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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 20th, 2016
From	Julia A. Beaver, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	208692 N/A
Applicant	Exelixis, Inc.
Date of Submission	December 22nd, 2015
PDUFA Goal Date	June 22nd, 2016
Proprietary Name / Established (USAN) names	CABOMETYX™ (cabozantinib)
Dosage forms / Strength	60mg, 40mg, 20mg tablets
Applicant Proposed Indication(s)	CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy.
Recommended:	Approval
Recommended Indication(s)/Population(s)	CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

Material Reviewed/Consulted	Names of discipline reviewers/Team Leaders
Regulatory Project Manager	Rajesh Venugopal/Christy Cottrell
Medical Officer Reviewer	Harpreet Singh and Michael Brave/ Julia Beaver
Statistical Review	Joyce Chen/ Shenghui Tang
Pharmacology Toxicology Review	Elias Zahalka/ Todd Palmby
CMC Review	Xing Wang – Drug Product and Substance Xiao Chen/ Anamitro Banerjee(Acting Branch Chief) – Drug Product
Micro process Reviewer	Ying Zhang/Jennifer Maguire
Facilities	Laura Fontan/Zhihao Peter Qiu
Biopharmaceutics	Fang Wu/Kimberly Raines
Clinical Pharmacology Review	Pengfei Song/ Qi Liu
Pharmacometrics Review	Chao Liu/ Yaning Wang
DMPP/OPDP	Nazia Fatima/Jessica Cleck Derenick
OSI	Lauren Iacono-Connors/ Susan Thompson
OSE/DMEPA	Tingting Gao/Alice (Chi-Ming) Tu
OSE/DRM	Carolyn Yancey/ Naomi Redd
OSE RPM	Frances Fahnbulleh
DEPI	Steven Bird
Patient Labeling	Rowe Medina/Barbra Fuller
Safety	Susan Jenny/ Katherine Fedenko

DMPP= Division of Medical Policy Programs, OPDP= Office of Prescription Drug Promotion OSI=Office of Scientific Investigations, OSE= Office of Surveillance and Epidemiology DMEPA=Division of Medication Error Prevention and Analysis, DRM= Division of Risk Management, DEPI=Division of Epidemiology, DPMH= Division of Pediatric and Maternal Health.

1. Introduction

On December 22nd, 2015, Exelixis Inc. completed the rolling submission of a New Drug Application (NDA) for Cabometyx™ (cabozantinib) indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received one prior therapy. During the review, the indication was amended to the following: "Cabometyx is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy".

The recommendation for approval of cabozantinib is primarily based on data from one randomized, open-label, multicenter study in 658 patients with advanced RCC who had received at least one prior anti-angiogenic therapy (Trial XL184-308). Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group. Patients were randomized 1:1 to receive either cabozantinib (N=330) administered at 60mg orally daily, or everolimus (N=328) administered at 10mg orally daily.

The major efficacy outcome was progression-free survival (PFS) as assessed by a blinded independent radiology review committee (IRC) in the first 375 randomized patients. Statistically significant improvement was observed in PFS with a median PFS of 7.4 months [95% Confidence Interval (CI): 5.6, 9.1] in the cabozantinib arm and 3.8 months (95% CI: 3.7, 5.4) in the everolimus arm [HR: 0.58 (95% CI 0.45, 0.74), stratified log-rank p-value <0.0001, per IVRS]. Other efficacy endpoints were overall survival (OS) and objective response rate (ORR) in the Intent-to-Treat (ITT) population. At the time of PFS analysis, the OS data was not mature and no statistically significant difference was seen. However, a second interim analysis was conducted with more mature data and a statistically significant difference in OS was demonstrated with a median OS of 21.4 months (95% CI: 18.7, not estimable) in the cabozantinib arm and 16.5 months (95% CI: 14.7, 18.8) in the everolimus arm (HR: 0.66, 95% CI: 0.53, 0.83; stratified log-rank p-value =0.0003, per IVRS) representing a median difference in OS of 4.9 months. ORR showed a statistically significant improvement in the cabozantinib arm compared to the everolimus arm with a 17% ORR (95% CI: 13, 22) and 3% ORR (95% CI: 2, 6) respectively.

The safety profile of cabozantinib was assessed in the 331 patients receiving at least one dose of cabozantinib and was consistent with the prior approval of cabozantinib in medullary thyroid cancer (MTC) as well as other multi-target kinase inhibitors. The most commonly reported (≥25%) adverse reactions were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation. Serious adverse events (SAEs) occurred in 40% of cabozantinib-treated patients and 43% of everolimus-treated patients. Sixty percent of patients who received cabozantinib required dose reductions compared to 24% on the everolimus arm. Dose reductions occurred most commonly due to diarrhea (16%), PPES (11%), Fatigue (10%) and Hypertension (8%). Adverse reactions led to study treatment discontinuation in 10% of patients receiving cabozantinib and in 10% of patients receiving everolimus.

A review issue revolved around the potential need for a dose-finding postmarketing requirement (PMR). However, after careful review described in this document, it was not felt that there was need for a further assessment of a known serious risk related to the use of the drug, and there was a concern about the potential for decreased efficacy with decreased doses; therefore, a dose finding PMR was not recommended.

In conclusion, cabozantinib demonstrated efficacy over everolimus in a population of patients with advanced RCC who have received prior anti-angiogenic therapy. The improvement in PFS and OS of cabozantinib over everolimus was statistically significant and clinically meaningful. The safety profile at a dose of 60mg orally daily was acceptable for the population studied. Therefore the overall benefit: risk profile is favorable to support approval.

This document summarizes the reviews and conclusion of each review discipline. There were no major disagreements among the recommendations of the review disciplines involved with this application.

2. Background

Pathophysiology of Condition
Renal cell carcinoma is a serious and life-threatening condition. In 2015, it is estimated that there will be 61,560 new cases and 14,080 deaths from RCC in the U.S (SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer 2015). Advanced RCC is most commonly treated with anti-angiogenic therapy in the first line setting, and after progression, the median PFS and OS can be as little as 5 and 20 months, respectively (Drugs@FDA: affinitor USPI and everolimus USPI). There is an unmet medical need to improve clinical outcomes in advanced RCC.

Existing (or Available) Therapies
There are three currently approved therapies for advanced RCC in the second line setting: everolimus, axitinib, and nivolumab. Everolimus is a mTOR inhibitor which demonstrated a median PFS improvement over placebo of 4.9 vs. 1.9 months. Axitinib a tyrosine kinase inhibitor demonstrated a median PFS improvement over sorafenib of 6.7 vs. 4.7 months. Nivolumab, an immunotherapy was approved in 2015 with an median OS benefit over everolimus of 25 vs. 19.6 months.

Product Information
Cabozantinib is an orally bioavailable multi-targeted kinase inhibitor with activity against MET (hepatocyte growth factor receptor protein) and VEGFR2 (vascular endothelial growth factor receptor), as well as other receptors that have been implicated in tumor pathobiology, including AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2.

Regulatory Background

- **June 10, 2005-** IND 72,596 submitted.
- **November 29, 2012**- cabozantinib (Cometriq) was approved for the treatment of patients with progressive, metastatic, medullary thyroid cancer (MTC).
- **January 17, 2013-** FDA and the Applicant discussed a proposal regarding a planned registration study in advanced RCC. FDA agreed on the design of Trial XL184-308, including the choice of comparator arm and the use of PFS as the primary endpoint with a robust evaluation of OS as a secondary end point.
- **February 27, 2013-** Protocol XL184-308, A Phase III, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Patients with Metastatic Renal Cell Carcinoma that is Refractory to or has Progressed after prior VEGFR Tyrosine Kinase Inhibitor Therapy was submitted to the IND.
- **September 13, 2013-** The Applicant discussed with FDA a tablet formulation of cabozantinib.
- **April 8, 2015-** Fast Track Designation was granted for treatment of patients with advanced renal cell carcinoma who have received one prior therapy.
- **August 21, 2015-** Breakthrough Therapy Designation was granted based on preliminary evidence from Trial XL184-308 which indicated that the treatment effect of cabozantinib may represent a substantial improvement over existing therapies for the treatment of advanced renal cell carcinoma after prior VEGFR-TKI therapy.
- **September 2, 2015-** FDA stated that a review of additional OS analysis would occur during the NDA review. The Applicant stated that additional PK reports would be submitted after the initial filing. FDA also stated that a 120-Day Safety update was not required, and recommended a rolling NDA submission.
- **October 13, 2015-** Rolling NDA submission initiated for the treatment of patients with metastatic RCC after prior VEGFR TKI therapy.
- **December 22, 2015-** final NDA component (Clinical) of the rolling NDA submission was submitted.

3. CMC/Device

The clinical CMC reviewers (Xing Wang Ph.D.), Application Technical Lead (Xiao Chen, Ph.D.), and Branch Chief (Anamitro Banerjee Ph.D.) concluded that the NDA is recommended for approval. Adequate data were provided for the manufacture and controls of the drug substance and drug product. The Office of Compliance issued an overall "acceptable" recommendation for all facilities used for manufacturing and control of the drug substance. Although cabozantinib had been previously approved in a capsule formulation for metastatic MTC, the current NDA was for a cabozantinib tablet formulation which will be commercialized under a different trade name and with a different indication. As NDA 208692 is for a new dosage form of an active ingredient that has been approved or marketed in the United States in a different dosage form, the NDA is a Type 3 NDA and not deemed a supplemental application. The following summary of chemistry assessments is excerpted from the CMC reviews.

General product quality considerations

Drug Substance:
CABOMETYX is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. The chemical name of cabozantinib (*S*)-malate is *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate.
The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. The proposed commercial manufacturing process is a (b) (4) (b) (4) (b) (4) The drug substance specification includes testing for appearance, identity, assay/ordinary impurities, (b) (4) content, four GTIs, water content, residual solvents, inorganic impurities, crystal form, heavy metals and particle size distribution. Updated long term stability data was submitted that includes (b) (4) (b) (4) data stored at (b) (4) The applicant retested a (b) (4) retest date for cabozantinib (*S*)-malate at the recommended storage conditions of (b) (4), which was deemed acceptable.

Drug Product:
The drug product is provided as immediate release tablets with three strengths containing a (b) (4) with each tablet consisting of (b) (4) (b) (4) Drug Substance with microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The 20mg, 40mg, and 60mg tablets are coated with an (b) (4) Yellow film coating (b) (4). All excipients in the cabozantinib tablets are compendial grade and consist of non-novel excipients. The formulation components and composition have not been modified throughout the course of development. All cabozantinib tablet batches used in clinical studies have always been manufactured from Drug Substance batches containing predominantly (b) (4) (b) (4) (b) (4) the tablets (20-mg, 40-mg, and 60-mg strengths) is a 60-cc HDPE bottle in a 30-count configuration. The drug product specification proposed per ICH Q6H consists of testing for Appearance, Identification, Potency, Impurities, Content Uniformity, water content, dissolution, Genotoxic impurities (GTIs) and Microbial limits. Content uniformity, dissolution and GTIs are considered critical quality attributes.

Long term stability data including up to 36 months at 25 °C/60%RH for the drug product batches manufactured with a process representative of the proposed commercial manufacturing process and at the intended commercial site (Patheon, Mississauga, Ontario, Canada) were

submitted. A 36 month shelf life is granted for the drug product stored at 25°C (77°F), excursions permitted to 15° to 30 °C (59° to 86°F).

Biopharmaceutical:
Cabozantinib is classified as a BCS Class 2 (low solubility, high permeability) that demonstrates a pH-dependent solubility profile. Cabozantinib (XL184 free base) was determined to be practically insoluble in water (<0.0001 mg/mL) and polymorphic. The applicant did not request a BE waiver. Besides the approved capsule formulation (COMETRIQ®, NDA 203756), a tablet formulation (20 mg, 40 mg and 60 mg) was later developed and was used in the biopharmaceutical Trial XL184-308. All of the drug product batches were manufactured at the intended commercial site (Patheon, Mississauga, Ontario, Canada). The tablet formulation did not change between that used in Trial XL184-308 and the proposed commercial drug product. The proposed dissolution method and the revised acceptance criteria ((b) (4) % at 15 min.) for the dissolution test are found to be acceptable.

Facilities review/inspection:
The Office of Compliance issued an overall acceptable recommendation on for all manufacturing and testing facilities during the review cycle.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer, Elias Zahalka Ph.D., and the team leader, Todd Palmby, Ph.D., state that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval and that no additional nonclinical pharmacology/toxicology studies are needed. The following summary of nonclinical pharmacology and toxicology assessments are abstracted from their reviews.

General nonclinical pharmacology/toxicology considerations
In support of the proposed indication, toxicology data from the initial NDA 203756 (metastatic MTC) as well as new nonclinical studies were submitted to NDA 208692. Refer to the nonclinical review from NDA 203756. During NDA 208692 it was determined that in addition to other tyrosine kinases included in the MTC cabozantinib label, ROS1, TYRO3, and MER kinases were also inhibited by cabozantinib and therefore these were added to the drug label.

Carcinogenicity
In fulfillment of a PMR for NDA 203756, the applicant submitted a 26-week mouse carcinogenicity study final report. The results showed that at the highest doses tested (1.2 fold the nominal MRHD of 60mg/day of cabozantinib), cabozantinib did not result in test article-related increases in the incidence of neoplastic lesions. At 15 mg/kg/day, non-neoplastic microscopic findings were reported in the spleen (lymphocyte depletion), glandular stomach (hyperplasia of the epithelium), duodenum (hyperplasia of the epithelium) and pancreas (zymogen depletion). Cabozantinib was not mutagenic or clastogenic.

Reproductive toxicology
Reproductive toxicology data was reviewed under NDA 203756; based on findings from animal studies and its mechanism of action, cabozantinib can cause fetal harm when administered to a pregnant woman. Further information on animal studies reviewed under NDA 203756 are reflected in the drug label.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/pharmacometrics reviewers (Pengfei Song, Ph.D. and Chao Liu, Ph.D.) and team leaders (Qi Liu, Ph.D. and Jingyu Yu Ph.D.), concluded that there are no outstanding clinical pharmacology issues that preclude approval. One clinical pharmacology Postmarketing Commitment (PMC) was agreed to with the applicant. The following information was abstracted from the Clinical Pharmacology reviews and the cabozantinib label.

General clinical pharmacology/biopharmaceutics considerations
In the current RCC submission, the applicant provided new clinical pharmacology 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; hepatic impairment study (XL184-003), a renal impairment study (XL184-017), and a drug-drug interaction study evaluating the effect of gastric pH modification (XL184-018). In addition, PK data from the randomized Trial XL184-308 was reviewed. The formulation used in Trial XL184-308 and recommended for approval in advanced RCC is a tablet formulation which differs from the capsule formulation previously approved for MTC (see Section 3).

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 3 hours post-dose. The predicted terminal half-life of cabozantinib tablets 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. Steady-state exposure ($C_{min,ss}$) was 1260 ng/mL, 44.4% 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.

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 to minimize the risk of any clinically-meaningful effect on food intake on plasma exposure.

Drug-drug interactions
The drug-drug interaction evaluation with respect to induction and inhibition of CYP enzymes and P-gp was conducted under NDA 203756 (MTC). Cabozantinib is a substrate of CYP3A4 *in vitro.* Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 38%. Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to

healthy subjects decreased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 77%. Although cabozantinib is an inhibitor of CYP2C8 *in vitro,* no clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} 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. Inhibition of CYP2C9 *in vitro* had a minimal effect on cabozantinib metabolite formation. *In vitro,* inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes *in vitro*. Cabozantinib is an inducer of CYP1A1 mRNA *in vitro*; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

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. 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.

Pathway of elimination
Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational ^{14}C-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.

Evaluation of intrinsic factor potentially affecting elimination
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 was not considered clinically important. Covariates determined to have a non-significant effect on CL/F were age (32-86), 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). Mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 as estimated by MDRD) did not demonstrate a clinically relevant difference in the pharmacokinetics of cabozantinib. Cabozantinib exposure (AUC_{0-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.

Demographic interactions/special population
The pharmacokinetics of cabozantinib has not been studied in the pediatric population

Thorough QT study or other QT assessment
The effect of orally administered cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC 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 the MTC application had a confirmed QTcF > 500 ms nor did any cabozantinib-treated patients in Trial 184-308.

Exposure-response relationships

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 advanced RCC.

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 daily 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.

Given the frequency of dose reductions, further modeling and simulations were undertaken in order to better inform the acceptability of the 60mg dose. These simulations indicated that lower starting doses such as 40 mg or 20 mg daily have the potential to compromise efficacy although dose reductions may be lower. Modeling showed that the potential reduction in tumor size would be effected for dose reduction with a median percent change of tumor size from baseline of -4.45% with 20mg, -9.1% with 40 mg, and -11.9% with 60mg. These reductions in tumor size correlate to an ORR of 8.7%, 15.6%, and 19.1% with the 20mg, 40mg, and 60mg dose respectively. A dose higher than 60 mg daily is not considered appropriate, given the 60% rate of dose reductions at this dose; a lower dose may result in compromised benefit. Therefore, dose selection of 60 mg daily was deemed acceptable.

Other notable issues

The formulation used in trial XL184-308 and recommended for approval in advanced RCC is a tablet formulation which differs from the capsule formulation previously approved for MTC (see Section 3). 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%. For C_{max}, the upper limit of the 90% CI (131.65%) was outside upper limit of 125.00%. Therefore, although the systemic exposure following cabozantinib capsule and tablet formulations are similar, bioequivalence could not be concluded. A 19% increase in the C_{max} of the tablet formulation compared to the

capsule formulation was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet and capsule formulations.

Cross-study PK analysis indicated similar steady-state exposures ($C_{trough,ss}$) at different doses across patient populations of MTC (140 mg capsules), advanced 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 PMC was requested and agreed upon with the applicant to evaluate the potential impact of tumor types, (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.

6. Clinical Microbiology

The microbiology review by Ying Zhang, Ph.D. concluded that there were no outstanding microbiology issues that preclude approval and no additional studies were needed. The drug product was tested for microbial limits and these were found reasonable for the immediate release tablet formulation per ICH Q6H. Microbial limit testing was conducted at batch release and on stability studies on representative batched; all data met the acceptance criteria. Therefore, commercial batches will be tested for microbial limit testing (b) (4)

7. Clinical/Statistical- Efficacy

Michael Brave M.D. was the primary clinical reviewer of efficacy for this application. Joyce Cheng Ph.D., and TL Shenghui Tang Ph.D., were the statistical reviewers for this application. There were no disagreements between the CDTL and clinical or statistical reviewers with respect to efficacy analyses. The NDA is primarily supported by PFS, OS, and ORR results from a single, open-label, multicenter, international trial, Trial XL184-308, entitled "**A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) Versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy**".

Study Design:
Trial XL184-308 randomized 658 patients (1:1) to receive either cabozantinib (N=330) administered orally at 60 mg daily or everolimus (N=328) administered orally at 10 mg daily. The open-label, multicenter (182 sites in 24 counties including the U.S.) trial was conducted in patients with advanced RCC who had received at least 1 prior anti-angiogenic therapy. Patients had to have a Karnofsky Performance Score (KPS) $\geq$ 70%. Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group. Patients were treated until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator.

The primary objective of the study was PFS by RECIST v1.1 as assessed by IRC among the first 375 patients randomized (Primary Endpoint Intent-to-Treat Population or PITT). PFS was defined as the time from randomization to the earlier of the following events: documented progressive disease (PD) per RECIST v1.1 or death due to any cause. Key secondary endpoints included OS as defined as the time from first dose until death due to any cause and ORR per RECIST v1.1 as assessed by IRC. The primary PFS and secondary OS analyses by the Applicant were stratified by data collected on the electronic Case Report Forms (eCRFs). To follow the ITT principle, FDA conducted additional analyses based on IVRS.

Protocol Deviations

The number of applicant defined important (could put a subjects safety at risk or impact the interpretation of the study results) violations was similar between arms (approximately 23% in each arm). Important eligibility violations accounted for 11% of these in both arms. These deviations were generally related to laboratory value collection times, time of last anti-angiogenic therapy, and QTc values, and were unlikely to have impacted the results of the trial. The primary PFS analysis by the Applicant was stratified by data collected on the eCRFs. A concordance analysis of eCRF- and IVRS-based stratification values revealed some discrepancies, with 3% discordant Number of Prior VEGFR-TKIs and 11% MSKCC prognostic criteria discordance in the cabozantinib PITT population. However, the review team performed analyses based on both stratification by eCRF and IVRS for PFS and OS, and results remained consistent (see Efficacy Results below).

Patient Demographics and Disease Characteristics

All patients had RCC with a clear cell component by histology or cytology. The majority of the patients were male (75%), with a median age of 62 years. Sixty-nine percent (69%) received only one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 46% favorable (0 risk factors), 42% intermediate (1 risk factor), and 13% poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%). Approximately 5% of patients had prior PD-L1 or PD-1 blocking antibodies. In general the treatment arms were balanced with respect to age, gender, race, ethnicity, enrollment region, number of prior therapies, MSKCC risk factors, prior cancer therapies.

Patient Disposition

Overall there were 658 patients enrolled at 182 sites in 24 countries (200 patients were enrolled in the US). Table 1 summarizes the reason for treatment discontinuation.

Table 1: Patient Disposition

	ITT Population		PITT Population	
	Cabozantinib N = 330	Everolimus N = 328	Cabozantinib N = 187	Everolimus N = 188
Treatment ongoing	133 (40%)	67 (20%)	56 (30%)	33 (18%)
Discontinued treatment	197 (60%)	261 (80%)	131 (70%)	155 (82%)
Progressive disease	122 (37%)	158 (48%)	82 (44%)	92 (49%)
Adverse event	32 (10%)	31 (9%)	21 (11%)	20 (11%)
Clinical deterioration	28 (8%)	51 (16%)	18 (10%)	29 (16%)
Withdrawal by subject	6 (2%)	11 (3%)	3 (2%)	7 (4%)
Physician decision	5 (2%)	2 (1%)	4 (2%)	2 (1%)
Lack of efficacy	3 (1%)	0 (0%)	2 (1%)	0 (0%)
Protocol violation	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
No study treatment given	0 (%)	5 (2%)	0 (0%)	3 (2%)
Sponsor decision	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Other	0 (0%)	1 (<%)	0 (0%)	1 (1%)

Patients on the everolimus arm received more subsequent kinase inhibitors than the cabozantinib arm, 41% vs. 16% respectively. And patients on the cabozantinib arm received more subsequent everolimus, 23% versus 4% respectively. No patients received subsequent PD-L1 or PD-1 blocking antibodies.

Efficacy Results

At the time of the data cutoff date of May 22nd, 2015, 247 PFS events were reported. The minimum time of follow-up was 10.7 months. There was a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the everolimus arm with a 3.6 month difference in median PFS (7.4 versus 3.8 months respectively). The hazard ratio adjusted for stratification factors was 0.59 (95% CI: 0.46, 0.76; stratified log-rank p-value < 0.0001) per eCRF and 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value < 0.0001) per IVRS.

At the time of the primary PFS analysis, a pre-specified interim analysis of OS was conducted at 202 deaths and showed a trend of longer OS however the p-value of ≤0.0019 (49% information fraction) required to achieve statistical significance was not reached. A second unplanned interim analysis of OS was conducted for the ITT population at 320 deaths representing 78% of the 408 deaths required for the pre-specified primary analysis of OS. The minimum time of follow-up was 13 months. There was a 4.9 month improvement in median OS (21.4 vs. 16.5 months) for subjects in the cabozantinib arm compared with the everolimus arm. The hazard ratio adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified log-rank p-value = 0.0003) per eCRF and 0.66 (95% CI: 0.53, 0.83; stratified log-rank p-value = 0.0003) per IVRS. The p-value of ≤ 0.0163 (78% information fraction) required to achieve statistical significance at the time of this unplanned second interim analysis was reached. Stratified hazard ratios calculated per eCRF and per IVRS were consistent and both p-values reached the p-value required for statistical significance. The review team decided in order to follow the ITT principle the IVRS stratified data would be presented in the label for both PFS and OS (see Table 2 and 3). ORR results were statistically significant and supportive of

cabozantinib activity with confirmed ORR as assessed by IRC of 17% (95% CI 13%, 22%) in the cabozantinib arm and 3% (95% CI: 2%, 6%) in the everolimus arm (see Table 3).

Table 2: Progression-Free Survival (First 375 Randomized)

Endpoint	CABOMETYX	Everolimus
	N = 187	N = 188
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

Table 3: Overall Survival and Objective Response Rate (ITT)

Endpoint	CABOMETYX	Everolimus
	N = 330	N = 328
Median OS (95% CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value[1]	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value[2]	p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)
[2] chi-squared test

Sensitivity Analyses

A sensitivity analysis for PFS per IRC using the full ITT population was consistent with the PITT population showing a statistically significant 3.5 month median PFS improvement over the everolimus arm (7.4 versus 3.9) with a stratified hazard ratio of 0.52 (95% CI: 0.43, 0.64; stratified log-rank p-value <0.0001) per eCRF and 0.51 (95% CI: 0.41, 0.62; stratified log-rank p-value <0.0001) per IVRS. In addition, PFS and ORR results as assessed per investigator were consistent with the PFS and ORR results as assessed by IRC. In the PITT population, the IRC and investigator agreed 76% of the time for the cabozantinib arm and 72% of the time for the everolimus arm. In the ITT population, they agreed 77% of the time for the cabozantinib arm and 74% of the time for the everolimus arm.

The review team also calculated the difference between treatment arms in terms of median PFS using several alternative patient groupings and censoring schemes (see statistical and clinical review for more details) and the hazard ratios for PFS were similar.

Subgroup Analyses

The PFS and OS benefit in the cabozantinib arm held across these various subgroups except for PFS in females in the PITT population (n=45), and a select few small subgroups including Latin America (PITT: n=7, ITT: n=12), Black or African American (PITT: n=6, ITT: n=9),

and Race Not Reported (PITT: n=16, ITT: n=37). No conclusions should be drawn based on these subgroups as numbers were small, post-hoc and not prespecified. Note that the PFS benefit was seen in females when considering the full ITT population. No outlier subgroup was observed.

8. Safety

Harpreet Singh, M.D. was the primary clinical reviewer of safety for this application. There were no disagreements between the CDTL and clinical reviewer with respect to safety analyses. The safety database included the randomized clinical Trial XL184-308 in advanced RCC (331 patients treated with cabozantinib and 322 patients treated with everolimus). In addition the review team reviewed safety information from other cabozantinib clinical trials including two trials conducted in metastatic prostate cancer and the trial resulting in the approval of cabozantinib for mMTC. The safety database and duration of cabozantinib exposure were sufficient to characterize the safety of cabozantinib in advanced RCC and the safety results demonstrate an acceptable safety profile for the advanced RCC indication after prior treatment with anti-angiogenic therapy. No clinical safety related Postmarketing Requirements or Commitments are recommended.

Deaths
On Trial XL184-308, Fifteen deaths were reported within 30 days of the last cabozantinib dose. Eight deaths were attributed to progressive disease, five deaths were due to cognitive deterioration, pneumonia, hemorrhage, cardiac failure, and urosepsis, and two deaths were due to sudden cardiac death. Twenty three deaths occurred within 30 days of the last dose of everolimus.

SAEs
Serious adverse events (SAE) were reported in 40% of patients. The most common serious adverse events (greater than or equal to 2%) were abdominal pain, pleural effusion, diarrhea, nausea, anemia, acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. Forty three percent of patients on the everolimus arm experienced an SAE.

Discontinuations
Adverse reactions led to study treatment discontinuation in 10% of patients receiving cabozantinib and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with cabozantinib were decreased appetite (2%) and fatigue (1%).

Dose Reductions
The dose was reduced in 60% of patients receiving cabozantinib and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received 20 mg cabozantinib as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with cabozantinib were: diarrhea (16%), PPES (11%), Fatigue (10%) and Hypertension (8%). Adverse reactions led to study treatment being held in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Given the high rate of dose reductions, the review

team focused a detailed assessment of the adverse reactions leading to dose reduction. The median time to dose reduction was 55 days and while 60% had dose reductions, only 10% required dose discontinuation demonstrating the ability of clinicians to appropriately modify the dose. In addition, of the patients whose dose was reduced only two had grade 4 toxicity indicating that the dose was able to be reduced appropriately for lower grade toxicity before it reached a life-threatening safety concern. In addition only 10% of the total patients requiring dose reductions experienced SAEs as the cause for dose reduction. Given the potential for decreased efficacy (see Section 5) and the fact that the adverse events requiring dose reduction did not appear to pose a serious risk to patients, the review team is not requiring any postmarketing studies but labelling will include instructions for appropriate dose modification.

General AEs

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients included, in order of decreasing frequency: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were hypertension, fatigue, diarrhea, palmar-plantar erythrodysesthesia syndrome, and anemia.

Laboratory tests

Laboratory abnormalities occurring in ≥25% of patients who received cabozantinib are summarized in Table 4.

Table 4: Laboratory Abnormalities Occurring in ≥25% of Patients Who Received Cabozantinib

Test	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistry				
AST increased	74	3	40	<1
ALT increased	68	3	32	<1
Creatinine increased	58	<1	71	0
Triglycerides increased	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
ALP increased	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
GGT increased	27	5	43	9
Hematology				
White blood cells decreased	35	<1	31	<1
Absolute neutrophil count decreased	31	2	17	<1
Hemoglobin decreased	31	4	71	17
Lymphocytes decreased	25	7	39	12
Platelets decreased	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0

Immunogenicity
Not applicable as immunogenicity was not studied.

Special safety concerns
The safety profile of cabozantinib in RCC appeared similar to the previously characterized profile of the MTC formulation as well as other VEGF TKIs. Patients treated with the 60 mg tablet formulation used in the RCC study experienced fewer events such as GI perforations and fistulas compared to those treated with the 140 mg capsule formulation in the MTC trial. However, the rates of other adverse events, such as diarrhea, hypertension, and PPES were similar across tumor types.

In Trial XL184-308, the incidence of Grade ≥ 3 hemorrhagic events was 2.1% in cabozantinib-treated patients and 1.6% in everolimus-treated patients. Two fatal hemorrhages occurred in Trial XL184-308. Fistulas were reported in 1.2% (including 0.6% anal fistula) of cabozantinib-treated patients and 0% of everolimus-treated patients. Gastrointestinal (GI) perforations were reported in 0.9% of cabozantinib-treated patients and 0.6% of everolimus-treated patients. No

fatal perforations or fistulas occurred in Trial XL184-308 although fatal events did occur in the MTC and prostate cancer trials. Venous thromboembolism was reported in 7.3% of cabozantinib-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of cabozantinib-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of cabozantinib-treated patients and 0.3% of everolimus-treated patients. There was not an adverse reaction in Trial XL184-308 which was considered appropriate for a black box warning.

9. Advisory Committee Meeting

This application was not referred to an advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Cabozantinib was granted a full pediatric waiver for advanced RCC on March 23rd, 2016.

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)
Based on the review of the eCRFs and narratives, the primary data submitted to this application was found to be reliable for the primary analyses of safety and efficacy. The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

Financial Disclosures
Disclosure of financial interests of the investigators who conducted the clinical trials was submitted in the FDA form 3454. No investigators had any disclosures.

Good Clinical Practice
The Applicant states that the trial was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol, amendments, and patient informed consent received appropriate approval by the IRB/IEC prior to initiation of trial at the site. No breaches of the conditions and principles of GCP in connection with the trial or protocol were reported.

OSI audits
The Office of Scientific Investigations inspected four clinical sites chosen based on number of enrolled patients. OSI also inspected two CROs. Interim classification for all sites was no action indicated.

Other discipline consults
The follow FDA Offices and Divisions supplied subject matter expertise by consulting on this application; DMPP/OPDP, DMEPA, DRM, and Patient Labeling. No issues were identified that precluded recommendations for approval for this application.

12. Labeling

Proprietary name
The proposed proprietary name for cabozantinib is Cabometyx. DMEPA notified DOP1 that the name Cabometyx was acceptable from a look-alike and sound-alike perspective. No objections to the name Cabometyx were identified by OPDP or the clinical review team during the review cycle.

Physician labeling
This CDTL agreed with the recommendations made by the review teams that are described below. All sections were revised for brevity and clarity. Labeling changes made in agreement with the applicant in the course of the review include the following high-level changes:

- Black Box: After discussion with the applicant it was agreed that the black box warnings for hemorrhage and fistula/perforations that were included in the cabozantinib MTC formulation label would not be included in this label due to a difference in safety profile of these events as not as serious or common in the RCC application.
- Section 1 Indications and Usage:
  - The indication statement was changed (b) (4) (b) (4) to the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy to better reflect the population studied in Trial XL184-308.
- Section 5 Warnings and Precautions: In comparison to the cabozantinib MTC label, wound complications and proteinuria were not included from warnings and precautions due to differences in trial data with the change in formulation and the change in patient population. Diarrhea was added to this section due to frequency of the adverse reaction as well as frequency of dose reductions resulting from diarrhea. The warnings and precautions were ordered to reflect seriousness.
- Section 14 Clinical Studies: This section was simplified with respect to data presentation. The pITT population and the ITT population were specified. PFS and OS results using IVRS data was included.

Clinical pharmacology, non-clinical and CMC sections were updated from the prior cabozantinib MTC formulation label to reflect updated labeling recommendations as well as updated information submitted to this NDA.

Carton and immediate container labels
The carton and immediate container labels were revised for clarity and understandability in conjunction with CMC and DMEPA.

Patient labeling/Medication guide
The PPI was revised for clarity, brevity, and understandability in conjunction with OPDP and recommendations. No Medication guide was required.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The recommendation of this Cross Discipline Team Leader is for approval of NDA 208692. All review teams recommended approval or reported that there were no findings that would preclude approval. The recommended indication is as follows:

> CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

Risk Benefit Assessment
Advanced RCC is a serious and life-threatening disease which carries a poor prognosis. The recommendation for approval of cabozantinib is primarily based on data from one randomized, open-label, multicenter study in 658 patients with advanced RCC who had received at least one prior anti-angiogenic therapy. Patients were randomized 1:1 to receive either cabozantinib (N=330) administered at 60mg orally daily, or everolimus (N=328) administered at 10mg orally daily. PFS as assessed by IRC in the PITT population demonstrated a statistically significant improvement in median PFS of 7.4 months (95% CI: 5.6, 9.1] in the cabozantinib arm and 3.8 months (95% CI: 3.7, 5.4) in the everolimus arm [HR: 0.58 (95% CI 0.45, 0.74), stratified log-rank p-value <0.0001, per IVRS]. An OS benefit in a second interim analysis was demonstrated with a median OS of 21.4 months (95% CI: 18.7, not estimable) in the cabozantinib arm and 16.5 months (95% CI: 14.7, 18.8) in the everolimus arm (HR: 0.66, 95% CI: 0.53, 0.83; stratified log-rank p-value =0.0003, per IVRS) representing a median difference in OS of 4.9 months. The OS and PFS results are statistically significant and clinically meaningful. ORR results demonstrating a statistically significant improvement in the cabozantinib arm compared to the everolimus arm with a 17% ORR (95% CI: 13, 22) and 3% ORR (95% CI: 2, 6) respectively are supportive of cabozantinib activity. Despite other available therapies in this setting, everolimus, an approved drug for advanced RCC, is an appropriate active comparator.

The safety profile of cabozantinib was assessed in the 331 patients receiving at least one dose of cabozantinib and was consistent with the prior approval of cabozantinib in medullary thyroid cancer (MTC) as well as other multi-target kinase inhibitors. The most commonly reported (≥25%) adverse reactions were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation. Serious adverse events (SAEs) occurred in 40% of cabozantinib-treated patients

and 43% of everolimus-treated patients. Despite the fact that 60% percent of patients who received cabozantinib required dose reductions, only 10% of patients required treatment discontinuation. A detailed analysis of the adverse reactions resulting in dose reduction did not identify a serious risk, a signal of a serious risk, or an unexpected serious risk related to the use of the drug and therefore criteria for a safety PMR under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (created by Section 901, in Title IX of the Food and Drug Administration Amendments Act of 2007) were not met. In addition, exposure response and pharmacometric modeling showed a potential for decreased activity with a lower dose. Labeling will clearly state dose reduction instructions as well as describe the frequency of dose reductions seen in Trial XL184-308 to inform practitioners.

The improvement in PFS and OS of cabozantinib over everolimus was statistically significant and clinically meaningful. The safety profile of cabozantinib at 60mg daily is acceptable for the population studied. Cabozantinib for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy demonstrates a favorable benefit: risk profile with enough evidence to recommend approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No post-market risk management activities are necessary at this time (other than those required for all NDAs such as described in 21 CFR 314.81). The proposed label contains patient counseling information for trained prescribing physicians.

Recommendation for other Postmarketing Requirements and Commitments

One postmarketing commitment (PMC) from clinical pharmacology was agreed upon with the applicant. The PMC is as follows:

3063-1 Combine all available pharmacokinetics (PK) data from different patient populations and healthy subjects in an integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

Final Report Submission: 06/16

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

/s/

JULIA A BEAVER
04/20/2016