NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA) and Switzerland's Swissmedic. While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

Application Type	Efficacy Supplement – SE1
Application Number(s)	NDA 208692-S017
Priority or Standard	Standard
Submit Date(s)	May 21, 2024; June 3, 2024
Received Date(s)	May 21, 2024; June 3, 2024
PDUFA Goal Date	April 3, 2025
Division/Office	Division of Oncology 2 / Office of Oncologic Drugs
Review Completion Date	*Electronic Stamp Date*
Established Name	cabozantinib
(Proposed) Trade Name	Cabometyx
Pharmacologic Class	Kinase inhibitor
Code name	XL184
Applicant	Exelixis, Inc.
Formulation(s)	Tablets (20, 40, 60 mg)
Dosing Regimen	60 mg orally once daily for adult and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg, or 40 mg orally once daily for pediatric patients 12 years of age and older with bodyweight less than 40 kg.
Applicant Proposed Indication(s)/Population(s)	Adult patients with previously treated, locally advanced/unresectable or metastatic, well- or moderately - differentiated pancreatic or extra-pancreatic neuroendocrine tumors
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	- Adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors. - Adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors.

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OCP = Office of Clinical Pharmacology
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology

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DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
DRISK = Division of Risk Management

Project Orbis #141 Partners

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Clinical Assessors	(b) (6)
Regulatory Project Managers	

Swissmedic (SMC, Switzerland) Review Team	
Clinical Assessor	(b) (6)
Clinical Peer Assessor	
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(b) (6)	

Glossary

AE	adverse event
AERS	adverse events reporting system
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	adequate tumor assessment
ATC	anatomical therapeutic chemical
ATE	arterial thrombotic events
BIRC	blinded independent review committee
BOR	best overall response
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcome Assessment
CRADA	Cooperative Research and Development Agreement
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography

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CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
DBP	diastolic blood pressure
DCR	disease control rate
DOR	duration of response
DSMB	Data and Safety Monitoring Board
DTC	differentiated thyroid carcinoma
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
epNET	extra-pancreatic neuroendocrine tumor
ETM	Events to Monitor
GEP	gastroenteropancreatic
GCP	Good Clinical Practice
GI	gastrointestinal
HCC	hepatocellular carcinoma
HR	hazard ratio
IA	interim analysis
IND	Investigational New Drug
ITT	intent-to-treat
IxRS	interactive web/voice response system
LR	log-rank test
Lu-177	lutetium-177
MAH	marketing authorization holder
MDS	multilineage dysplasia
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NET	neuroendocrine tumor
NPACT	nonprotocol anticancer therapy
NR	not reached
OCE	Oncology Center of Excellence
Oct LAR	octreotide long acting release
OPEN	Oncology Patient Enrollment Network
ORR	objective response rate

OS	overall survival
PBL	post-baseline
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMB	Pharmaceutical Management Branch
pNET	pancreatic neuroendocrine tumor
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRRT	peptide receptor radionuclide therapy
PT	preferred term
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	reversible posterior leukoencephalopathy syndrome
RPSFT	rank-preserving structural failure time
RTK	receptor tyrosine kinase
RTOR	Real-Time Oncology Review Pilot Program
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SoD	sum of diameters
SPEER	specific protocol exceptions to expedited reporting
SSA	somatostatin analog
SSTR	somatostatin receptor
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TMA	thrombotic microangiopathy
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Cabozantinib is an oral, small-molecule multi-kinase inhibitor that targets several receptor tyrosine kinases including MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Cabozantinib is marketed under two distinct trade names, Cabometyx (tablet formulation) and Cometriq (capsule formulation), which are not bioequivalent or interchangeable.

CABOMETYX is currently approved for the treatment of patients with:

- advanced renal cell carcinoma,
- advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab
- hepatocellular carcinoma who have been previously treated with sorafenib, and
- locally advanced or metastatic differentiated thyroid cancer* that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible (*this indication is for adult and pediatric patients 12 years of age and older)

COMETRIQ is currently approved for the treatment of patients with progressive, metastatic medullary thyroid cancer.

The Applicant is seeking FDA approval of CABOMETYX for the treatment of:

- adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET), and
- adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET).

The Applicant's proposed recommended dosage regimen for the proposed indications is:

- 60 mg orally once daily for adult and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg, and
- 40 mg orally once daily for pediatric patients 12 years of age and older with bodyweight less than 40 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant provide substantial evidence of effectiveness to support the traditional approval of cabozantinib for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic and extra-pancreatic neuroendocrine tumors.
The recommendation for traditional approval is based on the results of CABINET (Study A021602), which demonstrated that treatment with cabozantinib resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to placebo in the indicated patient populations.

CABINET is a randomized (2:1), double-blind, placebo-controlled, multicenter study of cabozantinib in US patients with unresectable, locally advanced or metastatic well-differentiated neuroendocrine tumors who had disease progression following receipt of FDA-approved therapy for their tumor. A total of 298 patients were randomized to the pNET or epNET cohort prior to the data cutoff (DCO) of August 24, 2023, which is the date of study unblinding. Patients received cabozantinib as a single agent administered at 60 mg once daily (the approved monotherapy dose for other cancer indications) or placebo.

The primary objective was to evaluate the efficacy of cabozantinib based on radiographic PFS per blinded independent radiology review committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 compared with placebo. Secondary endpoints included overall survival, investigator-assessed PFS and overall response rate (ORR) per RECIST v1.1. Overall, 298 patients were randomized in the trial, including 199 patients in the epNET cohort (134 in the cabozantinib arm) and 99 patients in the pNET cohort (64 in the cabozantinib arm) per the intent-to-treat (ITT) population.

Due to incorrect recording of tumor type during use of the Oncology Patient Enrollment Network (“OPEN”) registration that relied on an interactive voice/web response system (IxRS) to enroll patients, there were 3 patients with epNET who were misclassified as pNET patients and randomized to the pNET cohort, and 7 patients with pNET who were misclassified as epNET patients and randomized to the epNET cohort. Due to the prognostic value of primary tumor origin in patients with neuroendocrine tumors, the FDA’s assessment of efficacy in CABINET is based upon results of analyses in which patients are categorized according to their true tumor type (as verified in their case report form or per “electronic data capture [EDC]”), resulting in 132 patients with epNET and 66 patients with pNET who were treated with cabozantinib.

Using a study population with the corrected tumor classification, in the epNET cohort, a 4.3-month improvement in median PFS was observed in the cabozantinib arm, with a median PFS of 8.5 months (95% CI: 6.8, 12.5) compared to 4.2 months (95% CI: 3.0, 5.7) for the placebo arm. The hazard ratio (HR) for PFS in patients with epNET was 0.4 (95% CI: 0.26, 0.61; p-value

<0.0001). An overall survival (OS) analysis was conducted when 123 deaths were observed in the epNET cohort (DCO September 4, 2024); the OS results were not mature with 83 (63%) deaths occurring in the cabozantinib arm and 40 (60%) occurring in the placebo arm, yielding an OS HR of 1.05 (95% CI: 0.71, 1.54). Notably, 37% of patients receiving placebo crossed over to open-label treatment with cabozantinib upon confirmed disease progression, which may impact interpretability of the OS outcomes.

In the pNET cohort, a 10.5-month improvement in median PFS was observed in the cabozantinib arm, with a median PFS of 13.8 months (95% CI: 8.9, 17.0), compared to 3.3 months (95% CI: 2.8, 5.7) for the placebo arm. The HR for PFS in patients with pNET was 0.22 (95% CI: 0.12, 0.41; p-value <0.0001). The OS data for the pNET cohort were not mature, with 32 (48%) deaths occurring in the cabozantinib arm and 17 (52%) deaths occurring in the placebo arm, resulting in an OS HR of 1.01 (95% CI: 0.55, 1.83). Fifty-two percent of patients in the placebo arm crossed over to the cabozantinib arm upon confirmed disease progression, which may impact interpretability of OS outcomes.

Although CABINET was conducted as a single randomized controlled trial, it may be considered as two adequate well-controlled trials conducted in parallel in related patient populations of epNET and pNET; the results of each cohort may serve as confirmatory evidence. For example, the effect on PFS observed in the results of the pNET cohort support the results of the epNET cohort and provide confirmatory evidence of effectiveness for the epNET indication. The similarity of the epNET and pNET indications, cabozantinib's mechanism of action in these diseases, and the use of the same primary efficacy endpoint of PFS in these two disease reinforce the appropriateness of use of clinical trial data from the epNET and pNET cohorts as confirmatory evidence for each other (as described in the draft 2023 FDA Guidance for Industry: "Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence).

Supportive evidence for this approval is also derived from strong mechanistic evidence of cabozantinib's treatment effect in NETs, which are vascular tumors exhibiting high expression of several proangiogenic molecules including VEGF, a major driver of NET pathophysiology, that is directly targeted by cabozantinib (Terris et al., 1998; Zhang et al., 2007). Additionally, this application is supported by evidence of effectiveness of another drug (a multi-tyrosine kinase inhibitor targeting kinases including VEGFR and PDGFR) from a related pharmacologic class for a related indication (treatment of pNETs).

The evidence submitted meets the statutory evidentiary standard for traditional approval. Treatment with cabozantinib demonstrated a statistically significant and clinically meaningful improvement in PFS over placebo among patients with advanced, well-differentiated NETs who have had progressive disease after receiving FDA-approved therapy. Although pediatric data were not provided in this submission, there is clinical experience with cabozantinib in pediatric

patients with cancer, including in the Children's Oncology Group Study ADVL1622 which enrolled patients as young as 2 years of age with various malignancies, as described in the medical literature (Akshintala et al., 2021). Given the similarity of NETs in adolescents compared to adult patients, the known mechanism of action of cabozantinib, and available weight-based modeling, the review team agrees with the inclusion of patients 12 years of age and older in the proposed indication.

The statistically significant and clinically meaningful improvement in PFS in patients treated with cabozantinib, in conjunction with a manageable safety profile allows for a favorable benefit:risk assessment in the aforementioned patient populations. Of note, this is the first agent to be approved specifically for the treatment of patients with NETs that have progressed after prior treatment with an FDA-approved therapy. The review team recommends traditional approval of cabozantinib for adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic or extra-pancreatic neuroendocrine tumors.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Cabozantinib is an oral, small-molecule multi-kinase inhibitor that targets several receptor tyrosine kinases including MET, VEGFR-1, -2 and -3, AXL, RET, and ROS1. It is currently approved in the US for the treatment of patients with advanced renal cell carcinoma, hepatocellular carcinoma, differentiated thyroid carcinoma, and medullary thyroid carcinoma. Data from the CABINET trial (also referred to as Study A021602), conducted by the National Cancer Institute (NCI) Alliance research team, were provided as the primary evidence in support of the proposed indications of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET) and extrapancreatic neuroendocrine tumors (epNET).

Neuroendocrine tumors (NETs) are a rare, heterogeneous group of tumors that vary in location, grade, and hormone secretion (resulting in classification as functional vs. non-functional tumors) (Oronsky et al., 2017). These tumors comprise approximately 2% of all malignancies and according to an analysis of the SEER database, the incidence of NETs in the United States was approximately 7 cases per 100,000 people in the year 2012 with a current estimated prevalence of 175,000 (Dasari et al., 2017). The therapeutic approach to NETs varies, depending largely on the tumor type and stage of disease. When possible, patients with localized low to intermediate grade NETs undergo surgery with curative intent; however, patients with advanced or metastatic disease may require medical management. FDA-approved systemic treatments to suppress tumor growth include somatostatin analogs (lanreotide), targeted agents (everolimus, sunitinib), and peptide receptor radionuclide therapy (PRRT) with lutetium Lu 177 dotatate. There is no drug specifically approved for the treatment of NETs that have progressed on prior systemic therapy. Further, there is no clear evidence-based consensus supporting a specific sequence of therapies for the treatment of advanced or metastatic NETs.

CABINET is a randomized (2:1), double-blind, placebo-controlled, multicenter study conducted in the US evaluating cabozantinib in adult patients with unresectable, locally advanced or metastatic well-differentiated NETs who had disease progression after prior treatment with FDA-approved therapy for their tumor. Patients were assigned to one of two cohorts, pNET or epNET, according to tumor origin. The primary endpoint was progression-free survival (PFS) per blinded independent radiology review committee (BIRC) according to RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 compared to placebo. Secondary endpoints included overall survival, investigator-assessed PFS and overall response rate (ORR) per RECIST v1.1.

Patients received cabozantinib as a single agent administered once daily at 60 mg (the approved monotherapy dose for other cancer indications) or placebo. Patients who were assigned to the placebo arm were permitted to crossover to receive open-label treatment with cabozantinib upon confirmed disease progression by real-time central review. The study opened in 2018, and a total of 298 patients were randomized and treated prior to the data cutoff (DCO) of August 24, 2023, which is the date of study unblinding.

Due to the misallocation of some patients to the incorrect cohort in the intent-to-treat (ITT) population, and given the prognostic value of tumor origin (pNET vs. epNET), the FDA's assessment of efficacy data from CABINET was based on the corrected study population using patients' verified tumor type according to electronic data capture (EDC).

- Pancreatic Neuroendocrine Tumors
  According to the corrected efficacy population, the pNET cohort consisted of 66 patients in the cabozantinib arm and 33 patients in the placebo arm. The median PFS (mPFS) by BIRC was 13.8 months (95% CI: 8.9, 17) in the cabozantinib arm versus 3.3 months (95% CI: 2.8, 5.7) in the placebo arm. The PFS HR was 0.22 (95% CI: 0.12, 0.41) with a p-value of <0.0001 favoring the cabozantinib arm. Results of a descriptive analysis of overall survival (DCO September 4, 2024) were considered immature by FDA with interpretability complicated by substantial crossover of patients from the placebo arm to open-label cabozantinib treatment; however, this analysis did not suggest a detriment in OS in patients with pNET who received cabozantinib.

  The most common adverse reactions occurring in ≥20% of patients with pNET treated with cabozantinib were fatigue, increased AST, increased ALT, hypertension, diarrhea, rash, stomatitis, musculoskeletal pain, hyperglycemia, nausea, platelet count decreased, dysgeusia, neutrophil count decreased, abdominal pain, decreased appetite, hemoglobin decreased, dizziness, hypophosphatemia hypothyroidism, vomiting, increased ALP, and lymphocyte count decreased. Safety analyses were notable for a higher rate of thromboembolic events in the pNET cohort (19%) compared to 4% in the epNET cohort, which is likely related to the underlying disease. Overall, the adverse reactions observed in the cabozantinib arm of the pNET cohort were largely in line with the known safety profile of cabozantinib.

- Extrapancreatic Neuroendocrine Tumors
  According to the corrected efficacy population, the epNET cohort consisted of 132 patients in the cabozantinib arm and 67 patients in the placebo arm. The mPFS by BIRC was 8.5 months (95% CI: 6.8, 12.5) for cabozantinib-treated patients compared to 4.2 months (95%

CI: 3.0, 5.7) in patients receiving placebo. The PFS HR was 0.4 (95% CI: 0.26, 0.61) with a p-value of <0.0001 favoring the cabozantinib arm. Results of a descriptive analysis of overall survival (DCO September 4, 2024) were considered immature by the FDA with interpretability complicated by substantial crossover of patients from the placebo arm to open-label cabozantinib treatment; however, this analysis does not suggest a detriment in OS in patients with epNET who received cabozantinib.

The most common adverse reactions in ≥20% of patients with epNET treated with cabozantinib were fatigue, increased AST, diarrhea, hypertension, increased ALT, platelet count decreased, rash, stomatitis, nausea, white blood cell count decreased, neutrophil count decreased, musculoskeletal pain, dysgeusia, hypothyroidism, decreased appetite, hemoglobin decreased, hyperglycemia, abdominal pain, increased ALP, lymphocyte count decreased, weight decreased, blood creatinine increased, hypoalbuminemia, blood bilirubin increased, hypocalcemia, hypokalemia, and hypomagnesemia. The adverse reactions observed in the cabozantinib arm of the epNET cohort were generally consistent with the known safety profile of cabozantinib.

Although the CABINET trial did not enroll pediatric patients, there is clinical experience with cabozantinib in pediatric patients with cancer, including the Children's Oncology Group Study ADVL1622 which enrolled patients as young as 2 years of age with various malignancies, as described in the medical literature (Akshintala et al., 2021). Given the similarity of NETs in adolescents compared to adult patients, the known mechanism of action of cabozantinib, and available weight-based modeling, the FDA determined that the inclusion of patients 12 years of age and older in the indication statement was appropriate based on the totality of the data submitted.

The risks of cabozantinib in patients with advanced NETs are acceptable due to the serious and potentially life-threatening nature of the disease in the proposed population. The safe use of cabozantinib can be adequately implemented by oncologists through instructions in product labeling as oncologists are trained in the management of serious toxicities and familiar with adverse effects associated with TKIs such as cabozantinib.

In conclusion, the submitted data meets the statutory standard for demonstration of substantial evidence of effectiveness. The statistically significant and clinically meaningful improvement in PFS in patients treated with cabozantinib, in the context of a manageable safety profile allows for a favorable benefit:risk assessment for the treatment of patients with advanced NETs. Importantly, this is the first agent to be approved specifically for the treatment of patients with NET that has progressed after receipt of FDA-approved therapy. The review team recommends traditional approval of cabozantinib for adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic or extra-pancreatic neuroendocrine tumors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neuroendocrine tumors (NETs) are rare, heterogeneous tumors that vary in location, grade, and hormone secretion. NETs represent approximately 2% of all malignancies with an estimated prevalence in the US of 175, 000 and an incidence that is rising globally (Dasari et al., 2017). • NETs arise from neuroendocrine cells and are described as highly vascular tumors, exhibiting overexpression of vascular endothelial growth factor (VEGF). These tumors can originate throughout the body, most commonly in the gastrointestinal tract, lungs, and pancreas. NETs can be broadly classified as functional or non-functional depending on whether the tumor produces and releases peptide hormones that cause a characteristic carcinoid syndrome (e.g., skin flushing, diarrhea, wheezing, etc.). • There is a spectrum of clinical behavior for NETs, which can act as indolent tumors that follow a prolonged clinical course with a low risk of distant metastases, even without treatment, or they can be clinically aggressive and spread quickly as seen with poorly differentiated neuroendocrine carcinomas (NECs). • Primary tumor site is considered to have prognostic bearing. According to a 2018 study of SEER data by Da Man et al., patients with NETs in the rectum tend to have the best prognosis, followed by those with NETs in the small intestine, lung/bronchus, stomach, and colon, while those with pancreatic tumors had the highest risk of mortality. Poorer survival outcomes in patients with pNETs may be related to a greater proportion of these patients having distant stage disease. • Hallet et al. have reported that approximately 20% of patients have metastatic NET at initial diagnosis. The 10-year overall survival is ~68% for	NETs are a rare, serious and potentially life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with localized disease, ~18% for patients with metastases at presentation, and ~19% for patients with metastatic spread after initial diagnosis.	
Current Treatment Options	• The treatment approach to NETs depends on the tumor type, stage of disease, and presence of symptoms. The primary treatment for patients with localized disease is surgery with curative intent, whereas for patients with metastatic disease at diagnosis, chronic medical management may be pursued instead. • To relieve symptoms associated with NETs, patients are treated with somatostatin analogs (SSAs) including octreotide or lanreotide. Systemic therapies to suppress tumor growth are often initiated after disease progression or can be used as alternatives to first-line therapy. FDA-approved systemic treatments to suppress tumor growth include SSAs (lanreotide), targeted agents (everolimus, sunitinib), and peptide receptor radionuclide therapy (PRRT) with lutetium Lu 177 dotatate. • There are no drugs specifically approved for the treatment of NETs that have progressed on prior systemic therapy. There is no clear evidence-based consensus supporting a particular sequence of therapies for the treatment of advanced or metastatic NETs. Patients with advanced or metastatic NETs may also be considered for clinical trials when appropriate.	NETs are treated with SSAs for symptomatic disease and surgical resection, when possible, for localized tumor. Patients with distant disease may be managed with systemic treatments to suppress tumor growth including lanreotide, everolimus, sunitinib, and PRRT with lutetium Lu 177 dotatate. There is no clear consensus on the ideal sequence of therapies for patients with advanced or metastatic NETs. There are no FDA-approved drugs specifically for patients with NET that has progression on prior systemic therapy.
Benefit	• The primary efficacy data supporting this application is derived from the 198 patients treated with cabozantinib in CABINET, a randomized, double-blind, placebo-controlled, multicenter trial conducted in the US in adult patients with unresectable, locally advanced or metastatic well-differentiated NETs who had disease progression after prior treatment with FDA-approved therapy. Patients were allocated to one of two cohorts, pNET	The submitted evidence meets the statutory evidentiary standard for traditional approval. The PFS improvement observed with cabozantinib in both cohorts is statistically significant and clinically meaningful for patients with previously treated, advanced,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or epNET, according to tumor origin, and randomized to receive either cabozantinib at a dose of 60 mg or placebo orally once daily. Patients assigned to placebo treatment were permitted to crossover and receive open-label cabozantinib treatment upon confirmed disease progression. • The primary endpoint was progression-free survival (PFS) per blinded independent radiology review committee (BIRC) according to RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 compared to placebo. Secondary endpoints included overall survival, investigator-assessed PFS and overall response rate (ORR) per RECIST v1.1. • The pNET cohort included 66 patients in the cabozantinib arm and 33 patients in the placebo arm. The median PFS (mPFS) by BIRC was 13.8 months (95% CI: 8.9, 17.0) in the cabozantinib arm versus 3.3 months (95% CI: 2.8, 5.7) in the placebo arm. The PFS HR was 0.22 (95% CI: 0.12, 0.41) with a p-value of <0.0001 favoring the cabozantinib arm. • The epNET cohort included 132 patients in the cabozantinib arm and 67 patients in the placebo arm. The mPFS by BIRC was 8.5 months (95% CI: 6.8, 12.5) for cabozantinib-treated patients compared to 4.2 months (95% CI: 3.0, 5.7) in patients receiving placebo. The PFS HR was 0.4 (95% CI: 0.26, 0.61) with a p-value of <0.0001 favoring the cabozantinib arm. • Results of descriptive analyses of overall survival (DCO September 4, 2024) for both cohorts were considered immature with interpretability complicated by substantial crossover of patients; however, these analyses did not suggest a detriment in OS in patients with NET who received cabozantinib.	well-differentiated NETs. Although CABINET did not enroll pediatric patients, due to the similarity of NETs in adolescents compared to adult patients, the known mechanism of action of cabozantinib, and available weight-based modeling, the inclusion of patients 12 years of age and older in the indication statement was acceptable based on the totality of the data submitted. A PMC will be issued to assess survival follow-up of patients in the CABINET trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety populations analyzed in CABINET consisted of cabozantinib-treated patients in the individual cohorts (pNET vs. epNET) and the pooled subset of cabozantinib-treated patients from across both cohorts. Overall, the adverse reactions observed in patients with NETs were consistent with the known safety profile of cabozantinib in other cancer clinical trials. • The most common (≥20%) adverse reactions in the pooled safety population (n=195) were fatigue, AST increased, ALT increased, hypertension, diarrhea, rash, platelet count decreased, stomatitis, nausea, musculoskeletal pain, hypothyroidism, decreased appetite, dysgeusia, white blood cell count decreased, neutrophil count decreased, hyperglycemia, anemia, abdominal pain, blood ALP increased, lymphocyte count decreased, weight decreased, vomiting, and hypophosphatemia. • The most frequent (≥5%) Grade 3 or higher treatment-emergent adverse reactions in the cabozantinib-treated patient population included hypertension (26%), fatigue (14%), diarrhea (9%), abdominal pain (7%), musculoskeletal pain (6%) and rash (6%). The leading treatment-emergent serious adverse reactions reported in ≥2% of this pooled safety population were thromboembolic events, abdominal pain, musculoskeletal pain, vomiting, nausea, sepsis, fatigue, diarrhea, blood bilirubin increased, anemia, hemorrhage, and hypothyroidism. • Fatal adverse reactions among patients receiving cabozantinib occurred only in the epNET cohort (4.5%) including hepatic failure, multi-organ dysfunction, gastrointestinal hemorrhage, cardiac arrest, ruptured ascending aortic aneurysm, and sudden death not otherwise specified, occurring in one patient each. • Notable findings included the greater frequency of thromboembolic events	The treatment-emergent adverse reactions observed with cabozantinib administration in patients with previously treated, advanced NETs in CABINET were similar to those observed in clinical trials of cabozantinib in currently approved cancer indications. No new safety concerns were identified during review that require risk management beyond the current labeling. The observations of more frequent thromboembolic events in the pNET cohort and a greater rate of hypertension overall in the pooled safety population are likely related to the pathophysiology of NETs as thrombotic risk is higher in patients with pancreatic tumors and hypertension is a known complication in patients with functional tumors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in the pNET cohort (19%) compared to the epNET cohort (4%), and the higher rate of hypertension including Grade 3 events in patients with NETs (65%; 26% Grade 3) compared to that in the combined population of clinical trial patients for the other approved cancer indications described Section 5 of in the drug label (37%; 16% Grade 3 and <1% Grade 4). • No novel safety signals were identified during review of this sNDA.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			☐	Patient reported outcome (PRO)	
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			
	☐	Patient preference studies (e.g., submitted studies or scientific publications)			
	☐	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				
x	Patient experience data was not submitted as part of this application.				

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Neuroendocrine tumors (NET) represent a heterogenous group of malignancies characterized histologically by architectural, cytologic and immunohistochemical features reminiscent of non-malignant neuroendocrine cells (Klimstra et al, 2015). Clinicopathologically, NETs are classified by site of origin, stage, grade and other histologic characteristics. Well-differentiated NETs are classified into low, intermediate, and high grade based on mitotic rate and Ki-67 index, with higher levels being associated with a more aggressive clinical course and worse prognosis (Rindi et al, 2022; Panzuto et al, 2011). Although NETs arise most commonly in the GI tract (48%), lung (25%), and pancreas (9%), they may also occur in the breast, prostate, thymus, and skin (Hallet et al, 2015). NETs arising in the pancreas (pNETs) are genomically and prognostically distinct from extra-pancreatic NETs (epNETs), and the treatment paradigm is therefore dichotomized between these two groups (Halperin et al, 2015).

Similar to other malignant diseases, potential tumor-derived risks may occur based on the primary or metastatic disease location of NETs: hemoptysis, recurrent pneumonia due to bronchial obstruction, and compression syndromes (ie, dysphagia) for NETs arising in the lung; abdominal pain, obstruction, and GI bleeding for NETs arising in the GI tract. In addition, NETs may be non-functional or functional with secretion of bioactive amines and peptide hormones including serotonin, glucagon, insulin, and gastrin leading to carcinoid syndrome and other syndromes related to hormone excess. Classically, symptoms from serotonin hypersecretion include flushing, hypotension, bronchospasm, and diarrhea (Lips et al, 2003). NET-related symptoms may persist for long periods (median, 9.2 years) before an accurate diagnosis is made, placing a substantial symptom burden on patients (Vinik et al, 2010). In addition, patients with metastatic NET present unique treatment challenges due to the lack of cure in advanced stage and complications such as bowel ischemia/perforation and carcinoid heart disease. Indeed, carcinoid heart disease occurs in approximately 50% of patients with the carcinoid syndrome and usually heralds a worsening prognosis due to right heart failure caused by severe dysfunction of the tricuspid and pulmonary valves (Bhattacharyya et al, 2007). Finally, NETs and in particular pNETs carry an increased risk of venous thromboembolic disease likely due to high expression of pro-angiogenic factors and endothelial dysfunction (Wójcik-Giertuga et al, 2023). As a result of this symptom burden, both global and US based studies of health-related quality of life have demonstrated significant worsening compared to the general population including physical and emotional well-being (Beaumont et al, 2012; Singh et al, 2016).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of neuroendocrine tumors (NETs). NETs are a rare, heterogeneous group of tumors that vary in location, grade, and hormone secretion (resulting in classification of functional vs. non-functional tumors). These tumors comprise approximately 2% of all malignancies with a female preponderance of 2.5:1 (Oronsky et al., 2017). According to a retrospective analysis of the Surveillance, Epidemiology and End Results (SEER) database that identified approximately 65, 000 adult patients with NETs between 1973 and 2012, the incidence of NETs in the US was approximately 1 case per 100,000 people in 1973 and increased to nearly 7 cases per 100,000 people by 2012 with a current estimated prevalence of 175,000 (Dasari et al., 2017). The steady rise in the incidence of NETs is likely due in part to greater clinician awareness and advances in diagnostic imaging leading to more frequent detection of early-stage disease.

Based on clinical behavior, histology and proliferation rate, well-differentiated NETs are generally considered indolent, although a subset of tumors with low-grade appearance can behave similarly to more aggressive, high-grade lesions (poorly differentiated neuroendocrine carcinomas).

Anatomic distribution of NETs may vary across different countries and ethnicities (Das & Dasari, 2021). In the US, NETs most commonly develop in the gastrointestinal tract (~65%), primarily in the small intestine and rectum, followed by the lung (~25%) and pancreas. Other sites include the thymus, thyroid, adrenal glands, breast, skin, and genitourinary system, with some cases presenting from metastasis of an occult primary (Sultana et al., 2023). Approximately 12-22% of patients have metastatic disease at presentation.

As noted by the Applicant, the tumor origin bears clinical significance due to variability in survival among patients with NETs originating at different primary sites. In the population-based study of approximately 65,000 US patients with NETs, the best median overall survival (OS) among site groups was observed in NETs of the appendix (>30 years) and rectum (~25 years), while NETs of the lung (5.5 years) and pancreas (3.6 years) had the worst median OS (Dasari et al., 2017). When accounting for stage, for patients with distant metastases, patients with a primary site in the small intestine had the best median OS (5.8 years), whereas NETs in the lung (6 months) and colon (4 months) had the worst median OS. Similarly, in another SEER database analysis in ~74,000 patients, patients with NETs in the rectum had the best prognosis, followed by those with NETs in the small intestine, lung/bronchus, stomach and colon, whereas patients with NETs in the pancreas had the highest risk of mortality (Man et al., 2018).

2.2. Analysis of Current Treatment Options

Management of NETs is dependent on primary tumor location, grade, presence of symptoms, somatostatin receptor (SSTR) positivity, stage, and disease burden. Locoregional therapies such as surgery and liver-directed therapies may be used for symptom control as well as for curative

intent (NCCN [Neuroendocrine and Adrenal Tumors], 2023; Pavel et al, 2021; Baudin et al, 2021). For locally advanced/unresecatble and metastatic disease, several agents have been FDA approved based on progression-free survival (PFS) benefit seen in placebo controlled randomized studies many of which allowed for crossover upon progression. For initial treatment of both epNET and pNET, the somatostatin analogue (SSA) lanreotide has been shown to improve PFS compared with placebo (Caplin et al, 2014) and therefore SSAs are typically the first-line therapy to control the growth of well-differentiated NETs. Beyond this, the treatment paradigms for progressive advanced pNET and epNET are distinct. For patients with progressive pNET, approved treatment options include the mTOR inhibitor everolimus (Yao et al, 2011), the tyrosine kinase inhibitor sunitinib (Raymond et al, 2011) and for patients with SSTR+ disease, the radionuclide lutetium-177 (Lu-177) dotatate (Strosberg et al, 2017). For patients with progressive epNET, approved treatment options include everolimus and Lu-177 dotatate for SSTR+ disease (Yao et al, 2016a; Strosberg et al, 2017). In addition, cytotoxic chemotherapy including but not limited to temozolomide-based or platinum-based regimens are considered appropriate treatment options for patients with bulky disease, aggressive or symptomatic NETs although not specifically FDA approved (NCCN Guidelines Version 1.2023; Halfdanarson et al, 2020). Applicant Table 1 summarizes the results of the landmark trials and approved systemic therapies for NET.

Published literature is lacking to inform superiority of one targeted agent over another in the treatment of advanced epNET and pNET. Several retrospective studies support the efficacy of everolimus over sunitinib in pNET (Daskalakis et al, 2019; Angelousi et al, 2017; Yoo et al, 2017; Liu et al, 2016). Furthermore, Lu-177 dotatate treated patients showed an improved PFS compared to sunitinib in a randomized phase 2 study (Baudin et al, 2022). Therefore, everolimus and Lu-177 dotatate appear to be used more frequently in earlier lines of therapy than sunitinib for the treatment of advanced pNET (Stiefel et al, 2023).

Applicant Table 1: Approved Agents in pNET and epNET

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Sunitinib (SUTENT® and generics)	Treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult patients with unresectable locally advanced or metastatic disease	2011; Full approval	37.5 mg taken orally once daily	Comparators (n): Sunitinib (n=86) vs placebo (n=85) Prim EP: mPFS (mos); HR (95% CI): 10.2 vs 5.4; 0.43 (0.27, 0.67) Sec EP: mOS (mos); HR (95% CI): NR vs. NR; 0·41 (0.19, 0.89) Sec EP: ORR (%): 9.3% vs 0% Raymond et al, 2011; Faivre et al, 2017; Sutent® Prescribing	Hepatotoxicity, cardiovascular events, QT prolongation, hypertension, hemorrhagic events, tumor lysis syndrome, TMA, proteinuria, dermatologic toxicities, RPLS, thyroid dysfunction, hypoglycemia, ONJ, impaired wound healing, embryofetal toxicity
Everolimus (AFINITOR®)	Treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (pNET) with unresectable, locally advanced or metastatic disease.	2011; Full approval	10 mg orally once daily	Comparators (n): Everolimus (n=207) vs placebo (n=203) Prim EP: mPFS (mos); HR (95% CI): 11.0 vs 4.6; 0.35 (0.27, 0.45) Sec EP: mOS (mos); HR (95% CI): 44.0 vs. 37.7; 0.94 (0.73, 1.2) Sec EP: ORR (%): 5% vs 2% Yao et al, 2011; Yao et al, 2016a ; Afinitor® Prescribing	Non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing, metabolic disorders, myelosuppression, reduced immune response with vaccination, radiation sensitization, embryo-fetal toxicity

Lanreotide acetate (Somatuline Depot)	Treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs	2014; Full approval	120mg subcutaneous every 4 weeks	Comparators (n): Lanreotide (n=101) vs placebo (n=103) Prim EP: mPFS (mos); HR (95% CI): NR vs 18.0; 0.47 (0.3, 0.73) Sec EP: mOS (mos); Not available Caplin at al, 2014; Somatuline Depot® Prescribing	Cholelithiasis, hyperglycemia and hypoglycemia, cardiovascular abnormalities, thyroid function abnormalities
Everolimus (AFINITOR®)	Treatment of adult patients with progressive, well-differentiated, non-functional NET of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease	2016; Full approval	10 mg orally once daily	Comparators (n): Everolimus (n=205) vs placebo (n=97) Prim EP: mPFS (mos); HR (95% CI): 11.0 vs 3.9; 0.48 (0.35, 0.67) Sec EP: mOS (mos); NR vs. NR; 0.73; (0.48, 1.11) Sec EP: ORR (%): 2% vs 1% Yao et al, 2016b; Afinitor® Prescribing	Non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing, metabolic disorders, myelosuppression, reduced immune response with vaccination, radiation sensitization, embryo-fetal toxicity
Lutetium-177 dototate (LUTATHERA)	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors	2018; Full approval; priority review; orphan drug desgnation	7.4 GBq (200 mCi) every 8 weeks (± 1 week) for a total of 4 doses.	Comparators (n): Lu-177+Oct LAR 30mg (n=116) vs Oct LAR 60mg (n=113) Prim EP: mPFS (mos); HR (95% CI): NR vs 8.4; 0.21 (0.13, 0.32) Sec EP: mOS (mos); HR (95% CI): 48.0 vs. 36.3; 0·84 (0.60,1.17) ORR (%): 18% vs 3% Strosberg et al, 2017; Strosberg et al, 2021; Lutathera Prescribing	Risk from radiation exposure, myelosuppression, secondary MDS and leukemia, renal toxicity, hepatotoxicity, hypersensitivity reaction, neuroendocrine hormonal crisis, embryofetal toxicity, risk of infertility

CI, confidence interval; EP, endpoint; GEP, gastroenteropancreatic; GBq, gigabecquerel; HR, hazard ratio; mos, months, GI, gastrointestinal; m, median; MDS, multilineage dysplasia; mCi, millicurie; NR, not reached; Oct LAR, octreotide long acting release; Osteonecrosis of the jaw; ORR, objective response rate; PFS, progression-free survival; Prim EP, primary endpoint; Sec EP, secondary endpoint; SSTR, somatostatin receptor; RPLS, Reversible posterior leukoencephalopathy syndrome; TMA, thrombotic microangiopathy

The Applicant's Position:

Current FDA approved therapies are limited and have not shown efficacy in patients who have received prior targeted therapies Applicant Table 1 shows the important efficacy outcomes and prior systemic therapies of pivotal trials for sunitinib, everolimus and Lu-177 dotatate leading to FDA approval. Clinical outcomes remain poor in this patient population with significant mortality and morbidity due to NET related symptoms. The CABINET trial uniquely evaluated a heavily pretreated population as patients were required to have received at least 1 prior FDA approved therapy (excluding SSAs). Given that progression of NETs is associated with increasing grade and dedifferentiation over time (Zhang et al, 2022) and that systemic treatment is associated with further dedifferentiation and secondary acquisition of genomic and molecular abnormalities (Cordero-Hernandez et al, 2024; Shi et al, 2022), specific clinical trials are needed to demonstrate efficacy of treatments in patients with advanced NET whose disease has progressed on prior lines of FDA-approved therapy.

Although Lu-177 dotatate, everolimus and sunitinib are approved agents for pNET, the respective phase 3 studies that demonstrated improved PFS with these agents compared with placebo were conducted primarily in patients who had not received prior molecularly targeted therapy and therefore the efficacy of these agents after other targeted therapies is unknown (Raymond et al, 2011, Yao et al, 2011, Strosberg et al, 2017). Similarly, in patients with GI NET, evidence to support the efficacy of everolimus or Lu-177 dotatate after prior therapies is currently lacking (Yao et al, 2016a; Strosberg et al, 2017). In lung NET, there is no currently approved therapy following progression on everolimus. Everolimus, sunitinib and Lu-177 dotatate were all approved between 2011 and 2018, before the routine use of SSAs, VEGFR TKIs, everolimus or peptide receptor radionuclide therapies (PRRTs), and therefore the studies were conducted in a population of patients that had not received prior therapies outside of cytotoxic chemotherapy. The results of the CABINET trial address this unmet need of improving PFS in patients with relapsed/refractory NET who have received prior therapies.

Although FDA-approved treatment options exist depending on the primary tumor site location of NETs, not every available systemic therapy may be appropriate for a patient. Careful consideration of disease burden, aggressiveness, accompanying hormone secretion, symptoms, SSTR status, comorbidities, and toxicities of therapies guide treatment decisions on next lines of therapy. Furthermore, there are specific considerations related to each of the FDA approved therapies. Everolimus is not FDA-approved for patients with functional GI NET and may not be appropriate for patients with GI NET and carcinoid syndrome. Lu-177 dotatate requires sufficient SSTR expression and treatment places significant burden on patients requiring frequent travel to or extended stays at specialized centers, avoiding contact with children due to the potential for emitted radiation (Hope et al, 2019) and carries the risk of developing secondary hematological malignancies (Lutathera USPI). Sunitinib treatment in pNET patients is associated with toxicity which often requires treatment discontinuation (Angelousi et al, 2017; Raymond et al, 2011).

The FDA's Assessment:

The FDA agrees with the Applicant's statement that the therapeutic approach to NETs varies, depending largely on the tumor type, stage of disease, and presence of symptoms. When possible, the mainstay of treatment for localized low to intermediate grade NETs is surgery with curative intent; however, many patients with NETs have metastatic disease at diagnosis (Hofland J, et al. 2020). As a result, surgical intervention may not be feasible and chronic medical management may be pursued instead.

To relieve symptoms associated with NETs, patients are treated with somatostatin analogs (SSA) including octreotide or lanreotide. Systemic therapies to suppress tumor growth are often initiated after disease progression or can be used as alternatives to first-line therapy. These treatments include lanreotide, if not already administered; the targeted agents everolimus, an mTOR kinase inhibitor, or the multi-kinase inhibitor sunitinib; peptide receptor radionuclide therapy (PRRT) with the radiolabeled SSA lutetium Lu 177 dotatate; and cytotoxic chemotherapy regimens. In patients with liver-predominant disease, directed procedures (e.g., ablative therapy, transarterial embolization, selective radiotherapy, yttrium-90 microspheres) may be considered in leu of systemic treatment (Dasari et al., 2017). Additionally, patients with advanced or metastatic NETs may be considered for clinical trials when appropriate.

The FDA concurs with the Applicant's listing of therapies approved in the U.S. for the treatment of NETs as shown in Applicant **Error! Reference source not found.**. Everolimus, sunitinib and lanreotide were approved by the FDA on the basis of placebo-controlled trials that demonstrated a benefit in progression-free survival (PFS) in patients who had not received prior systemic therapy for their disease. Lutetium Lu 177 dotatate was also approved on the basis of PFS benefit; however, the study supporting this approval (NETTER-1) compared the combination of Lutetium Lu 177 and long-acting octreotide vs. long-acting octreotide alone.

As noted by the Applicant, there is no clear evidence-based consensus supporting a specific sequence of therapies for the treatment of advanced or metastatic NETs (NCCN Guidelines, 202). Although several guidelines on the management of NETs have been published by expert national and international groups (including the National Comprehensive Cancer Network [NCCN], North American Neuroendocrine Tumor Society [NANETS], and European Neuroendocrine Tumor Society [ENETS]) over the last two decades, universal agreement on the systemic treatment of NETs has not been reached. Accordingly, there is heterogeneity in the therapeutic approaches taken by clinicians and may be influenced by the generally slow-growing nature of these tumors (particularly when compared to other rapidly progressing cancers) and patient preference (e.g., tolerance of adverse effects).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs). It is provided as both capsules and tablets. The capsule and tablet formulations are not bioequivalent or interchangeable.

CABOMETYX® (cabozantinib) tablets, for oral use, is approved in the US for the indications presented in Applicant Table 2.

Applicant Table 2: Cabometyx® FDA Approvals

Indications	Approved
Treatment of subjects with RCC who have received prior anti-angiogenic therapy	25 April 2016
Treatment of subjects with advanced RCC.	19 December 2017
Treatment of subjects with HCC who have been previously treated with sorafenib.	14 January 2019
Treatment in combination with nivolumab, for the first-line treatment of subjects with advanced RCC.	22 January 2021
Treatment of adult and pediatric subjects 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.	17 September 2021

DTC, differentiated thyroid cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

Cometriq® (cabozantinib) capsules, for oral use, are approved in the US for the indication presented in Applicant Table 3.

Applicant Table 3: Cometriq® FDA Approval

Indications	Approved
Treatment of subjects with progressive, metastatic medullary thyroid cancer (MTC).	29 November 2012

MTC, medullary thyroid cancer.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key regulatory interaction regarding cabozantinib in NET tumors related to this sNDA is provided below. The Phase 3 CABINET study (Randomized, Double-Blinded Phase III Study of **CAB**ozantinib versus Placebo **I**n Patients with Advanced **NE**uroendocrine **T**umors After Progression on Prior Therapy; NCT03375320) was sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and conducted by the Alliance for Clinical Trials in Oncology ("Alliance"). Exelixis, the manufacturer and the US marketing authorization holder (MAH) of cabozantinib, provided cabozantinib for this study.

Applicant Table 4: Key Regulatory Milestones

Date	Regulatory Milestone
01 Dec 2017	New IND (137656) was submitted by Alliance including Protocol A021602
29 Dec 2017	Alliance received IND 137656 "Study May Proceed" letter
15 Mar 2018	FDA Type B, EOP2 meeting with the Alliance to obtain input on adequacy of Protocol A021602 to support the development of cabozantinib for the treatment of patients with neuroendocrine tumors (NETs).
09 Aug 2023	Alliance informed FDA about interim results of study A021602 via email
16 Aug 2023	FDA provided comments to the Alliance on the interim analysis results for Protocol A021602 (CABINET study) under IND 137656
24 Aug 2023	Alliance responded to the FDA comments via email.
25 Oct 2023	A Type B pre-NDA meeting request was submitted to the Exelixis cabozantinib parent IND 72,596
12 Dec 2023	Exelixis received Type B pre-NDA meeting Preliminary Comments issued by FDA
04 Mar 2024	Exelixis submitted Fast Track Designation request for both pNET and epNET indications to the IND 72,596
07 Mar 2024	Exelixis submitted Orphan Drug Designation request for pNET
11 Mar 2024	Per FDA request, Exelixis re-submitted two separate Fast Track Designation requests for pNET and epNET indications to the IND 72,596
15 Mar 2024	Exelixis submitted and amendment to agreed iPSP
29 Mar 2024	Exelixis submitted Orphan Drug Designation request for unresectable, locally advanced, or metastatic previously treated (b) (4)
01 Apr 2024	Exelixis submitted formal RTOR request to the IND 72,596 as part of the meeting package for the Type B Pre-sNDA meeting

Date	Regulatory Milestone
06 May 2024	Fast Track Designations were granted for both pNET and epNET indications
08 May 2024	Type B Pre-sNDA meeting Preliminary Comments issued by FDA
21 May 2024	Fast Track Rolling Review submission package #1 for CABINET sNDA submitted to FDA
03 Jun 2024	Final Complete Submission sNDA Package for CABINET submitted to FDA along with request for Priority Review

DCTD, Division of Cancer Treatment and Diagnosis; FDA, Food and Drug Administration;IND, Investigational New Drug; iPSP, Initial Pediatric Study Plan; RTOR, Real-Time Oncology Review Pilot Program; sNDA, supplemental New Drug Application.

The FDA's Assessment:

The FDA agrees with the Applicant's listing of key presubmission and submission regulatory activity and highlights the interactions listed below. The FDA has also provided a summary of important correspondence with the Applicant pertaining to additional overall survival data that was obtained during review of the application.

- December 1, 2017: The Division of Cancer Treatment and Diagnosis (DCTD) submitted IND 137656 including Protocol A021602, entitled "Randomized, Double-blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Everolimus (CABINET)." The IND went into effect on December 29, 2017.

- May 15, 2018 (End of Phase 2 Meeting): The DCTD requested a meeting to obtain input from FDA regarding the adequacy of Study A021602 (CABINET) to support the development of cabozantinib for the treatment of patients with NETs. Discussion at this meeting addressed several aspects of the study including two planned interim analyses for futility that were to be performed when 33% and 66% of the projected number of events occurred in CABINET. The FDA reiterated their concern (previously communicated April 5, 2017, and January 29, 2018) that interim analysis of progression-free survival (PFS) may not be sufficiently robust, and therefore susceptible to overestimation.

  The FDA stated the following: "An interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, or disagreements between imaging reviewers. Stopping a trial based on interim PFS results (which may not be verifiable after adjudication) may lead to challenges with interpreting the data, especially if treatment is changed based on interim results. FDA discourages the proposed plan of conducting the interim analysis for superiority since an interim PFS analysis may not provide an accurate estimate of the treatment effect size due to immature data included in the analysis. Also, there may not

be adequate data to evaluate safety, duration of benefit, and important subgroups."

- August 9, 2023 (Email correspondence): The DCTD informed the FDA via email that "based on an interim review, the Drug Safety Monitoring Board (DSMB) has recommended early termination of Protocol A021602 filed under IND 137656 due to positive results/efficacy." Top-line summary data was subsequently provided for both the pNET and epNET cohorts. The FDA was notified that based on the results of the first interim analysis for the pNET cohort and the second interim analysis for the epNET cohort, on July 28, 2023, the Alliance DSMB "voted unanimously to release the study results, terminate accrual to the trial and recommended unblinding of patients" and permit crossover of placebo patients to receive cabozantinib. Of note, although the study's primary endpoint was evaluation of response per blinded independent radiology review committee (BIRC), the DSMB's decision was based primarily on review of investigator assessed PFS due to reported discordance between real-time central review and the retrospective batched central review (BIRC), and as there was a backlog in readings by the BIRC.

- August 16, 2023 (Email correspondence): In reference to the interim analysis results and the DSMB's recommendation to unblind the CABINET study, the FDA informed the DCTD that the FDA is unable to advise them on study conduct and whether they should unblind CABINET; however, the FDA cautioned that "results of interim analyses may not provide an accurate estimate of the treatment effect size due to data immaturity, particularly those that are based on a small number of PFS events as in the pancreatic NET cohort." Additionally, the FDA noted that "a high degree of crossover and/or censoring after disease progression could make the results of the OS analysis difficult to interpret."

- May 14, 2024 (Pre-sNDA meeting): The FDA communicated to the Applicant the main issues that will be considered during the review of an sNDA submission including early termination of the study and its impact on the FDA's ability to reliably interpret efficacy data, potential uncertainty regarding the efficacy results based on discordance between investigator assessments and BIRC assessments as well as between BIRC and real-time central review assessments, and finally the potential for incomplete blinding due to the well-known toxicity profile of cabozantinib.

- September 3, 2024 (Email correspondence): Given the immaturity of overall survival (OS) data from CABINET, the FDA requested the Applicant to submit the results of an additional descriptive analysis of OS during the review cycle.

- November 4, 2024, and December 5, 2024 (Email correspondence): The Applicant provided an additional descriptive OS analysis with a data cutoff (DCO) of September 4,

2024 (previous DCO was August 24, 2023) for each cohort (pNET and epNET) using the intent-to-treat (ITT) population. The Applicant acknowledged that this updated OS analysis was based on a data snapshot without a rigorous sweep of survival data and therefore may not have captured all survival events.

- November 22, 2024 (Informal teleconference): Based upon the OS data snapshot provided and the uncertainty of the OS estimate with a hazard ratio exceeding 1 and wide confidence intervals, FDA determined that an Oncologic Drugs Advisory Committee (ODAC) meeting would be necessary to discuss the benefit:risk assessment of cabozantinib for the proposed indications and the concern for a potential safety signal due to drug toxicity. The FDA informed the Applicant of its decision to hold an ODAC.

- December 16, 2024 (Email correspondence): The Applicant confirmed with the Alliance study team that updated survival status was required for 47 patients and agreed to conduct a complete OS sweep of all patients using the DCO of September 4, 2024.

- December 19, 2024 (Informal teleconference): The FDA met with the Applicant to discuss the timeline for the OS data sweep and the Applicant's response to a statistical information request. Subsequently, the Applicant agreed to provide the requested OS data for the unplanned analysis by January 6, 2025.

- January 6, 2025 (Email correspondence): The Applicant provided updated OS data using the DCO of September 4, 2024. The Applicant confirmed that this was the first full, rigorous complete sweep of OS data. These datasets included source data verified OS information that was captured up to the DCO for all patients currently in survival follow-up.

- January 8, 2025 (Informal teleconference): The FDA informed the Applicant that an ODAC was no longer deemed necessary after review of the updated results provided in the complete OS data sweep.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Refer to the Clinical Inspection Summary, dated December 30, 2024, for full details. Briefly, two clinical investigators (CIs), Drs. Jonathan Strosberg (Site #FL065) and Edward Wolin (Site #NY021), as well as the imaging Contract Research Organization, (b) (4) were selected for inspection. Inspections of the CIs, Drs. Strosberg

and Wolin, and the imaging CRO revealed no discrepancies or regulatory violations regarding study conduct, data integrity, Good Clinical Practice (GCP), or regulatory compliance. Based on these inspections, Study A021602 (CABINET) appears to have been conducted adequately, and the data generated by the inspected CIs and the imaging CRO and submitted by the Applicant, Exelixis, appear acceptable in support of the proposed indications.

4.2. Product Quality

This section is not applicable for this supplemental application.

4.3. Clinical Microbiology

This section is not applicable for this supplemental application.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant proposed to expand the pNET and epNET indications to pediatric patients 12 years of age and older. The effectiveness of cabozantinib in pediatric patients 12 years of age and older is supported by clinical efficacy and safety data from Study A021602 (CABINET) in adults at 60 mg once daily (QD) with additional population pharmacokinetic data demonstrating that the AUC and Cmax of cabozantinib is expected to be similar between adults and pediatric patients aged 12 years and older at the proposed dosages (i.e., 40 mg QD with body weight < 40 kg; 60 mg QD with body weight ≥ 40 kg), and by sufficient similarity in the disease in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

In addition, the population PK analysis demonstrated that there is no clinically relevant difference of cabozantinib PK parameters based on tumor types. The population PK analysis is sufficient to support the proposed dosages of cabozantinib in pediatric patients. **Error! Reference source not found.**

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in sNDA 208692 and recommends approval. There are no clinical pharmacology-related postmarketing requirements (PMR) or postmarketing commitments (PMC). The key review issues and recommendations are summarized below.

FDA Table 5: Key Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendation
Error! Reference source not found. Recommended dosages	Adult and pediatric patients 12 years of age and older with body weight greater than or equal to 40 kg: 60 mg QD Pediatric patients 12 years of age and older with bodyweight less than 40 kg: 40 mg QD

	The population PK analysis in this submission is sufficient to support the proposed dosages in pediatric patients with pNET or epNET. Please refer to Section 19.4 for additional details.
Labeling	Use of CABOMETYX in pediatric patients aged 12 years and older with NETs is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages. The systemic exposures to cabozantinib in pediatric patients 12 years and older at the recommended dosages are expected to be comparable to the exposure in adults at the dose of CABOMETYX 60 mg once daily.

6.2. Summary of Clinical Pharmacology Assessment

The Applicant's Position:

Results from clinical pharmacology studies of cabozantinib were included in the original cabozantinib tablet (Cabometyx®) marketing application. The clinical PK of cabozantinib was assessed in 11 clinical pharmacology studies: a hepatic impairment study (Study XL184-003), a renal impairment study (Study XL184-017), four drug interaction studies of cabozantinib with rifampin (rifampicin; Study XL184-006), ketoconazole (Study XL184-007), rosiglitazone (Study XL184-008), and esomeprazole (Study XL184-018); and four biopharmaceutic studies consisting of two bioequivalence studies (Studies XL184-010 and XL184-016), a food effect study (XL184-004), and a comparative bioavailability study of two different tablet strengths (Study XL184-020). The above studies used cabozantinib capsules, with the exception of Studies XL184-018 and XL184-020 which were performed with tablets. The tablet and capsule formulations are not bioequivalent or interchangeable. In the eleventh clinical pharmacology study (XL184-012), cabozantinib was dosed as a formulated solution in a mass balance study in healthy subjects. The clinical pharmacology of cabozantinib 60 mg QD has been well characterized as part of NDA 208, 692, and is not discussed further here. No new clinical pharmacology studies were conducted since the initial application, and therefore, these results are not discussed further. The PK of cabozantinib 60 mg QD has been extensively studied. The collection of PK samples was optional in the CABINET study, and only a subset of subjects contributed samples for analysis, resulting in a limited dataset. No population PK or exposure-response analyses were conducted.

The FDA's Assessment:

FDA agrees with the Applicant's position. Please refer to the Multi-Disciplinary Review and

Evaluation of the original NDA 208692 submission for a full FDA assessment. Please refer to FDA's assessment in Section **Error! Reference source not found.** and Section 19.4 regarding updates to the population PK analysis in this submission to support the proposed dosages in pediatric patients 12 years of age and older.

6.2.1. General Dosing and Therapeutic Individualization

6.2.1.1. General Dosing

The Applicant's Position:

The 60-mg QD (once daily) dose of cabozantinib has been extensively investigated in clinical trials and has been approved, as monotherapy, in the US and Europe for treatment of subjects with renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer. Further, this dose was evaluated in subjects with epNET and pNET in the Investigator sponsored Phase 2 study NCT01466036 (Chan et al, 2017) and the phase 3 CABINET study. This dose was determined to be associated with objective tumor responses and encouraging PFS, while allowing for two protocol-specified levels of dose reduction (40 mg and 20 mg) to maximize individual subject tolerability.

The FDA's Assessment:

FDA agrees with the Applicant's position. Please refer to the Mult-Disciplinary Review and Evaluation of the original NDA 208692 submission for a full FDA assessment. Please refer to FDA's assessment in Section **Error! Reference source not found.** and Section 19.4 regarding updates to the population PK analysis in this submission to support the proposed dosages in pediatric patients 12 years of age and older.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Applicant Table 6 presents details of the CABINET study that supports the safety and efficacy in the proposed indication.

Applicant Table 6: Listing of Clinical Trials Relevant to this Application

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety – Pivotal Study CABINET						
A021602/ CABINET	NCT03375320	Phase 3, multicenter, randomized, double-blind study of cabozantinib (60 mg daily) versus matched placebo in subjects with locally advanced/unresecatble or metastatic epNET or pNET whose disease had progressed after prior FDA-approved therapy.	Cabozantinib 60 mg qd, oral Matching placebo, oral	**Primary:** PFS per RECIST 1.1 by BIRC **Secondary:** ORR, OS, Safety and tolerability of cabozantinib versus placebo	Until disease progression, intolerance to therapy, or withdrawal of consent.	epNET: 203 subjects were enrolled (134 cabozantinib, 69 placebo) pNET: 95 subjects were enrolled (64 cabozantinib, 31 placebo).	Subjects with locally advanced/unresectable or metasatic, well or moderately differentiated epNET (including gastrointestinal [GI], lung, thymus, other, or unknown primary site) or pNET whose disease had progressed after prior FDA-approved therapy (excluding somatostatin analogs)	62 sites in 1 country (United States)

BIRC, blinded independent review committee; epNET, extra-pancreatic neuroendocrine tumors; ORR, objective response rate; OS, overall survival; pNET, pancreatic neuroendocrine tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; qd, once daily

The FDA's Assessment:
The FDA agrees with the Applicant's description of the key clinical study, Study A021602, hereafter referred to as CABINET, a US-based study that was initiated in 2018, as outlined in Applicant Table 6. For this supplemental NDA (sNDA), the primary clinical data for the FDA's analysis of efficacy were based on data from 298 patients with advanced, previously treated epNET (n=203) or pNET (n=95) who enrolled in CABINET, using a DCO of August 24, 2023, which was the date of study unblinding. Patients were randomized (2:1) to treatment with cabozantinib or placebo. Patients receiving placebo were eligible to crossover and receive open-label cabozantinib upon confirmed disease progression (PD) by real-time central review to confirm local assessment of PD. Patients receiving cabozantinib were treated with the monotherapy dose of 60 mg orally once daily approved for other cancer indications.

The FDA's safety analyses were based on 293 patients (199 in the epNET cohort; 94 in the pNET cohort) who were treated in the study, of which 195 patients received cabozantinib and 98 patients received placebo. The FDA's source data for these safety analyses was the Applicant's safety update and implemented a DCO of August 24, 2023. The individual safety populations receiving cabozantinib were 63 patients from the pNET cohort and 132 patients from the epNET cohort with an integrated safety population of 195 patients.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. CABINET (A021602; NCT03375320)

Trial Design

The Applicant's Description:

The CABINET study (A021602; NCT03375320) is a randomized, placebo-controlled Phase 3 study designed by the lead investigators and conducted by the Alliance for Clinical Trials in Oncology ("Alliance") under the NCI-CTEP US Investigational New Drug (IND) application. It was funded by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP). Exelixis, the manufacturer of cabozantinib, has a Cooperative Research and Development Agreement (CRADA) with NCI-CTEP and provided cabozantinib for this study. The dose and formulation of cabozantinib used in the CABINET study was as approved for single-agent therapy in renal cell, hepatocellular and differentiated thyroid carcinoma. Exelixis did not participate in the design or conduct of the trial and did not have access to study data until after the top-line analyses of the study primary endpoint were announced by the Alliance in August 2023.

The study was intended for registrational purpose and included blinded independent central image review for the primary endpoint of PFS and real time review to confirm local assessment of progression prior to potential crossover from placebo to open-label cabozantinib.

Key details of the study design, primary endpoints, and status of the CABINET study are summarized in Applicant Table 7.

Applicant Table 7: Overview of CABINET Phase 3 Study (A021602) in Subjects with Advanced Neuroendocrine Tumors after Progression on Prior Systemic Therapy

Study/Phase/Status	**A021602 (CABINET) NCT03375320/ Phase 3/ ongoing (full CSR)**
Treatment	Three 20-mg oral tablets (60 mg total) of cabozantinib or matched-placebo daily in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent.
Study Population	• Well- or moderately-differentiated NETs of pancreatic (pNET) and extra pancreatic/ carcinoid (epNET) origin by local pathology. • Locally advanced/unresectable or metastatic disease. • ≥ 18 years • ECOG 0-2 • Measurable disease per RECIST 1.1 • RECIST progression within 12 months prior to study entry. • Progressed after receiving or intolerance leading to treatment discontinuation of at least one FDA-approved line of therapy (except somatostatin analogs). ○ Prior lines of therapy included one of the following: everolimus, sunitinib, or Lu-177 dotatate (pNET); everolimus (lung NET); everolimus or Lu-177 dotatate (GI NET)
Number of Subjects Treatment	• **Planned:** 395 Subjects (210 epNET, 185 pNET) • **Actual:** ○ **Efficacy Analyses (ITT Population)**: 298 subjects • epNET: 203 (134 cabozantinib, 69 placebo) • pNET: 95 (64 cabozantinib, 31 placebo) ○ **Safety Analyses (Safety Population):** 293 subjects • epNET: 199 (132 cabozantinib, 67 placebo) • pNET: 94 subjects (63 cabozantinib, 31 placebo)
Primary Objective	PFS per RECIST 1.1 by a blinded independent review committee (BIRC)
Secondary Objectives	OS; ORR per RECIST 1.1 by BIRC; safety and tolerability of cabozantinib versus placebo

BIRC, blinded independent review committee; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; epNET, extra-pancreatic neuroendocrine tumor (carcinoid tumor); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Subjects were accrued into 2 cohorts which were randomized separately: epNET and pNET. In this double-blinded study, subjects in both NET cohorts were randomized in a 2:1 fashion to

receive either treatment with cabozantinib or matched placebo. As with other pivotal NET studies in this treatment setting outlined in Module 2.5, Table 1, placebo was chosen due to the lack of prospective data regarding the efficacy of available agents in patients who progressed after FDA-approved therapy. Subjects in the CABINET study were required to have progressed or be intolerant to at least one FDA approved therapy (except somatostatin analogs).

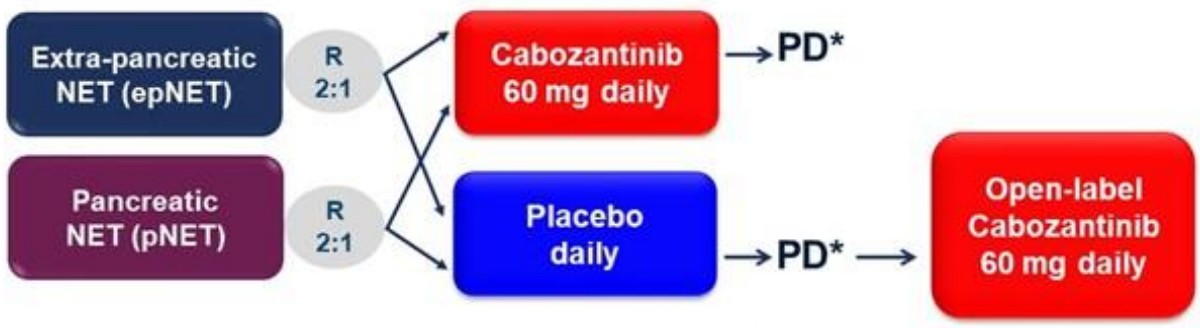
In the epNET cohort, randomization was stratified by concurrent somatostatin analog use: yes vs no and primary tumor site (midgut GI/unknown vs non-midgut GI/lung/other). In the pNET cohort, randomization was stratified by concurrent somatostatin analog use: yes vs no and prior sunitinib therapy: yes vs no.

Subjects received blinded treatment until disease progression, unacceptable toxicity, withdrawal of consent or death. Subjects were evaluated every 12 weeks by radiographic imaging for response and progression (as determined by RECIST 1.1). Radiographic images were assessed both locally and per batched BIRC. In addition, real time blinded central review for confirmation of progressive disease was performed. If radiographic progressive disease was the final determination by real time central review, then protocol therapy was discontinued. If radiographic progressive disease was not the final determination by the real time central review, then protocol treatment was to be continued. At the time of centrally confirmed radiographic disease progression, subjects were unblinded to treatment assignment, and those on placebo could elect to crossover to open-label cabozantinib treatment following re-registration and upon meeting the requirements for continuing with treatment on study. Crossover from placebo to open-label cabozantinib was allowed after Protocol Update #2 (version date 24 July 2020, implemented by sites on 15 Nov 2020). At the time of implementation of Protocol Update 2, 80 subjects had been randomized between both cohorts with 28 subjects randomized to placebo. A total of 12 placebo-treated subjects (6 epNET, 6 pNET) had disease progression prior to Protocol Update #2 and therefore did not have the option to crossover from placebo to open label cabozantinib.

Enrolled subjects were followed for tumor response and survival every 12 weeks until disease progression or the start of new anticancer therapy, and then for survival every 6 months until 8 years after registration or until death, whichever came first. Subjects with global deterioration of health status (not related to study treatment or other medical condition) requiring discontinuation of treatment without objective evidence of disease progression at the time of discontinuation, were encouraged to continue radiologic imaging every 12 weeks until disease progression (or start of a new anticancer therapy).

Applicant Figure 1 provides a schema of the CABINET study design.

Applicant Figure 1: CABINET Study Schema



Abbreviations: PD, progressive disease; R, randomized
*Unblinding and crossover from placebo to open-label cabozantinib allowed after confirmation of PD by real time central radiology review.

The FDA's Assessment:

The FDA agrees with the Applicant's description of CABINET. The Applicant did not participate in the design or conduct of the trial and states they did not have access to study data until after the top-line analyses of the study primary endpoint were reported by the Alliance study team in August 2023.

Regarding the comparator arm, the FDA did not object to Alliance's selection of placebo during discussion of the trial design in 2017 as there is no approved therapy for patients with pNET or epNET whose disease had progressed on prior therapy; however, the study's informed consent document was reviewed to confirm inclusion of available therapies (e.g., peptide receptor radionuclide therapy) that patients may choose to receive to treat their disease.

Additionally, as described in the subsection "Protocol Amendments", the FDA notes that the trial was initially designed as a study for patients with NETs who had progressed on prior everolimus and did not originally permit crossover. The study protocol was later modified to permit patients to have progressed on other prior FDA-approved therapies and to allow patients in the placebo arm to crossover to open label treatment with cabozantinib upon confirmed disease progression, likely in response to issues with patient accrual.

Key Eligibility Criteria

The Applicant's Description:

Applicant Table 8: Key Entry Criteria in the CABINET (A021602) Study

Documentation of disease	• Histological documentation: Well- or moderately-differentiated neuroendocrine tumors of pancreatic (pNET) and non-pancreatic (ie, extra pancreatic or carcinoid; epNET) origin by local pathology. • Subjects were required to have disease progression by RECIST 1.1 within 12 months prior to study entry.
Staging	• Locally advanced/unresectable or metastatic disease.
Age	• ≥ 18 years
Performance status	• ECOG 0-2
Measurable disease	• Subjects must have measurable disease per RECIST 1.1 (Eisenhauer et al, 2009) by computed tomography (CT) scan or magnetic resonance imaging (MRI).
Extent of prior anticancer therapy	• Subjects must have had disease progression after receiving or intolerance leading to treatment discontinuation of at least one FDA-approved line of therapy (except somatostatin analogs). Prior lines of therapy were to have included one of the following: everolimus, sunitinib, or lutetium Lu-177 dotatate in subjects with pNET; everolimus in subjects with lung NET; everolimus or lutetium Lu-177 dotatate in subjects with GI NET. • Prior treatment with somatostatin analogs was allowed, and continuation of treatment with somatostatin analogs while on cabozantinib/placebo was allowed provided that the subject had been on a stable dose for at least 2 months prior to enrollment.
Patient history	• Prior treatment with cabozantinib was not allowed. • No thromboembolic events within 6 months of registration (incl. stroke, TIA, DVT, & PE). • No uncontrolled hypertension within 14 days of registration (defined as SBP ≥150 mmHg and/or DBP ≥ 90 mmHg despite optimal medical management). • No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of registration including, but not limited to: – No GI perforation within 6 months of registration. – No known tumor with invasion into the GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration.

DBP, diastolic blood pressure; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; PE, pulmonary embolism; RECIST, Response Evaluation Criteria in Solid Tumor; SBP, systolic blood pressure; TIA, transient ischemic attack; ULN, upper limit of normal

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of key eligibility criteria for CABINET.

Other relevant eligibility criteria are listed below:

- Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma without specification of differentiation status, adenocarcinoid tumor, or goblet cell carcinoid tumor were not eligible.
- Patients with well-differentiated grade 3 neuroendocrine tumor were eligible.
- Patients with functional or nonfunctional tumors were allowed.
- Patients with active brain metastases or cranial epidural disease were not permitted to participate in the study.

Study Endpoints

The Applicant's Description:

The CABINET study objectives and endpoints along with the definitions of the endpoints are provided below in Applicant Table 9. All study endpoints were pre-specified.

Applicant Table 9: CABINET: Study Endpoints

Efficacy Endpoints	Definition
Primary	
PFS	The primary endpoint was PFS based on BIRC assessessment using RECIST v1.1. PFS is defined as the time from randomization to the earlier of disease progression per RECIST 1.1 or death due to any cause
Secondary	
ORR	ORR is defined as the proportion of subjects whose best response was either confirmed CR or PR
OS	OS is defined as the time from randomization to death from any cause
Safety and tolerability of cabozantinib versus placebo	Safety was assessed through AEs and SAEs; deaths; ECOG performance status;. The Alliance independent data monitoring committee monitored safety and accrual on a regular basis.
Additional	
DOR	DOR was defined as the time from the tumor assessment that first documents PR or CR until the date of documented radiographic progression, per RECIST 1.1, or death. Only subjects with confirmed CR or PR were included in this analysis separately within each cohort.
DCR	DCR was defined as the proportion of subjects with a BOR of CR, PR or SD. A method similar that used for ORR was used to analyze DCR.

AEs, adverse events; BIRC, blinded independent radiology committee; BOR, best overall response; CR, complete response; DOR, duration of response; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, response-evaluation criteria in solid tumors; SAEs, serious adverse events

The primary endpoint was PFS, defined as the time from randomization to first radiographic documentation of disease progression as determined by batched retrospective independent radiograph review, or death by any cause; and the secondary endpoint was OS, defined as time from randomization to death due to any cause. The choice of PFS as the primary endpoint, rather than OS, was based on the observed long survival times after progression in many subjects, thus making PFS a feasible and relevant endpoint in the Phase 3 trial (Kulke et al, 2011; Singh et al, 2023). Following real time centrally confirmed disease progression, subjects who had been taking placebo could elect to crossover to open-label cabozantinib.

The FDA's Assessment:

The FDA agrees with the description of the primary, secondary and additional endpoints in CABINET, as presented in this section. PFS has been used as the primary efficacy endpoint, with

OS as a secondary endpoint, in clinical trials that have supported FDA approval of therapies for patients with neuroendocrine tumors. CABINET allowed patients in the placebo arm to crossover to receive treatment with open-label cabozantinib upon radiographic disease progression according to real time central review. This may impact the assessment of OS by potentially obscuring the true treatment effect.

Statistical Analysis Plan and Amendments

The Applicant's Description:

This study was sponsored by CTEP and conducted by the Alliance group. Statistical analyses are based on Alliance SAP v2.0 (14 August 2023) and Exelixis' addendum to SAP 2.0 (26 February 2024). Statistical analyses and programming were conducted retrospectively by Exelixis as part of this regulatory submission. The Exelixis SAP addendum documents changes from the Alliance SAP v2 with additional specified analyses. The Exelixis SAP addendum was developed after the analysis of interim results and study unblinding and prior to Exelixis' receipt of the data from the 01 March 2024 data snapshot. Primary analyses are based on the cutoff date of 24 August 2023; 24 August 2023 corresponds to the date the study was unblinded and placebo subjects were allowed to crossover to cabozantinib if eligible. The unblinding was performed based on Data and Safety Monitoring Board (DSMB) recommendation after reviewing the first interim analysis results for the pNET cohort and second interim analysis for epNET cohort and performed by the Alliance.

The FDA's Assessment:

The efficacy results in this marketing application were submitted based on an initial data cut-off (DCO) date of Aug 24, 2023, the date of unblinding, when all patients in the placebo arm were allowed to crossover to the open-label cabozantinib arm. Statistical analysis plans dated after the unblinding were considered to be ad-hoc and exploratory. Several FDA recommendations were implemented in the ad-hoc or addendum analyses plans, and FDA has utilized results from these recommended analyses as supportive results for the overall evaluation of efficacy.

Further, the FDA notes that the DSMB's decision to unblind the study was primarily based on the review of investigator assessed PFS due to reported discordance between the real-time central review and the retrospective batched central review (BIRC) and a backlog in imaging evaluation by the BIRC.

***Analysis Populations**:*

The following analysis populations were used for the statistical analyses of the data and applied to both epNET and pNET cohorts:

Intent-to-Treat (ITT) Population: The ITT population consisted of all subjects within each cohort (epNET and pNET) who were randomized. The ITT population was used to analyze disposition,

demography, baseline characteristics, primary efficacy analysis, secondary efficacy analyses, protocol deviations, and ad-hoc endpoints. Subjects were grouped based on the treatment they were assigned during randomization.

ITT Population and Randomized for ≥ 6 Months: All subjects in the ITT population randomized at least 6 months before the data cutoff date were included in a PFS sensitivity analysis. Subjects were grouped based on the treatment they were assigned during randomization.

Safety Population: The Safety population consisted of all subjects who received at least 1 dose of any study medication. This population was used for exposure and safety analyses. Subjects were grouped based on the actual treatment received.

A per-protocol population was not defined or planned for this study.

The following 3 data sets of safety analyses for treatment-emergent AEs (TEAEs) and study treatment exposures were summarized as follows:

1. Data obtained from subjects in the blinded treatment phase (excluding data obtained in the open-label phase from subjects in the placebo arm who crossed over to open-label cabozantinib after disease progression)

2. Only data obtained during the open-label phase from subjects who crossed over from placebo to open-label cabozantinib

3. Data obtained from all subjects during the blinded treatment phase and the open-label cabozantinib treatment phase

The FDA's Assessment:

In general, the FDA agrees with the definitions of the analysis populations used in CABINET. Of note, the study enrolled patients using an "OPEN" registration system, a web-based Oncology Patient Enrollment Network system relying on an interactive voice/web response system (IxRS). Using this system, there were 3 epNET patients misclassified as pNET patients who were randomized to the pNET cohort, and 7 pNET patients misclassified as epNET patients who were randomized in the epNET cohort.

The FDA's analyses used both the ITT population (which includes misallocated patients per IxRS) and the population after correcting for misclassified tumor type (reflecting correct allocation according to patient's actual tumor type per electronic data capture). The efficacy results in the US prescriber information are derived from the population after correcting for tumor type and using source verified stratification factors for analyses. This review presents efficacy results from both populations.

Primary Endpoint:

Progression-free Survival per BIRC:

The primary objective of this study was to determine whether cabozantinib compared with placebo significantly improved PFS in subjects with either epNETor pNET whose disease had progressed after prior FDA-approved therapy. The primary endpoint of PFS is defined as the time from randomization to the earlier of either the date of radiographic progression per BIRC or the date of death due to any cause. The analysis is performed independently for each cohort (epNET and pNET). The prespecified primary analysis of PFS is based on 203 (134 cabozantinib, 69 placebo) subjects with epNET, and 95 (64 cabozantinib, 31 placebo) subjects with pNET. The data cutoff date for this event-driven analysis was 24 August 2023; a total of 111 events (55%) and 57 events (60%) were reported by this date in the epNET and pNET cohorts, respectively. Only radiographic progression events determined by BIRC per RECIST 1.1 and deaths prior to progression were counted as events.

A type 1 error spend of two-sided 0.002 (ie, one-sided 0.001) was prespecified for each protocol-defined futility analysis, and two-sided 0.046 (ie, one-sided 0.023) was prespecified for the final primary analysis of PFS within each disease cohort and using the stratification factors at randomization. As the DSMB recommended early unblinding of the study at the interim analysis, the PFS analysis herein compares the treatment arms with the two-sided significance level of 0.002 (one-sided significance level of 0.001). The HR for PFS was estimated using a stratified Cox proportional hazards model, with the 95% CI for the HR provided. Results from an unstratified analysis were also provided. Kaplan-Meier (K-M) methodology was used to estimate the median PFS for each treatment arm, and Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS for each treatment arm.

The FDA's Assessment:

The FDA agrees that the primary endpoint in each cohort in CABINET was PFS based on BIRC assessment using RECIST v1.1. PFS was defined as the time from randomization to the first radiographic documentation of disease progression, per RECIST 1.1, as determined by BIRC, or death from any cause. See Applicant Table 10 below for the descriptions of censoring rules for the primary and sensitivity analyses of the primary endpoint. FDA agrees with the estimation methods used for the primary endpoint presented in this section.

The primary efficacy analysis of PFS was planned after 149 PFS events in the pNET cohort and after 164 PFS events in the epNET cohort. The trial was designed to have 90% power to detect a PFS hazard ratio (HR) of 0.57 (medians: 5.0 vs. 8.8 months) using a one-sided alpha of 0.025 in pNET cohort and 90% power to detect a PFS HR of 0.58 (medians: 7.0 vs. 12.0 months) using a one-sided alpha of 0.025 in the epNET cohort. Two interim analyses (IAs) for futility were planned for each cohort after 33% (IA1) and 66% (IA2) of the planned number of PFS events had occurred. The Applicant allocated a one-sided alpha of 0.001 for each interim analysis because

the stopping rules were defined by analyses of PFS, which is also the primary endpoint for efficacy.

Patient enrollment in CABINET was terminated on August 7, 2023, following the DSMB's recommendation based primarily on investigator-assessed PFS benefit and no concerns regarding detriment in overall survival observed at the time of planned IA1 (33% information fraction [IF] for PFS) in the pNET cohort and IA2 (66% IF for PFS) in the epNET cohort. At the time of enrollment termination, a total of 95 patients of the planned 185 patients in the pNET cohort, and 203 patients of the planned 210 patients in the epNET cohort were enrolled. The NDA submission is based on the DCO of August 24, 2023, i.e., the date of unblinding when all eligible patients in the placebo arm were allowed to crossover to the open-label cabozantinib arm. See Section 8.1.2 "Interim Analysis" for additional information regarding the DSMB recommendation.

Primary PFS and Sensitivity Analyses:

Applicant Table 10 summarizes the PFS analyses documented in Alliance SAP 2.0 dated 14 August 2023 and the additional analyses Exelixis performed for PFS as documented in the Exelixis SAP addendum.

Applicant Table 10: Summary of PFS Primary and Sensitivity Analyses

Analysis Type	Description of the Primary and Sensitivity Analyses of PFS[a]	Comment
Primary (PFS-EP1)	Primary PFS endpoint defined as the time from randomization to the first radiographic documentation of disease progression, per RECIST 1.1 determined by BIRC, or death from any cause, using censoring rules per the FDA guidance. Symptomatic deterioration alone does not constitute a PFS event. Subjects who do not have a PFS event prior to initiation of the new concomitant or subsequent NPACT (including crossover therapy of cabozantinib for placebo subjects) will be censored for PFS at the last adequate tumor assessment date which is prior to initiation of the NPACT. Subjects with PD or death following 2 or more consecutive missing tumor assessments will be censored at the date of the last ATA prior to the missing scans.	PFS-EP1/2/3 were specified in the Alliance SAP 2.0 (14 August 2023). Note: Exelixis addendum to SAP 2.0 (26 Feb 2024) included censoring of 2 or more consecutive missing tumor assessments.
Sensitivity[a] (PFS-EP2)	The PFS according to investigator assessment	
Sensitivity[a] (PFS-EP3)	For subjects with a PFS event related to the results of a scan performed prior to the time of scheduled restaging, the PFS	

	event will be dated on the date of the next scheduled radiology restaging assessment.	
Sensitivity[a] (PFS-EP4)	Using disease allocation and stratification factors at randomization collected per EDC	These additional analyses (EP4-6, EA1-3) were added to the Exelixis addendum to SAP 2.0 (26 Feb 2024).
Sensitivity [a] (PFS-EP5)	Using a data cutoff date based on the protocol and SAP-defined number of events for the two cohorts interim analyses, respectively, (109 events for epNET cohort 2nd interim analysis and 50 for pNET cohort 1st interim analysis per independent central review, ie, BIRC imaging assessments, or death from any cause), if the number of events are met before or on 24 August 2023. In the case that multiple events occur on the same date and all of them could be counted as the specified event, all these events occurred on the same date will be included in the analysis.	
Sensitivity[a] (PFS-EP6)	Only include subjects randomized at least 6 months before 24 August 2023	
Sensitivity[a] (PFS-EA1)	Initiation of new NPACT (including crossover therapy) is treated as an event at the date of the initiation of the NPACT	
Sensitivity[a] (PFS-EA2)	Subjects whose PD or deaths occurred after two or more consecutive missing scans are treated as having an event at the last ATA before missing scans. Initiation of new NPACT (including crossover therapy) is treated as an event at the date of the initiation of the new NPACT	
Sensitivity[a] (PFS-EA3)	Symptomatic deterioration as an event at the date of the symptomatic deterioration. Initiation of new NPACT (including crossover therapy) are treated as an event at the date of the initiation of the NPACT	
Sensitivity[a] (PFS-EA4)	Ignore missing tumor assessment scans	PFA-EA4 is a separate sensitivity analysis in the Exelixis addendum to SAP 2.0 (14 August 2023). Note: Ignoring missing tumor assessments was included in the primary analysis of PFS per the Alliance SAP 2.0 (14 August 2023).

ATA, adequate tumor assessment; EDC, electronic data capture; BIRC, blinded independent review committee; NPACT, nonprotocol anticancer therapy; PFS, progression-free survival, SAP, statistical analysis plan

[a.] For primary analysis, a complete description is provided. For sensitivity analyses, the difference between the primary analysis and particular sensitivity is noted.

Source: CABINET CSR Appendix 16.1.9

The FDA's Assessment:

The FDA agrees with the Applicant's descriptions of the censoring rules for the primary and sensitivity analyses of the primary endpoint of BIRC assessed PFS.

Secondary Endpoints:

Overall Survival

Per FDA's guidance for survival analysis, a nominal alpha will be spent for each of the descriptive analyses conducted prior to the final analysis of OS. Overall survival at the final analysis will be compared between treatment arms using the stratified log-rank test at a one-sided significance level of 0.023 (ie, two-sided significance level of 0.046). A hierarchical approach will be used to control for family-wise type-I error rate for the final analysis of OS and will be formally tested only if the primary efficacy endpoint, PFS, is statistically significantly different between the 2 treatment arms within each cohort. As OS data were immature and had not reached the prespecified number of events for the final analysis by the data cutoff date for this submission, a nominal alpha of two-sided significance level 0.002 (ie, one-sided significance level 0.001) was used to compare the two treatment arms. The distribution of OS was estimated using the K-M methodology. The median OS, along with the 95% CIs, was estimated for the two treatment groups. Additionally, OS rate at 12 months, 24 months and 36 months, along with the 95% CIs, was estimated for the two treatment groups. The stratified Cox regression was used to estimate the HR of OS, along with the 95% CI. Primary analysis of OS was defined as the time from the randomization to the date of death due to any cause or the last known alive date. Subjects who were alive by the data cutoff date were censored at the last known alive date. Deaths prior to the data cutoff date are included in the analysis.

Besides these OS analyses specified in the Alliance SAP 2.0, the Exelixis SAP addendum added:

- Sensitivity analysis performed by censoring subjects who received concomitant or subsequent NPACT (including crossover therapy of cabozantinib for placebo subjects) at the date of the initiation of the NPACT.
- Sensitivity analysis using the disease allocation and randomization stratification factors collected per electronic case report form (eCRF) collected in electronic data capture (EDC)
- Rank-preserving structural failure time (RPSFT) model to adjust for the effect of the crossover of subjects.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the estimation methods for OS and the additional sensitivity analyses plan as presented in this section. To preserve statistical integrity,

the FDA recommended the Applicant allocate a nominal alpha for each of the interim OS analyses. The Applicant chose to spend an alpha of 0.001 at each analysis.

Objective Response Rate

ORR (ie, referred to as "radiographic response rate" in the protocol and Alliance SAP 2.0) was defined as the proportion of subjects with a BOR of confirmed CR or PR as assessed per RECIST 1.1 by BIRC. The study protocol did not specify the required minimal interval between the initial response and the subsequent confirmatory scan and the minimal interval for meeting BOR of SD. However, the analyses used a minimum of 28 days between confirmatory scan and the scan that the initial response was identified for reporting confirmed BOR and confirmed ORR as per RECIST 1.1. The analyses also used the minimal interval of 6 weeks (42 days) for meeting BOR of SD, ie, to be classified as BOR of SD, at least one timepoint response of SD must be documented ≥ 42 days after randomization.

Point estimates of ORR with confidence intervals (CIs) were calculated using Clopper Pearson method. The difference in ORR between the two treatment arms within each disease cohort and associated confidence intervals are provided, and ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were also performed.

Imaging assessments evaluated per batched BIRC review and per Investigator are provided.

ORR was performed based on the ITT analysis population.

Additional Endpoints:

Duration of Objective Response

Duration of objective response is defined as the time from the tumor assessment that first documents CR or PR until the date of documented radiographic progression, per RECIST 1.1 or death. Only subjects with CR or PR were included in this analysis, separately for each NET cohort.

- Duration of objective response (months) = (earliest date of progression, death or censoring – date of first documented objective response + 1)/30.4375

The duration of objective response was analyzed using the Kaplan-Meier method on ITT populations with a response of CR or PR.

Disease Control Rate

DCR is defined as proportion of subjects with BOR of CR, PR or SD. Analysis of DCR will use a similar method to ORR (for estimation and 95% CI).

The FDA's Assessment:

The FDA agrees with the Applicant's descriptions of the secondary and other endpoints. The Clopper Pearson method is considered appropriate for calculating confidence intervals for estimated ORRs.

Protocol Amendments
The Applicant's Description:

The original protocol, dated 24 May 2018 was updated 5 times. Key changes in each update are described below:

Protocol Amendment 1 dated 19 April 2019, had the following change:

- Revised Section 9.4 of the protocol to include the updated cabozantinib comprehensive AEs and potential risks list (version 2.4; dated, December 17, 2018).

Protocol Amendment 2, dated 24 July 2020, had the following key changes:

- Broadened the eligibility criteria to include subjects who had progressed after a prior therapy (prior to this update, the criterion had specified progression after everolimus).
- The stratification factors for the epNET cohort regarding the primary site were modified as follows for completeness and clarity:
  - Definition of the midgut was changed to "jejunum, ileum, appendix, cecum, ascending colon, hepatic flexure" (replacing "duodenum, jejunum, ileum, appendix, cecum").
  - The term "Unknown" was expanded to "Unknown primary site".
  - Definition of the non-midgut was changed to "duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon" (replacing "non-cecum colon").
  - The term "Other known primary site not listed" replaced the term "Other".
- Changed the title of the study to reflect the above criterion change: replaced the term "after progression with everolimus" with the term "after progression on prior therapy".

- Added re-registration criteria to reflect the addition of a re-registration step for crossover to open-label treatment for subjects randomized to placebo upon central confirmation of progression.
- Modified study schema to include the re-registration step.
- Updated the protocol throughout to reflect the allowance of crossover to open-label cabozantinib upon central confirmation of disease progression and the allowance for progression on any prior therapy, not just everolimus

  Note: At the time of Protocol Update 2, 29 subjects were on study (10 of whom were on placebo): 19 in the epNET cohort (12 in cabozantinib arm and 5 in placebo arm) and 10 in the pNET cohort (5 in each cabozantinib and placebo arm).

Protocol Amendment 3, dated 01 August 2022, had administrative changes only.

Protocol Amendment 4, dated 07 December 2022, had the following key changes:

- Clarified that subjects with neuroendocrine carcinoma without specification of differentiation status were not eligible for the study; and that subjects with well-differentiated grade 3 NET were eligible.
- Updated definition of functional tumor from “a clinical hormone syndrome” to “symptoms or a clinical syndrome related to hormone secretion by tumor”.
- Modified timing for discontinuation of strong CYP3A4 inducers from at least 14 days prior “to the start of study treatment” to at least 14 days prior “to registration on the study”.
- Added to the study calendar that re-registration was to occur ≤ 28 days of local determination of disease progression while receiving blinded therapy with central confirmation of PD; also added that labs were to be completed ≤ 28 days prior to re-registration.
- Added that for subjects who cross over to receive open-label therapy, imaging submission should continue every 12 weeks until progression on open-label therapy.
- Added that the real time central review imaging readers were to be blinded to the subject’s treatment but could access clinical history.
- Added that in the event of disagreement between the local and central imaging reads, adjudication could be requested. Further, added that the adjudicator’s decision would be used as the retrospective, batched central review decision for the purpose of the primary study endpoint.

- Clarified the frequency of progression follow-up at the end of treatment/intervention (ie, every 12 weeks ± 1 week).
- For the secondary endpoint of radiographic response rate, clarified that the radiographic response was to be confirmed.

Protocol Amendment 5, dated 03 February 2023, had the following key changes:

- Updated various sections (Cancer Trials Suport Unit [CTSU] contact information; subject registration; data and specimen submission; Rave-CTEP-AERS integration) with CTSU template language.
- Removed allowance for diagnostic CT in the setting of PET/CT
- Updated text regarding cabozantinib initial supply to allow sites to order initial blinded/subject-specific investigational supplies for the initial subject order.

The FDA's Assessment:
The FDA agrees with the Sponsor's summary of protocol amendments and key updates. Introduction of crossover in Protocol Amendment 2 is likely to impact interpretability of the OS endpoint, which is a secondary endpoint.

Additionally, during review of the sNDA submission, the Alliance study team submitted Protocol Amendment 6 to IND 137656 on November 22, 2024. The major change in this amendment was the addition of the following risks to its current listing of comprehensive adverse events and potential risks (CAEPR):

- Added new risk:
  - Less likely: Musculoskeletal and connective tissue disorder (bone metaphyseal dysplasia)
  - Rare but serious: Endocrine disorders (thyroid dysfunction)

Further, the informed consent document was updated to include a new risk of potential growth interference in children or adolescents in the condensed risk profile for cabozantinib with risk frequency cited as "occasional".

8.1.2. Study Results

Interim Analysis

The CABINET study opened for enrollment 18 July 2018. Two interim analyses (IAs) for futility were planned for each cohort after 33% (IA1) and 66% (IA2) of the planned number of PFS events had occurred. Alpha spending of one-sided 0.001 (ie, two-sided 0.002) for efficacy was included for each interim analysis based on FDA guidance. On 17 May 2023, the DSMB

reviewed the timing of the protocol planned interim analyses. The DSMB unanimously recommended using the local site/investigator assessment of PFS for the futility interim analysis given that the study was double-blinded and the batched BIRC review of tumor assessments was lagging.

At the 28 July 2023 meeting, the DSMB reviewed the interim analyses for PFS per investigator assessment for the pNET (IA1) and epNET (IA2) cohorts and available BIRC assessments (Applicant Table 11). The results were based on a clinical cutoff date of 18 July 2023, at this cutoff date, 200 of a total of planned 210 subjects had been enrolled in the epNET cohort and 95 of a total of planned 185 subjects had been enrolled in the pNET cohort. The DSMB noted a significant improvement in PFS by investigator assessment for patients receiving treatment with cabozantinib compared with placebo in both the epNET and pNET cohorts. Per investigator assessment, median PFS in the epNET cohort was 8.2 months for cabozantinib vs 3.2 months for placebo and in the pNET cohort 13.7 months for cabozantinib vs 3.0 months for placebo. The results were consistent using available BIRC results. No detriment to OS was observed with cabozantinib treatment compared with placebo.

Applicant Table 11: Interim PFS by Investigator and BIRC Review (28 July 2023 DSMB)

Analysis Population	N (Cabozantinib and Placebo)	No. of events	Stratified HR (95% CI)	Log-rankp-value
Extra-Pancreatic NET				
IA2 by Investigator[a]	175	109	0.41 (0.27, 0.62)	<0.0001
All available data by BIRC[b]	200	81	0.47 (0.29, 0.77)	0.0008
Pancreatic NET				
IA1 by Investigator[c]	82	50	0.25 (0.12, 0.49)	<0.0001
All available data by BIRC[b]	95	37	0.26 (0.12, 0.57)	0.0002

BIRC, blinded independent review committee; CI, confidence interval; DSMB, Data and Safety Monitoring Board; HR, hazard ratio; IA, interim analysis; NET, neuroendocrine tumors

a. Data cutoff 13 Dec 2022
b. Data cutoff 18 July 2023
c. Data cutoff 02 Dec 2022

Source: Alliance DSMB meeting 28 July 2023. Alliance data on file.

Based on the significant clinical benefit observed in subjects enrolled in the cabozantinib treatment arms versus placebo in both NET cohorts, the DSMB voted unanimously to recommend release of the study results, termination of accrual, unblinding of all subjects still being treated on the study to enable potential crossover of subjects on the placebo treatment arms to receive open-label cabozantinib treatment, and termination of the trial from further DSMB monitoring. Following the DSMB recommendation, the Alliance stopped enrollment into the study on 07 August 2023. The data were shared with the FDA by the Alliance on 09 August 2023. Investigators and subjects were unblinded on 24 August 2023. The results were

presented at the European Society of Medical Oncology Congress in October 2023 (Chan et al, 2023).

Exelixis subsequently collaborated with the Alliance to obtain and review the study data, and initiated activities to prepare for regulatory submissions. These activities included: facilitating data review, developing an Exelixis statistical analysis plan (SAP) addendum to the Alliance SAP version 2.0 to include analyses required for an ICH-compliant study report suitable for regulatory review, programming submission analysis data sets, performing the analyses described in the SAP and addendum, and authoring the regulatory clinical study report.

Additional minor changes occurring throughout the study conduct are described in the protocol.

The FDA's Assessment:

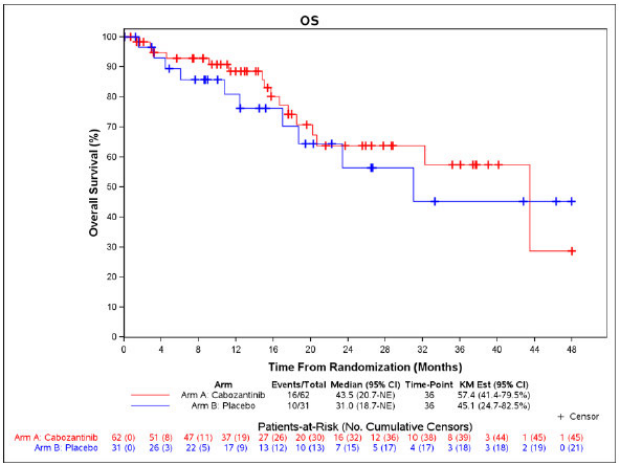
In general, the FDA agrees with Applicant's description of the interim analyses. The FDA did not independently verify these results. The FDA notes that the trial did not have a pre-specified analysis plan for early efficacy claims. The FDA advised the Applicant to spend nominal alpha for each interim futility analysis as the stopping rules were defined by analyses of the primary endpoint for efficacy, PFS. The Applicant allocated an alpha of 0.001 for each interim analysis.

On July 28, 2023, the data safety and monitoring board (DSMB) reviewed results from the IA1 for pNET and IA2 for epNET. The DSMB report indicated that the conditional power to reject the null hypothesis in the epNET cohort was 99.99 based on the investigator assessed PFS results observed at IA2, and was 99.95 in the pNET cohort based on the investigator assessed PFS results observed at IA1 (Source: Applicant's response to FDA information request, dated December 10, 2024). Neither of the cohorts were fully enrolled at the time of these analyses.

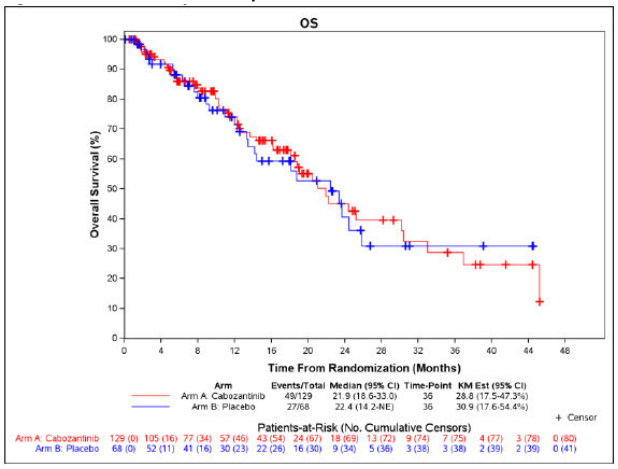
Based on the clinical benefit observed at the time of the pre-specified interim futility analysis, the DSMB recommended releasing the trial results, terminating patient accrual, and unblinding all patients still being treated on the trial to enable potential crossover of patients on the placebo treatment arms to receive open-label cabozantinib treatment. The overall survival results at the time of interim futility analyses of PFS that were presented to the DSMB review are provided in FDA Figure 2 below.

FDA Figure 2. Kaplan-Meier Plots of Overall Survival at Interim Futility Analyses of PFS – pNET and epNET

pNET cohort



epNET cohort



Source: Applicant's response to FDA information request, dated December 10, 2024; DCO: 06/16/2023

The primary efficacy results supporting this marketing application are based on the interim PFS and OS analyses with a data cutoff date of August 24, 2023. During the review, the FDA requested updated data on overall survival with additional follow-up time. The Applicant submitted updated OS results based on a data cutoff date of September 04, 2024, when a rigorous complete sweep of the OS data was performed (see Efficacy Results below).

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted by the Alliance for Clinical Trials in Oncology ("Alliance"), a member of the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN). The Alliance is comprised of academic and community institutions and their affiliates which conduct cancer treatment and cancer control/prevention studies and related research according to their Policies and Procedures and in accordance with all applicable federal, state and local laws and regulations including, without limitation, FDA regulations and guidelines for Good Clinical Practice (GCP).

The FDA's Assessment:

The FDA acknowledges the Alliance study team's statement of compliance with Good Clinical Practice (GCP) guidelines and other applicable laws and regulations.

Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed (see Section 19.2). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Subinvestigators) participating in the CABINET clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:
The FDA agrees that financial disclosures were provided by the Applicant. Refer to Section 19.2 for additional details. In the FDA's assessment, concern for potential investigator bias was mitigated by implementation of a blinded independent central review to evaluate the primary efficacy endpoint of PFS and the key secondary endpoint of ORR.

Patient Disposition

Data:
The first subject was randomized on 26 October 2018. As of the clinical cutoff date 24 August 2023, a total of 298 subjects (ITT population) were randomized to receive study treatment: 203 subjects in the epNET cohort (134 to cabozantinib treatment and 69 to placebo treatment) and 95 subjects in the pNET Cohort (64 to cabozantinib treatment and 31 to placebo treatment). In the epNET cohort, the median time to follow-up was 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm. In the pNET cohort, the median time to follow-up was 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm.

As of the 24 August 2023, in the epNET cohort, 111 subjects (83%) in the cabozantinib arm and 60 subjects (87%) in the placebo arm had discontinued study treatment, primarily due to disease progression (39% cabozantinib, 55% placebo) or an AE (25% and 13%, respectively). Two subjects in each arm never received any treatment before discontinuation. A total of 22 (32%) subjects from the placebo arm crossed-over to open-label cabozantinib treatment following real-time centrally confirmed disease progression. The median duration of exposure (including dose holds) was 5.37 months (range: 0.1–32.4 months) in the cabozantinib arm and 2.79 months (range: 0.5–22.8 months) in the placebo arm (not including crossover).

As of the 24 August 2023, in the pNET cohort, 49 subjects (77%) in the cabozantinib arm and 29 subjects (94%) in the placebo arm had discontinued study treatment, primarily due to disease progression (44% cabozantinib, 74% placebo) or an AE (16% cabozantinib and 0% placebo. One subject in cabozantinib arm did not receive study treatment. Twelve (39%) subjects from the placebo arm crossed-over to open-label cabozantinib treatment following real-time centrally confirmed disease progression. The median duration of exposure

(including dose holds) was 8.28 months (range: 0.1–37.8 months) in the cabozantinib arm and 2.86 months (range: 0.1 –11.2 months) in the placebo arm (excluding crossover phase).

Subject disposition for epNET cohort is summarized below in Applicant Table 12.

Applicant Table 12: Study CABINET: Subject Disposition (ITT population) - epNET

	Cabozantinib (N=134)	Placebo (N=69)
ITT Population	134 (100%)	69 (100%)
Subjects randomized but never received any study treatment	2 (1.5%)	2 (2.9%)
Subjects active on study treatment at data cutoff	21 (16%)	12 (17%)
Subjects active on blinded therapy	21 (16%)	7 (10%)
Subjects active on open-label therapy	0	5 (7.2%)
Discontinued study treatment in the blinded therapy phase	111 (83%)	60 (87%)
Primary reason for discontinuation from study treatment in the blinded therapy phase		
Adverse Event/Side Effects/Complications	34 (25%)	9 (13%)
Alternative therapy	5 (3.7%)	1 (1.4%)
Death on study	6 (4.5%)	3 (4.3%)
Disease progression, relapse during active treatment	52 (39%)	38 (55%)
Subject off-treatment for other complicating disease	1 (0.7%)	1 (1.4%)
Subject withdrawal/refusal after beginning protocol therapy	7 (5.2%)	4 (5.8%)
Other[a]	6 (4.5%)	4 (5.8%)
Discontinued survival follow-up	68 (51%)	41 (59%)
Primary reason for discontinuation of survival follow-up		
Death (as of data cutoff date)	60 (45%)	37 (54%)
Subject withdrawal of consent from all follow-up visits	8 (6.0%)	4 (5.8%)
Follow-up (months)		
Mean (SD)	24.40 (14.351)	24.21 (14.584)
Median (range)	23.34 (0.6 – 56.8)	23.00 (1.2 – 57.6)
25^{th}, 75^{th} percentiles	12.88, 31.34	12.91, 31.51
Placebo subjects crossed over to treatment with open-label cabozantinib	NA	22 (32%)

epNET, extra-pancreatic neuroendocrine tumor; ITT, intent-to-treat; NA, not applicable; SD, standard deviation

Note: The data are based on a data cutoff date of 24-AUG-2023.
Follow-up (months) = (the data cutoff date – the date of randomization +1)/30.4375.
[a] In the cabozantinib arm, 'other' included the following: clinical progression (2 subjects), worsening of non-target lesion (1 subject), loss of consciousness (1 subject), poor performance status (1 subject), and non-compliance (1 subject). In the placebo arm, 'other' included the following: clinical progression (3 subjects) and increase in tumor lesion size (liver nodule) (1 subject).
Source: CABINET CSR, Section 10.1 epNET (Table 14.1.3.1.b.1); ADaM datasets: ADSL.

Subject disposition for pNET cohort is summarized below in Applicant Table 13.

Applicant Table 13: Study CABINET: Subject Disposition (ITT population) – pNET

	Cabozantinib (N=64)	**Placebo (N=31)**
ITT Population	64 (100%)	31 (100%)
Subjects randomized but never received any study treatment	1 (1.6%)	0
Subjects active on study treatment at data cutoff	14 (22%)	8 (26%)
Subject active on blinded therapy	14 (22%)	2 (6.5%)
Subject active on open-label therapy	0	6 (19%)
Discontinued study treatment in the blinded therapy phase	49 (77%)	29 (94%)
Primary reason for discontinuation from study treatment in the blinded therapy phase		
Adverse event/side effects/complications	10 (16%)	0
Alternative therapy	1 (1.6%)	0
Disease progression, relapse during active treatment	28 (44%)	23 (74%)
Subject Off-Treatment for Other Complicating Disease	2 (3.1%)	0
Subject withdrawal/refusal after beginning protocol therapy	5 (7.8%)	4 (13%)
Other[a]	3 (4.7%)	2 (6.5%)
Discontinued survival follow-up	23 (36%)	13 (42%)
Primary reason for discontinuation of survival follow-up		
Death (as of data cutoff date)	21 (33%)	11 (35%)
Subjects withdrawal of consent from all follow-up visits	2 (3.1%)	2 (6.5%)
Follow-up (months)		
N	64	31
Mean (SD)	25.68 (14.624)	27.62 (15.918)
Median (range)	23.21 (1.7–58.0)	25.20 (2.4–55.6)

	Cabozantinib (N=64)	**Placebo (N=31)**
25th, 75th percentiles	15.85, 36.50	15.41, 41.92
Placebo subjects crossed over to and treated with open-label cabozantinib	NA	12 (39%)

ITT, intent-to-treat; NA, not applicable; pNET, pancreatic neuroendocrine tumor; SD, standard deviation
Note: The data are based on a data cutoff date of 24-AUG-2023.
Follow-up (months) = (the data cutoff date > the date of randomization +1)/30.4375.
[a] In the cabozantinib arm, 'other' included the following: clinical progression (1 subject), physician discretion (1 subject), and treatment hold for > 28 days (1 subject).
In the placebo arm, 'other' included the following: treatment hold for > 28 days (1 subject) and palliative care (1 subject).
Source: CABINET CSR, Section 10.1 pNET (Table 14.1.3.1.a.1); ADaM datasets: ADSL.

The Applicant's Position:

The patient disposition was as expected for these patient populations.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of patient disposition in CABINET. In both the pNET and epNET cohorts, the percentages of primary reason for discontinuation from study treatment in the blinded therapy phase due to adverse event/side effects/complications appear to be numerically higher in the cabozantinib arm as compared to the placebo arm (epNET: 25% in the cabozantinib arm vs. 13% in the placebo arm; pNET: 16% in the cabozantinib arm vs. 0% in the placebo arm).

In the Applicant's presentation, follow-up time was defined as time from the date of randomization to data cut-off plus 1 day. In FDA's calculation, follow-up time is defined as time from the date of randomization to date of death or last known date alive plus 1 day. In the ITT population, the median follow-up times in the pNET cohort were 17.2 months (range: 0.7, 58.0 months) in the cabozantinib arm and 17.1 months (range: 1.6, 55.6 months) in the placebo arm. The median follow-up times in the epNET cohort were 12.5 months (range: 0.6, 53.0 months) in the cabozantinib arm and 12.4 months (range: 0.7, 51.2 months) in the placebo arm.

Protocol Violations/Deviations

Data:

Applicant Table 14: Study CABINET: Summary of Critical and Major Protocol Deviations (ITT populations) – epNET

	Cabozantinib (N=134)	Placebo (N=69)	Total (N=203)
Subjects with any Critical or Major Deviations	11 (8.2%)	9 (13%)	20 (9.9%)
Critical deviations			
Eligibility: Other criteria not met	0	1 (1.4%)	1 (0.5%)
Major deviations			
Eligibility: Other criteria not met	1 (0.7%)	3 (4.3%)	4 (2.0%)
Other[a]	2 (1.5%)	2 (2.9%)	4 (2.0%)
Study Procedure: Other	1 (0.7%)	2 (2.9%)	3 (1.5%)
Eligibility: Lab criteria not met	1 (0.7%)	1 (1.4%)	2 (1.0%)
Study Drug Deviation: Other	1 (0.7%)	1 (1.4%)	2 (1.0%)
Study Drug Deviation: Study drug continued when study drug should have been discontinued per protocol	1 (0.7%)	0	1 (0.5%)
Study Drug Deviation: Received incorrect study treatment, including incorrect order of administration	0	1 (1.4%)	1 (0.5%)
Study Drug Deviation: Treatment/dose outside of protocol specified window	1 (0.7%)	0	1 (0.5%)
Study Procedure: Efficacy (Disease) Assessment Method Different From Baseline	1 (0.7%)	0	1 (0.5%)
Study Procedure: Efficacy (Disease) Assessment Out of Protocol Window	0	1 (1.4%)	1 (0.5%)
Study Procedure: Omitted Efficacy (Disease) Assessment	1 (0.7%)	0	1 (0.5%)
Study Procedure: Other Significant Protocol Deviation Affecting Efficacy	1 (0.7%)	0	1 (0.5%)

epNET, extra-pancreatic neuroendocrine tumor; ITT, intent-to-treat

[a] Other includes prohibited concomitant medication, consent by unauthorized personnel, missing imaging assessments and investigational product accountability issues

Source: CABINET CSR, Section 10.2 epNET (Table 14.1.2.2.b); ADaM dataset: ADSL; SDTM dataset: DV.

Applicant Table 15: Study CABINET: Summary of Critical and Major Protocol Deviations (ITT populations) – pNET

	Cabozantinib (N=64)	Placebo (N=31)	Total (N=95)
Subjects with any Critical or Major Deviations	6 (9.4%)	3 (9.7%)	9 (9.5%)
Major			
Study Procedure: Other	3 (4.7%)	1 (3.2%)	4 (4.2%)
Other[a]	1 (1.6%)	1 (3.2%)	2 (2.1%)
Study Drug Deviation: Received Incorrect Study Treatment, Including Incorrect Order of Administration	1 (1.6%)	1 (3.2%)	2 (2.1%)
Eligibility: Other Criteria Not Met	0	1 (3.2%)	1 (1.1%)
Informed Consent Not Appropriately Documented: Informed Consent Not Appropriately Documented	1 (1.6%)	0	1 (1.1%)
Study Drug Deviation: Continuation of Study Drug When Study Drug Should Have Been Discontinued Per Protocol	1 (1.6%)	0	1 (1.1%)
Study Drug Deviation: Other	1 (1.6%)	0	1 (1.1%)
Study Drug Deviation: Significant Deviation From Planned Dose (± 20%)	1 (1.6%)	0	1 (1.1%)

ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumor
[a] Other includes delayed radiology submission for real-time review and protected health information disclosure
Source: CABINET CSR, Section 10.2 pNET (Table 14.1.2.2.a); ADaM dataset: ADSL; SDTM dataset: DV.

The Applicant's Position:

A per-protocol population was not defined or planned for this study. Subjects with critical or major deviations were approximately 10% for both cohorts. Based on the compelling hazard ratios observed, protocol deviations were not likely to affect the study results or the conclusions of the primary analysis.

The FDA's Assessment:

The FDA agrees with the data presented in Applicant Table 14 and Applicant Table 15.

Per the protocol,

- A critical deviation was defined as "any condition, practice, process, or pattern that adversely affected the rights, safety, or well-being of the subject and/or the quality and integrity of the data; it includes serious violations of safeguards in place to ensure safety of a subject and/or manipulation and intentional misrepresentation of data."

- A major deviation was defined as "a variance from protocol-specified procedures or practices that made the resulting data questionable."

According to the clinical study report, in the epNET cohort, 20 patients (11 [8.2%] in the cabozantinib arm and 9 [13%] in the placebo arm) had at least one critical or major protocol deviation; of which the only critical protocol deviation was for a patient in the placebo arm ("other eligibility criteria not met"). The most frequently reported major protocol deviations involved ''other eligibility criteria not met" (1 patient [0.7%] in the cabozantinib arm and 3 patients in the placebo arm [4.3%]) and "other" (2 patients [1.5%] in the cabozantinib arm and 2 patients [2.9%] in the placebo arm). The "other" deviations that were reported in more than one patient included "other study procedure," "a lab eligibility criterion was not met," and "another study drug deviation."

In the pNET cohort, 9 patients (6 [9.4%] in the cabozantinib arm and 3 [9.7%] in the placebo arm) had at least 1 protocol deviation and all were categorized as major. The most frequently reported major protocol deviations involved "study procedure" (3 patients [4.7%] in the cabozantinib arm and 1 patient in the placebo arm [3.2%]), "other" which included delayed radiology submission for real-time review and protected health information disclosure (1 patient (1.6%) in the cabozantinib arm and 1 patient in the placebo arm [3.2%]), and a study drug deviation involving incorrect study treatment and incorrect order of administration (1 patient [1.6%] in the cabozantinib arm and 1 patient [3.2%] in the placebo arm).

Individual reasons for protocol deviations were reviewed and are not expected to affect the overall interpretability of study results.

Table of Demographic Characteristics

Data:

Applicant Table 16: Study CABINET: Demographics and Baseline Characteristics (ITT population) - epNET

	Cabozantinib (N=134)	**Placebo (N=69)**
Age (years)		
Mean (SD)	62.9 (11.97)	63.4 (10.35)
Median (range)	66.0 (28 – 86)	66.0 (30 – 82)
Age Category (years)		
< 65	60 (45%)	31 (45%)
≥ 65	74 (55%)	38 (55%)

	Cabozantinib (N=134)	**Placebo (N=69)**
65 to < 75	57 (43%)	30 (43%)
75 to < 85	16 (12%)	8 (12%)
≥ 85	1 (0.7%)	0
Sex		
Male	60 (45%)	38 (55%)
Female	74 (55%)	31 (45%)
Ethnicity		
Hispanic or Latino	8 (6.0%)	9 (13%)
Not Hispanic or Latino	125 (93%)	56 (81%)
Not Reported	0	3 (4.3%)
Unknown	1 (0.7%)	1 (1.4%)
Race		
White	115 (86%)	55 (80%)
Black or African American	9 (6.7%)	7 (10%)
Asian	3 (2.2%)	1 (1.4%)
Not Reported	2 (1.5%)	4 (5.8%)
Unknown	5 (3.7%)	2 (2.9%)
Body Mass Index		
N	133	69
Mean (SD)	27.24 (6.274)	27.49 (5.484)
Median (range)	26.95 (12.5 – 51.7)	27.14 (18.8 – 44.6)
ECOG PS (as reported on the OPEN registration system)		
0	49 (37%)	32 (46%)
1	84 (63%)	36 (52%)
2	1 (0.7%)	1 (1.4%)
Stratification factors per OPEN registration system		
Concurrent somatostatin analog use (yes)	92 (69%)	48 (70%)
Primary Site		
Midgut/Unknown primary site	74 (55%)	38 (55%)

	Cabozantinib (N=134)	Placebo (N=69)
Non-midgut GI/Lung/Other known primary site not listed	60 (45%)	31 (45%)
Stratification Factors per EDC		
Concurrent somatostatin analog use (yes)	73 (54%)	43 (62%)
Primary Site		
Midgut/Unknown primary site	63 (47%)	28 (41%)
Non-midgut GI/Lung/Other known primary site not listed	67 (50%)	38 (55%)

ECOG PS, Eastern Cooperative Oncology Group performance status; EDC, electronic data capture; GI, gastrointestinal; OPEN, Oncology Patient Enrollment Network; SD, standard deviation
Note: 7 pNET subjects (4 cabozantinib, 3 placebo) incorrectly allocated to the epNET cohort through the OPEN registration system are not included the summary of Primary Site of Stratification Factors per EDC.
Source: CABINET CSR, Section 11.2.1 epNET (Table 14.1.4.1.b.1); ADaM Dataset: ADSL.

Applicant Table 17: Study CABINET: Demographics and Baseline Characteristics (ITT population) - pNET

	Cabozantinib (N=64)	Placebo (N=31)
Age (years)		
Mean (SD)	59.4 (11.44)	62.0 (10.16)
Median (range)	59.5 (29–79)	64.0 (39–79)
Age Category 1 (years)		
< 65	40 (63%)	16 (52%)
≥ 65	24 (38%)	15 (48%)
65 to < 75	21 (33%)	12 (39%)
75 to < 85	3 (4.7%)	3 (9.7%)
≥ 85	0	0
Gender		
Male	37 (58%)	18 (58%)
Female	27 (42%)	13 (42%)
Ethnicity		
Hispanic or Latino	2 (3.1%)	2 (6.5%)
Not Hispanic or Latino	61 (95%)	26 (84%)

	Cabozantinib (N=64)	Placebo (N=31)
Not Reported	1 (1.6%)	2 (6.5%)
Unknown	0	1 (3.2%)
Race		
White	54 (84%)	25 (81%)
Black or African American	3 (4.7%)	3 (9.7%)
Asian	4 (6.3%)	0
American Indian or Alaska Native	1 (1.6%)	0
Native Hawaiian or Other Pacific Islander	1 (1.6%)	0
Not Reported	0	2 (6.5%)
Unknown	0	1 (3.2%)
Multiple	1 (1.6%)	0
Body Mass Index (BMI)		
N	64	31
Mean (SD)	27.05 (5.610)	28.19 (8.253)
Median (range)	26.02 (17.5–42.5)	27.99 (15.9–52.4)
ECOG PS (as reported on the OPEN registration system)		
0	35 (55%)	15 (48%)
1	28 (44%)	16 (52%)
2	1 (1.6%)	0
Stratification Factors per OPEN registration system		
Concurrent Somatostatin Analog Use (yes)	35 (55%)	17 (55%)
Prior Sunitinib Therapy (yes)	17 (27%)	9 (29%)
Stratification Factors per EDC		
Concurrent Somatostatin Analog Use (yes)	36 (56%)	17 (55%)
Prior Sunitinib Therapy (yes)	18 (28%)	7 (23%)

ECOG, Eastern Cooperative Oncology Group; EDC, electronic data capture; ITT, intent-to-treat; OPEN, Oncology Patient Enrollment Network; pNET, pancreatic neuroendocrine tumor; SD, standard deviation
Source: CABINET CSR, Section 11.2.1 epNET (Table 14.1.4.1.a.1); ADaM Dataset: ADSL.

The Applicant's Position:

Demographic characteristics were consistent with those patients with epNET and pNET seen in

clinical practice and were well balanced between treatment arms.

The FDA's Assessment:

The FDA agrees with the Sponsor's presentation of demographics and baseline disease characteristics based on the ITT population of 298 patients, as shown in Applicant Table 16 and Applicant Table 17. All patients were enrolled in the US. In summary, the key demographics of the study patients in CABINET are consistent with those expected in the US population and are generally balanced across study arms, with minor exception. With respect to race and ethnicity, most patients in this study were White. The ECOG performance score was 0 or 1 in nearly all study patients.

epNET
In the epNET cohort, due to the various tumor types included, an obvious trend with respect to sex or age is not expected. Neuroendocrine tumors, depending on their location of origin, can manifest earlier or later in life with an estimated age range of diagnosis spanning 50 to 70 years of age. The majority of patients are diagnosed at age 60 or later, as reflected by the median age of 66 years for both arms of the epNET cohort. The study arms were well matched by the stratification factors of concurrent somatostatin analog (SSA) use, present in the majority (~70%) of patients, and the primary tumor site, which was "non-midgut GI/lung/other known primary site not listed" for most patients.

pNET
Pancreatic tumors are slightly more common in men than women, and the median age of diagnosis of these tumors is approximately 60 years; these observations are consistent with findings in the pNET cohort. The pNET cohort did, however, have a greater percentage of patients under the age of 65 who were treated with cabozantinib (63%) than compared to the placebo arm (52%). Although this imbalance could potentially impact study results, as younger patients are generally expected to have better survival outcomes, it is worth noting that all patients in this study had advanced disease that had progressed after prior treatment. The study arms were well matched by the stratification factors of concurrent SSA use (yes for 55% of patients), and prior sunitinib therapy in approximately 28% of patients.

Three epNET patients were misclassified as pNET patients and 7 pNET patients were misclassified as pNET, and therefore assigned to the incorrect study cohort. After correcting for misclassified tumor types, the total number of pNET and epNET patients were 99 (66 in cabozantinib arm and 33 in placebo arm) and 199 (132 in cabozantinib arm and 67 in placebo arm), respectively.

In the 99 patients in pNET cohort, the median age was 60 years (range: 29 to 79); 57% were male; 83% were White, 6% Black or African American, 4% Asian, 1% American Indian or Alaska Native, 1% Native Hawaiian or other Pacific Islander, 1% multiple races, 4% not reported or unknown; and 5% were Hispanic or Latino.

In the 199 patients in epNET cohort, the median age was 66 years (range: 28 to 86), 51% were female; 84% were White; 8% were Black or African American; 2.0% were Asian; 6% had race unknown or race not reported; and 8% were Hispanic or Latino.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Key cancer history, baseline disease status and prior anticancer therapies are provided below in Applicant Table 18, Applicant Table 19, Applicant Table 20, and Applicant Table 21.

As per NCI/CTEP Alliance standards, data on concomitant medications, outside of NPACT and concurrent SSA use, were not collected.

Applicant Table 18: Study CABINET: Cancer History and Baseline Disease Status (ITT population) - epNET

	Cabozantinib (N=134)	Placebo (N=69)
Tumor type[a]		
epNET	130 (97%)	66 (96%)
Histologic Type		
Carcinoid Tumor	85 (63%)	54 (78%)
Atypical carcinoid tumor	26 (19%)	11 (16%)
Not Specified[b]	19 (14%)	1 (1.4%)
pNET[c]	4 (3.0%)	3 (4.3%)
Time from initial diagnosis of the primary tumor to randomization (months)		
N	134	67
Mean (SD)	89.7 (77.15)	90.5 (63.40)
Median (Range)	64.7 (9–489)	75.9 (14–340)
Primary tumor site		
Pancreas	4 (3.0%)	3 (4.3%)
Lung	27 (20%)	12 (17%)
Stomach	3 (2.2%)	2 (2.9%)
Small bowel (including Duodenum, Jejunum, Ileum)	37 (28%)	29 (42%)
Appendix	1 (0.7%)	0
Cecum	3 (2.2%)	0
Non-cecum colon	2 (1.5%)	0
Rectum	5 (3.7%)	6 (8.7%)
Thymus	6 (4.5%)	4 (5.8%)
Unknown[d]	22 (16%)	2 (2.9%)
Other[e]	24 (18%)	11 (16%)
Functional (hormone secretion) status		
Functional Tumor	41 (31%)	25 (36%)
Non-Functional Tumor	75 (56%)	34 (49%)
Unknown	18 (13%)	10 (14%)
Tumor Grade		
Grade 1	37 (28%)	15 (22%)

	Cabozantinib (N=134)	Placebo (N=69)
Grade 2	86 (64%)	48 (70%)
Grade 3	8 (6.0%)	5 (7.2%)
Unknown[b]	3 (2.2%)	1 (1.4%)
Histologic differentiation		
Well differentiated	118 (88%)	61 (88%)
Moderately differentiated	6 (4.5%)	5 (7.2%)
Poorly differentiated	0	0
Not specified[b]	10 (7.5%)	3 (4.3%)
Status of primary tumor by investigator		
Resected, no residual tumor	45 (34%)	31 (45%)
Resected, residual tumor	25 (19%)	13 (19%)
Resected, recurrent tumor following surgery to remove primary tumor	7 (5.2%)	4 (5.8%)
Unresected	40 (30%)	19 (28%)
Primary tumor status is unknown	17 (13%)	2 (2.9%)

epNET, extra-pancreatic neuroendocrine tumor; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumor; SD, standard deviation

[a] 7 subjects with a diagnosis of pNET were misallocated during enrollment to the epNET cohort

[b] Eligible epNET subjects were required to meet only ONE of the following criteria: 1) well- or moderately differentiated NET; 2) low- or intermediate-grade NET; or 3) carcinoid or atypical carcinoid tumor.

[c] Subjects with pNET who were misallocated to the epNET cohort were as follows:
Randomized to the cabozantinib arm: (b) (6)
Randomized to the placebo arm: (b) (6)

[d] Exact primary tumor location could not be identified but a diagnosis of epNET was made

[e] Other includes small bowel, mesenteric, ampullary, midgut, hindgut, biliary tract, larynx, pre-sacral, kidney and ethmoid sinus.

Source: Table 14.1.6.1.b.1; ADaM Datasets: ADSL, ADTR, ADCD

Applicant Table 19: Study CABINET: Prior Anticancer Therapies (ITT population) - epNET

	Cabozantinib (N=134)	Placebo (N=69)
Receipt of prior systemic anticancer therapy[a, b]	134 (100%)	69 (100%)
PRRT	81 (60%)	41 (59%)
Lu-177 dotatate	80 (60%)	41 (59%)
Other peptide receptor radionuclide therapy	1 (0.7%)	0
Everolimus	96 (72%)	44 (64%)

	Cabozantinib (N=134)	Placebo (N=69)
Anti-VEGFR TKI	7 (5.2%)	6 (8.7%)
Sunitinib	4 (3.0%)	1 (1.4%)
Other anti-VEGFR TKI	3 (2.2%)	5 (7.2%)
Cytotoxic chemotherapy regimens	51 (38%)	23 (33%)
Temozolomide +/- capecitabine	43 (32%)	20 (29%)
Streptozocin based combination	1 (0.7%)	0
Cisplatin/carboplatin-based combination	11 (8.2%)	8 (12%)
Other cytotoxic chemotherapy regimens	10 (7.5%)	4 (5.8%)
Other	10 (7.5%)	2 (2.9%)
Receipt of prior locoregional therapies	45 (34%)	29 (42%)
Hepatic artery embolization	38 (28%)	25 (36%)
Ablation	10 (7.5%)	7 (10%)
Other	2 (1.5%)	3 (4.3%)
Prior somatostatin analog use	124 (93%)	64 (93%)
Lanreotide	53 (40%)	33 (48%)
Octreotide	90 (67%)	47 (68%)
Number of prior systemic anti-cancer regimens[c] (excluding SSAs)		
N	134	69
Mean (SD)	1.9 (1.04)	1.8 (1.07)
Median (Range)	2.0 (1–5)	2.0 (1–6)
25th, 75th Percentiles	1.0, 3.0	1.0, 2.0
0	0	0
1	59 (44%)	33 (48%)
2	40 (30%)	21 (30%)
≥ 3	35 (26%)	15 (22%)

ATC, anatomical therapeutic chemical; CRF, case report form; epNET, extra-pancreatic neuroendocrine tumor; ITT, intent-to-treat; Lu-177, lutetium-177; PRRT, peptide receptor radionuclide therapy; SD, standard deviation; SSA, somatostatin analog; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; WHO, World Health Organization

[a] More than one category may be self-reported by the subject.

[b] As reported on the 'On-Study Prior Systemic Therapy' CRF: summarized by ATC Class Text and WHO Drug base substance preferred name

[c] A regimen was defined as a unique systemic anticancer therapy, excluding SSAs.

Source: Table 14.1.7.1.b.1; ADaM Datasets: ADSL, ADCM

Applicant Table 20: Study CABINET: Cancer History and Baseline Disease Status (ITT population) - pNET

	Cabozantinib (N=64)	Placebo (N=31)
Tumor type[a]		
pNET	62 (97%)	30 (97%)
epNET[b]	2 (3.1%)	1 (3.2%)
Histologic Type		
Carcinoid Tumor	1 (1.6%)	1 (3.2%)
Not Specified[c]	1 (1.6%)	0
Time from initial diagnosis of the primary tumor to randomization (months)		
N	64	31
Mean (SD)	85.7 (48.38)	86.1 (53.85)
Median (Range)	71.3 (18–214)	73.6 (18–230)
25th, 75th Percentiles	48.2, 118.2	43.8, 117.4
Primary tumor site		
Pancreas	62 (97%)	30 (97%)
Stomach[a]	1 (1.6%)	0
Small bowel (including Duodenum, Jejunum, Ileum)[a]	1 (1.6%)	0
Cecum[a]	0	1 (3.2%)
Functional (hormone secretion) status		
Functional Tumor	11 (17%)	5 (16%)
Non-Functional Tumor	48 (75%)	22 (71%)
Unknown	5 (7.8%)	4 (13%)
Tumor Grade		
Grade 1	14 (22%)	7 (23%)
Grade 2	39 (61%)	19 (61%)
Grade 3	8 (13%)	3 (9.7%)
Unknown[c]	3 (4.7%)	2 (6.5%)
Histologic differentiation		
Well differentiated	59 (92%)	30 (97%)
Moderately differentiated	4 (6.3%)	0

	Cabozantinib (N=64)	Placebo (N=31)
Poorly differentiated	0	0
Not specified	1 (1.6%)	1 (3.2%)
Status of primary tumor by investigator		
Resected, no residual tumor	21 (33%)	10 (32%)
Resected, residual tumor	13 (20%)	2 (6.5%)
Resected, recurrent tumor following surgery to remove primary tumor	4 (6.3%)	3 (9.7%)
Unresected	26 (41%)	16 (52%)

epNET, extra-pancreatic neuroendocrine tumor; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumor; SD, standard deviation

[a] 3 subjects with a diagnosis of epNET were misallocated during enrollment to the pNET cohort

[b] Subjects with epNET who were misallocated to the pNET cohort were as follows:
Randomized to the cabozantinib arm: (b) (6)
Randomized to the placebo arm: (b) (6)

[c] Eligible pNET subjects were required to meet only ONE of the following criteria: 1) well- or moderately differentiated NET; 2) low- or intermediate-grade NET; or 3) carcinoid or atypical carcinoid tumor.

Source: Table 14.1.6.1.a.1; ADaM Datasets: ADSL, ADCD, ADTR

Applicant Table 21: Study CABINET: Prior Anticancer Therapies (ITT population) - pNET

	Cabozantinib (N=64)	Placebo (N=31)
Receipt of prior systemic anticancer therapy[a, b]	64 (100%)	31 (100%)
PRRT	38 (59%)	18 (58%)
Lu-177 dotatate	38 (59%)	18 (58%)
Other peptide receptor radionuclide therapy	0	0
Everolimus	51 (80%)	25 (81%)
Anti-VEGFR TKI	19 (30%)	8 (26%)
Sunitinib	18 (28%)	7 (23%)
Other anti-VEGFR TKI	1 (1.6%)	1 (3.2%)
Cytotoxic chemotherapy regimens	44 (69%)	18 (58%)
Temozolomide +/- capecitabine	43 (67%)	16 (52%)
Streptozocin based combination	2 (3.1%)	0
Cisplatin/carboplatin-based combination	1 (1.6%)	2 (6.5%)
Other cytotoxic chemotherapy regimens	9 (14%)	7 (23%)
Other	6 (9.4%)	3 (9.7%)

	Cabozantinib (N=64)	Placebo (N=31)
Receipt of prior locoregional therapies	36 (56%)	10 (32%)
Hepatic artery embolization	28 (44%)	8 (26%)
Ablation	13 (20%)	5 (16%)
Other	1 (1.6%)	0
Prior somatostatin analog use	63 (98%)	30 (97%)
Lanreotide	27 (42%)	15 (48%)
Octreotide	48 (75%)	21 (68%)
Number of prior systemic anticancer regimens[c] (excluding SSAs)		
N	64	31
Mean (SD)	2.7 (1.54)	2.6 (1.74)
Median (Range)	3.0 (1–8)	2.0 (1–7)
25th, 75th Percentiles	1.0, 3.5	1.0, 4.0
0	0	0
1	17 (27%)	10 (32%)
2	14 (22%)	9 (29%)
≥ 3	33 (52%)	12 (39%)

ATC, anatomical therapeutic chemical; CRF, case report form; Lu-177, lutetium-177; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SD, standard deviation; SSA, somatostatin analog; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; WHO, World Health Organization

[a] More than one category may be self-reported by the subject.

[b] As reported on the 'On-Study Prior Systemic Therapy' CRF: summarized by ATC Class Text and WHO Drug base substance preferred name

[c] A regimen was defined as a unique systemic therapy, excluding SSAs.

Source: Table 14.1.7.1.a.1; ADaM Datasets: ADSL, ADCM

The FDA's Assessment:

The FDA agrees with the Sponsor's presentation of cancer history, baseline disease status and history of anticancer therapies based on the ITT population of 298 patients, as shown above. In summary, CABINET enrolled patients with progressive, well-differentiated, non-functional tumors that were primarily Grade 2. Study arms were fairly balanced with respect to the types of anticancer therapies received and the number of prior regimens. Patients with pNET had particularly refractory disease.

epNET

In the epNET cohort (n=203), most patients had carcinoid, well differentiated, non-functional tumors with the majority being Grade 2. The primary tumor site, in order of descending frequency, was as follows: small bowel (including duodenum, jejunum, ileum), lung, unknown,

rectum, thymus, stomach, cecum, non-cecum colon and appendix. These disease characteristics align with what is typically observed in US patients with epNET. Of note, as previously mentioned in the FDA's review, there were seven patients with an actual tumor type of pNET who were misallocated to this cohort (4 to the cabozantinib arm and 3 to the placebo arm).

Most patients in this cohort had undergone resection of primary tumor with no residual tumor at the time of original surgery; approximately 40% had previously received locoregional therapy (primarily hepatic artery embolization); and nearly all had used SSA. Approximately 45% had received one prior systemic anti-cancer regimen, with fewer patients receiving two or three prior regimens. The study arms were generally well balanced in terms of previous anti-cancer therapies; most commonly everolimus (64-72%), followed by peptide receptor radionuclide therapy with Lu-177 dotatate (~60%), and cytotoxic chemotherapy regimens (33-38%) including CAPTEM (temozolomide +/- capecitabine).

pNET

In the pNET cohort (n=95), the majority of patients had well-differentiated, non-functional Grade 2 tumors. Three patients who had an actual tumor type of epNET cohort who were erroneously randomized to this cohort (2 to the cabozantinib arm and 1 to the placebo arm).

Most patients in this cohort had unresected tumor and had received prior locoregional therapy (primarily hepatic artery embolization); and nearly all had received SSA. The majority of patients in this cohort had received 3 or more prior systemic anticancer regimens. The most commonly used anticancer therapies were everolimus (~80%), cytotoxic chemotherapy regimens (58-69%), peptide receptor radionuclide therapy with Lu-177 dotatate (~58%), and other anti-VEGFR tyrosine kinase inhibitors (TKIs) including sunitinib.

Findings in the Study Population with Correct Tumor Allocation per Electronic Data Capture

Based on the correctly classified tumor type, that is, in the 99 patients with pNET, 27% had received one prior systemic therapy, 26% had received two prior systemic therapies and 46% had received three or more prior systemic therapies. In the 199 patients with epNET, 46% had received one prior systemic therapy, 29% had received two prior systemic therapies and 25% had received three or more prior systemic therapies. For epNET patients, the primary sites of tumor were small bowel (34%) including duodenum, jejunum & ileum; lung (20%); thymus (5%); rectum (6%); cecum (2.0%); stomach (3.0%); non-cecum colon (1.0%); appendix (0.5%); others (18%); and unknown (12%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance:

The NCI-CTEP Pharmaceutical Management Branch (PMB) distributed study treatment to sites and mandated that each site maintain drug accountability records for investigational agents according to NCI-CTEP PMB guidelines. Agent disposition was documented on a Drug Accountability Record Form. In addition, subjects completed a daily medication diary, recording the number of tablets taken each day; this diary was reviewed by site personnel at each study visit. Subject compliance with outpatient study treatment regimens was assessed by the site using drug dispensing and return records, progress notes about dose reductions/holds, and subject interview. These data were not directly recorded on case report forms (CRFs); rather, CRFs captured the date of first dose, date of last dose, and the date and dose of all Investigator-directed changes in study treatment (eg, dose reduction, dose hold, resumption of treatment).

Concomitant Therapy:

As per Alliance standards, data on concomitant medications, outside of NPACT and concurrent SSA use, were not collected.

Rescue Medication Use:

Not Applicable

The FDA's Assessment:

The FDA concurs with the Applicant's summary of treatment compliance and acknowledges that data on concomitant medications outside of non-protocol anticancer therapy (NPACT) and concurrent somatostatin analog (SSA) use were not collected per Alliance practice.

As outlined in the CABINET protocol, concomitant SSA use was permitted (provided that patients had been on a stable dose for at least two months) and was applied as a stratification factor (yes/no) for all study patients. Other planned concurrent investigational agents or other tumor-directed therapies (e.g., chemotherapy, radiation) were not allowed while patients were on study.

Efficacy Results

Data:

Extra-Pancreatic Neuroendocine Tumors (epNET)

epNET Summary of Efficacy

Applicant Table 22 summarizes the key primary and secondary endpoint results from the epNET cohort of the CABINET study.

Applicant Table 22: Study CABINET: epNET Summary of Efficacy (ITT Population)

	Cabozantinib N=134	Placebo N=69
PFS by BIRC (primary endpoint)		
Events, n (%)	71 (53)	40 (58)
Median PFS, months (95% CI)	8.48 (7.46, 12.45)	3.98 (3.02, 5.68)
HR (95% CI); p-value[a]	0.38 (0.25, 0.58); p < 0.0001	
3-month PFS Rates, % (95% CI)	90.3 (83.2, 94.5)	64.6 (51.2, 75.1)
6-month PFS Rates, % (95% CI)	64.1 (53.9, 72.6)	28.8 (15.8, 43.2)
12-month PFS Rates, % (95% CI)	40.6 (30.2, 50.8)	10.3 (2.1, 26.1)
18-month PFS Rates, % (95% CI)	19.2 (10.2, 30.4)	NE (NE, NE)
OS		
Events, n (%)	60 (45)	37 (54)
Median OS, months (95% CI)	21.95 (18.60, 30.19)	19.71 (13.37, 24.48)
HR (95% CI); p-value[a]	0.86 (0.56, 1.31); p = 0.4871	
6-month OS Rates, % (95% CI)	85.9 (78.3, 91.0)	87.7 (76.9, 93.6)
12-month OS Rates, % (95% CI)	75.5 (66.5, 82.5)	73.5 (60.3, 82.9)
24-month OS Rates, % (95% CI)	46.4 (35.4, 56.7)	38.5 (24.8, 52.0)
36-month OS Rates, % (95% CI)	32.2 (20.2, 44.8)	23.4 (10.2, 39.6)
Confirmed ORR by BIRC[b]		
n (%)	7 (5.2)	0.0 (0.0)
95% CI	(2.1, 10.5)	(0.0, 5.2)
Confirmed ORR treatment difference (95% CI)[c]	5.2% (1.5%, 9.0%); p = 0.0524	
Confirmed BOR[d]		
Confirmed CR, n (%)	0	0

	Cabozantinib N=134	Placebo N=69
Confirmed PR, n (%)	7 (5.2)	0
SD, n (%)	87 (65)	37 (54)
PD, n (%)	15 (11)	24 (35)
Unable to evaluate, n (%)	0	1 (1.4)
Missing, n (%)	25 (19)	7 (10)
No qualifying post-baseline assessments on or before PFS censoring or event date, n (%)[e]	23 (17)	6 (8.7)
SD or non-CR/non-PD not meeting minimum criteria (> 42 days) from randomization, n (%)	2 (1.5)	1 (1.4)
DOR by BIRC		
Median, months (95% CI)	8.26 (4.47, NE)	NE (NE, NE)

BIRC, blinded independent review committee; BOR, best overall response; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; DOR, duration of response; HR, hazard ratio; NE, not evaluable; OPEN, Oncology Patient Enrollment Network; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut /Unknown vs. Non-midgut GI /Lung/Other].
[a] Hazard ratios were calculated from a stratified Cox proportional hazards model stratified (per OPEN). p-values are from log-rank test.
[b] Confirmed Objective Response Rate (ORR-Confirmed) is defined as proportion of subjects with best overall response of confirmed CR or confirmed PR. There were no CRs reported in the epNET cohort.
[c] Using asymptotic confidence limits based on large number theorem. p-value from stratified CMH test
[d] Confirmed BOR is derived based on RECIST criteria 1.1. Only responses prior to PFS-EP1 are considered. Protocol did not define minimal interval between initial response scan and confirmatory scan; for calculation purpose, minimum 28 days is used.
[e] Reasons in the cabozantinib arm: first scheduled imaging timepoint after the clinical cutoff date, adverse event, death, withdrawal, no study treatment given, and other complicating disease. In the placebo arm: no study treatment given, adverse event, death, first scheduled imaging timepoint after the clinical cutoff date, and other (death)
Source: CABINET CSR Tables 14.2.1.1.2, 14.2.2.1.b, 14.2.3.1.b, 14.2.3.2.b; ADaM Datasets: ADSL, ADRS, ADTR, ADTTE.

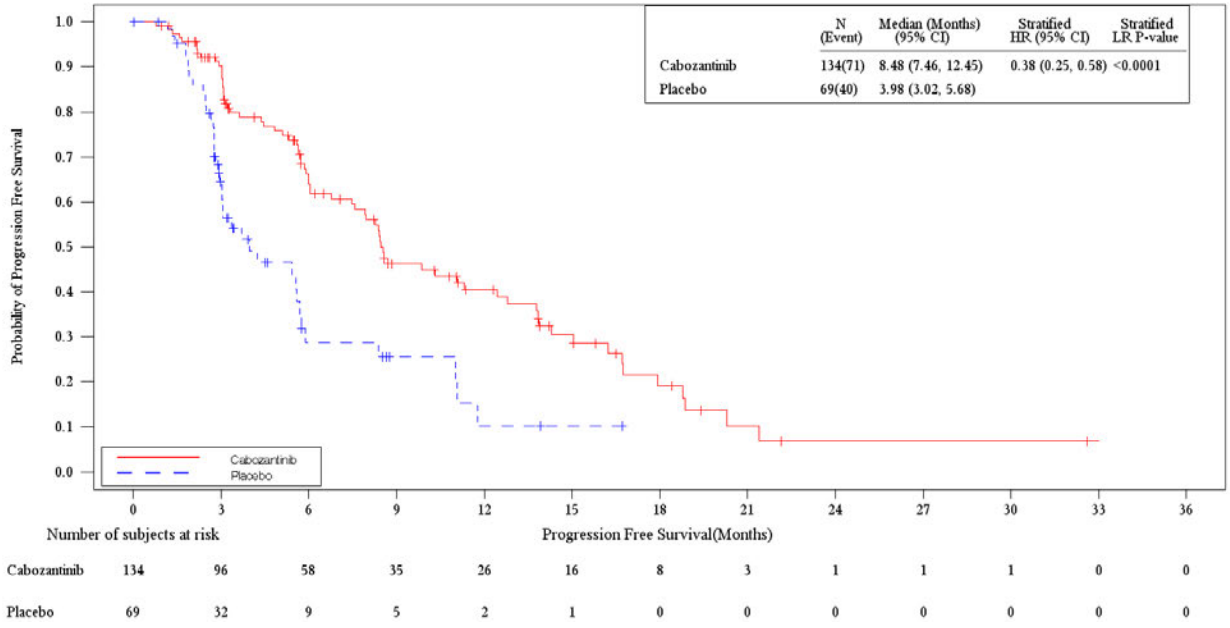
epNET – Primary Endpoint (Including Sensitivity Analyses)

epNET Primary Analysis of Progression-free Survival per RECIST 1.1 by BIRC

As of the 24 August 2023 cutoff date, 71 subjects (53%) in the cabozantinib arm, and 40 subjects (58%) placebo arm, had events, demonstrating a 62% reduction in the risk of disease progression or death in the cabozantinib arm versus the placebo arm, stratified HR: 0.38 (95% CI: 0.25, 0.58; stratified 2-sided $p < 0.0001$).

The Kaplan-Meier estimate of median PFS was 8.48 months (95% CI: 7.46, 12.45) cabozantinib, 3.98 months (95% CI: 3.02, 5.68) placebo with an estimated 4.5-month difference in medians between treatment arms. The 6-, 12-, and 18-month event free rates were 64.1%, 40.6%, and 19.2%, respectively, in the cabozantinib arm and 28.8%, 10.3%, and not estimable (NE) in the placebo arm

Applicant Figure 3: Study CABINET: epNET Kaplan-Meier Plot of Progression-Free Survival by BIRC through 24 August 2023



+ indicates a censored observation; CI, confidence interval; HR, hazard ratio; LR, log-rank test
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes/No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
Source: CABINET CSR Figure 14.2.1.1.2; ADaM Datasets: ADSL, ADTTE.

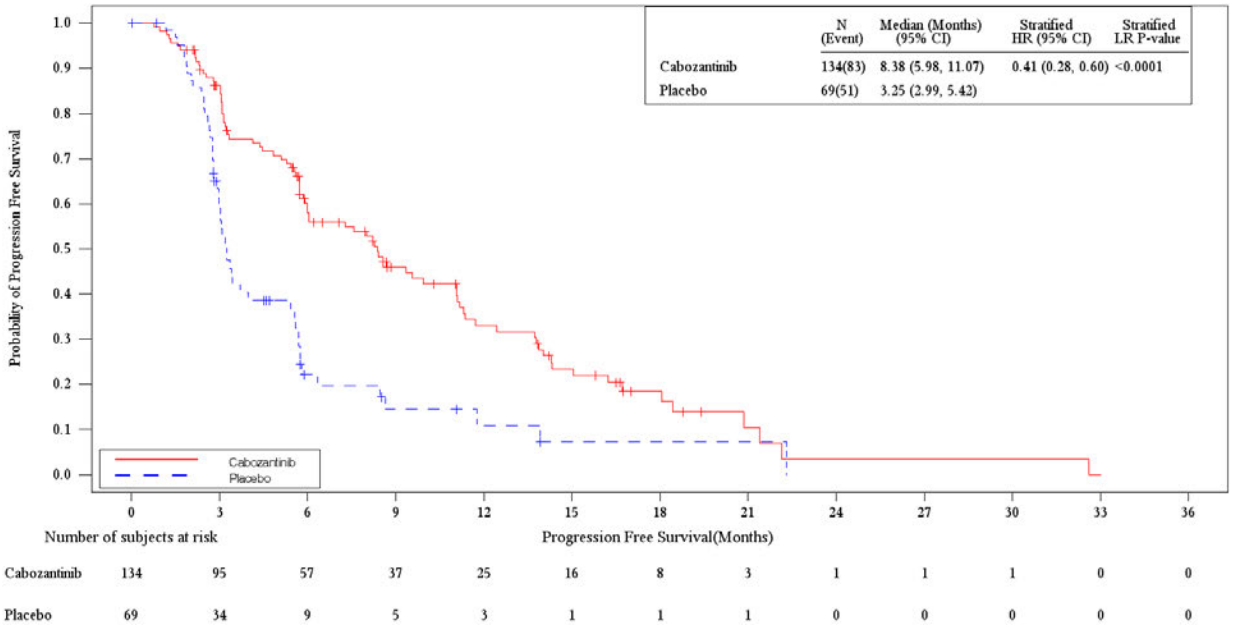
epNET Sensitivity Analysies: Progression-free Survival per RECIST 1.1 by Investigator (Sensitivity Analysis)

As of the 24 August 2023 cutoff date, 83 subjects (62%) in the cabozantinib arm and 51 subjects (74%) in the placebo arm had events. The sensitivity analysis of PFS (PFS-EP2) by Investigator showed a highly consistent treatment effect compared to BIRC assessment: a 59% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm stratified HR: 0.41 (95% CI: 0.28, 0.60; stratified 2-sided $p < 0.0001$).

The Kaplan-Meier estimate of median PFS per RECIST 1.1 using FDA-recommended censoring rules was 8.38 months (95% CI: 5.98, 11.07) in the cabozantinib arm compared with 3.25 months (95% CI: 2.99, 5.42) in the placebo arm, an estimated 5.13-month difference in medians between treatment arms (Applicant Figure 4). The 6-, 12-, and 18-month event free rates were

58.1%, 33.0%, and 18.5%, respectively, in the cabozantinib arm and 22.2%, 10.8%, and 7.2%, respectively, in the placebo arm.

Applicant Figure 4: Study CABINET: epNET Kaplan-Meier Plot of Progression-Free Survival by Investigator through 24 August 2023



CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LR, log-rank test
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes/No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
+ indicates a censored observation.
Source: CABINET CSR Figure 14.2.1.2.2; ADaM Datasets: ADSL, ADTTE.

epNET Additional Sensitivity Analyses: Progression-free Survival

Sensitivity analyses of PFS by BIRC (EP3 through EP6 and EA1 through EA4) all supported the robustness of the treatment effect estimate from the primary analysis, demonstrating a 59% to 65% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm. Although differences in cohort allocation and stratification existed between the OPEN registration system and EDC, a sensitivity analysis using disease allocation and stratification factors per EDC (EP4) showed consistent results with the primary analysis (HR 0.40; 95% CI: 0.26, 0.62).

Applicant Table 23: Study CABINET: epNET: Summary of Primary and Sensitivity Analyses of PFS (ITT Population)

Analysis of PFS by BIRC unless noted otherwise	Treatment Arm	Events, n (%)	K-M Estimate of Median PFS (95% CI)	K-M Estimate of 6-, 12-, 18-Month Event-free Rates	Stratified HR (95% CI) [1]	Stratified 2-sided p-value
EP1: Primary analysis	Cabozantinib (N=134)	71 (53%)	8.48 (7.46, 12.45)	64.1%, 40.6%, 19.2%	0.38 (0.25, 0.58)	< 0.0001
	Placebo (N=69)	40 (58%)	3.98 (3.02, 5.68)	28.8%, 10.3%, NE		
EP2: Investigator-assessed	Cabozantinib (N=134)	83 (62%)	8.38 (5.98, 11.07)	58.1%, 33.0%, 18.5%	0.41 (0.28, 0.60)	< 0.0001
	Placebo (N=69)	51 (74%)	3.25 (2.99, 5.42)	22.2%, 10.8%, 7.2%		
EP3: With early events dated as occurring at the scheduled restaging assessment	Cabozantinib (N=134)	59 (44%)	10.32 (8.31, 13.83)	71.8%, 46.1%, 25.4%	0.37 (0.23, 0.60)	< 0.0001
	Placebo (N=69)	34 (49%)	5.55 (2.96, 5.75)	34.2%, 18.2%, NE		
EP4: Using disease allocation and stratification factors collected at randomization per EDC	Cabozantinib (N=132)	69 (52%)	8.48 (6.77, 12.45)	63.0%, 39.8%, 19.9%	0.40 (0.26, 0.62)	< 0.0001
	Placebo (N=67)	39 (58%)	4.24 (3.02, 5.75)	30.7%, 11.1%, NE		
EP5: Using protocol- and SAP-defined number of events (109 for epNET) for 2nd interim analysis [2]	Cabozantinib (N=134)	71 (53%)	8.48 (7.46, 12.45)	64.1%, 40.6%, 19.2%	0.38 (0.25, 0.58)	< 0.0001
	Placebo (N=69)	40 (58%)	3.98 (3.02, 5.68)	28.6%, 10.2%, NE		
	Cabozantinib (N=120)	68 (57%)	8.57 (7.59, 12.78)	65.9%, 41.8%, 19.8%	0.37 (0.24, 0.58)	< 0.0001

Analysis of PFS by BIRC unless noted otherwise	Treatment Arm	Events, n (%)	K-M Estimate of Median PFS (95% CI)	K-M Estimate of 6-, 12-, 18-Month Event-free Rates	Stratified HR (95% CI) [1]	Stratified 2-sided p-value
EP6: Only include subjects randomized for at least 6 months before 24 August 2023	Placebo (N=64)	38 (59%)	4.24 (3.02, 5.75)	29.8%, 10.6%, NE		
EA1: Initiation of NPACT (including crossover therapy) was treated as an event at the date of the start of the NPACT	Cabozantinib (N=134)	98 (73%)	7.95 (5.98, 8.94)	58.6%, 34.5%, 12.5%	0.37 (0.25, 0.53)	< 0.0001
	Placebo (N=69)	55 (80%)	3.88 (3.02, 5.03)	19.1%, 4.4%, NE		
EA2: PD or death occurring after ≥ 2 missing scans were treated as events at the more recent ATA before the missing scans Initiation of NPACT (including crossover therapy) was treated as an event at the date of the start of the NPACT	Cabozantinib (N=134)	99 (74%)	7.95 (5.91, 8.71)	57.8%, 34.0%, 12.3%	0.35 (0.24, 0.49)	< 0.0001
	Placebo (N=69)	60 (87%)	3.71 (2.96, 4.47)	16.9%, 3.9%, NE		
EA3: Symptomatic deterioration and initiation of a new NPACT were treated as events at the respective start dates	Cabozantinib (N=134)	98 (73%)	8.11 (5.91, 8.94)	57.7%, 34.6%, 12.5%	0.36 (0.25, 0.51)	< 0.0001
	Placebo (N=69)	58 (84%)	3.71 (2.92, 4.63)	17.8%, 4.1%, NE		
EA4: Missing tumor scans were ignored	Cabozantinib (N=134)	72 (54%)	8.54 (7.46, 12.45)	64.2%, 41.2%, 18.3%	0.40 (0.26, 0.60)	< 0.0001
	Placebo (N=69)	43 (62%)	4.24 (3.02, 5.75)	33.3%, 15.8%, NE		

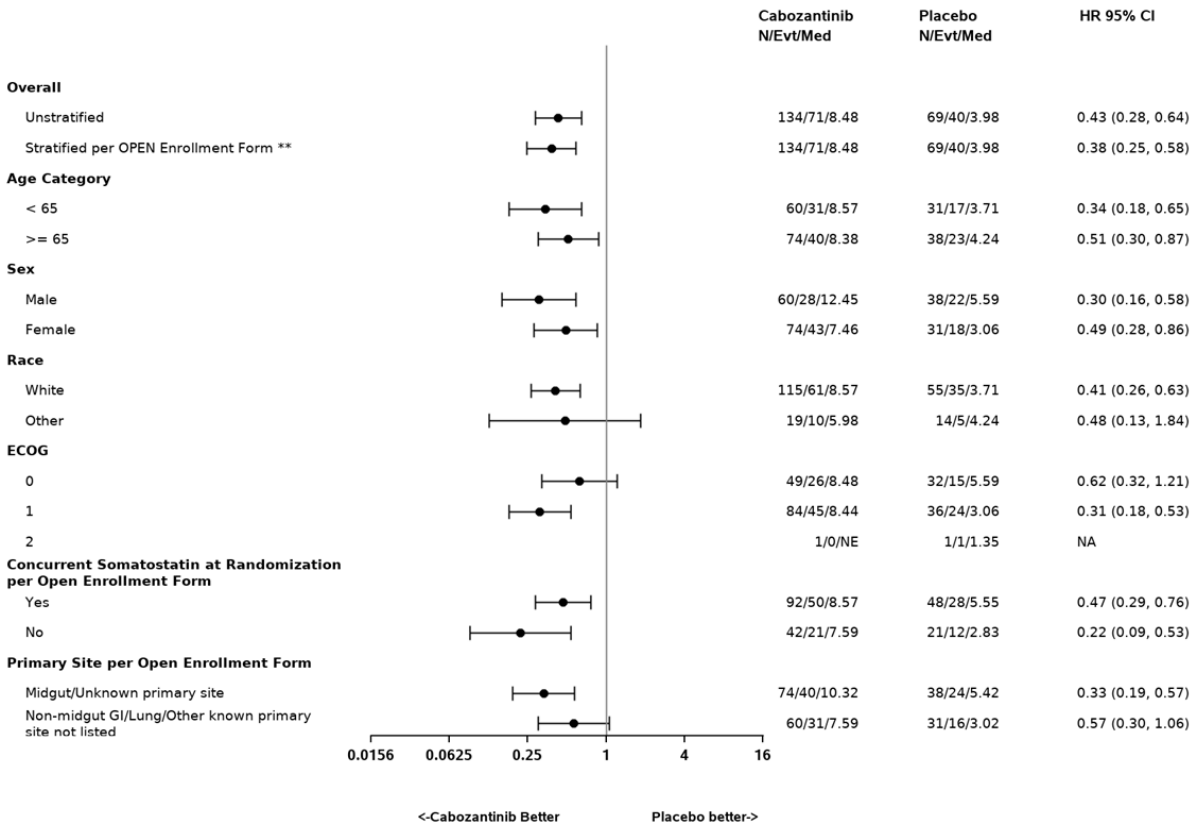
ATA, adequate tumor assessment; BIRC, blinded independent review committee; CI, confidence interval; EDC, electronic data capture; GI, gastrointestinal; HR, hazard ratio; ITT, intent-to-treat; K-M, Kaplan-Meier; NE, not estimable; NPACT, nonprotocol anticancer therapy; PD, progressive disease; PFS, progression-free survival; SAP, statistical analysis plan
p-values are from log-rank test.

Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
[1] Hazard ratios were calculated from Cox proportional hazards model.
[2] PFS-EP5, 3 events (109th through 111th) occurred on the same date.
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
Source: CABINET CSR Tables 14.2.1.1.2, 14.2.1.2.2, 14.2.1.3.2, 14.2.1.4.2, 14.2.1.5.2, 14.2.1.6.2, 14.2.1.7.2, 14.2.1.8.2, 14.2.1.9.2, 14.2.1.10.2; ADaM Datasets: ADSL, ADTTE.

epNET Subgroup Analysis of PFS per RECIST 1.1 by BIRC

For BIRC-assessed response, the results of the subgroup analysis including but not limited to prior therapies and histologic type were consistent with the primary analysis of PFS, favoring cabozantinib. All HRs were < 1; and for most subgroups, the upper bound of the 95% CI was < 1. The subgroup analyses of the BIRC-assessed analyses of PFS are displayed in Applicant Figure 5.

Applicant Figure 5: Study CABINET: epNET Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC (ITT Population)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; GI, gastrointestinal; HR, hazard ratio; ITT, intent to treat; IxRS, interactive voice/web response system (ie, the OPEN registration system); Med, median; N, number of subjects; NA, not applicable; OPEN, Oncology Patient Enrollment Network

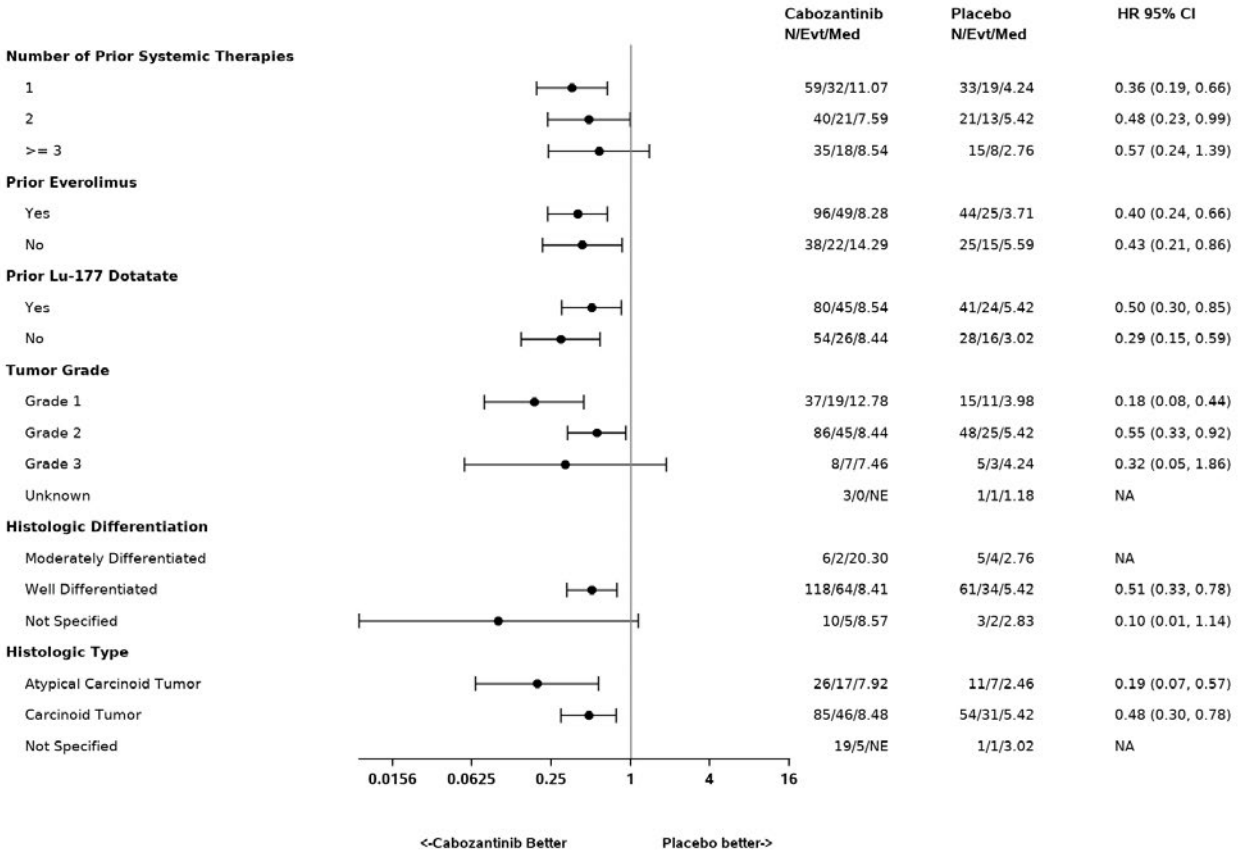
Hazard ratio and 95% CI Estimates from unstratified Cox proportional hazards model are presented for all subgroups

**Stratification factors are as follows: (1) concurrent somatostatin analog use (yes, no) and (2) primary site (midgut/unknown vs non-midgut GI/lung/other).

Source: CABINET CSR Figure 14.2.7.2.b; ADaM Datasets: ADSL, ADTTE.

continued

Applicant Figure 5: Study CABINET: epNET Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC (ITT Population) (Continued)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; GI, gastrointestinal; HR, hazard ratio; ITT, intent to treat; IxRS, interactive voice/web response system (ie, the OPEN registration system); Med, median; N, number of subjects; NA, not applicable; OPEN, Oncology Patient Enrollment Network
Hazard ratio and 95% CI Estimates from unstratified Cox proportional hazards model are presented for all subgroups
**Stratification factors are as follows: (1) concurrent somatostatin analog use (yes, no) and (2) primary site (midgut/unknown vs non-midgut GI/lung/other).
Source: CABINET CSR Figure 14.2.7.2.b; ADaM Datasets: ADSL, ADTTE.

Comparison of Disease Progression by BIRC and Investigator

Discordance rates between investigator assessments and BIRC assessments were similar between the two treatment arms with disagreement on progressive disease (PD) status observed in 33% and 37% of cabozantinib and placebo subjects, respectively. Additional results for disagreement on PD date and discrepancy rates are summarized below in Applicant Table 24. Discordance rates were generally balanced between the treatment arms regardless of discordance measure.

Applicant Table 24: Study CABINET: epNET: Summary of Discordance between Investigator and BIRC

Discordance Measure	Cabozantinib (N = 111)	Placebo (N = 63)
Disagreement on PD status	37/111 (33%)	23/63 (37%)
Disagreement on PD date within 2 weeks	46/111 (41%)	27/63 (43%)
Disagreement on PD date within 4 weeks	44/111 (40%)	27/63 (43%)
Early discrepancy rate [a]	27/67 (40%)	18/46 (39%)
Late discrepancy rate [b]	21/48 (44%)	15/33 (45%)

BIRC, blinded independent review committee; PD, progressive disease; NET, neuroendocrine tumor
ITT subjects with at least one post-baseline tumor assessment per investigator and BIRC were included in the analysis.

[a] Early discrepancy rate is the percentage of subjects for whom investigator declared PD while BIRC did not or PD date by investigator was earlier than by BIRC out of subjects who were declared PD by investigator. Denominator is the number of subjects who were declared PD by investigator.

[b] Late discrepancy rate is the percentage of subjects for whom BIRC declared PD while investigator did not or PD date by investigator was later than by BIRC out of subjects for whom investigator and BIRC had discordances on PD status or PD date. Denominator is the number of subjects for whom investigator and BIRC had discordances on PD status or PD date.

Source: CABINET CSR Table 14.2.8.1.b; ADaM Datasets: ADSL, ADRS

Results of the discordance analyses are similar to meta-analysis reviews comparing central blinded radiology to local radiology (in open label and double-blind controlled clinical trials in oncology) (Amit et al, 2011; Mannino et al, 2013). Consistency of PFS results between the BIRC and local investigator evaluation supports robustness and lack of bias in the estimation of the PFS treatment effect.

Comparisons of batched BIRC vs real-time central review and investigator vs real-time central review were also performed. The real-time central assessments and the batched BIRC assessments were performed by different readers. The disagreement between real-time central review and investigator-assessed progression was small and balanced between treatment arms.

The Applicant's Position:

In the epNET cohort, the study met its primary efficacy endpoint of PFS by BIRC for the epNET cohort. The statistically significant prolongation of PFS observed represent a clinically meaningful improvement over placebo. The efficacy benefit in PFS provided by cabozantinib was observed consistently across multiple sensitivity analyses as well as in key pre-specified subgroups, including those based on stratification factors.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the efficacy results for the primary endpoint of BIRC-assessed PFS per RECIST 1.1, and results from the sensitivity and subgroup analyses in the ITT population in the epNET cohort. The efficacy results are based on 68% of the planned PFS events for the final analysis in epNET cohort. A clinically significant BIRC-assessed PFS improvement for cabozantinib over placebo was observed at the time of this analysis. The Kaplan-Meier plots of BIRC-assessed PFS by treatment arm appeared to separate early and the separation of the curves continued over the entire follow-up time.

To evaluate the robustness of the treatment effect in PFS and any potential impact of censoring, additional analyses of PFS by BIRC were conducted in the ITT population. For the primary analysis of PFS, patients were censored if they did not have a PFS event, received concomitant or subsequent non-protocol anti-cancer therapy including crossover therapy prior to a PFS event or experienced a PFS event after two or more consecutive missing tumor assessments. Reasons for censoring for the primary analysis of PFS are provided in FDA Table **25** below.

FDA Table 25. BIRC assessed PFS Analysis in epNET in ITT Population - Reasons for Censoring

Reasons for censoring, n(%)	Cabozantinib (n=134)	Placebo (n=69)
Two or more missing adequate tumor assessments prior to event	1 (0.8)	5 (7)
No event and did not crossover	20 (15)	7 (10)
No event prior and after crossover	0	6 (9)
No post-baseline adequate tumor assessments	15 (11)	2 (2.9)
Systemic non-protocol anti-cancer therapy	27 (20)	9 (13)

Source: FDA analysis of the Applicant's submitted data (adtte); DCO: 09/04/2024

One patient (0.8%) in the cabozantinib arm and 5 (7%) patients in the placebo arm were censored due to two or more consecutive missing tumor assessments. Two sensitivity analyses (EA2 and EA4 in Applicant Table 23) were conducted by the Applicant and verified by the FDA. One sensitivity analysis (EA2) treated PD or deaths as events and another (EA4) ignored the missing tumor assessments. Results from both sensitivity analyses were consistent with the results from the primary BIRC-assessed PFS analysis.

Eleven percent of the patients in the cabozantinib arm and 2.9% patients in the placebo arm were censored due to no post-baseline adequate tumor assessments. FDA performed a sensitivity analysis in the ITT population considering patients with no post-baseline adequate tumor assessments having an event in the cabozantinib arm and censored in the placebo arm at the time of randomization. BIRC-assessed PFS result from this analysis (PFS HR: 0.55 [95% CI: 0.37, 0.83]) was supportive of the results observed in the primary analysis.

Twenty percent of patients in the cabozantinib arm and 13% of patients in the placebo arm were censored for BIRC-assessed PFS analysis due to receipt of non-protocol anticancer therapy (NPACT) prior to disease progression. The most common reasons for initiation of NPACT in these patients were determination of disease progression per investigator assessment and/or real-time central review and toxicity. The Applicant conducted a sensitivity analysis considering receipt of non-protocol anticancer therapy as an event in both treatment arms as presented under EA1 in Applicant Table 23. FDA also performed a conservative analysis of BIRC-assessed PFS considering receipt of systemic non-protocol anticancer therapy as an event in the cabozantinib arm and censored in the placebo arm. PFS results from both Applicant's and FDA's analyses were supportive (EA1 PFS HR: 0.37 [95% CI: 0.25, 0.53]; FDA analysis PFS HR: 0.53 [95% CI: 0.35, 0.79]) of the results observed in the primary analysis of PFS. PFS results appeared to be consistent with that of the investigator-assessed PFS analysis and across sensitivity analyses presented above. PFS results across the selected subgroups were also supportive of the results observed in the primary and sensitivity analyses.

FDA considered results from the landmark analyses of PFS to be descriptive only.

During the review, the Applicant assessed and updated the timing and completeness of subsequent anti-cancer therapy based on the same DCO of Aug 24, 2024 (Source: Response to FDA information request, dated Feb 07, 2025). This resulted in one additional patient in the cabozantinib arm in the epNET cohort being censored for initiation of non-protocol anti-cancer therapy before documented disease progression in the BIRC assessed PFS analysis. Based on this updated data, the BIRC assessed PFS results in the epNET cohort, correcting for misclassified tumor type and based on verified stratification factors per electronic data capture, are provided in FDA Table **26** below. **These PFS results are included in the US prescribing information**.

FDA Table 26. BIRC-assessed PFS Results in Patients with epNET in CABINET

	Cabozantinib (N=132)	Placebo (N=67)
Number of Events (%)	68 (52)	39 (58)
Median (95% CI)[1], in months	8.5 (6.8, 12.5)	4.2 (3.0, 5.7)
Hazard Ratio (95% CI)[2]	0.40 (0.26, 0.61)	
p-value[3]	<0.0001	

CI, confidence interval
[1]Kaplan-Meier method
[2]Stratified Cox proportional hazards model stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other)
[3]Stratified log-rank test stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other) (compared to one-sided alpha=0.001)
Source: FDA analysis of the Applicant's submitted data (adtte); DCO: 09/04/2024

Investigator assessed PFS was a secondary endpoint in the trial. The discordance rates in PD status between the investigator assessed PFS and BIRC assessed PFS were above 30% in both arms (33% for cabozantinib and 37% for placebo). To further explore the discordance between investigator and BIRC assessment, the FDA also assessed the real-time central review adjudication process. According to the protocol, real-time central review was set up to adjudicate investigator-assessed disease progression to minimize potential bias in investigator assessments. The disagreement in PD status by real time central review and investigator assessments was 23% in cabozantinib arm and 20% in the placebo arm.

While the discordance between the investigator assessed disease progression and BIRC assessed disease progression was relatively high, the distribution of the disagreement in the PD status and the timing of the PD appears to be balanced between treatment arms. Additionally, the distribution of the early discrepancy and late discrepancy rates appear to be similar between treatment arms. This mitigated FDA's concerns regarding the discordance between investigator and BIRC-assessed PFS results and interpretability of the trial results.

In addition, FDA notes that imaging with CT and MRI with assessments by RECIST criteria have well-described limitations in NETs given their generally slow-growing nature and commonly observed areas of necrosis, fibrosis, or inflammation within tumors (Galgano 2021). These challenges in conventional imaging techniques may contribute to increased discordance between investigators and assessors.

For further details regarding statistical challenges refer to Section 8.3 for major statistical issues

Data:

Pancreatic Neuroendocrine Tumors (pNET)

pNET Summary of Efficacy

Applicant Table 27 summarizes the key primary and secondary endpoint results from the pNET cohort of the CABINET study.

Applicant Table 27: Study CABINET: pNET Summary of Efficacy (ITT Population)

	Cabozantinib N=64	Placebo N=31
PFS by BIRC (primary endpoint)		
Events, n (%)	32 (50)	25 (81)
Median PFS, months (95% CI)	13.83 (8.87, 16.95)	4.47 (3.02, 5.75)

	Cabozantinib N=64	Placebo N=31
HR (95% CI); p-value[a]	0.23 (0.12, 0.42); p < 0.0001	
3-month PFS Rates, % (95% CI)	87.9 (76.2, 94.0)	70.0 (50.3, 83.1)
6-month PFS Rates, % (95% CI)	71.4 (56.9, 81.7)	24.0 (10.0, 41.3)
12-month PFS Rates, % (95% CI)	53.8 (38.1, 67.1)	0.0 (NE, NE)
18-month PFS Rates, % (95% CI)	29.7 (15.3, 45.6)	0.0 (NE, NE)
OS		
Events, n (%)	21 (33)	11 (35)
Median OS, months (95% CI)	40.08 (20.70, NE)	31.11 (18.76, NE)
HR (95% CI); p-value[a]	0.95 (0.45, 2.00); p = 0.8852	
6-month OS Rates, % (95% CI)	91.7 (81.1, 96.5)	89.9 (71.7, 96.6)
12-month OS Rates, % (95% CI)	88.0 (76.4, 94.1)	82.5 (62.9, 92.3)
24-month OS Rates, % (95% CI)	65.3 (49.6, 77.2)	61.8 (38.0, 78.8)
36-month OS Rates, % (95% CI)	56.5 (38.5, 71.0)	44.5 (18.7, 67.7)
Confirmed ORR by BIRC[b]		
n (%)	12 (19)	0.0 (0.0)
95% CI	(10.1, 30.5)	(0.0, 11.2)
Confirmed ORR treatment difference (95% CI); p-value[c]	18.8 (9.2, 28.3); p = 0.0115	
Confirmed BOR[d]		
Confirmed CR, n (%)	0	0
Confirmed PR, n (%)	12 (19%)	0
SD, n (%)	39 (61%)	17 (55%)
PD, n (%)	5 (7.8%)	12 (39%)
Unable to evaluate, n (%)	0	0
Missing, n (%)	8 (13%)	2 (6.5%)
No qualifying post-baseline assessments on or before PFS censoring or event date, n (%)[e]	8 (13%)	2 (6.5%)
DOR by BIRC		
Median, months (95% CI)	11.20 (5.78, NE)	NE (NE, NE)

BIRC, blinded independent review committee; BOR, best overall response; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; DOR, duration of response, NE, not evaluable; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

Stratification factors for pNET: 1.Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).

[a] Hazard ratios were calculated from a stratified Cox proportional hazards model stratified (per OPEN). p-values are from log-rank test.

[b] Confirmed Objective Response Rate (ORR-Confirmed) is defined as proportion of subjects with best overall response of confirmed CR or confirmed PR. There were no CRs reported in the pNET cohort.

[c] Using asymptotic confidence limits based on large number theorem.

[d] Confirmed BOR is derived based on RECIST criteria 1.1. Only responses prior to PFS-EP1 are considered. Protocol did not define minimal interval between initial response scan and confirmatory scan; for calculation purpose, minimum 28 days is used.

[e] Reasons in the cabozantinib arm: adverse event, other (death), withdrawal, no study treatment give, and first scheduled imaging timepoint after the clinical cutoff date. In the placebo arm: other (death) and withdrawal.

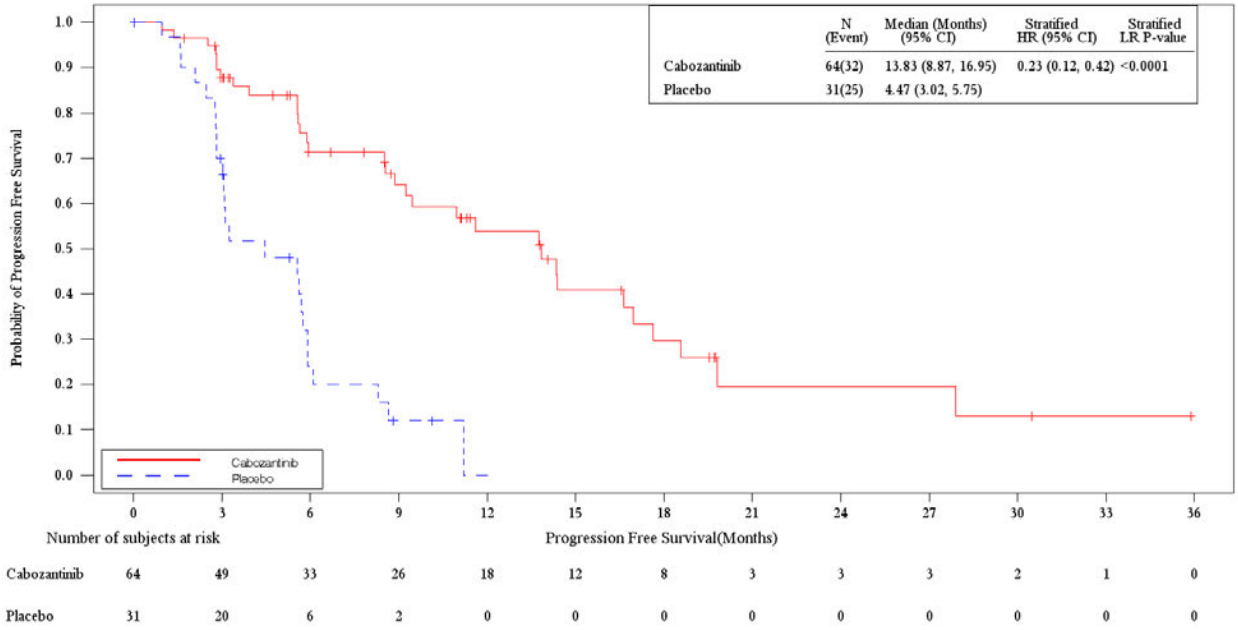
Source: CABINET Clinical Overview Section 4.2.5; CSR Tables 14.2.1.1.1, 14.2.2.1a, 14.2.3.1a, 14.2.3.2a; ADaM Datasets: ADSL, ADTR, ADRS, ADTTE.

pNET – Primary Endpoint (Including Sensitivity Analyses)

pNET Primary Analysis of Progression-free Survival per RECIST 1.1 by BIRC

As of the 24 August 2023 cutoff date, 32 subjects (50%) in the cabozantinib arm and 25 subjects (81%) in the placebo arm had events, . demonstrating a 77% reduction in the risk of disease progression or death in the cabozantinib arm versus the placebo arm, stratified HR: 0.23 (95% CI: 0.12, 0.42; stratified 2-sided $p < 0.0001$). The Kaplan-Meier median PFS per RECIST 1.1 was 13.83 months (95% CI: 8.87, 16.95 cabozantinib, 4.47 months (95% CI: 3.02, 5.75)placebo, , an estimated 9.4-month difference in the medians between treatment arms. The 6-, 12-, and 18-month event free rates were 71.4%, 53.8%, and 29.7%, respectively, in the cabozantinib arm and 24.0%, 0%, and 0%, in the placebo arm.

Applicant Figure 6: Study CABINET: pNET Kaplan-Meier Plot of Progression-Free Survival Primary by BIRC through 24 August 2023



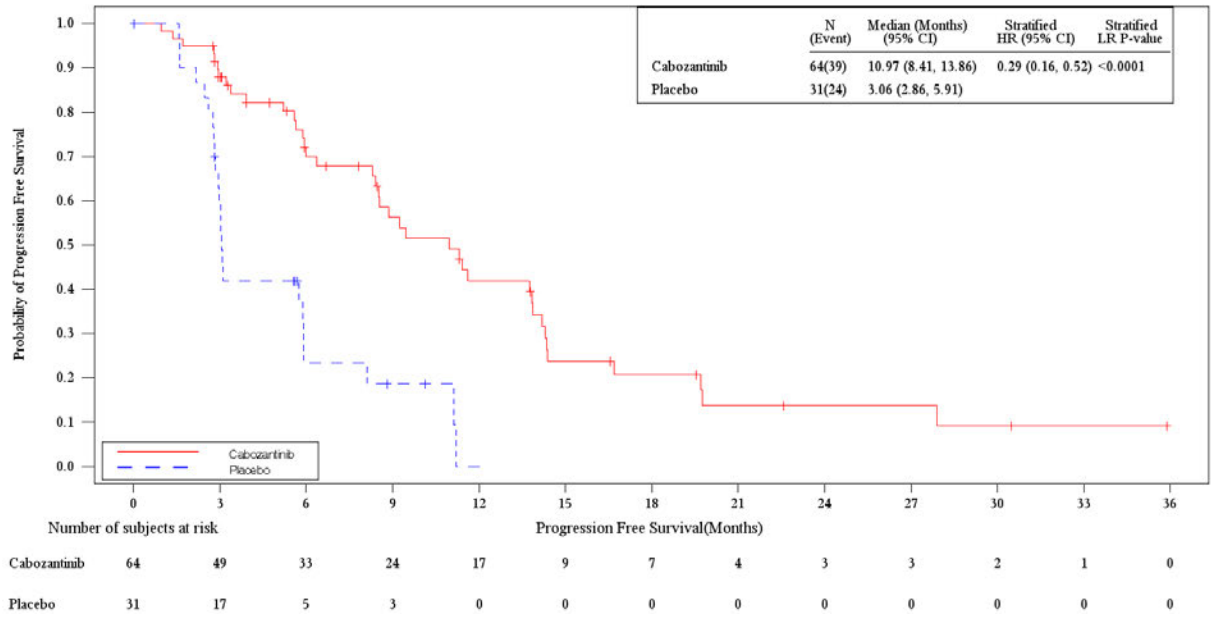
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LR, log-rank test
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
+ indicates a censored observation.
Source: CABINET CSR Figure 14.2.1.1.1; ADaM Datasets: ADSL, ADTTE.

pNET Sensitivity Analysies: Progression-free Survival per RECIST 1.1 by Investigator

As of the 24 August 2023 cutoff date, 39 subjects (61%) in the cabozantinib arm and 24 subjects (77%) in the placebo arm had events. The sensitivity analysis of PFS (PFS-EP2) by Investigator showed a highly consistent treatment effect compared to BIRC assessment: a 71% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm, stratified HR: 0.29 (95% CI: 0.16, 0.52; stratified 2-sided $p < 0.0001$).

The Kaplan-Meier estimate of median PFS per RECIST 1.1 using FDA-recommended censoring rules was 10.97 months (95% CI: 8.41, 13.86) in the cabozantinib arm compared with 3.06 months (95% CI: 2.86, 5.91) in the placebo arm and estimated 7.9-month difference in medians between treatment arms. The 6-, 12-, and 18-month event free rates were 69.9%, 41.9%, and 20.7%, respectively, in the cabozantinib arm and 23.3%, 0.0%, and 0.0%, respectively, in the placebo arm.

Applicant Figure 7: Study CABINET: pNET Kaplan-Meier Plot of Progression-Free Survival by Investigator through 24 August 2023



CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LR, log-rank test
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
+ indicates a censored observation.
Source: CABINET CSR Figure 14.2.1.2.1; ADaM datasets: ADSL, ADTTE.

pNET Additional Sensitivity Analyses: Progression-free Survival

Additional sensitivity analyses of PFS (EP3 through EP6 and EA1 through EA4) all supported the primary analysis and all showed consistent results with the BIRC assessment ($p < 0.0001$)), demonstrating a 71% to 78% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm. Although differences in cohort allocation and stratification existed between the OPEN registration system and EDC, a sensitivity analysis using disease allocation and stratification factors per EDC (EP4) showed consistent results with the primary analysis (HR 0.22; 95% CI: 0.12, 0.41).

Applicant Table 28: Study CABINET: pNET: Summary of Primary and Sensitivity Analyses of PFS (ITT Population)

Analysis of PFS by BIRC unless noted otherwise	Treatment Arm	Events, n (%)	K-M Estimate of Median PFS (95% CI)	K-M Estimate of 6-, 12-, 18-Month Event-free Rates	Stratified HR (95% CI) [1]	Stratified 2-sided p-value
EP1: Primary analysis	Cabozantinib (N=64)	32 (50%)	13.83 (8.87, 16.95)	71.4%, 53.8%, 29.7%	0.23 (0.12, 0.42)	< 0.0001
	Placebo (N=31)	25 (81%)	4.47 (3.02, 5.75)	24.0%, 0.0%, 0.0%		
EP2: Investigator-assessed	Cabozantinib (N=64)	39 (61%)	10.97 (8.41, 13.86)	69.9%, 41.9%, 20.7%	0.29 (0.16, 0.52)	< 0.0001
	Placebo (N=31)	24 (77%)	3.06 (2.86, 5.91)	23.3%, 0.0%, 0.0%		
EP3: With early events dated as occurring at the scheduled restaging assessment	Cabozantinib (N=64)	29 (45%)	16.59 (11.07, 18.56)	76.7%, 61.2%, 35.4%	0.23 (0.12, 0.46)	< 0.0001
	Placebo (N=31)	20 (65%)	5.55 (2.83, 6.11)	33.7%, 0.0%, 0.0%		
EP4: Using disease allocation and stratification factors collected at randomization per EDC	Cabozantinib (N=66)	34 (52%)	13.83 (8.87, 16.95)	72.9%, 54.6%, 28.3%	0.22 (0.12, 0.41)	< 0.0001
	Placebo (N=33)	26 (79%)	3.25 (2.83, 5.75)	20.6%, 0.0%, 0.0%		
EP5: Using protocol- and SAP-defined number of events (50 for pNET) for 1st interim analysis	Cabozantinib (N=64)	28 (44%)	14.36 (8.87, 17.64)	74.8%, 53.8%, 29.9%	0.22 (0.11, 0.43)	< 0.0001
	Placebo (N=31)	22 (71%)	4.47 (2.83, 5.91)	28.0%, 0.0%, 0.0%		
	Cabozantinib (N=64)	31 (48%)	13.83 (8.87, 16.95)	72.2%, 54.5%, 30.1%	0.22 (0.12, 0.43)	< 0.0001

Analysis of PFS by BIRC unless noted otherwise	Treatment Arm	Events, n (%)	K-M Estimate of Median PFS (95% CI)	K-M Estimate of 6-, 12-, 18-Month Event-free Rates	Stratified HR (95% CI) [1]	Stratified 2-sided p-value
EP6: Only include subjects randomed for at least 6 months before 24 August 2023	Placebo (N=31)	23 (74%)	4.47 (2.83, 5.91)	26.1%, 0.0%, 0.0%		
EA1: Initiation of NPACT (including crossover therapy) was treated as an event at the date of the start of the NPACT	Cabozantinib (N=64)	45 (70%)	9.23 (5.95, 13.83)	62.9%, 39.8%, 22.9%	0.28 (0.16, 0.48)	< 0.0001
	Placebo (N=31)	29 (94%)	4.47 (3.02, 5.75)	24.5%, 0.0%, 0.0%		
EA2: PD or death occurring after ≥ 2 missing scans were treated as events at the more recent ATA before the missing scans, or initiation of NPACT (including crossover therapy) was treated as an event at the date of the start of the NPACT	Cabozantinib (N=64)	46 (72%)	9.23 (5.95, 13.77)	62.0%, 39.2%, 22.6%	0.29 (0.17, 0.50)	< 0.0001
	Placebo (N=31)	29 (94%)	4.47 (3.02, 5.75)	24.5%, 0.0%, 0.0%		
EA3: Symptomatic deterioration and initiation of a new NPACT were treated as events at the respective start dates	Cabozantinib (N=64)	46 (72%)	8.87 (5.95, 11.60)	62.9%, 36.1%, 19.7%	0.28 (0.17, 0.48)	< 0.0001
	Placebo (N=31)	29 (94%)	4.47 (3.02, 5.75)	24.5%, 0.0%, 0.0%		
EA4: Missing tumor scans were ignored	Cabozantinib (N=64)	33 (52%)	13.83 (8.87, 16.95)	71.9%, 54.8%, 28.4%	0.22 (0.12, 0.41)	< 0.0001
	Placebo (N=31)	25 (81%)	4.47 (3.02, 5.75)	24.0%, 0.0%, 0.0%		

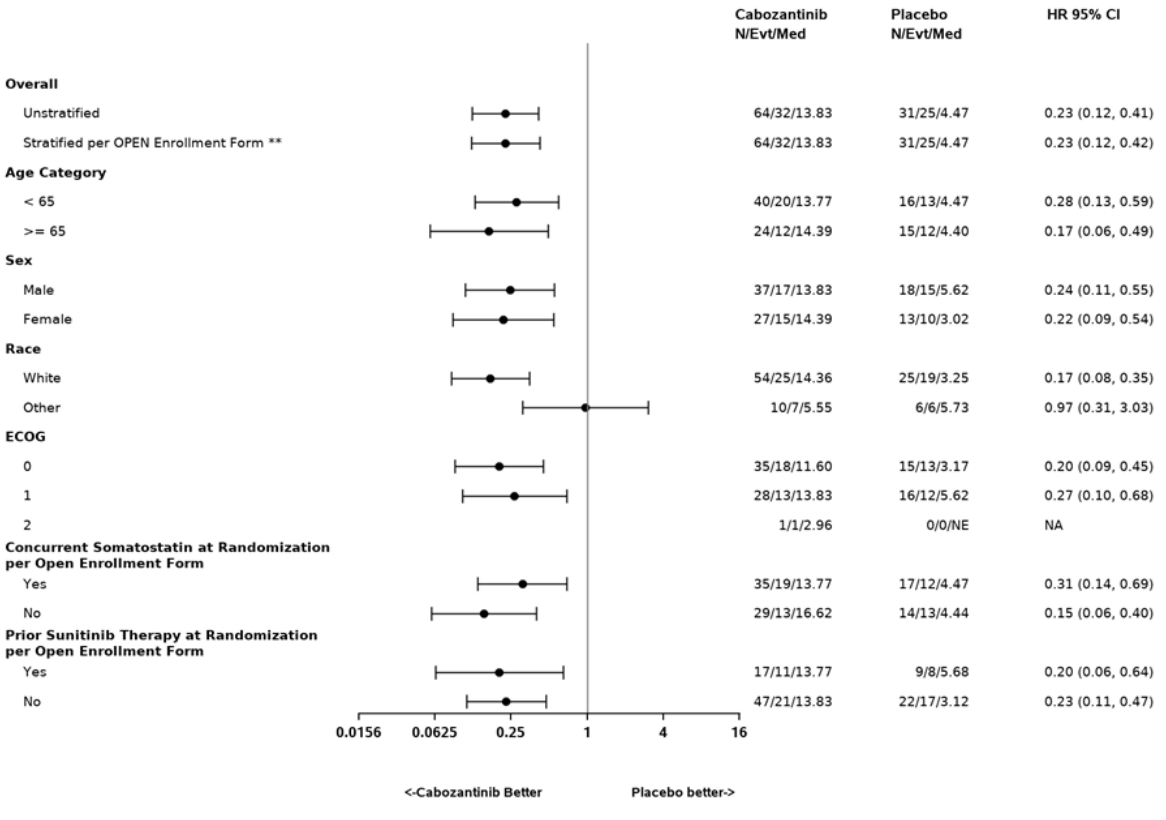
CI, confidence interval; HR, hazard ratio; EDC, electronic data capture; ITT, intent-to-treat; K-M, Kaplan-Meier; NE, not estimable; NPACT, nonprotocol anticancer therapy
p-values are from log-rank test.
[1] Hazard ratios were calculated from Cox proportional hazards model.

Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
Source: CABINET CSR Tables 14.2.1.1.2, 14.2.1.2.2, 14.2.1.3.2, 14.2.1.4.2, 14.2.1.5.2, 14.2.1.6.2, 14.2.1.7.2, 14.2.1.8.2, 14.2.1.9.2, 14.2.1.10.2; ADaM datasets: ADSL, ADTTE.

pNET Subgroup Analysis of PFS per RECIST 1.1 by BIRC

For BIRC-assessed response, the results of the subgroup analysis including but not limited to stratification factors and prior systemic therapies were consistent with the primary analysis of PFS, favoring cabozantinib. All HRs were < 1; and for most subgroups, the upper bound of the 95% CI was < 1. The subgroup analyses of the BIRC-assessed analyses of PFS are displayed in and summarized in Applicant Figure 8.

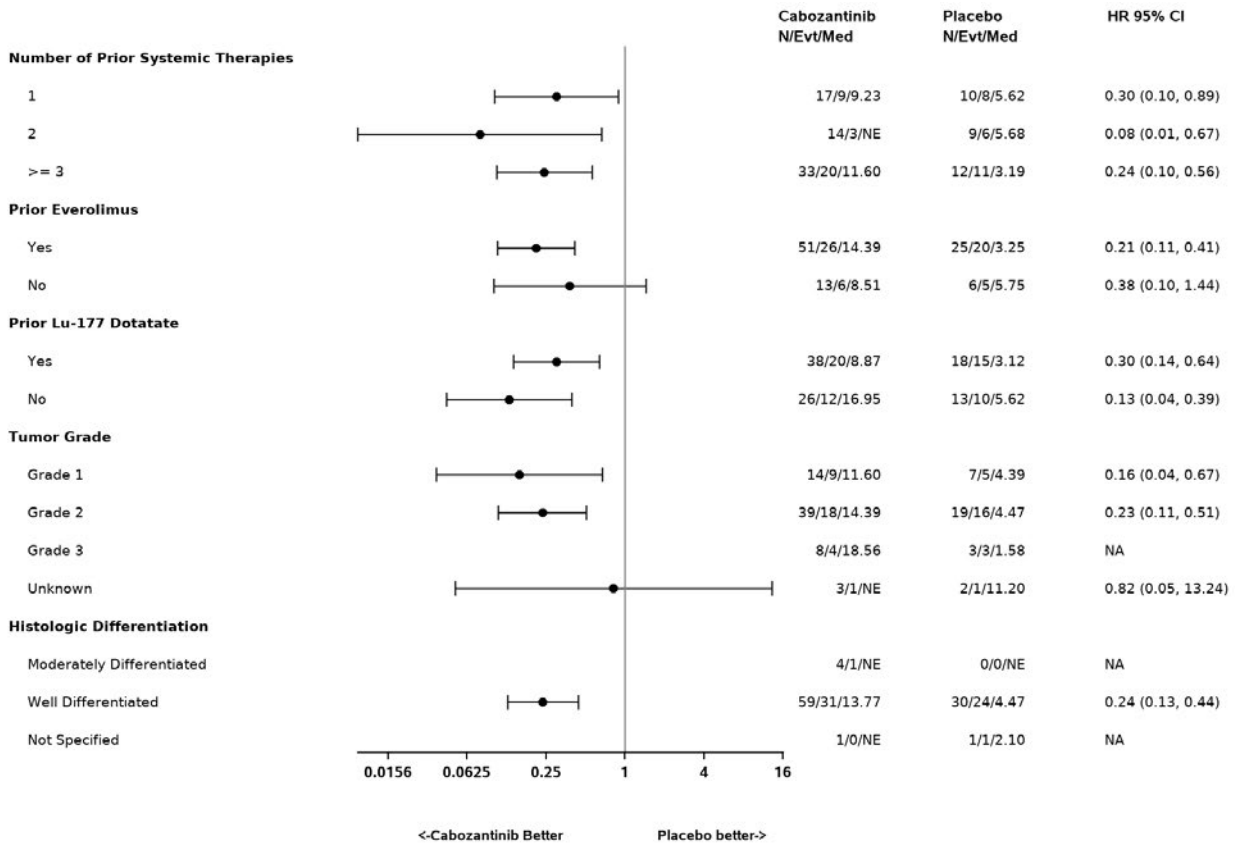
Applicant Figure 8: Study CABINET: pNET Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; HR, hazard ratio; ITT, intent to treat; Med, median; N, number of subjects; NA, not applicable; OPEN, Oncology Patient Enrollment Network
Hazard ratio and 95% CI Estimates from unstratified Cox proportional hazards model are presented for all subgroups
**Stratification factors are as follows: (1) concurrent somatostatin analog use (yes, no) and (2) prior sunitinib therapy (Yes, No).
Source: CABINET CSR Figure 14.2.7.1.a; ADaM Datasets: ADSL, ADTTE.

continued

Applicant Figure 8: Study CABINET: pNET: Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC (Continued)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; HR, hazard ratio; ITT, intent to treat; Med, median; N, number of subjects; NA, not applicable; OPEN, Oncology Patient Enrollment Network
Hazard ratio and 95% CI Estimates from unstratified Cox proportional hazards model are presented for all subgroups
**Stratification factors are as follows: (1) concurrent somatostatin analog use (yes, no) and (2) prior sunitinib therapy (Yes, No).
Source: CABINET CSR Figure 14.2.7.1.a; ADaM Datasets: ADSL, ADTTE.

Comparison of Disease Progression by BIRC and Investigator

Discordance rates between investigator assessments and BIRC assessments were generally similar between the two arms with disagreement on PD status observed in 29% and 28% of cabozantinib and placebo subjects, respectively. Additional measures are summarized below (Applicant Table 29) with a slightly higher late discrepancy rate noted on the placebo arm relative to cabozantinib and slightly higher early discrepancy rate noted on the cabozantinib arm which would suggest bias favoring the placebo arm, although sample size was limited.

Applicant Table 29: Study CABINET: pNET: Summary of Discordance between Investigator and BIRC

Discordance Measure	Cabozantinib (N = 56)	Placebo (N = 29)
Disagreement on PD status	16/56 (29%)	8/29 (28%)
Disagreement on PD date within 2 weeks	21/56 (38%)	12/29 (41%)
Disagreement on PD date within 4 weeks	20/56 (36%)	12/29 (41%)
Early discrepancy rate[a]	14/34 (41%)	6/23 (26%)
Late discrepancy rate [b]	7/21 (33%)	7/13 (54%)

BIRC, blinded independent review committee; PD, progressive disease; NET, neuroendocrine tumor
ITT subjects with at least one post-baseline tumor assessment per investigator and BIRC were included in the analysis.

[a] Early discrepancy rate is the percentage of subjects for whom investigator declared PD while BIRC did not or PD date by investigator was earlier than by BIRC out of subjects who were declared PD by investigator. Denominator is the number of subjects who were declared PD by investigator

[b] Late discrepancy rate is the percentage of subjects for whom BIRC declared PD while investigator did not or PD date by investigator was later than by BIRC out of subjects for whom investigator and BIRC had discordances on PD status or PD date. Denominator is the number of subjects for whom investigator and BIRC had discordances on PD status or PD date

Source: CABINET CSR Table 14.2.8.1.a; ADaM datasets: ADSL, ADRS.

Comparisons of batched BIRC vs real-time central review and investigator vs real-time central review were also performed. The real-time central assessments and the batched BIRC assessments were performed by different readers. The disagreement between real-time central review and investigator-assessed progression was small and balanced between treatment arms.

The Applicant's Position:

In the pNET cohort, the study met its primary efficacy endpoint of PFS by BIRC for the epNET cohort. The statistically significant prolongation of PFS observed represent a clinically meaningful improvement over placebo. The efficacy benefit in PFS provided by cabozantinib was observed consistently across multiple sensitivity analyses as well as in key pre-specified subgroups, including those based on stratification factors.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the efficacy results for the primary endpoint of BIRC-assessed PFS per RECIST 1.1, and results from the sensitivity and subgroup analyses in the ITT population in the pNET cohort. The efficacy results are based on 38% of the planned PFS events for the final analysis in pNET cohort. The pNET cohort did not fully enroll due early discontinuation of the enrollment and this interim PFS analysis is

considered the final PFS analysis. A significant improvement in BIRC assessed PFS for the patients treated with cabozantinib over placebo was observed at the time of this analysis. The Kaplan-Meier plots of BIRC assessed PFS by treatment arms appeared to separate early and the separation of the curves continued over the entire follow-up time.

To evaluate the robustness of the treatment effect in PFS and impact of censoring, additional analyses of PFS by BIRC were conducted in the ITT population. For the primary analysis of PFS, patients were censored if they did not have a PFS event, received concomitant or subsequent non-protocol anti-cancer therapy including crossover therapy prior to a PFS event or experienced a PFS event after two or more consecutive missing tumor assessments. Reasons for censoring for the primary analysis of PFS are provided in Table 30 below.

FDA Table 30. BIRC assessed PFS Analysis in pNET in ITT Population - Reasons for Censoring

Reasons for censoring, n(%)	Cabozantinib (n=64)	Placebo (n=31)
Two or more missing adequate tumor assessments prior to event	1 (2.0)	0
No event and did not crossover	14 (22)	1 (3.2)
No event prior and after crossover	0	1 (3.2)
No post-baseline adequate tumor assessments	4 (6)	1 (3.2)
Systemic non-protocol anti-cancer therapy	13 (20)	3 (10)

Source: FDA analysis of the Applicant's submitted data (adtte.xpt); DCO: 09/04/2024

Six percent of the patients in the cabozantinib arm and 3.2% patients in the placebo arm were censored due to no post-baseline adequate tumor assessments. FDA performed a conservative sensitivity analysis in the ITT population considering patients with no post-baseline adequate tumor assessments as having an event in the cabozantinib arm and censored in the placebo arm at the time of randomization. The BIRC-assessed PFS result from this analysis (PFS HR: 0.29 [95% CI: 0.16, 0.52]) was consistent with the results observed in the primary analysis.

Similarly, the impact of non-protocol anti-cancer therapy was evaluated. Twenty percent of patients in the cabozantinib arm and 10% of patients in the placebo arm were censored due to receipt of non-protocol anticancer therapy (NPACT) prior to disease progressions. The most common reasons for initiation of NPACT in these patients were determination of disease progression per investigator assessment and/or real-time central review, toxicity, and patient withdrawal or refusal to continue protocol therapy. The Applicant conducted a sensitivity analysis considering receipt of non-protocol anticancer therapy as an event in both treatment arms as presented under EA1 in Applicant Table 28; the results of EA1 are supportive of the analysis according to the primary PFS censoring rule. BIRC-assessed PFS results from the sensitivity analysis considering receipt of systemic non-protocol anticancer therapy as an event in the cabozantinib arm and censored in the placebo arm was also consistent (PFS HR: 0.34

[95% CI: 0.19, 0.59]) with the PFS results observed in the primary analysis. PFS results also appeared to be consistent with that of the investigator-assessed PFS analysis and across sensitivity analyses presented above. PFS results across the selected subgroups were also supportive of the results observed in the primary and sensitivity analyses.

FDA considered results from the landmark analyses of PFS to be descriptive only.

During the review, the Applicant assessed and updated the timing and completeness of subsequent anti-cancer therapy based on the same DCO of August 24, 2024 (Source: Response to FDA information request, dated February 7, 2025). This resulted in one additional patient in the cabozantinib arm in the pNET cohort being censored for initiation of non-protocol anti-cancer therapy before documented progression in the BIRC-assessed PFS analysis. Based on this updated data, the BIRC-assessed PFS results in pNET cohort, correcting for misclassified tumor type and based on verified stratification factors per electronic data capture, are provided in FDA Table 31 below. **These PFS results are included in the US prescribing information.**

FDA Table 31. BIRC assessed PFS Results in Patients with pNET in CABINET

	Cabozantinib (N=66)	Placebo (N=33)
Progression-Free Survival (PFS)		
Number of events (%)	33 (50)	26 (79)
Median (95% CI)[1], in months	13.8 (8.9, 17.0)	3.3 (2.8, 5.7)
Hazard Ratio (95% CI)[2]	0.22 (0.12, 0.41)	
p-value[3]	<0.0001	

CI, confidence interval
[1]Kaplan-Meier method
[2]Stratified Cox proportional hazards model stratified by concurrent somatostatin analog (SSA) use (yes/no) and prior sunitinib therapy (yes/no)
[3]Stratified log-rank test stratified by concurrent somatostatin analog (SSA) use (yes/no) and prior sunitinib therapy (yes/no) (compared to one-sided alpha=0.001)
Source: FDA analyses of the Applicant submitted data (adtte, adsl); DCO: 09/04/2024

Investigator-assessed PFS was a secondary endpoint. Similar to the epNET cohort, real-time central review confirmation was utilized to adjudicate investigator-assessed PFS to reduce potential bias. The disagreement in PD status by real time central review and investigator assessments in the cabozantinib arm was 18% and was 13% in the placebo arm. The distribution of disagreements, that is, when PD was determined by investigator and not by real-time central review or vice-versa, appear to be balanced between treatment arms.

While the discordance between investigator-assessed disease progression and BIRC-assessed disease progression was relatively high, the distribution of the disagreement in the PD status and the timing of the PD appears to be well balanced between treatment arms. Additionally, the distribution of the early discrepancy rate was numerically higher in the cabozantinib arm and late discrepancy was higher in placebo arm. The impact of these discrepancies should be interpreted with caution due to the small number of PFS events observed at the time of the PFS analysis.

For further details regarding statistical challenges refer to Statistical Issues section below.

Data Quality and Integrity

The Applicant's Position:

The study was conducted by the Alliance for Clinical Trials in Oncology ("Alliance"), a member of the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN). The Alliance is comprised of academic and community institutions and their affiliates which conduct cancer treatment and cancer control/prevention studies and related research according to their Policies and Procedures and in accordance with all applicable federal, state and local laws and regulations including, without limitation, FDA regulations and guidelines for GCP.

The FDA's Assessment:
The FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the efficacy of cabozantinib in patients with advanced neuroendocrine tumors. The FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the NDA and all requests were addressed appropriately.

Efficacy Results – Secondary and other relevant endpoints

Data:

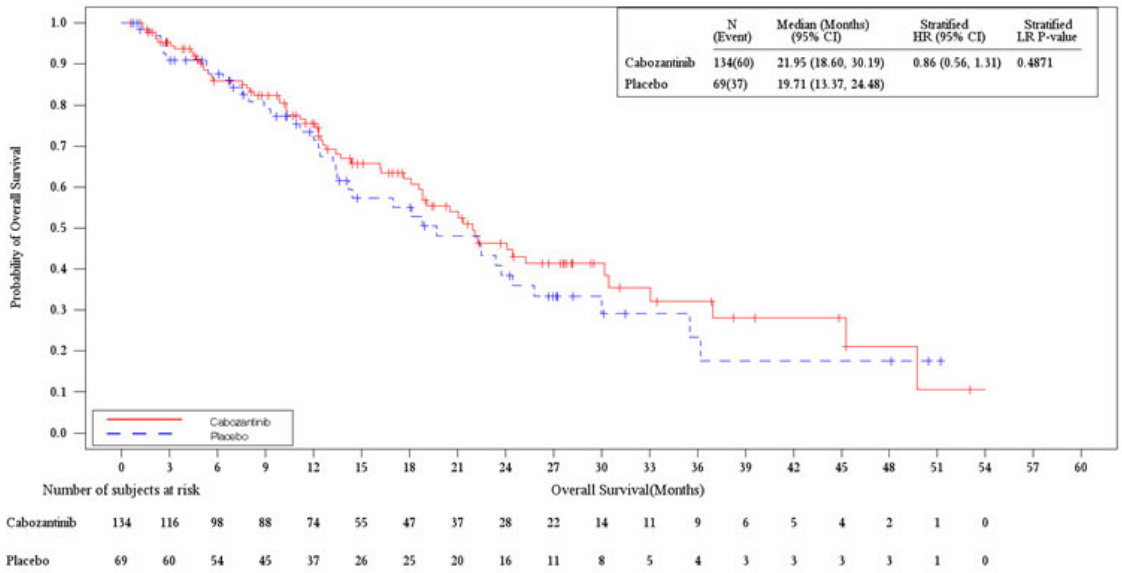
epNET – Secondary and Other Relevant Endpoints

epNET Overall Survival –Secondary Endpoint

As of the 24 August 2023 cutoff date, 97 deaths (60 subjects [45%] cabozantinib arm, 37 subjects [54%] placebo arm) were reported. At the time of the cutoff date, OS supported the primary endpoint of PFS per RECIST 1.1 by BIRC, showing a trend toward improvement in the cabozantinib arm compared with the placebo arm (HR = 0.86 [95% CI: 0.56, 1.31]; p = 0.4871), although OS results are immature (97 of 203 subjects [48%] with OS events) and confounded by 22 of the 69 placebo subjects (32%) having crossed over to open label cabozantinib treatment after progression. The median duration of OS for the cabozantinib subjects was 21.95 months

(95% CI: 18.60, 30.19) compared to 19.71 months (13.37, 24.48) for the placebo subjects. Kaplan-Meier estimates showed that at most time points, the proportion of subjects estimated to be event-free was greater in the cabozantinib arm compared with the placebo arm (Applicant Figure 9). Results of the subgroup analyses of OS were generally consistent to that for the entire population and suggest no detriment in OS.

Applicant Figure 9: Study CABINET: epNET Kaplan-Meier Plot of Overall Survival through 24 August 2023



+ indicates a censored observation; CI, confidence interval; HR, hazard ratio; LR, log-rank test
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes/No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
Source: CABINET CSR Figure 14.2.2.1b; ADaM Dataset: ADSL, ADTTE.

The FDA's Assessment:

Overall survival (OS) in the epNET cohort was planned to be hierarchically tested after 155 OS events, if PFS was statistically significant. At the time of the NDA submission, a descriptive analysis of OS based on the DCO of August 24, 2023, when 63% of the planned OS events in epNET were observed, was submitted. The OS HR was 0.86 (95% CI: 0.56, 1.31). The K-M plots of OS do not indicate a potential OS detriment in the cabozantinib arm. During the review of this NDA, an updated descriptive analysis of OS with approximately an additional year of follow-up (DCO: Sep 04, 2024) was performed and submitted. The observed OS information fraction at the time of this analysis was 81%; 41% of patients from the placebo arm had crossed over to open-label cabozantinib. The OS results of this analysis are provided in FDA Table 32 and FDA Figure 10, respectively. FDA considered these results to be descriptive only.

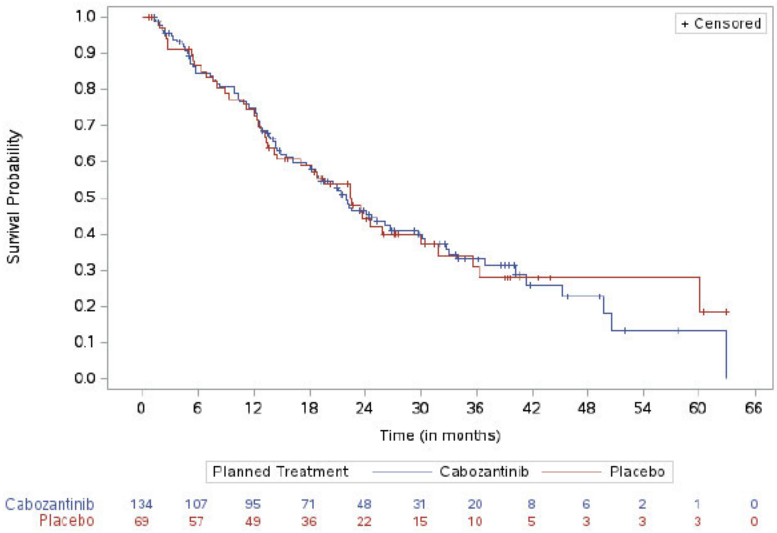
FDA's assessment of overall survival based on the descriptive analyses of OS does not appear to indicate there is an OS detriment in patients with epNET treated with cabozantinib. However, these results should be interpreted with caution as OS data was not fully mature and crossover may have impacted the results. Of the total 69 patients in the placebo arm, 20% of patients received crossover treatment only, 33% received other non-protocol anticancer therapy only, 12% received both, and 35% received none. Forty-five percent of patients on the cabozantinib arm received other non-protocol anti-cancer therapy.

FDA Table 32. Updated Overall Survival Results in the ITT Population - epNET

	epNET	
	Cabozantinib N=134	Placebo N=69
Overall Survival (OS)[1]		
Deaths (%)	84 (63%)	42 (61%)
Median, months (95% CI)	22.0 (17.6, 29.6)	22.5 (14.2, 30.0)
Hazard Ratio (95% CI)[2]	1.04 (0.71, 1.52)	
Information fraction	81%	
Crossover	41%	

[1]Updated descriptive analysis of OS; [2] From stratified Cox regression model
Source: FDA analysis of the Applicant's submitted data (ADSL, ADTTE); DCO: 09/04/2024

FDA Figure 10. Kaplan-Meier Plots of Updated Overall Survival Results in the ITT Population - epNET



Source: FDA analysis of the Applicant's submitted data (ADSL, ADTTE)
DCO: 09/04/2024

FDA also conducted additional analyses of OS correcting for tumor type and stratification factors by excluding misclassified patients from the respective cohorts and correctly classifying the misclassified patients. Three epNET patients were misclassified as pNET patients and 7

pNET patients were misclassified as epNET patients. These analyses also used the source verified values of stratification factors rather than values assigned by randomization. Results from these analyses yielded similar OS HRs to those observed in the ITT population (FDA Table 33).

FDA Table 33. Selected Sensitivity Analyses of OS - epNET

	OS HR (95% CI)
PA: OS in ITT	1.04 (0.71, 1.52)
SA 1: Excluding misclassified patients and correcting for stratification factors	1.04 (0.70, 1.54)
SA 2: Correctly classifying misclassified patients and correcting for stratification factors	1.05 (0.71, 1.54)

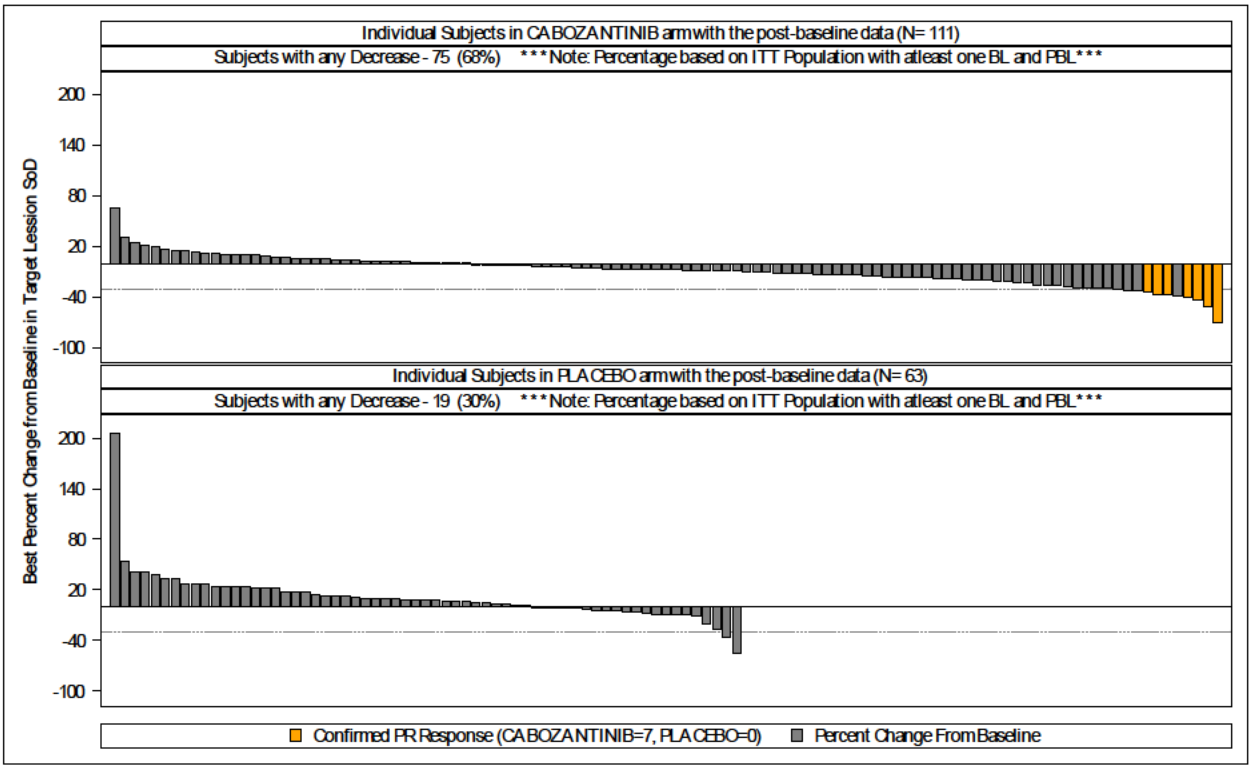
OS, overall survival; HR, hazard ratio; ITT, intent to treat
Source: FDA analyses of the Applicant submitted data (adsl, adtte); DCO: 09/04/2024

Approximately 15% (20/134) patients in the cabozantinib arm and 10% (7/69) of the patients in the placebo arm were mis-stratified at the time of randomization as concurrent somatostatin analogue users, and 0.75% (1/134) patients in the cabozantinib arm and 2.9% (2/69) patients in the placebo arm were mis-stratified as non-users. Six percent (8/134) of patients in the cabozantinib arm and no patients in the placebo arm were mis-stratified as “NON-MIDGUT GI/LUNG/OTHER KNOWN PRIMARY SITE NOT LISTED” as the primary tumor site. Thirteen percent (18/134) of patients in the cabozantinib arm and 12% (8/69) patients in the placebo arm were mis-stratified as “MIDGUT/UNKNOWN PRIMARY SITE” as the primary rumor sites. The OS HR in the ITT population using sourced verified stratification factors was 1.04 (95% CI: 0.70, 1.54). In the USPI, the HR for OS (SA 2) for the correctly classified patient cohort was reported.

epNET Objective Response Rate per RECIST 1.1 by BIRC–Secondary Endpoint

In the cabozantinib arm 7 subjects (5.2%) had a confirmed PR, no CRs were reported, giving a confirmed ORR of 5.2% (95% CI: 2.1%, 10.5). No subject in the placebo arm had a confirmed response (ORR of 0% :95% CI: 0%, 5.2%). The difference in confirmed ORR was 5.2% (95% CI: 1.5%, 9.0%, p-value = 0.0524). The median time from randomization to confirmed response was 5.52 months (range: 2.8–8.4 months in the cabozantinib arm. The best percentage change in BIRC-assessed tumor target lesion size from baseline is shown in Applicant Figure 11. The proportion of subjects in the cabozantinib arm who had a postbaseline reduction in tumor target lesion size was higher than that observed in the placebo arm (68% vs 30%).

Applicant Figure 11: Study CABINET: epNET Waterfall Plot of Best Percentage Change in Sum of Tumor Target Lesion Size Since Baseline by BIRC



BL, baseline; ITT, intent-to-treat; PBL, post-baseline
Source: CABINET CSR Figure 14.2.3.2.b; ADaM Dataset: ADSL, ADTR, ADRS.

epNET Objective Response Rate by Investigator

In the cabozantinib arm 5 subjects (3.7%) had a confirmed PR, no CRs were reported, giving a confirmed ORR of 3.7% (95% CI: 1.2%, 8.5%). In the placebo arm, 1 subject (1.4%) had a confirmed PR, no CRs were reported (ORR 1.4%, 95% CI: 0.0%, 7.8%). The treatment difference in confirmed ORR was 2.3% (95% CI: −2.0%, 6.6%; p-value = 0.3652).

The proportion of subjects in the cabozantinib arm who had a postbaseline reduction in tumor size was higher than that observed in the placebo arm (72% vs 17%).

The median time from randomization to confirmed objective response was 3.02 months (range: 2.8–8.2) for the 5 subjects with a confirmed objective response in the cabozantinib arm and 3.09 months for the 1 subject in the placebo arm.

epNET Additional Endpoints

epNET Duration of Objective Response

Duration of Objective Response by BIRC

Of the 7 subjects in the cabozantinib arm who had a BIRC-assessed confirmed PR, 5 either had subsequent disease progression (n=4) or died (n=1). The Kaplan-Meier estimate of the median DOR, per BIRC, was 8.26 months (95% CI: 4.47, not estimable), and the 3-, 6-, and 12- month event-free rates were 100.0%, 50.0%, and 25.0%, respectively. No subject in the placebo arm had either a CR or PR.

The median time from randomization to confirmed objective response was 5.52 months (range: 2.8–8.4 months) for the 7 subjects with a confirmed objective response in the cabozantinib arm.

Duration of Objective Response by Investigator

Of the 5 subjects in the cabozantinib arm who had an investigator-assessed confirmed PR, all 5 had subsequent disease progression. The Kaplan-Meier estimate of median DOR, per the investigator, was 10.74 months (95% CI: 5.32, not estimable), and the 3-, 6- and 12-, month event-free rates were 100.0%, 80.0%, and 20.0%, respectively. One subject in the placebo arm had a confirmed PR subsequently progressed after 5.59 months.

epNET Disease Control Rate

Disease Control Rate by BIRC

The BIRC-assessed DCR was 70% (95% CI: 61.6%, 77.7%) in the cabozantinib arm and 54% (95% CI: 41.2%, 65.7%) in the placebo arm. The difference in DCR between treatment arms was 16.5% (95% CI: 2.4%, 30.6%).

Disease Control Rate by Investigator

The investigator-assessed DCR was 65% (95% CI: 56.2%, 73.0%) in the cabozantinib arm and 41% (95% CI: 28.9%, 53.1%) in the placebo arm. The difference in DCR between treatment arms was 24.3% (95% CI: 10.2%, 38.5%).

The Applicant's Position:

Analyses of OS gave a HR of 0.86 (95% CI: 0.56, 1.31; p = 0.4871) for the epNET cohort supporting no detriment. OS results are immature and confounded by crossover of placebo subjects to open label cabozantinib after progression (32% in the epNET cohort).

Efficacy is supported by the fact that objective responses were increased and were durable in cabozantinib treated subjects. ORR by BIRC in epNET showed an improved response with cabozantinib over placebo, with a treatment difference of 5.2% (95% CI: 1.5%, 9.0%, p-value = 0.0524. Median duration of response with cabozantinib per BIRC was 8.26 months (95% CI: 4.47, NE).

The FDA's Assessment:

According to the SAP, ORR was not planned to be formally tested and results are considered descriptive only. In addition, given the small number of responders in both the cabozantinib and the placebo arm, it is challenging to interpret results of ORR and DOR. FDA Table 34 lists the duration of responses for responders assessed by BIRC or investigator in the cabozantinib arm (no responders were observed in the placebo arm). In addition, FDA does not consider DCR to be an acceptable regulatory endpoint. Results of these endpoints are considered exploratory only.

FDA Table 34. Listing of Duration of Response by BIRC in the epNET Cohort

Duration of response (in months)	Event/censoring
12.1	PD
2.8	Censored
4.6	Death
4.5	PD
5.5	PD
5.6	Censored
11.1	PD

PD, disease progression
Source: FDA analysis of the Applicant's submitted data (adtte); DCO: 09/04/2024

For FDA comments regarding overall survival in epNET cohort, see FDA comments above under section **epNET Overall Survival –Secondary Endpoint.**

Data:

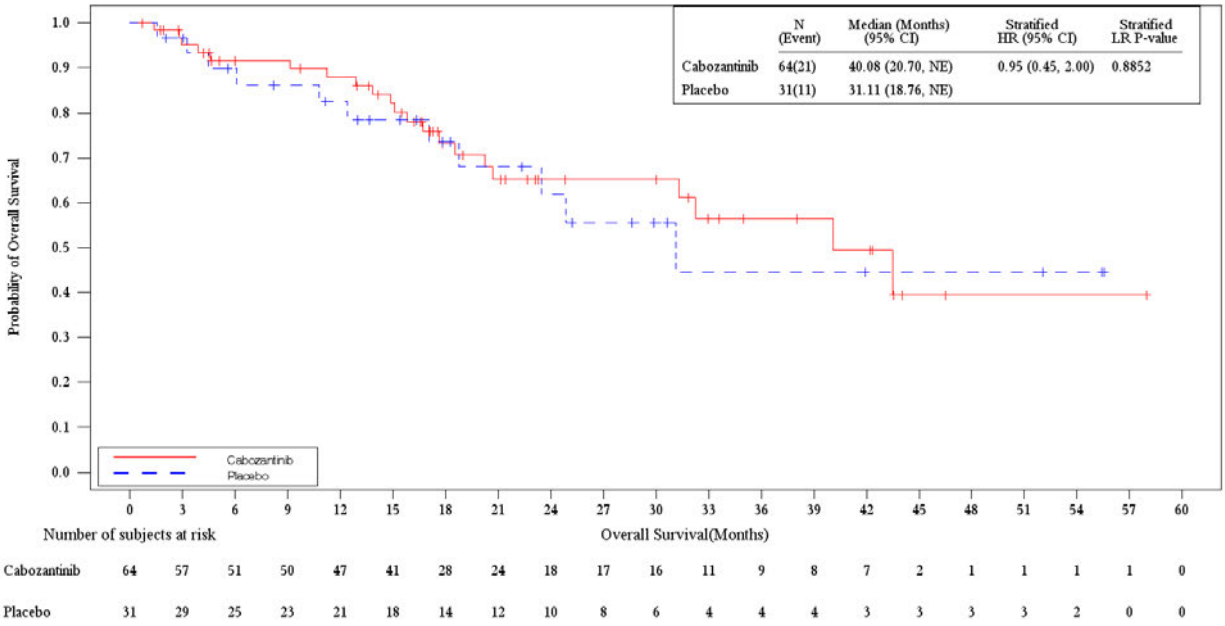
pNET – Secondary and other relevant endpoints

pNET Overall Survival –Secondary Endpoint

As of the 24 August 2023 cutoff date, 32 deaths (21 subjects [33%] in the cabozantinib arm and 11 subjects [35%] in the placebo arm) were reported. The OS at the time of the cutoff date appeared similar between treatment arms (HR = 0.95 [95% CI: 0.45, 2.00]; p = 0.8852). The OS results are immature (32 of 95 subjects [34%] with OS events) and confounded by 12 out of 31 placebo subjects (39%) having crossed over to cabozantinib treatment after progression. The median duration of OS was 40.08 months (20.70, NE) and 31.11 months (18.76, NE) for the cabozantinib and placebo subjects, respectively. Kaplan-Meier estimates of event-free rates were similar between treatment arms at all time points (Applicant Figure 12).

The subgroup analyses of OS showed that age, gender, race, primary site per open enrollment form, and prior Lu-177 dotatate use were consistent with that for the entire population and suggested no detriment in OS

Applicant Figure 12: Study CABINET: pNET Kaplan-Meier Plot of Overall Survival through 24 August 2023



CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LR, log-rank test
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
+ indicates a censored observation.
Source: CABINET CSR Figure 14.2.2.1a; ADaM Datasets: ADSL, ADTTE.

The FDA's Assessment:

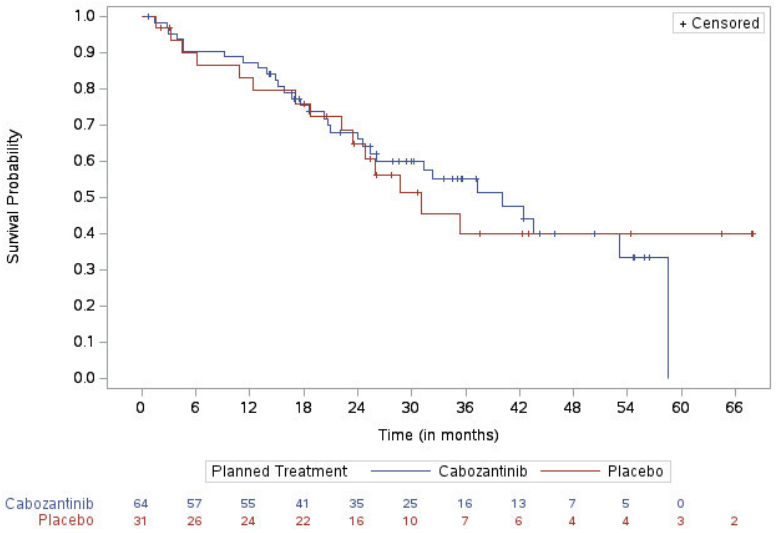
Overall survival in pNET cohort was planned to be hierarchically tested after 155 OS events, if PFS was statistically significant. OS was descriptively analyzed at the time of the NDA submission based on a DCO of August 24, 2023, when 21% of the planned OS events in pNET were observed. The OS HR was below 1.0 with the upper limit of the 95% CI exceeding 1.0. The K-M plots of OS did not appear to indicate a potential OS detriment in the cabozantinib arm. This OS analysis was performed based on a snapshot of OS data with the DCO of August 24, 2023. An updated descriptive analysis of OS with approximately an additional year of follow-up (DCO: September 4, 2024) and a rigorous sweep of OS data was performed. The observed OS information fraction at the time of this analysis was 30%, and 45% patients from placebo arm crossed over to open label cabozantinib arm. The OS HR in this analysis was 1.11. OS results from this analysis are provided in FDA Table 35 & FDA Figure 13, respectively.

FDA Table 35. Updated Overall Survival Results in ITT population – pNET Cohort

	pNET	
	Cabozantinib N=64	Placebo N=31
Overall Survival (OS)[1]		
Deaths (%)	31 (48%)	15 (48%)
Median, months (95% CI)	40.1 (25.4, NE)	31.1 (22.2, NE)
Hazard Ratio (95% CI)[2]	1.11 (0.59, 2.09)	
Information fraction	30%	
Crossover	45%	

[1]Updated descriptive analysis of OS; [2]From stratified Cox regression model
Source: FDA analysis of the Applicant's submitted data (ADSL, ADTTE); DCO: 09/04/2024

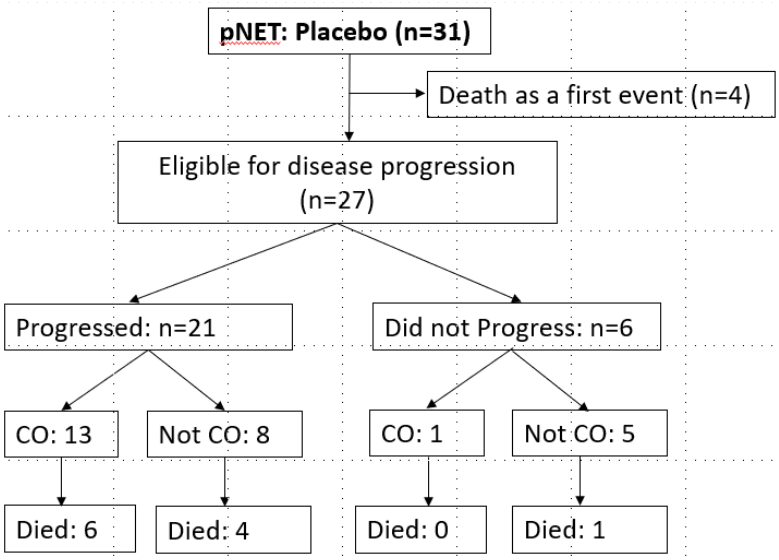
FDA Figure 13. Kaplan-Meier Plots of Updated Overall Survival Results – pNET Cohort



Source: FDA analysis of the Applicant's submitted data (ADSL, ADTTE)

Descriptive analyses were done to characterize survival outcomes in placebo arm patients who had disease progression versus those who did not. The distribution of deaths in crossover patients with disease progression or without disease progression appeared to be numerically similar. A similar finding was observed in patients without crossover as presented in FDA Figure 14 below. While these analyses provide additional information regarding OS in placebo arm, there are inherent differences in the patients who are eligible and choose to crossover and those who are not eligible or do not choose to crossover.

FDA Figure 14. Distribution of OS Events in Placebo Arm in pNET Cohort



The primary analysis set included 3 epNET patients misclassified as pNET patients and excluded 7 pNET patients misclassified as epNET patients. FDA conducted additional analyses of OS correcting for misclassified tumor type and stratification factors in pNET cohort. The analyses included estimation after excluding misclassified patients from the respective cohorts, and correctly classifying the misclassified patients. These analyses also used the source verified values of stratification factors rather than values assigned by randomization. After correcting for the tumor type and using source verified stratification factors, the OS HR in the pNET cohort was 1.01 (95% CI: 0.55, 1.83). Results from these sensitivity analyses are provided in FDA Table 36.

FDA Table 36. Selected Sensitivity Analyses of OS – pNET Cohort

	OS HR (95% CI)
PA: OS in ITT	1.11 (0.59, 2.09)
SA 1: Excluding misclassified patients and correcting for stratification factors [1]	1.08 (0.56, 2.07)
SA 2: Correctly classifying misclassified patients and correcting for stratification factors [1]	1.01 (0.55, 1.83)

OS, overall survival; HR, hazard ratio; CI, confidence interval; PA, primary analysis; ITT, intent-to-treat; SA, sensitivity analysis; DCO: 09.04.2024;
[1] Three epNET patients were misclassified as pNET patients and 7 pNET patients were misclassified as pNET
Source: FDA analysis of the Applicant's submitted data (ADSL, ADTTE)

Approximately 5% (3/64) patients in the cabozantinib arm and 6% (2/31) of the patients in the placebo arm were mis-stratified at the time of randomization as concurrent somatostatin analogue users, and 6% (4/64) patients in the cabozantinib arm and 6% (2/31) patients in the placebo arm were mis-stratified as non-users. Approximately one and a half percent (1/64) of patients in the cabozantinib arm and 6% (2/31) patients in the placebo arm were mis-stratified as receiving prior sunitinib therapy whereas 3.13% (2/64) of patients in the cabozantinib arm and no patients in the placebo arm were mis-stratified as receiving no prior sunitinib therapy. The OS HR in the ITT population using source verified stratification factors was 1.07 (95% CI: 0.57, 2.01). Given the OS data in the pNET cohort is limited and correcting for misclassified patients and stratification factors reduced the point estimate of OS HR from 1.11 to 1.01, a listing of the outcomes of these patients is provided in FDA Table 37.

FDA Table 37. OS Outcomes in Patients with Mis-classified Tumor Types in CABINET

Patient ID	Correctly classified cohort	Time to cross-over (in months)	Time to OS event (in months)	Censoring event
(b) (6)	pNET	NA	5.7	Death
	pNET	3.0	8.0	Death
	pNET	3.8	12.8	Death
	pNET	NA	18.1	Death
	pNET	NA	21.4	Alive
	pNET	NA	22.2	Death
	pNET	3.4	22.4	Death
	epNET	NA	16.7	Death
	epNET	NA	23.5	Death
	epNET	NA	53.2	Death

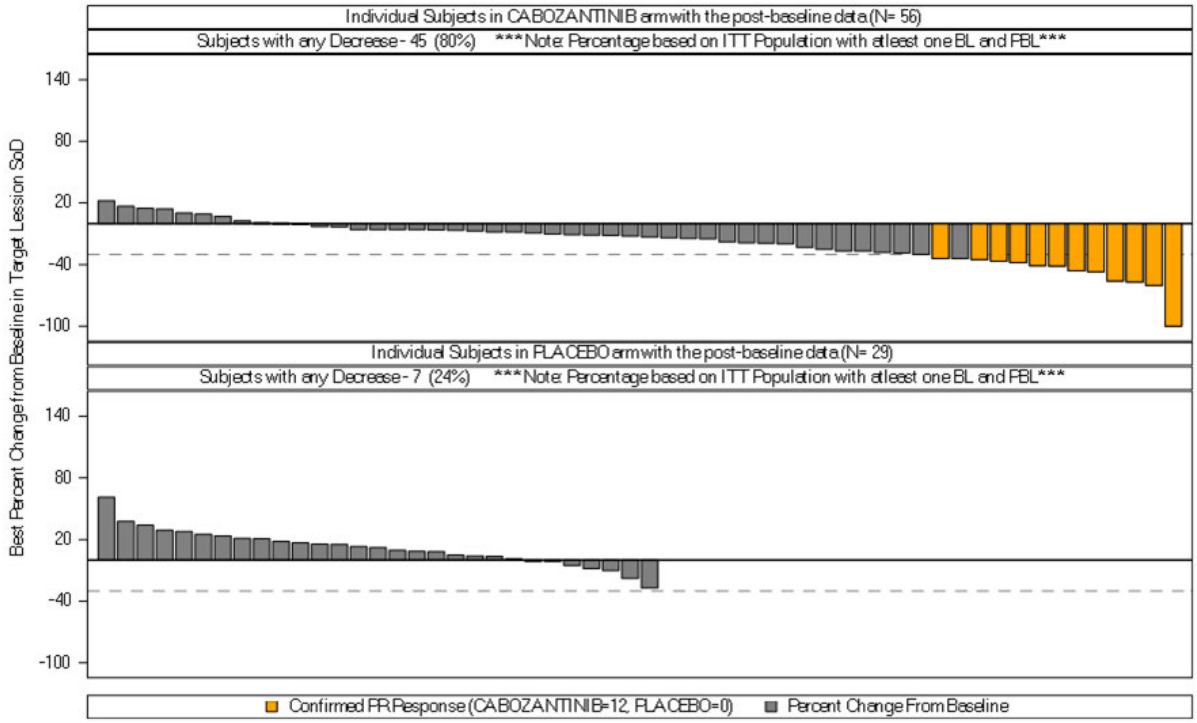
NA, not applicable
Source: FDA analysis of the Applicant's submitted data (adsl, adtte); DCO: 09/04/2024

In the USPI, the HR for OS (SA 2) by correctly classified patient cohort was reported. FDA's overall assessment of OS, based on the descriptive analyses, does not appear to indicate an OS detriment in patients treated with cabozantinib in pNET patients. These OS results should be interpreted with caution as the data were not fully mature and crossover may have impacted true characterization of treatment effect on the OS. Of the 31 patients in the placebo arm, 26% patients received crossover treatment only, 32% received other non-protocol anticancer therapy only, 13% received both, and 29% received none. A total of 53% of patients on the cabozantinib arm received other non-protocol anticancer therapy.

pNET Objective Response Rate per RECIST 1.1 by BIRC–Secondary Endpoint

As per the 24 August 2023 cutoff date, In the cabozantinib arm 12 subjects (19%) had a confirmed PR, giving a confirmed ORR of 19% (95% CI: 10.1%, 30.5%). No subject in the placebo arm had a confirmed response (ORR of 0%:95% CI: 0%, 11.2%). The difference in confirmed ORR was 18.8% (95% CI: 9.2%, 28.3%, p-value = 0.0115). The median time from randomization to confirmed response was 5.78 months (range: 2.8–8.7) in the cabozantinib arm The best percentage change in BIRC-assessed tumor target lesion size from baseline is shown in Applicant Figure 15. The proportion of subjects in the cabozantinib arm who had a postbaseline reduction in tumor target lesion size was higher than that observed in the placebo arm (80% vs 24%).

Applicant Figure 15: Study CABINET: pNET Waterfall Plot of Best Percentage Change in Sum of Tumor Target Lesions from Baseline by BIRC



BL, baseline; ITT, intent to treat; PBL, postbaseline; PR, partial response; SoD, sum of diameters
Source: CABINET CSR Figure 14.2.3.1.a; ADaM Datasets: ADSL,, ADTR, ADRS.

pNET Objective Response Rate by Investigator

In the cabozantinib arm, confirmed ORR was 7.8% (95% CI: 2.6%, 17.3%): 5 subjects (7.8%) had a confirmed PR. No subject in the placebo arm had either a CR or PR (ORR of 0.0% (95% CI:

0.0%, 11.2%). The treatment difference in confirmed ORR was 7.8% (95% CI: 1.2%, 14.4%; p-value = 0.1218).

The median time from randomization to confirmed objective response was 5.45 months (range: 3.0–6.2) for the 5 subjects with a confirmed objective response in the cabozantinib arm.

The proportion of subjects in the cabozantinib arm who had a postbaseline reduction in tumor size was higher than that observed in the placebo arm (87% vs 21%).

pNET Additional Endpoints

pNET Duration of Objective Response

Duration of Objective Response per BIRC

Of the 12 subjects in the cabozantinib arm who had a BIRC-assessed confirmedPR, 6 either had subsequent disease progression (n=5) or died (n=1). The Kaplan-Meier estimate of the median DOR, per BIRC, was 11.20 months (95% CI: 5.78, not estimable), and the 3-, 6-, and 12-month event-free rates were 100.0%, 88.9%, and 32.4%, respectively. No subject in the placebo arm had either a CR or PR.

Duration of Objective Response per Investigator

Of the 5 subjects in the cabozantinib arm who had an investigator-assessed confirmed PR, 4 had subsequent disease progression. The Kaplan-Meier estimate of median DOR, per the investigator, was 16.59 months (95% CI: 5.55, not estimable), and the 3-, 6- 12-, and 18-month event-free rates were 100.0%, 80.0%, 60.0%, and 30.0%, respectively. No subject in the placebo arm had a confirmed response.

pNET Disease Control Rate

Disease Control Rate by BIRC

The BIRC-assessed DCR was 80% (95% CI: 67.8%, 88.7%) in the cabozantinib arm and 55% (95% CI: 36.0%, 72.7%) in the placebo arm. The difference in DCR between treatment arms was 24.8% (95% CI: 4.7%, 44.9%).

Disease Control Rate by Investigator

The investigator-assessed DCR was 78% (95% CI: 66.0%, 87.5%) in the cabozantinib arm and 42% (95% CI: 24.5%, 60.9%) in the placebo arm. The difference in DCR between treatment arms was 36.2% (95% CI: 16.1%, 56.3%).

The Applicant's Position:

Analyses of OS gave a HR of 0.95 (95% CI: 0.45, 2.00; p = 0.8852) for the pNET cohort supporting no detriment. OS results are immature and confounded by crossover of placebo subjects to open label cabozantinib after progression (39% in the pNET cohort).

Efficacy is supported by the fact that objective responses were increased and were durable in cabozantinib treated subjects in both cohorts. ORR by BIRC in pNET showed an improved response with cabozantinib over placebo, with a treatment difference 18.8% (95% CI: 9.2%, 28.3%, p-value = 0.0115). Median duration of response with cabozantinib per BIRC was 11.20 months (95% CI: 5.78, NE) in pNET

The FDA's Assessment:

According to the SAP, ORR was not planned to be formally tested and will be considered descriptive only. In addition, given the small number of responders in both the cabozantinib and the placebo arm, it is challenging to interpret results of ORR and DOR. During the review, the Applicant assessed and updated the timing and completeness of subsequent anti-cancer therapy based on the same DCO of August 24, 2024 (Source: Response to FDA information request, dated February 7, 2025). This resulted in one additional patient in the cabozantinib arm in the pNET cohort being censored for initiation of non-protocol anti-cancer therapy before documented progression by the BIRC. Based on this updated data, the listing of BIRC assessed DOR results in pNET cohort, correcting for misclassified tumor type are provided in FDA Table 38. There were no responders observed in the placebo arm. In addition, FDA does not consider DCR as a regulatory endpoint. Results of these endpoints are considered exploratory only.

FDA Table 38. Listing of Duration of Response by BIRC in pNET Based on Correctly Classified Tumor Type

Duration of response (in months)	Event/censoring
11.2	PD
2.8	Censored
11.1	Censored
11.4	PD
2.7	Censored
6.1	PD
2.8	Censored
16.6	Censored
8.3	PD
8.3	Censored
15.8	Death
2.8	Censored

Source: FDA analysis of the Applicant's submitted data (adtte); DCO: 09/04/2024

For FDA comments regarding overall survival in pNET cohort, see FDA comments above under section **epNET Overall Survival –Secondary Endpoint.**

Dose/Dose Response

The Applicant's Position:

Cabozantinib tablets at a dose of 60 mg once daily has been extensively investigated in clinical trials and has been approved, as monotherapy, in the US and Europe for treatment of subjects with renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer. Further, this dose was evaluated in subjects with epNET (n=41) and pNET (n=20) in a Phase 2 study (Chan et al, 2017), which showed that treatment with cabozantinib was tolerated and associated with encouraging PFS and objective tumor responses, warranting further evaluation in subjects with epNET and pNET.

Thus in the CABINET trial, an assigned cabozantinib dose of 60 mg once daily was determined to be an effective dosing regimen for epNET and pNET subjects, while allowing for two protocol-specified levels of dose reduction (40 mg and 20 mg) to maximize individual subject tolerability

The FDA's Assessment:
Please refer to Section 6.2 for additional details regarding the FDA's analysis of dose/dose response.

Durability of Response

Data and The Applicant's Position:

epNET Cohort:

Of the 7 subjects in the cabozantinib arm who had a BIRC-assessed confirmed PR , 4 had subsequent disease progression, and 1 died. The Kaplan-Meier estimate of the median DOR, per BIRC, was 8.26 months (95% CI: 4.47, NE), and the 3-, 6-and 12-month event-free rates were 100.0%, 50.0% and 25.0% respectively. No subject in the placebo arm had either a CR or PR.

pNET Cohort:

Of the 12 subjects in the cabozantinib arm who had a BIRC-assessed confirmed PR, 6 either had subsequent disease progression (n=5) or died (n=1). The Kaplan-Meier estimate of the median DOR, per BIRC, was 11.20 months (95% CI: 5.78, not estimable), and the 3-, 6- and 12-month event-free rates were 100.0%, 88.9%, 32.4%, and NE, respectively (Source: Table 14.2.3.2a). No subject in the placebo arm had either a CR or PR.

The FDA's Assessment:

See FDA's Assessment under Sections on "Objective Response Rate per RECIST 1.1 by BIRC – Secondary Endpoint" for both epNET and pNET cohorts.

Persistence of Effect

The Applicant's Position:

In both the epNET and pNET cohorts, PFS per RECIST 1.1 by BIRC (primary endpoint) Kaplan-Meier curves separated early, and the observed benefits were consistent at 3, 6-, 12-, 18- and 24-month landmark estimates. Objective responses by BIRC were only seen with cabozantinib treatment and in addition, responses were durable with median DOR of 8.26 months (95% CI: 4.47, NE) in the epNET cohort and 11.20 months (95% CI: 5.78, NE) in the pNET cohort. At the time of the data cutoff, there were more subjects who were receiving blinded study treatment with cabozantinib (16% epNET and 22% pNET) versus placebo (10% epNET and 6.5% pNET).

The FDA's Assessment:
See FDA's Assessment under Sections on "Overall Survival – Secondary Endpoint" and "Objective Response Rate per RECIST 1.1 by BIRC – Secondary Endpoint" for both epNET and pNET cohorts.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
The Applicant's Position:

Not Applicable

The FDA's Assessment:
The FDA agrees.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not Applicable

The FDA's Assessment:
The FDA agrees.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
This application is supported by efficacy data from the randomized (2:1), double-blind, placebo-controlled trial CABINET evaluating cabozantinib in US patients with advanced, well-differentiated neuroendocrine tumors that have progressed after prior FDA-approved therapy. The primary evidence of effectiveness of cabozantinib in patients with epNETs and pNETs is the demonstration of a clinically meaningful and statistically significant improvement in PFS in the cabozantinib arm compared to the placebo arm in the respective cohorts.

Based on the study population with the corrected tumor classification according to EDC, the

median PFS (mPFS) by BIRC in the epNET cohort was 8.5 months (95% CI: 6.8, 12.5) for cabozantinib-treated patients compared to 4.2 months (95% CI: 3.0, 5.7) in patients receiving placebo. The PFS HR was 0.40 (95% CI: 0.26, 0.61) with a p-value of <0.0001 favoring the cabozantinib arm. In the pNET cohort, the mPFS by BIRC was 13.8 months (95% CI: 8.9, 17.0) in the cabozantinib arm versus 3.3 months (95% CI: 2.8, 5.7) in the placebo arm. The PFS HR was 0.22 (95% CI: 0.12, 0.41) with a p-value of <0.0001 favoring the cabozantinib arm. Subgroup analyses also suggest efficacy in patients regardless of disease characteristics including tumor origin and number of prior systemic therapies, as well as demographic factors including age, race, and sex.

Although CABINET was unblinded prior to reaching its originally planned number of PFS events, resulting in a low information fraction for PFS in the pNET cohort, the efficacy results from the epNET cohort were considered supportive of the PFS benefit observed in the pNET cohort due to the similarity of the disease in the pNET and epNET patient populations and the drug's proposed mechanism of action in NETs.

Updated overall survival results (DCO September 4, 2024) from the clinical trial obtained during review of the application were considered immature by the FDA with interpretability complicated by substantial crossover of patients from the placebo arm to open-label cabozantinib treatment; however, descriptive analyses appear to indicate that a detriment in OS was not observed in patients receiving cabozantinib.

Based on the review of clinical data from CABINET, the clinical and statistical review teams conclude that the Applicant provided substantial evidence of effectiveness of cabozantinib in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors that have progressed on prior FDA-approved therapy. Due to the similarity of these NETs in adolescents compared to adult patients, the mechanism of action of cabozantinib, and available weight-based modeling, the review team agrees with the inclusion of patients 12 years of age and older in the proposed indication.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Refer to the FDA's assessment in the "Integrated Review of Effectiveness".

Additional Efficacy Considerations

The FDA's Assessment:
The FDA has no additional comments.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Refer to the FDA's assessment in the "Integrated Review of Effectiveness".

8.2. Review of Safety

Data:

The primary support for the safety and benefit-risk profile for cabozantinib in this indication is data as of the cutoff date 24 August 2023 (date of study unblinding) from the CABINET Study (Alliance Study A021602; NCT03375320; Applicant Table 39).

Applicant Table 39: Clinical Study Data Contributing to the Summary of Clinical Safety (Safety Population)

Study (Phase)	Data cut-off	Study Title	Number of Subjects

A021602 (CABINET)
(Phase 3)
	24 August 2023	Randomized, Double-Blind Phase 3 Study of Cabozantinib (IND 137656) versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET)	epNET Cohort
			• 199 treated subjects
			  ○ 132 Cabozantinib 60 mg
			  ○ 67 Placebo
			pNET Cohort
			• 94 treated subjects
			  ○ 63 Cabozantinib 60 mg
			  ○ 31 Placebo

CSR, clinical study report; epNET, extra-pancreatic neuroendocrine tumor (carcinoid tumor); IND, Investigational New Drug; pNET, pancreatic neuroendocrine tumor

The Applicant's Position:

The safety database allowed for a comprehensive and adequate assessment of the safety profile of cabozantinib in this patient population. The safety of cabozantinib at the 60 mg dose has been well characterized and previously evaluated in NDA 208,692.

The FDA's Assessment:
The FDA agrees with the Sponsor's general presentation of the safety database and the data cutoff used for analyses. Refer to Sections 8.2.1 and 8.2.2 for the FDA's safety review.

8.2.1. Safety Review Approach

Data:

The safety evaluation relies solely on the safety data from the double-blinded, randomized, CABINET pivotal study. Safety data from all treated patients (cabozantinib or placebo) in the double-blind period of the is presented. Safety analyses were based on the randomized disease cohort (epNET or pNET). As previously agreed between the NCI/CTEP Alliance and the Agency selective safety information was collected for this study. The protocol-specified safety data collection practices are summarized below. A safety window of 30 days after last treatment dose was used for all treated subjects in each treatment group. AEs occurring more than 30 days after treatment discontinuation were only collected if they were possibly, probably, or definitely related to study treatment.

For each AE, attribution to protocol treatment and severity grading (per the Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) was performed. AEs (ie, verbatim terms) were mapped to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA; version 26.1). A treatment-emergent AE (TEAE) was defined as an AE observed on or after Cycle 1 or those collected on the late AE CRF. No comparison to AEs present at baseline was performed for evaluating whether or not an AE was treatment emergent. Related TEAEs were those AEs with an Investigator attribution of causality as possible, probable, or definite.

Alliance/NCI-CTEP Data Collection Procedures

For data collection and reporting of AEs the following standard procedures per Alliance/NCI-CTEP were employed:

- Certain AEs were considered "expected" (referred to as solicited events) and included the following: ALT/AST increased, diarrhea, fatigue, hyperglycemia, hypertension, hypothyroidism, mucositis oral, neutrophil count decreased, palmar-plantar erythrodysesthesia (PPE) syndrome, platelet count decreased, and rash maculo-papular. Solicited events were collected at baseline and each treatment cycle. Note: Grade 1 events that were not solicited, were not required to be reported.
- Safety assessments included laboratory tests (hematology, chemistry, and urinalysis), physical examinations (including vital sign measurements), ECOG performance status, and electrocardiogram (ECG) recordings. Laboratory abnormalities, vital signs, body weight, ECG readings, were not collected in the clinical database; clinically significant findings and solicited events were to be reported as AEs.

- Events that met the protocol definition of serious were submitted directly to the NCI-CTEP adverse events reporting system (AERS) by the Investigator. Expedited reporting was required for SAEs that occurred within 30 days of the last dose of study treatment. Specific protocol exceptions to expedited reporting (SPEER) stated that certain events only required expedited reporting if the outlined grade was exceeded (Protocol Table 6 [Appendix 16.1.1.1]). In addition, standard CTEP procedures allowed investigators to exercise clinical judgement and declare any event to be nonserious and therefore not requiring expedited reporting. Further, lower grade AEs (ie, Grade 1, 2, or 3) not resulting in hospitalization could also be reported as SAEs if these were important medical events at the discretion of the investigator.

Dose modifications (reductions or holds) were recorded on both the treatment intervention CRF and AE CRF; however, the AE CRF only captured one action taken for each AE (ie dose reduction or hold) per cycle resulting in a lower rate of dose modifications per AE CRF compared with the treatment intervention CRF.

Analysis of Events to Monitor for Cabozantinib

ETMs are a defined set of AEs which allow to collect events known to be associated with TKIs or VEGF pathway inhibition, that have potentially serious consequences, or warranted ongoing routine surveillance. These comprise gastrointestinal (GI) perforation, fistula, abscess all, intra-abdominal and pelvic abscess, ≥ Grade 3 hemorrhage, venous and mixed thrombotic events, arterial thrombotic events (ATE), wound complications, hypertension, osteonecrosis, palmar-plantar erythrodysesthesia (PPE), proteinuria, posterior reversible encephalopathy syndrome (PRES), diarrhea, and QT prolongation.

Treatment Categories/Pooling

The following treatment categories were defined for safety analyses:

Treatment Category	Description	epNET (N)	pNET (N)
Cabozantinib Only	Subjects randomized and treated with cabozantinib in the blinded phase of study	132	63
Placebo Only	Subjects randomized and treated with placebo during blinded phase of study	67	31
All Cabozantinib	All subjects treated with cabozantinib at any time, including crossover from placebo to open-label cabozantinib after progressive disease	154	75
Placebo Crossover to Cabozantinib	Subjects randomized and treated with placebo who crossed over from placebo to cabozantinib	22	12

epNET, extra-pancreatic neuroendocrine tumor (carcinoid tumor); pNET, pancreatic neuroendocrine tumor

Safety reports using these treatment categories were presented individually for each epNET and pNET cohort. For selected safety reports the information was pooled from both cohorts (pooled epNET + pNET double-blind and pooled epNET + pNET including crossover).

The Applicant's Position:

The safety review approach was considered comprehensive and adequate to identify and quantify the key differences in the safety profile between cabozantinib and placebo.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary safety data included in the submission. As noted by the Applicant, adverse events in CABINET were monitored and reported according to the protocol specified plan and as per Alliance standard procedures for clinical studies.

The following were captured as per study protocol:

- "Expected" adverse events that were solicited including decreased neutrophil and platelet count, increased ALT/AST, palmar-plantar erythrodysesthesia syndrome, maculo-papular rash, hyperglycemia, hypothyroidism, hypertension, fatigue, diarrhea, and oral mucositis;
- Grade ≥2 treatment-emergent adverse events (i.e., occurring up to 30 days after treatment discontinuation) regardless of attribution;
- Grade ≥2 AEs occurring later than 30 days after treatment discontinuation if at least possibly related to study treatment; and
- Clinically important laboratory values were reported as AEs/serious adverse events (SAEs).

Notably, not all Grade 1 AEs were recorded, and laboratory values were not captured in the case report form (CRF).

These data limitations were discussed with the FDA during the pre-sNDA meeting and were considered acceptable in the context of the well-studied safety profile of cabozantinib.

The FDA's safety review focused largely on data from patients treated with cabozantinib during the double-blinded portion of CABINET (DCO of August 24, 2023), although safety data were also considered from patients who crossed over from placebo to cabozantinib. The pooled safety population for the FDA's analysis consists of the 195 patients from the epNET (n=132) and pNET (n=63) cohorts who were initially randomized to treatment with cabozantinib at the study dose of 60 mg orally once daily.

The FDA's evaluation of safety included analysis of the submitted clinical study report, datasets, line listings, and electronic CRFS. Additionally, reports of serious adverse events (SAEs) and the reported adverse events of special interest (referred to as events to monitor or "ETMs" by the Applicant) were also reviewed.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Applicant Table 40: Study CABINET: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug (cabozantinib 60 mg or matching placebo) in this development program for the indication under review epNET Cohort N=199 pNET Cohort N=94 (N is the sum of all available numbers from the columns below)				
Cohorts	epNET		pNET	
Clinical Trial Groups	Cabozantinib	Placebo	Cabozantinib	Placebo
Controlled trials conducted for this indication (Study CABINET)[2]	132	67 (22)[3]	63	31 (12)[3]

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] number of patients noted in the paranthesis in the placebo arm are those who crossed over from placebo to open label cabozantinib after real time confirmation of PD.

The Applicant's Position:
The overall exposure to cabozantinib is considered adequate for the comprehensive assessment of comparison to placebo.

The FDA's Assessment:
The FDA agrees with the Sponsor's summary of overall exposure.

Using the DCO of August 24, 2023, a total of 195 patients in CABINET had received at least one dose of cabozantinib per randomization. Based on initial study assignment, the median duration of cabozantinib exposure in the epNET cohort was 5.4 months (range: 0.1 – 32.4) with a median average daily dose of 42.9 mg and median dose intensity of 71%. Dose reductions were reported for 66% of the 132 patients in this arm, and dose interruptions occurred in 83%.

In the pNET cohort, the median duration of cabozantinib exposure was 8.3 months (range: 0.1 – 37.8), and the median average daily dose was 41.4 mg and median dose intensity of 69%. Dose reductions were reported for 68% of the 63 patients in this arm, and dose interruptions occurred in 86%. Refer to subsection "Adequacy of the safety database" for additional details.

The FDA agrees that the overall exposure to cabozantinib in the epNET and pNET cohorts of CABINET permits an adequate assessment of the drug's safety profile in patients who are representative of the intended target population.

Relevant characteristics of the safety population:

Data:

Demographic characteristics of the study population were representative of the previously treated pNET and epNET patient population seen in clinical practice and were well balanced between treatment arms in both cohorts (Applicant Table 16 and Applicant Table 17).

The Applicant's Position:

The safety database includes a clearly defined population that is sufficiently diverse to adequately represent and characterize the safety profile in the target population.

The FDA's Assessment:
The FDA agrees with the Applicant's overview of the key demographic and baseline disease characteristics provided for the overall study population (n=298). The demographics and disease characteristics of the study population are representative of patients with advanced neuroendocrine tumors, fairly balanced between study arms in each cohort, and permit sufficient assessment of safety in the proposed indications. Refer to the FDA's assessment in Section 8.1.2 for additional details.

Adequacy of the safety database:

Data:

As of 24 August 2023, 293 subjects were treated (195 cabozantinib and 98 placebo) in this study, including 199 subjects in the epNET cohort and 94 subjects in the pNET cohort.

In the epNET cohort, the median duration of exposure (including dose holds) was 5.37 months (range: 0.1–32.4 months) in the cabozantinib arm and 2.79 months (range: 0.5-22.8 months) in the placebo arm (excluding crossover phase). The median average daily dose of cabozantinib was 42.86 mg, and the median dose intensity was 71.43%. Compliance with placebo tablets was 100%.

In the pNET cohort, the median duration of exposure (including dose holds) was 8.28 months (range: 0.1–37.8 months) in the cabozantinib arm and 2.86 months (range: 0.1 –11.2 months) in the placebo arm (excluding crossover phase). The median average daily dose of cabozantinib

was 41.36 mg, and the median dose intensity was 68.93%. Compliance with placebo tablets was > 99%.

In pooled epNET + pNET data including crossover, the median duration of exposure (including dose holds) for subjects who received cabozantinib was 5.49 months (range: 0.1 – 37.8 months) The median average daily dose of cabozantinib was 42.64 mg, and the median dose intensity was 71.06%.

The Applicant's Position:

The available safety database allows for an adequate assessment of the overall safety profile of cabozantinib in the intended population at the target dose.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the adequacy of the safety database to evaluate the safety profile of cabozantinib in patients with advanced, well-differentiated neuroendocrine tumors.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The study was conducted by the Alliance for Clinical Trials in Oncology ("Alliance"), a member of the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN). The Alliance is comprised of academic and community institutions and their affiliates which conduct cancer treatment and cancer control/prevention studies and related research according to their Policies and Procedures and in accordance with all applicable federal, state and local laws and regulations including, without limitation, FDA regulations and guidelines for GCP.

The Applicant's Position:

No meaningful concerns were observed in the quality and integrity of the submitted datasets and individual case narratives. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant.

The FDA's Assessment:
The FDA agrees with the Applicant's position. No meaningful concerns were identified in the quality and integrity of the submitted clinical study reports, datasets, and case report forms. The FDA was able to complete a comprehensive analysis of safety data. The NDA submission

contains all required components of the electronic common technical document (eCTD). See Section 8.1.2 "Data Quality and Integrity" for the FDA's assessment of overall data quality and integrity in this sNDA. Further, refer to Section 4.1 "Office of Scientific Investigation" for a summary of clinical site inspections.

Categorization of Adverse Event

Data:

Interpretation of the safety data must be in the setting of the study data collection methods. Laboratory abnormalities, vital signs, body weight, ECG readings, were not collected in the clinical database; however safety profile of cabozantinib has been well characterized. In this study, the safety profile observed with cabozantinib was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of AEs to study treatment
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs associated with study drug discontinuation, dose reduction, and/or study drug interruption , and ETMs.
- Fredquency and type of AE in key intrinsic and extrinsic factors (ie, age, race, ECOG PS, etc)

The Applicant's Position:

In general, the categorization of AEs was considered appropriate for evaluating the safety data in the targeted population.

The FDA's Assessment:

As noted in the clinical study report, safety in CABINET was assessed through capture of adverse events (AEs), including serious adverse events (SAEs) and deaths; laboratory tests; physician examinations, including vital sign measurements; ECOG performance status; and electrocardiogram recordings.

AEs were categorized by severity grading using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. and attribution to protocol treatment by the investigator from baseline through 30 days after the patient's last treatment date. AEs occurring more than 30 days after treatment discontinuation were recorded only if they were possibly, probably, or definitely related to study treatment. AEs were mapped to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA; version 26.1).

A treatment-emergent adverse event (TEAE) was defined as an adverse event observed on or

after Cycle 1 or those collected on the late AE CRF. No comparison to AEs present at baseline was performed for evaluating whether or not an AE was treatment-emergent, thus TEAEs included symptoms that could have been present at baseline.

As described in Section 8.2.1, certain AEs were considered "expected" (referred to as solicited events) by the Applicant and included known safety signals observed with cabozantinib treatment including hypertension, diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome. Additionally, the Applicant analyzed adverse events of special interest referred to as "ETMs" (events to monitor such as GI perforation, fistula, hemorrhage, thrombotic events, etc.) that are known to be associated with TKIs or VEGF pathway inhibition and may have serious consequences or warrant ongoing routine surveillance.

The FDA considers the Applicant's strategy for categorization of adverse event data to be acceptable.

Routine Clinical Tests

The Applicant's Position:
Not Applicable

The FDA's Assessment:
The CABINET protocol required the collection of routine clinical tests including laboratory monitoring (e.g., hematology and chemistry studies) and urine studies as specified in the study calendar. The FDA notes that additional assessments included electrocardiograms and routine physical examinations at study visits.

Overall, the frequency and scope of these routine clinical tests was considered adequate to assess the safety of cabozantinib in the proposed indications.

8.2.4. Safety Results

Data:

epNET Summary of Safety

In the epNET cohort, 199 subjects received study treatment (Safety population), 132 subjects in the cabozantinib arm and 67 subjects in the placebo arm. Seven subjects (4 randomized to cabozantinib and 3 randomized to placebo) had a diagnosis of pNET and were misallocated during registration to the epNET cohort. Summarized safety results for the 199 epNET subjects (Applicant Table 41) were reflective of known safety profile of cabozantinib as monotherapy to date.

Applicant Table 41: Study CABINET: epNET Summary of Adverse Events (Safety Population)

Safety Parameter	Cabozantinib N=132 n (%)	Placebo N=67 n (%)
Deaths and primary reason for death at any time during study[a]	58 (44)	25 (37)
Tumor (progressive disease)	35 (27)	13 (19)
Treatment-related[b]	0	0
Unknown	14 (11)	7 (10)
Other	9 (6.8)	5 (7.5)
Deaths ≤ 30 days after the date of last dose of study treatment	9 (6.8)	4 (6.0)
Tumor (progressive disease)	5 (3.8)	3 (4.5)
Treatment-related[b]	0	0
Unknown	2 (1.5)	0
Other[c]	2 (1.5)	1 (1.5)
Dose reductions due to an AE (all-causality)[d]	82 (62)	5 (7.5)
AEs leading to a dose hold (all-causality)[e]	106 (80)	25 (37)
AEs leading to a treatment discontinuation (all-causality)[e]	36 (27)	12 (18)

	ADVERSE EVENTS			
	All grades	Grade 3-4	All grades	Grade 3-4
All-causality SAEs	58 (44)	43 (33)	27 (40)	16 (24)
Treatment-related SAEs	38 (29)	26 (20)	14 (21)	10 (15)
All-causality AEs ≥ 20% in any treatment arm	132 (100)	89 (67)	67 (100)	27 (40)
Fatigue	95 (72)	19 (14)	38 (57)	6 (9.0)
AST increased	93 (70)	5 (3.8)	14 (21)	1 (1.5)
Diarrhoea	86 (65)	14 (11)	28 (42)	3 (4.5)
Hypertension	84 (64)	34 (26)	25 (37)	4 (6.0)
ALT increased	83 (63)	1 (0.8)	12 (18)	1 (1.5)
Platelet count decreased	68 (52)	2 (1.5)	8 (12)	1 (1.5)
Nausea	52 (39)	3 (2.3)	14 (21)	0

Safety Parameter	Cabozantinib N=132 n (%)		Placebo N=67 n (%)	
Stomatitis[f]	51 (39)	5 (3.8)	7 (10)	0
WBC count decreased	49 (37)	4 (3.0)	3 (4.5)	0
Neutrophil count decreased	45 (34)	4 (3.0)	4 (6.0)	0
PPE syndrome	45 (34)	4 (3.0)	4 (6.0)	0
Decreased appetite	44 (33)	2 (1.5)	10 (15)	1 (1.5)
Dysgeusia	43 (33)	0	1(1.5)	0
Hypothyroidism	41 (31)	0	2 (3.0)	0
Anaemia	39 (30)	3 (2.3)	13 (19)	0
Blood alkaline phosphatase increased	38 (29)	6 (4.5)	20 (30)	4 (6.0)
Hyperglycaemia	36 (27)	1 (0.8)	23 (34)	1 (1.5)
Lymphocyte count decreased	36 (27)	12 (9.1)	11 (16)	1 (1.5)
Weight decreased	36 (27)	6 (4.5)	5 (7.5)	0
Abdominal pain	34 (26)	11 (8.3)	27 (40)	4 (6.0)
Blood creatinine increased	31 (23)	0	8 (12)	1 (1.5)
Treatment-related AEs ≥ 20% in any treatment arm	130 (98)	78 (59)	56 (84)	17 (25)
AST increased	86 (65)	4 (3.0)	11 (16)	0
Fatigue	80 (61)	17 (13)	28 (42)	5 (7.5)
ALT increased	77 (58)	1 (0.8)	8 (12)	0
Diarrhoea	72 (55)	14 (11)	20 (30)	3 (4.5)
Hypertension	69 (52)	27 (20)	13 (19)	2 (3.0)
Platelet count decreased	58 (44)	1 (0.8)	5 (7.5)	1 (1.5)
Stomatitis[f]	48 (36)	5 (3.8)	6 (9.0)	0
Nausea	46 (35)	2 (1.5)	11 (16)	0
WBC count decreased	46 (35)	4 (3.0)	2 (3.0)	0
PPE syndrome	45 (34)	4 (3.0)	4 (6.0)	0
Dysgeusia	42 (32)	0	1 (1.5)	0
Decreased appetite	40 (30)	2 (1.5)	8 (12)	0
Neutrophil count decreased	38 (29)	4 (3.0)	2 (3.0)	0
Hypothyroidism	34 (26)	0	1 (1.5)	0

Safety Parameter	Cabozantinib N=132 n (%)		Placebo N=67 n (%)	
Lymphocyte count decreased	30 (23)	5 (3.8)	6 (9.0)	0
Anaemia	28 (21)	2 (1.5)	7 (10)	0
Weight decreased	28 (21)	3 (2.3)	3 (4.5)	0
Blood alkaline phosphatase increased	26 (20)	3 (2.3)	10 (15)	3 (4.5)
All-causality ETMs (group terms)[g,h]	110 (83)	48 (36)	34 (51)	13 (19)
Abscess	2 (1.5)	0	0	0
Arterial thromboembolic events	2 (1.5)	2 (1.5)	0	0
Fistula	1 (0.8)	0	0	0
GI perforation	1 (0.8)	1 (0.8)	0	0
Haemorrhage ≥ Grade 3[i]	2 (1.5)	1 (0.8)	1 (1.5)	1 (1.5)
Hepatotoxicity	6 (4.5)	3 (2.3)	1 (1.5)	0
Hypertension	85 (64)	35 (27)	25 (37)	4 (6.0)
Intra-abdominal and pelvic abscess	1 (0.8)	0	0	0
Osteonecrosis	4 (3.0)	1 (0.8)	0	0
PPE Syndrome	45 (34)	4 (3.0)	4 (6.0)	0
PRES (RPLS)	1 (0.8)	1 (0.8)	0	0
Proteinuria	11 (8.3)	0	3 (4.5)	0
QT Prolongation	12 (9.1)	7 (5.3)	5 (7.5)	5 (7.5)
Renal failure	1 (0.8)	1 (0.8)	2 (3.0)	2 (3.0)
Venous and Mixed Thromboembolic events	5 (3.8)	4 (3.0)	1 (1.5)	1 (1.5)
Wound complication	5 (3.8)	1 (0.8)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase CRF, case report form; ETM, event to monitor; PPE, palmar-plantar erythrodysaesthesia; PRES; posterior reversible encephalopathy syndrome; RPLS, reversible posterior leukoencephalopathy syndrome; SAE, serious adverse event
At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
Preferred terms in **bold** font are **solicited adverse events**.
[a] Deaths recorded on the patient status CRF.
[b] Investigators could only select a single primary reason for death on the patient status CRF but could attribute Grade 5 AEs as possibly or probably related to study treatment on the AE CRF. As such, related Grade 5 AEs were reported in the epNET cohort (4 subjects [3.0%] cabozantinib vs 1 subject [1.5%] placebo) but treatment-related deaths were not selected as a primary reason for death on the patient status CRF .

[c] The category of 'other' for deaths ≤ 30 days after the last dose of study treatment included multiorgan failure (1 subject) and respiratory failure due to metastatic tumor (1 subject) both in the cabozantinib arm. In the placebo arm 1 subject experienced cardiopulmonary arrest.
[d] The data presented for AEs leading to dose reductions were recorded on the treatment intervention CRF.
[e] The data presented for AEs leading to a dose hold or treatment discontinuation were recorded on the AE CRF.
[f] Equivalent to solicited term "mucositis oral" which was coded to stomatitis.
[g] Events to Monitor group terms are ordered alphabetically.
[h] Grade 5 ETMs were reported for 4 subjects (3.0%) in the cabozantinib arm under the PTs haemorrhage, hepatic failure, cardiac arrest, and sudden death (n=1 each). No Grade 5 ETMs were reported in the placebo arm.
[i] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.
Source: CABINET CSR Table Table 14.3.1.5.1.1.b, Table 14.3.1.5.6.1.b, Table 14.3.1.6.2.1.b, 14.3.1.15.1.1.b, Table 14.3.2.1.1.b.1, Table 14.3.2.1.3.1.b, Table 14.3.2.2.1.b, Table 14.3.1.1.5.b.1; ADaM Datasets: ADSL, ADAE, ADAEETM, ADEXSUM.

pNET Summary of Safety

A total of 94 subjects received study treatment (Safety population) were randomized, 63 to cabozantinib treatment and 31 to placebo. Three subjects (2 randomized to cabozantinib and 1 randomized to placebo) had a diagnosis of epNET and were misallocated during registration to the pNET cohort. Summarized safety results of the blinded treatment phase for the 94 subjects are presented in Applicant Table 42 and are reflective of the known safety profile of cabozantinib as monotherapy to date.

Applicant Table 42: Study CABINET: pNET Summary of Adverse Events (Safety Population)

Safety Parameter	Cabozantinib N=63 n (%)	Placebo N=31 n (%)
Deaths and reason for death at any time during the study[a]	21 (33)	8 (26)
Tumor (progressive disease)	15 (24)	5 (16)
Treatment-related	0	0
Unknown	5 (7.9)	2 (6.5)
Other	1 (1.6)	1 (3.2)
Deaths ≤ 30 days after the date of last dose of study treatment	1 (1.6)	0
Tumor (progressive disease)[b]	1 (1.6)	0
Treatment-related	0	0
Unknown	0	0
Other	0	0
Dose reductions due to an AE (all causality)[c]	42 (67)	4 (13)

Safety Parameter	Cabozantinib N=63 n (%)		Placebo N=31 n (%)	
AEs leading to a dose hold (all causality)[d]	52 (83)		13 (42)	
AEs leading to treatment discontinuation (all causality)[d]	12 (19)		3 (9.7)	
	ADVERSE EVENTS			
	All grades	Grade 3-4	All grades	Grade 3-4
All-causality SAEs	29 (46)	24 (38)	7 (23)	6 (19)
Treatment-related SAEs	23 (37)	18 (29)	2 (6.5)	2 (6.5)
All-causality AEs ≥ 20% in any treatment arm	63 (100)	46 (73)	31 (100)	14 (45)
Fatigue	50 (79)	9 (14)	19 (61)	2 (6.5)
AST increased	48 (76)	1 (1.6)	15 (48)	0
ALT increased	46 (73)	1 (1.6)	12 (39)	1 (3.2)
Diarrhoea	40 (63)	4 (6.3)	7 (23)	0
Hypertension	40 (63)	14 (22)	15 (48)	4 (13)
Stomatitis[e]	30 (48)	4 (6.3)	3 (9.7)	0
PPE syndrome	27 (43)	6 (9.5)	4 (13)	0
Nausea	24 (38)	5 (7.9)	10 (32)	1 (3.2)
Hyperglycaemia	21 (33)	2 (3.2)	13 (42)	1 (3.2)
Platelet count decreased	21 (33)	0	6 (19)	0
Dysgeusia	18 (29)	0	2 (6.5)	0
Anaemia	16 (25)	1 (1.6)	10 (32)	0
Hypophosphataemia	16 (25)	0	2 (6.5)	0
Vomiting	16 (25)	4 (6.3)	5 (16)	0
Decreased appetite	15 (24)	2 (3.2)	6 (19)	0
Dizziness	15 (24)	0	1 (3.2)	0
Abdominal pain	14 (22)	2 (3.2)	5 (16)	2 (6.5)
Lymphocyte count decreased	14 (22)	5 (7.9)	5 (16)	0
Neutrophil count decreased	14 (22)	1 (1.6)	2 (6.5)	0
Blood alkaline phosphatase increased	13 (21)	2 (3.2)	7 (23)	0

Safety Parameter	Cabozantinib N=63 n (%)		Placebo N=31 n (%)	
Blood thyroid stimulating hormone increased	13 (21)	0	0	0
Treatment-related AEs				
≥ 20% in any treatment arm	62 (98)	41 (65)	26 (84)	7 (23)
Fatigue	47 (75)	7 (11)	12 (39)	1 (3.2)
ALT increased	40 (63)	1 (1.6)	8 (26)	0
AST increased	40 (63)	1 (1.6)	8 (26)	0
Diarrhoea	37 (59)	4 (6.3)	3 (9.7)	0
Hypertension	34 (54)	12 (19)	7 (23)	3 (9.7)
Stomatitis[e]	29 (46)	4 (6.3)	2 (6.5)	0
PPE syndrome	27 (43)	6 (9.5)	3 (9.7)	0
Nausea	24 (38)	5 (7.9)	7 (23)	1 (3.2)
Platelet count decreased	19 (30)	0	3 (9.7)	0
Dysgeusia	18 (29)	0	2 (6.5)	0
Neutrophil count decreased	14 (22)	1 (1.6)	1 (3.2)	0
Blood alkaline phosphatase increased	13 (21)	0	2 (6.5)	0
Blood thyroid stimulating hormone increased	13 (21)	0	0	0
Hypophosphataemia	13 (21)	0	2 (6.5)	0
Vomiting	13 (21)	4 (6.3)	3 (9.7)	0
Anaemia	12 (19)	0	7 (23)	0
All-causality ETMs (group terms)[f]	54 (86)	31 (49)	19 (61)	6 (19)
Arterial thromboembolic events	1 (1.6)	1 (1.6)	0	0
Fistula	1 (1.6)	0	0	0
Haemorrhage ≥ Grade 3[g]	2 (3.2)	2 (3.2)	0	0
Hepatotoxicity	4 (6.3)	4 (6.3)	1 (3.2)	1 (3.2)
Hypertension	42 (67)	16 (25)	15 (48)	4 (13)
Osteonecrosis	2 (3.2)	0	0	0
PPE syndrome	27 (43)	6 (9.5)	4 (13)	0
Proteinuria	5 (7.9)	1 (1.6)	0	0

Safety Parameter	Cabozantinib N=63 n (%)		Placebo N=31 n (%)	
QT Prolongation	4 (6.3)	3 (4.8)	1 (3.2)	0
Renal failure	1 (1.6)	1 (1.6)	1 (3.2)	1 (3.2)
Venous and Mixed Thromboembolic events	12 (19)	7 (11)	1 (3.2)	0
Wound complication	1 (1.6)	0	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRF, case report form; ETM, event to monitor; pNET, pancreatic neuroendocrine tumor; PPE, palmar-plantar erythrodysaesthesia; SAE serious adverse event
MedDRA 26.1 was used for coding.
At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
Preferred terms in **bold** font are **solicited events**.
[a] Deaths recorded on the patient status CRF.
[b] A single death occurred in the cabozantinib arm of the pNET cohort due to tumor per the patient status CRF within 30 days of last dose but was not entered as a Grade 5 AE on the AE CRF.
[c] The data presented for AEs leading to dose reductions were recorded on the treatment intervention CRF
[d] The data presented for AEs leading to a dose hold or treatment discontinuation were recorded on the AE CRF.
[e] Equivalent to solicited term "mucositis oral" which was coded to stomatitis.
[f] Events to Monitor group terms or ordered alphabetically.
[g] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.
Source: CABINET CSR Table 14.3.1.5.1.1.a, Table 14.3.1.5.6.1.a, Table 14.3.1.6.2.1.a, Table 14.3.1.15.1.1.a, Table 14.3.2.1.1.a.1, Table 14.3.2.1.3.1.a, Table 14.3.2.2.1.a, Table 14.3.1.1.5.a.1;ADaM Datasets: ADSL, ADAE, ADAEETM, ADEXSUM.

Deaths

The Applicant's Position:

epNET Deaths

A total of 83 deaths were reported in the Safety population during the blinded treatment phase (58 [44%] in the cabozantinib arm, 25 [37%] in the placebo arm). Disease progression was the most common cause of death in both treatment arms (27% and 19% respectively) and most deaths occurred > 30 days after the last dose of study drug. There were 4 subjects, 3.0% versus 1 subject, 1.5% who experienced Grade 5 related AEs that occurred within 30 days of the last dose, respectively.

Nine subjects (6.8%) in the cabozantinib arm and 4 subjects (6.0%) in the placebo arm experienced a Grade 5 event ≤ 30 days after the last dose of study drug. Grade 5 events that occurred for > 1 subject were death (2 subjects [1.5%] cabozantinib) and disease progression (2 subjects [1.5%] cabozantinib, 2 subjects [3.0%] placebo).

On the AE CRF, there were 4 treatment-related Grade 5 AEs reported in the cabozantinib arm (cardiac arrest, death, GI hemorrhage, and sudden death) and 1 treatment-related Grade 5 event in the placebo arm (disease progression). For all four Grade 5 cases in the cabozantinib arm, the investigator also assessed tumor as an alternative cause of death.

pNET Deaths

A total of 29 deaths were reported in the Safety Population during the blinded treatment phase, 21 (33%) in the cabozantinib arm and 8 (26%) in the placebo arm. Disease progression was the most common cause of death in both treatment arms (24% and 16% respectively) and most deaths occurred > 30 days after the last dose of study drug.

There were no related Grade 5 AEs reported. One subject in the cabozantinib arm died within 30 days of last dose due to tumor (per the patient status CRF); this death was not recorded in the AE CRF.

Grade 5 Adverse Events within 30 days of Last Dose of Study Drug

epNET Cohort

In the epNET cohort, Grade 5 AEs were reported for 9 subjects (6.8%) in the cabozantinib arm and 4 subjects (6%) in the placebo arm. Grade 5 AEs that occurred for > 1 subject were death (2 subjects [1.5%] cabozantinib) and disease progression (2 subjects [1.5%] cabozantinib, 2 subjects [3.0%] placebo). Grade 5 AEs considered related to study drug by the Investigator occurred for 4 subjects (3.0%) in the cabozantinib arm and 1 subject (1.5%) in the placebo arm who crossed over to open-label cabozantinib treatment. Treatment-related Grade 5 AEs were cardiac arrest, death, GI hemorrhage, and sudden death in the cabozantinib arm, and disease progression in the placebo arm.

pNET Cohort

In the pNET cohort, no subjects had a Grade 5 AE. However, one subject in the cabozantinib arm died due to tumor (per the patient status CRF) after study drug discontinuation; this death was not recorded in the AE CRF.

The FDA's Assessment:

Summary of Safety

An overview of the FDA's analysis of treatment-emergent adverse events and dose modification or drug discontinuation occurring during the blinded study period (DCO August 24, 2023) is shown below in FDA Table 43. As anticipated, the frequencies of adverse events and their severity are higher in the cabozantinib-treated patients than patients receiving placebo; however, the rates of higher grade AEs and SAEs are notable for patients in the placebo arm at 46% and 35%, respectively. With the exception of Grade 5 events, which were notably higher in

the epNET cohort, the rates of higher grade AEs and SAEs were closely matched between the cabozantinib arms of both cohorts. For further details regarding FDA's assessment of adverse event data reported in CABINET, refer to the subsection "Treatment-emergent Adverse Events and Adverse Reactions" further below in this review.

Similarly, dose modification or discontinuation occurred at notably higher rates in the cabozantinib-treated patients, although dose interruptions were fairly common (40%) in placebo treated patients as well.

FDA Table 43: Overview of TEAEs and Dose Modification or Drug Discontinuation

	epNET Cabozantinib N=132 n (%)	epNET Placebo N=67 n (%)	pNET Cabozantinib N=63 n (%)	pNET Placebo N=31 n (%)	Combined Cabozantinib N=195 n (%)	Combined Placebo N=98 n (%)
Incidence of TEAEs, n (%)						
Any TEAE	132 (100)	67 (100)	63 (100)	31 (100)	195 (100)	98 (100)
Grade ≥3	98 (74)	31 (46)	46 (73)	14 (45)	144 (74)	45 (46)
Serious TEAEs	58 (44)	27 (40)	29 (46)	7 (23)	87 (45)	34 (35)
Grade 5 (including PD)	9 (6.8)	4 (6)	1 (1.6)	0	11 (5.6)	4 (4.1)
TEAEs Leading to Dose Modification or Discontinuation, n (%)						
Dose reduction	50 (38)	4 (6)	31 (49)	5 (16)	81 (42)	9 (9)
Dose interruption	107 (81)	26 (39)	52 (83)	13 (42)	159 (82)	39 (40)
Discontinuation	37 (28)	13 (19)	12 (19)	3 (10)	49 (25)	16 (16)

Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

Acknowledging the limitations of cross-trial comparisons, patients treated with cabozantinib for other cancer indications in clinical studies, as documented in the drug label, also experienced frequent adverse events and exhibited similar rates of dose interruption, reduction and drug discontinuation.

Death Analysis

The FDA agrees with the Applicant's general overview of deaths as presented in Applicant Table 41 and Applicant Table 42. The majority of deaths in CABINET were attributed to progressive disease and most occurred greater than 30 days after the last dose of study drug.

Per the FDA's analysis, there were 15 treatment-emergent deaths in total that occurred during the blinded portion of the study (DCO August 24, 2023), as shown in FDA Table 44 below. In the epNET cohort, there were eight deaths reported as Grade 5 adverse events (including causes of death that were not otherwise specified), with seven deaths occurring in the cabozantinib arm and 1 in the placebo arm. The remainder of deaths in the epNET cohort were due to disease progression. In the pNET cohort, there was a single treatment-emergent death due to progressive disease in the cabozantinib arm, with no deaths occurring in the placebo arm.

FDA Table 44: Analysis of Deaths Within 30 Days of Study Drug During the Blinded Study Period

	epNET Cabozantinib N=132 n (%)	**epNET Placebo N=67 n (%)**	**pNET Cabozantinib N=63 n (%)**	**pNET Placebo N=31 n (%)**
Within 30 days after last dose	9 (6.8)	4 (6)	1 (1.6)	0
Due to progressive disease	2 (1.5)	3 (4.4)	1 (1.6)	0
Due to adverse event	7* (5.3)	1** (1.5)	0	0

Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26
*Two treatment-emergent deaths in the epNET cabozantinib arm were reported as "sudden death" and "death"
**This patient's Grade 5 adverse event was reported as "death"

The FDA examined causes of death for study patients based on death narratives submitted by the Applicant. An overview of treatment-emergent deaths due to a cause other than malignant disease in patients treated with cabozantinib and occurring during the blinded study period is summarized in FDA Table 45 below, followed by brief summaries of narratives for these patients. In general, these deaths were attributable or at least possibly related to cabozantinib treatment as several fatal adverse events are known adverse reactions to the drug.

FDA Table 45: Overview of Treatment-Emergent Deaths (Excluding Disease Progression) in Cabozantinib-Treated Patients

Study Arm	Subject ID	Age/Gender	Study Day of Death	Grade 5 AE	FDA Assessment of Relatedness to Study Drug
epNET/Cabo	(b) (6)	77 yo M	31	Ruptured ascending aortic aneurysm	Yes
epNET/Cabo		66 yo M	31	Sudden death	Possibly
epNET/Cabo		54 yo F	343	Death	No
epNET/Cabo		57 yo M	561	Hepatic failure	Possibly
epNET/Cabo		75 yo M	303	Multiple organ dysfunction syndrome	Possibly
epNET/Cabo		80 yo M	28	Gastrointestinal hemorrhage	Yes
epNET/Cabo		73 yo F	167	Cardiac arrest	Possibly

Patient (b) (6) was a 77-year-old male with epNET (primary tumor site: jejunum) who died on study day 31 (0 days after receiving last dose of cabozantinib). He had widely metastatic disease to lymph nodes, liver and bone, and was previously treated with everolimus and Lu-177 dotatate. He had a history of hypertension and a prior thromboembolic event. The patient was found collapsed by his spouse and was originally reported to have a Grade 5 event of "death NOS" that was later revised by the Applicant to "ruptured ascending aortic aneurysm" when additional information was obtained.

FDA Reviewer Comment: The reviewer attributes this death to cabozantinib as labeled adverse reactions include "arterial (including aortic) aneurysms, dissections and rupture" per postmarketing experience, and hemorrhage which is a warning.

Patient (b) (6) was a 66-year-old male with epNET (primary tumor site: rectum) and liver metastases who died on study day 31 (3 days after receiving last dose of cabozantinib). He had been previously treated with everolimus, Lu-177 dotatate, and sunitinib malate. The patient's medical history was notable for hypertension, Type 2 diabetes mellitus, hyperlipidemia and smoking. The patient was found "slumped over in his bathroom" with no signs of homicide or suicide. The exact cause of death was unknown. An autopsy was not performed. The patient was reported to have a Grade 5 event of "sudden death NOS".

FDA Reviewer Comment: The reviewer considers this death to be possibly related to cabozantinib given the inability to ascribe the death to a cause unrelated to the drug.

Patient (b) (6) was a 54-year-old female with epNET (primary tumor site: ileum) who died on study day 343 (29 days after receiving last dose of cabozantinib). The patient had extensive metastases to the lymph nodes, liver, bone, spleen and pelvis. She had previously been treated with everolimus, Lu-177 dotatate, and chemotherapy (capecitabine and temozolomide). On study day 314, the patient's cabozantinib was discontinued due to progressive disease. Two weeks later, the patient was admitted to the hospital for Grade 3 hepatic failure and Grade 3 sepsis, and diagnosed with a Grade 3 urinary tract infection and Grade 3 encephalopathy. The patient recovered from these medical issues, and was later hospitalized again for Grade 4 hepatic failure and Grade 3 dehydration requiring intervention. The patient subsequently died due to an unknown cause. An autopsy was not performed.

FDA Reviewer Comment: The cause of death was not known; however, the case narrative provided is supportive of death likely due to disease progression.

Patient (b) (6) was a 57-year-old male with epNET (primary tumor site: ileum) and lymph node and liver metastases who died on study day 561 (27 days after receiving last dose of cabozantinib). He was previously treated with everolimus and Lu-177 dotatate and had a medical history of hypertension. Ten days prior to his death, the patient was noted to have hepatic failure in the context of disease progression. He was subsequently transferred to hospice care, and 5 days later was reported to have a Grade 5 event of "hepatic failure". An autopsy was not performed.

FDA Reviewer Comment: Although the reviewer considers this death to be likely related to worsening of underlying disease, possible attribution to cabozantinib cannot be ruled out as hepatotoxicity is a known adverse reaction.

Patient (b) (6) was a 75-year-old male with epNET (primary tumor site: ileum) and lymph node and liver metastases who died on study day 303 (7 days after receiving last dose of cabozantinib). He was previously treated with everolimus, Lu-177 dotatate, and octreotide, and had a medical history of hypotension. The week before his death, the patient experienced a Grade 3 fall due to syncope and was hospitalized for surgery due to an injury sustained to his right lower extremity. While hospitalized, he experienced fainting episodes, abdominal pain, and began to decline clinically. A CT scan performed showed concern for bowel ischemia likely causing septic shock. The patient ultimately died from "multiple organ dysfunction syndrome".

FDA Reviewer Comment: The patient's death is likely due to the underlying event of bowel ischemia. Although bowel ischemia is also a potential sequelae of small bowel neuroendocrine tumor, it is also an adverse event that has been reported in patients treated with cabozantinib; therefore, the role of cabozantinib in this patient's death cannot be ruled out.

Patient (b) (6) was an 80-year-old male with epNET (primary tumor site: unknown) who died on study day 28 (8 days after receiving last dose of cabozantinib). He had widely metastatic disease to the lymph node, liver, abdominal wall, brain, and lungs, and was previously treated with everolimus and chemotherapy (capecitabine and temozolomide). On study day 23, the patient was hospitalized for Grade 3 pulmonary embolism and was started on anticoagulation treatment. His heparin drip was temporarily held for possible thoracentesis for a large pleural effusion; however, the patient developed sudden onset of blurred vision and was noted to have multiple cerebral infarcts from embolic processes, prompting restarting of the heparin drip. The patient later developed progressive shortness of breath and experienced hematemesis with a suspected upper GI bleed, requiring intubation. Due to the patient's poor premorbid condition, the family decided to withdraw care. The patient eventually died from a large bleed reported as a Grade 5 event of "gastrointestinal hemorrhage" and resultant shock. An autopsy was not performed.

FDA Reviewer Comment: The reviewer attributes this death to cabozantinib as hemorrhage, including gastrointestinal bleeding, is an established safety signal that is labeled. Cabozantinib is also likely to have contributed to the patient's intercurrent thrombotic events of pulmonary embolism and stroke.

Patient (b) (6) was a 73-year-old female with epNET (primary tumor site: ileum) who died on study day 167 (14 days after receiving last dose of cabozantinib). She had widely metastatic disease to the lymph nodes, liver, brain, and lungs, and was previously treated with everolimus and Lu-177 dotatate. On study day 161, the patient was hospitalized for Grade 3 abdominal pain and Grade 3 generalized muscle weakness. During the hospitalization, she experienced two episodes of bradycardia and syncope, requiring intubation. The patient was being evaluated for a pacemaker possibly due to tachycardia/bradycardia syndrome, and subsequently went into atrial fibrillation and experienced cardiac arrest. An autopsy was not performed.

FDA Reviewer Comment: Possible attribution of this patient's death to cabozantinib cannot be ruled out as cardiac dysfunction has been reported as a rare adverse event in patients treated with cabozantinib.

Additionally, the FDA reviewed treatment-emergent deaths in patients who crossed over from placebo to open-label treatment with cabozantinib following confirmed disease progression. This analysis was notable for a 79-year-old patient (ID (b) (6)) with epNET (primary tumor site of the lung) and metastases to the liver and CNS who had a Grade 5 event of intestinal perforation approximately 28 days into his cabozantinib course. This patient's death is likely attributed to cabozantinib given the temporality and that bowel perforation is a known safety signal associated with the drug.

Serious Adverse Events

Data:

Frequently reported SAEs regardless of causality that occurred during the Standard Safety Observation Period (within 30 days of last dose) are presented for the epNET cohort (Applicant Table 46), for the pNET cohort (Applicant Table 47).

epNET:

SAEs were collected per NCI CTEP/Alliance standards. SAEs that were reported for 44% of subjects in the cabozantinib arm and 40% of subjects in the placebo arm: hypertension (6.1% cabozantinib, 1.5% placebo), abdominal pain (5.3% vs 6.0%), diarrhea (3.0%, 4.5%), and vomiting (3.0% in both treatment arms) were the most frequently reported SAEs.

Related SAEs were reported in 29% and 21% of subjects in the cabozantinib and placebo arms, respectively: hypertension (6.1% cabozantinib, 0% placebo) was the most frequently reported treatment-related SAE.

Applicant Table 46: Study CABINET: Serious Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Arm (epNET; Double-Blind)

Preferred Term	Cabozantinib Only (N = 132) n (%)	Placebo (N = 67) n (%)
Number of Subjects With at Least One Event	58 (44)	27 (40)
Hypertension	8 (6.1)	1 (1.5)
Abdominal pain	7 (5.3)	4 (6.0)
Diarrhoea	4 (3.0)	3 (4.5)
Vomiting	4 (3.0)	2 (3.0)
Anaemia	3 (2.3)	0
Back pain	3 (2.3)	1 (1.5)
Blood bilirubin increased	3 (2.3)	2 (3.0)
Fatigue	3 (2.3)	3 (4.5)
Muscular weakness	3 (2.3)	0
Nausea	3 (2.3)	2 (3.0)
Pulmonary embolism	3 (2.3)	1 (1.5)
Sepsis	3 (2.3)	0
Syncope	3 (2.3)	3 (4.5)
Disease progression	2 (1.5)	2 (3.0)

Preferred Term	Cabozantinib Only (N = 132) n (%)	Placebo (N = 67) n (%)
Dyspnoea	2 (1.5)	3 (4.5)
Acute kidney injury	1 (0.8)	2 (3.0)
Hyperglycemia	1 (0.8)	2 (3.0)
Hypokalemia	1 (0.8)	2 (3.0)
Small intestinal obstruction	1 (0.8)	2 (3.0)

epNET, extra-pancreatic neuroendocrine tumor
Note: MedDRA 26.1 was used for coding.
Note: Preferred terms in **bold** font are solicited events.
Source: CABINET CSR Table 14.3.2.1.3.1.b; ADaM Datasets: ADSL, ADAE.

pNET:

SAEs were collected per NCI CTEP/Alliance standards. SAEs were reported in 46% of subjects in the cabozantinib arm compared with 23% in the placebo arm: Frequently reported SAEs were vomiting (6.3% cabozantinib, 0% placebo), embolism, hypoxia, and nausea (each reported for 4.8% of subjects in the cabozantinib arm and no subject in the placebo arm), and small intestinal obstruction (1.6% cabozantinib, 9.7% placebo).

Related SAEs were reported in for 37% of subjects in the cabozantinib arm and 6.5% of subjects in the placebo arm: vomiting (6.3% cabozantinib, 0% placebo) was the most frequently reported treatment-related SAE.

Applicant Table 47: Study CABINET: Serious Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Arm (pNET; Double-Blind)

Preferred Term	Cabozantinib Only (N = 63) n (%)	Placebo (N = 31) n (%)
Number of Subjects With at Least One Event	29 (46)	7 (23)
Vomiting	4 (6.3)	0
Embolism	3 (4.8)	0
Hypoxia	3 (4.8)	0
Nausea	3 (4.8)	0
Sepsis	3 (4.8)	0
Abdominal pain	2 (3.2)	1 (3,2)
Blood bilirubin increased	2 (3.2)	0
Fatigue	2 (3.2)	0

Preferred Term	**Cabozantinib Only (N = 63) n (%)**	**Placebo (N = 31) n (%)**
Hyperkalemia	2 (3.2)	0
Hypertension	2 (3.2)	0
Pulmonary embolism	2 (3.2)	0
Acute kidney injury	1 (1.6)	1 (3.2)
Hepatic failure	1 (1.6)	1 (3.2)
Small intestinal obstruction	1 (1.6)	3 (9.7)
Cholangitis	0	2 (6.5)
Craniotomy	0	1 (3.2)

pNET, pancreatic neuroendocrine tumor
Note: MedDRA 26.1 was used for coding.
Note: Preferred terms in **bold** font are solicited events.
Source: CABINET CSR Table 14.3.2.1.3.1.a; ADaM Datasets: ADSL, ADAE.

The Applicant's Position:

While the number of SAEs were higher for the cabozantinib arms, the SAE reporting procedures for this study allowed reporting of lower grade events at the discretion of the Investigator. In addition, subjects were heavily pretreated and had high tumor burden. Also, the study included subjects with functional NETs who are known to have significant symptom burden. Therefore, rates of AEs and dose modifications in the cabozantinib arm should be viewed in the context of the increased event rates on the placebo arm. Of note, dose holds were common in the subjects randomized to placebo, suggesting the subject population under study had significant co-morbidity associated with advanced neuroendocrine disease.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of SAE data for both the epNET and pNET cohorts. The FDA concurs that SAEs were more frequent in patients treated with cabozantinib and acknowledges that the SAE rate of 23-40% in the placebo arms likely reflects the advanced nature of patients' heavily pretreated disease. Additional clinically significant SAEs occurring <2% in patients treated with cabozantinib included events of hemorrhage, cerebrovascular accident, intestinal obstruction, cardiac arrest, and posterior reversible encephalopathy syndrome (PRES).

Based upon review of SAE reports, the FDA considers many of the SAEs to be related to cabozantinib exposure (e.g., thromboembolic events, hypertension, hepatic failure are known side effects) or potentially attributable to the underlying disease (e.g., possible complications of epNETs include bowel obstruction). No new safety signals were identified.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

epNET:

The data presented for treatment discontinuations were recorded on the AE CRF.

Study treatment was discontinued due to an AE for 27% of subjects in the cabozantinib arm and 18% of subjects in the placebo arm. AEs that led to treatment discontinuation were considered by the investigator as related to treatment for 26% of subjects in the cabozantinib arm and 12% of subjects in the placebo arm. In the cabozantinib arm, AEs leading to treatment discontinuation that were reported for ≥ 3.0% of subjects were diarrhea (4.5%), fatigue (3.8%), and AST increased (3.0%); these AEs were also most frequently considered related to treatment. In the placebo arm, AEs leading to treatment discontinuation that were reported for > 1 subject were diarrhea (4.5%), abdominal pain (3.0%), and memory impairment (3.0%); these AEs were also most frequently considered related to treatment.

pNET:

The data presented for treatment discontinuations were recorded on the AE CRF.

Study treatment was discontinued due to an AE for 19% of subjects in the cabozantinib arm and 9.7% of subjects in the placebo arm. Related AEs leading to treatment discontinuation were reported in 14% and 3.2% of subjects, respectively. AEs leading to treatment discontinuation that were reported for > 1 subject were pulmonary embolism (3.2% [also considered treatment related]) in the cabozantinib arm and fatigue (6.5% [considered related for 3.2% of subjects]) in the placebo arm.

The Applicant's Position:

The frequency of all causality AEs and treatment discontinuations due to AEs were higher with cabozantinib compared with placebo treatment. Although the frequency of treatment discontinuation was higher with cabozantinib, there was a notable frequency of treatment-related AEs and treatment discontinuation due to investigator-assessed treatment-related AEs in the placebo arm, which indicates the study included a highly symptomatic NET population.

The FDA's Assessment:

The FDA agrees with the rate of discontinuation due to an adverse reaction cited by the Applicant for the pNET cohort (19%) and notes a minor discrepancy in the rate stated for the epNET cohort, which per the FDA's analysis was 28% (not 27%). The FDA also notes that the overall rate of drug discontinuation in the cabozantinib-treated patients (n=195) was 25%, compared to 16% in the placebo-treated patients (n=98), underscoring the level of morbidity of the CABINET study population.

Additional adverse reactions that resulted in permanent discontinuation of cabozantinib in the pNET cohort included acute kidney injury, rash, dyspnea, fistulas, hemorrhage, cardiac arrest, musculoskeletal pain, COVID-19 infection, Cushing's syndrome, pneumonia, proteinuria, and myocardial infarction. Additional adverse reactions that resulted in permanent discontinuation of cabozantinib in the epNET cohort included increased ALT, blood bilirubin increased, rash, thromboembolic events, hypertension, increased ALP, nausea and stomatitis. Most of the aforementioned adverse reactions have been observed with cabozantinib treatment and are described in the drug label. No new safety signals were identified.

Dose Interruption/Reduction Due to Adverse Effects

Data:

epNET:

The data presented for AEs leading to dose modifications were recorded on the AE CRF.

Adverse events led to a dose reduction for 38% of subjects in the cabozantinib arm and 6% of subjects in the placebo arm. In the cabozantinib arm, the most frequently reported AEs that led to a dose reduction were solicited AEs: PPE syndrome (9.8% of subjects), diarrhea (7.6%), and fatigue (7.6%). In the placebo arm, fatigue (4.5%) was the only AE that led to a dose reduction for > 1 subject.

Adverse events that led to a dose hold were reported for 80% of subjects in the cabozantinib arm and 37% of subjects in the placebo arm. In the cabozantinib arm, the most frequently reported AEs that led to a dose hold were solicited AEs: fatigue (21% of subject), diarrhea (20%), and PPE syndrome (17%). In the placebo arm, blood bilirubin increased (7.5%) and dyspnea (6.0%) were the most frequently reported AEs that led to a dose hold.

Adverse events led to a dose modification (reduction or hold) for 86% of subjects in the cabozantinib arm and 40% of subjects in the placebo arm. In both the cabozantinib and placebo arms, the most frequently reported AEs that led to a dose modification were solicited AEs: fatigue (25% cabozantinib, 7.5% placebo) and diarrhea (23% cabozantinib, 6.0% placebo). These were followed in the cabozantinib arm by the solicited AE of PPE syndrome (20% vs 0% placebo). In the placebo arm, other frequently reported AEs that led to a dose modification were blood bilirubin increased (7.5%), abdominal pain (6.0%) and dyspnea (6.0%)

pNET:

The data presented for AEs leading to dose modifications were recorded on the AE CRF.

Adverse events led to a dose reduction for 49% of subjects in the cabozantinib arm and 16% of subjects in the placebo arm. In the cabozantinib arm, the most frequently reported AEs that led to a dose reduction were solicited AEs: PPE syndrome (19% of subjects), fatigue (14%), hypertension (7.9%), and stomatitis (7.9%). In the placebo arm, fatigue (9.7%) was the only AE that led to a dose reduction for > 1 subject.

In the pNET cohort, AEs that led to a dose hold were reported for 83% of subjects in the cabozantinib arm and 42% of subjects in the placebo arm. In the cabozantinib arm, the most frequently reported AEs that led to a dose hold were the same solicited AEs as those reported for epNET: PPE syndrome (21% of subjects), diarrhea (17%), and fatigue (16%). In the placebo arm, small intestinal obstruction (9.7%), fatigue (6.5%), and nausea (6.5%) were the only AEs that led to a dose hold for > 1 subject.

In the pNET cohort, AEs led to a dose modification for 89% of subjects in the cabozantinib arm and 52% of subjects in the placebo arm. In the cabozantinib arm, the most frequently reported AEs that led to a dose modification were PPE syndrome (27% of subjects), fatigue (25%), diarrhea (19%), and hypertension (16%). In the placebo arm, the most frequently reported AEs that led to a dose modification were fatigue (13%) and small intestinal obstruction (9.7%).

The Applicant's Position:

epNET and pNET:

The incidence of AEs leading to dose interruption, dose reduction or dose modification (interruption or reduction) were higher in the cabozantinib arm relative to placebo. However, dose modification rates were similar to that observed in other cabozantinib monotherapy studies. Although the frequency of dose modifications was higher with cabozantinib, there was a notable frequency of modifications in the placebo arm, which indicates the study included a highly symptomatic NET population.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of dose interruption and reduction in CABINET, including the most frequent adverse reactions that led to dose modification, with minor discrepancies in some rates as noted.

In the epNET cohort, per the FDA's analysis dose interruptions due to adverse reaction occurred in 81% (not 80%) of patients in the cabozantinib arm and 39% (not 37%) of patients in the placebo. Additionally, diarrhea led to dose interruption in 21% (not 20%) of cabozantinib-treated patients. Hypertension was another clinically significant adverse reaction that required dose reduction in ≥5% of patients in the cabozantinib arm.

In the pNET cohort, the FDA notes additional adverse reactions that resulted in dose interruption ≥5% of patients in the cabozantinib arm, beyond those mentioned by the Applicant, include thromboembolic events, nausea, hypertension, increased ALT, blood bilirubin increased, musculoskeletal pain, stomatitis, vomiting and increased AST.

As stated by the Applicant, the frequency of dose modification (interruption or reduction) was higher in cabozantinib-treated patients relative to patients receiving placebo; however, the rate

of dose interruption in the placebo arms (n=98) was substantial at 40%, indicating the symptom and disease burden of those enrolled in the study.

Significant Adverse Events

Data:
Events to Monitor

A set of Events to Monitor (ETM) known to be associated with tyrosine kinase inhibitors (TKIs) or vascular endothelial growth factor (VEGF) pathway inhibition, that have potentially serious consequences, or warranted ongoing routine surveillance were analyzed. These comprise GI perforation, fistula, abscess–all, intra-abdominal and pelvic abscess, ≥ Grade 3 hemorrhage, venous and mixed thrombotic events, arterial thrombotic events (ATE), wound complications, hypertension, osteonecrosis, PPE, proteinuria, posterior reversible encephalopathy syndrome (PRES) (reversible posterior leukoencephalopathy syndrome [RPLS]), diarrhea, and QT prolongation.

epNET:

ETMs were reported for 83% of subjects in the cabozantinib arm. By grouped term and preferred term, hypertension was the most frequently reported ETM (64%). Other frequently reported grouped terms were PPE syndrome (34%), and QT prolongation (9.1%).

Grade 3/4 ETMs were reported for 36% of subjects in the cabozantinib arm and most frequently included the ETM grouped term of hypertension (27%).

Grade 4 ETMs were only reported in the cabozantinib arm (4 subjects [3.0%]) and included the following grouped terms: arterial thromboembolic events (1 subject [0.8%] who had both an acute myocardial infarction and coronary artery occlusion), hepatotoxicity (1 subject [0.8%] with hepatic failure); QT prolongation (1 subject [0.8%] who had both a cardiac arrest and torsades de pointes); and venous and mixed thromboembolic events (2 subjects [1.5%]: 1 with a cerebrovascular accident and 1 with a pulmonary embolism).

Grade 5 ETMs were only reported in the cabozantinib arm (4 subjects [3.0%]). Grade 5 ETMs consisted of the following events (PTs): GI hemorrhage, hepatic failure, cardiac arrest, and sudden death (1 subject each).

pNET:

ETMs were reported for 86% of subjects in the cabozantinib arm and 61% of subjects in the placebo arm. By grouped term and preferred term, hypertension was the most frequently reported ETM in both treatment arms (grouped term: 67% cabozantinib, 48% placebo; PT: 63% cabozantinib, 48% placebo). Other frequently reported grouped terms were PPE syndrome (43% vs 13%), venous and mixed thrombotic events (19% vs 3.2%).

Grade 3/4 ETMs were reported for 49% of subjects in the cabozantinib arm and 19% of subjects in the placebo arm and most frequently included hypertension (22% vs 13%). The grouped term venous or mixed thrombotic events included 7 subjects with Grade ≥ 3 events, all of which were considered possibly or probably related, with the PTs embolism (4 subjects), pulmonary embolism (3 subjects), and embolism venous (1 subject).Grade 4 ETMs were only reported in the cabozantinib arm (2 subjects [3.2%] vs 0% in the placebo arm) and included arterial thromboembolic events (1 subject [1.6%] who had a myocardial infarction), QT prolongation (1 subject [1.6%] with cardiac arrest), and venous and mixed thromboembolic events (1 subject [1.6%] with a pulmonary embolism).

No Grade 5 ETMs were reported in either treatment arm in the pNET cohort

The Applicant's Position:

The incidence of ETMs reported in Study CABINET were generally consistent with those observed in previous cabozantinib studies. The evaluation of the data from Study CABINET did not identify any new safety signals.

The FDA's Assessment:

Overall, the FDA agrees with the Applicant's description of the ETMs, a subset of clinically significant adverse events selected for analysis based on the safety profile of cabozantinib.

epNET Cohort

For further context regarding the Applicant's observation of "QT prolongation" in ~9% of study patients receiving cabozantinib, "QT prolongation" was observed in 7.5% of the placebo-treated patients. As noted in the clinical study report, the grouped term (GT) "QT prolongation" encompassed preferred terms of "cardiac arrest", "electrocardiogram QT prolonged", "sudden death", "syncope", "torsades de pointes", and "ventricular arrhythmia"; corresponding rates of events listed by arm are shown in FDA Table 48 below.

FDA Table 48: Treatment-emergent QT Prolongation Cases in epNET Cohort

	Cabozantinib N=132 n (%)			**Placebo N=67 n (%)**		
	Any Grade	**Gr 3-4**	**Gr 5**	**Any Grade**	**Gr 3-4**	**Gr 5**
GT: QT Prolongation	12 (9.1)	7 (5.3)	2 (1.5)	5 (7.5)	5 (7.5)	0
Cardiac arrest	2 (1.5)	1 (0.8)	1 (0.8)	0	0	0

Electrocardiogram QT prolonged	3 (2.3)	1 (0.8)	0	0	0	0
Sudden death	1 (0.8)	0	1 (0.8)	0	0	0
Syncope	5 (3.8)	5 (3.8)	0	5 (7.5)	5 (7.5)	0
Torsades de pointes	1 (0.8)	1 (0.8)	0	0	0	0
Ventricular arrhythmia	1 (0.8)	0	0	0	0	0

Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

All events of "electrocardiogram QT prolonged" were Grades 1-3 and nonserious. Per the FDA's analysis, the patient who had both a cardiac arrest (Grade 4) and torsades de pointes (Garde 4) was a 51 -year-old male with metastatic epNET (primary tumor site: small bowel) with history of hypertension and hypercholesterolemia who was being treated with cabozantinib. He experienced a Grade 4 acute myocardial infarction (ST elevation MI) in the setting of a coronary artery occlusion without QTc prolongation (QTc <500).

For additional information regarding Grade 5 ETMs in CABINET, which were limited to the cabozantinib arm of the epNET cohort, refer to the FDA's "Death Analysis" above in Section 8.2.4.

pNET Cohort

Regarding "QT prolongation" in the pNET cohort, there were 4 patients (6.3%) affected in the cabozantinib arm, and one patient (3.2%) in the placebo arm. The Grade 4 case highlighted by the Applicant was a 65-year-old male with pNET and liver metastases, previously treated with everolimus, Lu-177 dotatate, sunitinib and chemotherapy (capecitabine and temozolomide), and receiving cabozantinib in CABINET. The patient experienced Grade 4 cardiac arrest, requiring CPR and defibrillation, in the setting of a Grade 4 myocardial infarction due to a flow limiting lesion in the left anterior descending artery and narrowing of the right coronary artery. The patient underwent stenting and discontinued cabozantinib.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

epNET:

The most frequently reported AEs were fatigue (72% cabozantinib vs 57% placebo), AST increased (70% vs 21%), diarrhea (65% vs 42%), hypertension (64% vs 37%), ALT increased (63% vs 18%), and platelet count decreased (52% vs 12%) (Applicant Table 49).

Applicant Table 49: Study CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects in Either Treatment Arm (epNET; Double-Blind)

Preferred Term	Cabozantinib Only (N = 132) n (%)			Placebo (N = 67) n (%)		
	All	Grade 3/4	Grade 5	All	Grade 3/4	Grade 5
Subjects with at least 1 AE, n (%)	132 (100)	89 (67)	9 (6.8)	67 (100)	27 (40)	4 (6)
Fatigue	95 (72)	19 (14)	0	38 (57)	6 (9.0)	0
AST increased	93 (70)	5 (3.8)	0	14 (21)	1 (1.5)	0
Diarrhoea	86 (65)	14 (11)	0	28 (42)	3 (4.5)	0
Hypertension	84 (64)	34 (26)	0	25 (37)	4 (6.0)	0
ALT increased	83 (63)	1 (0.8)	0	12 (18)	1 (1.5)	0
Platelet count decreased	68 (52)	2 (1.5)	0	8 (12)	1 (1.5)	0
Nausea	52 (39)	3 (2.3)	0	14 (21)	0	0
Stomatitis[a]	51 (39)	5 (3.8)	0	87(10)	0	0
WBC count decreased	49 (37)	4 (3.0)	0	3 (4.5)	0	0
Neutrophil count decreased	45 (34)	4 (3.0)	0	4 (6.0)	0	0
PPE syndrome	45 (34)	4 (3.0)	0	4 (6.0)	0	0
Decreased appetite	44 (33)	2 (1.5)	0	10 (15)	1 (1.5)	0
Dysgeusia	43 (33)	0	0	1 (1.5)	0	0
Hypothyroidism	41 (31)	0	0	2 (3.0)	0	0
Anaemia	39 (30)	3 (2.3)	0	13 (19)	0	0
Blood alkaline phosphatase increased	38 (29)	6 (4.5)	0	20 (30)	4 (6.0)	0
Hyperglycaemia	36 (27)	1 (0.8)	0	23 (34)	1 (1.5)	0
Lymphocyte count decreased	36 (27)	12 (9.1)	0	11 (16)	1 (1.5)	0
Weight decreased	36 (27)	6 (4.5)	0	5 (7.5)	0	0
Abdominal pain	34 (26)	11 (8.3)	0	27 (40)	4 (6.0)	0
Blood creatinine increased	31 (23)	0	0	8 (12)	1 (1.5)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; epNET, extra-pancreatic neuroendocrine tumor (carcinoid tumor); PPE, palmar-plantar erythrodysaesthesia; WBC, white blood cell
Note: MedDRA 26.1 was used for coding.
Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis
Source: CABINET CSR Table 14.3.1.5.6.1.b; ADaM Datasets: ADSL, ADAE.

pNET:

The most frequently reported AEs were solicited: fatigue (79% cabozantinib vs 61% placebo), AST increased (76% vs 48%), and ALT increased (73% vs 39%) (Applicant Table 50).

Applicant Table 50: Study CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects in Either Treatment Arm (pNET; Double-Blind)

	Cabozantinib Only (N = 63) n (%)			Placebo (N = 31) n (%)		
Preferred Term	**All**	**Grade 3/4**	**Grade 5**	**All**	**Grade 3/4**	**Grade 5**
Subjects with at least 1 AE, n (%)	63 (100)	46 (73)	0	31 (100)	14 (45)	0
Fatigue	50 (79)	9 (14)	0	19 (61)	2 (6.5)	0
AST increased	48 (76)	1 (1.6)	0	15 (48)	0	0
ALT increased	46 (73)	1 (1.6)	0	12 (39)	1 (3.2)	0
Diarrhoea	40 (63)	4 (6.3)	0	7 (23)	0	0
Hypertension	40 (63)	14 (22)	0	15 (48)	4 (13)	0
Stomatitis[a]	30 (48)	4 (6.3)	0	3 (9.7)	0	0
PPE syndrome	27 (43)	6 (9.5)	0	4 (13)	0	0
Nausea	24 (38)	5 (7.9)	0	10 (32)	1 (3.2)	0
Hyperglycaemia	21 (33)	2 (3.2)	0	13 (42)	1 (3.2)	0
Platelet count decreased	21 (33)	0	0	6 (19)	0	0
Dysgeusia	18 (29)	0	0	2 (6.5)	0	0
Anaemia	16 (25)	1 (1.6)	0	10 (32)	0	0
Hypophosphataemia	16 (25)	0	0	2 (6.5)	0	0
Vomiting	16 (25)	4 (6.3)	0	5 (16)	0	0
Decreased appetite	15 (24)	2 (3.2)	0	6 (19)	0	0
Dizziness	15 (24)	0	0	1 (3.2)	0	0
Abdominal pain	14 (22)	2 (3.2)	0	5 (16)	2 (6.5)	0
Lymphocyte count decreased	14 (22)	5 (7.9)	0	5 (16)	0	0
Neutrophil count decreased	14 (22)	1 (1.6)	0	2 (6.5)	0	0
Blood alkaline phosphatase increased	13 (21)	2 (3.2)	0	7 (23)	0	0
Blood thyroid stimulating hormone increased	13 (21)	0	0	0	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; pNET, pancreatic neuroendocrine tumor; PPE, palmar-plantar erythrodysaesthesia
Note: MedDRA 26.1 was used for coding.

Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis
Source: CABINET CSR Table 14.3.1.5.6.1.a; ADaM Datasets: ADSL, ADAE.

The Applicant's Position:

For labeling purposes, adverse reactions (grouped by system organ class [SOC] and presented by CTCAE grade) for the proposed regimen that were reported in > 20% in cabozantinib treated subjects in CABINET were included in Section 6.1 of the United States Prescribing Information USPI).

In the epNET cohort, the most common adverse reactions occurring in ≥ 20% of CABOMETYX-treated patients in order of decreasing frequency were fatigue, increased AST, diarrhea, hypertension, increased ALT, platelet count decreased, nausea, stomatitis, white blood cell count decreased, neutrophil count decreased, dysgeusia, PPE, decreased appetite, hypothyroidism, anemia, lymphocyte count decreased, rash, weight decreased, blood creatinine increased, hypoalbuminemia, hypocalcemia, hypokalemia, blood bilirubin increased, and hypomagnesemia. Serious adverse reactions occurred in 44% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included hypertension, anemia, back pain, muscular weakness, pulmonary embolism, and sepsis.

In the pNET cohort, the most common adverse reactions occurring in ≥ 20% of CABOMETYX-treated patients, in order of decreasing frequency were: fatigue, increased AST, increased ALT, hypertension, diarrhea, stomatitis, PPE, nausea, platelet count decreased, dysgeusia, neutrophil count decreased, vomiting, hypophosphatemia, abdominal pain, decreased appetite, dizziness, rash, lymphocyte count decreased, and increased blood TSH. Serious adverse reactions occurred in 46% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included vomiting, embolism, hypoxia, nausea, sepsis, blood bilirubin increased, fatigue, hyperkalemia, hypertension, and pulmonary embolism.

The FDA's Assessment:
See FDA Table 51 and FDA Table 52 for the FDA's analysis of the most common treatment-emergent adverse events observed in patients who received cabozantinib in the epNET and pNET cohorts, respectively. The FDA noted generally minor discrepancies in the rates reported by the Applicant that are likely related to use of slightly differing grouped terms.

The leading adverse reactions for both cohorts included fatigue, hypertension, diarrhea, rash (including PPE), stomatitis, nausea, abdominal pain, vomiting, and hypothyroidism. The adverse reactions observed in patients with neuroendocrine tumors are largely consistent with the known safety profile of cabozantinib and may also reflect manifestations of the underlying disease (e.g., gastrointestinal-related complaints of abdominal pain, nausea and vomiting).

The FDA notes that thromboembolic events occurred at a higher rate (19%) in patients with pNET compared to 4% in patients with epNET which is likely a reflection of the increased

thrombotic risk observed in patients with a pancreatic primary that has been described in medical literature (Wojcik-Giertuga et al., 2023). Additionally, although hypertension is a known adverse reaction reported with cabozantinib treatment, the rate of hypertension and higher-grade events in patients treated with cabozantinib in CABINET (65%; including 26% Grade 3 events) was found to be substantially higher than the 37% rate (16% Grade 3 and <1% Grade 4) observed in the combined clinical trial patient population described in Section 5 of the cabozantinib drug label. Based on this discrepancy, the "Hypertension and Hypertensive Crisis" warning was updated to include the frequency of hypertension occurring in CABINET for clinician and patient awareness. Due to the limited sample size in CABINET, generalizations cannot be made regarding hypertension in patients with NETs versus other approved cancer indications for cabozantinib; however, the presence of functional NETs in approximately 33% of the epNET cohort and 17% of the pNET cohort is likely to contribute to the higher prevalence of hypertension in this patient population.

Overall, no novel safety signals were identified during review of this sNDA. For the FDA's review of laboratory assessments, refer to the subsection "Laboratory Findings".

FDA Table 51: Adverse Reactions (≥15%) in Patients with epNET Who Received Cabozantinib

Adverse Reaction	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
	Percentage (%) of Patients			
General				
Fatigue[2]	73	14	58	9
Edema[3]	16	1.5	10	0
Gastrointestinal				
Diarrhea[4]	65	11	42	4.5
Stomatitis[5]	40	3.8	10	0
Nausea	39	2.3	21	0
Abdominal pain[6]	29	9	43	8
Vomiting	17	2.3	10	1.5
Vascular				
Hypertension[7]	64	27	37	6
Skin and Subcutaneous Tissue				
Rash[8]	50	3.0	10	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	36	8	33	1.5
Endocrine System				
Hypothyroidism[10]	34	0	4.5	0
Metabolism and Nutrition				
Decreased appetite	33	1.5	15	1.5

Adverse Reaction	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
Nervous System				
Dysgeusia[11]	35	0	1.5	0
Dizziness[12]	17	0	6	0
Investigations				
Weight decreased	27	4.5	8	0
Respiratory, Thoracic, and Mediastinal				
Cough[13]	17	0	10	0

[1] NCI CTCAE Version 5.0
[2] Includes fatigue, asthenia
[3] Includes edema, edema peripheral, generalized edema, localized edema, periorbital edema, face edema, eye edema
[4] Includes diarrhea, colitis
[5] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis
[6] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain
[7] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension
[8] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, rash macular, rash pustular, dermatitis bullous, dermatitis, erythema multiforme, rash maculo-papular, dermatitis contact, erythema, dermatitis psoriasiform
[9] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort
[10] Includes hypothyroidism, blood thyroid stimulating hormone increased
[11] Includes dysgeusia, taste disorder, ageusia, anosmia
[12] Includes dizziness, vertigo
[13] Includes cough, upper-airway cough syndrome, productive cough
Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

FDA Table 52: Adverse Reactions (≥15%) in Patients with pNET Who Received Cabozantinib

Adverse Reaction	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades[1]	Grade 3 or 4	All Grades[1]	Grade 3 or 4
	Percentage (%) of Patients			
General				
Fatigue[2]	79	14	61	6
Vascular				
Hypertension[3]	67	25	55	16
Thromboembolic events[4]	19	11	3.2	0
Gastrointestinal				
Diarrhea[5]	63	6	23	0
Stomatitis[6]	49	6	10	0
Nausea	37	8	32	3.2
Abdominal pain[7]	25	3.2	16	6

Adverse Reaction	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades[1]	Grade 3 or 4	All Grades[1]	Grade 3 or 4
Vomiting	25	6	16	0
Dyspepsia[8]	16	0	6	0
Skin and Subcutaneous Tissue				
Rash[9]	57	11	23	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[10]	41	1.6	19	0
Nervous System				
Dysgeusia[11]	30	0	6	0
Dizziness[12]	25	0	3.2	0
Endocrine disorders				
Hypothyroidism[13]	25	0	3.2	0
Metabolism and Nutrition				
Decreased appetite	25	3.2	19	0
Investigations				
Weight decreased	19	3.2	10	0
Respiratory, Thoracic, and Mediastinal				
Dyspnea[14]	16	0	3.2	0

[1] NCI CTCAE Version 5.0
[2] Includes fatigue, asthenia
[3] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension
[4] Includes thromboembolic event, pulmonary embolism, embolism, deep vein thrombosis, vena cava thrombosis, embolism venous, embolism arterial
[5] Includes diarrhea, colitis
[6] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis
[7] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain
[8] Includes dyspepsia, gastroesophageal reflux disease
[9] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, erythema multiforme, rash macular, rash maculo-papular, rash pustular, dermatitis, dermatitis bullous, dermatitis contact, erythema, dermatitis psoriasiform
[10] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort
[11] Includes dysgeusia, taste disorder, ageusia, anosmia
[12] Includes dizziness, vertigo
[13] Includes hypothyroidism, blood thyroid stimulating hormone increased
[14] Includes dyspnea, dyspnea exertional
Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

Additionally, clinically relevant adverse reactions occurring at a frequency of <15% in patients

receiving cabozantinib in CABINET included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, and hair color changes.

Laboratory Findings

Data:

Not Applicable

The Applicant's Position:

Clinical laboratory assessments were evaluated at intervals throughout the study, but these data were not collected in the clinical database, except for clinically significant findings which were required to be reported as AEs and specified laboratory parameters (ie, AST increases, ALT increases, neutrophil count decreases, platelet count decreased, blood thyroid stimulating hormone increased, etc.), which were required to be reported as solicited AEs

The FDA's Assessment:
The FDA acknowledges the Applicant's position. As per Alliance study practice, laboratory assessments were not routinely captured and only recorded if occurring as adverse events during the conduct of CABINET.

See FDA Table 53 and FDA Table 54 for the FDA's analysis of select laboratory abnormalities that were reported as adverse reactions in patients who received cabozantinib in the epNET and pNET cohorts, respectively. The most frequently observed laboratory-related adverse reactions were increased liver enzymes, decreased blood counts (including platelets, white blood cells, neutrophils, lymphocytes), decreased hemoglobin, hyperglycemia, increased ALP, and increased blood creatinine. These laboratory abnormalities are consistent with the clinical experience of cabozantinib treatment in other oncologic indications. No new laboratory-related safety signals were identified in patients with neuroendocrine tumors.

FDA Table 53: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with epNET Who Received Cabozantinib

	CABOMETYX (N=132)		Placebo (N=67)	
Laboratory Abnormality	**All Grades[1] (%)**	**Grade 3 or 4 (%)**	**All Grades[1] (%)**	**Grade 3 or 4 (%)**
Chemistry				
Increased AST	70	3.8	21	1.5
Increased ALT	63	0.8	18	1.5

Hyperglycemia[2]	30	0.8	39	1.5
Increased ALP[3]	29	4.5	30	6
Blood creatinine increased	23	0	12	1.5
Blood bilirubin increased[4]	20	3	10	6
Hypoalbuminemia[5]	20	0.8	9	0
Hypocalcemia[6]	20	0	4.5	0
Hypokalemia[7]	20	2.3	10	1.5
Hypomagnesemia[8]	20	0.8	4.5	0
Hypophosphatemia[9]	19	0.8	4.5	0
Hyponatremia[10]	16	2.3	7	1.5
Hematology				
Platelet count decreased[11]	55	1.5	13	1.5
White blood cell count decreased[12]	37	3	4.5	0
Neutrophil count decreased[13]	36	3	6	0
Hemoglobin decreased[14]	30	2.3	19	0
Lymphocyte count decreased[15]	28	9	18	1.5

[1] NCI CTCAE Version 5.0
[2] Includes hyperglycemia, blood glucose increased
[3] Includes blood alkaline phosphatase, blood alkaline phosphatase increased
[4] Includes blood bilirubin increased, hyperbilirubinemia
[5] Includes hypoalbuminemia, blood albumin decreased
[6] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased
[7] Includes hypokalemia, blood potassium decreased
[8] Includes hypomagnesemia, blood magnesium decreased
[9] Includes hypophosphatemia, blood phosphorus decreased
[10] Includes hyponatremia, blood sodium decreased
[11] Includes platelet count decreased, thrombocytopenia
[12] Includes white blood cell count decreased, leukopenia
[13] Includes neutrophil count decreased, neutropenia
[14] Includes hemoglobin decreased, anemia
[15] Includes lymphocyte count decreased, lymphopenia
Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

FDA Table 54: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with pNET Who Received Cabozantinib

	CABOMETYX (N=63)		**Placebo (N=31)**	
Laboratory Abnormality	**All Grades[1] (%)**	**Grade 3 or 4 (%)**	**All Grades[1] (%)**	**Grade 3 or 4 (%)**
Chemistry				
Increased AST	76	1.6	48	0
Increased ALT	75	1.6	39	3.2

Hyperglycemia[2]	37	3.2	48	3.2
Hypophosphatemia[3]	25	0	6	0
Increased ALP[4]	22	3.2	23	0
Hypocalcemia[5]	17	0	3.2	0
Hyponatremia[6]	16	1.6	16	0
Blood bilirubin increased[7]	14	4.8	6	3.2
Hyperkalemia[8]	14	1.6	10	0
Hypoalbuminemia[9]	14	0	10	0
Hypoglycemia[10]	11	0	6	0
Hypomagnesemia[11]	11	0	6	0
Hypokalemia[12]	10	1.6	3.2	0
Hematology				
Platelet count decreased[13]	37	0	19	0
Neutrophil count decreased[14]	27	1.6	6	0
Hemoglobin decreased[15]	25	1.6	32	0
Lymphocyte count decreased[16]	22	8	16	0
White blood cell count decreased[17]	19	1.6	3.2	0

[1] NCI CTCAE Version 5.0
[2] Includes hyperglycemia, blood glucose increased
[3] Includes hypophosphatemia, blood phosphorus decreased
[4] Includes blood alkaline phosphatase, blood alkaline phosphatase increased
[5] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased
[6] Includes hyponatremia, blood sodium decreased
[7] Includes blood bilirubin increased, hyperbilirubinemia
[8] Includes hyperkalemia, blood potassium increased
[9] Includes hypoalbuminemia, blood albumin decreased
[10] Includes hypoglycemia, blood glucose decreased
[11] Includes hypomagnesemia, blood magnesium decreased
[12] Includes hypokalemia, blood potassium decreased
[13] Includes platelet count decreased, thrombocytopenia
[14] Includes neutrophil count decreased, neutropenia
[15] Includes hemoglobin decreased, anemia
[16] Includes lymphocyte count decreased, lymphopenia
[17] Includes white blood cell count decreased, leukopenia
Source: ADSL (Subject-Level Analysis Dataset) – 2024-08-26, ADAE (Adverse Event Analysis Dataset) – 2024-08-26

Vital Signs

Data:

Not Applicable

The Applicant's Position:

Vital signs (blood pressure, pulse), physical examination, and ECG assessments were performed at intervals throughout the study. Laboratory abnormalities and vital signs were not collected in the clinical database; clinically significant findings and solicited events were to be reported as AEs (ie, hypertension, blood pressure increased).

The FDA's Assessment:
The FDA acknowledges the Applicant's position. As per Alliance study practice, vital sign measurements were not routinely captured and only recorded if occurring as adverse events during the conduct of CABINET. Refer to the sub-section "Treatment Emergent Adverse Events and Adverse Reactions" for additional information.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Interpretation of the safety data must be in the setting of the study data collection methods, disease status, as well as the symptom burden of the subject population. A subset of AEs known to be associated with cabozantinib were solicited (eg, ALT/AST increased, diarrhea, fatigue, and hypertension, etc) during the study, and this may have resulted in a higher-than-expected frequency in both the cabozantinib and placebo arms. While the number of SAEs were higher for the cabozantinib arms, the SAE reporting procedures for this study allowed reporting of lower grade events at the discretion of the Investigator. In addition, subjects were heavily pretreated and had high tumor burden. Also, the study included subjects with functional NETs who are known to have significant symptom burden. Therefore, rates of AEs and dose modifications in the cabozantinib arm should be viewed in the context of the increased event rates on the placebo arm. Of note, dose holds were common in the subjects randomized to placebo, suggesting the subject population under study had significant co-morbidity associated with advanced neuroendocrine disease. Treatment was discontinued due to an AE in the epNET cohort for 27% vs 18% of subjects in the cabozantinib and placebo treatment arms, respectively, and in the pNET cohort for 19% vs 9.7% of subjects, respectively. Although the frequency of treatment discontinuation was higher with cabozantinib, there was a notable frequency of treatment-related AEs and treatment discontinuation due to investigator-assessed treatment-related AEs in the placebo arm, which indicates the study included a highly symptomatic NET population and the blind was effective.

In general, the safety profile for cabozantinib was similar between the epNET and pNET populations, with the possible exception of a higher incidence of venous thromboembolism in the pNET cohort, which may be secondary to underlying disease. In addition, among the 32 total crossover subjects (randomized to placebo and crossed over to open-label cabozantinib after disease progression), safety results were consistent with those from subjects who were randomized to cabozantinib.

Overall, in both epNET and pNET cohorts, there were no new safety findings from this study for cabozantinib as monotherapy. Adverse events were effectively managed through dose modifications, and the safety profile was consistent with prior studies with single-agent cabozantinib treatment, with no new safety concerns emerging from this study in patients with epNET or pNET. The manageable and well characterized safety profile support a positive benefit-risk profile of cabozantinib for the management of patients previously treated for pNET and epNET. After an internal pharmacovigilance review, Exelixis believes that the results of the CABINET study do not warrant any update to Warnings and Precautions of the current Cabometyx label.

The FDA's Assessment:
Overall, the FDA agrees with the Applicant's assessment of safety in CABINET, including general trends regarding clinically significant adverse reactions observed in patients with neuroendocrine tumors and the symptomatic disease burden of the study population as evidenced by notable rates of adverse reactions and dose modifications in the placebo arms. The rates of dose interruption, dose reduction, and drug discontinuation in CABINET were fairly similar to those observed in other clinical trials of cabozantinib for the approved oncologic conditions described in the drug label. The FDA concurs that no new safety signals were observed in patients with neuroendocrine tumors.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Not Applicable

The Applicant's Position:

Not Applicable

The FDA's Assessment:
Not applicable as the Applicant did not submit clinical outcome assessment data for the FDA's evaluation.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

The following factors were examined for incidence of AEs and ETMs in CABINET.

- Sex (male, female)
- Age group at screening (< 65 years, 65-74 years, 75-84 years, and ≥ 85 years)
- Race (White, Black/African-American, Asian, other)
- ECOG performance status at baseline (0, ≥ 1)

The incidence of AEs or ETMs reported in cabozantinib-treated subjects in CABINET was generally similar between males and females in the cabozantinib arm, with the following exceptions:

- The incidence of the nausea and vomiting in the cabozantinib arm was reported more frequently in female subjects (45% and 24%) than in male subjects (28% and 14%). The incidence of hypophosphatemia was reported more frequently in male subjects (27%) than in female subjects (16%).
- The ETM of hemorrhage (≥ Grade 3) was reported more frequently in male subjects (3.5%) than in female subjects (0%) in the cabozantinib arm. The ETM of hemorrhage (≥ Grade 3) and venous and mixed thromboembolic events were reported more frequently in male subjects (hemorrhage [≥ Grade 3]: 3.5%; VTE: 12%) than in female subjects (0%; 4.3%) in the cabozantinib arm.

There were no significant differences in incidence of AEs or ETMs reported in cabozantinib-treated subjects in the pooled all cabozantinib group and was generally similar between across age groups.

Most subjects (83% cabozantinib, 80% placebo in CABINET were White.

The incidence of AEs was generally similar between baseline ECOG performance status in the cabozantinib arm with the following exceptions. The AEs of white blood cell (WBC) count decreased and hypokalemia were more frequently reported in subjects with baseline ECOG of ≥ 1 than in subjects with baseline ECOG of 0.

The Applicant's Position:

Reported AEs and ETMs across subgroup analyses of sex, age group, race, and baseline ECOG performance status were generally similar to those observed in all subjects who received cabozantinib.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of safety analyses by demographic subgroups. As the subgroups are small in size, the FDA cautions that generalizations regarding safety across subgroups cannot be adequately supported. No major safety concerns were identified in these subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

Data:
Not applicable

The Applicant's Position:
Not Applicable

The FDA's Assessment:
The FDA agrees as no specific safety studies were performed for this application.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:
Not Applicable

The Applicant's Position:
Not Applicable

The FDA's Assessment:
The FDA agrees as no carcinogenicity or tumor development studies were conducted for this application.

Human Reproduction and Pregnancy
Data:
No new information is provided in this application

The Applicant's Position:
Not Applicable

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth
Data:

epNET and pNET are rare in the pediatric population.

The Applicant's Position:
(b) (6)
.

The FDA's Assessment:
The FDA acknowledges that neuroendocrine tumors are rare in the pediatric population. As described in Section 10 "Pediatrics", in the initial Pediatric Study Plan (iPSP) for cabozantinib, the Applicant requested a partial waiver from pediatric study requirements in patients less than 12 years of age; the FDA considered this request to be appropriate as the necessary studies would be impossible or highly impracticable.

Although pediatric patients were not enrolled in the CABINET study, adolescent patients are included in the proposed indication based on extrapolation from data in adults with NETs and acceptable dose modeling. Refer to Section 10 for additional details.

The FDA also notes that as previously described in the "Pediatric Use" subsection of the drug label, "physeal widening has been observed in children with open growth plates when treated with cabozantinib" and that "physeal and longitudinal growth monitoring is recommended in children with open growth plates." As confirmed by the Applicant in correspondence during the sNDA review, there have been no cases of growth delay or premature growth plate fusion that have been observed with cabozantinib treatment in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:

No AEs of overdose were reported in the clinical database or Exelixis cabozantinib global safety database of CABINET. Clinical data are not available to evaluate the effect on disease or clinical biomarkers after withdrawal of cabozantinib.

The Applicant's Position:
There is no specific treatment for overdose of cabozantinib and possible symptoms of overdose have not been established.

The FDA's Assessment:
The FDA concurs with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data:

Cabozantinib capsules (Cometriq) were first approved on 29 November 2012 in the US for the treatment of patients with progressive, metastatic MTC at a dose of 140 mg qd and were subsequently approved in the EU and UK for the treatment of adults with progressive, unresectable locally advanced or metastatic MTC.

Cabozantinib tablets (Cabometyx) have been approved in the US, EU, Japan, and other regions at a dose of 60 mg qd for the treatment of patients with advanced RCC (different patient populations depending on region) and patients with HCC who have previously been treated with sorafenib. Cabozantinib tablets (40 or 60 mg depending on body surface area [BSA]) are also approved in the US for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine (RAI)-refractory or ineligible. Additionally, the use of cabozantinib is approved in the EU and other regions as a second-line treatment in adult patients with locally advanced or metastatic DTC who have progressed during or after prior systemic therapy and are radioactive iodine-refractory or ineligible. Cabozantinib tablets are also approved in the US and EU for patients with advanced RCC, as a first-line treatment in combination with nivolumab. Through 28 November 2023, the estimated number of patients treated with cabozantinib exceeds 179,545 patients in the postmarketing setting, including approximately 4530 treated with Cometriq and approximately 175,015 treated with cabozantinib alone or in combination with nivolumab .

The Applicant's Position:

Postmarketing data for cabozantinib are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, individually as expedited reports as well as periodically in aggregate reports to global health authorities. Through 28 November 2023, the reviewed postmarketing safety data are consistent with the known safety profile of cabozantinib and confirm the clinical trial safety data for cabozantinib. The safety profile of cabozantinib in the postmarketing setting remains favorable and similar to the profile established during clinical trials

The FDA's Assessment:
The FDA agrees with the Applicant's summary of safety in the postmarketing setting and that it is consistent with the known safety profile of cabozantinib based on clinical trial data.

8.2.11. Integrated Assessment of Safety

Data:
Not Applicable

The Applicant's Position:

Safety analysis was focused soley on data from the CABINET study.

The FDA's Assessment:

The most commonly reported (≥20% incidence) treatment-emergent adverse reactions occurring in the 195 patients treated with cabozantinib across the epNET and pNET cohorts of CABINET were fatigue, AST increased, ALT increased, hypertension, diarrhea, rash, platelet count decreased, stomatitis, nausea, musculoskeletal pain, hypothyroidism, decreased appetite, dysgeusia, white blood cell count decreased, neutrophil count decreased, hyperglycemia, anemia, abdominal pain, blood ALP increased, lymphocyte count decreased, weight decreased, vomiting, and hypophosphatemia. The most frequent (≥5%) Grade 3 or higher treatment-emergent adverse reactions in the cabozantinib-treated patient population included hypertension (26%), fatigue (14%), diarrhea (9%), abdominal pain (7%), musculoskeletal pain (6%) and rash (6%). The leading treatment-emergent serious adverse reactions reported in ≥2% of this pooled safety population were thromboembolic events, abdominal pain, musculoskeletal pain, vomiting, nausea, sepsis, fatigue, diarrhea, blood bilirubin increased, anemia, hemorrhage, and hypothyroidism. Fatal adverse reactions occurred in only in the epNET cohort (4.5%), including hepatic failure, multi-organ dysfunction, gastrointestinal hemorrhage, cardiac arrest, ruptured ascending aortic aneurysm, and sudden death not otherwise specified, occurring in one patient each.

Cabozantinib was discontinued in 25% of patients treated across the two cohorts: primarily for diarrhea, fatigue, rash, and elevated liver enzymes (AST and ALT). Similarly, drug interruption was most commonly due to diarrhea (20%), fatigue (19%), and rash (18%). Lastly, dose reduction was mainly due to rash (13%), fatigue (10%), and hypertension (8%).

Although cross-trial comparisons should be interpreted with caution due to variability in study populations, in general, the FDA considers the safety profile of single-agent cabozantinib in patients with advanced NETs to be similar to that observed in clinical trials for other approved cancer indications (i.e., patients with renal cell carcinoma, hepatocellular carcinoma and thyroid carcinoma) and predominantly consistent with adverse reactions documented with use of related in-class TKIs (e.g., those targeting VEGFR). Notable findings from the FDA's review of safety data from cabozantinib-treated patients in CABINET were related to the greater frequency of thromboembolic events in the pNET cohort (19%) compared to the epNET cohort (4%), and the higher rate of hypertension including Grade 3 events in patients with NETs (65%; 26% Grade 3) compared to that in the combined population of clinical trial patients for the other approved cancer indications described Section 5 of in the drug label (37%; 16% Grade 3 and <1% Grade 4). Both of these observations are likely related to the pathophysiology of the underlying disease as thrombotic risk is higher in patients with pancreatic tumors and hypertension is a known complication in patients with functional tumors. Overall, no novel safety signals were identified during review of this sNDA.

In summary, the FDA considers the safety profile of cabozantinib to be acceptable for the treatment of patients with previously treated advanced NETs, who will be treated by

oncologists who are experienced in managing such toxicities.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The efficacy results for the marketing application are submitted from CABINET trial, a Phase 3, randomized, double-blind, placebo-controlled trial of cabozantinib for the treatment of patients with previously treated, locally advanced/unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET) or extra-pancreatic neuroendocrine tumors (epNET). The primary endpoint was progression-free survival (PFS), per RECIST v1.1 criteria, according to blinded independent review committee (BIRC). Two interim analyses (IAs) for futility were planned for each cohort after 33% (IA1) and 66% (IA2) of the planned number of PFS events had occurred. OS was a secondary endpoint and was planned to be tested hierarchically only if the PFS analysis is statistically significant. The primary OS analysis in each cohort was planned after 155 OS events in the respective cohort.

The trial did not have a pre-specified analysis plan for early efficacy claims. FDA advised the Sponsor to allocate a nominal alpha for each interim futility analysis as the stopping rules were based on analyses of the primary endpoint for efficacy, PFS. This recommendation was intended as an acknowledgement of the analysis of efficacy data during the futility assessment. The Applicant allocated an alpha of 0.001 for each interim analysis.

On July 28, 2023, the Alliance DSMB reviewed results from the IA1 for pNET and IA2 for epNET. The report indicated that the conditional power to reject the null hypothesis was 99.99% based on the investigator assessed PFS results observed at IA2 in the epNET and was 99.95% based on the investigator assessed PFS results observed at IA1 in the pNET cohort. Based on the strong clinical benefit observed at the time of pre-specified interim futility analysis, the DSMB recommended to release the trial results, terminate patient accrual, unblind treatment assignment of all the patients still being treated on the trial to enable potential crossover of patients on the placebo treatment arms to receive open-label cabozantinib treatment.

There are three major challenges associated with PFS in this application. First, assessing the accuracy of the results from the interim analyses that were pre-defined for futility assessment was a major review issue. These analyses were conducted well before the final analysis of PFS, especially for the pNET cohort. There were 33% investigator assessed PFS events at the time of IA1 of pNET cohort and 66% investigator assessed PFS events at the time of IA2 of epNET cohort. NDA submission included BIRC assessed PFS data, with 38% PFS IF in pNET cohort and 68% PFS IF in epNET cohort. Results of such early interim analyses, particularly in the pNET cohort, may be liable to overestimation of the treatment effect size due to data immaturity.

Second, there was a relatively high discordance observed between investigator assessments and BIRC assessments of PFS. In epNET, the disagreement between PD status was 33% in the cabozantinib arm and 37% in the placebo arm. The rate of disagreement on PD status within 4 weeks was approximately 40% in cabozantinib arm and 43% in the placebo arm. While the discordance rate is relatively high, the distribution of the discordance rate by treatment arm and the distribution of early discrepancy rate (40% in cabozantinib arm vs 39% in the placebo arm) and late discrepancy rate (44% in cabozantinib arm vs. 45% in the placebo arm) do not appear to alter the interpretation of treatment effect of cabozantinib on BIRC-assessed PFS in epNET cohort. In the pNET cohort, the disagreement between PD status was 29% in the cabozantinib arm and 28% in the placebo arm. The disagreement of PD within 4 weeks was approximately 36% in cabozantinib arm and 41% in the placebo arm. While the discordance rate is relatively high, the distribution of the discordance rate by treatment arm and the distribution of early discrepancy rate (41% in cabozantinib arm vs 26% in the placebo arm) and late discrepancy rate (33% in cabozantinib arm vs. 54% in the placebo arm) do not appear to alter the interpretation of the treatment effect of cabozantinib on BIRC-assessed PFS in pNET cohort. The sensitivity analyses performed by the Applicant and the FDA also suggest robustness of the estimated treatment effects.

Finally, tumor assessments were performed every 12 weeks (3 months). In the ITT population, the median BIRC assessed PFS was 4.0 months in the placebo arm and 8.5 months in the cabozantinib arm in the epNET cohort. In the pNET cohort, the median PFS was 4.5 months in the placebo arm and 13.8 months in the cabozantinib arm. Given the imaging interval was 3 months and the median improvement in BIRC assessed PFS in epNET cohort was 4.5 months, the FDA requested additional analysis of PFS in the epNET cohort to assess an impact of the timing of the imaging interval on the PFS benefit. In a response to FDA information request, the Applicant provided sensitivity analyses results to address this issue, which included a post-hoc analysis of PFS using interval censoring method. According to Applicant's analysis, the PFS HR in epNET was 0.42 (95% CI: 0.28, 0.61). Results from this analysis is consistent with the results observed in the primary analysis of PFS.

The early termination of enrollment in the trial also resulted in a limited data set and challenges in interpretation of overall survival outcomes, especially within the pNET cohort. Additionally, high rate of patients in the placebo arm choosing to crossover to receive cabozantinib or other post-progression therapies following radiographic progression. While sensitivity analyses alleviate some concerns regarding a potential detrimental effect, the actual treatment effect on OS remains unclear. The OS follow-up is ongoing with the final analyses in both cohorts projected to be performed based on a DCO of April 2026. This may provide further insight on the effect of cabozantinib on OS.

Despite the challenges in interpretation of BIRC assessed PFS results from early interim analyses (in particular for the pNET cohort), discordance between the investigator and BIRC assessments of PD, and median PFS in control arm close to imaging interval, the treatment benefit on PFS

appeared to be consistent across various sensitivity and subgroup analyses. Although the relatively low PFS information fraction may have led to an overestimate of the magnitude of PFS effect, the consistently strong effect observed in both pNET and epNET cohorts strengthens the results and provides additional support in demonstrating efficacy of cabozantinib for the treatment of patients with previously treated, locally advanced/unresectable or metastatic, well- differentiated pNET or epNET.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the evaluation of clinical data from CABINET, the review team recommends traditional approval of cabozantinib for the treatment of adult and pediatric patients 12 years and older with unresectable, locally advanced or metastatic, well-differentiated pancreatic and extrapancreatic neuroendocrine tumors. The primary basis for the FDA's recommendation is the clinically meaningful and statistically significant improvement in PFS observed in patients treated with cabozantinib compared to those who received placebo, in the context of the drug's manageable safety profile.

The treatment strategy for NETs varies depending on the tumor type, stage of disease and presence of symptoms. Systemic therapies to inhibit tumor growth are frequently initiated after disease progression or can be used as alternatives to first-line therapy. FDA-approved agents for the treatment of NETs include lanreotide, everolimus, sunitinib, and PRRT with lutetium Lu-177 dotatate, all of which were approved primarily on the basis of PFS benefit. For patients with advanced disease that has progressed on prior systemic therapy, such as the study population in CABINET, there is no drug that has been specifically approved for the second-line setting. Additionally, there is no clear evidence-based consensus supporting a sequence of therapies for the treatment of advanced or metastatic NETs, and patients may be considered for clinical trials when appropriate.

The main evidence of effectiveness of cabozantinib in the proposed indications is derived from CABINET, a randomized (2:1), double blind, placebo-controlled multicenter study which enrolled adult patients in the US with advanced, well-differentiated NETs that progressed after prior treatment with FDA-approved therapy other than SSAs. The study's primary endpoint is PFS according to BIRC per RECIST v1.1. The FDA considers PFS to be an acceptable endpoint in this disease setting and may represent a direct clinical benefit depending on the magnitude of the treatment effect and the risk-benefit of the investigational treatment compared to available therapies.

The efficacy population according to verified tumor type consists of 198 patients randomized to treatment with cabozantinib 60 mg once daily across the epNET and pNET cohorts. A statistically significant and clinically meaningful improvement in median PFS per BIRC according to RECIST v1.1 was observed in patients receiving cabozantinib in both cohorts. The mPFS

benefit was 4.3 months in the epNET cohort with a PFS HR of 0.4 (95% CI: 0.26, 0.61; p-value <0.0001) favoring the cabozantinib arm, and the mPFS benefit was 10.5 months in the pNET cohort with a PFS HR of 0.22 (95% CI: 0.12, 0.41; p-value <0.0001) favoring the cabozantinib arm. Additionally, descriptive analyses of overall survival (OS) data appear to indicate that a detriment in OS was not observed in patients treated with cabozantinib.

The pooled safety population in CABINET included 195 patients with epNET and pNET who received cabozantinib. The most commonly-reported treatment-emergent adverse reactions occurring in these patients were fatigue, AST increased, ALT increased, hypertension, diarrhea, rash, platelet count decreased, stomatitis, nausea, musculoskeletal pain and hypothyroidism. Thromboembolic events occurred more frequently in patients with pNET, and hypertension was noted to occur at a substantial rate of 65% in the pooled safety population; these findings are likely related to the underlying pathophysiology of neuroendocrine tumors. No new safety signals were identified during the review of this sNDA. The FDA considers the safety profile of single agent cabozantinib in patients with advanced NETs to be acceptable, acknowledging that patients will be treated by oncologists who are experienced in managing the drug's known toxicities.

In conclusion, the clinical and statistical review teams recommend traditional approval of cabozantinib at a dose of 60 mg orally once daily for the treatment of adolescent and adult patients with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic and extrapancreatic neuroendocrine tumors. The submitted data meet the statutory standard for demonstration of substantial evidence of effectiveness, and the benefit-risk assessment of cabozantinib is favorable. Due to the similarity of NETs in adolescents compared to adult patients, the mechanism of action of cabozantinib, and available weight-based modeling, the review team agrees with the inclusion of patients 12 years of age and older in the proposed indications. Notably, cabozantinib represents the first agent to be approved specifically for the treatment of patients with neuroendocrine tumor that has progressed following prior systemic therapy.

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

As described in Section 3.2 ("Summary of Presubmission/Submission Regulatory Activity"), the FDA considered holding an Oncologic Drugs Advisory Committee (ODAC) meeting to discuss the benefit:risk assessment of cabozantinib for the treatment of patients with advanced neuroendocrine tumors. The main issue of concern was the uncertainty regarding updated overall survival (OS) results (DCO September 4, 2024) provided in November 2024 for the intent-to-treat population (ITT) in CABINET, with hazard ratios exceeding 1 and wide confidence intervals for both cohorts, particularly patients with pNET, highlighting concern for a potential safety signal due to drug toxicity. The FDA was informed that these updated OS results were based on a snapshot, and not a complete sweep of OS data. Therefore, FDA subsequently requested a full sweep of OS data (DCO September 4, 2024) be completed, and the Applicant provided the results of that analysis in January 2025.

The results of the complete sweep showed reduction in the OS point estimate for the ITT population. Additionally, an analysis of this OS data in which the cohort allocation was corrected according to a patient's primary tumor origin per electronic data capture (i.e., the three misclassified epNET patients were included in the pNET cohort, and the seven misclassified pNET patients were included in the epNET cohort) indicated further reduction in the pNET OS point estimate and narrowing of the confidence intervals. Acknowledging the PFS benefit demonstrated in CABINET, the limited number of events observed due to early study unblinding, and the difficulty in interpreting OS outcomes given the extent of crossover in the study, the FDA determined that the information from the full OS sweep sufficiently mitigated its concerns regarding a potential safety signal due to drug toxicity; consequently, the FDA determined an ODAC was no longer necessary.

10 Pediatrics

The Applicant's Position:
Pediatric studies of cabozantinib for the treatment of extra-pancreatic or pancreatic neuroendocrine tumors are highly impractical to conduct as the conditions are not common in the pediactic population

The FDA's Assessment:
On June 6, 2024, cabozantinib was granted orphan designation for the treatment of pNETs.

In July 2024, the Applicant submitted an Agreed iPSP for previously treated pNETs and epNETs to the FDA for review by the division and the Oncology Center of Excellence (OCE) Pediatric Review Committee. The study plan proposed partial waiver of pediatric assessments in children younger than 12 years of age on the basis that the necessary studies would be impossible or highly impracticable because the number of such patients is so small or geographically dispersed. The FDA agreed that a partial waiver from pediatric study requirements in children younger than 12 years of age was appropriate based on the rationale provided by the Applicant.

The iPSP also proposed extrapolation of pharmacokinetic (PK) data for pediatric patients 12 years of age and older as the course of NETs and the effects of drugs in this class (TKIs) are expected to be sufficiently similar in adults and adolescent patients. The Applicant agreed to provide a summary of the cabozantinib PK data from CABINET, along with analyses supporting dosing justification for adults and extrapolation to adolescents with pNET and epNET based on PPK and exposure-response analyses.

The FDA confirms that the Applicant submitted the agreed upon PK data from CABINET and that this data was adequate to inform weight-based dosing in adolescent patients and support extension of the marketing indication to adolescent patients.

11 Labeling Recommendations

Data: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights	Updated to reflect changes made to the Full Prescribing Information	Added Recent Major Changes.
1 Indications and Usage	Added new indications for epNET and pNET	Separated the 2 indications (epNET and pNET) for clarity.
2.1 Important Dosage Information		Revised to include Recommended Evaluation and Testing Before Initiating CABOMETYX.
2.5 Recommended Dosage for Neuroendocrine Tumors	Added new section recommended dosage for epNET and pNET	Since the dosage is the same for differentiated thyroid cancer (DTC), epNET and pNET, we deleted the proposed (b) (4) and added Neuroendocrine Tumors to Section 2.4
5 WARNINGS AND PRECAUTIONS		Revised to include the risk statement at the beginning of each subsection. Note that subsections of WARNINGS that do not have adverse reaction incidence for CABINET study are such because the incidence was less than, or not significantly different from what is already reported in the label.
5.4 Warnings and Precautions - Hypertension and Hypertensive Crisis		Added adverse reaction incidences for CABINET study.
5.14 Warnings and	Added CABINET study	Agreed.

Precautions – Hypocalcemia		
6.1 Adverse Reactions	• Added CABINET study to introductory paragraph • Added new subsection for Neuroendocrine Tumors (CABINET ADR data)	Text revised for consistency with current labeling practices and all numbers adjudicated or revised based on FDA analysis.
8.4 Pediatric Use		Added neuroendocrine tumors (NETs)
8.5 Geriatric Use	Added outcomes from CABINET study for patients ≥ 65 years of age	Agreed.
12.2 Pharmacodynamics	Updated to include CABINET study	Agreed.
14 Clinical Studies	Added new subsection 14.4 with efficacy information for CABINET study	FDA revised for clarity and brevity. All numbers adjudicated or revised based on FDA analysis.
Medication Guide		
What is CABOMETYX	Added epNET and pNET indications	The medication guide was reviewed and revised by the Patient Labeling Team, Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis.

The Applicant's Position:

Based on the results of the CABINET study, the Applicant proposes the changes described in the table above for the CABOMETYX Prescribing Information and Medication Guide. The proposed changes above reflect changes from the version approved on 20 Sep 2023

The FDA's Assessment:

The revised labeling has been agreed upon with the Applicant to convey adequate information for the safe and effective use of CABOMETYX.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of cabozantinib are considered acceptable in the indication patient populations due to the serious and potentially life-threatening nature of advanced, previously treated, neuroendocrine tumors. As the safety profile of cabozantinib has been well-documented, the safe use of cabozantinib can be adequately implemented in the post-market setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following postmarketing commitment (PMC) will be included in the approval letter. Refer to the approval letter for requested milestones.

Complete survival follow-up of patients in the CABINET trial to further characterize the efficacy and clinical benefit of cabozantinib in adult patients with previously treated, unresectable, locally advanced or metastatic, well- or moderately-differentiated pancreatic or extra-pancreatic neuroendocrine tumors.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

Financial disclosure information was provided for clincal investigators involved in the covered clinical study CABINET. Three investigators had disclosable financial interests or arrangements under the significant payments of other sorts financial disclosure category. No concerns were raised regarding the overall integrity of the study data.

Covered Clinical Study (Name and/or Number):* CABINET study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,102		
Number of investigators who are Sponsor employees (including both full-time and part-time		

<table>
<tr><td colspan="3">employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
Significant payments of other sorts: 3
Proprietary interest in the product tested held by investigator: 0
Significant equity interest held by investigator in study: 0
Sponsor of covered study: _____ / Exelixis (applicant)</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☒</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

In accordance with the Code of Federal Regulations (CFR) Title 21, Part 54, the Applicant submitted a financial disclosure certification document (FDA Form 3454) in Module 1.3.4. The document lists 1099 of the 1102 investigators who participated in CABINET and had no financial disclosures. The remaining three investigators (b) (4) were included in FDA Form 3455 for receipt of significant payments (speaker fees) from the Applicant.

Per the FDA's review, relevant details are summarized below:

- (b) (4) Received speaker fees of approximately $27K. (b) (4) enrolled (b) (4)
- (b) (4) Received speaker fees of approximately $33K. (b) (4) enrolled (b) (4)
- (b) (4) Received speaker fees of approximately $65K. (b) (4) enrolled (b) (4)

To mitigate concerns about potential bias, the Applicant highlighted that both the primary

efficacy endpoint of PFS and the key secondary endpoint of ORR were both assessed by blinded independent central review.

Also, the following aspects of CABINET provide further support to minimize potential bias that may result from the financial interests mentioned above:

- The trial was double-blinded and conducted by multiple investigators at numerous study sites
- Centralized study monitoring
- Predetermined statistical analysis plan

The FDA agrees that the use of BICR and the other aspects highlighted above sufficiently address any concerns about potential bias in CABINET. The FDA also reviewed site-specific safety and efficacy data for the study sites of the investigators with financial disclosures and did not identify any major outliers in the data concerning for bias.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No additional nonclinical pharmacology/toxicology submitted with this application

The FDA's Assessment:
Not applicable

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

The FDA's Assessment:
Executive Summary:

In the current submission, a PopPK analysis of cabozantinib in adults with NET from the pivotal trial, CABINET, was conducted, along with predictions of cabozantinib in a virtual population of adolescents. Simulations to evaluate adolescent dosage were also performed.

The previously developed cabozantinib PopPK model, based on 8 historical cabozantinib clinical studies, adequately described the PK of cabozantinib in 151 participants with NET (including epNET and pNET) from CABINET. This model was a 2-compartment model with a first-order elimination and a dual absorption process.

Tumor type had no detectable impact on cabozantinib PK parameters. The cabozantinib exposures observed in the NET population in CABINET were comparable to those in other

tumor types for which cabozantinib is indicated.

The 60 mg QD dose of cabozantinib was deemed appropriate for adolescents weighing > 40 kg, as this body weight is well-represented in the evaluated adult population across cancer types, and no clinically meaningful relationship was identified between cabozantinib clearance (CL/F) and body weight.

With conservative allometric scaling assumptions for CL/F and V/F, the predicted exposures in adolescents weighing less than 40 kg and receiving 40 mg QD of cabozantinib (instead of 60 mg QD) better aligned with the exposures observed in adults receiving 60 mg QD.

19.4.1.1. PopPK model

Objectives:

The primary objectives of the PopPK analysis were to assess the predictive performance of the prior cabozantinib PopPK model using PK data in CABINET from participants with NET treated with orally administered cabozantinib, evaluate effects of NET tumor types (epNET and pNET) on cabozantinib exposure, as well as predict cabozantinib exposures in a virtual population of adolescents (> 12 years old) to inform cabozantinib dosing in adolescents with NET.

Model Development:

Data:

Participants with NET in CABINET who were randomized to the experimental arm (no crossover from placebo to active), received at least one dose of cabozantinib, and who had valid cabozantinib PK results were included in this PPK analysis.

Table 1. Summary of Baseline Demographics

	pNET (N=51)	epNET (N=100)	Overall (N=151)
Age (y)			
Mean (SD)	60.3 (10.4)	62.5 (11.3)	61.7 (11.0)
Median [Min, Max]	60.0 [34.0, 79.0]	65.0 [32.0, 86.0]	64.0 [32.0, 86.0]
Body Weight (kg)			
Mean (SD)	81.3 (17.7)	79.0 (21.5)	79.8 (20.3)
Median [Min, Max]	80.2 [50.6, 129]	78.1 [36.0, 146]	79.8 [36.0, 146]
Sex			
Male	32 (62.7%)	41 (41.0%)	73 (48.3%)
Female	19 (37.3%)	59 (59.0%)	78 (51.7%)
Race			
White	45 (88.2%)	87 (87.0%)	132 (87.4%)
Black	2 (3.9%)	5 (5.0%)	7 (4.6%)
Asian	3 (5.9%)	2 (2.0%)	5 (3.3%)
Other	1 (2.0%)	0 (0%)	1 (0.7%)

Source: Table 5. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Methodology:

Prior Cabozantinib PopPK Model

A population pharmacokinetic (PPK) model was previously developed for cabozantinib tablet using the results from 8 clinical studies (XL184-020, XL184-306, XL184 307, XL184-308, XL184-309, XL184-311, XL184-021, and CA2099ER).

A 2-compartment model with a first-order elimination and a dual-absorption processes was used to describe the PK of cabozantinib. Based on observing double peaks in cabozantinib pharmacokinetic profile in Study XL184-020 after a single oral-dose administration, the absorption of cabozantinib was described using a dual absorption model: one portion of the dose was modeled as a zero-order release to the depot followed by a first order absorption to the central compartment, and the other portion was absorbed directly into the central compartment at a zero order after a long delay. The covariates of body weight on apparent clearance (CL/F) and volume of the central compartment (Vc/F), and sex on CL/F were included in the model, but they were deemed not clinically meaningful. The estimated exponent for the relationship between body weight and CL/F and Vc/F were 0.0885 and 1.04, respectively.

External Model Validation on Data from CABINET

The previously developed PopPK model for cabozantinib with the tablet formulation was externally validated based on cabozantinib PK data from CABINET. Goodness-of-fit (GOF) diagnostic plots included PRED versus DV, individual predicted concentrations (IPRED) versus DV, and conditional weighted residuals (CWRES) versus PRED or time were used to assess the predictive performance of the model. Prediction-corrected visual predictive check (pcVPC) was performed.

Adolescent Virtual Population

A virtual NET population of 4800 adolescents, evenly split between 2400 boys and 2400 girls, aged 12 to under 18 years was constructed. This was done using a normal distribution sampling of 200 participants for each half-year age group per each sex, based on the 2000 Center for Disease Control and Prevention (CDC) Growth Charts for the United States.

Adolescent Simulations

Steady-state simulations were performed for the 4800 adolescent participants using the parameter estimates from the final PPK model based on a daily dose of 40 or 60 mg. The interindividual random effects (η) for ith simulated adolescent sampling was based on a multivariate normal distribution from the variance-covariance matrix in PPK variance omega block (ω2).

Since the final population pharmacokinetic (PPK) model parameter estimates indicated a shallow relationship between body weight and clearance, two approaches were employed to visualize and estimate the potential impact of body weight on cabozantinib exposure in adolescents:

1) For adolescents weighing > 40 kg, the simulation applied the final PPK model parameter estimates.
2) For adolescents weighing < 40 kg, the simulation applied allometric-scaling exponent of 0.75 for CL/F and 1 for V2/F and V3/F parameters.

Results:

<u>External Validation:</u>

The previously developed PopPK model for cabozantinib with the tablet formulation was externally validated using cabozantinib PK data from CABINET. Goodness-of-fit plots (Figure 3) of the model suggested that the previously developed model described cabozantinib PK in CABINET adequately. Conditional weighted residuals (CWRES) were scattered around 0 when examined versus population predicted cabozantinib (PRED), time after dose, and time after first

dose. Individual predicted concentrations (IPRED) had good alignment with the observed values, suggesting that cabozantinib exposures calculated using the individual PK parameters were adequate to predict the observed exposures in CABINET.

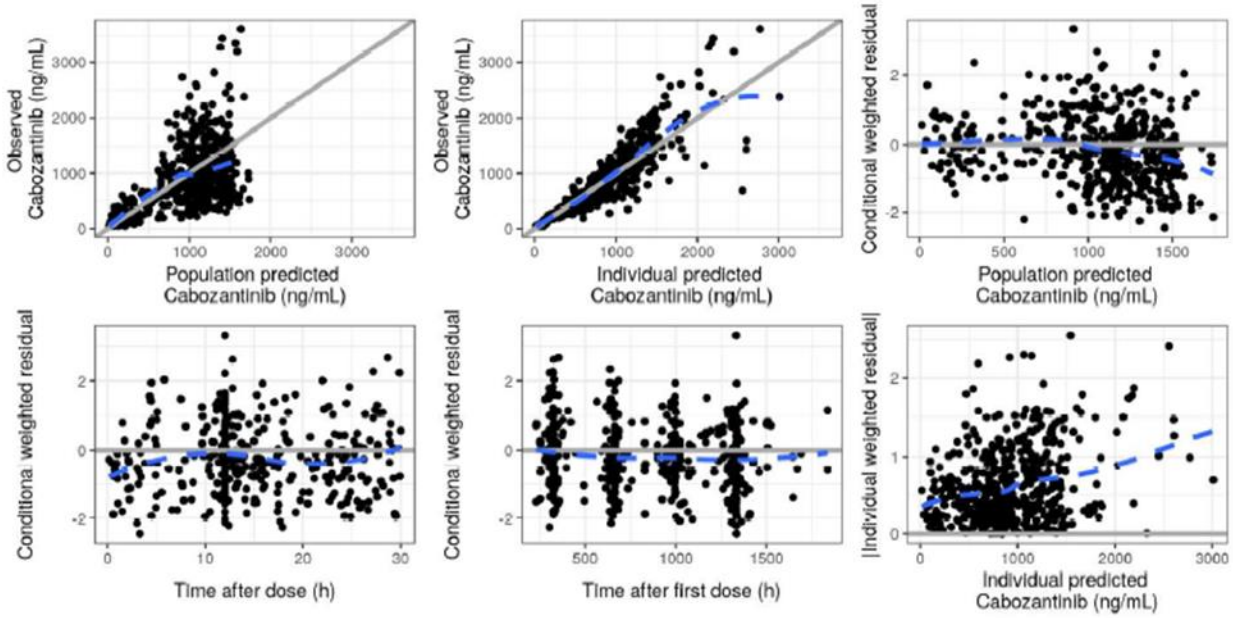
Table 2. Final Parameter Estimates of the Cabozantinib Final PopPK Model

Parameter	**Estimate**
CL/F (L/h)	2.06
V2/F (L)	103
Q/F (L/h)	19.3
V3/F (L)	192
KA (1/h)	0.826 (FIX)
ALAG1 (h)	0.359 (FIX)
D1 (h)	0.385 (FIX)
ALAG2 (h)	22.2 (FIX)
D2 (h)	5.94 (FIX)
F1 Fraction	0.709 (FIX)
Sigma proportional HV	0.217
Sigma additive HV	-0.351
Sigma proportional patients	0.302
Sigma additive patients	53.7
WEIGHT ON CL/F	0.0885
WEIGHT ON V2/F and V3/F	1.04
Female on CL/F	-0.201

IIV CL/F	0169
IIV V2/F	0.13
IIV V3	--
IIV KA1	0.373
IIV D1	0.159
IIV F1	0.424

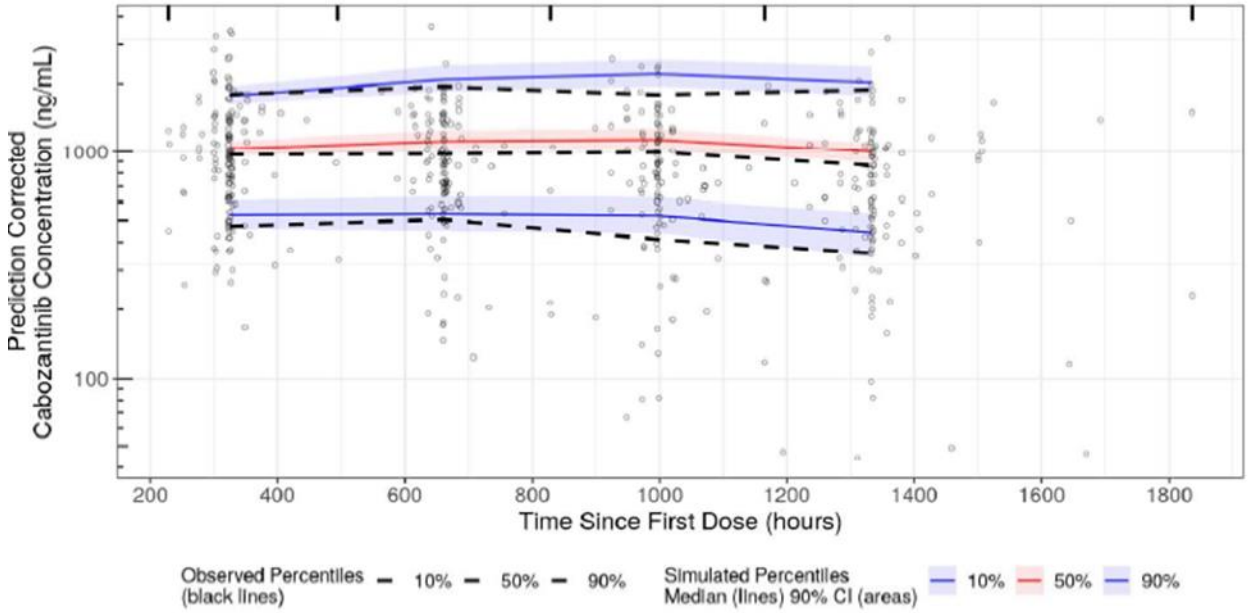
Source: Reviewer's analysis

Figure 1. Goodness of Fit of the Cabozantinib Final PopPK Model (CABINET)



Source: Figure 3. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Figure 2. Prediction-Corrected Visual Predictive Checks of the Cabozantinib Final PopPK Model (CABINET)



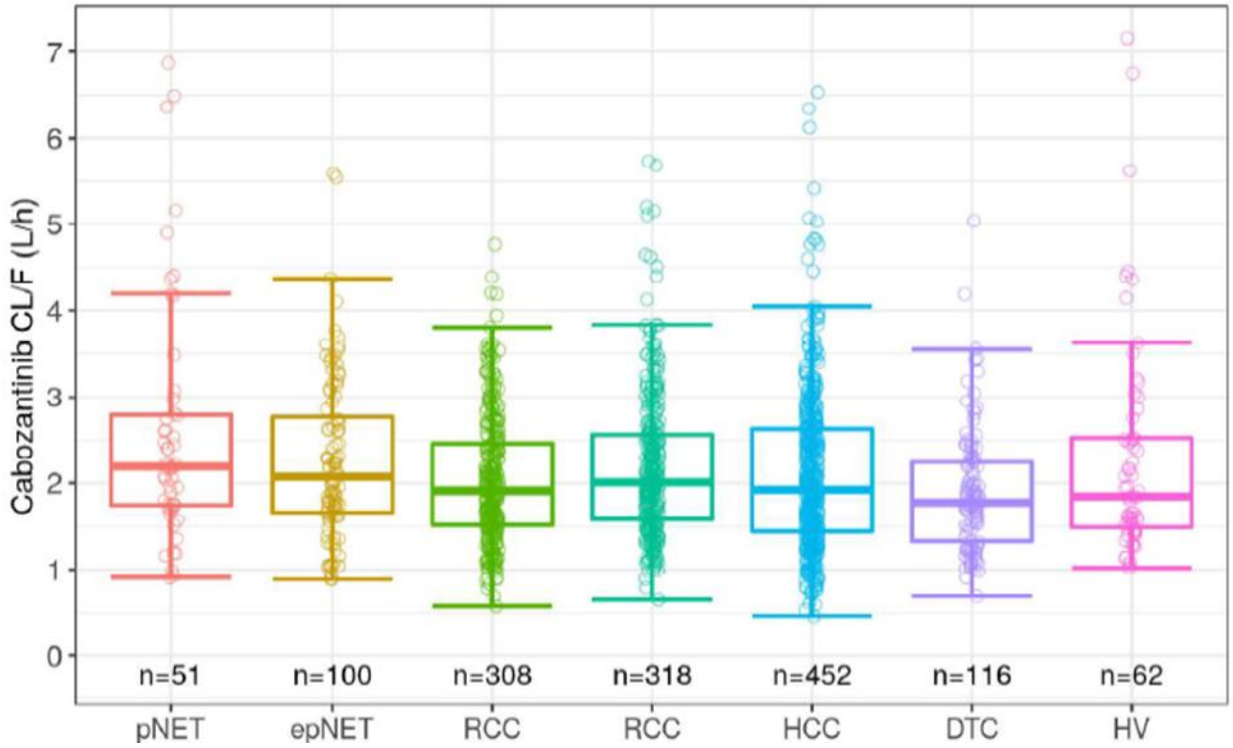
Source: Figure 4. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Effect of Cancer Types on Cabozantinib PK:

The effect of covariates on cabozantinib exposure was visualized by examining post-hoc CL/F

by participants with different tumor types including NET and healthy volunteers are compared in **Figure 3**. Results from the studies used to build the previously developed PPK model and CABINET are included in the comparison. CL/F in NET including pNET and epNET is similar in participants with the different tumor types.

Figure 3. Post-Hoc CL/F by Evaluated Population (Healthy Volunteers and Participants with Different Tumor Types)



Source: Reviewer's analysis to confirm Figure5. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Adolescent Simulations:

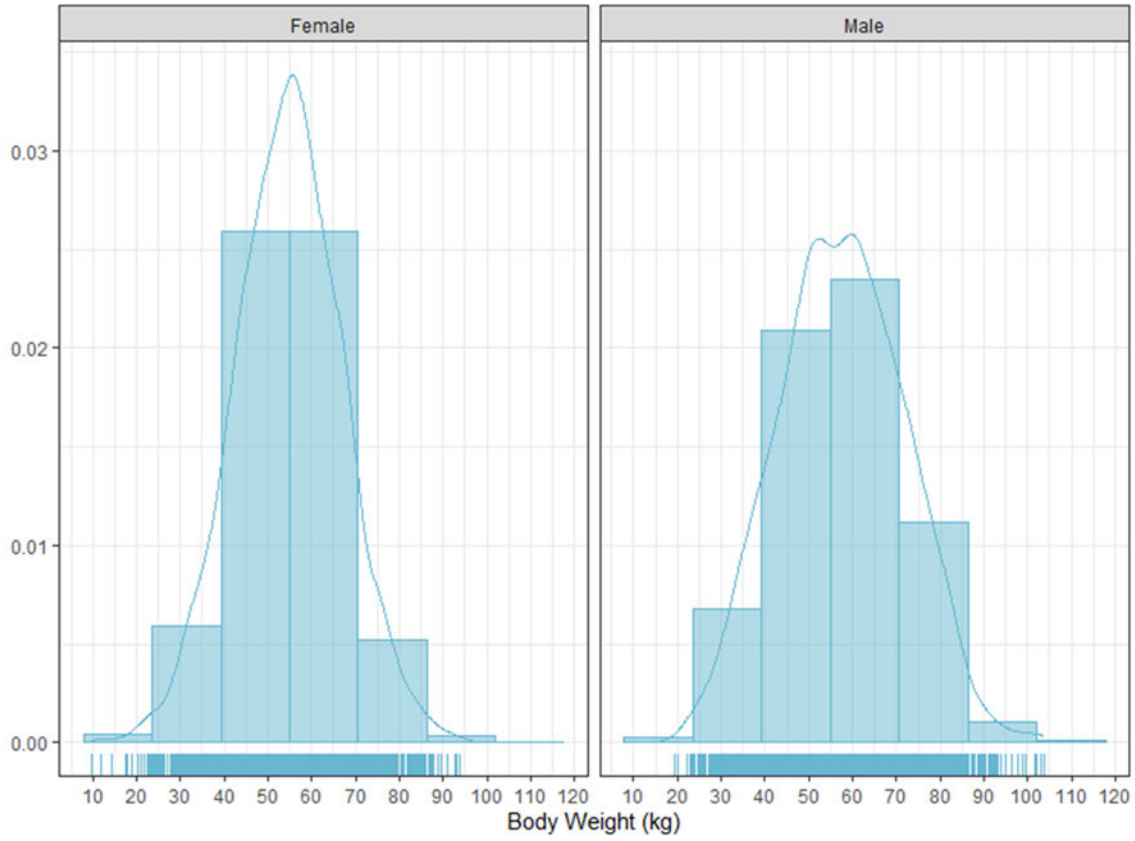
A virtual population of 4800 adolescents from 12 to less than 18 years of age were sampled from a normal distribution based on the CDC Growth Chart. These adolescent body weights were binned in ordinal categories (**Table 3, Figure 4**). 11.5% of adolescents in the virtual population weigh less than 40 kg.

Table 3. Summary of Simulated Virtual Adolescents with Varying Body Weights

Adolescent Weight Bins	Overall (N=4800)
<35 kg	281 (5.9%)
[35-40) kg	272 (5.7%)
[40-50) kg	1027 (21.4%)
[50-60) kg	1384 (28.8%)
[60-70) kg	1118 (23.3%)
[70-78) kg	456 (9.5%)
[78-110) kg	262 (5.5%)

Source: Reviewer's analysis to confirm Table 8. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Figure 4. Simulated Virtual Adolescents with Varying Body Weights (by Sex)



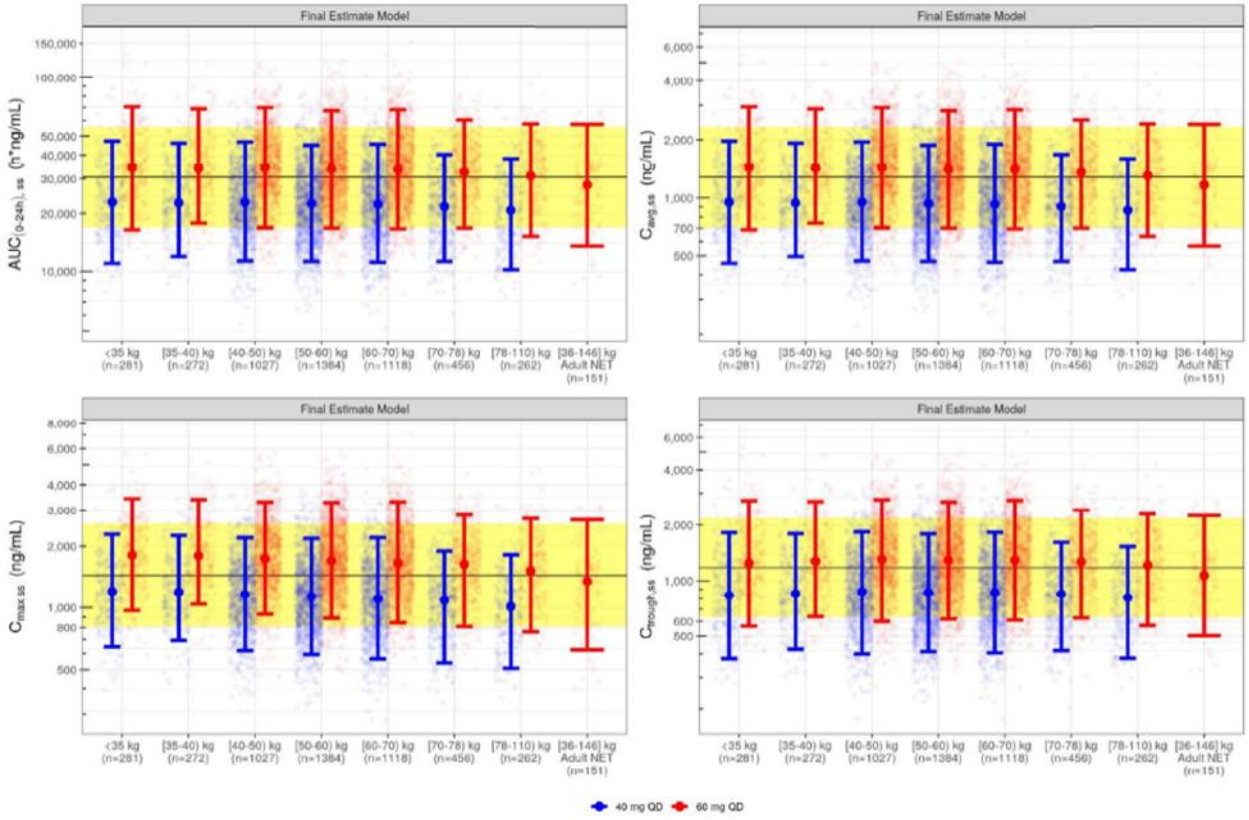
Source: Reviewer's analysis

Adolescent Simulations and Dose Selection:

Using the final PPK model, the median and 90% prediction intervals (5th and 95th percentile) for cabozantinib exposures (AUC(0-24h),ss, Cavg,ss, Cmax,ss, and Ctrough,ss) for adolescents across body weights receiving 60 mg QD (**Figure 5)** were predicted to be within the simulated adult exposures receiving the same daily dose of 60 mg.

The predicted exposures for 40 mg QD in adolescents were lower than those in adult cancer patients receiving 60 mg QD. This was expected since the estimated exponent in the final PPK model of body weight effect on CL/F was 0.0885, which resulted in minimal effect of body weight on predicted steady cabozantinib exposure. The major influencing factor for drug exposures is the dosage.

Figure 5. Predicted Steady-state Adolescent Cabozantinib Exposures Using the Final PPK Model

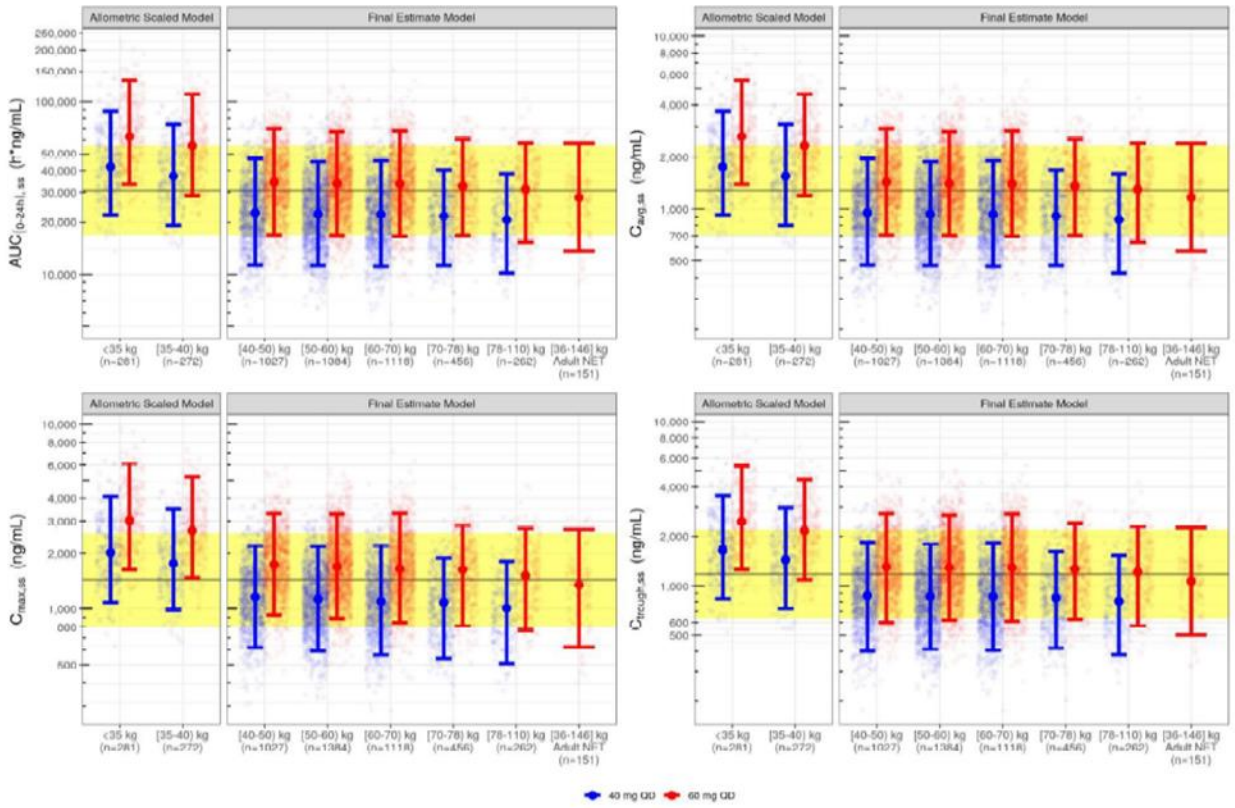


Source: Reviewer's analysis to confirm Figure 7. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

Figure 6 presents simulations for adolescents with body weights > 40 kg using the final PPK model, and for those < 40 kg using the final PPK model but with allometric exponents of 0.75 for CL/F. With this conservative simulation scenario, adolescents with body weights < 40 kg and receiving cabozantinib 60 mg QD were predicted to have higher cabozantinib plasma exposures relative to adults receiving the same daily dose. For adolescents weighing less than 40 kg and

receiving 40 mg QD of cabozantinib, the predicted adolescent exposures had better overlap with exposures for adults receiving 60 mg QD.

Figure 6. Predicted Steady-state Adolescent Cabozantinib Exposures Using the Final PPK Model



Source: Reviewer's analysis to confirm Figure 8. Cabozantinib Population PK Report for XL184-CABINET.PPK.001

The previously developed cabozantinib PopPK model adequately described the PK of cabozantinib in 151 patients with neuroendocrine tumors (NET), including epNET and pNET, in the CABINET study.

Tumor type had no detectable impact on cabozantinib PK parameters. Cabozantinib exposures observed in the NET population in CABINET were comparable to those in other tumor types for which cabozantinib has previously been evaluated.

The adult dose of cabozantinib 60 mg QD is appropriate for adolescents with body weight ≥ 40 kg. This weight range is well represented within the adult population evaluated across cancer types, and no clinically meaningful relationship was observed between cabozantinib clearance (CL/F) and body weight.

Extrapolating adult exposures to adolescents weighing < 40 kg using an allometric scaling approach for CL/F (with an exponent of 0.75) provides a conservative estimate of the maximum

anticipated body weight effect on cabozantinib CL/F in this population. With conservative allometric scaling assumptions for CL/F and volume of distribution (V/F), the predicted exposures in adolescents weighing < 40 kg receiving 40 mg QD of cabozantinib (instead of 60 mg QD) better aligned with the exposures observed in adults receiving 60 mg QD.
This adolescent dosage selection for cabozantinib aligns with the FDA's 2019 guidance for industry, which recommends that adolescents < 40 kg receive a body weight (BW) or body surface area (BSA) adjusted dose (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-inclusion-adolescent-patients-adult-oncology-clinical-trials)

19.4.2. Exposure-Response Analysis

The Applicant's Position:
No additional data submitted with this application

The FDA's Assessment:
Not applicable.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Please refer to Section 8.2.

NDA 208692-S017 Signature Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Wentao Fu, PhD	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** ☒Authored ☐Approved
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Master Pharmacokineticist	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ☐ Authored ☒ Approved
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Clinical Reviewer	Sonia Singh, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** ☒ Authored ☒ Approved
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Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** ☒ Authored ☒ Approved
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Biometrics Reviewer	Arup Sinha, PhD	CDER/OTS/OB/DBV	Sections: 8	**Select one:** ☒ Authored ☐ Approved
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Supervisory Mathematical Statistician	Anup Amatya, PhD	CDER/OTS/OB/DBV	Sections: 8	**Select one:** ☐ Authored ☒ Approved
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Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OND/OOD/DOII	Section: 11	**Select one:** ☒ Authored ☐ Approved
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Deputy Division Director (Clinical)	Nicole Drezner, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** ☒ Authored ☒ Approved
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