)	81.1	76.3	73.40
Progressive Disease (PD)	10.2	8.10	7.50

Source: Adapted from Study No. XL184-308.ER.002 - Memorandum

Reviewer's comment: Monte Carlo simulation was used to generate the virtual dosing history and time course of tumor sizes. As the sponsor developed the exposure-dose-alternation model and exposure-tumor dynamics separately, the potential association between the probability to respond (efficacy) and likelihood to have severe AEs could not be incorporated into the model and thus be reproduced by generating virtual population. Simulations using post-hoc estimates are able to address this issue to some extent. In addition, as sponsor mentioned, subject drop out due to progressive disease, death or consent censoring was not considered in generating the virtual dosing history, which may make the simulated dose reduction rate higher than observed.

3 APPENDIX – IR TO SPONSOR

Please address the following questions and submit the dataset regarding the exposure-response (ER) analysis:

1. Please use the exposure-efficacy/safety analyses to assess whether a lower dose of cabozantinib can achieve efficacy similar to the 60 mg dose, but has less toxicity. In addition to ORR, PFS and OS, the longitudinal continuous tumor size should be analyzed in the following way to evaluate a lower dose:

a. Develop an exposure-response model for the time course of tumor size for cabozantinib in RCC patients. Longitudinal drug exposure based on the actual doses should be used.

b. Develop a longitudinal exposure – AE model. Sponsor may treat all dose-altering/interrupting AEs as one repeatable event.

c. Simulate the dose modification/interruption scenario with a lower starting dose levels (such as 12mg) using the exposure-AE model developed in step b and the current dose adjustment algorithm.

d. Sponsor could also assess the net benefit of adding an up-titration option to the current titration algorithm.

e. Based on the dose simulated from step c, individual longitudinal exposure can be simulated based on the individual PK parameters from the population PK model. The individual exposure can be used to simulate the time course of tumor size with the lower starting doses.

2. Please submit a dataset for FDA reviewer's analysis as SAS transport files (*.xpt) with define.pdf files. The dataset should include:

a. Time and reasons for each dose adjustment and interruption;

b. Types of co-medications at time point when each dose interruption and adjustment happens;

c. Dose level after each modification.

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/s/

PENGFEI SONG
04/14/2016

CHAO LIU
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JINGYU YU
04/14/2016

QI LIU
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NAM ATIQUR RAHMAN
04/14/2016
I agree with the review team's recommendation.