Amsterdam, 19 June 2025
EMA/CHMP/138089/2025
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: CABOMETYX

International non-proprietary name: Cabozantinib

Procedure No. EMEA/H/C/004163/II/0040

Marketing authorisation holder (MAH) Ipsen Pharma

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2025. Reproduction is authorised provided the source is acknowledged.

Table of contents

List of abbreviations

AE	adverse event
AERS	adverse events reporting system
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	adequate tumour assessment
BIRC	blinded independent review committee
BOR	best overall response
BP	blood pressure
BSC	best supportive care
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
CVA	cerebrovascular accident
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DOR	duration of response
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	emergency department
EDC	electronic data capture
epNET	extra-pancreatic neuroendocrine tumour (carcinoid tumour)
ETM	event to monitor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
IRB	Institutional Review Board
IROC	Imaging and Radiation Oncology Core
ITT	intent-to-treat
LAD	left anterior descending artery
LMWH	low molecular weight heparin
Lu-177	lutetium-177
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NPACT	nonprotocol anticancer therapy
NE	Not evaluable/estimable

NET	neuroendocrine tumour
NOS	Not otherwise specified
OPEN	Oncology Patient Enrollment Network
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
pNET	pancreatic neuroendocrine tumour
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRRT	peptide receptor radionuclide therapy
PT	preferred term
QTc	corrected QT interval
QTcF	corrected QT interval calculated by the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SOC	system organ class
SPEER	specific protocol exemptions to expedited reporting
SSA	somatostatin analogue
SSTR	somatostatin receptor
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell count
WHO-DD	World Health Organization-drug dictionary

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Ipsen Pharma submitted to the European Medicines Agency on 2 September 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adult patients with progressive extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours after prior systemic therapy for CABOMETYX based on final results from study CABINET (A021602). This is a multicenter, two-arm, randomised, double-blind, placebo-controlled phase 3 study investigating cabozantinib versus placebo in patients with advanced Neuroendocrine Tumors (NET). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0309/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0309/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ingrid Wang Co-Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	2 September 2024
Start of procedure:	14 September 2024
CHMP Rapporteur Assessment Report	8 November 2024
PRAC Rapporteur Assessment Report	15 November 2024
CHMP Co-Rapporteur Assessment	20 November 2024
PRAC members comments	20 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	02 December 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2024
Request for supplementary information (RSI)	12 December 2024
CHMP Rapporteur Assessment Report	25 February 2025
PRAC Rapporteur Assessment Report	25 February 2025
PRAC members comments	5 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur Assessment Report	20 March 2025
Request for supplementary information (RSI)	27 March 2025
CHMP Rapporteur Assessment Report	26 May 2025
CHMP members comments	10 May 2025
Updated CHMP Rapporteur Assessment Report	12 June 2025
An Oral explanation took place on	17 June 2025
The CHMP adopted a Similarity Assessment Report	19 June 2025
Opinion	19 June 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

State the claimed the therapeutic indication

Neuroendocrine Tumours (NET)

CABOMETYX is indicated for the treatment of adult patients with progressive extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours after prior systemic therapy.

Epidemiology

Neuroendocrine tumours represent a heterogenous group of malignancies characterised 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. Based on a retrospective, population-based study using nationally representative data from the Surveillance, Epidemiology and End Results (SEER) program, the highest incidence rates were 1.49 per 100 000 in the lung, 3.56 per 100 000 in gastroenteropancreatic sites, and 0.84 per 100 000 in NETs with an unknown primary site (Dasari et al, 2017).

Biologic features

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).

Clinical presentation

Extra-pancreatic neuroendocrine tumours (epNET) can arise in multiple organs most commonly in the GI tract (48%) and lung (25%). epNETs are increasing in incidence and prevalence and are therefore a significant public health issue. They can cause significant morbidity due to symptoms from hormone secretion (e.g., carcinoid syndrome) or tumour burden. Prognosis of metastatic epNET is poor ranging from median OS of 5 months (lung) to 40 months (small bowel) (Hallet et al, 2015).

Pancreatic NETs (pNET) are thought to arise from the islet cells of the pancreas and are relatively rare accounting for approximately 10% of all NETs (Halperin et al, 2015). Compared to other NETs, pNETs are less commonly functional but may secrete a wider variety of hormones including glucagon, insulin and gastrin. Clinically, pNETs are classified primarily by stage with more than a third of patients having metastatic disease, and an additional 20% having disease that is locally advanced (Panzuto et al, 2011).

Similar to other malignant diseases, potential tumour-derived risks may occur based on the primary or metastatic disease location of NETs: hemoptysis, recurrent pneumonia due to bronchial obstruction, and compression syndromes (i.e. 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). 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).

Management

Management of NETs is dependent on primary tumour 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 Guidelines Version 1.2023; Pavel et al, 2021; Baudin et al, 2021). For locally advanced and metastatic disease, several agents have been approved in the EU and US based on PFS benefit seen in placebo controlled randomized studies. For the initial treatment of well-differentiated epNET and pNET, the somatostatin analogues (SSA) lanreotide and octreotide are considered to be first line therapy having shown PFS improvement compared with placebo (Caplin et al, 2014; Rinke et al, 2017). Beyond this, the treatment paradigms for progressive advanced epNET and pNET are distinct.

pNET: Approved treatment options include everolimus (Yao et al, 2011), sunitinib (Raymond et al, 2011) and for patients with SSTR+ disease, lutetium-177 (Lu-177) dotatate (Strosberg et al, 2017).

epNET: Approved treatment options include everolimus (though the efficacy of everolimus has not been established in most functional NETs) 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 approved in the EU or US (NCCN Guidelines Version 1.2023; Halfdanarson et al, 2020).

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). In the current treatment landscape, there are no data from randomized controlled trials supporting efficacy for any agent in patients whose disease has progressed on prior lines of approved therapy.

Unmet medical need

Treatment options for relapsed and progressive NET remain limited and therefore an unmet need is present given most patients acquire resistance to the current approved targeted therapies. Clinical outcomes remain poor in this patient population with significant mortality and morbidity due to NET related symptoms.

Table 1. Landmark Trials of Approved Agents in Extra-Pancreatic or Pancreatic NET

Product name	Relevant indication	Year and approval type	Dosing/Administration	Efficacy Information	Important safety and tolerability issues	Study Name and Reference
Somatostatin analogues						
SOMATULINE Autogel **(Lanreotide)**	Unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs	2014 Full approval	120 mg SQ every 4 weeks	Lanreotide (n=101) vs placebo (n=103) Prim EP: PFS (mos); HR (95% CI): NR vs 18.0; 0.47 (0.3, 0.73) Sec EP: mOS (mos); Not available	Cholelithiasis, hyperglycemia and hypoglycemia, cardiovascular abnormalities, thyroid function abnormalities	CLARINET Caplin et al, 2014 Somatuline Autogel® Prescribing
mTOR inhibitors						
AFINITOR **(Everolimus)**	Progressive pNET and progressive, well-differentiated, non-functional NET of GI or lung origin that are unresectable, locally advanced or metastatic	2011 (pNET) Full approval 2016 (GI, lung NET) Full approval	10 mg po qd	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% 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%	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	RADIANT-3 RADIANT-4 Yao et al, 2016c Afinitor® Prescribing
VEGFR TKIs						
SUTENT (Sunitinib maleate)	Progressive, well-differentiated pNET with unresectable locally advanced or metastatic disease	2011 Full approval	37.5 mg po qd	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%	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	SUN-1111 Raymond et al, 2011; Sutent® Prescribing

Product name	Relevant indication	Year and approval type	Dosing/Administration	Efficacy Information	Important safety and tolerability issues	Study Name and Reference
Peptide receptor radionuclide therapy						
LUTATHERA **(Lutetium Lu-177 dotatate)**	SSTR-positive GEP NET	2018 Full approval	7.4 GBq (200 mCi) IV every 8 weeks for a total of 4 doses	Lu-177+Oct LAR 30mg (n=116) vs Oct LAR 60 mg (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%	Risk from radiation exposure, myelosuppression, secondary MDS and leukemia, renal toxicity, hepatotoxicity, hypersensitivity reaction, neuroendocrine hormonal crisis, embryofetal toxicity, risk of infertility	NETTER-1 Strosberg et al, 2017 Strosberg et al, 2021 Lutathera Prescribing

2.1.2. About the product

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumour cell proliferation and/or tumour neovascularization, including VEGFR2, MET, RET, and KIT. Cabozantinib targets also include TYRO3, AXL, and MER (TAM family kinases), which are implicated in promoting suppression of an antitumour immune response.

Cabometyx is available as film-coated tablets which contain 20 mg, 40 mg or 60 mg cabozantinib. The recommended dose of CABOMETYX is 60 mg once daily.

Currently approved indications:

Renal cell carcinoma (RCC)
CABOMETYX is indicated as monotherapy for advanced renal cell carcinoma
- as first-line treatment of adult patients with intermediate or poor risk (see section 5.1),
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy (see section 5.1).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

Hepatocellular carcinoma (HCC)
CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Differentiated thyroid carcinoma (DTC)
CABOMETYX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The pivotal study of this application (CABINET) was sponsored by the NCI (Bethesda, MD) and conducted by the Alliance for Clinical Trials in Oncology (Alliance) in the United States (US). Scientific advice by EMA has not been requested. The FDA reviewed the protocol and gave advice to NCI (DCTD) in the period 2018-2024. The most important subject for discussion was the possibility of using a

planned interim analysis as the primary analysis. The FDA discouraged the plan for conducting a superiority interim analysis. On several occasions, FDA stated that the planned interim analysis based on 66% of events may not provide for a reliable estimate of the treatment effect. The interim analysis of PFS may not be sufficiently robust and therefore susceptible to overestimation. The 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. Also, there may not be adequate data to evaluate safety, duration of benefit, and important subgroups. In response to this advice, the protocol was amended to no longer include an interim analysis for superiority. However, two interim analyses for futility at 33% and 66% of the projected number of events were kept. Contrary to the FDA advice, this application is based on an interim analysis (see *Conduct of the study*). The sponsor was advised to collect sparse PK samples in all patients treated in the cabozantinib arm to perform population PK and exposure-response analyses for the proposed new indication.

2.1.4. General comments on compliance with GCP

The pivotal study is declared to have been conducted in accordance with the ethical principles of Good Clinical Practice and the International Council on Harmonisation Harmonised Tripartite Guideline.

The MAH has provided information that FDA has inspected two study sites as well as IROC Ohio (Alliance Imaging Core Lab) where the blinded review of images was performed. There were no findings of great concern.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The total refined fraction of marked penetration for the previous indications is 0.00024.

For the new indication, the treatment of neuroendocrine tumours (NETs), the prevalence rate in the UK is 9/100 000, and this seems to be a realistic worst-case scenario for EU countries. The incidence in Norway is 8.35/100 000, but for the calculation of the Fpen, the incidence in the UK is used. This results in 6112 patients in the UK, and a Fpen of 0.00009.

Adding the Fpen for NETs to the Fpen for the previous indications, results in a total Fpen of 0.000325.

This results in a PECsurfacewater of 0.00975 µg/L, which is below the action limit of 0.01 µg/L and Cabometyx is not a PBT substance as log Kow does not exceed 4.5.

Substance (INN/Invented Name): cabozantinib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	<4.5	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B

Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00975 µg/L	µg/L	> 0.01 threshold: N

2.2.2. Discussion on non-clinical aspects

No new non-clinical data but a discussion on "Ecotoxicity/environmental risk assessment" have been submitted in this application, which is considered acceptable.

Cabozantinib is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, cabozantinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatment arms (Test Product(s): Dosage Regimen, Route of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Duration of Treatment	Data cut-off date	Type of Report
Efficacy Safety	A021602 (CABINET)	Module 5.3.5.1	The primary objective of this study was to determine whether cabozantinib compared with placebo significantly improved PFS in subjects with either advanced extra- pancreatic neuroendocrine tumors (epNET; ie, carcinoid tumors) or pancreatic NET (pNET) whose disease had progressed after prior therapy.	Phase 3 Multicenter, randomized, double-blind placebo-controlled trial in 2 separate cohorts (epNET and pNET) Primary endpoints: • PFS per RECIST 1.1 by BIRC	**Cabozantinib:** Oral cabozantinib (60 mg) once daily (qd) **Placebo**: Oral cabozantinib-matched placebo once daily	epNET cohort ITT population: 203 **cabozantinib**: 134 **placebo**: 69 pNET cohort ITT population: 95 **cabozantinib**: 64 **placebo**: 31	Subjects with either advanced epNET or pNET whose disease had progressed after prior therapy.	Subjects received blinded treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Crossover to cabozantinib was permitted after PD per RECIST 1.1 confirmed by blinded real-time central review.	CCO (24 Aug 2023)	Final CSR

Abbreviations: BIRC=blinded independent radiology committee, CCO=clinical cut off, CSR=clinical study report, epNET=extra-pancreatic neuroendocrine tumors, ITT=intend to treat, PFS=progression-free survival, pNET=pancreatic neuroendocrine tumors, RECIST=Response Evaluation Criteria in Solid Tumors

2.3.2. Pharmacokinetics

The clinical pharmacokinetics (PK) of cabozantinib have been characterised for other tumour types in previous submissions (Chan et al, 2017). The PK analysis in the CABINET study was optional and no population PK or exposure-response analyses were conducted for this application.

Methods

Blood samples for cabozantinib measurements were collected only in subjects who consented to participate to the optional A021602-PP1 substudy. Approximately 5 ml of peripheral blood for cabozantinib trough concentrations were collected from subjects prior to receiving their first cabozantinib dosage (as 20 mg tablets) on Cycle 1 Day 1 (C1D1) and then obtained during clinic visits on Cycle 1 Day 15 (C1D15), Cycle 2 Day 1 (C2D1), Cycle 2 Day 15 (C2D15), and Cycle 3 Day 1 (C3D1) while still on protocol therapy but before receiving the scheduled daily dose (trough sample). Each cycle is 28 days.

Cabozantinib plasma concentrations were measured in subjects in both the cabozantinib and placebo treatment arms using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method implemented by the Alliance Pharmacology/Pharmacokinetic Core Laboratory at the University of Pittsburgh.

Subjects who had at least one reported plasma PK collection were included in the PK population. A total of 1052 PK records from 240 subjects were available. The PK analysis was performed on the PK Population, using all the concentration records that met the analysis eligibility requirements as described in the footnote to Table 2. After filtering for these eligible criteria, 424 PK records from 133 subjects were available for descriptive statistics.

Results

Summary PK data for epNET subjects, pNET subjects and for both cohorts combined are provided in Table 2. Individual and summary of cabozantinib plasma concentrations are presented by cohort (epNET and pNET) in Figure 1.

Figure 2 displays individual and summary cabozantinib plasma concentrations measured at C1D15 (corresponds to Week 3 Day 1, W3D1), C2D1 (W5D1) and C3D1 (W9D1), in subjects with different

tumour types receiving cabozantinib 60 mg once daily. The comparison includes subjects with renal cell carcinoma (RCC) enrolled in the METEOR study, subjects with hepatocellular carcinoma (HCC) enrolled in CELESTIAL study and subjects with differentiated thyroid carcinoma (DTC) enrolled in COSMIC-311 study.

Table 2. Summary Table of Cabozantinib Plasma PK Concentrations by Nominal Visit for Subjects in the Cabozantinib Arm (Subjects with Analysis Eligible Records[a])

Cabozantinib Concentration (ng/mL)												
	C1D15			C2D1			C2D15			C3D1		
	epNET (N=55)	pNET (N=31)	All (N=86)	epNET (N=82)	pNET (N=38)	All (N=120)	epNET (N=75)	pNET (N=35)	All (N=110)	epNET (N=73)	pNET (N=35)	All (N=108)
Mean	1020	1100	1050	927	816	892	934	784	886	784	640	737
(SD)	(569)	(692)	(613)	(601)	(520)	(577)	(544)	(543)	(546)	(560)	(439)	(526)
CV%	56%	63%	59%	65%	64%	65%	58%	69%	62%	72%	69%	71%
Median [Min, Max]	907 [0, 3350]	926 [362, 3440]	917 [0, 3440]	749 [0, 3600]	746 [0, 1970]	749 [0, 3600]	856 [0, 2390]	631 [0, 2570]	802 [0, 2570]	719 [0, 3200]	553 [0, 1800]	620 [0, 3200]

C, Cycle; CV%, coefficient of variation; D, day; Max, maximum; Min, minimum; mg Milligram; mL Milliliter; ng Nanogram; PK, pharmacokinetic; SD, standard deviation
a The PK analysis was performed on the PK Population, using all the concentration records that met the following analysis eligibility requirements:
1) The sample met stability requirements:
A. Samples stored more than >1090 days were excluded from the PK analysis
B. Samples received thawed or at room temperature were excluded from the PK analysis
C. Samples received as whole blood were excluded from the PK analysis
2) The PK concentration was measured at least 14 days after the first dose of cabozantinib, (ie, ≥ Study Day 15 relative to first cabozantinib dose)
3) The PK concentration was not missing
4) The PK plasma sample was associated with a planned visit (ie, was not unscheduled or taken during screening)
5) Dosing modifications prior to scheduled visits were included
6) Subject was originally assigned to experimental cabozantinib arm (ie, no crossover from placebo to active)
7) Subject consented to participate to the A021602-PP1 substudy

Figure 1. Individual and Summary Plasma PK Cabozantinib Concentrations Plotted Versus Nominal Visit by Cohort (epNET and pNET)

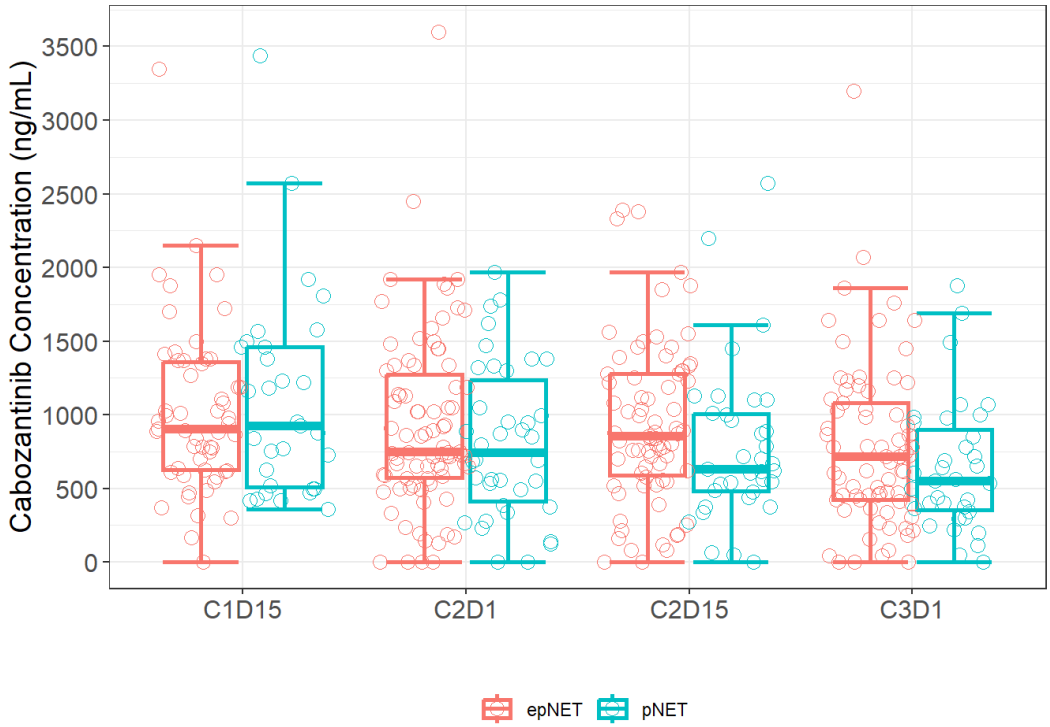


Figure 2. Individual and Summary Plasma PK Cabozantinib Concentrations Plotted Versus Nominal Visit from Monotherapy Cabozantinib 60 mg Once Daily Studies (METEOR [RCC], CELESTIAL [HCC], COSMIC-311 [DTC] and CABINET [NET])

2.3.3. Pharmacodynamics

Mechanism of action

Cabozantinib is an orally bioavailable inhibitor of multiple RTKs known to play important roles in tumour cell proliferation and/or tumour neovascularization, including VEGFR2, MET, RET, and KIT. Cabometyx is approved for single agent therapy in renal cell carcinoma, hepatocellular carcinoma and differentiated thyroid cancer.

Primary and secondary pharmacology

No new data have been submitted, but published literature have been provided to support a pharmacological rationale for effect in NETs.

A role for angiogenesis and VEGF-pathway signalling in NET is suggested by clinical observations that NETs are vascular tumours. Expression of VEGF has been demonstrated in epNET and pNET (Zhang et al, 2007; Terris et al, 1998). Increased expression of VEGFR2 has been demonstrated in tissue from GI NET tumours and the carcinoid BON cell line (Bowen et al, 2009; Silva et al, 2011). Additionally, pNETs show widespread expression of VEGFR2 and 3 in addition to PDGFRα and β, and KIT (Fjallskog et al, 2007; Fjallskog et al, 2003; Hansel et al, 2003). Preclinical data have demonstrated a role for MET activation in stimulating growth of pNETs in xenograft models, and a role for inhibition of MET in treatment (Krampitz et al, 2016; Reuther et al, 2016; Sennino et al, 2013; Sennino et al, 2012).

Tumour expression of MET has been correlated with reduction in overall survival (OS) in patients with pNET (Krampitz et al, 2016). In the RIPTag2 murine model of spontaneous pNET, treatment with an anti-VEGF antibody or sunitinib increases hypoxia, expression of HIF-1α, and activation of MET. This is associated with increased tumour invasion and metastasis, which can be reduced by either combining anti- VEGF pathway therapy with an inhibitor of MET or treatment with cabozantinib that simultaneously targets VEGFR2 and MET (Sennino et al, 2012).

2.3.4. Discussion on clinical pharmacology

PK sampling was optional, and only sparsely collected PK data have been presented. PK samples were obtained on the 1st and 15th day of each cycle prior to drug administration. This sparse sampling method only provides C_{trough} data, hence AUC and C_{max} in the sought population are currently not known. Based on the available C_{trough} data from the optional substudy A021602-PP1, exposure to cabozantinib seems comparable between subjects with epNET and pNET tumours. Moreover, trough exposure to cabozantinib in subjects with NET tumours seems comparable to other tumour types (RCC, HCC and DTC) in which cabozantinib monotherapy is indicated for (60 mg QD), indicating similar clearance across investigated patient populations. In addition, plasma concentrations for cabozantinib slightly decreased over time, in accordance with observations in previous studies for already approved indications. This decrease in exposure is likely caused by dose reduction or interruptions over time. No updated popPK model was provided.

No data on dose-exposure-response have been provided. According to the PK substudy protocol, population pharmacokinetic approaches would be used to explore the relationships of exposure versus dose modification, toxicity, and efficacy. However, no such analyses have been provided. Ideally, the dose-exposure-response should be investigated for each indication. Even if PK (plasma levels) is similar, exposure-response might differ depending on the tumour location. Moreover, there is a concern that a well-balanced dose has not been found, as already highlighted in previous assessment (i.e. II/05 and II/17). The clinical data show that approximately 2/3 of the patients in the study experienced dose reductions due to AEs, and the median dose actually received was 42.9 mg and 41.4 mg in the epNET or pNET cohorts, respectively (refer to assessment of clinical safety). The high frequency of dose modifications indicates poor tolerability, as previously discussed in other approved indications (RCC – in monotherapy and in combination with nivolumab, and HCC). The repeated pattern of dose reductions for several tumour types (RCC, HCC, DTC and NET) strengthens the concern that the chosen dose might be too high. The tolerability profile and benefit/risk balance may be improved with lower starting dose of cabozantinib. However, as lower doses have not been properly tested, and the dose-exposure-response relationships are not well characterised, it is unknown whether lower initial doses would maintain similar clinical efficacy. At the time of the approval of the extension of indication for RCC (EMEA/H/C/004163/II/0017), the applicant was recommended to prospectively investigate lower dose levels for cabozantinib in future studies. The MAH is reminded to further investigate dosing strategies as well as sources of variability in cabozantinib PK in future studies. Regarding this application, it is noted that the CABINET study was not conducted by the applicant, and therefore this issue is not pursued further as part of this procedure.

No new PD data have been provided. A scientific rationale for effect of cabozantinib on NETs has however been provided based on known mechanism of action, and by referring to literature data indicating beneficial effect of inhibition of both VEGFR2 and MET in animal models of NETs. Inhibition of VEGFR and MET leads to downstream inhibition of mTOR in tumour cells, with subsequent inhibition of angiogenesis. Considering that mTOR is also inhibited by sunitinib (inhibiting PDGFR and VEGFR, with downstream inhibition of mTOR) and everolimus (inhibits mTOR via FKBP12) approved for treatment of NET and pNET, a beneficial effect on cabozantinib on epNET and pNET could be expected.

2.3.5. Conclusions on clinical pharmacology

Cabozantinib PK in epNET/pNET patients are comparable to that in other cancer patient populations investigated earlier based on analysis of trough concentrations. The clinical pharmacology package is considered adequate for the current application.

2.4. Clinical efficacy

Based on the observed clinical activity of cabozantinib in NET from a Phase 2 study (NCT01466036, see 'Supportive study(ies)' section below), and the unmet need in the treatment of NET, the current Phase 3 study (CABINET) was designed to evaluate the effect of cabozantinib on PFS compared with placebo. This study included subjects with epNET and pNET who had received at least one prior FDA-approved systemic therapy. CABINET is the pivotal trial on this application.

2.4.1. Dose response study(ies)

No dose-response studies were conducted for this variation application. See clinical pharmacology section.

2.4.2. Main study

CABINET: Randomised, Double-Blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumours after Progression on Prior Therapy

This study was sponsored by the NCI (Bethesda, MD). The Alliance for Clinical Trials in Oncology (Alliance) conducted the study for registrational purposes at 62 investigative sites in the United States (US).

The Alliance Data and Safety Monitoring Board (DSMB) conducted regular reviews of safety data. The committee consisted of a patient advocate as well as a group of Alliance members with oncology or biostatistics expertise, and National Institutes of Health (NIH) representatives. Distribution and submission of safety reports during the study was the responsibility of the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP).

The Alliance was responsible for clinical conduct, clinical data management, and data analyses for the interim analyses. The Alliance prepared a statistical analysis plan that described the study design, endpoints, sample size, and study level type I error control. Exelixis prepared an Addendum to the Alliance SAP to include additional analyses including those requested by the US FDA.

Exelixis was responsible for biostatistical analyses, programming, and for preparation of the clinical study report.

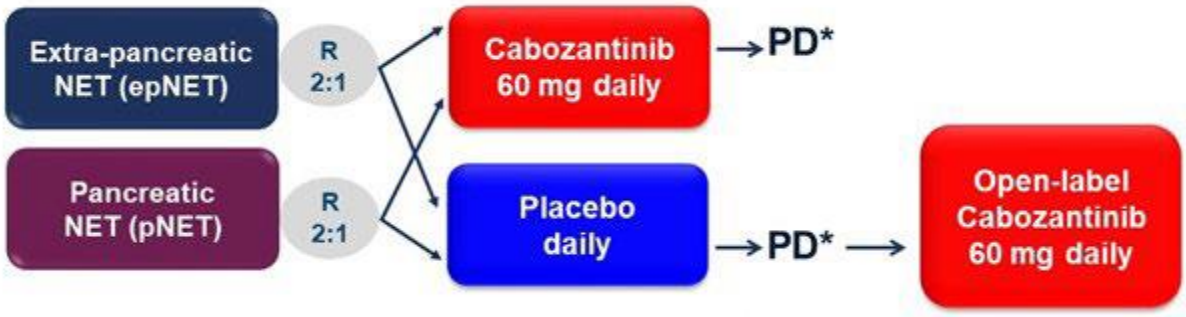
Radiographic images were centrally reviewed by an Imaging Central Review Panel, coordinated through Imaging and Radiation Oncology Core (IROC) Ohio (Columbus, OH).

The clinical study report for the Phase 3 study is based on preplanned interim analyses. Primary efficacy and safety analyses were performed based on a data cutoff date of 24 August 2023, which corresponds to the date of study-wide unblinding by Alliance and when all placebo subjects were eligible to cross over to cabozantinib (for more information see *Conduct of the study*).

Methods

Because of differences in biology and potential responsiveness to treatment, subjects with epNET and subjects with pNET tumour types were evaluated separately and enrolled into 2 separate cohorts to independently evaluate the efficacy and safety of cabozantinib.

Figure 3. Study schema



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

Study participants

Key eligibility criteria

Documentation of disease:

- Histological documentation: Well- or moderately differentiated neuroendocrine tumours of pancreatic (pNET) and non-pancreatic (i.e., extra pancreatic or carcinoid; epNET) origin by local pathology, including well-differentiated grade 3 NET.
- 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 analogues). 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 gastrointestinal (GI) NET.

- Prior treatment with somatostatin analogues was allowed, and continuation of treatment with somatostatin analogues while on cabozantinib/placebo was allowed provided that the subject had been on a stable dose for at least 2 months prior to enrolment.

Patient history:

- Prior treatment with cabozantinib was not allowed.
- No thromboembolic events within 6 months of registration (incl. stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), & pulmonary embolism (PE)).
- No uncontrolled hypertension within 14 days of registration (defined as systolic blood pressure (SBP) ≥150 mmHg and/or diastolic blood pressure (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 tumour with invasion into the GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration.

Treatments

Based on treatment assignment, subjects received either oral cabozantinib tablets at a dose of 60 mg (consisting of three 20-mg tablets) or matching placebo.

Study treatment was taken once daily during each 28-day treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The reason for discontinuation was documented, and the subject was followed (if the subject agreed) for response and survival until death or 8 years after registration (randomisation).

Subjects who had real-time centrally confirmed progression per RECIST 1.1 and had received placebo during blinded treatment could opt to receive open-label cabozantinib. Open-label treatment consisted of three 20-mg oral tablets (60 mg total) of cabozantinib taken once daily for each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were monitored for treatment response and toxicity.

Concomitant therapies

The following medication were allowed during treatment with cabozantinib/placebo:

- Somatostatin analogues (provided that the subject was on a stable dose for at least 2 months)
- Low dose aspirin ≤ 81 mg/day
- Anticoagulation with therapeutic doses of LMWH (provided that the subject was on a stable dose for at least 6 weeks prior to registration)

The following medication were not allowed during treatment with cabozantinib/placebo:

- Chronic concomitant treatment with strong CYP3A4 inhibitors or inducers (subjects were to discontinue these drugs at least 14 days prior to registration in the study)
- Other planned concurrent investigational agents or other tumour directed therapies (chemotherapy, radiation)
- Full dose oral anticoagulation/antiplatelet therapy
- Treatment with warfarin
- Anticoagulation in subjects with brain metastases

Objectives

The primary objective of this study was to determine whether cabozantinib compared with placebo significantly improved progression-free survival (PFS) in subjects with either epNET or pNET whose disease had progressed after prior therapy. Secondary objectives included comparisons between treatment groups of overall survival (OS), safety and tolerability, and overall radiographic response rate (ORR).

Outcomes/endpoints

Primary endpoint: PFS defined as the time from randomisation to the earlier of progressive disease (PD) per RECIST 1.1 or death due to any cause, determined by BIRC

Secondary endpoints:

- OS, defined as the time from randomisation to death from any cause
- ORR, defined as the proportion of subjects whose best response was either complete response (CR) or partial response (PR)
- Safety and tolerability of cabozantinib versus placebo

Additional endpoints:

- DOR, defined as the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1
- DCR, defined as the proportion of subjects with a best overall response (BOR) of CR, PR, or stable disease (SD)
- Concordance between the investigator and BIRC response assessments

Tumour assessments were performed at baseline and every 12 weeks (± 1 week) following the start of study treatment until evidence of progression.

The radiographic images were evaluated for tumour response or progression by the investigator as well as by a batched BIRC; both the investigator and BIRC reviews followed RECIST 1.1. In addition, PD was confirmed by blinded real-time central review. This review was incorporated due to challenges with interpreting radiology results of neuroendocrine tumours and due to a desire to minimise the chances of informative censoring of data related to a local investigator interpretation of PD followed by treatment discontinuation prior to central radiology interpretation of PD. The real-time assessments and the batched BIRC assessments were performed by different readers.

Real-time central review imaging readers were to be blinded to the subject's treatment but could access clinical history. At the time of real-time centrally confirmed radiographic disease progression (per RECIST 1.1), subjects were unblinded to treatment assignment, and those on placebo could elect to crossover to open-label cabozantinib treatment. If radiographic PD was not confirmed by real-time central review, subjects were to continue with blinded study treatment and undergo study treatment assessments according to the protocol.

In the event of disagreement between the local and central imaging reads, adjudication could be requested by the local site. If requested locally or centrally, the adjudicator could be put in touch with the local treating physician. The adjudicator's decision was used as the final central review decision for the interpretation and treatment/response determinations.

In the event of disagreement between central reviewers with previously recorded central review measurements, a blinded adjudication by another central reviewer would occur; the adjudicator was not the same radiologist that performed either of the central reviews in question. The adjudicator's decision was used as the retrospective, batched central review decision.

Multiphase CT scans (chest/abdomen/pelvis) were the preferred imaging modality. Equivalent modalities (MRI scan of the abdomen/pelvis with either chest X-ray or non-contrast chest CT) could have been used at the discretion of the treating physician. The same imaging modality used at baseline was to be used for all subsequent evaluations.

Subjects were followed for survival and second malignancy every 6 months until death or 8 years after registration (randomisation).

Sample size

For the **epNET** cohort the assumption that for PFS of 7 months for the placebo arm were based on results from the afinitor studies RADIANT-2 and RADIANT-4 (8.6 and 3.9 months, respectively). For the cabozantinib arm, a PFS of 12 months corresponding to a HR of 0.583 was assumed without any reference to literature or previous data. With otherwise similar assumptions as above, for the epNET cohort, assuming 35 months accrual, 4.286 % dropout, 11 months minimum follow up, a sample size of 210 patients (141:69) were to be recruited to provide 164 events for the final analysis of PFS.

Correspondingly for the **pNET** cohort the assumptions for PFS of the placebo arm of 5 months was based on the studies RADIANT-3 (afinitor vs placebo) and SUN-1111 (sunitinib vs placebo). For the cabozantinib arm, a PFS of 8.8 months corresponding to a HR of 0.568 was assumed without any reference to literature or previous data. Further assuming an accrual time of 31 months with 6 pts/mth, 4.32% of dropout, minimum follow-up in all other patients of 8 months, exponential survival, a one-sided log-rank test for superiority at alpha level 0.025, 90% power, two non-binding interim analyses for futility with a nominal spending of 0.001 alpha each analysis and a 2:1 patient allocation for cabozantinib and placebo, it was calculated that 185 patients (124:61) were to be recruited to provide 149 events for the final analysis of PFS.

Randomisation

Subjects were allocated to a cohort based on disease type (epNET vs pNET), and eligible patients were randomised 2:1 to cabozantinib or placebo using a permuted block schedule by means of a central Interactive Web Response System. Randomisation was stratified by Concurrent Somatostatin Analogue Use: (Yes - No), Prior Sunitinib Therapy: (Yes - No) for the pNET cohort. For the epNET cohort stratification included the factors Concurrent Somatostatin Analogue Use: (Yes - No), Primary Site [Midgut/Unknown primary site - Non-midgut GI/Lung/Other known primary site not listed].

Blinding (masking)

The study was performed double blind.

The subject treatment assignments were to remain blinded to the investigator and subject unless an event required emergency unblinding (e.g., a life-threatening unexpected AE that was at least possibly related to study treatment for which unblinding would influence treatment decisions or a medication error, such as an accidental overdose) or until there was a centrally confirmed disease progression. The steps for unblinding a subject upon progression were as follows: the imaging scan showing progression per RECIST 1.1 (except symptomatic deterioration) along with the local report were

submitted for real-time central review to IROC Ohio within 24 hours of local determination of progression; IROC Ohio was to confirm disease progression. This confirmation was then sent to the study site and the Alliance Statistics and Data Management Center. If unblinding and crossover were desired, the site was to notify the Alliance Registration Office to unblind the subject.

Statistical methods

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 randomised. The ITT was used to analyse disposition, demography, baseline characteristics, primary efficacy analysis, secondary efficacy analyses, protocol deviations, and additional endpoints. Subjects were grouped based on the treatment they were assigned during randomisation.

ITT Population and Randomised for ≥ 6 Months: All subjects in the ITT population randomised 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 randomisation.

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.

Primary Endpoint Analysis

The primary analysis of PFS was to be performed when a specified number of events had occurred: 149 and 164 PFS events for the pNET and epNET cohorts, respectively. For both cohorts, PFS was to be compared between treatment arms in the ITT population using the stratified log rank test at one-sided level 0.023 (see below Interim analyses/Multiplicity). The stratification factors as collected at enrolment were to be used for the analysis. The HR for PFS was to be estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR provided. Kaplan-Meier methodology was to be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves produced. Brookmeyer Crowley methodology was to be used to construct the 95% CI for the median PFS for each treatment arm. Patients who experienced progression per IROC review or died were to be treated as having an event at the assessment or death date, respectively. In the primary analysis, patients who did not have a PFS event were to be censored for PFS at the last disease assessment date which was prior to initiation of new anticancer therapy, patients without disease evaluations post baseline on day 1, and patients lost to follow up at the last disease assessment. Results from an unstratified analysis and the PFS according to investigator assessment were to be provided as sensitivity analyses. Later revisions of the analysis plan (Addendum to SAP 2.0, 26 Feb. 2024) added numerous sensitivity analyses, and changed the primary analysis to also censor patients with progression after two or more missing assessments. The PFS analyses provided are summarized in Table 3.

Table 3. Summary of PFS Primary and Sensitivity Analysis

Analysis Type	Description of the Primary and Sensitivity Analyses of PFS	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, PFS-EP2, and PFS-EP3 were specified in Alliance SAP 2.0, dated 14 Aug 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-EP6, EA1-EA3) were added to the Exelixis SAP 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 2 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 cabozantinib 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 cabozantinib crossover therapy) were treated as an event at the date of the initiation of the NPACT	
Sensitivity[a] (PFS-EA4)	Ignore missing imaging scans	PFS-EA4 is a separate sensitivity analysis of PFS per the Alliance SAP 2.0, dated 14 Aug 2023.

ATA, adequate tumour assessment; BIRC, blinded independent review committee; EDC, electronic data capture; epNET, extra-pancreatic neuroendocrine tumour; FDA, Food and Drug Administration; NPACT, non-protocol

anticancer therapy; PD, progressive disease; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour; SAP, statistical analysis plan
[a] For sensitivity analyses, changes from the primary PFS endpoint analysis are described.

Key Secondary Efficacy Analyses

For each cohort, OS was to be estimated using the method of Kaplan-Meier. The median OS, along with the 95% confidence intervals were to be presented, and a comparison between treatment arms using the stratified log-rank test at a one-sided cumulative 2.3% level of significance performed when approximately 155 OS events had been observed in each cohort, respectively. The stratified Cox regression was to be used to estimate the hazard ratio (HR) of OS, along with the 95% confidence interval. Patients who did not have an OS event were to be censored for OS at the date they were last known to be alive. The OS analyses within each cohort is planned to be conducted when approximately 155 OS events have been observed and a hierarchical approach is to be used to control for family-wise type-I error rate. It was planned that OS should be statistically tested only if the null hypothesis for the primary efficacy endpoint had been rejected for the respective cohort.

For each cohort, (confirmed) radiographic response rate, the proportion of patients with either (confirmed) CR or (confirmed) PR as their best response were initially to be estimated using point estimates and 95% confidence intervals (method according to Duffy and Santner). Radiographic response rate was to be compared between treatment arms using the 2-sample z-test to compare sample proportion at a one-sided 2.5% level of significance. A later revision of the analysis plan (SAP 2 Addendum, 26 Feb. 2024) altered this to using Clopper Pearson method for calculating the confidence intervals and statistical testing by stratified Cochran-Mantel-Haenszel (CMH) test primarily adjusting for the stratification factors from randomization, with the z-test and Fisher's exact test as sensitivity analyses. For patients who crossed over to open-label cabozantinib at centrally-confirmed PD, only disease assessments prior to crossover were to be considered. SAP 2.0 Addendum clarified that subjects who did not have any post-baseline tumour assessments were to be counted as non-responders.

The initial protocol and analysis plan included no sensitivity analyses for the secondary endpoints. Later revisions of the protocol and analysis plans (SAP 2.0 Addendum, 26 Feb. 2024) added analyses of progression by local investigator, OS and response rate by primary tumour site, OS comparison censoring at the initiation of NPACT and rank preserving structural failure time adjusting for treatment switching, sustained response/clinical benefit rate (at least 28 days apart) as sensitivity analyses, and duration of response in the ITT population by Kaplan-Meyer method in addition.

Subgroup analyses

Interaction p-values (interaction between treatment arms and specific subgroups) were planned to be used to determine whether the treatment effect was consistent. A p-value of < 0.1 would indicate that there is a differential treatment effect across different subgroups. The pre-planned subgroups initially were Prior Anti-VEGF Therapy (Yes vs. No) and Prior Targeted Radionucleotide Therapy (PRRT) (Yes vs. No).

A number of covariates were specified in the initial analysis plan:

- Age [<65, ≥65 years],
- Sex
- Race
- Baseline BMI
- Eastern Cooperative Oncology Group Performance Status (0, 1, 2)
- Tumour grade
- Functional (Hormone Secretion) Status: functional vs. non-functional
- Concurrent Somatostatin Analog Use: Yes vs. No

- Prior Sunitinib Therapy: Yes vs. No
- Primary Site: Midgut (duodenum, jejunum, ileum, appendix, cecum)/Unknown vs. Non-midgut GI (stomach, non-cecum colon, rectum)/Lung/Other [for carcinoid cohort only]

Later revisions of the analysis plan (SAP 3.0) added Ethnicity and Tumour differentiation as covariates and specified that subgroup analyses for PFS were to be performed for each covariate in both cohorts, except for prior sunitinib use which is only applicable in the pNET cohort.

Missing data

Other than for partial dates, missing data were not imputed and were treated as missing. SAP 2.0 Addendum clarified that subjects who did not have any post-baseline tumour assessments were to be counted as non-responders.

Interim analyses and Multiplicity

Two interim analyses for PFS futility were pre-planned for both disease cohorts when 33% and 66% of the projected number of events had occurred. A nominal alpha spending of one-sided 0.001 (ie, two-sided 0.002) for efficacy was included per interim analysis and the final analysis critical p-value therefore 0.023 for a one-sided test (or 0.046 for two-sided test). The analysis of OS was planned to use a hierarchical approach to control for family-wise type-I error rate allowing formally testing only if the null hypothesis for the primary efficacy endpoint, PFS, had been rejected, for each cohort, respectively.

Changes to the Planned Analyses

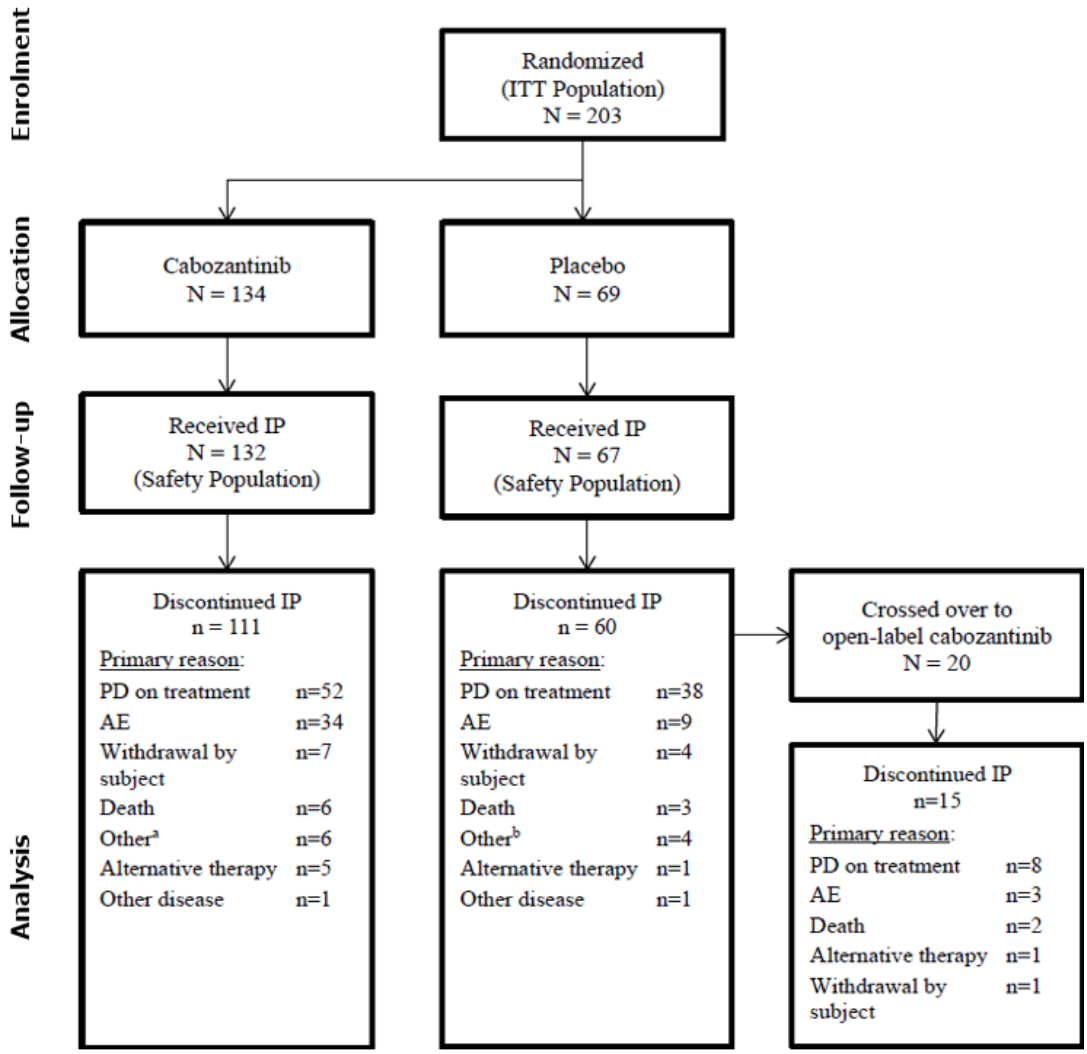
Changes from the planned analysis described in the Alliance SAP were provided in the addendum to the Alliance SAP version 2.0, dated 04 August 2023, prepared by Exelixis.

The SAP addendum (version 2.0, dated 26 February 2024) was prepared prior to database lock and no changes were made to that analysis plan.

Results

Participant flow

Figure 4. epNET: Participant flow



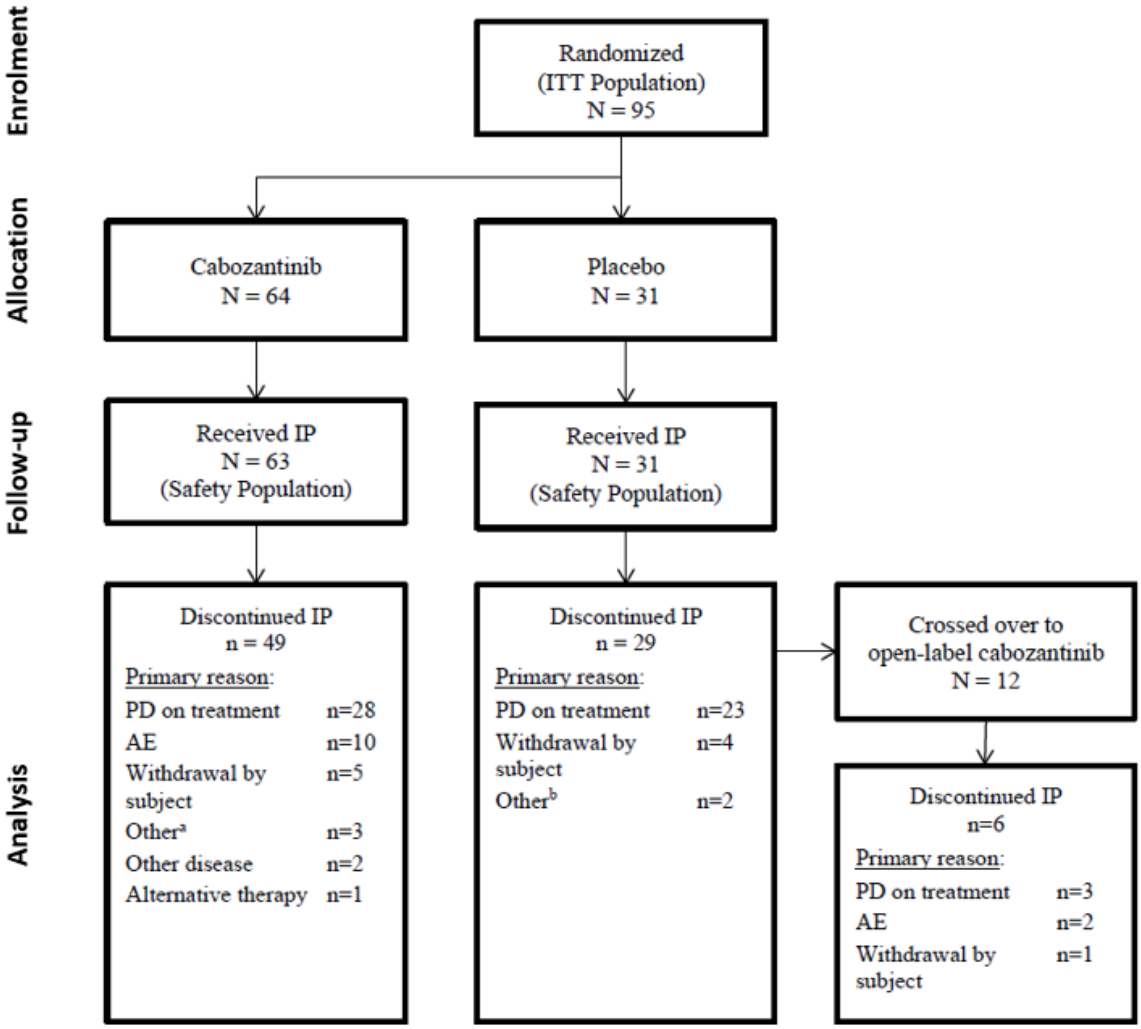
AE, adverse event; epNET, extra-pancreatic neuroendocrine tumour; IP, investigational product; ITT, intent-to-treat; PD, progressive disease
Note: Data are based on the cutoff date of 24 Aug 2023
a In the cabozantinib arm, 'other' included the following: clinical progression (2 subjects), worsening of non-target lesion (1 subject), loss of consciousness (1 subject), poor performance status (1 subject), and non-compliance (1 subject).
b In the placebo arm, 'other' included the following: clinical progression (3 subjects) and increase in tumour lesion size (liver nodule) (1 subject).

Table 4. epNET: Subject Disposition (ITT Population)

	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)
25th, 75th percentiles	12.88, 31.34	12.91, 31.51
Placebo subjects crossed over to treatment with open-label cabozantinib	NA	20 (29%)

ITT, intent to treat; NA, not applicable; SD, standard deviation
Follow-up (months) = (the data cutoff date – the date of randomisation +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).

Figure 5. pNET: Participant flow



Note: Data are based on the cutoff date of 24 Aug 2023
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).
b In the placebo arm, 'other' included the following: treatment hold for > 28 days (1 subject) and palliative care (1 subject).

Table 5. pNET: Subject Disposition (ITT Population)

	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)
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 tumour; 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 randomisation +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).

Recruitment

The study opened for enrolment on 18 July 2018. The first subject was randomised 26 October 2018. Patients were enrolled from 62 sites across the US.

Conduct of the study

In 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 interim analysis given that the study was double-blinded and independent central review of tumour assessments was lagging.

At the July 2023 DSMB meeting, the DSMB reviewed the interim analyses for PFS per investigator assessment for the pNET (1st interim analysis) and epNET (2nd interim analysis) cohorts and available

BIRC assessments. The results were based on a clinical cutoff date of 18 July 2023, at which time, 200 of a target of 210 subjects had been enrolled in the epNET cohort and 95 of a target of 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. The investigator-assessed PFS results were consistent with additional analyses using available BIRC results for both the pNET and epNET cohorts.

Table 6. Interim PFS by Investigator and BIRC Assessment (July 2023 Alliance DSMB)

	N (Cabozantinib and Placebo)	No. of Events	Stratified HR (95% CI)	Log-rank p-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 tumours; PFS, progression-free survival
a Data cutoff 13 Dec 2022
b Data cutoff 18 July 2023
c Data cutoff 02 Dec 2022

Based on this review, the DSMB voted unanimously to recommend termination of accrual and unblinding of the study to enable potential crossover for patients on the placebo treatment arms to receive open-label cabozantinib treatment. Following the DSMB recommendation, the Alliance stopped enrolment into the study on 07 August 2023. The DCO for the clinical study report is 24 August 2023.

Protocol amendments

Key changes to the original protocol, dated 24 May 2018:

Update 19 April 2019	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).
Update 24 July 2020	Broadened the eligibility criteria to include subjects who had progressed after a prior FDA-approved therapy (prior to this update, the criterion had specified progression after everolimus). 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. Modified stratification factors for clarity: • Definition of the midgut was changed to "jejunum, ileum, appendix, cecum, ascending colon, hepatic flexure" (replacing "duodenum, jejunum, ileum, appendix, cecum").

	• Definition of the non-midgut was changed to "duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon" (replacing "non-cecum colon").
Update 07 Dec. 2022	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. 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 (i.e., every 12 weeks ± 1 week). For the secondary endpoint of radiographic response rate, clarified that the radiographic response was to be confirmed.
Update 03 Feb. 2023	Removed allowance for diagnostic CT in the setting of PET/CT.

Protocol Deviations epNET

In the epNET cohort, 20 subjects (11 [8.2%] in the cabozantinib arm and 9 [13%] in the placebo arm) had at least 1 critical or major protocol deviation. A critical protocol deviation (other eligibility criteria not met) was reported for 1 subject (1.4%) in the placebo arm. No other critical protocol deviations were reported. The most frequently reported major protocol deviations involved other eligibility criteria not met (1 subject [0.7%] in the cabozantinib arm and 3 subjects [4.3%] in the placebo arm) and 'other' (2 subjects [1.5%] in the cabozantinib arm and 2 subjects [2.9%] in the placebo arm). Other major protocol deviations reported for > 1 subject overall included other study procedure (0.7% cabozantinib, 2.9% placebo), a lab eligibility criterion not met (0.7% cabozantinib, 1.4% placebo), and another study drug deviation (0.7% cabozantinib, 1.4% placebo).

Protocol Deviations pNET

In the pNET cohort, 9 subjects (6 [9.4%] in the cabozantinib arm and 3 [9.7%] in the placebo arm) had at least 1 protocol deviation. All protocol deviations were categorised as major, none was critical. Major protocol deviations reported for > 1 subject overall were other study procedure (4.7% cabozantinib, 3.2% placebo), 'other' (1.6% cabozantinib, 3.2% placebo), and a study drug deviation involving incorrect study treatment and incorrect order of administration (1.6% cabo., 3.2% placebo).

Baseline data

epNET cohort:

Table 7. epNET: Baseline Demographic Characteristics (ITT Population)

	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%)
65 to < 75	57 (43%)	30 (43%)
75 to < 85	16 (12%)	8 (12%)
≥ 85	1 (0.7%)	0
Gender		
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%)

	Cabozantinib (N=134)	Placebo (N=69)
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%)
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, Eastern Cooperative Oncology Group; EDC, electronic data capture; epNET, extra-pancreatic neuroendocrine tumour; GI, gastrointestinal; ITT, intent-to-treat; OPEN, Oncology Patient Enrolment Network; pNET, pancreatic neuroendocrine tumour; 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 in the summary of Primary Site of Stratification Factors per EDC.

Table 8. epNET: Cancer History and Baseline Disease Status (ITT Population)

	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

	Cabozantinib (N=134)	Placebo (N=69)
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%)
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 tumour; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumour; SD, standard deviation
a 7 subjects with a diagnosis of pNET were misallocated during enrolment 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 tumour.
c Six subjects with pNET were misallocated to the epNET cohort as follows: three to the cabozantinib arm, and three to the placebo arm
d Exact primary tumour 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.

Table 9. epNET: Summary of Metastatic Disease (ITT Population)

	Cabozantinib (N=134)	Placebo (N=69)
Extent of disease: metastatic	134 (100%)	69 (100%)
Extent of metastatic sites per investigator per EDC		
Nodal	92 (69%)	50 (72%)
Liver	119 (89%)	63 (91%)
Subcutaneous tissue	5 (3.7%)	1 (1.4%)
Abdominal wall	10 (7.5%)	6 (8.7%)
Bone	67 (50%)	33 (48%)
CNS/Brain	4 (3.0%)	3 (4.3%)
Lung	30 (22%)	13 (19%)
Other[a]	48 (36%)	23 (33%)
Number of metastatic sites per subject, reported by the investigator per EDC		
0	0	0
1	18 (13%)	5 (7.2%)
2	38 (28%)	27 (39%)
≥ 3	78 (58%)	37 (54%)
Metastatic site resected (yes)	43 (32%)	17 (25%)

CNS, central nervous system; EDC, electronic data capture; epNET, extra-pancreatic neuroendocrine tumour; ITT, intent-to-treat
a Common other sites included adrenal gland, breast, ovaries, kidney, mesentery/omentum/peritoneum, pancreas, and spleen

Table 10. epNET: Prior anticancer therapy (ITT Population)

	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%)
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]		
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 tumour; 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.

Prior external beam radiation therapy (excluding PRRT and radioembolization) of the primary tumour was received by 10% of subjects in the cabozantinib arm and 14% of subjects in the placebo arm; and external beam radiation therapy for metastatic sites was received by 22% of subjects in the cabozantinib arm and 17% of subjects in the placebo arm.

pNET cohort:

Table 11. pNET: Baseline Demographic Characteristics (ITT Population)

	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 (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%)
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		

	Cabozantinib (N=64)	Placebo (N=31)
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 Enrolment Network; pNET, pancreatic neuroendocrine tumour; SD, standard deviation

Table 12. pNET: Cancer History and Baseline Disease Status (ITT Population)

	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		

	Cabozantinib (N=64)	Placebo (N=31)
Well differentiated	59 (92%)	30 (97%)
Moderately differentiated	4 (6.3%)	0
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 tumour; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumour; SD, standard deviation
a 3 subjects with a diagnosis of epNET were misallocated during enrolment to the pNET cohort
b Three subjects with epNET were misallocated to the pNET cohort as follows: two were randomised to the cabozantinib arm, and one to the placebo arm
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 tumour.

Table 13. pNET: Summary of Metastatic Disease (ITT Population)

	Cabozantinib (N=64)	Placebo (N=31)
Extent of disease		
Locally advanced	1 (1.6%)	2 (6.5%)
Metastatic	63 (98%)	29 (94%)
Extent of metastatic sites per investigator per EDC		
Nodal	29 (45%)	17 (55%)
Liver	63 (98%)	29 (94%)
Abdominal wall	3 (4.7%)	2 (6.5%)
Bone	19 (30%)	7 (23%)
Lung	3 (4.7%)	2 (6.5%)
Other[a]	9 (14%)	4 (13%)
Number of metastatic sites per subject, reported by the investigator per EDC		
0	1 (1.6%)	2 (6.5%)
1	24 (38%)	9 (29%)
2	22 (34%)	11 (35%)
≥ 3	17 (27%)	9 (29%)
Metastatic site resected (yes)	18 (28%)	7 (23%)

EDC, electronic data capture; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumour
a Common other sites included ovaries, mesentery/omentum/peritoneum, spleen, and stomach

Table 14. pNET: Prior anticancer therapy (ITT Population)

	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%)
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		
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 tumour; 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.

Numbers analysed

Table 15. epNET. Analysis Populations

	Cabozantinib n (%)	Placebo n (%)
ITT Population[a]	134 (100%)	69 (100%)
Safety Population[b]	132 (100%)	67 (100%)

a Includes all randomised subjects
b Includes all randomised subjects who received at least 1 dose of study treatment

Table 16. pNET. Analysis Populations

	Cabozantinib n (%)	Placebo n (%)
ITT Population[a]	64 (100%)	31 (100%)
Safety Population[b]	63 (100%)	31 (100%)

a Includes all randomised subjects
b Includes all randomised subjects who received at least 1 dose of study treatment

Outcomes and estimation

epNET cohort:

At the DCO 24 Aug 2023, the median follow-up time was 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm.

Primary endpoint: PFS by BIRC

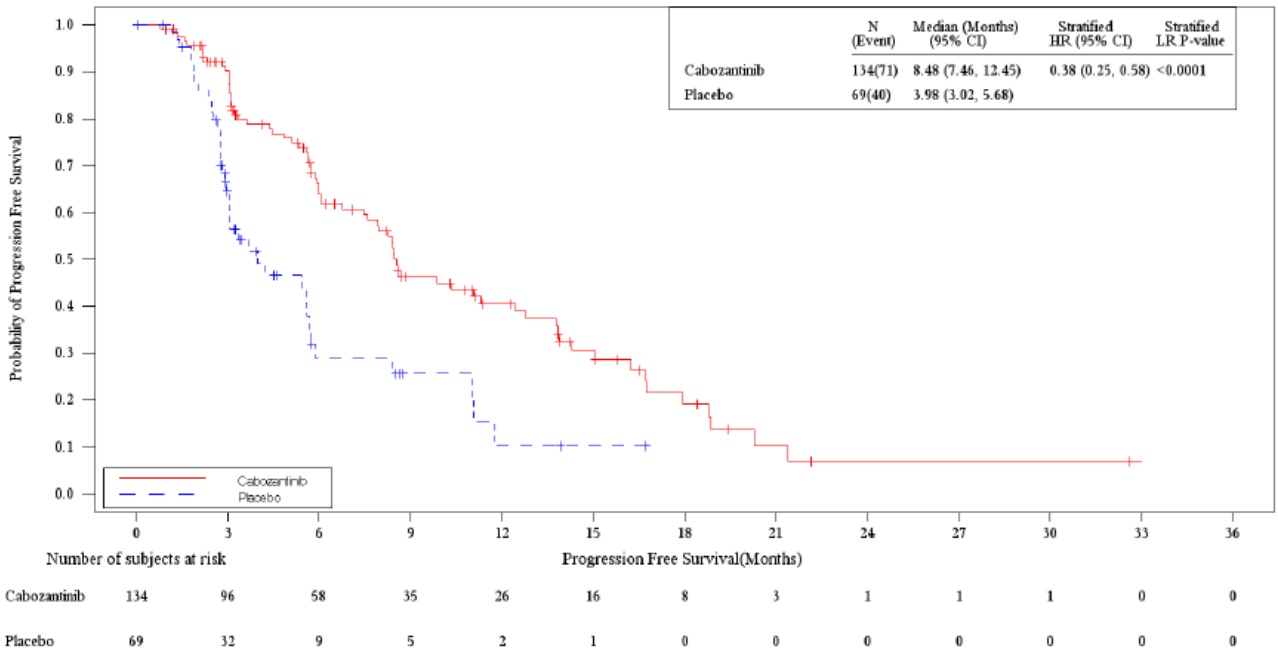
Table 17. epNET: Progression-Free Survival by BIRC (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=134)	Placebo (N=69)
Number (%) of Subjects		
Censored	63 (47%)	29 (42%)
NPACT	27 (20 %)	9 (13%)
2 or more missing ATA prior to event	1 (0.7%)	5 (7.2%)
No post baseline ATA	15 (11%)	2 (2.9%)
No Event and Did Not Crossover	20 (15%)	7 (10%)
Event	71 (53%)	40 (58%)
Death	18 (13%)	5 (7.2%)
Documented progression	53 (40%)	35 (51%)
K-M estimate (months)		
n	134	69

	Cabozantinib (N=134)	Placebo (N=69)
25th Percentile	5.09	2.76
Median (95% CI)	8.48 (7.46, 12.45)	3.98 (3.02, 5.68)
75th Percentile	16.72	11.01
Min, Max	0.03+, 32.59	0.03+, 16.72+
K-M landmark estimates and 95% CI of percent of subjects event-free at:		
3 months	90.3% (83.2%, 94.5%)	64.6% (51.2%, 75.1%)
6 months	64.1% (53.9%, 72.6%)	28.8% (15.8%, 43.2%)
12 months	40.6% (30.2%, 50.8%)	10.3% (2.1%, 26.1%)
18 months	19.2% (10.2%, 30.4%)	NE (NE, NE)
24 months	6.9% (1.5%, 18.2%)	NE (NE, NE)
Stratified (per OPEN) HR (95% CI)[a]	0.38 (0.25, 0.58)	
Stratified (per OPEN) 2-Sided p-value	<0.0001	

ATA, adequate tumour assessment; BIRC, blinded independent review committee; CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intent-to-treat; K-M, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; NPACT, nonprotocol anticancer therapy; OPEN, Oncology Patient Enrollment Network
Note: + indicates a censored observation.
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].
a Hazard ratios were calculated from Cox proportional hazards model.

Figure 6: epNET: Kaplan-Meier Plot of Progression-Free Survival by BIRC (DCO 24 August 2023)



BIRC, blinded independent review committee; CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test
Note: + indicates a censored observation.

Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].

epNET Sensitivity analyses of PFS

Sensitivity Analysis: Progression-Free Survival by Investigator

Per investigator assessments of progression and response with a cutoff date of 24 August 2023, PFS events occurred for 83 subjects (62%) in the cabozantinib arm and 51 subjects (74%) in the placebo arm. These results showed consistent results compared to the BIRC assessment, demonstrating a 59% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm, with a stratified HR of 0.41 (95% CI: 0.28, 0.60; stratified 2-sided $p < 0.0001$).

The Kaplan-Meier estimate of median PFS 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 (Table 18), an estimated 5.13-month difference in medians between treatment arms. 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.

Additional Sensitivity Analyses of PFS

Table 18. 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)[a]	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%	0.36 (0.23, 0.58)	< 0.0001
	Placebo (N=69)	35 (51%)	5.55 (2.92, 5.75)	33.6%, 17.9%, 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[b]	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		
EP6: Only include subjects randomized for at least 6 months before 24 August 2023	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
	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 tumour assessment; BIRC, blinded independent review committee; CI, confidence interval; EDC, electronic data capture; epNET, extra-pancreatic neuroendocrine tumour; 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

Note: p-values are from log-rank test.

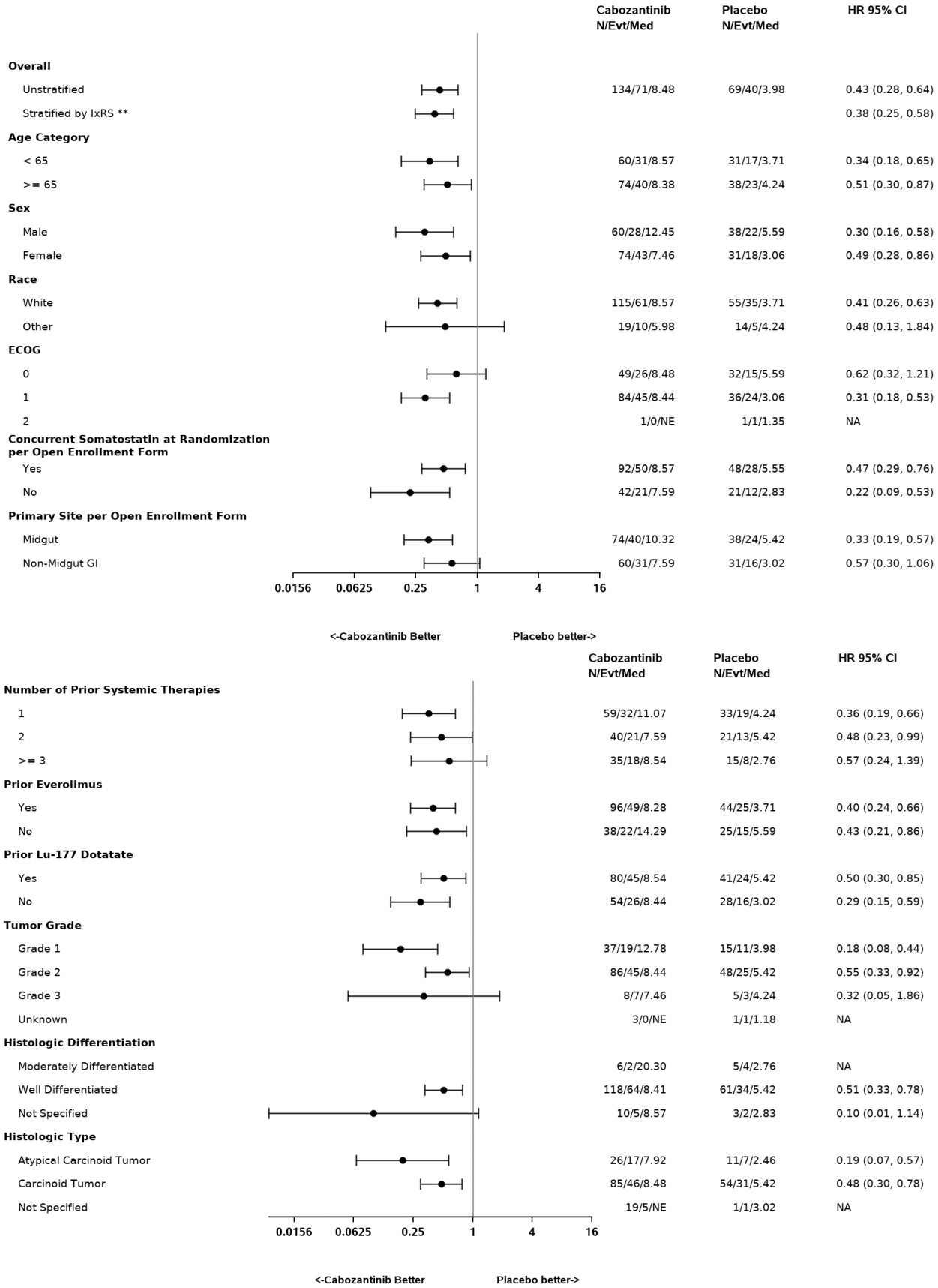
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].

a Hazard ratios were calculated from Cox proportional hazards model.

b PFS-EP5, 3 events (109th through 111th) occurred on the same date.

epNET Forest plot PFS

Figure 7. epNET: Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC



BIRC, blinded independent review committee; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; IxRS, interactive voice/web response system (ie, the OPEN registration system); Med, median; N, number of subjects; NA, not applicable; NE, not estimable; 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 analogue use (yes, no) and (2) primary site (midgut/unknown vs non-midgut GI/lung/other).

epNET PFS discordance

Table 19. epNET: Summary of Progressive Disease Discordance between Investigator and BIRC (ITT Population)

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%)

Note: ITT subjects with at least 1 postbaseline tumour 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.

Table 20. epNET: Summary of Discordance Between BIRC and Real-time Central Review and Investigator and Real-time Central Read (ITT Population)

Summary of Discordance Between BIRC and Real-time Central Review		
Discordance Measure	**Cabozantinib (N = 63)**	**Placebo (N = 46)**
Disagreement on PD status	18 (29%)	20 (43%)
BIRC PD/ Real Time Review Non-PD	3 (4.8%)	6 (13%)
BIRC non-PD/ Real Time Review PD	15 (24%)	14 (30%)
Summary of Discordance Between Investigator and Real Time Central read		
Discordance Measure	**Cabozantinib (N = 62)**	**Placebo (N = 46)**
Disagreement on PD status	14 (23%)	9 (20%)
Investigator PD/ Real Time Review Non-PD	12 (19%)	8 (17%)
Investigator non-PD/ Real Time Review PD	2 (3.2%)	1 (2.2%)

BIRC, blinded independent review committee; PD, progressive disease; ITT, intent to treat
ITT subjects with at least one post-baseline tumour assessment per batch retrospective BIRC and real time review were included in the analysis.

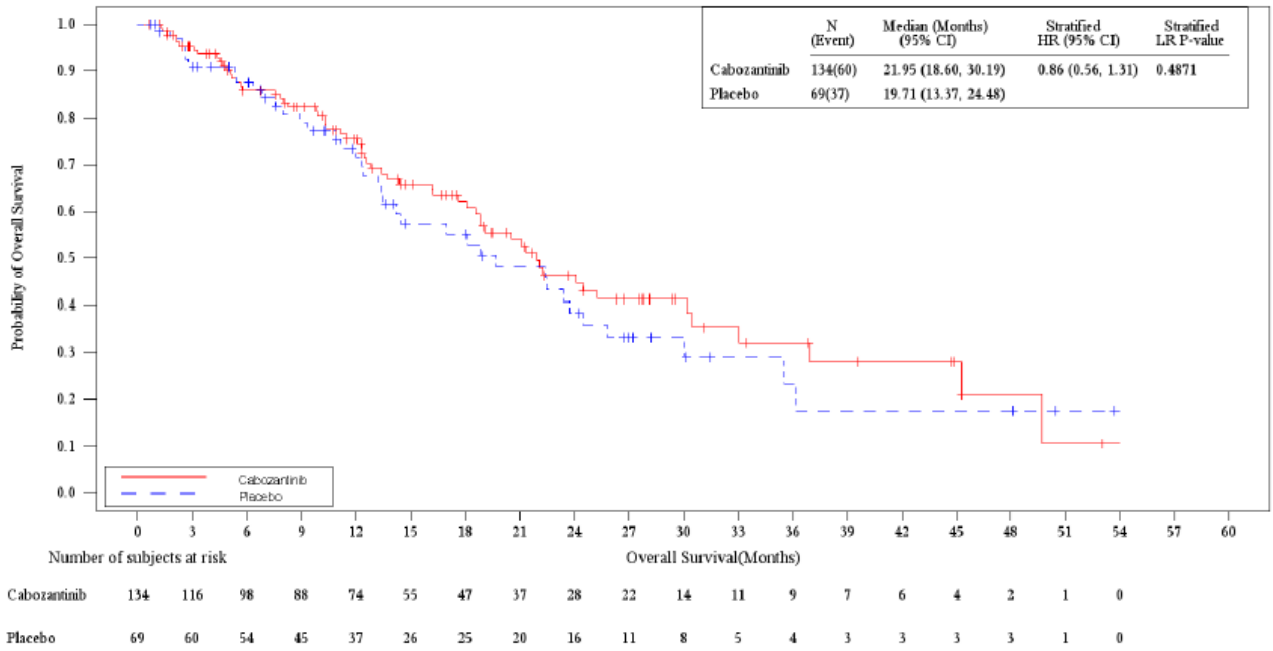
Secondary endpoint: OS

Table 21. epNET: Overall Survival (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=134)	Placebo (N=69)
Number (%) of Subjects		
Censored	74 (55%)	32 (46%)
Alive	67 (50%)	30 (43%)
Death after Data Cutoff date	7 (5.2%)	2 (2.9%)
Event: Death	60 (45%)	37 (54%)
K-M estimate (months)		
n	134	69
25th Percentile	12.09	11.17
Median (95% CI)	21.95 (18.60, 30.19)	19.71 (13.37, 24.48)
75th Percentile	45.27	35.52
Min, Max	0.59+, 53.03+	0.72+, 53.68+
K-M landmark estimates (95% CI) of percent of subjects event-free at:		
3 months	95.3% (89.9%, 97.9%)	90.9% (80.9%, 95.8%)
6 months	85.9% (78.3%, 91.0%)	87.7% (76.9%, 93.6%)
12 months	75.5% (66.5%, 82.5%)	73.5% (60.3%, 82.9%)
18 months	62.1% (51.8%, 70.8%)	55.1% (40.8%, 67.3%)
24 months	46.4% (35.4%, 56.7%)	38.5% (24.8%, 52.0%)
Stratified (per OPEN) 2-Sided p-value	0.4871	
Stratified (per OPEN) HR (95% CI)[a]	0.86 (0.56, 1.31)	

CI, confidence interval; epNET, extra-pancreatic neuroendrocrine tumour; HR, hazard ratio; ITT, intent-to-treat; K-M, Kaplan-Meier; Max, maximum; Min, minimum; OPEN, Oncology Patient Enrolment Network
Note: + indicates a censored observation.
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].
a Hazard ratios were calculated from Cox proportional hazards model.

Figure 8. epNET: Kaplan-Meier Plot of Overall Survival (ITT Population) (DCO 24 August 2023)



CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test
Note: + indicates a censored observation.
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].

Non-protocol anticancer therapy

The study considered NPACT to include systemic therapies as well as locoregional liver directed therapy and external beam radiation. Any NPACT was received by 37% and 58% of subjects in the cabozantinib and placebo arms, respectively (see table below).

At the time of the first OS analysis, 20 subjects (29%) had crossed over to open-label cabozantinib.

Table 22. epNET: Summary of nonprotocol anticancer therapy use (ITT Population)

	Cabozantinib Only (N=134)	Placebo (N=69)
Subjects who received any NPACT or crossed over to cabozantinib	50 (37%)	40 (58%)
Time from randomization to first NPACT or crossover to cabozantinib (months)		
n	50	40
Mean (SD)	10.0 (6.82)	6.4 (4.10)
Median (Range)	8.0 (1–34)	5.0 (3–23)
25th, 75th Percentiles	4.4, 14.5	4.1, 7.1
Subjects who received systemic NPACT or crossover cabozantinib	45 (34%)	38 (55%)
Time from randomization to first systemic anticancer therapy (months)		
N	45	38
Mean (SD)	10.2 (6.65)	6.6 (4.47)
Median (Range)	8.9 (1–34)	5.0 (3–23)
25th, 75th Percentiles	4.6, 13.9	4.0, 6.9
Crossover cabozantinib	NA	20 (29%)
PRRT	15 (11%)	3 (4.3%)
Everolimus	4 (3.0%)	3 (4.3%)
Anti-VEGFR TKI	7 (5.2%)	4 (5.8%)
Cytotoxic chemotherapy regimens	21 (16%)	8 (12%)
Other anticancer therapies	9 (6.7%)	3 (4.3%)

epNET, extra-pancreatic neuroendrocrine tumour; ITT, intent-to-treat; NPACT, nonprotocol anticancer therapy; PRRT, peptide receptor radionuclide therapy; SD, standard deviation; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor
Note: WHO Drug B3/Sep 2023 used for coding.

Sensitivity Analysis for OS: Censoring at initiation of NPACT

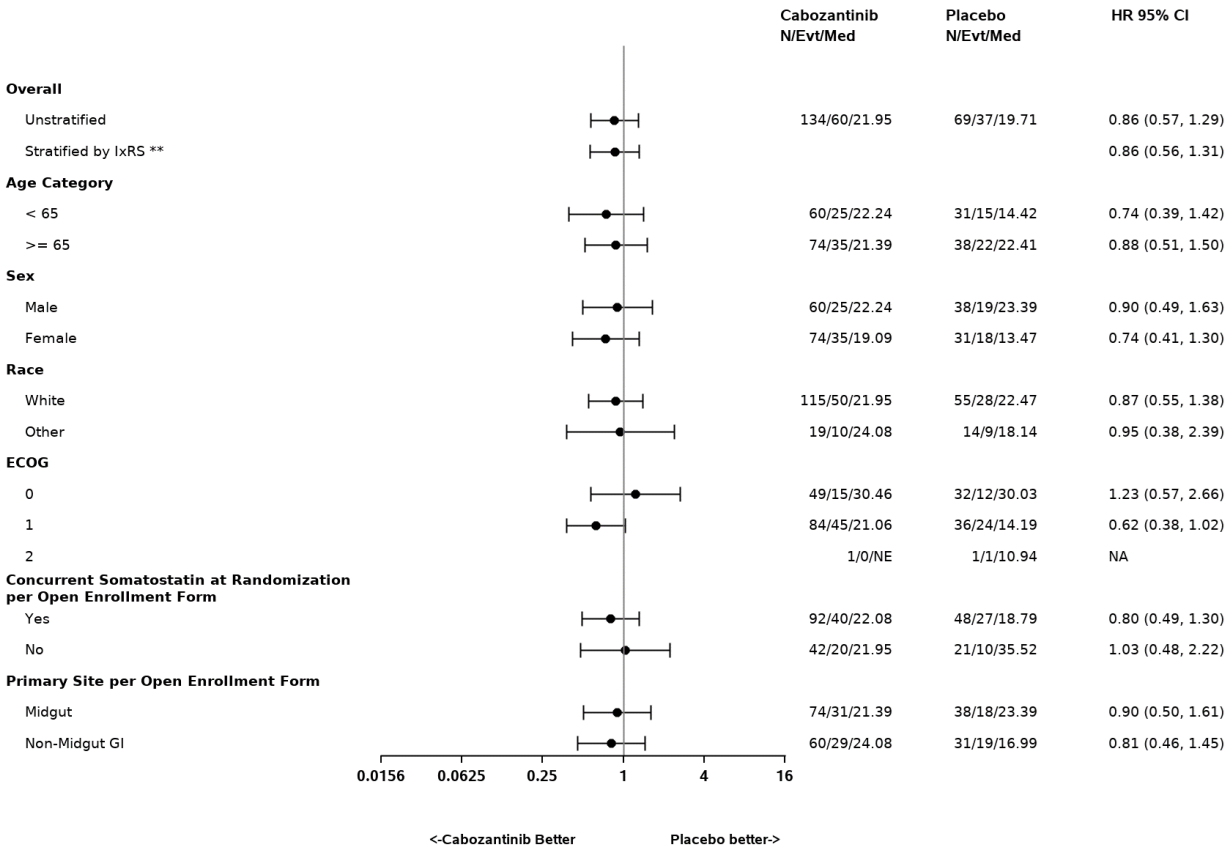
For this analysis, 73% of subjects in the cabozantinib arm and 78% of subjects in the placebo arm were censored, and 27% of subjects in the cabozantinib arm and 22% of subjects in the placebo arm died. The Kaplan-Meier estimate of median survival was 21.06 months (95% CI: 18.10, NE) in the cabozantinib arm and 23.39 months (95% CI: 13.37, NE) in the placebo arm, with an HR of 0.94 (95% CI: 0.50, 1.76; p = 0.8375).

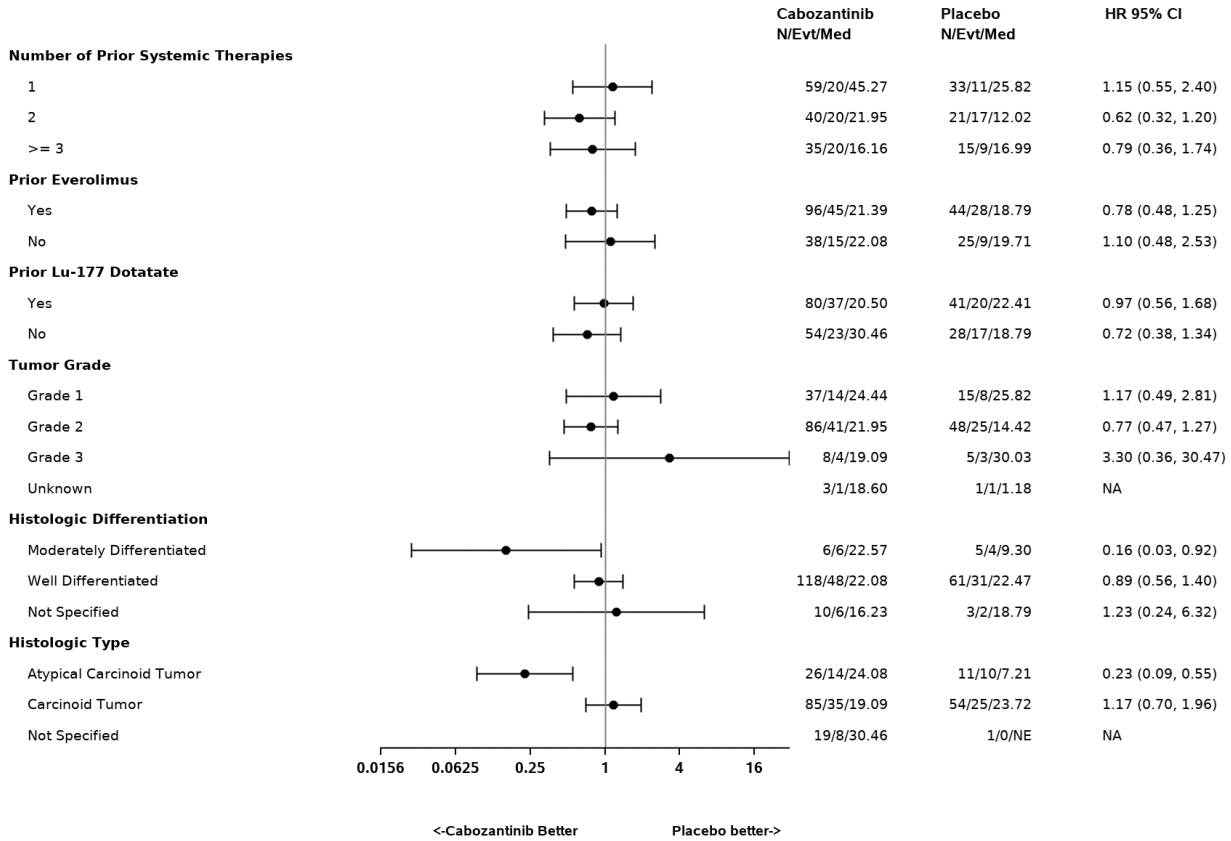
Sensitivity Analysis for OS: Effect of crossover based on a Rank-preserving Structural Failure Time Model

An analysis of OS adjusting for the effect of crossover based on an RPSFT model was performed. The Kaplan-Meier estimates of median survival were 21.95 months (95% CI: 18.60, 30.19) in the cabozantinib arm and 18.79 months (95% CI: 13.37, 24.48) in the placebo arm, with an HR of 0.81 (95% CI: 0.53, 1.23; p = 0.3205).

epNET Forest plot OS

Figure 9. epNET: Forest Plot of Subgroup Analysis of Overall Survival (ITT Population)





CI, confidence interval; Evt, number of subjects with events; ITT, intent-to-treat; Med, median; N, number of subjects; NA, not applicable; NE, not estimable; pNET, pancreatic neuroendocrine tumour. 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)

epNET Updated OS results

The MAH has provided updated OS analyses with DCO of 04 September 2024. The analysis of the epNET cohort provides an additional 29 events, i.e. an increase in the number of reported deaths from 97 to 126.

At the time of the updated OS analysis, approximately 52% of patients in the cabozantinib and 74% of patients in the placebo arm received crossover cabozantinib and/or at least one NPACT regimen. A total of 28 patients (41%) in the placebo arm had crossed over to cabozantinib treatment. For sensitivity analyses of OS, see *Ancillary analyses*.

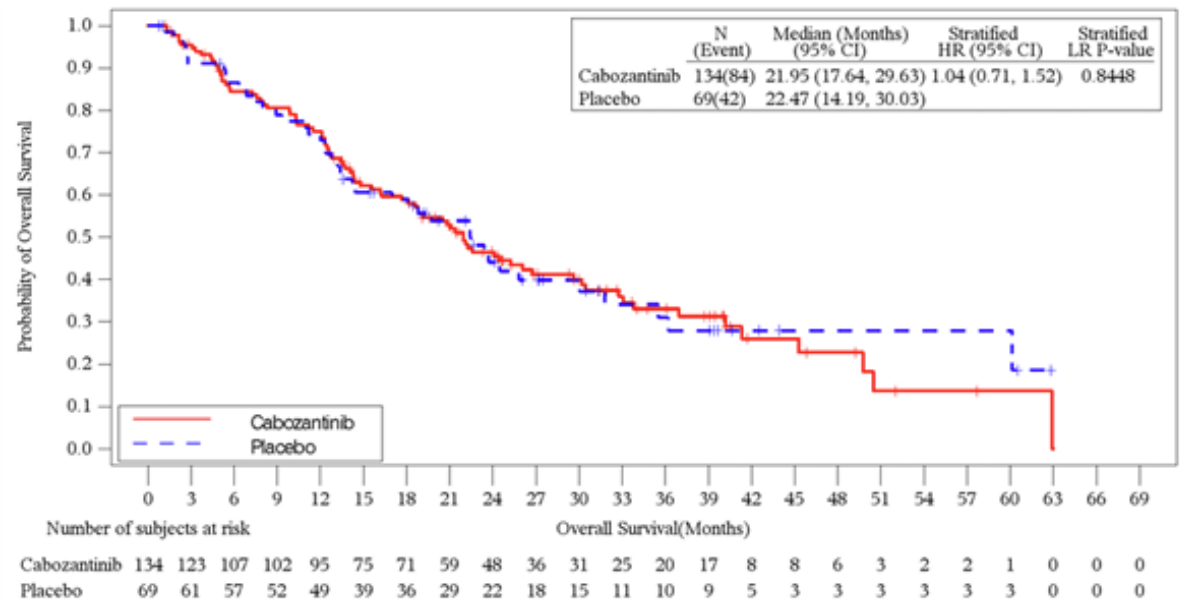
Table 23. epNET: Analysis of Overall Survival (ITT Population) (DCO 04 Sep 2024)

	Cabozantinib (N=134)	Placebo (N=69)
Number (%) of Patients		
Censored	50 (37%)	27 (39%)
Alive	49 (37%)	27 (39%)
Death after Data Cutoff date	1 (0.7%)	0
Event: Death	84 (63%)	42 (61%)
K-M estimate (months)		
n	134	69
25th Percentile	12.09	11.17
Median (95% CI)	21.95 (17.64, 29.63)	22.47 (14.19, 30.03)

	Cabozantinib (N=134)	Placebo (N=69)
75th Percentile	45.27	60.12
Min, Max	1.18+, 62.92	0.72+, 62.85+
K-M landmark estimates (95% CI) of percent of patients event-free at:		
3 months	95.5% (90.2%, 97.9%)	91.0% (81.1%, 95.9%)
6 months	84.5% (77.0%, 89.7%)	86.5% (75.6%, 92.7%)
12 months	75.0% (66.5%, 81.6%)	74.4% (62.0%, 83.2%)
18 months	58.9% (49.7%, 66.9%)	59.0% (46.1%, 69.8%)
24 months	46.5% (37.3%, 55.1%)	44.1% (31.3%, 56.2%)
36 months	33.0% (23.9%, 42.4%)	31.0% (18.5%, 44.4%)
Stratified (per OPEN) 2-Sided p-value	0.8448	
Stratified (per OPEN) Hazard Ratio (95% CI)[a]	1.04 (0.71, 1.52)	

Note: DCO is 04 September 2024
Note: + indicates censored observation.
Note: p-values are from log-rank test.
Note: Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut /Unknown. Non-midgut GI /Lung/Other].
[a] Hazard ratios were calculated from Cox proportional hazards model.
CI=confidence interval; DCO=data cutoff; epNET=extra-pancreatic neuroendocrine tumor; HR=hazard ratio; ITT=Intent-to-Treat; K-M=Kaplan-Meier; max=maximum; min=minimum; n=number; NE=Not estimable; OPEN=Oncology Patient Enrollment Network.

Figure 10. Kaplan-Meier Plot of Overall Survival (DCO 04 September 2024)



CI=confidence interval; epNET=extra-pancreatic neuroendocrine tumor; HR=hazard ratio; LR=log-rank.

Secondary endpoint: Objective Response Rate by BIRC

Table 24. epNET: Objective Response Rate by BIRC (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=134)	Placebo (N=69)
Subjects with measurable disease at baseline	133 (99%)	69 (100%)
Subjects with only non-target lesion at baseline	1 (0.7%)	0
Subjects with baseline and ≥ 1 postbaseline sum of diameters	111 (83%)	63 (91%)
Confirmed best overall response[a]		
Confirmed CR	0	0
Confirmed PR	7 (5.2%)	0
SD	87 (65%)	37 (54%)
PD	15 (11%)	24 (35%)
Unable to evaluate	0	1 (1.4%)
Missing	25 (19%)	7 (10%)
No qualifying post-baseline assessments on or before PFS censoring or event date[b]	23 (17%)	6 (8.7%)
SD or non-CR/non-PD not meeting minimum criteria (> 42 days) from randomization	2 (1.5%)	1 (1.4%)
Confirmed ORR (CR+PR), n (%)[c]	7 (5.2%)	0.0 (0.0%)
95% CI	(2.1%, 10.5%)	(0.0%, 5.2%)
Confirmed ORR treatment difference (95% CI)[d]	5.2% (1.5%, 9.0%)	
p-value from stratified CMH test	0.0524	

CMH, Cochran–Mantel–Haenszel; CR, complete response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease
a Confirmed best overall response is derived based on RECIST criteria 1.1. Only responses prior to PFS-EP1 are considered. The protocol did not define a minimal interval between the initial response scan and confirmatory scan; for calculation purposes, a minimum of 28 days was used.
b No qualifying post-baseline assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: first scheduled imaging timepoint after the clinical cutoff date (7 subjects), adverse event (6 subjects), death (4 subjects), withdrawal (3 subjects), no study treatment given (2 subjects), and other complicating disease (1 subject). In the placebo arm: no study treatment given (2 subjects), adverse event (1 subject), death (1 subject), first scheduled imaging timepoint after the clinical cutoff date (1 subject), and other (death) (1 subject).
c Confirmed Objective Response Rate (ORR-Confirmed) is defined as proportion of subjects with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods.
d Using asymptotic confidence limits based on large number theorem.

epNET Time to response by BIRC

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.

epNET Objective Response Rate by Investigator

Per investigator-assessment of tumour response, no subject in the cabozantinib arm had a confirmed CR and 5 subjects (3.7%) had a confirmed PR, giving a confirmed ORR of 3.7% (95% CI: 1.2%, 8.5%). In comparison, no subject in the placebo arm had a confirmed CR and 1 subject (1.4%) had a

confirmed PR, giving a confirmed ORR of 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 median time from randomisation 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 (range: 3.1–3.1) for the 1 subject in the placebo arm.

epNET Duration of Response

Of the 7 subjects in the cabozantinib arm who had a BIRC-assessed BOR of PR, 4 had subsequent documented disease progression, and 1 died. For these subjects, 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,

Of the 5 subjects in the cabozantinib arm who had an investigator-assessed BOR of PR, all 5 had subsequent documented progression. The Kaplan-Meier estimate of median DOR, per the investigator, was 10.74 months (95% CI: 5.32, NE), and the 3-, 6-, and 12-month event-free rates were 100.0%, 80.0%, and 20.0%, respectively.

epNET Disease Control rate

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 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.

pNET cohort:

At the DCO 24 Aug 2023, the median follow-time was 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm.

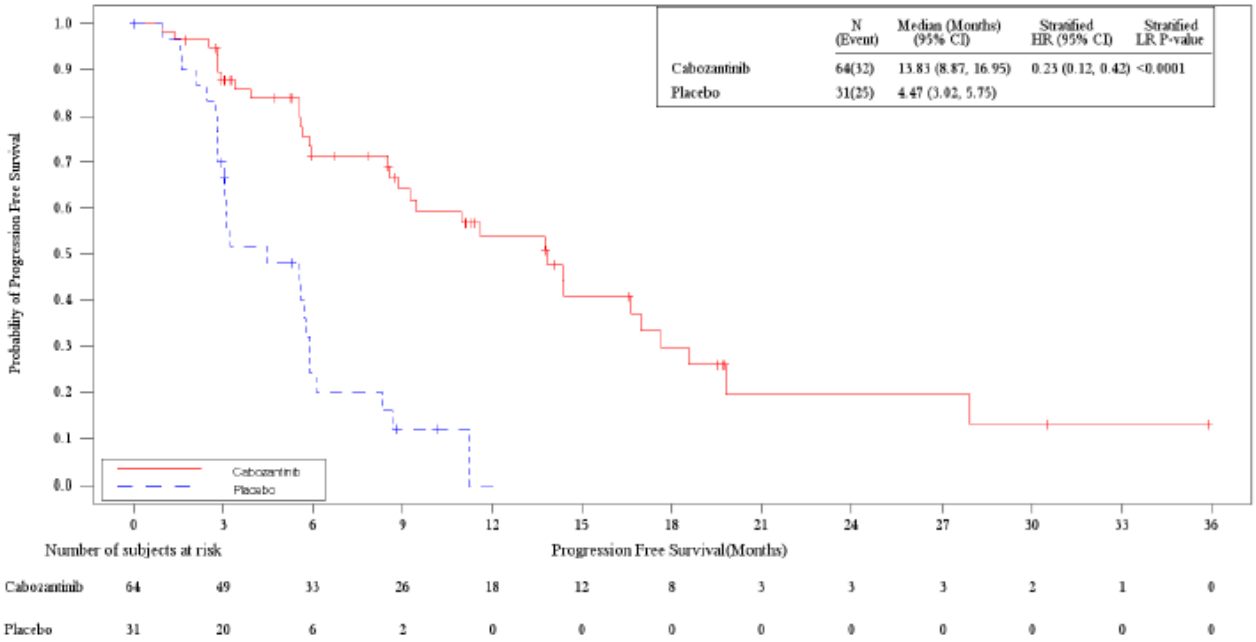
Primary endpoint: PFS by BIRC

Table 25. pNET: Progression-Free Survival by BIRC (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=64)	Placebo (N=31)
Number (%) of Subjects		
Censored	32 (50%)	6 (19%)
NPACT	13 (20%)	3 (9.7%)
2 or more missing ATA prior to event	1 (1.6%)	0
No post baseline ATA	4 (6.3%)	1 (3.2%)
No Event Prior and after Crossover	0	1 (3.2%)
No Event and Did Not Crossover	14 (22%)	1 (3.2%)
Event	32 (50%)	25 (81%)
Death	7 (11%)	4 (13%)
Documented progression	25 (39%)	21 (68%)
K-M estimate (months)		
n	64	31
25th Percentile	5.88	2.83
Median (95% CI)	13.83 (8.87, 16.95)	4.47 (3.02, 5.75)
75th Percentile	19.81	5.91
Min, Max	0.03+, 35.88+	0.03+, 11.20
K-M landmark estimates (95% CI) of percent of subjects event-free at:		
3 months	87.9% (76.2%, 94.0%)	70.0% (50.3%, 83.1%)
6 months	71.4% (56.9%, 81.7%)	24.0% (10.0%, 41.3%)
12 months	53.8% (38.1%, 67.1%)	0.0% (NE, NE)
18 months	29.7% (15.3%, 45.6%)	0.0% (NE, NE)
24 months	19.5% (6.7%, 37.1%)	0.0% (NE, NE)
Stratified (per OPEN) HR (95% CI)[a]	0.23 (0.12, 0.42)	
Stratified (per OPEN) 2-Sided p-value	< 0.0001	

ATA, adequate tumour assessment; NPACT, nonprotocol anticancer therapy; OPEN, Oncology Patient Enrolment Network;
Note: + indicates a censored observation. p-values are from log-rank test. Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
a Hazard ratios were calculated from Cox proportional hazards model.

Figure 11. pNET: Kaplan-Meier Plot of Progression-Free Survival by BIRC (DCO 24 August 2023)



BIRC, blinded independent review committee; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test pNET, pancreatic neuroendocrine tumour
Note: + indicates a censored observation
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).

pNET Sensitivity analyses of PFS

Sensitivity Analysis: Progression-Free Survival by Investigator

Per investigator assessments of progression and response with a cutoff date of 24 August 2023, PFS events occurred for 39 subjects (61%) in the cabozantinib arm and 24 subjects (77%) in the placebo arm. These results showed consistent results compared to the BIRC assessment, demonstrating a 71% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm, with a stratified HR of 0.29 (95% CI: 0.16, 0.52; stratified 2-sided $p < 0.0001$).

The Kaplan-Meier estimate of median PFS 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 (Table 36) 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.

Additional Sensitivity Analyses of PFS

Table 26. 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)[a]	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=58)	28 (48%)	14.36 (8.87, 17.64)	74.8%, 53.8%, 29.9%	0.22 (0.11, 0.43)	< 0.0001
	Placebo (N=29)	22 (76%)	4.47 (2.83, 5.91)	28.0%, 0.0%, 0.0%		
EP6: Only include subjects randomized for at least 6 months before 24 August 2023	Cabozantinib (N=57)	31 (54%)	13.83 (8.87, 16.95)	72.2%, 54.5%, 30.1%	0.22 (0.12, 0.43)	< 0.0001
	Placebo (N=28)	23 (82%)	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 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%		

ATA, adequate tumour 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; pNET, pancreatic neuroendocrine tumour; SAP, statistical analysis plan

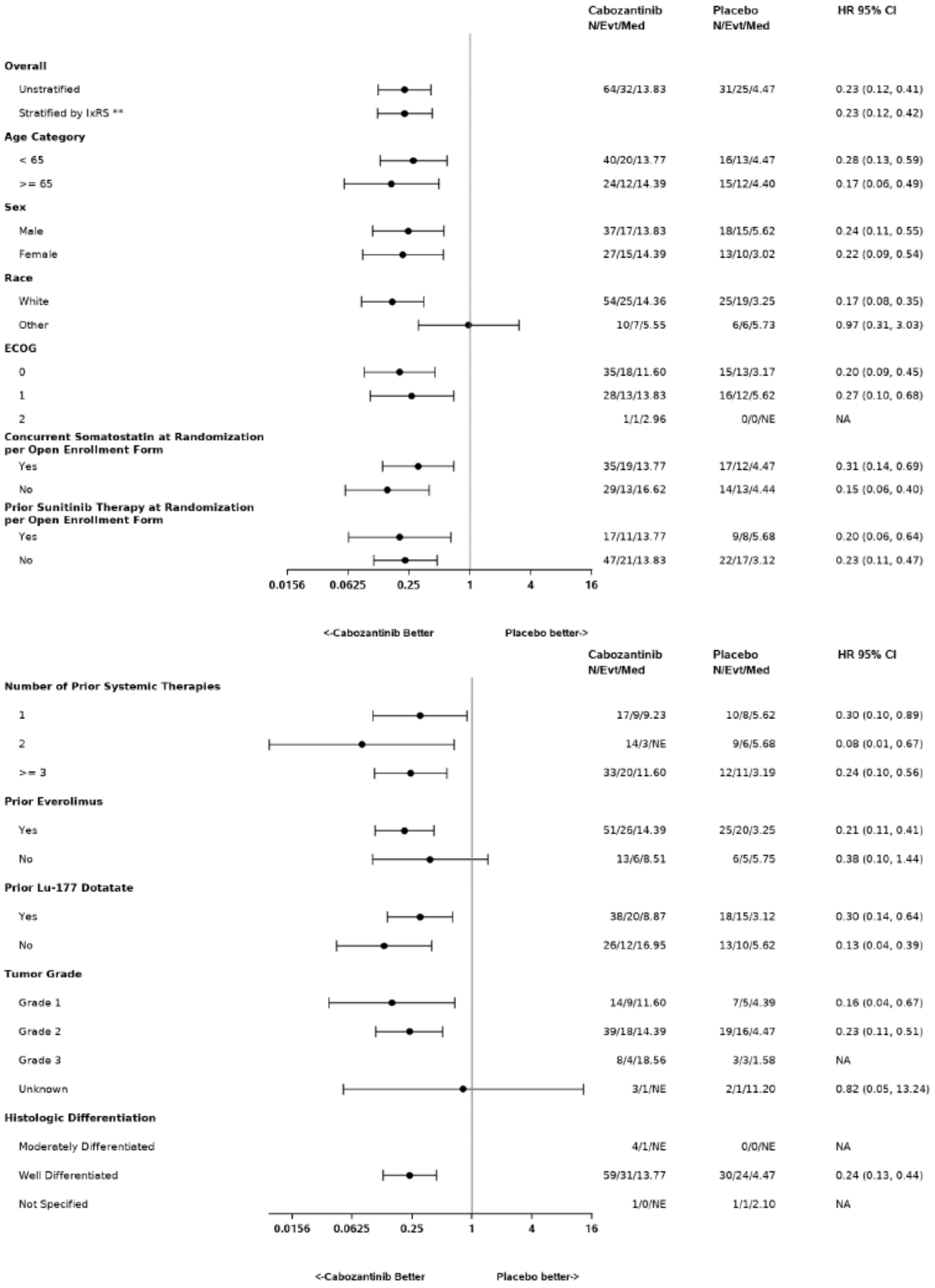
p-values are from log-rank test.

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

a Hazard ratios were calculated from Cox proportional hazards model.

pNET Forest plot PFS

Figure 12. pNET: Forest Plot of Subgroup Analysis of Progression-Free Survival by BIRC



BIRC, blinded independent review committee; ECOG, Eastern Cooperative Oncology Group; Evt, number of subjects with events; IxRS, interactive voice/web response system (ie, the OPEN registration system); Med, median; N, number of subjects; NA, not applicable; NE, not estimable; OPEN, Oncology Patient Enrollment Network; **Stratification factors are as follows: (1) concurrent somatostatin analog use (yes, no) and (2) prior sunitinib therapy (yes, no).

pNET PFS discordance

Table 27. pNET: Summary of Progressive Disease Discordance between Investigator and BIRC (ITT Population)

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%)

ITT subjects with at least 1 postbaseline tumour 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.

Table 28. pNET: Summary of Discordance Between BIRC and Real-time Central Review and Investigator and Real-time Central Read (ITT Population)

Discordance Measure	Cabozantinib (N = 29)	Placebo (N = 24)
Summary of Discordance Between BIRC and Real-time Central Review		
Disagreement on PD status	8 (28%)	4 (17%)
BIRC PD/ Real Time Review Non-PD	1 (3.4%)	1 (4.2%)
BIRC non-PD/ Real Time Review PD	7 (24%)	3 (13%)
Summary of Discordance Between Investigator and Real-Time Central Read		
Discordance Measure	**Cabozantinib (N = 28)**	**Placebo (N = 24)**
Disagreement on PD status	5 (18%)	3 (13%)
Investigator PD/ Real Time Review Non-PD	3 (11%)	2 (8.3%)
Investigator non-PD/ Real Time Review PD	2 (7.1%)	1 (4.2%)

BIRC, blinded independent review committee; ITT, intent to treat; PD, progressive disease
ITT subjects with at least one post-baseline tumour assessment per batch retrospective BIRC and real-time review were included in the analysis.

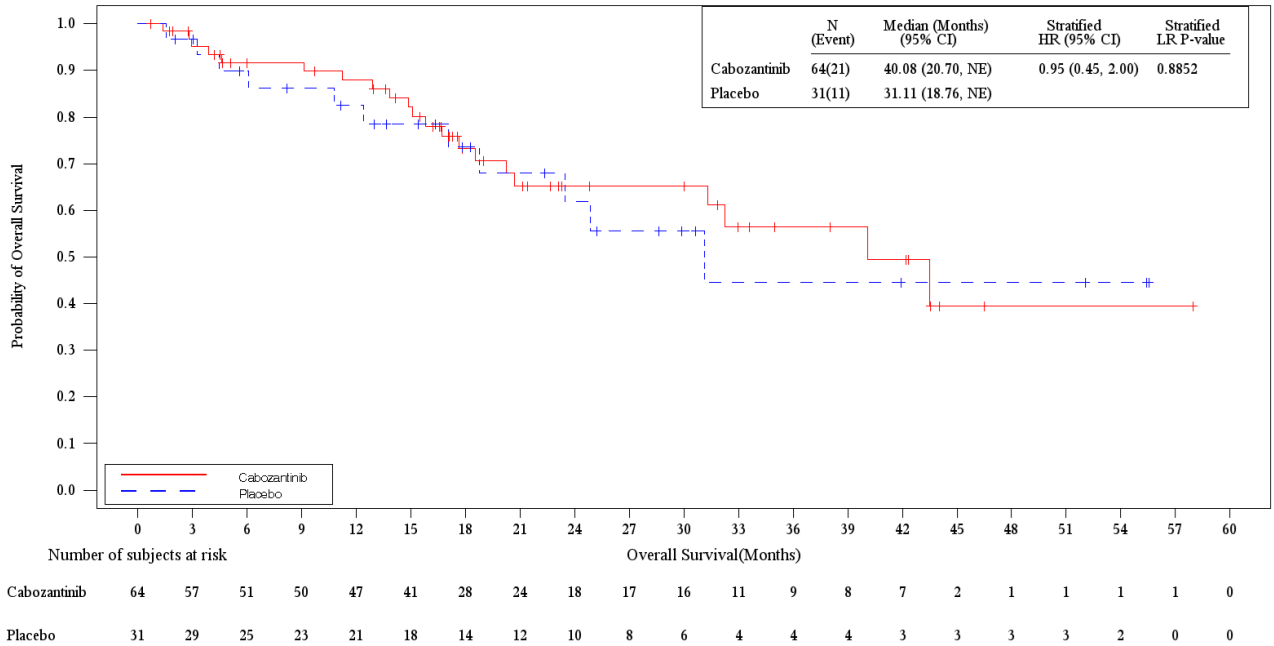
Secondary endpoint: OS

Table 29. pNET: Overall Survival (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=64)	Placebo (N=31)
Number (%) of Subjects		
Censored	43 (67%)	20 (65%)
Alive	39 (61%)	20 (65%)
Death after data cutoff date	4 (6.3%)	0
Event: Death	21 (33%)	11 (35%)
K-M estimate (months)		
n	64	31
25th Percentile	17.64	17.05
Median (95% CI)	40.08 (20.70, NE)	31.11 (18.76, NE)
75th Percentile	NE	NE
Min, Max	0.72+, 57.95+	1.58, 55.56+
K-M landmark estimates and 95% CI of percent of subjects event-free at:		
3 months	95.1% (85.5%, 98.4%)	96.8% (79.2%, 99.5%)
6 months	91.7% (81.1%, 96.5%)	89.9% (71.7%, 96.6%)
12 months	88.0% (76.4%, 94.1%)	82.5% (62.9%, 92.3%)
18 months	73.3% (58.8%, 83.4%)	73.7% (52.1%, 86.7%)
24 months	65.3% (49.6%, 77.2%)	61.8% (38.0%, 78.8%)
Stratified (per OPEN) 2-Sided p-value	0.8852	
Stratified (per OPEN) HR (95% CI)[a]	0.95 (0.45, 2.00)	

NE, not estimable; OPEN, Oncology Patient Enrollment Network;
+ indicates a censored observation. p-values are from log-rank test. Stratification factors for pNET:
1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
a Hazard ratios were calculated from Cox proportional hazards model.

Figure 13. pNET: Kaplan-Meier Plot of Overall Survival (ITT Population) (DCO 24 August 2023)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test; pNET, pancreatic neuroendocrine tumor
+ indicates a censored observation.
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).

Non-protocol anticancer therapy

Any NPACT was received by 39% and 58% of subjects in the cabozantinib and placebo arms, respectively (see table below).

At the time of the first OS analysis, 12 subjects (39%) had crossed over to open-label cabozantinib.

Table 30. pNET: Summary of nonprotocol anticancer therapy use (ITT Population)

	Cabozantinib Only (N=64)	Placebo (N=31)
Subjects who received any NPACT or crossed over to cabozantinib	25 (39%)	18 (58%)
Time from randomization to first NPACT or crossover to cabozantinib (months)		
n	25	18
Mean (SD)	11.4 (9.36)	7.7 (3.81)
Median (Range)	7.0 (2–41)	8.1 (2–14)
25th, 75th Percentiles	5.3, 13.7	3.7, 10.5
Subjects who received systemic nonprotocol anticancer therapy or crossover cabozantinib	25 (39%)	18 (58%)
Time from randomization to first systemic anticancer therapy (months)		
n	25	18
Mean (SD)	11.6 (9.25)	7.7 (3.81)
Median (Range)	8.3 (2–41)	8.1 (2–14)
25th, 75th Percentiles	5.8, 13.7	3.7, 10.5
Crossover cabozantinib	NA	12 (39%)
PRRT	8 (13%)	2 (6.5%)
Everolimus	2 (3.1%)	0
Anti-VEGFR TKI	5 (7.8%)	3 (9.7%)
Cytotoxic chemotherapy regimens	15 (23%)	0
Other anticancer therapies	4 (6.3%)	1 (3.2%)

NPACT, nonprotocol anticancer therapy; PRRT, peptide receptor radionuclide therapy; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor
Note: WHO Drug B3/Sep 2023 used for coding.

Sensitivity Analysis for OS: Censoring at initiation of NPACT

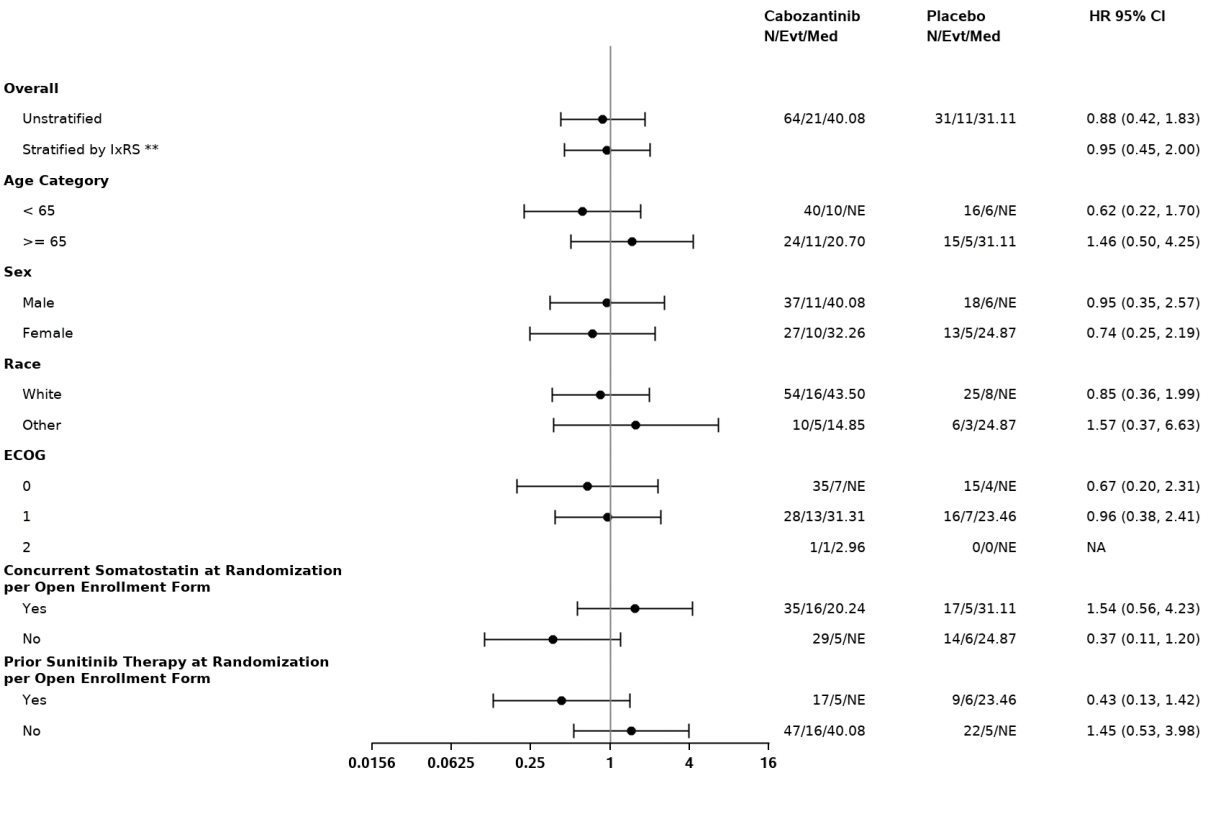
For this analysis, 81% of subjects in both treatment arms were censored, and 19% of subjects in both treatment arms had died. The Kaplan-Meier estimate of median survival was NA (95% CI: 20.24, NA) in the cabozantinib arm and 18.76 months (95% CI: 10.81, NA) in the placebo arm, with an HR of 0.65 (95% CI: 0.23, 1.81; p = 0.4052).

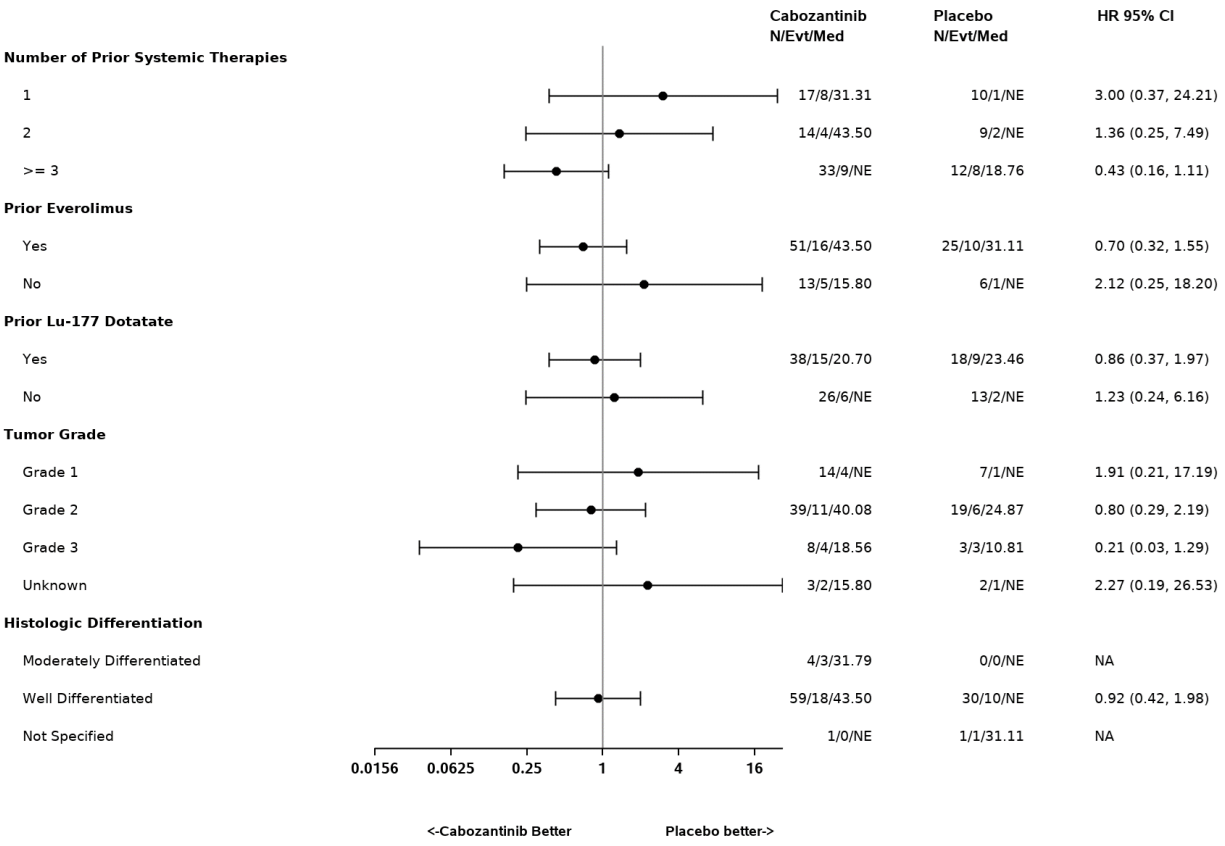
Sensitivity analysis for OS: Effect of crossover based on a Rank-preserving Structural Failure Time Model

An analysis of OS adjusting for the effect of crossover based on an RPSFT model was performed. The Kaplan-Meier estimates of median survival were 40.08 months (95% CI: 20.70, NE) in the cabozantinib arm and 31.11 months (95% CI: 18.76, NE) in the placebo arm, with an HR of 0.86 (95% CI: 0.41, 1.79; p = 0.6820).

pNET Forest plot OS

Figure 14. pNET: Forest Plot of subgroup analysis of Overall Survival (ITT Population)





CI, confidence interval; Evt, number of subjects with events; ITT, intent-to-treat; Med, median; N, number of subjects; NA, not applicable; NE, not estimable; pNET, pancreatic neuroendocrine tumour. **Stratification factors are as follows: (1) concurrent somatostatin analogue use (yes, no) and (2) prior sunitinib therapy (yes, no).

pNET Updated OS results

The updated OS analysis with DCO of 04 September 2024 provides an additional 14 events, i.e. an increase in the number of reported deaths from 32 to 46.

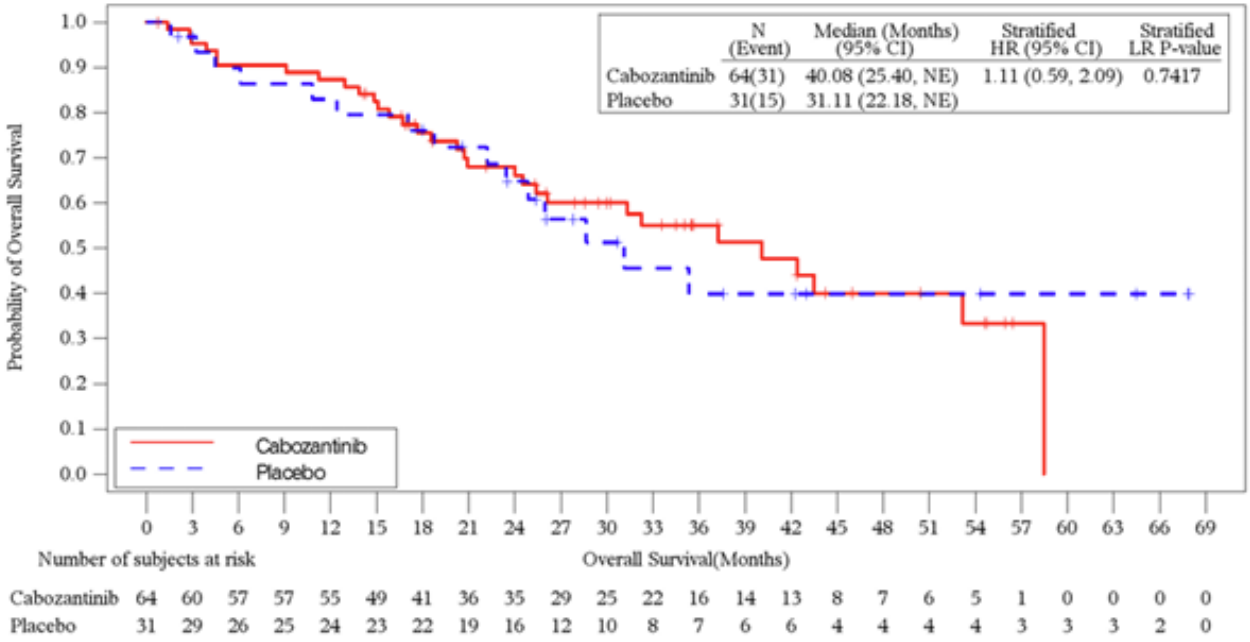
At the time of the updated OS analysis, approximately 61% of patients in the cabozantinib and 77% of patients in the placebo arm received crossover cabozantinib and/or at least one NPACT regimen. A total of 14 patients (45%) in the placebo arm had crossed over to cabozantinib treatment. For sensitivity analyses of OS, see *Ancillary analyses*.

Table 31. pNET: Analysis of Overall Survival (ITT Population) (DCO 04 Sep 2024)

	Cabozantinib (N=64)	**Placebo (N=31)**
Number (%) of Patients		
Censored	33 (52%)	16 (52%)
Alive	31 (48%)	15 (48%)
Death after Data Cutoff date	2 (3.1%)	1 (3.2%)
Event: Death	31 (48%)	15 (48%)
K-M estimate (months)		
n	64	31
25th Percentile	18.56	18.76
Median (95% CI)	40.08 (25.40, n/a)	31.11 (22.18, n/a)
75th Percentile	58.45	n/a
Min, Max	0.72+, 58.45	1.58, 67.94+
K-M landmark estimates (95% CI) of percent of patients event-free at:		
3 months	95.2% (86.0%, 98.4%)	96.8% (79.2%, 99.5%)
6 months	90.5% (80.0%, 95.6%)	89.9% (71.7%, 96.6%)
12 months	87.3% (76.2%, 93.4%)	82.9% (63.7%, 92.5%)
18 months	75.5% (62.7%, 84.5%)	76.0% (56.2%, 87.8%)
24 months	68.0% (54.4%, 78.3%)	64.8% (44.3%, 79.3%)
36 months	55.0% (40.6%, 67.3%)	39.9% (19.9%, 59.3%)
Stratified (per OPEN) 2-Sided p-value	0.7417	
Stratified (per OPEN) Hazard Ratio (95% CI)[a]	1.11 (0.59, 2.09)	

Note: DCO is 04 September 2024
Note: + indicates censored observation.
Note: p-values are from log-rank test.
Note: : Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib (Yes, No). aHazard ratios were calculated from Cox proportional hazards model.
CI=confidence interval; epNET=extra-pancreatic neuroendocrine tumor; HR=hazard ratio; ITT=Intent-to-Treat; K-M = Kaplan-Meier; max=maximum; min=minimum; n=number; NE=Not estimable; OPEN=Oncology Patient Enrollment Network.

Figure 15. pNET: Kaplan-Meier Plot of Overall Survival (DCO 04 September 2024)



CI=confidence interval; HR=hazard ratio; LR=log-rank; pNET=pancreatic neuroendocrine tumor

Secondary endpoint: Objective Response Rate by BIRC

Table 32. pNET: Objective Response Rate by BIRC (ITT Population) (DCO 24 Aug 2023)

	Cabozantinib (N=64)	Placebo (N=31)
Subjects with measurable disease at baseline	64 (100%)	31 (100%)
Subjects with baseline and at least one post-baseline sum of diameters	56 (88%)	29 (94%)
Confirmed best overall response[a]		
Confirmed CR	0	0
Confirmed PR	12 (19%)	0
SD	39 (61%)	17 (55%)
PD	5 (7.8%)	12 (39%)
Unable to evaluate	0	0
Missing	8 (13%)	2 (6.5%)
No qualifying post-baseline assessments on or before PFS censoring or event date[b]	8 (13%)	2 (6.5%)
Confirmed ORR (CR+PR)[c], n (%)	12 (19%)	0.0 (0.0%)
95% CI	(10.1%, 30.5%)	(0.0%, 11.2%)
Confirmed ORR treatment difference (95% CI)[d]	18.8% (9.2%, 28.3%)	
p-value from stratified CMH test	0.0115	

CMH, Cochran–Mantel–Haenszel; CR, complete response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

a Confirmed best overall response is derived based on RECIST criteria 1.1. Only responses prior to PFS-EP1 are considered. The protocol did not define a minimal interval between the initial response scan and confirmatory scan; for calculation purposes, a minimum of 28 days was used.
b No qualifying post-baseline assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: adverse event (2 subjects), other (death) (2 subjects), withdrawal (2 subjects), no study treatment give (1 subject), and first scheduled imaging timepoint after the clinical cutoff date (1 subject). In the placebo arm: other (death) (1 subject) and withdrawal (1 subject).
c Confirmed Objective Response Rate (ORR-Confirmed) is defined as proportion of subjects with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods.
d Using asymptotic confidence limits based on large number theorem.

pNET Time to response by BIRC

The median time from randomization to confirmed objective response was 5.78 months (range: 2.8–8.7) for the 12 subjects with a confirmed objective response in the cabozantinib arm.

pNET Objective Response Rate by Investigator

Per investigator-assessment of response, no subject in the cabozantinib arm had a confirmed CR and 5 subjects (7.8%) had a confirmed PR, giving a confirmed ORR of 7.8% (95% CI: 2.6%, 17.3%). In comparison, no subject in the placebo arm had either a confirmed CR or PR, giving a confirmed 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 randomisation 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.

pNET Duration of Response

Of the 12 subjects in the cabozantinib arm who had a BIRC-assessed BOR of PR, 6 either had subsequent documented disease progression (n=5) or died (n=1). For these subjects, the Kaplan-Meier estimate of the median DOR, per BIRC, was 11.20 months (95% CI: 5.78, NE), and the 3-, 6-, and 12-month event-free rates were 100.0%, 88.9%, and 32.4%, respectively.

Of the 5 subjects in the cabozantinib arm who had an investigator-assessed BOR of PR, 4 had subsequent documented progression. The Kaplan-Meier estimate of median DOR, per the investigator, was 16.59 months (95% CI: 5.55, NE), and the 3-, 6-, and 12-month event-free rates were 100.0%, 80.0%, and 60.0%, respectively.

pNET Disease Control Rate

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 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.

epNET and pNET QoL substudy

The applicant has provided the results of the QoL substudy of the CABINET study. Participation in this study was optional. The following questionnaires were used: EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ Gastrointestinal Neuroendocrine Tumours 21 (EORTC QLQ-GINET21) and Patient Global Impression of Change (PGIC). Responses were collected at trial registration and every 12 weeks until disease progression or the start of a new anticancer treatment.

Ancillary analyses

Reason for censoring

The Applicant provided further information on patients who were censored due to not having a post-baseline assessment and for receiving NPACT before a BIRC-assessed progression event or death, for both treatment arms and in both cohorts.

epNET

In the epNET cohort, 42 patients (31% of the ITT) in the cabozantinib arm and 11 patients (16% of the ITT) in the placebo arm were censored due to NPACT before a BIRC-assessed progression event or no post-baseline assessment. Of these patients, just over 80% discontinued treatment prior to being censored, with the most common reason for discontinuation being an AE/side effects/complications or disease progression (as determined by the investigator during active treatment).

It is noted that for the investigator-based progression, 14 patients (10% of the ITT) in the cabozantinib arm and 2 (3% of the ITT) in the placebo arm were censored for not having a post-baseline assessment, and 13 (9.7% of the ITT) and 6 (8.7% of the ITT) patients, respectively, were censored because they received NPACT. It is likely that informative censoring is present also in the investigator-based analysis, even though the rate of censoring due to NPACT is lower given progressions are investigator-determined.

pNET

In the pNET cohort, 17 patients (27% of the ITT) in the cabozantinib arm and 4 patients (13% of the ITT) in the placebo arm were censored due to NPACT before a BIRC-assessed progression event or no post-baseline assessment. 15/17 (88%) and 4/4 (100%) of the patients, respectively, discontinued allocated treatment before being censored. In the cabozantinib arm, the most common reason was again discontinuation due to AE or investigator-determined disease progression.

For the investigator-based assessment the same number of patients were censored due to a missing baseline assessment in each group and a slightly lower number (7 and 3) of patients in the cabozantinib arm and placebo arms, respectively, were censored due to receiving NPACT.

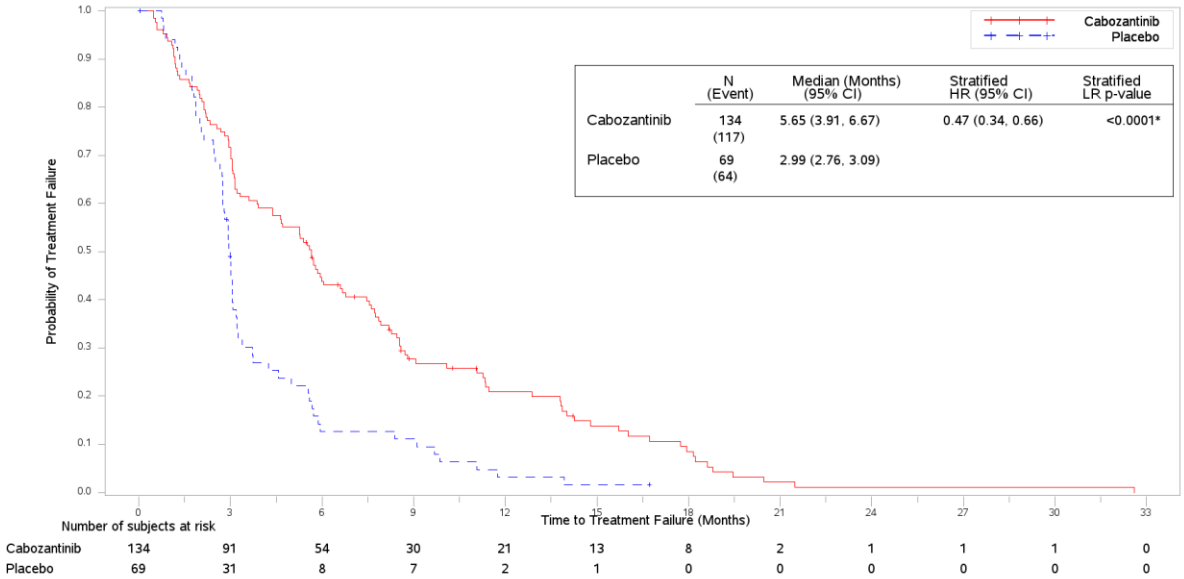
Time to treatment failure

Upon request, the MAH provided the results from a time to treatment failure analysis for which recorded treatment discontinuation for any reason was also considered to be an event. In this analysis the only remaining reasons for censoring were no post-baseline assessment (without known discontinuation) and no event and did not crossover.

epNET

When a composite strategy is used for intercurrent events of treatment discontinuation, 13% and 7.2% of patients from the cabozantinib and placebo arms, respectively, were event free of treatment failure at the time of analysis. In both treatment arms, the most common events were treatment discontinuation (62% in the cabozantinib arm and 52% in the placebo arm) and documented progression (23% in the cabozantinib arm and 39% in the placebo arm).

Figure 16. epNET: Kaplan-Meier Plot for Time to Treatment Failure (ITT Population)

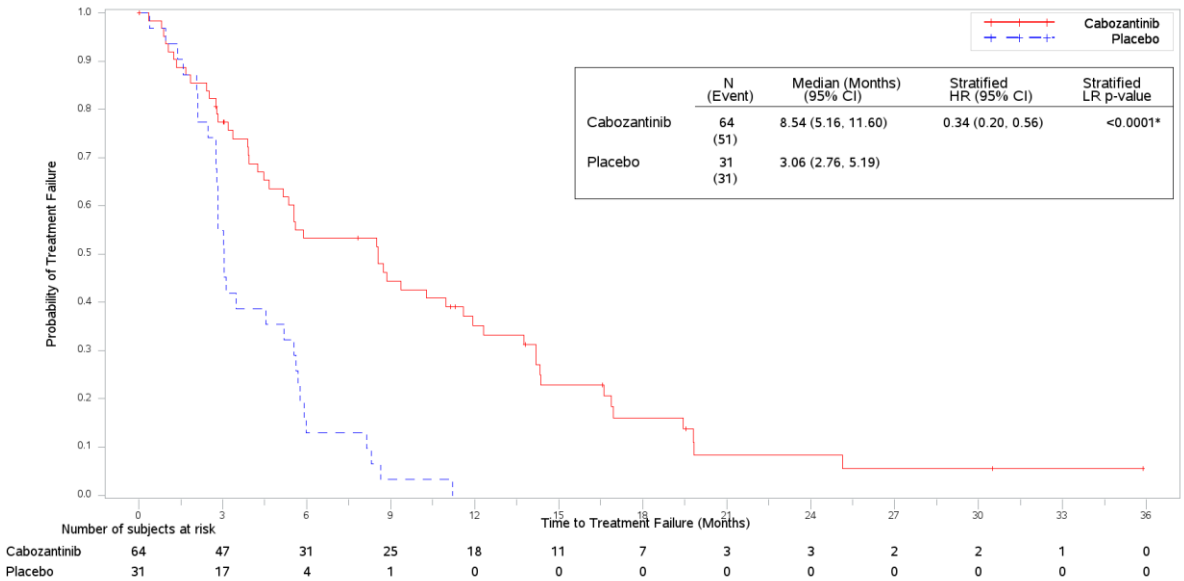


Abbreviations: CI=confidence interval; epNET=extrapancreatic neuroendocrine tumor; HR=hazard ratio; ITT=intent-to-treat.

pNET

At the time of the analysis, 20% and 0% of patients in the cabozantinib and placebo arms, respectively, were censored as they were event-free. In both treatment arms, the most common events were treatment discontinuation (52% in the cabozantinib arm and 45% in the placebo arm) and documented progression (28% in the cabozantinib arm and 55% in the placebo arm).

Figure 17. pNET: Kaplan-Meier Plot for Time to Treatment Failure (ITT Population)

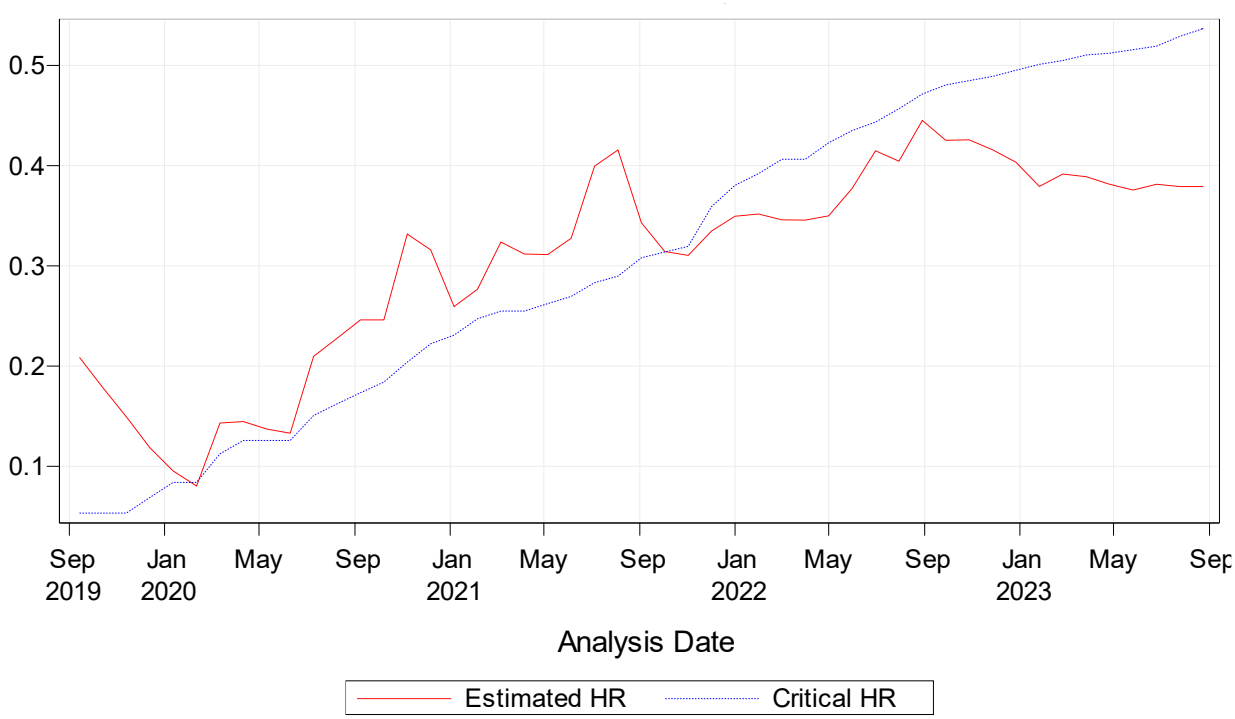


Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; pNET=pancreatic neuroendocrine tumor.

PFS stability

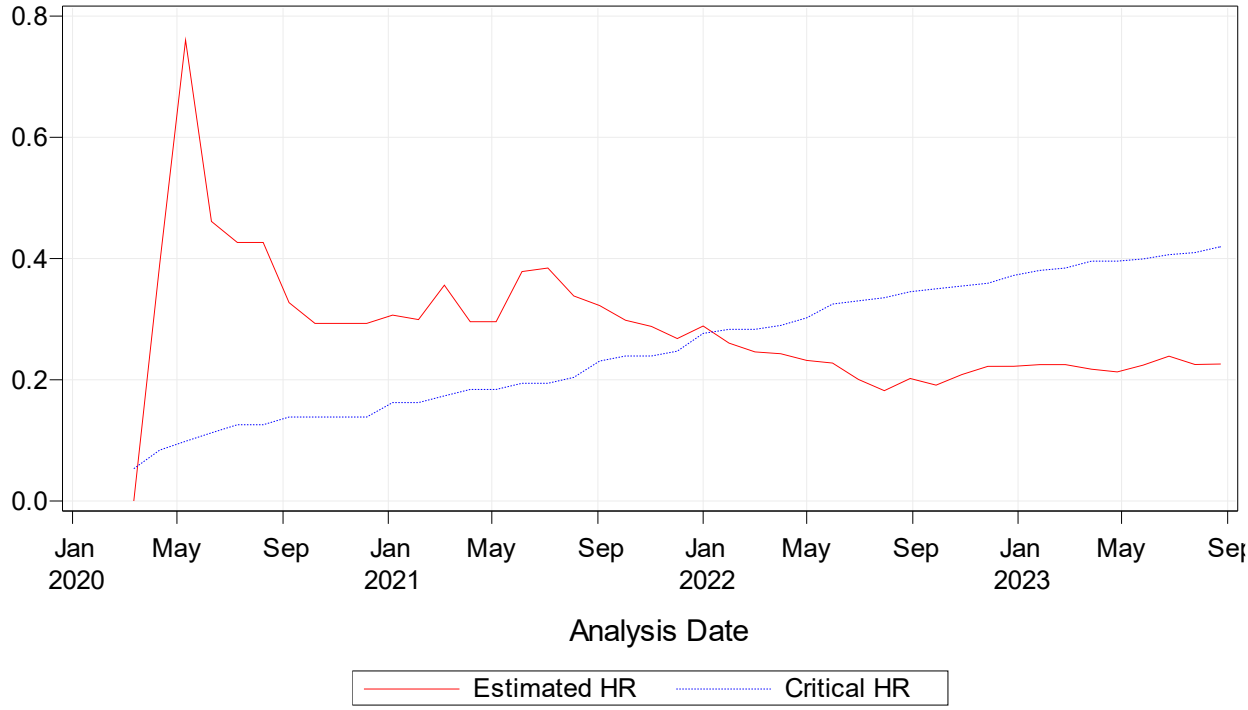
The MAH has generated an analysis showing the evolution of the estimated PFS HRs over time in the pNET and epNET cohorts during the study conduct period to investigate whether the primary endpoint PFS was performed with data that had stabilized, or whether the data were particularly favourable at this timepoint. The starting point is the CSR data cutoff date (24 August 2023) then, back dated cutoff dates were derived by monthly (30 days) base back to the date with at least 5 accrued events. Hazard ratios (HRs) are calculated for each of these a posteriori-defined cut-off dates to generate the graph.

Figure 18. epNET: Estimated Hazard Ratio Overtime (ITT Population)



HR=Hazard Ratio
Hazard ratios are calculated from stratified Cox proportional hazards model with data cutoff by analysis dates.
Critical hazard ratios are back calculated based on number of accrued events with one-sided alpha level of 0.001 by analysis dates.

Figure 19. pNET: Estimated Hazard Ratio Overtime (ITT Population)



HR=Hazard Ratio
Hazard ratios are calculated from stratified Cox proportional hazards model with data cutoff by analysis dates.
Critical hazard ratios are back calculated based on number of accrued events with one-sided alpha level of 0.001 by analysis dates.

PFS events outside of assessment window

The MAH has provided an additional sensitivity analysis of PFS where events in both arms outside the assessment window have been moved to the planned assessment time.

Table 33. epNET: Kaplan-Meier Analysis of Progression-Free Survival per IRC and Investigator (ITT Population)

epNET	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)[a]	Stratified Log-rank 2-sided p-value
Primary analysis IRC-assessed PFS	Cabozantinib (N=134)	71	8.48 (7.46, 12.45)	64.1%, 40.6%, 19.2%	0.38 (0.25, 0.58)	< 0.0001*
	Placebo (N=69)	40	3.98 (3.02, 5.68)	28.8%, 10.3%, NE		

epNET	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)[a]	Stratified Log-rank 2-sided p-value
IRC-assessed PFS adjusting to planned disease assessment time	Cabozantinib (N=134)	71	8.31 (8.31, 12.78)	62.6%, 42.9%, 22.1%	0.44 (0.29, 0.67)	0.0002*
	Placebo (N=79)	40	5.55 (2.79, 5.55)	35.4%, 12.6%, NE		
Investigator-assessed PFS	Cabozantinib (N=134)	83	8.38 (5.98, 11.07)	58.1%, 33.0%, 18.5%	0.41 (0.28, 0.60)	< 0.0001*
	Placebo (N=69)	51	3.25 (2.99, 5.42)	22.2%, 10.8%, 7.2%		
Investigator-assessed PFS adjusting to planned disease assessment time	Cabozantinib (N=134)	83	8.31 (5.55, 11.07)	57.5%, 35.1%, 20.7%	0.44 (0.30, 0.64)	< 0.0001*
	Placebo (N=69)	51	2.79 (2.79,5.55)	26.8%, 14.3%, 9.5		

*: met the critical two-sided p-value of 0.002.
[a] Hazard ratios were calculated from Cox proportional hazards model.
Stratification factor for epNET: 1. Concurrent somatostatin analog use (Yes or No) and 2. Primary tumor site (Midgut/Unknown vs. Non-midgut GI/Lung/Other)
Abbreviations: CI=confidence interval; CSR=clinical study report; epNET=extrapancreatic neuroendocrine tumor; GI=gastrointestinal; HR=hazard ratio; IRC=independent review committee; K-M=Kaplan-Meier; PFS=progression-free survival

Table 34. pNET: Kaplan-Meier Analysis of PFS per IRC and Investigator (ITT Population)

pNET	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)[a]	Stratified Log-rank 2-sided p-value
Primary analysis IRC-assessed PFS	Cabozantinib (N=64)	32	13.83 (8.87, 16.95)	71.4%, 53.8%, 29.7%	0.23 (0.12, 0.42)	< 0.0001*
	Placebo (N=31)	25	4.47 (3.02, 5.75)	24.0%, 0.0%, 0.0%		
IRC-assessed PFS	Cabozantinib (N=64)	32	13.83 (8.31,17.64)	72.3%, 55.9%, 32.2%	0.24 (0.13, 0.44)	<0.0001*

adjusting to planned disease assessment time	Placebo (N=31)	25	4.47 (2.79, 5.55)	26.4%, NE,NE		
Investigator-assessed PFS	Cabozantinib (N=64)	39	10.97 (8.41, 13.86)	69.9%, 41.9%, 20.7%	0.29 (0.16, 0.52)	< 0.0001*
	Placebo (N=31)	24	3.06 (2.86, 5.91)	23.3%, 0.0%, 0.0%		
Investigator-assessed PFS adjusting to planned disease assessment time	Cabozantinib (N=64)	39	11.07 (8.31, 13.83)	68.5%, 43.4%, 22.7%	0.32 (0.18, 0.57)	< 0.0001*
	Placebo (N=31)	24	2.79 (2.79, 5.55)	28.9%, NE,NE		

*: met the critical two-sided p-value of 0.002.
[1] Hazard ratios were calculated from Cox proportional hazards model.
Stratification factors for pNET: 1.Concurrent somatostatin analog use(Yes or No) and 2. Prior sunitinib therapy (Yes or No)
Abbreviations: CI=confidence interval; CSR=clinical study report; GI=gastrointestinal; HR=hazard ratio; IRC=independent review committee; K-M=Kaplan-Meier; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumor

OS sensitivity analyses adjusting for crossover

The MAH provided the results of three OS sensitivity analyses adjusting for crossover, i.e., a rank preserving structural failure time (RPSFTM) model, inverse probability of censoring weights (IPCW) and a two-stage estimation (TSE) method (Table 35).

Table 35. OS sensitivity analyses adjusting for crossover – RPSFT, ICPW and TSE

	epNET (N = 203) HR (95% CI)	**pNET (N = 95) HR (95% CI)**
RPSFT	1.07 (0.73, 1.57)	1.12 (0.60, 2.11)
IPCW	0.84 (0.53, 1.34)	1.32 (0.59, 2.94)
TSE	0.98 (0.67, 1.44)	0.99 (0.53, 1.87)
Primary OS	1.04 (0.71, 1.52)	1.11 (0.59, 2.09)

epNET=extra-pancreatic neuroendocrine tumor; IPCW=inverse probability of censoring weights; pNET=pancreatic neuroendocrine tumor; OS=overall survival; RPSFT=rank preserving structural failure time; TSE=two-stage estimation.

OS sensitivity analysis adjusting for misallocation

The MAH has provided a sensitivity analysis for OS using the latest data cut-off (04-Sep-2024) with disease allocation per eCRF collected in EDC, i.e. where patients misallocated to pNET/epNET have been re-allocated according to diagnosis. A total of 3 epNET patients were misallocated to the pNET cohort and 7 pNET patients were misallocated to the epNET cohort

Table 36. Summary of OS Results Based on the Patient's Primary Tumor Location (with Misallocation) vs OS Results Following Patient Reassignment (DCO 04 Sep 2024)

Cohort	Treatment Arm	Updated OS Data (with misallocation)		Updated OS Data (with reassigning)	
		Median, Mos	HR (95% CI)	Median, Mos	HR (95% CI)
epNET	Cabozantinib	21.95 (N=134)	Stratified: 1.04 (0.71, 1.52) Unstratified: 1.02 (0.70, 1.47)	21.95 (N=132)	Stratified: 1.05 (0.71, 1.54) Unstratified: 1.04 (0.71, 1.53)
	Placebo	22.47 (N=69)		23.39 (N=67)	
pNET	Cabozantinib	40.08 (N=64)	Stratified: 1.11 (0.59, 2.09) Unstratified: 0.99 (0.53, 1.85)	37.26 (N=66)	Stratified: 1.01 (0.55, 1.83) Unstratified: 0.91 (0.50, 1.64)
	Placebo	31.11 (N=31)		28.65 (N=33)	

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for trial CABINET

Title: Randomised, Double-Blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumours after Progression on Prior Therapy (CABINET)	
Study identifier	A021602

<table>
<tr><td>Design</td><td colspan="3">This was a Phase 3, randomised, double-blind study of cabozantinib (60 mg daily for each 28-day cycle) versus matched placebo in subjects with advanced epNET or pNET whose disease had progressed after prior therapy. Subjects were allocated to a cohort based on disease type (epNET or pNET), and within each cohort, subjects were randomised to a treatment (cabozantinib vs placebo) in a 2:1 ratio utilizing a permuted block schedule. Randomisation was stratified by the following cohort-specific factors:
• For subjects with epNET, stratification factors were:
- Concomitant somatostatin analogue use: yes vs no
- Primary site: Midgut (jejunum, ileum, appendix, cecum, ascending colon, hepatic flexure)/Unknown primary site vs Non-midgut GI (stomach, duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon, rectum)/Lung/Other known primary site not listed
• For subjects with pNET, stratification factors were:
- Concomitant somatostatin analogue use: yes vs no
- Prior sunitinib therapy: yes vs no
Subjects were to receive blinded treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects were evaluated every 12 weeks (± 1 week) by radiographic imaging for tumour response and progression (as determined by RECIST 1.1). Images were assessed both locally and per BIRC. In addition, PD was confirmed by blinded real-time central review. At the time of real-time centrally confirmed radiographic disease progression (per RECIST 1.1), subjects were unblinded to treatment assignment, and those on placebo could elect to crossover to open-label cabozantinib treatment following re-registration and satisfying all re registration criteria (ie, documentation of disease; not pregnant or nursing; laboratory values within the limits defined per eligibility criterion #9). If radiographic PD was not confirmed by real-time central review, subjects were to continue with blinded study treatment and undergo study treatment assessments according to the protocol. Subjects were followed for survival and progression every 12 weeks until 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.
<table><tr><td>Duration of main phase:</td><td>26 October 2018 (first subject randomized) – 24 August 2023 (data cutoff date)</td></tr><tr><td>Duration of Run-in phase:</td><td>not applicable</td></tr><tr><td>Duration of Extension phase:</td><td>not applicable</td></tr></table></td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td>Treatments groups</td><td colspan="2">epNET - cabozantinib arm</td><td>Cabozantinib was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent, with 134 subjects randomised in this group.</td></tr>
<tr><td></td><td colspan="2">epNET - placebo arm</td><td>Placebo was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent, with 69 subjects randomised in this group.</td></tr>
<tr><td></td><td colspan="2">pNET - cabozantinib arm</td><td>Cabozantinib was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent, with 64 subjects randomised in this group.</td></tr>
<tr><td></td><td colspan="2">pNET - placebo arm</td><td>Placebo was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent, with 31 subjects randomised in this group.</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>PFS</td><td>Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 by a blinded independent review committee (BIRC)</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>OS</td><td>Overall survival (OS), defined as the time from randomisation to death from any cause</td></tr>
</table>

	Secondary endpoint	ORR	Objective response rate (ORR), defined as the proportion of subjects whose best response was either complete response (CR) or partial response (PR)
	Additional endpoint	DOR	Duration of response (DOR), defined as the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1
Database lock	24 August 2023		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	*Analysis population:* Intent-to-Treat Population *Time point:* 24 August 2023 (data cut-off date)			
Descriptive statistics and estimate variability	Treatment group	epNET cohort		pNET cohort	
		epNET - cabozantinib arm	epNET - placebo arm	pNET - cabozantinib arm	pNET - cabozantinib arm
	Number of subjects	134	69	64	31
	PFS (median), month	8.48	3.98	13.83	4.47
	95% CI	7.46, 12.45	3.02, 5.68	8.87, 16.95	3.02, 5.75

Effect estimate per comparison	Primary endpoint – PFS	Comparison groups	epNET - cabozantinib vs placebo	pNET – cabozantinib vs placebo
		Hazard Ratio	0.38	0.23
		95% CI	0.25, 0.58	0.12, 0.42
		P-value	<0.0001	<0.0001

Analysis description	**Secondary analysis**			
Analysis population and time point description	*Analysis population:* Intent-to-Treat Population *Time point:* 24 August 2023 (data cut-off date)			
Descriptive statistics and estimate variability	Treatment group	epNET cohort		pNET cohort	
		epNET - cabozantinib arm	epNET - placebo arm	pNET - cabozantinib arm	pNET - cabozantinib arm
	Number of subject	134	69	64	31
	OS (median), month	21.95	19.71	40.08	31.11
	95% CI	18.60, 30.19	13.37, 24.48	20.70, NE	18.76, NE

Effect estimate per comparison	Secondary endpoint - OS	Comparison groups	epNET – cabozantinib vs placebo	pNET – cabozantinib vs placebo
		Hazard Ratio	0.86	0.95
		95% CI	0.56, 1.31	0.45, 2.00
		P-value	0.4871	0.8852

Analysis description	**Secondary analysis**			
Analysis population and time point description	*Analysis population:* Intent-to-Treat Population *Time point:* 24 August 2023 (data cutoff date)			
Descriptive statistics and estimate variability	Treatment group	epNET cohort		pNET cohort	
		epNET - cabozantinib arm	epNET - placebo arm	pNET - cabozantinib arm	pNET - cabozantinib arm

	Number of subject	134	69	64	31
	Confirmed ORR, %	5.2	0	19	0
	95% CI	2.1, 10.5	0, 5.2	10.1, 30.5	0, 11.2
Effect estimate per comparison	Secondary endpoint - ORR	Comparison groups	epNET – cabozantinib vs placebo	pNET – cabozantinib vs placebo	
		Confirmed ORR treatment difference, %	5.2	18.8	
		95% CI	1.5, 9.0	9.2, 28.3	
		P-value[1]	0.0524	0.0115	
Notes	[1] Based on CMH test				
Analysis description	**Other additional analysis**				
Analysis population and time point description	*Analysis population:* Intent-to-Treat Population *Time point:* 24 August 2023 (data cutoff date)				
Descriptive statistics and estimate variability	Treatment group	epNET cohort		pNET cohort	
		epNET - cabozantinib arm	epNET - placebo arm	pNET - cabozantinib arm	pNET - cabozantinib arm
	Number of subject	7	0	12	0
	DOR (median), month	8.26	NA	11.2	NA
	95% CI	4.47, NE	NA	5.78, NE	NA
Effect estimate per comparison	Additional endpoint – DOR	*Comparison groups*	*epNET – cabozantinib vs placebo*	pNET – cabozantinib vs placebo	
		Hazard Ratio	NA	NA	
		95% CI	NA	NA	
		P-value	NA	NA	

Supportive study(ies)

Phase 2 study NCT01466036:

The clinical activity of cabozantinib in patients with NET was evaluated in an investigator-sponsored Phase 2 study that included patients with advanced pNET and epNET, many of whom had progressed on prior therapy (Chan et al, 2017; Chan, NCT01466036). Patients were treated with cabozantinib starting at a dose of 60 mg daily and continued treatment until disease progression or development of unacceptable toxicity or withdrawal of consent. The primary endpoint of the study was radiographic response rate, as measured by RECIST v. 1.1 criteria. Objective radiographic responses to treatment were observed in 3/20 (15%) patients with pNET and 6/41 (15%) patients with epNET. The median PFS was 21.1 months (95% CI: 8.6, 32.0) in patients with pNET and 17.6 months (95% CI: 8.5, 23.8) in patients with epNET. With a median follow up time of 89.1 months, the median OS was 37.3 months (95% CI: 14.5, 70.7) in patients with pNET and 36.1 months (95% CI: 20.6, 65.5) in patients with epNET. Treatment-related adverse events (AEs) associated with cabozantinib in patients with NET were similar to what has been reported in other solid tumours.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided a Phase 3 study, CABINET, to support the extension of indication for Cabometyx to include treatment of patients with pancreatic NET (pNET) and extra-pancreatic NET (epNET) with cabozantinib at a daily dose of 60 mg.

CABINET was designed as a randomised, double-blind, placebo-controlled study with two cohorts, one which included patients with pNET and one which included patients with epNET, with efficacy and safety evaluated independently. Thus, while the pNET cohort is studying a rather homogenous group of patients disease-wise, the epNET cohort includes a wide variety of NETs. Subjects were randomised to cabozantinib or placebo in a 2:1 ratio with stratification according to concomitant somatostatin analogue treatment for both cohorts, for epNET according to primary site of NET, and for pNET according to prior sunitinib therapy.

The study participants were to be diagnosed with locally advanced/unresectable or metastatic disease with well- or moderately differentiated neuroendocrine tumours, including patients with well-differentiated Grade 3 NET.

The participants had to have progression after receiving, or intolerance leading to treatment discontinuation of at least one FDA-approved line of therapy (except somatostatin analogues). The study was not set up to capture the reason for stopping prior treatment, i.e. PD or intolerance. 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. These medicinal products are also approved in the EU and recommended by treatment guidelines in Europe (Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice, 2021). Originally, patients should have been treated with everolimus to be eligible. However, according to the MAH, the requirement for prior treatment with everolimus negatively affected enrolment to the study since many physicians and patients avoided everolimus due to limited efficacy and the toxicity profile. Furthermore, Lutathera became available as a treatment option in 2018. Consequently, the protocol was amended (24 July 2020) to allow patients that had been treated with at least one FDA-approved line of therapy and increase the accrual rate. Various treatments allowed before inclusion in the study reflect the heterogeneous population studied and adds to the complexity of the interpretation of the study outcome.

Placebo was chosen as comparator due to the lack of prospective data regarding the efficacy of available agents in patients with progressive disease after treatment with FDA-approved therapy. This is considered acceptable. Alternatively, best supportive care (BSC) could have been added to both study arms (as done in RADIANT-3 for everolimus, see EPAR for Afinitor II/0008). Albeit some concomitant treatments were prohibited, e.g. other anticancer therapy, (see *Concomitant therapies*) excluding BSC from the study plan has not deprived the patients of receiving necessary symptomatic treatment. In line with treatment guidelines and clinical practice concomitant somatostatin analogue treatment was allowed provided that the subject was on a stable dose for at least 2 months before enrolment. Thus, omitting BSC in the study arms is not considered unethical in that regard. Palliative radiation or surgery and non-protocol anticancer therapy (NPACT) if required would lead to censoring. Best standard of care including anticancer therapy as comparator arm could have been a possibility; however, blinding would have been challenging.

PFS based on BIRC assessment of images was the primary endpoint. Patients were evaluated every 12 weeks for tumour response and progression (as determined by RECIST 1.1). PFS has been accepted as primary endpoint in similar study populations and is considered acceptable also in this case provided there is no detrimental effect on overall survival. OS and ORR are secondary endpoints. OS data are only descriptive. To improve recruitment, the study protocol was amended (24 July 2020) to allow patients in the placebo arm to receive open-label cabozantinib treatment at the time of disease progression. Cross-over has not impacted the assessment of PFS but could have interfered with the interpretation of the OS data.

Although this was a double-blind study, there could be unintentional "unblinding" taking into consideration the known safety profile of cabozantinib. This might be of limited consequence for the study outcome since progressive disease had to be confirmed by real-time central review before taking patients off treatment. Although unaware of the given treatment, central real-time review reader could access clinical history (amendment to the protocol 07 Dec 2022) and thus, potentially not completely blinded.

Originally the study was planned to include 210 subjects in the epNET cohort and 185 subject in the pNET cohort. Two interim analyses (IA1, IA2) for PFS futility were pre-planned for both disease cohorts when 33% and 66% of the projected number of events had occurred. Stopping for efficacy was not planned, but a nominal alpha (0.001) was spent for efficacy for each interim. After reviewing results of IA1 for pNET and IA2 for epNET, the independent data safety monitoring board (DSMB) noted a significant improvement in PFS by investigator assessment for subjects receiving treatment with cabozantinib compared with placebo in both cohorts. The investigator assessment for PFS was used for the futility analysis since the BIRC review of tumour assessments was lagging. The result of the interim analysis was later confirmed in the analysis based on BIRC review (cut-off 18 July 2023). The DSMB voted unanimously to recommend termination of accrual and unblinding of the study to enable potential crossover for patients on the placebo treatment arms to receive open-label cabozantinib treatment (July 2023, *ad hoc* DSMB meeting). Following the DSMB recommendation, the Alliance stopped enrolment into the study on 07 August 2023. The MAH has submitted statistical reports forming the basis for the DSMB recommendation and explained that no formal minutes of the DSMB meeting (July 2023) exist as it was an *ad hoc* meeting, and that minutes were only produced for regularly scheduled DSMB meetings in accordance with the Alliance SOP. Although no formal minutes are provided, documentation covering the communication of the DSMB recommendation, and the Alliance SOP governing the process has been submitted in support (Alliance DSMB Report Procedure).

Accrual

At the termination of accrual after the interim analysis, the epNET cohort had almost reached full enrolment, i.e. 203 (134:69) of the planned 210 patients. However, in the pNET cohort which originally planned to include 185 subjects, only 95 (64:31) patients had been enrolled due to lower accrual rate than expected. The final analysis was initially planned to be performed when 164 and 149 events had occurred in patients with epNET and pNET, respectively. Based on the interim analysis with DCO 24 August 2023, the information fraction for efficacy is 68% in the epNET cohort pNET and 38% in the pNET cohort.

Baseline

Most key baseline demographics and baseline characteristics were balanced between arms in both the epNET and pNET cohorts. In both cohorts, most patients had well-differentiated NETs (>88%) of Grade 2 (>60%), and ECOG status 1 or 0. Nearly all patients had been treated with SSA before entering the study; 93% of patients in both arms of the epNET cohort and 98/97% in the pNET cohort. In both

cohorts, the large majority had disease progression within the last 6 months prior to randomisation, and most of them within the last month before study entry.

epNET population: The most common primary tumour sites were the small bowel (28% cabozantinib, 42% placebo) and lung (20% cabozantinib, 17% placebo). There was also a number of patients within the heterogenous categories Other and Unknown site, with patients in the latter category mainly in the cabozantinib arm (16% vs 2.9%). Any consequence for the outcome is not possible to determine. The heterogeneity in terms of primary tumour site is acknowledged based on the low incidence of neuroendocrine tumours overall. Furthermore, the efficacy of cabozantinib is not expected to differ according to tumour site per se. All subjects had metastatic disease, and a majority had ≥ 3 metastatic sites. 90% of the participants had metastatic disease in liver and 70% had metastatic site in lymph nodes. Approximately half of the patients had non-functional tumour. Median age was 66 years in both treatment arms.

All patients had received an FDA-approved systemic anticancer therapy, the most frequent of which were everolimus (72% in the cabozantinib arm, 64% in the placebo arm) and Lu-177 dotatate (60% vs 59%). Prior cytotoxic chemotherapy was received by 38% of subjects in the cabozantinib arm and 33% of subjects in the placebo arm. Subjects in both treatment arms had received a median of 2.0 prior systemic anticancer regimens (excluding SSAs). In this cohort, 44% and 48% of patients have received only one prior treatment other than SSA.

Concomitant treatment with SSA was allowed during the study and was received by 54% and 62% of the patients in the cabozantinib and placebo arm, respectively.

pNET population: Nearly all subjects had metastatic disease (>94%), with number of metastatic sites almost equally divided between 1, 2 >3 in both arms. 95% of the participants had metastasis in liver, whereas ~50% had metastatic site in lymph nodes. The majority of patients had non-functional tumour, 75% in the cabozantinib arm and 71% in the placebo arm. While keeping in mind the limited number of patients per treatment arm, the proportion of participants ≥ 65 years was 10% higher in the placebo arm than in the cabozantinib arm (48% vs 38%, respectively) and the difference in median age nearly five years (64 vs 59.5 years). As age is an important prognostic factor, this may have had some impact on the results, favouring cabozantinib.

All patients had received an FDA-approved systemic anticancer therapy prior to enrolment, the most frequent being everolimus (80% in the cabozantinib arm, 81% in the placebo arm) and Lu-177 dotatate (59% vs 58%). Sunitinib was priorly received by a relatively low fraction, 28% and 23%, respectively, despite FDA-approval since 2011. This may be explained by more frequent use of everolimus and Lu-177 dotatate in earlier lines of therapy (Stiefel et al, 2023), but also the late protocol amendment (24 July 2020) allowing entering patients that had been treated with at least one FDA-approved line of therapy (not only everolimus). Prior cytotoxic chemotherapy was received by 69% of subjects in the cabozantinib arm and 58% of subjects in the placebo arm. Subjects in the cabozantinib arm had received a median of 3 prior systemic anticancer regimens (excluding SSAs), while patients in the placebo arm had received median 2. This cohort is more heavily pretreated than the epNET cohort; 27% and 32% of the patients have received only one prior treatment other than SSA.

Concomitant treatment with SSA was received by 56% and 55% of the patients in the cabozantinib and placebo arm, respectively.

Altogether, the baseline data were similar between treatment arms of both cohorts apart from the age distribution in the pNET cohort where the placebo arm had an older population.

Efficacy data and additional analyses

Efficacy results epNET

At the time of the primary analysis, the median follow-up time was 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm.

Primary endpoint PFS epNET: An improvement with cabozantinib compared to placebo was reported for PFS assessed by BIRC using FDA-recommended censoring rules (censoring progression after NPACT or two missed assessments), i.e. 8.48 months (95% CI: 7.46, 12.45) in the cabozantinib arm compared with 3.98 months (95% CI: 3.02, 5.68) in the placebo arm; HR 0.38 (95% CI: 0.25, 0.58; stratified 2-sided $p < 0.0001$). This result was supported by the Investigator analysis and all sensitivity analyses described in the analysis plan, showing a 59% to 65% reduction in the risk of progression or death in the cabozantinib arm compared with the placebo arm. This included an analysis treating NPACT as an event (and ignoring intermittent missing assessments) (HR 0.35; 95% CI: 0.24, 0.49). The reported improvement in PFS is similar in magnitude to what has been observed for everolimus in earlier line of therapy of lung- and GI-NET (RADIANT-4 trial), and could be considered to be of clinical relevance.

An analysis of HR over time (see *Ancillary analyses*) indicating stabilisation of HR during the study conduct period, and that the PFS analysis was not performed at a "random high" was provided. Concerns have been raised regarding potential informative censoring due to high rates of censoring due to NPACT and missing post baseline assessments, which differed between treatment arms. Further details on the reasons for treatment discontinuation prior to the censoring events in these patients, (see *Ancillary analyses*), tipping point analyses, and analysis of time to treatment failure were provided.

The MAH provided tipping point analyses for IRC and Investigator assessed PFS under various assumptions of increase/decrease in the hazard rate for non-administratively censored patients in the treatment/placebo arms, respectively. Reversing the statistical significance of the primary PFS results (using a conventional one-sided alpha level of 0.025 as for all other sensitivity analyses), required large increases in hazard rates for the administratively censored patients in the treatment arm or large reductions in hazard rates for the corresponding patients in the placebo arm. Also, with a reduced one-sided alpha level of 0.001, for IRC-assessed PFS, the analyses showed that reversing the significance of the primary PFS results would require substantial changes in hazard rates, indicating limited impact from potential informative censoring. The tipping point analyses show that the PFS results are not impacted by the observed potential informative censoring to the extent that a different conclusion regarding the presence of an effect would change.

In the time to treatment failure analysis (see *Ancillary analyses*) for which recorded treatment discontinuation for any reason was also considered to be an event, the only remaining reasons for censoring were no post-baseline assessment (without known discontinuation) and no event and did not crossover. The hazard ratio for time to treatment failure was higher than the HR for PFS, as would be expected given the higher rate of additional events in the treatment arm compared to the placebo arm: TTF HR 0.48 (95% CI 0.34, 0.66). The Kaplan-Meier curve shows clear separation after the first planned assessment (see *Ancillary analyses*). These results provide reassurance that patients being (informatively) censored after treatment discontinuation or use of NPACT are not influencing the results to the extent that a different conclusion regarding the presence of an effect would change.

An additional sensitivity analysis of PFS where events in both arms have been moved to the planned assessment time was provided. The results are in line with the primary PFS analysis (see *Ancillary analysis*).

It is noted that more patients in the cabozantinib arm than in the placebo arm (18 [13%] vs 5 [7.2%]) had death as event in the PFS analysis for the epNET cohort. Most of these events (11 and 4) were due to progressive disease. Five of the deaths in the cabozantinib arm occurred within 30 days of the last dose of study treatment. Three of these are considered possibly related to cabozantinib. These patients had several comorbidities that may have contributed.

Results of the subgroup analysis were consistent with the primary analysis of PFS with HRs below 1. Stratification of the patients was performed according to primary site of the disease i.e. Midgut/Unknown primary site vs Non-midgut GI/Lung/Other known primary site not listed. With few patients per disease site, it is not possible to determine efficacy for all the individual sites.

Although unintentional unblinding could have occurred due to the known safety profile of cabozantinib, there are no clear indications of this.

An analysis of discordance between BIRC and Investigator in determination of progression was provided. The discordance rate was relatively high, but similar in the two treatment arms. There is no obvious favouring of cabozantinib in the investigator analysis.

Secondary endpoint OS epNET: K-M estimates of median survival were 21.95 months and 19.71 months in the cabozantinib and placebo arms, respectively, with HR 0.86 [95% CI: 0.56, 1.31] for the difference; p = 0.4871. At the time of the primary analysis (DCO 24 Aug 2023), the OS data were immature with 97 of 203 subjects (48%) having died. After progression, 20 of the 69 placebo subjects (29%) crossed over to open-label cabozantinib treatment. An analysis adjusting for the effect of crossover based on an RPSFT model resulted in a HR of 0.81 [95% CI: 0.53, 1.23]; p = 0.3205. Subgroup analyses of OS were generally consistent with that for the entire population with HR close to 1 for almost all subgroups. Variations are likely caused by the small population studied. More patients in the placebo arm received NPACT (including cabozantinib) than patients in the cabozantinib arm, 55% vs 34%.

Updated OS results were provided with DCO 04 September 2024, showing no clear differences between treatment arms and similar results to the primary analysis: HR 1.04 (95%CI: 0.71, 1.52). A sensitivity analysis for OS using the latest DCO, where patients mis-allocated to pNET/epNET at enrolment had been re-allocated according to diagnosis (see *Ancillary analyses*), was submitted. A total of 3 epNET patients were misallocated to the pNET cohort and 7 pNET patients were misallocated to the epNET cohort. For the epNET, cohort the results of this analysis were almost identical to the previously reported results.

In addition, sensitivity analyses aiming to account for crossover were also inconclusive regarding any potential detrimental effect of cabozantinib. For the epNET cohort, approximately 52% of patients in the cabozantinib arm and 74% of patients in the placebo arm received crossover cabozantinib and/or at least one NPACT, which likely contributed to the lack of difference in OS between the treatment arms, as reflected in the superimposable OS curves.

Overall, OS data showed no clear difference between treatment arms.

Secondary endpoint ORR epNET: There were no subjects with CR, but 7 subjects (5.2%) had a confirmed PR in the cabozantinib arm, giving a confirmed ORR of 5.2% (95% CI: 2.1%, 10.5%). In comparison, no subject in the placebo arm had response, giving an ORR of 0% (95% CI: 0%, 5.2%). Low ORR has also been observed with everolimus in less pretreated epNET (RADIANT-3 trial). The median time from randomisation to confirmed objective response was 5.52 months (range: 2.8–8.4 months) for the 7 subjects.

Efficacy results pNET

At the time of the primary analysis, the median follow-time was 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm.

Primary endpoint PFS pNET: An improvement with cabozantinib compared to placebo was reported for PFS assessed by BIRC using FDA-recommended censoring rules (censoring progression after NPACT or two missed assessments), i.e. 13.83 months (95% CI: 8.87, 16.95) in the cabozantinib arm compared with 4.47 months (95% CI: 3.02, 5.75) in the placebo arm; HR 0.23 (95% CI: 0.12, 0.42); stratified 2-sided $p < 0.0001$. The PFS in the placebo arm is in line with what has been previously reported for everolimus in less pretreated patients (RADIANT-3 trial) and for sunitinib (Study A6181111). This result was supported by the Investigator analysis and all sensitivity analyses described in the analysis plan, showing a 71% to 78% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm. This included an analysis treating NPACT as an event (and ignoring intermittent missing assessments) (HR 0.29; 95% CI: 0.17, 0.50). Furthermore, results of the subgroup analysis were consistent with the primary analysis of PFS with HRs below 1, including the small subgroup of patients who have received prior sunitinib (HR 0.20, 95%CI 0.06, 0.64). The early termination of enrolment and the limited number of events in this cohort is unfortunate and may have led to overestimation of PFS. However, analysis of HR over time (see *Ancillary analyses*) indicates stabilisation during the study conduct period, and that the PFS analysis was not performed at a random high.
The same concerns related to the potential for informative censoring raised for the epNET cohort were raised for the pNET cohort. The same additional analyses and information as for epNET (see *Ancillary analyses*) were provided. The results and conclusions were similar, apart from the BIRC-assessed PFS results for the pNET cohort which appeared more robust to the assumptions of censoring, while at a reduced alpha level of 0.001 the investigator-assessed PFS was more sensitive. The analysis of time to treatment failure are in line with the PFS analysis, i.e. TTF HR 0.34 (95% CI 0.20, 0.56) for the pNET cohort, providing reassurance that patients being (informatively) censored after treatment discontinuation or use of NPACT are not influencing the results to the extent that a different conclusion regarding the presence of an effect would change.

The results of an additional sensitivity analysis of PFS where events in both arms have been moved to the planned assessment time are in line with the primary PFS analysis (see *Ancillary analysis*).

The analysis of discordance between BIRC and Investigator in determination of PD shows a relatively large but similar discordance in the two treatment arms. There is no obvious favouring of cabozantinib in the investigator analysis.

Secondary endpoint OS pNET: K-M estimates of median survival were 40.08 months and 31.11 months in the cabozantinib and placebo arms, respectively, with HR 0.95 [95% CI: 0.45, 2.00] for the difference; $p = 0.8852$. At the time of primary analysis (DCO 24 Aug 2023), the OS data were immature with 33 of 95 subjects (35%) having died. After progression, 12 of the 31 placebo subjects (39%) crossed over to open-label cabozantinib treatment. An analysis adjusting for the effect of crossover based on an RPSFT model resulted in a HR of 0.86 [95% CI: 0.41, 1.79]; $p = 0.6820$. Subgroup analyses of OS were generally consistent with that for the entire population with HR close to 1 for almost all subgroups, although some of them above 1. Variations are likely caused by small subgroups. More patients in the placebo arm received NPACT (including cabozantinib) than patients in the cabozantinib arm, 58% vs 39%.

Updated OS results (DCO 24 September 2024) provided an increase in the number of reported deaths from 32 to 46 and a similar median OS, with HR of 1.11 (0.59, 2.09). Kaplan-Meier landmark estimates showed comparable survival rates at all timepoints through 24 months. The sensitivity analysis for OS using the latest DCO, where patients mis-allocated to pNET/epNET at enrolment had been re-allocated according to diagnosis (see *Ancillary analyses*) showed similar result as previously reported. It is noted

that for the pNET cohort, the confidence interval narrowed when compared to the previous analysis, i.e. from HR 1.11, 95% CI (0.59, 2.09), to HR 1.01, 95% CI (0.55, 1.83).

In addition, sensitivity analyses aiming to account for crossover were also inconclusive regarding any potential detrimental effect of cabozantinib. In the pNET cohort, approximately 61% of patients in the cabozantinib arm and 77% of patients in the placebo arm received crossover cabozantinib and/or at least one NPACT, which likely contributed to the lack of difference in OS between the treatment arms, as reflected in the overlapping OS curves.

Secondary endpoint ORR pNET: There were no subject with CR, but 12 subjects (19%) had a confirmed PR in the cabozantinib arm, giving a confirmed ORR of 19% (95% CI: 10.1%, 30.5%). In comparison, no subject in the placebo arm had response. The median time from randomisation to confirmed objective response was 5.78 months (range: 2.8–8.7 months) for the 12 subjects. The ORR is relatively low, but not lower than observed with everolimus and sunitinib.

QoL substudy

Overall health-related QoL remained relatively stable over time in both treatment arms of both cohorts (data not shown). The results should be interpreted with caution due to the limited data especially in the placebo arm. PGIC showed trend for improvement over time for both pNETs and epNETs with slight worsening at Week 60. Some of the known adverse effects of cabozantinib, e.g. diarrhoea and constipation, are reflected in the scores of EORTC QLQ-GINET21. Overall, cabozantinib seems to be acceptably tolerated by the patients participating in this sub-study, and there could be a slight improvement in overall QoL until progression of the disease in the studied patients.

Indication

The final wording of the indication took into account the studied population and the latest WHO classification by specifying 'well-differentiated', in line with other treatments approved for NET, i.e. Afinitor, Sutent and Lutathera, and that 'previous line of treatment' should specify 'other than a somatostatin analogue':

2.4.4. Conclusions on the clinical efficacy

The phase 3 CABINET study comparing treatment with cabozantinib vs placebo in previously treated patients with epNET and pNET, resulted in improved PFS compared to placebo for both cohorts. The placebo arms show similar PFS as registered for other placebo-controlled studies in the treatment of epNET and pNET in less pretreated patients.

The epNET cohort, although prematurely unblinded, had nearly reached preplanned number of patients. In contrast, the pNET cohort had only recruited half of the preplanned number of patients for the final analysis of PFS when the study was unblinded, and accrual was halted. The reported prolongation of PFS with cabozantinib vs placebo is considered of clinical relevance in this pretreated population for both cohorts. Support from secondary endpoints is however lacking. For both cohorts, the HR for OS is close to 1 with wide confidence intervals. Taking into consideration that more than 40% of the patients in the placebo arms crossed over to open label cabozantinib and patients of both treatment arms had access to other treatments post progression, an OS benefit is not expected to be demonstrated.

2.5. Clinical safety

Introduction

CABINET (A021602) is a multicenter, two-arm, randomised, double-blind, placebo-controlled phase 3 study investigating cabozantinib versus placebo in patients with progressive epNET and pNET. A total of 199 subjects received study treatment in the epNET cohort (132 cabozantinib, 67 placebo) and 94 subjects in the pNET cohort (63 cabozantinib, 31 placebo). These subjects comprised the Safety Population.

The CABINET study (A021602) is the focus of this submission. However, contextualise these data within the broader cabozantinib experience as monotherapy, pooled safety data from previously reported studies in the different indications is also provided; XL184-308 (METEOR; RCC), A031203 (Cabosun; RCC), XL184-309 (CELESTIAL; HCC), and XL184-311 (Cosmic-311; DTC).

Safety presentations include summaries of adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose reduction, and events to monitor (ETMs). AEs were reported every cycle and a safety window of 30 days after last treatment dose was used for all treated subjects in each treatment group.

Patient exposure

Subject disposition for the CABINET study is presented in Table 38.

Table 38. CABINET: Subject Disposition (epNET and pNET; Double-Blind)

	epNET		pNET	
	Cabozantinib (N = 132) n (%)	**Placebo (N = 67) n (%)**	**Cabozantinib (N = 63) n (%)**	**Placebo (N = 31) n (%)**
Safety Population	132 (100)	67 (100)	63 (100)	31 (100)
Subjects on active study treatment at data cutoff	21 (16)	12 (18)	14 (22)	8 (26)
Blinded therapy	21 (16)	7 (10)	14 (22)	2 (6.5)
Open-label therapy[a]	0	5 (7.5)	0	6 (19)
Discontinued study treatment in the blinded therapy phase	111 (84)	60 (90)	49 (78)	29 (94)
Primary reason for discontinuation from study treatment in the blinded therapy phase				
Adverse Event/Side Effects/Complications	34 (26)	9 (13)	10 (16)	0
Alternative Therapy	5 (3.8)	1 (1.5)	1 (1.6)	0
Death On Study	6 (4.5)	3 (4.5)	0	0
Disease Progression, Relapse During Active Treatment	52 (39)	38 (57)	28 (44)	23 (74)
Subject Off-Treatment for Other Complicating Disease	1 (0.8)	1 (1.5)	2 (3.2)	0
Subject Withdrawal/Refusal After Beginning Protocol Therapy	7 (5.3)	4 (6.0)	5 (7.9)	4 (13)
Other	6 (4.5)	4 (6.0)	3 (4.8)	2 (6.5)
Discontinued survival follow-up	66 (50)	39 (58)	22 (35)	13 (42)
Primary reason for discontinuation of survival follow-up				
Death (as of data cutoff date)	58 (44)	36 (54)	21 (33)	11 (35)
Subjects withdrawal of consent from all follow-up visits	8 (6.1)	3 (4.5)	1 (1.6)	2 (6.5)
Follow-up (months)				

	epNET		pNET	
	Cabozantinib (N = 132) n (%)	**Placebo (N = 67) n (%)**	**Cabozantinib (N = 63) n (%)**	**Placebo (N = 31) n (%)**
Mean (SD)	23.99 (14.391)	23.79 (14.751)	25.61 (14.627)	27.32 (15.883)
Median (range)	22.72 (0.5 – 56.5)	22.77 (0.8 – 56.8)	23.03 (1.4 – 57.8)	24.90 (2.3 – 55.4)
25^{th}, 75^{th} percentiles	12.57, 30.87	11.53, 33.41	15.77, 37.78	15.21, 41.53
Placebo subjects crossed over to treatment with open-label cabozantinib	NA	20 (30)	NA	12 (39)

[a] Per off-treatment form.
[b] In the cabozantinib arm (epNET cohort), '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 (epNET cohort), 'other' included the following: clinical progression (3 subjects) and increase in tumour lesion size (liver nodule) (1 subject). In the cabozantinib arm (pNET cohort), 'other' included the following: clinical progression (1 subject), physician discretion (1 subject), and treatment hold for > 28 days (1 subject).
In the placebo arm (pNET cohort), 'other' included the following: treatment hold for > 28 days (1 subject) and palliative care (1 subject).

Study treatment exposure for subjects who received cabozantinib or placebo in the double-blind phase in the epNET and pNET cohorts is summarised in Table 39. After disease progression, twenty subjects (30%) and twelve subjects (39%) from the placebo groups crossed over to treatment with open-label cabozantinib in the pNET and epNET cohorts, respectively. Exposure for the pooled groups, including crossover, is presented in Table 40.

Table 39. CABINET: Study Treatment Exposure (epNET and pNET; Double-Blind)

	epNET		pNET	
	Cabozantinib Only (N = 132)	**Placebo (N = 67)**	**Cabozantinib Only (N = 63)**	**Placebo (N = 31)**
Duration of exposure (months)[a]				
N	132	67	63	31
Mean (SD)	6.85 (5.999)	4.29 (3.988)	9.36 (8.053)	4.40 (3.071)
Median (range)	5.37 (0.1 – 32.4)	2.79 (0.5 – 22.8)	8.28 (0.1 – 37.8)	2.86 (0.1 – 11.2)
Average daily dose (mg/day)[b]				
N	131	66	63	31
Mean (SD)	43.13 (13.849)	56.70 (9.812)	42.37 (14.186)	55.21 (7.907)
Median (range)	42.86 (10.0 – 60.0)	60.00 (21.7 – 92.7)	41.36 (19.3 – 60.0)	59.54 (29.1 – 60.0)
Dose intensity (%)[c]				
N	131	66	63	31
Mean (SD)	71.89 (23.082)	94.50 (16.354)	70.62 (23.643)	92.01 (13.178)
Median (range)	71.43 (16.7–100.0)	100.00 (36.1–154.5)	68.93 (32.2–100.0)	99.24 (48.6–100.0)

Note: The dosing intervals with dose level of 'Other' and with 'If (Other), specify' field not quantifiable will be considered as dose level of unknown, and the corresponding dosing interval will not be taken into the calculation of the total dose received, average daily dose and dose intensity, but will be included in the derivation of the first dose and the last dose of study treatment to prevent underreporting for exposure and AE summaries.
[a] Duration of exposure = (Date of last dose or cutoff date – Date of first dose + 1)/30.4375.
[b] Average daily dose (mg/day) = total dose received (mg) / duration of exposure (days).
[c] Percent dose intensity of cabozantinib/placebo = 100*(average daily dose in mg/day) / (60 mg/day).

Table 40. CABINET: Study Treatment Exposure (Pooled epNET + pNET Double-Blind versus Pooled epNET + pNET Including Crossover)

	Cabozantinib Only (N = 195)	All Cabozantinib (N = 227)
Duration of exposure (months)[a]		
N	195	227
Mean (SD)	7.66 (6.813)	7.47 (6.634)
Median (range)	5.52 (0.1 – 37.8)	5.52 (0.1 – 37.8)
Average daily dose (mg/day)[b]		
N	194	226
Mean (SD)	42.89 (13.927)	43.18 (14.082)
Median (range)	42.44 (10.0 – 60.0)	42.64 (10.0 – 60.0)
Dose intensity (%)[c]		
N	194	226
Mean (SD)	71.48 (23.212)	71.96 (23.470)
Median (range)	70.73 (16.7 – 100.0)	71.06 (16.7 – 100.0)

Note: The dosing intervals with dose level of 'Other' and with 'If (Other), specify' field not quantifiable will be considered as dose level of unknown, and the corresponding dosing interval will not be taken into the calculation of the total dose received, average daily dose and dose intensity, but will be included in the derivation of the first dose and the last dose of study treatment to prevent underreporting for exposure and AE summaries.

[a] Duration of exposure = (Date of last dose or cutoff date – Date of first dose + 1)/30.4375.

[b] Average daily dose (mg/day)= total dose received (mg) / duration of exposure (days).

[c] Percent dose intensity of cabozantinib/placebo = 100*(average daily dose in mg/day) / (60 mg/day).

Study treatment modifications (Reductions or Hold)

Study treatment modifications (reductions or hold) for the Safety Population are summarized in Table 41.

Table 41. CABINET: Study Treatment Modifications (epNET and pNET; Double-Blind)

	epNET		pNET	
	Cabozantinib Only (N = 132)	Placebo (N = 67)	Cabozantinib Only (N = 63)	Placebo (N = 31)
Subjects with any dose modification, n (%)	112 (85)	33 (49)	56 (89)	16 (52)
Subjects with any dose reduction, n (%)	87 (66)	7 (10)	43 (68)	6 (19)
Subjects with any dose reduction due to an AE who received[a], n (%)	82 (62)	5 (7.5)	42 (67)	4 (13)
40 mg once daily, n (%)	79 (60)	4 (6.0)	40 (63)	4 (13)
20 mg once daily, n (%)	34 (26)	2 (3.0)	17 (27)	1 (3.2)
Time to dose reduction,				
Time (days) to 1st dose reduction, median (range)	50.5 (6 – 534)	31.0 (9–60)	47.5 (8–228)	16.5 (8–25)
Time (days) to 2nd dose reduction, median (range)	102.0 (42 – 427)	40.0 (40–40)	91.0 (24–202)	29.0 (29–29)
Subjects with any dose hold, n (%)	110 (83)	32 (48)	54 (86)	15 (48)

[a] Includes all-causality AEs

Demographics and Baseline Characteristics

Most key baseline demographics and baseline characteristics were balanced between arms in both the epNET and pNET cohorts. In the epNET cohort there was a lower number of male subjects (45% vs 55%) and a lower number of ECOG 0 subjects (37% vs 48%) in the cabozantinib arm compared to the placebo arm. In the pNET cohort, there was a higher number of ECOG 0 patients (54% vs 48%) in the cabozantinib arm compared to the placebo arm. Please refer to the efficacy section for further details on baseline demographics and characteristics.

Adverse events

Adverse events (AEs) were mapped to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA; version 26.1). AEs were to be reported every cycle and 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. A treatment-emergent AE (TEAE) was defined as an AE observed on or after Cycle 1 or those collected on the AE case report form (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. Related TEAEs were those AEs with an Investigator attribution of causality as possible, probable, or definite. For brevity, TEAEs are referred to as AEs. Certain AEs were considered "expected" (referred to as solicited events) and included the following: alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, diarrhoea, fatigue, hyperglycaemia, 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 collected but not required to be reported.

An overview of adverse events (AEs) for epNET and pNET, and for pooled epNET + pNET with and without crossover, is presented in Table 42 and Table 43, respectively.

Table 42. CABINET: Overview of Adverse Events (epNET and pNET; Double-Blind)

	epNET		pNET	
	Cabozantinib Only (N=132) n (%)	**Placebo (N=67) n (%)**	**Cabozantinib Only (N=63) n (%)**	**Placebo (N=31) n (%)**
AE	132 (100)	67 (100)	63 (100)	31 (100)
Related AE	130 (98)	56 (84)	62 (98)	26 (84)
SAE	68 (52)	28 (42)	35 (56)	10 (32)
Related SAE	52 (39)	16 (24)	30 (48)	4 (13)
Worst Grade 3 or 4 AE	89 (67)	26 (39)	46 (73)	14 (45)
Worst Grade 3 or 4 Related AE	78 (59)	18 (27)	41 (65)	7 (23)
Worst Grade 4 AE	9 (6.8)	1 (1.5)	7 (11)	0
Worst Grade 4 Related AE	8 (6.1)	1 (1.5)	6 (9.5)	0
Worst Grade 5 AE	9 (6.8)	5 (7.5)	0[a]	0
Worst Grade 5 Related AE	4 (3.0)	1 (1.5)	0	0
AE leading to dose reduction	50 (38)	5 (7.5)	31 (49)	5 (16)
AE leading to dose hold	106 (80)	25 (37)	52 (83)	13 (42)
AE leading to dose modification (reduction or hold)	113 (86)	28 (42)	56 (89)	16 (52)
AE leading to treatment discontinuation	36 (27)	13 (19)	12 (19)	3 (9.7)
Related AE leading to treatment discontinuation[b]	34 (26)	9 (13)	9 (14)	1 (3.2)
ETM Any Grade AE	111 (84)	37 (55)	54 (86)	19 (61)
ETM Worst Grade 3 or 4 AE	48 (36)	13 (19)	31 (49)	6 (19)
ETM Worst Grade 4 AE	4 (3.0)	0	2 (3.2)	0
ETM Worst Grade 5 AE	4 (3.0)	0	0	0

Note: Subjects counted only once within each category but may be counted in multiple categories.
[a] A single death occurred due to tumour during the safety reporting window but was not entered as a Grade 5 AE.
[b] The data presented for AEs leading to treatment discontinuation were recorded on the AE CRF

Table 43. CABINET: Overview of Adverse Events (Pooled epNET + pNET Double-Blind versus Pooled epNET + pNET Including Crossover)

	Cabozantinib Only (N = 195) n (%)	All Cabozantinib (N = 227) n (%)
AE	195 (100)	227 (100)
Related AE	192 (98)	224 (99)
SAE	87 (45)	102 (45)
Related SAE	61 (31)	65 (29)
Worst Grade 3 or 4 AE	135 (69)	156 (69)
Worst Grade 3 or 4 Related AE	119 (61)	133 (59)
Worst Grade 4 AE	16 (8.2)	17 (7.5)
Worst Grade 4 Related AE	14 (7.2)	15 (6.6)
Worst Grade 5 AE	9 (4.6)	10 (4.4)
Worst Grade 5 Related AE	4 (2.1)	5 (2.2)
AE leading to dose reduction	81 (42)	96 (42)
AE leading to dose hold	158 (81)	178 (78)
AE leading to dose modification (reduction or hold)	169 (87)	191 (84)
AE leading to treatment discontinuation[a]	48 (25)	55 (24)
Related AE leading to treatment discontinuation	43 (22)	47 (21)
ETM Any Grade AE	164 (84)	195 (86)
ETM Worst Grade 3 or 4 AE	79 (41)	90 (40)
ETM Worst Grade 4 AE	6 (3.1)	7 (3.1)
ETM Worst Grade 5 AE	4 (2.1)	5 (2.2)

Note: Subjects may be counted multiple times in different categories due to having experienced multiple AEs.
[a] The data presented for AEs leading to treatment discontinuation were recorded on the AE CRF.

Treatment-Emergent Adverse Events

Summaries of AEs reported for ≥ 20% of subjects in either treatment arm are provided for the epNET cohort (Table 44), pNET cohort (Table 45), and pooled epNET + pNET with and without crossover subjects (Table 46 and Table 47). AEs included symptoms that could have been present at baseline.

Table 44. CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects (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)**	**26 (39)**	**5 (7.5)**
Fatigue	95 (72)	19 (14)	0	39 (58)	6 (9.0)	0
AST increased	93 (70)	5 (3.8)	0	15 (22)	1 (1.5)	0
Diarrhoea	86 (65)	14 (11)	0	28 (42)	3 (4.5)	0
Hypertension	84 (64)	34 (26)	0	27 (40)	4 (6.0)	0
ALT increased	83 (63)	1 (0.8)	0	15 (22)	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	8 (12)	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	2 (3.0)	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	21 (31)	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

Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Table 45. CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects (pNET; Double Blind)

Preferred Term	Cabozantinib Only (N = 63) n (%)			Placebo (N = 31) n (%)		
	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

Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Table 46. CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects (Pooled epNET + pNET; Double-Blind)

Preferred Term	Cabozantinib Only (N = 195) n (%)			Placebo (N = 98) n (%)		
	Grade			Grade		
	All	3/4	5	All	3/4	5
Number of Subjects With at Least One Event	195 (100)	135 (69)	9 (4.6)	98 (100)	40 (41)	5 (5.1)
Fatigue	145 (74)	28 (14)	0	58 (59)	8 (8.2)	0
AST increased	141 (72)	6 (3.1)	0	30 (31)	1 (1.0)	0

Preferred Term	Cabozantinib Only (N = 195) n (%)			Placebo (N = 98) n (%)		
	Grade			Grade		
	All	3/4	5	All	3/4	5
ALT increased	129 (66)	2 (1.0)	0	27 (28)	2 (2.0)	0
Diarrhoea	126 (65)	18 (9.2)	0	35 (36)	3 (3.1)	0
Hypertension	124 (64)	48 (25)	0	42 (43)	8 (8.2)	0
Platelet count decreased	89 (46)	2 (1.0)	0	14 (14)	1 (1.0)	0
Stomatitis[a]	81 (42)	9 (4.6)	0	11 (11)	0	0
Nausea	76 (39)	8 (4.1)	0	24 (24)	1 (1.0)	0
PPE syndrome	72 (37)	10 (5.1)	0	8 (8.2)	0	0
Dysgeusia	61 (31)	0	0	4 (4.1)	0	0
WBC count decreased	61 (31)	5 (2.6)	0	4 (4.1)	0	0
Decreased appetite	59 (30)	4 (2.1)	0	16 (16)	1 (1.0)	0
Neutrophil count decreased	59 (30)	5 (2.6)	0	6 (6.1)	0	0
Hyperglycaemia	57 (29)	3 (1.5)	0	36 (37)	2 (2.0)	0
Anaemia	55 (28)	4 (2.1)	0	23 (23)	0	0
Blood alkaline phosphatase increased	51 (26)	8 (4.1)	0	28 (29)	4 (4.1)	0
Hypothyroidism	51 (26)	0	0	3 (3.1)	0	0
Lymphocyte count decreased	50 (26)	17 (8.7)	0	16 (16)	1 (1.0)	0
Abdominal pain	48 (25)	13 (6.7)	0	32 (33)	6 (6.1)	0
Weight decreased	48 (25)	8 (4.1)	0	8 (8.2)	0	0
Hypophosphataemia	39 (20)	1 (0.5)	0	5 (5.1)	0	0
Vomiting	39 (20)	7 (3.6)	0	12 (12)	1 (1.0)	0

Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Table 47. CABINET: Frequent Adverse Events Regardless of Causality Occurring in ≥ 20% of Subjects (Pooled epNET + pNET Double-Blind versus Pooled epNET + pNET Including Crossover)

Preferred Term	Cabozantinib Only (N = 195) n (%)			All Cabozantinib (N = 227) n (%)		
	Grade			Grade		
	All	3/4	5	All	3/4	5
Number of Subjects With at Least One Event	195 (100)	135 (69)	9 (4.6)	227 (100)	156 (69)	10 (4.4)
Fatigue	145 (74)	28 (14)	0	166 (73)	31 (14)	0
AST increased	141 (72)	6 (3.1)	0	161 (71)	7 (3.1)	0
ALT increased	129 (66)	2 (1.0)	0	147 (65)	2 (0.9)	0
Hypertension	124 (64)	48 (25)	0	145 (64)	53 (23)	0
Diarrhoea	126 (65)	18 (9.2)	0	144 (63)	19 (8.4)	0
Platelet count decreased	89 (46)	2 (1.0)	0	100 (44)	3 (1.3)	0
Stomatitis[a]	81 (42)	9 (4.6)	0	94 (41)	10 (4.4)	0
PPE syndrome	72 (37)	10 (5.1)	0	90 (40)	11 (4.8)	0
Nausea	76 (39)	8 (4.1)	0	84 (37)	9 (4.0)	0
Dysgeusia	61 (31)	0	0	71 (31)	0	0
Decreased appetite	59 (30)	4 (2.1)	0	68 (30)	4 (1.8)	0
Hyperglycaemia	57 (29)	3 (1.5)	0	68 (30)	3 (1.3)	0
WBC count decreased	61 (31)	5 (2.6)	0	68 (30)	5 (2.2)	0
Neutrophil count decreased	59 (30)	5 (2.6)	0	67 (30)	6 (2.6)	0
Anaemia	55 (28)	4 (2.1)	0	62 (27)	4 (1.8)	0
Blood alkaline phosphatase increased	51 (26)	8 (4.1)	0	60 (26)	9 (4.0)	0
Hypothyroidism	51 (26)	0	0	59 (26)	0	0
Weight decreased	48 (25)	8 (4.1)	0	58 (26)	10 (4.4)	0
Abdominal pain	48 (25)	13 (6.7)	0	56 (25)	15 (6.6)	0
Lymphocyte count decreased	50 (26)	17 (8.7)	0	55 (24)	17 (7.5)	0
Hypophosphataemia	39 (20)	1 (0.5)	0	49 (22)	1 (0.4)	0
Vomiting	39 (20)	7 (3.6)	0	44 (19)	7 (3.1)	0

Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Treatment-Related Adverse Events

Treatment-related AEs are presented for the epNET cohort (Table 48) and pNET cohort (Table 49).

Table 48. CABINET: Treatment-Related Adverse Events Occurring in ≥ 20% of Subjects in Either Treatment Arm (epNET; Double-Blind)

	Cabozantinib Only (N=132) n (%)			Placebo (N=67) n (%)		
Preferred Term	**All**	**G3/4**	**G5**	**All**	**G3/4**	**G5**
Subjects with at least 1 event, n (%)	130 (98)	78 (59)	4 (3.0)	56 (84)	18 (27)	1 (1.5)
AST increased	86 (65)	4 (3.0)	0	12 (18)	0	0
Fatigue	80 (61)	17 (13)	0	29 (43)	5 (7.5)	0
ALT increased	77 (58)	1 (0.8)	0	10 (15)	0	0
Diarrhoea	72 (55)	14 (11)	0	20 (30)	3 (4.5)	0
Hypertension	69 (52)	27 (20)	0	14 (21)	2 (3.0)	0
Platelet count decreased	58 (44)	1 (0.8)	0	5 (7.5)	1 (1.5)	0
Stomatitis[a]	48 (36)	5 (3.8)	0	7 (10)	0	0
Nausea	46 (35)	2 (1.5)	0	11 (16)	0	0
WBC count decreased	46 (35)	4 (3.0)	0	2 (3.0)	0	0
PPE syndrome	45 (34)	4 (3.0)	0	4 (6.0)	0	0
Dysgeusia	42 (32)	0	0	2 (3.0)	0	0
Decreased appetite	40 (30)	2 (1.5)	0	8 (12)	0	0
Neutrophil count decreased	38 (29)	4 (3.0)	0	2 (3.0)	0	0
Hypothyroidism	34 (26)	0	0	1 (1.5)	0	0
Lymphocyte count decreased	30 (23)	5 (3.8)	0	6 (9.0)	0	0
Anaemia	28 (21)	2 (1.5)	0	7 (10)	0	0
Weight decreased	28 (21)	3 (2.3)	0	3 (4.5)	0	0
Blood alkaline phosphatase increased	26 (20)	3 (2.3)	0	11 (16)	3 (4.5)	0

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.

[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Table 49. CABINET: Treatment-Related Adverse Events Occurring in ≥ 20% of Subjects in Either Treatment Arm (pNET; Double-Blind)

	Cabozantinib Only (N=63) n (%)			Placebo (N=31) n (%)		
Preferred Term	**All**	**G3/4**	**G5**	**All**	**G3/4**	**G5**
Subjects with at least 1 event, n (%)	62 (98)	41 (65)	0	26 (84)	7 (23)	0
Fatigue	47 (75)	7 (11)	0	12 (39)	1 (3.2)	0
ALT increased	40 (63)	1 (1.6)	0	8 (26)	0	0
AST increased	40 (63)	1 (1.6)	0	8 (26)	0	0
Diarrhoea	37 (59)	4 (6.3)	0	3 (9.7)	0	0
Hypertension	34 (54)	12 (19)	0	7 (23)	3 (9.7)	0
Stomatitis[a]	29 (46)	4 (6.3)	0	2 (6.5)	0	0
PPE syndrome	27 (43)	6 (9.5)	0	3 (9.7)	0	0
Nausea	24 (38)	5 (7.9)	0	7 (23)	1 (3.2)	0
Platelet count decreased	19 (30)	0	0	3 (9.7)	0	0
Dysgeusia	18 (29)	0	0	2 (6.5)	0	0
Neutrophil count decreased	14 (22)	1 (1.6)	0	1 (3.2)	0	0
Blood alkaline phosphatase increased	13 (21)	0	0	2 (6.5)	0	0
Blood thyroid stimulating hormone increased	13 (21)	0	0	0	0	0
Hypophosphataemia	13 (21)	0	0	2 (6.5)	0	0
Vomiting	13 (21)	4 (6.3)	0	3 (9.7)	0	0
Anaemia	12 (19)	0	0	7 (23)	0	0

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Adverse Events by Severity

Frequently reported all-causality Grade 3/4 AEs are provided for the epNET cohort (Table 50) and pNET cohort (Table 51).

Table 50. CABINET: All-Causality Grade 3 or 4 Adverse Events Occurring in > 4% of Subjects in Either Treatment Arm (epNET; Double-Blind)

Preferred Term	**Cabozantinib Only (N=132) n (%)**	**Placebo (N=67) n (%)**
Subjects with at least 1 Grade 3 or 4 event, n (%)	89 (67)	26 (39)
Hypertension	34 (26)	4 (6.0)
Fatigue	19 (14)	6 (9.0)
Diarrhoea	14 (11)	3 (4.5)

Lymphocyte count decreased	12 (9.1)	1 (1.5)
Abdominal pain	11 (8.3)	4 (6.0)
Blood alkaline phosphatase increased	6 (4.5)	4 (6.0)
Dyspnoea	6 (4.5)	3 (4.5)
Weight decreased	6 (4.5)	0
Syncope	5 (3.8)	5 (7.5)
Blood bilirubin increased	3 (2.3)	4 (6.0)

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
Note: Preferred terms in **bold** font are solicited events.

Table 51. CABINET: All-Causality Grade 3 or 4 Adverse Events Occurring in > 4% Subjects in Either Treatment Arm (pNET; Double-Blind)

Preferred Term	**Cabozantinib Only (N=63) n (%)**	**Placebo (N=31) n (%)**
Subjects with at least 1 Grade 3 or 4 event, n (%)	46 (73)	14 (45)
Hypertension	14 (22)	4 (13)
Fatigue	9 (14)	2 (6.5)
PPE syndrome	6 (9.5)	0
Lymphocyte count decreased	5 (7.9)	0
Nausea	5 (7.9)	1 (3.2)
Diarrhoea	4 (6.3)	0
Embolism	4 (6.3)	0
Stomatitis[a]	4 (6.3)	0
Vomiting	4 (6.3)	0
Blood bilirubin increased	3 (4.8)	1 (3.2)
Blood pressure increased	3 (4.8)	0
Hypoxia	3 (4.8)	0
Pain	3 (4.8)	0
Pulmonary embolism	3 (4.8)	0
Sepsis	3 (4.8)	0
Abdominal pain	2 (3.2)	2 (6.5)
Small intestinal obstruction	1 (1.6)	2 (6.5)
Cholangitis	0	2 (6.5)

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
Note: Preferred terms in **bold** font are solicited events.
[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Serious adverse event/deaths/other significant events

Deaths

In CABINET, 114 subjects died during the blinded treatment phase as of the data cutoff. An overview of deaths and primary reason for death is provided in Table 52. Investigators could only select a single primary reason for death on the death CRF but could attribute Grade 5 AEs as possibly or probably related to study drug 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 (Table 53), but drug-related deaths were not selected as a primary reason for death. Of note, no subject in the pNET cohort had a treatment-related Grade 5 AE.

Table 52. CABINET: Deaths and Primary Reason for Death (epNET and pNET; Double-Blind)

Preferred Term	epNET		pNET	
	Cabozantinib Only (N = 132) n (%)	Placebo (N = 67) n (%)	Cabozantinib Only (N = 63) n (%)	Placebo (N = 31) n (%)
Alive	74 (56)	40 (60)	42 (67)	23 (74)
Died	58 (44)	27 (40)	21 (33)	8 (26)
Primary Death Reason				
Tumour (Progressive Disease)	35 (27)	14 (21)	15 (24)	5 (16)
Drug-related	0	0	0	0
Unknown	14 (11)	8 (12)	5 (7.9)	2 (6.5)
Other	9 (6.8)	5 (7.5)	1 (1.6)	1 (3.2)
Death ≤ 30 days after the date of last dose of study treatment	9 (6.8)	5 (7.5)	1 (1.6)	0
Primary Death Reason				
Tumour (Progressive Disease)	5 (3.8)	4 (6.0)	1 (1.6)	0
Drug-related	0	0	0	0
Unknown	2 (1.5)	0	0	0
Other[a]	2 (1.5)	1 (1.5)	0	0
Death > 30-100 days after the date of last dose of study treatment	16 (12)	2 (3.0)	6 (9.5)	4 (13)
Primary Death Reason				
Tumour (Progressive Disease)	11 (8.3)	1 (1.5)	5 (7.9)	3 (9.7)
Drug-related	0	0	0	0
Unknown	2 (1.5)	0	0	1 (3.2)
Other[b]	3 (2.3)	1 (1.5)	1 (1.6)	0
Death >100 days after the date of last dose of study treatment	33 (25)	20 (30)	14 (22)	4 (13)
Primary Death Reason				
Tumour (Progressive Disease)	19 (14)	9 (13)	9 (14)	2 (6.5)
Drug-related	0	0	0	0
Unknown	10 (7.6)	8 (12)	5 (7.9)	1 (3.2)
Other[c]	4 (3.0)	3 (4.5)	0	1 (3.2)

[a] The category of 'other' for deaths ≤ 30 days after the last dose of study treatment included the following:
In the epNET cohort, cabozantinib arm: multiorgan failure (1 subject) and respiratory failure due to metastatic tumour (1 subject).

[b] The category of 'other' for deaths > 30-100 days after the last dose of study treatment included the following:
In the epNET cohort, cabozantinib arm: acute cardiac tamponade (1 subject), COVID-19, extremity swelling, inferior vena cava occlusion and stenosis, and pleural effusions (1 subject), and stroke (1 subject).
In the epNET cohort, placebo arm: dyspnea and hypoglycemia from chronic medical disease (1 subject).
In the pNET cohort, cabozantinib arm: acute sepsis, metabolic encephalopathy, acute renal failure (1 subject).
[c] The category of 'other' for deaths > 100 days after the last dose of study treatment included the following:
In the epNET cohort, cabozantinib arm: acute respiratory failure with hypoxia, septic shock (1 subject), progressive disease (1 subject), septic shock secondary to cancer (1 subject), encephalitis (pembrolizumab) (1 subject).
In the epNET cohort, placebo arm: septic/cardiogenic shock (1 subject), pneumotosis intestinalis and portal venous gas leading to cardiac arrest (1 subject), and died of disease (1 subject).
In the pNET cohort, placebo arm: septic shock due to urinary tract infection (1 subject).

Table 53. CABINET: Grade 5 Adverse Events Occurring Within 30 Days of the Last Dose of Study Drug (epNET and pNET; Double-Blind)

Preferred Term	epNET		pNET	
	Cabozantinib Only (N = 132) n (%)	Placebo (N = 67) n (%)	Cabozantinib Only[a] (N = 63) n (%)	Placebo (N = 31) n (%)
Subjects with a Grade 5 AE	9 (6.8)	5 (7.5)	0	0
Death	2 (1.5)	2 (3.0)	0	0
Disease progression	2 (1.5)	2 (3.0)	0	0
Cardiac arrest	1 (0.8)	0	0	0
GI haemorrhage	1 (0.8)	0	0	0
Hepatic failure	1 (0.8)	0	0	0
Multiple organ dysfunction syndrome	1 (0.8)	0	0	0
Sudden death	1 (0.8)	0	0	0
Neuroendocrine carcinoma	0	1 (1.5)	0	0

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
[a] A single death occurred due to tumour during the safety reporting window but was not entered as a Grade 5 AE.

Treatment-related Grade 5 AEs for the 4 subjects in the cabozantinib arm of the epNET cohort are described below.

- 80-year-old male with epNET, received cabozantinib from 01 April 2019 through 21 April 2019 (held from 22 April 2019 to 29 April 2019 then discontinued). The subject experienced pulmonary embolism Grade 3 serious about 23 days after initiating treatment with cabozantinib and was hospitalized. Five days after admission, the subject had a cerebrovascular accident (Grade 3 serious) and gastrointestinal bleeding which ultimately led to death (Grade 5). The Investigator assessed cerebrovascular accident, GI haemorrhage, and pulmonary embolism as serious and possibly related to cabozantinib and possibly related to the underlying carcinoid tumour of the lung; gastrointestinal haemorrhage was also probably related to heparin therapy; and cerebrovascular accident was also considered probably related to pulmonary embolus.

- 66-year-old male with epNET, received cabozantinib from 16 January 2020 through 15 February 2020. On 15 Feb 2020, the subject experienced sudden death (Grade 5). There were no signs of homicide or suicide. The exact cause of death was unknown. The Investigator assessed the sudden death not otherwise specified (NOS) as serious and possibly related to cabozantinib and epNET.

- 73-year-old female with epNET, received cabozantinib from 12 July 2021 through 12 December 2021 (held from 13 December 2021 until 26 December 2021 then discontinued). The subject was hospitalized on 20 December 2021 due to abdominal pain (Grade 3,

serious) and generalized muscle weakness (Grade 3, serious). While in hospital on 26 December 2021, the subject went into atrial fibrillation and had a cardiac arrest. The subject was taken off life support systems and died a few hours later. The cause of death was reported as cardiac arrest, which was considered by the Investigator as possibly related to cabozantinib.

- 77-year-old male with epNET, received cabozantinib from 30 April 2022 through 30 May 2022. On 29 May 2022, the subject complained of severe abdominal pain and diarrhoea with loud bowel sounds the night before. On 30 May 2022 in the morning, the subject was found collapsed, was taken to the emergency room, and was pronounced dead (death not otherwise specified [NOS], Grade 5). The cause of death was unknown. The Investigator assessed the death NOS as serious and possibly related to cabozantinib and epNET.

The treatment-related Grade 5 AE for the 1 subject randomised to placebo is described below:

- A 66-year-old female with epNET, received placebo from 29 April 2019 through 12 May 2019 (held from 13 May 2019 until 11 June 2019 then discontinued). On 04 June 2019, the subject developed vaginal haemorrhage (Grade 2, serious), while on anticoagulation for pulmonary embolism which resulted in hospitalization. During hospitalisation functional status declined. Due to progression of disease and significant symptoms, comfort-oriented care was requested. On 10 June 2019, the subject was transferred to hospital progressive care unit for management of end-of-life symptoms. Symptoms were appropriately controlled. On 11 June 2019, the subject died due to disease progression (Grade 5).

Other Serious Adverse Events

Serious adverse events occurring in ≥ 2% of subjects in either treatment arm are presented in Table 54 (epNET), Table 55 (pNET), Table 56 (pooled pNET+epNET) and Table 57 (pooled pNET+epNET including crossover).

Table 54. 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 serious 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)
Death	2 (1.5)	2 (3.0)
Disease progression	2 (1.5)	2 (3.0)
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)

Note: Preferred terms in **bold** font are solicited events.

Table 55. 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 serious 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
Hyperkalemia	2 (3.2)	0
Hypertension	2 (3.2)	1 (1.6)
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)

Note: Preferred terms in **bold** font are solicited events.

Table 56. CABINET: Serious Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Arm (Pooled epNET + pNET; Double-Blind)

Preferred Term	Cabozantinib Only (N = 195) n (%)	Placebo (N = 98) n (%)
Number of subjects with at least one serious event	87 (45)	34 (35)
Hypertension	10 (5.1)	1 (1.0)
Abdominal pain	9 (4.6)	5 (5.1)
Vomiting	8 (4.1)	2 (2.0)
Nausea	6 (3.1)	2 (2.0)
Sepsis	6 (3.1)	0
Blood bilirubin increased	5 (2.6)	2 (2.0)
Diarrhoea	5 (2.6)	3 (3.1)
Fatigue	5 (2.6)	3 (3.1)
Pulmonary embolism	5 (2.6)	1 (1.0)
Anaemia	4 (2.1)	0
Dyspnoea	3 (1.5)	3 (3.1)
Syncope	3 (1.5)	3 (3.1)
Acute kidney injury	2 (1.0)	3 (3.1)
Death	2 (1.0)	2 (2.0)
Disease progression	2 (1.0)	2 (2.0)
Hyperglycaemia	2 (1.0)	2 (2.0)
Hypokalaemia	2 (1.0)	2 (2.0)
Small intestinal obstruction	2 (1.0)	5 (5.1)
Cholangitis	0	2 (2.0)

Note: Preferred terms in **bold** font are solicited events.

Table 57. CABINET: Serious Adverse Events Occurring in ≥ 2% of Subjects (Pooled epNET + pNET Double-Blind versus Pooled epNET + pNET Including Crossover)

Preferred Term	Cabozantinib Only (N = 195) n (%)	All Cabozantinib (N = 227) n (%)
Number of Subjects With at Least One SAE	87 (45)	102 (45)
Hypertension	10 (5.1)	11 (4.8)
Abdominal pain	9 (4.6)	10 (4.4)
Vomiting	8 (4.1)	9 (4.0)
Fatigue	5 (2.6)	6 (2.6)
Nausea	6 (3.1)	6 (2.6)
Sepsis	6 (3.1)	6 (2.6)
Blood bilirubin increased	5 (2.6)	5 (2.2)
Diarrhoea	5 (2.6)	5 (2.2)
Pulmonary embolism	5 (2.6)	5 (2.2)
Anaemia	4 (2.1)	4 (1.8)

Note: Preferred terms in **bold** font are solicited events.

Treatment-Related Serious Adverse Events

Frequently reported treatment-related SAEs are summarized in Table 58 and Table 59.

Table 58. CABINET: Treatment-Related Serious Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Arm (epNET; Double-Blind)

Preferred Term	Cabozantinib Only (N=132)	Placebo (N=67)
Subjects with at least 1 related SAE, n (%)	38 (29)	14 (21)
Hypertension	8 (6.1)	0
Diarrhoea	3 (2.3)	3 (4.5)
Fatigue	3 (2.3)	3 (4.5)
Pulmonary embolism	3 (2.3)	1 (1.5)
Acute kidney injury	1 (0.8)	2 (3.0)
Abdominal pain	0	2 (3.0)

Note: Preferred terms in **bold** font are solicited events.

Table 59. CABINET: Treatment-Related Serious Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Arm (pNET; Double-Blind)

Preferred Term	Cabozantinib Only (N=63)	Placebo (N=31)
Subjects with at least 1 related SAE, n (%)	23 (37)	2 (6.5)
Vomiting	4 (6.3)	0
Embolism	3 (4.8)	0
Hypoxia	3 (4.8)	0
Nausea	3 (4.8)	0
Abdominal pain	2 (3.2)	1 (3.2)
Pulmonary embolism	2 (3.2)	0
Small intestinal obstruction	0	2 (6.5)

Note: Preferred terms in **bold** font are solicited events.

Other Significant Adverse Events

Adverse Events That Led to a Dose Modification (Reduction or Hold)

For subjects in the **epNET** cohort, AEs led to a dose modification (reduction or hold) for 86% of subjects in the cabozantinib arm and 42% of subjects in the placebo arm. In both treatment arms, the most frequently reported AEs that led to a dose modification were solicited AEs: fatigue (25% cabozantinib, 7.5% placebo) and diarrhoea (23% cabozantinib, 6.0% placebo). In the cabozantinib arm, these were followed 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 dyspnoea (6.0%).

For subjects 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 solicited AEs: PPE syndrome (27% of subjects), fatigue (25%), diarrhoea (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%).

Adverse Events that led to a dose reduction and a dose hold are presented in Table 60 and Table 61, respectively.

Table 60. CABINET: Adverse Events Occurring in > 5% of Subjects That Led to a Dose Reduction (epNET and pNET; Double-Blind)

	epNET		pNET	
Preferred Term	**Cabozantinib Only (N=132) n (%)**	**Placebo (N=67) n (%)**	**Cabozantinib Only (N=63) n (%)**	**Placebo (N=31) n (%)**
Subjects with at least 1 AE leading to dose reduction, n (%)	50 (38)	5 (7.5)	31 (49)	5 (16)
PPE syndrome	13 (9.8)	0	12 (19)	0
Diarrhoea	10 (7.6)	1 (1.5)	2 (3.2)	1 (3.2)
Fatigue	10 (7.6)	3 (4.5)	9 (14)	3 (9.7)
Hypertension	8 (6.1)	1 (1.5)	5 (7.9)	0
Stomatitis[a]	6 (4.5)	0	5 (7.9)	0

[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Adverse Events That Led to a Dose Hold

Table 61. CABINET: Adverse Events Occurring in > 5% of Subjects That Led to a Dose Hold (epNET and pNET; Double-Blind)

	epNET		pNET	
Preferred Term	**Cabozantinib Only (N=132) n (%)**	**Placebo (N=67) n (%)**	**Cabozantinib Only (N=63) n (%)**	**Placebo (N=31) n (%)**
Subjects with at least 1 AE leading to dose hold, n (%)	106 (80)	25 (37)	52 (83)	13 (42)
Fatigue	28 (21)	2 (3.0)	10 (16)	2 (6.5)
Diarrhoea	27 (20)	3 (4.5)	11 (17)	1 (3.2)
PPE syndrome	22 (17)	0	13 (21)	0
Hypertension	18 (14)	0	6 (9.5)	0
Stomatitis[a]	13 (9.8)	0	4 (6.3)	0
Nausea	11 (8.3)	1 (1.5)	7 (11)	2 (6.5)
Abdominal pain	9 (6.8)	3 (4.5)	1 (1.6)	1 (3.2)
AST increased	9 (6.8)	1 (1.5)	4 (6.3)	0
Vomiting	8 (6.1)	2 (3.0)	4 (6.3)	1 (3.2)
ALT increased	6 (4.5)	0	6 (9.5)	0
Blood bilirubin increased	6 (4.5)	5 (7.5)	5 (7.9)	0
Dyspnoea	3 (2.3)	4 (6.0)	1 (1.6)	0
Small intestinal obstruction	1 (0.8)	0	1 (1.6)	3 (9.7)

[a] Equivalent to solicited term "mucositis oral" which was coded to stomatitis

Events to Monitor

Events to monitor (ETMs) represent medical events that reflect the known pharmacology of cabozantinib or other drugs in the same pharmacologic class or are otherwise considered important to characterising the safety profile of cabozantinib.

ETMs, regardless of causality were summarised through 30 days of last dose for the epNET cohort (Table 62), pNET cohort (Table 63), and pooled epNET + pNET with and without crossover subjects (Table 64).

Each ETM is a grouped clinical term comprising a broad set of AEs that are related pathophysiologically. Certain events have been associated with cabozantinib and vascular endothelial growth factor receptor (VEGFR)-TKIs, including solicited AE of hypertension, and grouped ETM terms of venous and mixed thromboembolic events and QT prolongation.

For **epNET**, Grade 4 ETMs were only reported in the cabozantinib arm (4 subjects [3.0%] vs 0% in the placebo arm) 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%] vs 0% in the placebo arm): GI haemorrhage, hepatic failure, cardiac arrest, and sudden death (1 subject each).

Table 62. CABINET: Incidence of Events to Monitor (epNET; Double-Blind)

	Cabozantinib Only (N=132) n (%)		Placebo (N=67) n (%)	
ETM Grouped Term	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Number of subjects with at least 1 ETM	110 (83)	48 (36)	36 (54)	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)[a]	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)	27 (40)	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

Note: Grade 5 ETMs were reported for 4 subjects (3.0%) in the cabozantinib arm under the following PTs: GI hemorrhage, hepatic failure, cardiac arrest, and sudden death (n = 1 each). No Grade 5 ETMs were reported in the placebo arm.
[a] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.

For **pNET**, Grade 4 ETMs were only reported in the cabozantinib arm (2 subjects [3.2%] vs 0% in the placebo arm) and included the following grouped terms: 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.

Table 63. CABINET: Incidence of Events to Monitor (pNET; Double-Blind)

	Cabozantinib Only (N=63) n (%)		**Placebo (N=31) n (%)**	
ETM Grouped Term	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Number of subjects with at least 1 ETM	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)[a]	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
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

Note: No Grade 5 ETMs were reported in either treatment arm.
[a] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.

Table 64. CABINET: Incidence of Events to Monitor (Pooled epNET + pNET Double-Blind versus Pooled epNET + pNET Including Crossover)

	Cabozantinib Only N = 195 n (%)			All Cabozantinib N = 227 n (%)		
	Grade			Grade		
	Any	3 or 4	5	Any	3 or 4	5
Number of subjects with at least 1 ETM	164 (84)	79 (41)	4 (2.1)	194 (85)	90 (40)	5 (2.2)
Abscess	2 (1.0)	0	0	2 (0.9)	0	0
Arterial thromboembolic events	3 (1.5)	3 (1.5)	0	3 (1.3)	3 (1.3)	0
Fistula	2 (1.0)	0	0	3 (1.3)	1 (0.4)	0
GI perforation	1 (0.5)	1 (0.5)	0	3 (1.3)	2 (0.9)	1 (0.4)
Haemorrhage (Grade ≥ 3)[a]	4 (2.1)	3 (1.5)	1 (0.5)	4 (1.8)	3 (1.3)	1 (0.4)
Hepatotoxicity	10 (5.1)	7 (3.6)	1 (0.5)	11 (4.8)	8 (3.5)	1 (0.4)
Hypertension	127 (65)	51 (26)	0	148 (65)	56 (25)	0
Intra-abdominal and pelvic abscess	1 (0.5)	0	0	1 (0.4)	0	0
Osteonecrosis	6 (3.1)	1 (0.5)	0	7 (3.1)	2 (0.9)	0
PPE syndrome	72 (37)	10 (5.1)	0	90 (40)	11 (4.8)	0
PRES (RPLS)	1 (0.5)	1 (0.5)	0	1 (0.4)	1 (0.4)	0
Proteinuria	16 (8.2)	1 (0.5)	0	19 (8.4)	1 (0.4)	0
QT Prolongation	16 (8.2)	10 (5.1)	2 (1.0)	18 (7.9)	12 (5.3)	2 (0.9)
Renal failure	2 (1.0)	2 (1.0)	0	2 (0.9)	2 (0.9)	0
Venous and Mixed Thromboembolic events	17 (8.7)	11 (5.6)	0	18 (7.9)	11 (4.8)	0
Wound complication	6 (3.1)	1 (0.5)	0	6 (2.6)	1 (0.4)	0

[a] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.

Median time to the first occurrence of ETMs in pooled epNET + pNET including crossover is summarised in Table 65.

Table 65. CABINET: Time to First Occurrence of Events to Monitor (Pooled epNET + pNET Including Crossover)

ETM	Time to First Occurrence of ETM Median (25th, 75th Percentile), (days)
	All Cabozantinib (N=227)
Abscess	70.0 (55.0, 85.0)
Arterial thromboembolic events	134.0 (107.0, 578.0)
Fistula	135.0 (83.0, 213.0)
GI perforation	151.0 (146.0, 169.0)
Haemorrhage (Grade ≥ 3)[a]	98.5 (51.0, 191.5)
Hepatotoxicity	330.0 (119.0, 477.0)
Hypertension	15.0 (8.0, 29.0)
Intra-abdominal and pelvic abscess	85.0 (85.0, 85.0)
Osteonecrosis	55.0(15.0, 339.0)
PPE syndrome	57.0 (28.0, 132.0)
PRES (RPLS)	42.0 (42.0, 42.0)
Proteinuria	115.0 (84.0, 336.0)
QT prolongation	60.0 (35.0, 168.0)
Renal failure	224.5 (83.0, 366.0)
Venous and mixed thromboembolic events	76.5 (37.0, 165.0)
Wound complication	222.0 (120.0, 353.0)

[a] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3.

Hypertension

The solicited AE of hypertension (grouped ETM term) occurred in 64% and 67% of cabozantinib-treated subjects in the epNET and pNET cohorts by grouped term compared with 40% and 48% of subjects in the placebo arm.

In the **epNET** cohort, Grade ≥ 3 PTs within the grouped term of hypertension consisted of hypertension (34 subjects [26%] cabozantinib, 4 subjects [6.0%] placebo) and blood pressure increased (2 subjects [1.5%] cabozantinib, 0% placebo). Among the cabozantinib-treated subjects, 8 had Grade ≥ 3 serious events. Of those, 1 subject had an additional Grade 3 event of PRES, and 1 subject had an additional Grade 4 cerebrovascular accident (CVA). Abbreviated narratives for these 2 subjects are below. The remaining cases did not require expedited reporting (per protocol).

- One subject had a Grade 3 hypertension that required hospitalisation for blood pressure control. At the same time, the subject complained of headaches and was diagnosed with PRES (Grade 3, serious, probably related) on magnetic resonance imaging (MRI). Hypertension was treated with diltiazem and cabozantinib was discontinued.
- One subject had a Grade 3 hypertension and a Grade 4 CVA (possibly related) which required hospitalisation. The subject had a medical history of hypertension, hyperlipidaemia, tobacco use and chronic kidney disease and presented with acute onset left hemiplegia, left facial droop, dysarthria, and blood pressure of 190/110 mmHg. A head computed tomography (CT) showed no acute haemorrhage and moderate basal ganglia calcification and was diagnosed with a lacunar infarct. Cabozantinib was discontinued and alternative anticancer therapy was initiated approximately 3 months later.

In the **pNET** cohort, Grade ≥ 3 PTs within the grouped term of hypertension consisted of hypertension (14 subjects [22%] cabozantinib, 4 subjects [13%] placebo) and blood pressure increased (3 subjects [4.8%] cabozantinib, 0% placebo). Of these subjects, 2 had serious events: one subject had additional Grade ≥ 3 events, and the other subject had a serious Grade 1 event that did not require expedited reporting.

Venous and Mixed Thromboembolic Events (VTE)

Using the grouped ETM term, venous and mixed thrombotic AEs regardless of causality were reported in, epNET: 5 (3.8%) subjects; pNET: 12 (19%) subjects in the cabozantinib arm, compared with epNET: 1 (1.5%) subject; pNET: 1 (3.2%) subject in the placebo arm.

For the CABINET study, events reported using the nonspecific term "thromboembolic event" were coded to the PT embolism. Per CTCAE v5.0 severity grades for thromboembolic events are as follows: Grade 1 venous thrombosis (e.g., superficial thrombosis); Grade 2 venous thrombosis (e.g., uncomplicated deep vein thrombosis [DVT]); Grade 3 thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus); Grade 4 life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency). Thus, pulmonary embolism is reflected as a Grade ≥ 3 embolism in some subjects.

In the **epNET** cohort, 5 subjects (3.8%) had a venous or mixed embolic event in the cabozantinib arm. Grade ≥ 3 events were reported for 4 subjects (3.0%), which included pulmonary embolism events for 3 (2.3%) subjects and are described below:

- One subject had a Grade 3 pulmonary embolism (possibly related). During the first cycle of cabozantinib treatment, the subject developed right arm weakness/dysesthesia and subsequently presented to the emergency department with cough, dyspnoea, tachycardia when he was diagnosed with pulmonary embolism. The subject subsequently lost vision and was diagnosed with multiple cerebral vascular accidents.
- One subject had a Grade 3 pulmonary embolism (possibly related). The subject was hospitalised 19 days after the last dose of cabozantinib and pulmonary embolism was found incidentally on restaging imaging.
- One subject had a Grade 4 pulmonary embolism (definitely related). The subject had a history of hyperlipidaemia and prior tobacco use and presented to the hospital with chest pain and shortness of breath during Cycle 4 of cabozantinib treatment. Subsequently, the subject was diagnosed with pulmonary embolism in the right artery which required hospitalisation.

In the **pNET** cohort, 12 (19%) venous or mixed thrombotic events regardless of causality occurred in cabozantinib-treated subjects. This included 7 subjects with Grade ≥ 3 events, all of which were considered possibly or probably related, with the PTs embolism (n = 4), embolism venous (n = 1) and pulmonary embolism (n = 3) as follows:

- One subject had a Grade 3 embolism and Grade 3 embolism venous (same event coded to 2 different PTs, both possibly related) which were nonserious events during Cycle 3 of cabozantinib treatment.
- One subject had a Grade 4 pulmonary embolism (definitely related) requiring hospitalisation after presenting with dyspnoea, pleuritic chest pain, generalized fatigue, and nausea and high blood pressure during Cycle 2 of cabozantinib treatment. CT scan of chest showed extensive filling defects within the pulmonary arterial system.

- One subject had a Grade 3 embolism event (possibly related) after undergoing a protocol scheduled CT which found pulmonary emboli during Cycle 6 of cabozantinib treatment. This was an incidental finding, and the subject was asymptomatic.
- One subject had a Grade 3 pulmonary embolism event (probably related) after undergoing a protocol scheduled CT which showed pulmonary emboli during Cycle 3 of cabozantinib treatment. The subject had a past medical history of diabetes. The subject was asymptomatic and pulmonary emboli were an incidental finding.
- One subject had a Grade 3 embolism event (possibly related). One week after being diagnosed with coronavirus disease 2019 (COVID-19), the subject presented with severe pain in the right side of the chest and shortness of breath during Cycle 2 of cabozantinib treatment. The subject had a past medical history which included paroxysmal atrial fibrillation, hypertension, hypercholesterolemia, diabetes mellitus, follicular lymphoma. CT of the chest showed bilateral pulmonary emboli, and hepatic metastases had increased in volume.
- One subject had a Grade 3 embolism event (probably related). The subject presented with pain in the right calf which developed after a prolonged car ride during Cycle 7 of cabozantinib treatment. The subject denies worsening shortness of breath, but CT angiogram of the chest showed central low attenuation within the segmental arteries of the right upper lobe, most compatible with pulmonary emboli.
- One subject had a Grade 3 pulmonary embolism and Grade 3 DVT events (both possibly related). The subject presented to a local emergency department with shortness of breath and CT angiography showed acute saddle pulmonary emboli requiring hospitalization during Cycle 2 of cabozantinib treatment. Of note, the past medical history included prior COVID-19 infection, prior DVT, diabetes, hypertension, fatty liver, and neuropathy.

Since patients with NET are known to exhibit a higher thromboembolic risk, in particular those with pancreatic origin (Wójcik-Giertuga et al, 2023), the underlying disease may have been a contributing factor for the reported cases of pulmonary embolism.

QT Prolongation

There was no protocol-specified requirement to verify post-baseline QT prolongation with repeat electrocardiogram (ECG) assessments or to confirm ECG results by independent central review. The ETM grouped term of QT prolongation occurred in 9.1% and 6.3% cabozantinib-treated subjects in the epNET and pNET cohorts compared with 7.5% and 3.2% in the placebo arm.

In the **epNET** cohort, the grouped ETM term QT prolongation included Grade 3 syncope for 5 subjects in the cabozantinib arm; electrocardiogram QT prolonged (Grades 1, 2, and 3, all nonserious) for 3 subjects in the cabozantinib arm, all with concurrent SSA; and a nonserious Grade 1 ventricular arrythmia in 1 subject in the cabozantinib arm. In addition, 2 subjects had cardiac arrest, and 1 subject had sudden death, as follows:

- One subject had a Grade 5 sudden death event (possibly related). The subject completed Cycle 1 of cabozantinib treatment in Feb 2020 and missed a follow-up appointment the following day. The subject was found deceased a few days later.
- One subject had Grade 4 cardiac arrest and Grade 4 Torsades des pointes events (both probably related) during Cycle 5 of cabozantinib treatment. The subject had a past medical history of hypercholesterolemia and hypertension and initially presented to the emergency department after awakening with chest pain and was subsequently diagnosed with ST-segment

elevation myocardial infarction due to proximal left anterior descending artery occlusion. Torsades des pointes occurred without QT prolongation.

- One subject had a Grade 5 cardiac arrest event (possibly related) during Cycle 6 of cabozantinib treatment. The subject was hospitalised for abdominal pain (Grade 3, serious) and generalised muscle weakness (Grade 3, serious). During hospitalisation, the subject experienced 2 episodes of bradycardia and syncope. Subsequently the subject went into atrial fibrillation and experienced a cardiac arrest. The subject was taken off life support systems and died a few hours later.

In the pNET cohort, there were 3 nonserious events of electrocardiogram QT prolonged (2 were Grade 3 and one was Grade 1). In addition, there was a single Grade 4 cardiac arrest event as follows:

- One subject had a Grade 4 cardiac arrest event (probably related) during Cycle 4 of cabozantinib treatment. The subject experienced chest pain and was admitted to the hospital, then went into cardiac arrest (Grade 4, serious), which required cardiopulmonary resuscitation and defibrillation. The subject was diagnosed with myocardial infarction (Grade 4, serious). Coronary arteriogram showed a mid-left anterior descending artery flow limiting lesion and a long segment of high-grade narrowing of 70% or more in the right coronary artery.

Other Clinically Significant Adverse Events

Hypothyroidism

In the epNET cohort, the solicited AE of hypothyroidism occurred in 41 subjects (31%) in the cabozantinib arm and 2 subjects (3.0%) in the placebo arm. No event in either treatment arm was Grade ≥ 3. For 1 subject (0.8% vs 0% placebo) in the cabozantinib arm, hypothyroidism was serious. In the pNET cohort, the solicited AE of hypothyroidism occurred in 10 subjects (16%) in the cabozantinib arm and 1 subject (3.2%) in the placebo arm. No event in either treatment arm was Grade ≥ 3 or serious.

Pregnancy

There were no events of pregnancy on study in either cohort.

Second Primary Malignancies

There were no new second primary malignancies reported in either cohort.

Laboratory findings

Clinical laboratory assessments were evaluated at intervals throughout the study, but these data were not collected in the clinical database; clinically significant findings and solicited events were to be reported as AEs. Owing to the difference in collection of data, there was a higher incidence of laboratory-associated AEs in the CABINET study compared to other studies based on pooled analysis.

Safety observations in placebo crossover subjects

As noted previously, 20 subjects in the epNET cohort and 12 subjects in the pNET cohort crossed over from the placebo arm to open-label cabozantinib following confirmed disease progression. An overview of study treatment exposure is presented in Table 66. Among crossover subjects, the median duration

of exposure to cabozantinib was 4.62 vs 4.81 months for subjects in the epNET and pNET cohorts, respectively. The median average daily dose of cabozantinib was 55.23 mg vs 44.22 mg, respectively.

Table 66. CABINET: Study Treatment Exposure (epNET and pNET; Placebo Crossover to Cabozantinib)

	epNET	pNET
	Cabozantinib (N = 20)	**Cabozantinib (N = 12)**
Duration of exposure (months)[a]		
Mean (SD)	5.71 (4.540)	7.39 (6.611)
Median (range)	4.62 (0.9–14.3)	4.81 (0.9–20.7)
Average daily dose (mg/day)[b]		
Mean (SD)	44.94 (16.471)	44.94 (13.182)
Median (range)	55.23 (22.1–60.0)	44.22 (22.9–60.0)
Dose intensity (%)[c]		
Mean (SD)	74.91 (27.452)	74.89 (21.970)
Median (range)	92.06 (36.8–100.0)	73.71 (38.2–100.0)

Note The dosing intervals with dose level of 'Other' and with 'If (Other), specify' field not quantifiable will be considered as dose level of unknown, and the corresponding dosing interval will not be taken into the calculation of the total dose received, average daily dose and dose intensity, but will be included in the derivation of the first dose and the last dose of study treatment to prevent underreporting for exposure and AE summaries.
[a] Duration of exposure = (Date of last dose or cutoff date - Date of first dose + 1)/30.4375.
[b] Average daily dose (mg/day)= total dose received (mg) / duration of exposure (days).
[c] Percent dose intensity of cabozantinib/placebo = 100*(average daily dose in mg/day) / (60 mg/day).

An overview of adverse events among the crossover subjects is provided in Table 67.

A comprehensive comparison algorithm was implemented to compare datasets derived based on the original CSR algorithm versus an updated algorithm for calculating the date of the last and first dose in the double-blind and/or open label (crossover) period. The comparison identified 3 placebo subjects whose reported AEs were partially misclassified under the double-blind period but would have been attributed to cabozantinib during the crossover period. A review of the reported AEs from these 3 subjects did not identify any new safety concerns related to cabozantinib.

Table 67. CABINET: Overview of Adverse Events (epNET and pNET; Placebo Crossover to Cabozantinib)

	Placebo Crossover to Cabozantinib	
Subjects experiencing any of the following, n (%)	**From epNET Cohort (N = 20) n (%)**	**From pNET Cohort (N = 12) n (%)**
AE	20 (100)	12 (100)
Related AE	20 (100)	12 (100)
SAE	11 (55)	4 (33)
Related SAE	2 (10)	2 (17)
Worst Grade 3 or 4 AE	13 (65)	8 (67)
Worst Grade 3 or 4 related AE	6 (30)	8 (67)
Worst Grade 4 AE	0	1 (8.3)
Worst Grade 4 related AE	0	1 (8.3)

Subjects experiencing any of the following, n (%)	Placebo Crossover to Cabozantinib	
	From epNET Cohort (N = 20) n (%)	From pNET Cohort (N = 12) n (%)
Worst Grade 5 AE	1 (5.0)	0
Worst Grade 5 related AE	1 (5.0)	0
AE leading to dose reduction	9 (45)	6 (50)
AE leading to dose hold	12 (60)	8 (67)
AE leading to dose modification (reduction or hold)	13 (65)	9 (75)
AE leading to treatment discontinuation[a]	4 (20)	3 (25)
Related AE leading to treatment discontinuation	2 (10)	2 (17)
ETM any Grade AE	19 (95)	11 (92)
ETM worst Grade 3 or 4 AE	7 (35)	4 (33)
ETM worst Grade 4 AE	0	1 (8.3)
ETM worst Grade 5 AE	1 (5.0)	0

[a] The data presented for AEs leading to treatment discontinuation were recorded on the AE CRF.

Safety observations in other studies

Safety results from the CABINET Study and the pooled studies (cabozantinib 60-mg treatment arms of Studies XL184-308, XL184-309, CABOSUN [A031203] and XL184-311) are provided to present the observations in the NET population (CABINET) in context with respect to the broader cabozantinib safety experience.

Adverse events, ETMs and serious adverse events

An overview of AEs in the cabozantinib arm of the CABINET and pooled studies is provided in Table 68. Although the studies each included a cabozantinib 60-mg treatment arm, cross-CABINET and pooled-study comparison should be done with caution due to differences in the study population, study design, and time of follow-up. Furthermore, AE management guidance evolved over time with increasing familiarity with the safety profile of cabozantinib and TKIs in general.

Table 68. CABINET, Pooled Studies (XL184-308, A031203 [CABOSUN], XL184-309, and XL184-311): Overview of Adverse Events (Safety Population)

	CABINET (N = 195)	Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)
AE	195 (100.0%)	1077 (99.0%)
Related AE	192 (98.5%)	1037 (95.3%)
Serious AE	87 (44.6%)	529 (48.6%)
Serious related AE	61 (31.3%)	202 (18.6%)
Worst grade 3 or 4 AE	135 (69.2%)	736 (67.6%)
Worst grade 3 or 4 related AE	119 (61.0%)	665 (61.1%)
Worst grade 4 AE	16 (8.2%)	98 (9.0%)
Worst grade 4 related AE	14 (7.2%)	48 (4.4%)
Worst grade 5 AE	9 (4.6%)	139 (12.8%)

	CABINET (N = 195)	Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)
Worst grade 5 related AE	4 (2.1%)	11 (1.0%)

A summary of frequent AEs (≥ 10%) of any grade in the cabozantinib arm of the CABINET study compared with the pooled studies is provided in Table 69.

To assess the impact of disease-specific confounding effects on the high incidence of AEs, a comparison of the placebo arm of CABINET to the placebo arm of the two studies that used placebo as a comparator (XL184-309 and XL184-311) was performed. There was a higher incidence of AEs in the placebo arm of the CABINET study compared to the pooled placebo arm (results not shown).

Table 69. CABINET, Pooled Studies (XL184-308, A031203 [CABOSUN], XL184-309, and XL184-311): Summary of Frequent Adverse Events (≥ 10% Incidence [any grade] or ≥ 2% [Grade 3-4] in the CABINET Study) by Preferred Term (Safety Population)

	CABINET (N = 195)			Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)		
System Organ Class Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 N (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**
Number of Subjects With at Least One Event	195 (100.0)	135 (69.2)	16 (8.2)	1077 (99.0)	736 (67.6)	98 (9.0)
Fatigue	145 (74.4)	28 (14.4)	0	533 (49.0)	112 (10.3)	0
Aspartate aminotransferase increased	141 (72.3)	6 (3.1)	0	264 (24.3)	68 (6.3)	6 (0.6)
Alanine aminotransferase increased	129 (66.2)	2 (1.0)	1 (0.5)	230 (21.1)	39 (3.6)	2 (0.2)
Diarrhoea	126 (64.6)	18 (9.2)	0	690 (63.4)	114 (10.5)	1 (0.1)
Hypertension	124 (63.6)	48 (24.6)	0	380 (34.9)	174 (16.0)	2 (0.2)
Platelet count decreased	89 (45.6)	2 (1.0)	0	103 (9.5)	24 (2.2)	5 (0.5)
Stomatitis	81 (41.5)	9 (4.6)	0	202 (18.6)	27 (2.5)	0
Nausea	76 (39.0)	8 (4.1)	0	415 (38.1)	33 (3.0)	0
Palmar-plantar erythrodysaesthesia syndrome	72 (36.9)	10 (5.1)	0	497 (45.7)	136 (12.5)	0
Dysgeusia	61 (31.3)	0	0	140 (12.9)	2 (0.2)	0
White blood cell count decreased	61 (31.3)	5 (2.6)	0	37 (3.4)	8 (0.7)	0
Decreased appetite	59 (30.3)	4 (2.1)	0	502 (46.1)	48 (4.4)	0
Neutrophil count decreased	59 (30.3)	5 (2.6)	0	52 (4.8)	14 (1.3)	2 (0.2)
Hyperglycaemia	57 (29.2)	3 (1.5)	0	51 (4.7)	3 (0.3)	1 (0.1)
Anaemia	55 (28.2)	4 (2.1)	0	163 (15.0)	48 (4.4)	2 (0.2)
Blood alkaline phosphatase increased	51 (26.2)	8 (4.1)	0	78 (7.2)	20 (1.8)	0
Hypothyroidism	51 (26.2)	0	0	140 (12.9)	2 (0.2)	0
Lymphocyte count decreased	50 (25.6)	17 (8.7)	0	28 (2.6)	6 (0.6)	1 (0.1)
Abdominal pain	48 (24.6)	13 (6.7)	0	182 (16.7)	26 (2.4)	1 (0.1)
Weight decreased	48 (24.6)	8 (4.1)	0	272 (25.0)	23 (2.1)	0
Hypophosphataemia	39 (20.0)	1 (0.5)	0	86 (7.9)	30 (2.8)	1 (0.1)
Vomiting	39 (20.0)	7 (3.6)	0	300 (27.6)	14 (1.3)	0

System Organ Class Preferred Term	CABINET (N = 195)			Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)		
	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 N (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)
Blood creatinine increased	36 (18.5)	1 (0.5)	0	58 (5.3)	5 (0.5)	0
Dizziness	36 (18.5)	0	0	121 (11.1)	4 (0.4)	0
Hypocalcaemia	35 (17.9)	0	0	97 (8.9)	27 (2.5)	7 (0.6)
Rash maculo-papular	35 (17.9)	0	0	33 (3.0)	2 (0.2)	0
Blood bilirubin increased	34 (17.4)	6 (3.1)	2 (1.0)	85 (7.8)	25 (2.3)	6 (0.6)
Hypoalbuminaemia	32 (16.4)	0	0	103 (9.5)	6 (0.6)	0
Hypokalaemia	31 (15.9)	4 (2.1)	1 (0.5)	114 (10.5)	35 (3.2)	3 (0.3)
Hypomagnesaemia	31 (15.9)	1 (0.5)	1 (0.5)	135 (12.4)	30 (2.8)	17 (1.6)
Hyponatraemia	31 (15.9)	4 (2.1)	1 (0.5)	75 (6.9)	48 (4.4)	4 (0.4)
Dyspnoea	29 (14.9)	6 (3.1)	0	174 (16.0)	31 (2.8)	0
Headache	26 (13.3)	1 (0.5)	0	133 (12.2)	5 (0.5)	0
Muscle spasms	26 (13.3)	0	0	105 (9.7)	1 (0.1)	0
Oedema peripheral	23 (11.8)	1 (0.5)	0	128 (11.8)	5 (0.5)	0
Blood thyroid stimulating hormone increased	22 (11.3)	0	0	42 (3.9)	1 (0.1)	0
Cough	22 (11.3)	0	0	170 (15.6)	2 (0.2)	0
Dry mouth	22 (11.3)	0	0	89 (8.2)	1 (0.1)	0
Dysphonia	22 (11.3)	1 (0.5)	0	203 (18.7)	7 (0.6)	0
Back pain	21 (10.8)	5 (2.6)	0	143 (13.1)	19 (1.7)	0
Gastrooesophageal reflux disease	21 (10.8)	0	0	54 (5.0)	1 (0.1)	0
Constipation	20 (10.3)	0	0	224 (20.6)	4 (0.4)	0
Muscular weakness	14 (7.2)	5 (2.6)	0	31 (2.8)	5 (0.5)	0
Embolism	8 (4.1)	4 (2.1)	0	11 (1.0)	7 (0.6)	2 (0.2)
Pain	8 (4.1)	4 (2.1)	0	62 (5.7)	16 (1.5)	1 (0.1)
Blood pressure increased	7 (3.6)	5 (2.6)	0	11 (1.0)	2 (0.2)	0
Pulmonary embolism	6 (3.1)	6 (3.1)	2 (1.0)	29 (2.7)	20 (1.8)	1 (0.1)
Sepsis	6 (3.1)	6 (3.1)	2 (1.0)	10 (0.9)	6 (0.6)	4 (0.4)
Hypoxia	5 (2.6)	4 (2.1)	0	1 (0.1)	0	0
Syncope	5 (2.6)	5 (2.6)	0	25 (2.3)	20 (1.8)	0

Solicited AEs for Cabinet are **bolded**.
Solicited AE for the Cabinet only: Hyperglycaemia, Hypothyroidism, Stomatitis, Rash maculo-papular
Solicited AE for the Cabosun only: Blood bilirubin increased, Electrocardiogram QT prolonged, Pancreatitis
Solicited AE for both studies: Alanine aminotransferase increased, Aspartate aminotransferase increased, Diarrhoea, Fatigue, Hypertension, Neutrophil count decreased, Palmar-plantar erythrodysaesthesia syndrome, Platelet count decreased

A comparison of ETM incidences in the CABINET study and the pooled studies is presented in Table 70.

Table 70. CABINET, Pooled Studies (XL184-308, A031203 [CABOSUN], XL184-309, and XL184-311): Incidence of Adverse Events to Monitor Occurring in ≥ 0.5% of Subjects in CABINET by ETM and Preferred Term (Safety Population)

	CABINET (N = 195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)			
ETM Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of Subjects With at Least One Event	184 (94.4)	87 (44.6)	5 (2.6)	3 (1.5)	946 (86.9)	483 (44.4)	25 (2.3)	17 (1.6)
Hypertension	127 (65.1)	51 (26.2)	0	0	394 (36.2)	180 (16.5)	2 (0.2)	0
Hypertension	124 (63.6)	48 (24.6)	0	0	380 (34.9)	174 (16.0)	2 (0.2)	0
Blood pressure increased	7 (3.6)	5 (2.6)	0	0	11 (1.0)	2 (0.2)	0	0
Blood pressure systolic increased	2 (1.0)	0	0	0	0	0	0	0
Diarrhea	126 (64.6)	18 (9.2)	0	0	690 (63.4)	114 (10.5)	1 (0.1)	0
Diarrhoea	126 (64.6)	18 (9.2)	0	0	690 (63.4)	114 (10.5)	1 (0.1)	0
PPE syndrome	72 (36.9)	10 (5.1)	0	0	497 (45.7)	136 (12.5)	0	0
Palmar-plantar erythrodysaesthesia syndrome	72 (36.9)	10 (5.1)	0	0	497 (45.7)	136 (12.5)	0	0
Venous and Mixed Thromboembolic events	17 (8.7)	11 (5.6)	3 (1.5)	0	86 (7.9)	49 (4.5)	6 (0.6)	4 (0.4)
Embolism	8 (4.1)	4 (2.1)	0	0	11 (1.0)	7 (0.6)	2 (0.2)	0
Pulmonary embolism	6 (3.1)	6 (3.1)	2 (1.0)	0	29 (2.7)	20 (1.8)	1 (0.1)	2 (0.2)
Deep vein thrombosis	3 (1.5)	0	0	0	14 (1.3)	5 (0.5)	0	0
Cerebrovascular accident	2 (1.0)	1 (0.5)	1 (0.5)	0	5 (0.5)	4 (0.4)	1 (0.1)	1 (0.1)
Embolism venous	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Proteinuria	16 (8.2)	1 (0.5)	0	0	106 (9.7)	25 (2.3)	1 (0.1)	0
Proteinuria	15 (7.7)	1 (0.5)	0	0	102 (9.4)	22 (2.0)	0	0
Protein urine present	1 (0.5)	0	0	0	3 (0.3)	0	0	0
QT Prolongation	16 (8.2)	10 (5.1)	2 (1.0)	2 (1.0)	45 (4.1)	26 (2.4)	1 (0.1)	1 (0.1)
Electrocardiogram QT prolonged	6 (3.1)	3 (1.5)	0	0	9 (0.8)	1 (0.1)	0	0

	CABINET (N = 195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)			
ETM Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Syncope	5 (2.6)	5 (2.6)	0	0	25 (2.3)	20 (1.8)	0	0
Cardiac arrest	3 (1.5)	2 (1.0)	2 (1.0)	1 (0.5)	0	0	0	0
Sudden death	1 (0.5)	0	0	1 (0.5)	0	0	0	0
Torsade de pointes	1 (0.5)	1 (0.5)	1 (0.5)	0	0	0	0	0
Ventricular arrhythmia	1 (0.5)	0	0	0	2 (0.2)	0	0	0
Osteonecrosis	6 (3.1)	1 (0.5)	0	0	41 (3.8)	12 (1.1)	0	0
Tooth infection	6 (3.1)	1 (0.5)	0	0	19 (1.7)	3 (0.3)	0	0
Tooth abscess	1 (0.5)	0	0	0	10 (0.9)	3 (0.3)	0	0
Wound complication	6 (3.1)	1 (0.5)	0	0	33 (3.0)	8 (0.7)	1 (0.1)	0
Wound complication	3 (1.5)	0	0	0	1 (0.1)	0	0	0
Impaired healing	1 (0.5)	0	0	0	7 (0.6)	1 (0.1)	0	0
Skin wound	1 (0.5)	0	0	0	1 (0.1)	0	0	0
Wound infection	1 (0.5)	1 (0.5)	0	0	5 (0.5)	3 (0.3)	0	0
Haemorrhage (≥ Grade 3)	4 (2.1)	3 (1.5)	0	1 (0.5)	56 (5.1)	48 (4.4)	5 (0.5)	8 (0.7)
Gastrointestinal haemorrhage	1 (0.5)	0	0	1 (0.5)	7 (0.6)	7 (0.6)	0	0
Haemorrhoidal haemorrhage	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Oesophageal haemorrhage	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Rectal haemorrhage	1 (0.5)	1 (0.5)	0	0	2 (0.2)	2 (0.2)	0	0
Arterial thromboembolic events	3 (1.5)	3 (1.5)	2 (1.0)	0	15 (1.4)	10 (0.9)	2 (0.2)	2 (0.2)
Acute myocardial infarction	1 (0.5)	1 (0.5)	1 (0.5)	0	2 (0.2)	2 (0.2)	1 (0.1)	0
Coronary artery occlusion	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.1)	1 (0.1)	0	0
Embolism arterial	1 (0.5)	1 (0.5)	0	0	1 (0.1)	1 (0.1)	0	0

	CABINET (N = 195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)			
ETM Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Myocardial infarction	1 (0.5)	1 (0.5)	1 (0.5)	0	0	0	0	0
Abscess	2 (1.0)	0	0	0	32 (2.9)	16 (1.5)	2 (0.2)	0
Anal abscess	1 (0.5)	0	0	0	6 (0.6)	5 (0.5)	1 (0.1)	0
Tooth abscess	1 (0.5)	0	0	0	10 (0.9)	3 (0.3)	0	0
Fistula	2 (1.0)	0	0	0	16 (1.5)	5 (0.5)	0	1 (0.1)
Anal fistula	1 (0.5)	0	0	0	11 (1.0)	4 (0.4)	0	0
Biliary fistula	1 (0.5)	0	0	0	0	0	0	0
Gastrointestinal perforation	1 (0.5)	1 (0.5)	0	0	14 (1.3)	11 (1.0)	5 (0.5)	1 (0.1)
Spontaneous bacterial peritonitis	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Intra-abdominal and pelvic abscess	1 (0.5)	0	0	0	12 (1.1)	9 (0.8)	2 (0.2)	0
Anal abscess	1 (0.5)	0	0	0	6 (0.6)	5 (0.5)	1 (0.1)	0
PRES (RPLS)	1 (0.5)	1 (0.5)	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0
Posterior reversible encephalopathy syndrome	1 (0.5)	1 (0.5)	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0

Only selected ETMs are considered: ETMs: Gastrointestinal Perforation, Fistula, Abscess Intra-Abdominal and Pelvic Abscess, Haemorrhage, Arterial Thrombotic Events, Venous and Mixed/Unspecified Thrombotic Events, Wound Complications, Hypertension, Osteonecrosis, PPES, Proteinuria, RPLS, Diarrhoea, QT Prolongation
Solicited AEs for Cabinet are **bolded**.

A summary of frequent SAEs (≥ 2% incidence) in the cabozantinib arm in the CABINET study compared with the pooled studies is provided in in Table 71 (regardless of causality) and

Table 72 (treatment-related).

Table 71. CABINET, Pooled Studies (XL184-308, A031203 [CABOSUN], XL184-309, and XL184-311): Summary of Serious Adverse Events (≥ 2% Incidence) by SOC and Preferred Term (Safety Population)

	CABINET (N = 195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)			
System Organ Class Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of Subjects With at Least One Event	87 (44.6)	67 (34.4)	11 (5.6)	9 (4.6)	529 (48.6)	340 (31.3)	55 (5.1)	139 (12.8)
Gastrointestinal disorders	27 (13.8)	21 (10.8)	0	1 (0.5)	138 (12.7)	103 (9.5)	12 (1.1)	4 (0.4)
Abdominal pain	9 (4.6)	9 (4.6)	0	0	19 (1.7)	16 (1.5)	1 (0.1)	0
Vomiting	8 (4.1)	7 (3.6)	0	0	15 (1.4)	6 (0.6)	0	0
Nausea	6 (3.1)	5 (2.6)	0	0	12 (1.1)	6 (0.6)	0	0
Diarrhoea	5 (2.6)	3 (1.5)	0	0	21 (1.9)	17 (1.6)	1 (0.1)	0
General disorders and administration site conditions	17 (8.7)	8 (4.1)	0	6 (3.1)	96 (8.8)	53 (4.9)	8 (0.7)	19 (1.7)
Fatigue	5 (2.6)	4 (2.1)	0	0	15 (1.4)	13 (1.2)	0	0
Vascular disorders	16 (8.2)	12 (6.2)	0	0	37 (3.4)	28 (2.6)	5 (0.5)	1 (0.1)
Hypertension	10 (5.1)	7 (3.6)	0	0	13 (1.2)	12 (1.1)	2 (0.2)	0
Metabolism and nutrition disorders	14 (7.2)	10 (5.1)	2 (1.0)	0	60 (5.5)	51 (4.7)	15 (1.4)	0
Infections and infestations	13 (6.7)	12 (6.2)	3 (1.5)	0	99 (9.1)	77 (7.1)	12 (1.1)	12 (1.1)
Sepsis	6 (3.1)	6 (3.1)	2 (1.0)	0	10 (0.9)	6 (0.6)	4 (0.4)	3 (0.3)
Investigations	13 (6.7)	7 (3.6)	1 (0.5)	0	20 (1.8)	17 (1.6)	6 (0.6)	0
Blood bilirubin increased	5 (2.6)	4 (2.1)	1 (0.5)	0	4 (0.4)	3 (0.3)	2 (0.2)	0
Nervous system disorders	11 (5.6)	8 (4.1)	1 (0.5)	0	65 (6.0)	48 (4.4)	6 (0.6)	3 (0.3)
Musculoskeletal and connective tissue disorders	10 (5.1)	8 (4.1)	0	0	42 (3.9)	36 (3.3)	0	0
Respiratory, thoracic and mediastinal disorders	10 (5.1)	7 (3.6)	2 (1.0)	0	79 (7.3)	50 (4.6)	4 (0.4)	7 (0.6)
Pulmonary embolism	5 (2.6)	5 (2.6)	2 (1.0)	0	15 (1.4)	12 (1.1)	1 (0.1)	2 (0.2)
Cardiac disorders	6 (3.1)	5 (2.6)	2 (1.0)	1 (0.5)	18 (1.7)	10 (0.9)	2 (0.2)	4 (0.4)

	CABINET (N = 195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N = 1088)			
System Organ Class Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Hepatobiliary disorders	5 (2.6)	4 (2.1)	2 (1.0)	1 (0.5)	38 (3.5)	23 (2.1)	6 (0.6)	14 (1.3)
Blood and lymphatic system disorders	4 (2.1)	2 (1.0)	0	0	25 (2.3)	21 (1.9)	4 (0.4)	0
Anaemia	4 (2.1)	2 (1.0)	0	0	18 (1.7)	14 (1.3)	2 (0.2)	0

Note: Solicited AEs for Cabinet are **bolded**.

Table 72. CABINET, Pooled Studies (XL184-308, A031203 [CABOSUN], XL184-309, and XL184-311): Summary of Serious Adverse Events Related to Treatment (≥ 2% Incidence) by SOC and Preferred Term (Safety population)

	CABINET (N=195)				Cabozantinib pool (XL184-308 + CABOSUN + XL184-309 + XL184-311) (N=1088)			
System Organ Class Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of Subjects With at Least One Event	61 (31.3)	44 (22.6)	9 (4.6)	4 (2.1)	202 (18.6)	167 (15.3)	26 (2.4)	11 (1.0)
Gastrointestinal disorders	16 (8.2)	11 (5.6)	0	1 (0.5)	64 (5.9)	52 (4.8)	6 (0.6)	2 (0.2)
Vomiting	5 (2.6)	5 (2.6)	0	0	7 (0.6)	4 (0.4)	0	0
Diarrhoea	4 (2.1)	3 (1.5)	0	0	20 (1.8)	16 (1.5)	1 (0.1)	0
Nausea	4 (2.1)	4 (2.1)	0	0	7 (0.6)	4 (0.4)	0	0
Vascular disorders	14 (7.2)	11 (5.6)	0	0	23 (2.1)	20 (1.8)	4 (0.4)	0
Hypertension	9 (4.6)	7 (3.6)	0	0	13 (1.2)	12 (1.1)	2 (0.2)	0
General disorders and administration site conditions	9 (4.6)	5 (2.6)	0	2 (1.0)	24 (2.2)	19 (1.7)	0	1 (0.1)
Fatigue	4 (2.1)	3 (1.5)	0	0	10 (0.9)	10 (0.9)	0	0
Respiratory, thoracic and mediastinal disorders	9 (4.6)	6 (3.1)	2 (1.0)	0	21 (1.9)	16 (1.5)	0	2 (0.2)
Pulmonary embolism	5 (2.6)	5 (2.6)	2 (1.0)	0	11 (1.0)	9 (0.8)	0	1 (0.1)
Investigations	8 (4.1)	3 (1.5)	0	0	9 (0.8)	8 (0.7)	2 (0.2)	0
Metabolism and nutrition disorders	7 (3.6)	5 (2.6)	2 (1.0)	0	38 (3.5)	36 (3.3)	10 (0.9)	0
Cardiac disorders	5 (2.6)	4 (2.1)	2 (1.0)	1 (0.5)	4 (0.4)	3 (0.3)	0	0
Infections and infestations	4 (2.1)	4 (2.1)	2 (1.0)	0	22 (2.0)	18 (1.7)	2 (0.2)	1 (0.1)

Note: Solicited AEs for Cabinet are bolded.

Treatment modification and discontinuation

An overview of AEs leading to dose modification and discontinuation is presented in Table 73 and Table 74, respectively. Study A031203 (CABOSUN) is not included in the pooled studies as AEs leading to dose modification or treatment discontinuation were not recorded in the study CRF.

Table 73. CABINET, Pooled Studies (XL184-308, XL184-309, and XL184-311): AEs Leading to Dose Modification in ≥ 1% of Subjects by SOC and Preferred Term (Safety Population)

System Organ Class Preferred Term	CABINET (N = 195)				Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N = 1010)			
	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)
Number of Subjects With at Least One Event	169 (86.7)	101 (51.8)	6 (3.1)	1 (0.5)	867 (85.8)	628 (62.2)	59 (5.8)	2 (0.2)
Gastrointestinal disorders	92 (47.2)	37 (19.0)	0	1 (0.5)	402 (39.8)	160 (15.8)	5 (0.5)	0
Diarrhoea	43 (22.1)	15 (7.7)	0	0	235 (23.3)	85 (8.4)	1 (0.1)	0
Stomatitis	24 (12.3)	9 (4.6)	0	0	49 (4.9)	16 (1.6)	0	0
Nausea	21 (10.8)	6 (3.1)	0	0	86 (8.5)	14 (1.4)	0	0
Vomiting	14 (7.2)	4 (2.1)	0	0	61 (6.0)	8 (0.8)	0	0
Abdominal pain	12 (6.2)	8 (4.1)	0	0	37 (3.7)	12 (1.2)	0	0
Oral pain	3 (1.5)	0	0	0	3 (0.3)	0	0	0
Rectal haemorrhage	3 (1.5)	1 (0.5)	0	0	7 (0.7)	1 (0.1)	0	0
Abdominal pain upper	2 (1.0)	0	0	0	11 (1.1)	2 (0.2)	0	0
Constipation	2 (1.0)	0	0	0	3 (0.3)	1 (0.1)	0	0
Small intestinal obstruction	2 (1.0)	2 (1.0)	0	0	1 (0.1)	1 (0.1)	0	0
Dyspepsia	1 (0.5)	0	0	0	15 (1.5)	1 (0.1)	0	0
General disorders and administration site conditions	56 (28.7)	24 (12.3)	0	0	303 (30.0)	133 (13.2)	3 (0.3)	1 (0.1)
Fatigue	49 (25.1)	22 (11.3)	0	0	152 (15.0)	72 (7.1)	0	0
Pain	4 (2.1)	3 (1.5)	0	0	9 (0.9)	3 (0.3)	0	0
Oedema peripheral	3 (1.5)	0	0	0	7 (0.7)	0	0	0
Pyrexia	2 (1.0)	0	0	0	19 (1.9)	2 (0.2)	0	0
Asthenia	0	0	0	0	74 (7.3)	32 (3.2)	0	0
General physical health deterioration	0	0	0	0	15 (1.5)	10 (1.0)	3 (0.3)	1 (0.1)
Mucosal inflammation	0	0	0	0	44 (4.4)	13 (1.3)	0	0
Investigations	49 (25.1)	21 (10.8)	2 (1.0)	0	204 (20.2)	129 (12.8)	14 (1.4)	0
Aspartate aminotransferase increased	16 (8.2)	4 (2.1)	0	0	69 (6.8)	48 (4.8)	2 (0.2)	0
Alanine aminotransferase increased	15 (7.7)	0	0	0	54 (5.3)	27 (2.7)	0	0
Blood bilirubin increased	11 (5.6)	5 (2.6)	2 (1.0)	0	18 (1.8)	9 (0.9)	1 (0.1)	0
Neutrophil count decreased	7 (3.6)	4 (2.1)	0	0	15 (1.5)	10 (1.0)	1 (0.1)	0

System Organ Class Preferred Term	CABINET (N = 195)				Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N = 1010)			
	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood alkaline phosphatase increased	6 (3.1)	2 (1.0)	0	0	3 (0.3)	2 (0.2)	0	0
Weight decreased	5 (2.6)	3 (1.5)	0	0	35 (3.5)	7 (0.7)	0	0
Platelet count decreased	4 (2.1)	1 (0.5)	0	0	29 (2.9)	15 (1.5)	1 (0.1)	0
Blood pressure increased	3 (1.5)	2 (1.0)	0	0	1 (0.1)	0	0	0
Electrocardiogram QT prolonged	3 (1.5)	2 (1.0)	0	0	2 (0.2)	1 (0.1)	0	0
Blood creatinine increased	2 (1.0)	0	0	0	7 (0.7)	1 (0.1)	0	0
Lymphocyte count decreased	2 (1.0)	0	0	0	3 (0.3)	1 (0.1)	0	0
Lipase increased	1 (0.5)	1 (0.5)	0	0	12 (1.2)	9 (0.9)	3 (0.3)	0
Amylase increased	0	0	0	0	12 (1.2)	10 (1.0)	2 (0.2)	0
Gamma-glutamyltransferase increased	0	0	0	0	12 (1.2)	7 (0.7)	1 (0.1)	0
Skin and subcutaneous tissue disorders	48 (24.6)	10 (5.1)	0	0	299 (29.6)	135 (13.4)	0	0
Palmar-plantar erythrodysaesthesia syndrome	44 (22.6)	10 (5.1)	0	0	246 (24.4)	120 (11.9)	0	0
Blister	3 (1.5)	0	0	0	6 (0.6)	3 (0.3)	0	0
Skin exfoliation	2 (1.0)	0	0	0	4 (0.4)	0	0	0
Skin ulcer	2 (1.0)	0	0	0	15 (1.5)	8 (0.8)	0	0
Rash	1 (0.5)	0	0	0	16 (1.6)	5 (0.5)	0	0
Vascular disorders	41 (21.0)	23 (11.8)	0	0	111 (11.0)	81 (8.0)	2 (0.2)	0
Hypertension	32 (16.4)	19 (9.7)	0	0	98 (9.7)	76 (7.5)	1 (0.1)	0
Hypotension	5 (2.6)	2 (1.0)	0	0	2 (0.2)	0	0	0
Embolism	3 (1.5)	1 (0.5)	0	0	0	0	0	0
Deep vein thrombosis	2 (1.0)	0	0	0	4 (0.4)	1 (0.1)	0	0
Metabolism and nutrition disorders	22 (11.3)	9 (4.6)	1 (0.5)	0	155 (15.3)	69 (6.8)	13 (1.3)	0
Decreased appetite	5 (2.6)	2 (1.0)	0	0	95 (9.4)	22 (2.2)	0	0
Hypokalaemia	5 (2.6)	3 (1.5)	1 (0.5)	0	8 (0.8)	5 (0.5)	1 (0.1)	0
Dehydration	4 (2.1)	1 (0.5)	0	0	15 (1.5)	5 (0.5)	0	0
Hypomagnesaemia	3 (1.5)	0	0	0	13 (1.3)	7 (0.7)	3 (0.3)	0
Hyperkalaemia	2 (1.0)	1 (0.5)	0	0	1 (0.1)	1 (0.1)	0	0
Hyponatraemia	2 (1.0)	1 (0.5)	0	0	17 (1.7)	14 (1.4)	3 (0.3)	0
Hypophosphataemia	2 (1.0)	1 (0.5)	0	0	5 (0.5)	3 (0.3)	1 (0.1)	0
Nervous system disorders	21 (10.8)	1 (0.5)	0	0	79 (7.8)	31 (3.1)	4 (0.4)	0
Dizziness	14 (7.2)	0	0	0	12 (1.2)	0	0	0
Dysgeusia	2 (1.0)	0	0	0	12 (1.2)	2 (0.2)	0	0
Infections and infestations	20 (10.3)	8 (4.1)	3 (1.5)	0	113 (11.2)	57 (5.6)	9 (0.9)	1 (0.1)

System Organ Class Preferred Term	CABINET (N = 195)				Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N = 1010)			
	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 4 n (%)	Grade 5 n (%)
COVID-19	4 (2.1)	0	0	0	3 (0.3)	1 (0.1)	0	0
Sepsis	4 (2.1)	4 (2.1)	2 (1.0)	0	3 (0.3)	2 (0.2)	1 (0.1)	0
Tooth infection	4 (2.1)	1 (0.5)	0	0	7 (0.7)	1 (0.1)	0	0
Herpes zoster	2 (1.0)	0	0	0	1 (0.1)	0	0	0
Pneumonia	2 (1.0)	0	0	0	23 (2.3)	15 (1.5)	4 (0.4)	1 (0.1)
Musculoskeletal and connective tissue disorders	18 (9.2)	8 (4.1)	0	0	60 (5.9)	20 (2.0)	0	0
Back pain	7 (3.6)	4 (2.1)	0	0	11 (1.1)	3 (0.3)	0	0
Muscular weakness	3 (1.5)	2 (1.0)	0	0	3 (0.3)	0	0	0
Pain in extremity	3 (1.5)	1 (0.5)	0	0	11 (1.1)	4 (0.4)	0	0
Arthralgia	2 (1.0)	1 (0.5)	0	0	10 (1.0)	1 (0.1)	0	0
Flank pain	2 (1.0)	0	0	0	1 (0.1)	0	0	0
Muscle spasms	2 (1.0)	0	0	0	9 (0.9)	0	0	0
Respiratory, thoracic and mediastinal disorders	17 (8.7)	6 (3.1)	0	0	102 (10.1)	41 (4.1)	2 (0.2)	0
Dyspnoea	5 (2.6)	1 (0.5)	0	0	27 (2.7)	9 (0.9)	0	0
Oropharyngeal pain	4 (2.1)	0	0	0	6 (0.6)	0	0	0
Hypoxia	3 (1.5)	2 (1.0)	0	0	0	0	0	0
Pulmonary embolism	3 (1.5)	3 (1.5)	0	0	12 (1.2)	10 (1.0)	0	0
Dysphonia	1 (0.5)	0	0	0	13 (1.3)	3 (0.3)	0	0
Psychiatric disorders	10 (5.1)	3 (1.5)	0	0	23 (2.3)	7 (0.7)	1 (0.1)	0
Anxiety	4 (2.1)	1 (0.5)	0	0	1 (0.1)	0	0	0
Confusional state	2 (1.0)	0	0	0	9 (0.9)	3 (0.3)	0	0
Eye disorders	5 (2.6)	0	0	0	5 (0.5)	0	0	0
Visual impairment	2 (1.0)	0	0	0	1 (0.1)	0	0	0
Blood and lymphatic system disorders	4 (2.1)	1 (0.5)	0	0	51 (5.0)	37 (3.7)	3 (0.3)	0
Anaemia	3 (1.5)	1 (0.5)	0	0	11 (1.1)	7 (0.7)	1 (0.1)	0
Thrombocytopenia	1 (0.5)	0	0	0	23 (2.3)	15 (1.5)	0	0
Injury, poisoning and procedural complications	4 (2.1)	1 (0.5)	0	0	27 (2.7)	11 (1.1)	0	0
Wound complication	2 (1.0)	0	0	0	0	0	0	0
Renal and urinary disorders	4 (2.1)	1 (0.5)	0	0	55 (5.4)	26 (2.6)	1 (0.1)	0
Chromaturia	2 (1.0)	0	0	0	1 (0.1)	0	0	0
Proteinuria	1 (0.5)	0	0	0	40 (4.0)	17 (1.7)	0	0
Cardiac disorders	3 (1.5)	1 (0.5)	0	0	13 (1.3)	6 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.0)	1 (0.5)	0	0	21 (2.1)	17 (1.7)	1 (0.1)	0
Hepatobiliary disorders	0	0	0	0	25 (2.5)	21 (2.1)	1 (0.1)	0
Reproductive system and breast disorders	0	0	0	0	14 (1.4)	5 (0.5)	0	0

Note: Solicited AEs for Cabinet are bolded.

Table 74. CABINET, Pooled Studies (XL184-308, XL184-309, and XL184-311): AEs Leading to Discontinuation in ≥ 1% of Subjects by SOC and Preferred Term (Safety Population)

System Organ Class Preferred Term	CABINET (N = 195)				Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N = 1010)			
	Any Grade n(%)	Grade 3-4 n(%)	Grade 4 n(%)	Grade 5 n(%)	Any Grade n(%)	Grade 3-4 n(%)	Grade 4 n(%)	Grade 5 n(%)
Number of Subjects With at Least One Event	48 (24.6)	29(14.9)	10 (5.1)	1 (0.5)	312 (30.9)	180 (17.8)	30 (3.0)	46 (4.6)
Gastrointestinal disorders	11 (5.6)	5 (2.6)	0	0	58 (5.7)	21 (2.1)	5 (0.5)	3 (0.3)
Diarrhoea	6 (3.1)	2 (1.0)	0	0	15 (1.5)	2 (0.2)	0	0
Nausea	2 (1.0)	0	0	0	8 (0.8)	0	0	0
Stomatitis	2 (1.0)	0	0	0	1 (0.1)	0	0	0
Investigations	8 (4.1)	3 (1.5)	1 (0.5)	0	26 (2.6)	12 (1.2)	2 (0.2)	0
Aspartate aminotransferase increased	4 (2.1)	1 (0.5)	0	0	6 (0.6)	4 (0.4)	0	0
Blood bilirubin increased	3 (1.5)	1 (0.5)	0	0	6 (0.6)	4 (0.4)	2 (0.2)	0
Alanine aminotransferase increased	2 (1.0)	1 (0.5)	1 (0.5)	0	3 (0.3)	1 (0.1)	0	0
Blood alkaline phosphatase increased	2 (1.0)	1 (0.5)	0	0	0	0	0	0
General disorders and administration site conditions	7 (3.6)	2 (1.0)	0	1 (0.5)	85 (8.4)	42 (4.2)	4 (0.4)	8 (0.8)
Fatigue	5 (2.6)	1 (0.5)	0	0	29 (2.9)	14 (1.4)	0	0
Asthenia	0	0	0	0	12 (1.2)	6 (0.6)	0	0
General physical health deterioration	0	0	0	0	27 (2.7)	13 (1.3)	3 (0.3)	3 (0.3)
Vascular disorders	6 (3.1)	4 (2.1)	0	0	11 (1.1)	5 (0.5)	1 (0.1)	1 (0.1)
Hypertension	2 (1.0)	2 (1.0)	0	0	5 (0.5)	3 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	5 (2.6)	4 (2.1)	2 (1.0)	0	22 (2.2)	11 (1.1)	2 (0.2)	2 (0.2)
Pulmonary embolism	3 (1.5)	3 (1.5)	2 (1.0)	0	2 (0.2)	2 (0.2)	0	0
Dyspnoea	2 (1.0)	1 (0.5)	0	0	6 (0.6)	3 (0.3)	0	0
Nervous system disorders	4 (2.1)	2 (1.0)	1 (0.5)	0	29 (2.9)	19 (1.9)	3 (0.3)	2 (0.2)
Cardiac disorders	3 (1.5)	3 (1.5)	2 (1.0)	0	6 (0.6)	2 (0.2)	0	3 (0.3)
Cardiac arrest	2 (1.0)	2 (1.0)	2 (1.0)	0	0	0	0	0
Infections and infestations	3 (1.5)	1 (0.5)	0	0	24 (2.4)	13 (1.3)	6 (0.6)	6 (0.6)
Skin and subcutaneous tissue disorders	3 (1.5)	0	0	0	19 (1.9)	11 (1.1)	0	0
Palmar-plantar erythrodysaesthesia syndrome	3 (1.5)	0	0	0	14 (1.4)	9 (0.9)	0	0
Hepatobiliary disorders	2 (1.0)	1 (0.5)	1 (0.5)	0	18 (1.8)	9 (0.9)	3 (0.3)	7 (0.7)
Metabolism and nutrition disorders	2 (1.0)	2 (1.0)	2 (1.0)	0	23 (2.3)	13 (1.3)	3 (0.3)	0
Renal and urinary disorders	2 (1.0)	2 (1.0)	0	0	13 (1.3)	7 (0.7)	0	2 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.5)	1 (0.5)	0	0	18 (1.8)	11 (1.1)	0	0

System Organ Class Preferred Term	CABINET (N = 195)				Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N = 1010)			
	Any Grade n(%)	Grade 3-4 n(%)	Grade 4 n(%)	Grade 5 n(%)	Any Grade n(%)	Grade 3-4 n(%)	Grade 4 n(%)	Grade 5 n(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	28 (2.8)	14 (1.4)	2 (0.2)	10 (1.0)
Hepatocellular carcinoma	0	0	0	0	11 (1.1)	5 (0.5)	2 (0.2)	5 (0.5)

Note: Solicited AEs for Cabinet are bolded.

Deaths

In the CABINET study, death was reported for 40.5% of subjects versus 62.2% of subjects in the pooled studies.

Disease progression was the most common cause of death in both the CABINET study (63.3%, labeled as tumour) and the pooled studies (73.3%, labeled as progression of disease under study). There were many different PTs reported under disease progression. In the CABINET study, other causes of death were recorded as unknown (24.1%) and other (12.7%). In the pooled studies, other causes of death were other (16.8%), tumour (3.7%), unknown (0.7%), progression of DTC (0.6%), and death due to an unknown cause, DTC disease progression, and progression of thyroid cancer (2 subjects [0.3%] each). No other cause of death was reported in more than 1 subject in the pooled studies.

Clinical Laboratory Evaluations

As mentioned further above, clinically significant laboratory abnormalities and solicited events in CABINET were to be reported as AEs. A summary of abnormal laboratory data is presented in Table 75. CABOSUN was excluded as its laboratory data was collected similarly to CABINET.

Table 75. CABINET, Pooled Studies (XL184-308, XL184-309, and XL184-311): Summary of Abnormal Laboratory Data (≥ 10% Incidence [any grade] or ≥ 2% [grade 3-4] in the CABINET Study) by Preferred Term (Safety Population)

Preferred Term	Cabinet (N=195)		Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N=1010)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Aspartate aminotransferase increased	141 (72.3)	6 (3.1)	217 (21.5)	66 (6.5)
Aspartate aminotransferase increased (from lab)	N.A.	N.A.	765 (75.7)	138 (13.7)
Alanine aminotransferase increased	129 (66.2)	2 (1.0)	187 (18.5)	35 (3.5)
Alanine aminotransferase increased (from lab)	N.A.	N.A.	734 (72.7)	79 (7.8)
Platelet count decreased	89 (45.6)	2 (1.0)	73 (7.2)	23 (2.3)
Platelet count decreased (from lab)	N.A.	N.A.	413 (40.9)	61 (6.0)
Neutrophil count decreased	59 (30.3)	5 (2.6)	40 (4.0)	14 (1.4)
Neutrophil count decreased (from lab)	N.A.	N.A.	398 (39.4)	52 (5.1)
Hyperglycaemia	57 (29.2)	3 (1.5)	35 (3.5)	3 (0.3)
Hyperglycaemia (from lab)	N.A.	N.A.	416 (41.2)	25 (2.5)
Anaemia	55 (28.2)	4 (2.1)	137 (13.6)	47 (4.7)

	Cabinet (N=195)		Cabozantinib pool (XL184-308 + XL184-309 + XL184-311) (N=1010)	
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**
Anaemia (from lab)	N.A.	N.A.	367 (36.3)	47 (4.7)
Blood alkaline phosphatase increased	51 (26.2)	8 (4.1)	68 (6.7)	20 (2.0)
Blood alkaline phosphatase increased (from lab)	N.A.	N.A.	421 (41.7)	47 (4.7)
Lymphocyte count decreased	50 (25.6)	17 (8.7)	18 (1.8)	5 (0.5)
Lymphocyte count decreased (from lab)	N.A.	N.A.	330 (32.7)	105 (10.4)
Hypophosphataemia	39 (20.0)	1 (0.5)	68 (6.7)	23 (2.3)
Hypophosphataemia (from lab)	N.A.	N.A.	228 (22.6)	77 (7.6)
Blood creatinine increased	36 (18.5)	1 (0.5)	39 (3.9)	3 (0.3)
Blood creatinine increased (from lab)	N.A.	N.A.	147 (14.6)	10 (1.0)
Hypocalcaemia	35 (17.9)	0	83 (8.2)	25 (2.5)
Hypocalcaemia (from lab)	N.A.	N.A.	157 (15.5)	37 (3.7)
Blood bilirubin increased	34 (17.4)	6 (3.1)	74 (7.3)	25 (2.5)
Blood bilirubin increased (from lab)	N.A.	N.A.	262 (25.9)	45 (4.5)
Hypoalbuminaemia	32 (16.4)	0	88 (8.7)	6 (0.6)
Hypoalbuminaemia (from lab)	N.A.	N.A.	454 (45.0)	19 (1.9)
Hypokalaemia	31 (15.9)	4 (2.1)	102 (10.1)	34 (3.4)
Hypokalaemia (from lab)	N.A.	N.A.	224 (22.2)	56 (5.5)
Hypomagnesaemia	31 (15.9)	1 (0.5)	118 (11.7)	28 (2.8)
Hypomagnesaemia (from lab)	N.A.	N.A.	278 (27.5)	48 (4.8)
Hyponatraemia	31 (15.9)	4 (2.1)	64 (6.3)	41 (4.1)
Hyponatraemia (from lab)	N.A.	N.A.	364 (36.0)	107 (10.6)

Solicited AEs for CABINET are **bolded**.
Solicited AE for the CABINET: Alanine aminotransferase increased, Aspartate aminotransferase increased, Diarrhea, Fatigue, Hyperglycaemia, Hypertension, Hypothyroidism, Neutrophil count decreased
Palmar-plantar erythrodysaesthesia syndrome, Platelet count decreased, Rash maculo-papular, Stomatitis
Only post baseline records with CTC grade > baseline CTC grade are included. This does not apply to the CABINET study since no laboratory data were recorded for this study.
For studies 308 and 309, CTCAE Version 4 is used. For study 311, CTCAE version 5 is used. CTCAE is not applicable for the CABINET study since no laboratory data were recorded for this study. All lab abnormalities are therefore noted as "NA" in the CABINET group.

Safety in special populations

Intrinsic Factors

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)
- Baseline ECOG performance status at baseline (0, ≧ 1)

Extrinsic Factors

No additional extrinsic factors were evaluated for this report.

Safety related to drug-drug interactions and other interactions

Drug-drug interaction studies have been carried out in vitro, and in the clinic, and were part of the original Cabometyx filing. No further drug interaction studies have been conducted. Clinical

pharmacology data in special populations and studies of drug-drug interactions and drug metabolism for cabozantinib are summarized in the cabozantinib prescribing information.

Discontinuation due to adverse events

Adverse events leading to treatment discontinuation are presented for the epNET cohort (Table 76), pNET cohort (Table 77), and pooled epNET + pNET including crossover (Table 78).

Table 76. CABINET: Adverse Events Occurring in ≥ 2% of Subjects Leading to Treatment Discontinuation in Either Treatment Arm (epNET; Double-Blind)

	Cabozantinib Only (N = 132) n (%)		Placebo (N = 67) n (%)	
Preferred Term	**All**	**Grade 3/4**	**All**	**Grade 3/4**
Number of subjects with at least 1 AE leading to treatment discontinuation, n (%)	36 (27)	21 (16)	13 (19)	9 (13)
Diarrhoea	6 (4.5)	2 (1.5)	3 (4.5)	1 (1.5)
Fatigue	5 (3.8)	1 (0.8)	0	0
AST increased	4 (3.0)	1 (0.8)	0	0
Blood bilirubin increased	3 (2.3)	1 (0.8)	1 (1.5)	0
Abdominal pain	1 (0.8)	1 (0.8)	2 (3.0)	1 (1.5)
Memory impairment	0	0	2 (3.0)	1 (1.5)

Table 77. CABINET: Adverse Events Occurring in ≥ 2% of Subjects Leading to Treatment Discontinuation in Either Treatment Arm (pNET; Double-Blind)

	Cabozantinib Only (N = 63) n (%)		Placebo (N = 31) n (%)	
Preferred Term	**All**	**Grade 3/4**	**All**	**Grade 3/4**
Number of subjects with at least 1 AE leading to treatment discontinuation, n (%)	12 (19)	8 (13)	3 (9.7)	2 (6.5)
Pulmonary embolism	2 (3.2)	2 (3.2)	0	0
Decreased appetite	0	0	1 (3.2)	0
Fatigue	0	0	2 (6.5)	1 (3.2)
Hepatic failure	0	0	1 (3.2)	1 (3.2)

Table 78. CABINET: Adverse Events Occurring in ≥ 2% of Subjects Leading to Treatment Discontinuation (Pooled epNET + pNET Including Crossover)

Preferred Term	All Cabozantinib (N = 227) n (%)		
	Grade		
	All	3/4	5
Number of subjects with at least 1 AE leading to treatment discontinuation	55 (24)	33 (15)	2 (0.9)
Diarrhoea	7 (3.1)	2 (0.9)	0
Fatigue	6 (2.6)	1 (0.4)	0

Safety to support product information

To provide current safety information, safety data from the cabozantinib arm of the CABINET study (n=227, including crossover) were added to cabozantinib data from previously pooled studies (n=1 128), resulting in a dataset of 1 355 subjects. The finalisation of this approach involved the following steps:

- Algorithmic identification of TEAEs frequently observed (≥ 10% occurrence) in the cabozantinib arm of the CABINET study.
- Identification of TEAEs with at least a 5% higher occurrence in the cabozantinib arm compared to the placebo arm, or with a frequency of ≥ 2% for grade 3/4 TEAEs in the cabozantinib arm from CABINET.
- Identification of TEAEs with a frequency of ≥ 5% higher in the cabozantinib arm across the pooled studies.
- Analysis of the cabozantinib monotherapy pool, including data from XL184-308, CABOSUN, XL184 309, and XL184-311.
- Analysis of an expanded cabozantinib pool, which also includes data from the CABINET study.
- Evaluation of all AEs that did not meet the algorithmic criteria on an event-by-event basis to assess potential causality to cabozantinib.
- Use of medical judgment to determine if an AE should be classified as an adverse drug reaction (ADR), considering factors such as reporting frequency, comparison to placebo, and pharmacological consistency with cabozantinib.

The following modifications to the EU Summary of Product Characteristics (SmPC) in use at the time of this submission are proposed following analysis of data:

- A detailed review led to the inclusion of three PTs in the ADR table: flatulence, hypotension, and allergic rhinitis.
- The PT of white blood cell count decreased, already present in the Patient Information Leaflet (PIL), was added to the ADR table under section 4.8 for consistency.
- Frequencies were updated for arthralgia, hypocalcaemia, and blood alkaline phosphatase increased from common to very common.

A copy of the proposed ADR table in Section 4.8 of the SmPC, including the incidence in the total dataset of n=1355 patients is provided below.

Table 79. Adverse Drug Reactions (ADRs) Reported in Clinical Trials or After Post-Marketing Use in Patients Treated with Cabozantinib in Monotherapy

Infections and infestations	
Common	abscess (2.5%), pneumonia (5.0%)
Blood and lymphatic disorders	
Very common	anaemia (17.8%), thrombocytopenia (21.8%)
Common	neutropenia (4.2%), lymphopenia (1.3%)
Endocrine disorders	
Very common	hypothyroidism* (14.8%)
Metabolism and nutrition disorders	
Very common	decreased appetite (42.7%), hypomagnesaemia (13.1%), hypokalaemia (11.1%), hypoalbuminaemia (10.6%), hypocalcaemia (10.6%)
Common	dehydration (4.6%), hypophosphataemia (10%), hyponatraemia (8.4%), hyperkalaemia (4.3%), hyperbilirubinemia (1.4%), hyperglycaemia (8.8%), hypoglycaemia (2.3%)
Nervous system disorders	
Very common	dysgeusia (15.8%), headache (12.3%), dizziness (12.0%)
Common	peripheral neuropathy[a] (2.0%)
Uncommon	seizure (0.5%), cerebrovascular accident (0.5%), posterior reversible encephalopathy syndrome (0.1%)
Ear and labyrinth disorders	
Common	tinnitus (1.8%)
Cardiac disorders	
Uncommon	acute myocardial infarction (0.2%)
Vascular disorders	
Very common	hypertension (40.6%), haemorrhage[c*] (21.2%)
Common	venous thrombosis[d] (7.7%), hypotension[e] (5.5%), embolism (1.5%)
Uncommon	hypertensive crisis (0.2%), arterial thrombosis (1.4%), embolism arterial (0.1%)
Not known	aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	
Very common	dysphonia (17.1%), dyspnoea (15.6%), cough (14.5%)
Common	pulmonary embolism (2.7%), rhinitis allergic[e] (1.7%)
Uncommon	pneumothorax (0.8%)
Gastrointestinal disorders	
Very common	diarrhoea* (62.7%), nausea (37.5%), vomiting (25.8%), stomatitis (22.4%), constipation (18.9%), abdominal pain (17.8%), dyspepsia (10.4%)
Common	gastrointestinal perforation* (1.3%), pancreatitis (1.1%), fistula* (1.4%), gastroesophageal reflux disease (5.8%), haemorrhoids (2.6%), oral pain (3.5), dry mouth (8.5%), dysphagia (3.3%), flatulence[e] (5.5%)
Uncommon	glossodynia (0.5)
Hepatobiliary disorders	
Common	hepatic encephalopathy* (1.8%)
Uncommon	hepatitis cholestatic (0.1%)
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome (44.1%), rash[f] (22.6%)
Common	pruritus (6.3%), alopecia (7.6%), dry skin (8.4%), hair colour change (4.7%), hyperkeratosis (2.3%), erythema (2.5%)
Not known	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very common	pain in extremity (10.2%), arthralgia (12.5%)
Common	muscle spasms (10%)
Uncommon	osteonecrosis of the jaw (0.4%)
Renal and urinary disorders	
Common	proteinuria (9.5%)

General disorders and administration site conditions	
Very common	fatigue (52.3%), mucosal inflammation (12.9%), asthenia (15.8%), peripheral oedema (11.6%)
Investigations[e]	
Very Common	weight decreased (24.8%), serum ALT increased (28.3%), AST increased (32.0%), blood alkaline phosphatase increased (10.5%)
Common	GGT increased (5.2%), blood creatinine increased (7.4%), amylase increased (2.5%), lipase increased (2.4%), blood cholesterol increased (1.3%), blood triglycerides increased (2.5%), white blood cell count decreased (7.7%)
Injury, poisoning and procedural complications	
Uncommon	wound complications[g] (2.9%)

*See section 4.8 Description of selected adverse reactions for further characterisation.

[a] including polyneuropathy; peripheral neuropathy is mainly sensory

[b] Including epistaxis as the most commonly reported adverse reaction

[c] All venous thrombosis including deep vein thrombosis

[d] Based on the NET study (CABINET)

[e] Based on reported adverse reactions

[f] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic and drug eruption.

[g] Impaired healing, incision site complication and wound dehiscence

Post marketing experience

Through 28 November 2023, the estimated number of patients treated with cabozantinib exceeds 179,545 patients in the post marketing setting, including approximately 4530 treated with Cometriq and approximately 175,015 treated with cabozantinib alone or in combination with nivolumab (PSUR, 28Nov2023).

2.5.1. Discussion on clinical safety

The safety data supporting this extension of indication to include the treatment of adult patients with progressive extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours after prior systemic therapy for Cabometyx is based on final results from study CABINET. In addition, the safety results from CABINET were compared to pooled safety data from four previously reported registrational studies (n=1088) that each included a 60-mg treatment arm; XL184-308 (METEOR; RCC), A031203 (Cabosun; RCC), XL184-309 (CELESTIAL; HCC), and XL184-311 (Cosmic-311; DTC). The safety assessment approach, including pooling of data, is acceptable.

Data on concomitant medications, outside of non-protocol anticancer therapy and concurrent somatostatin analogue (SSA) use, were not collected. Concurrent SSAs were used by more than half of both cabozantinib- and placebo-treated patients in CABINET. The impact of this on the safety assessment is uncertain, but this uncertainty is (at least in part) negated by the randomised design of the study. No subgroup analysis for safety by concurrent use of SSA was provided. This is acceptable, as the safety profile of cabozantinib is well known.

Patient exposure

At total of 293 subjects were included in the safety population, 195 in the cabozantinib arm (epNET: n=132, pNET: n=63) and 98 in the placebo arm (epNET: n=67, pNET: n=31). The size of the defined safety population is limited but considered acceptable, although it is not sufficient for detection of rare adverse events. After disease progression, twenty subjects (30%) and twelve subjects (39%) from the placebo groups crossed over to treatment with open-label cabozantinib in the pNET and epNET cohorts, respectively.

In the **epNET** cohort, the median duration of exposure was longer in the cabozantinib arm (5.37

months, range: 0.1 – 32.4 months) vs the placebo arm (2.79 months, range: 0.5 – 22.8 months), which is likely in part due to crossover. The median average daily dose of study drug was considerably lower in the cabozantinib arm (42.86 mg/day) compared to the placebo arm (60.00 mg/day), as reflected in the median dose intensity of 71.43% and 100%, respectively. This is consistent with previous cabozantinib studies, and due to frequent dose modifications (reduction or hold) in the cabozantinib-treated subjects. It is noteworthy that the median daily dose upper range in the placebo arm is as high as 92.7 mg/day, and that the upper range of the median dose intensity is 154.5%. The median follow-up time was similar for both treatment arms, 22.72 months vs 22.77 months for cabozantinib and placebo, respectively.

The median duration of exposure in the **pNET** cohort was longer in the cabozantinib arm (8.28 months, range: 0.1 – 37.8 months) vs the placebo arm (2.86 months, range: 0.1 – 11.2 months), again, likely to at least be partly due to crossover. The median average daily dose of study drug was notably low in the cabozantinib arm (41.36 mg/day) compared to the placebo arm (60.00 mg/day), which is reflected in the median dose intensity of 68.93% and 99.24%, respectively, and again due to dose modifications. The median follow-up time was comparable for the cabozantinib (23.03 months) and placebo (24.90 months) arms.

Adverse events

Overall, the type of AEs reported are consistent with previously reported data for cabozantinib. All subjects experienced at least one AE, and the majority also had treatment-related AEs; 98% vs 84% for cabozantinib and placebo, in both the epNET and pNET cohorts. Safety data in the epNET and pNET cohorts are generally comparable and pooling of these data is thus considered acceptable. The incidence, type, and severity of AEs reported for the 32 crossover patients were overall consistent with those reported for the n=195 patients who received blinded cabozantinib treatment. Therefore, grouping together these (195+32=) 227 "All Cabozantinib" patients in CABINET for safety is acceptable. It is of note that the incidence of AEs, including treatment-related events, is high in the placebo arm, suggesting an overlap of AEs and symptoms of the NET disease.

Deaths

The incidence of all-cause mortality was comparable for cabozantinib and placebo. For **epNET** a total of 85 deaths were reported, 58 subjects (44%) in the cabozantinib arm and 27 subjects (40%) in the placebo arm. Most deaths, 27% vs 21%, were attributed to progressive disease and the majority occurred >30 days after the date of last dose of study treatment, yet 9 (6.8%) vs 5 (7.5%) subjects died within 30 days after the last dose. Of these, 4 subjects vs 1 subject had Grade 5 AEs considered as possibly related to study drug by the Investigator, in the cabozantinib arm and the placebo arm, respectively. Grade 5 AEs possibly related to study treatment in the cabozantinib arm were cardiac arrest, death (cause of death unknown, but according to the Investigator, possibly thromboembolic event), GI haemorrhage and sudden death (cause of death unknown, but possibly thromboembolic event according to the Investigator). These treatment related Grade 5 AEs are all (related to) known ADRs for cabozantinib. The single treatment-related Grade 5 AE in the placebo arm was disease progression. In the **pNET** cohort, a total of 29 deaths were reported, 21 subjects (33%) in the cabozantinib arm and 8 subjects (26%) in the placebo arm. None of the subjects had a grade 5 AE and only 1 subject died within 30 days after the date of last dose of study treatment (due to progressive disease).

Other serious adverse events

In the **epNET** cohort, SAEs regardless of causality were reported at a similar frequency in the cabozantinib (44%) and placebo (40%) arms. Hypertension (6.1% vs 1.5%), abdominal pain (5.3% vs 6.0%), diarrhoea (3.0%, 4.5%), and vomiting (3.0% in both treatment arms) were the most frequently reported SAEs in the cabozantinib arm and placebo arm, respectively. Treatment-related

SAEs were reported for 39% of subjects in the cabozantinib arm and as many as 24% of subjects in the placebo arm. The most frequent ones were hypertension (6.1% vs 0%), diarrhoea (2.3% vs 4.5%), fatigue (2.3% vs 4.5%) and pulmonary embolism (2.3% vs 1.5%), all of them considered sufficiently addressed in the SmPC. In the **pNET** cohort, SAEs were reported at a higher frequency in the cabozantinib arm (46%) compared to placebo (23%). Frequently reported SAEs were vomiting (6.3% cabozantinib vs 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). Treatment-related SAEs were reported for 48% of subjects in the cabozantinib arm and 13% of subjects in the placebo arm, the most frequent ones being vomiting (6.3% vs 0%), embolism (4.8% vs 0%), hypoxia (4.8% vs 0%), and nausea (4.8% vs 0%). Overall, frequently reported SAEs were similar for pooled **epNET + pNET**, with and without crossover, compared to the separate cohorts. Sepsis was reported in 3.1% of subjects but was not proposed to be included as an ADR in the cabozantinib SmPC, which is supported, based on the provided narratives where sepsis was assessed as unlikely related to study treatment (data not shown). It is noted that only for the SAEs hypertension (5.1% vs 1.0%), vomiting (4.1% vs 2.0%), sepsis (3.1% vs 0%), pulmonary embolism (2.6% vs 1.0%), and anaemia (2.1% vs 0%) the incidence for cabozantinib treated patients in CABINET was clearly higher than for placebo treated patients.

Dose modifications

AEs leading to dose modification (reduction or hold) were very frequently reported; epNET: 86%, pNET: 89% of subjects in the cabozantinib arm; epNET: 42%, pNET: 52% in the placebo arm. Dose reductions due to an AE were more frequent in the cabozantinib arm (epNET: 62%, pNET: 67%) compared to the placebo arm (epNET: 7.5%, pNET: 13%), while AEs leading to a dose hold were very common in both treatment arms, although more frequent in the cabozantinib arm (epNET: 80%, pNET: 83%) than in the placebo arm (epNET: 37%, pNET: 42%). Thus, dose modifications due to AEs are, as previously known, frequently reported for cabozantinib, suggesting poor tolerability of the 60 mg dose and resulting in a considerably lower median daily dose (42.64 mg for epNET+pNET). This is concerning from a safety perspective, nonetheless, it is in line with previously reported data. It is noted that AEs leading to dose modifications are common also in the placebo arm, yet this does not seem to notably affect the median daily dose.

Events to monitor (ETMs)

In the pooled **epNET + pNET** the overall incidence of reported ETMs in the cabozantinib arm was similar with or without crossover subjects (84% vs 85%, respectively), and comparable to the separate cohort-level analysis, except for Venous and Mixed Thromboembolic events, discussed below. The median time to first occurrence of ETMs varied from 15.0 days (hypertension) to 330.0 days (hepatotoxicity). PRES, osteonecrosis, PPE syndrome, QT prolongation, abscess and venous and mixed thromboembolic events and intra-abdominal and pelvic abscess had a median time to first occurrence of <90 days.

VTE: Venous and mixed thrombotic AEs (grouped ATM term) regardless of causality were unevenly reported in the different cohorts. In **epNET**, it was reported for 5 subjects (3.8%) in the cabozantinib arm and 1 subject (1.5%) in the placebo arm. In **pNET**, it was notably higher in the cabozantinib arm, 12 subjects (19%) vs 1 (3.2%) subject in the placebo arm. Most of events were reported as PTs embolism (epNET+pNET: 8 subjects) or pulmonary embolism (epNET+pNET: 6 subjects). Thromboembolic events are known risks of cabozantinib, as reflected in the SmPC sections 4.4 and 4.8. Regarding the higher frequency of venous and mixed thrombotic events observed in the pNET cohort compared to the epNET, the MAH states that patients with NET are known to exhibit a higher thromboembolic risk, in particular those with pancreatic origin, and suggests that the underlying disease may have been a contributing factor for the reported cases of pulmonary embolism. Although

this is acknowledged, it should be noted that only one (1) subject (3.2 %) in the pNET placebo arm experienced a thromboembolic event. The higher frequency of VTE in the pNET cohort is now reflected in the SmPC, section 4.4.

QT Prolongation: QT prolongation (ETM grouped term) was reported at a slightly higher frequency in the cabozantinib arm (epNET: 9.1%; pNET: 6.3%) compared to the placebo arm (epNET: 7.5%; pNET: 3.2%). Cardiac events, including Electrocardiogram QT prolonged (PT) and cardiac arrest (PT) are further discussed below. One subject presented with Torsades des pointes, which was assessed as probably related to study treatment by the Investigator. The event occurred without QT prolongation.

Safety observations in placebo crossover subjects

Overall, the incidence, type, and severity of AEs reported for subjects from the placebo arms of the epNET cohort and pNET cohort who crossed over to open-label cabozantinib after disease progression were consistent with those reported by subjects who received blinded cabozantinib treatment in each of the 2 cohorts.

CABINET compared to previously reported studies (pooled)
Overall, the safety profile of cabozantinib is comparable between the CABINET study and the pooled studies. It should be noted that there was a higher incidence of AEs, including treatment-related, in the placebo arm of the CABINET study compared to previously reported data from placebo arms, suggesting that some AEs are related to the NET disease.

A similar proportion of subjects in the cabozantinib arm of the CABINET and pooled studies had AEs considered as treatment related (98.5% vs 95.3%) or worst Grade 3/4 AEs (69.2% vs 67.6%). The most commonly reported AEs in the cabozantinib arm in the CABINET study, were reported at a higher incidence than in the pooled studies; fatigue (74.4% vs 49.0%), AST increased (72.3% vs 24.3 %), ALT increased (66.2% vs 21.1%), diarrhoea (64.6% vs 63.4%) and hypertension (63.6% vs 34.9%), respectively. There was a higher incidence of these AEs in the placebo arm of CABINET vs the pooled placebo arm of the two other studies that used placebo as a comparator (XL184-309 and 311; data not shown), suggesting that the higher incidence in CABINET could be due to the underlying condition/treated disease. In contrast, e.g., palmar-plantar erythrodysaesthesia (PPE) syndrome was less frequently observed in CABINET vs the pooled studies (36.9% vs 45.7%), due to unknown reasons. The incidence of laboratory-associated AEs was higher in the CABINET study than in the pooled studies, mainly due to the difference in collection of data, discussed below.

Overall, the frequency and severity of ETMs observed in the CABINET study were generally consistent with those of the pooled studies. A higher incidence of hypertension (ETM) was reported in the CABINET study (65.1 %) vs the pooled studies (36.2%), which is most likely due to the NET disease as reflected by the incidence (PT) in the placebo-groups in CABINET compared to the pooled studies (42.9% vs 7.7%) (data not shown). Hypertension, including how this is addressed in the SmPC, is further discussed below.

The ETM QT prolongation was more frequently reported in CABINET (8.2%) vs the pooled studies (4.1%), with the PT Electrocardiogram QT prolonged reported in 6 subjects (3.1%) vs 9 subjects (0.8%), respectively. Although the number of events is small and no QTC > 500 ms was identified, the MAH was requested to provide a causality assessment for electrocardiogram QT prolonged (PT). Based on the provided causality assessment, the MAH´s conclusion not to include Electrocardiogram QT prolonged as an ADR is endorsed. Furthermore, cardiac arrest as a PT was reported in 3 subjects (1.5%) in CABINET, compared to 0 subjects (0%) in the pooled studies. According to provided narratives, these events were assessed as possibly or probably related to study treatment by the

Investigator. Nevertheless, based on the provided data, the MAH´s conclusion that there is insufficient evidence to conclude on causality between cabozantinib and cardiac arrest, is supported.

The proportion of subjects with at least one SAE was similar for CABINET (44.6%) and the pooled studies (48.6%) and the overall incidence of SAEs was in general comparable. Serious treatment-related and Grade 4 treatment-related events were however more common in CABINET (31.3% and 7.2%) than in the pooled studies (18.6% and 4.4%), which is likely due to the underlying condition as discussed above. In contrast, Grade 5 AEs were more common in the pooled studies (4.6% vs 12.8%) while the rate of grade 5 related AEs was comparable (2.1 % vs 1%) for CABINET and the pooled studies, respectively.

The most frequent SAEs (regardless of causality) in the CABINET study were hypertension (5.1%), abdominal pain (4.6%), vomiting (4.1%), nausea and sepsis (3.1%, each), and in the pooled studies, diarrhoea (1.9%) and abdominal pain (1.7%). The most frequent treatment-related SAEs (≥ 2% incidence) in the CABINET study were hypertension (4.6%), vomiting (2.6%), pulmonary embolism (2.6%) and diarrhoea, nausea and fatigue (2.1% each), while in the pooled studies, diarrhoea (1.8% of subjects), hypertension (1.2%), and pulmonary embolism (1.0%) were the most reported. It is of note that five (5) subjects (2.6%) experienced treatment related cardiac disorders in CABINET, vs 4 subjects (0.4%) in the pooled studies.

Dose modifications are exceedingly frequent among subjects treated with cabozantinib, with similar proportions of subjects experiencing at least one AE that led to dose modifications in CABINET (86.7%) and the pooled studies (85.8%). Overall, at an SOC level, the frequencies for CABINET and the pooled studies leading to dose modifications were comparable. The frequency of subjects experiencing at least one AE that led to study treatment discontinuation was high, but comparable for CABINET (24.6%) and the pooled studies (30.9%). Almost all of the events in CABINET were considered treatment related (22%), however, a rather high incidence was observed also in the placebo arms (19% in epNET, 10% in pNET, data not shown), (again) suggesting a relation with the underlying condition/treated disease. For example, in the epNET cohort diarrhoea leading to treatment discontinuation was observed at an identical rate in cabozantinib and placebo treated patients (4.5% each). In the CABINET study, death was reported for 40.5% of subjects vs 62.2% of subjects in the pooled studies, with disease progression being most common cause of death.

Clinically significant laboratory abnormalities and solicited events in CABINET were to be reported as AEs rather than being collected in the clinical database as laboratory abnormalities, precluding a meaningful direct comparison between CABINET and the pooled studies of these parameters. However, when comparing the laboratory-associated any grade AEs of AST increased, ALT increased, platelet count decreased, neutrophil count decreased and hyperglycaemia, which had a higher incidence in CABINET compared to the pooled studies, their incidence was generally similar to the corresponding laboratory abnormality in the pooled studies.

Safety in special populations

The incidence of AEs or ETMs reported in cabozantinib-treated subjects in CABINET was generally similar between females and males, and between baseline ECOG performance status, with few exceptions. 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 patients (~80%) included in the CABINET study were White, hence, difficult to draw any conclusion with regards to differences according to race (data not shown).

Safety to support the product information

The updated SmPC is based on safety data from the n=227 "All Cabozantinib" patients from CABINET (including crossover), added to the cabozantinib 60-mg treatment data from four previously pooled studies (n=1128), resulting in a total dataset of n=1355 patients. These n=1128 patients are comprised of the study populations described at the start of this section (n=1088), but from XL184-311 in DTC an additional 40 patients who crossed over from the control arm to receive cabozantinib are included.

Overall, the safety profile of cabozantinib in the CABINET Study is consistent with the known safety profile of cabozantinib in monotherapy in various other tumour types including DTC, RCC and HCC. There were four new ADRs included with frequency common: flatulence, hypotension, allergic rhinitis and embolism. It was concluded that there was insufficient evidence to confirm a direct causal association between cabozantinib and the PTs cardiac arrest, hypoxia, and electrocardiogram QT prolonged, as discussed above. The MAH reinstated the PT of "white blood cell count decreased" in the SmPC, section 4.8, table 2. This ADR went missing due to an oversight at the time of submission of procedure EMEA/H/C/004163/II/0017 (II/17 EPAR). The correction by the MAH is endorsed.

Regarding ADR frequencies, hypocalcaemia (17.9% vs 8.9%) and blood alkaline phosphatase (26.2% vs 7.2%) were more frequent in the CABINET study compared to the pooled studies, respectively, and the ADR frequencies in the SmPC are revised from common to very common. In addition, the ADR frequency of arthralgia is revised from common to very common.

The subsection 'Summary of safety profile' in section 4.8 of the SmPC has been updated to list the most common serious ADRs (≥1% incidence) in the NET population based on safety information from CABINET. These ADRs include hypertension, fatigue, pulmonary embolism, vomiting, diarrhoea, nausea, and embolism.

2.5.2. Conclusions on clinical safety

New ADRs are included in the SmPC (flatulence, hypotension, embolism and allergic rhinitis). Consistent with previously reported studies, dose modifications were exceedingly frequent, resulting in a median average daily dose of 42.64 mg, which suggests poor tolerability of cabozantinib.

Overall, the safety profile of cabozantinib in NETs appears manageable and consistent with the known safety profile of cabozantinib, and no major safety concerns are raised for the NET population.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.3 with the following content:

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Gastrointestinal perforation • Gastrointestinal and nongastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Posterior reversible encephalopathy syndrome (PRES) • Osteonecrosis
Important Potential Risks	• Renal failure • Hepatotoxicity • Embryotoxicity • Carcinogenicity
Missing Information	None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Gastrointestinal perforation	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Gastrointestinal and nongastrointestinal fistula	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thromboembolic events	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8[a] PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Haemorrhage (Grade ≥3)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Wound complications	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Osteonecrosis	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Important potential risks		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Renal failure	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Embryotoxicity	**Routine risk minimisation measures:** SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.

PL= package leaflet; PRES=posterior reversible encephalopathy syndrome; SmPC=summary of product characteristics.

a Data in this section relate to events of pulmonary embolism, venous thrombosis and arterial thrombosis.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A user testing bridging approach was reviewed and accepted by EMA in the scope of the initial CABOMETYX MAA EMEA/H/C/004163/0000. Given that the proposed changes to the Cabometyx PL are not significant and were already tested in a previous user consultation of Cabometyx PL, a new user consultation is not deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final wording of the indication, as approved, is: Cabometyx is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.

3.1.2. Available therapies and unmet medical need

Currently, there are no approved treatments for patients whose disease has progressed on prior lines of approved therapy other than SSA.

Unmet medical need

Treatment options for relapsed and progressive NET remain limited and therefore an unmet need is present given most patients acquire resistance to the current approved targeted therapies. Clinical outcomes remain poor in this patient population with significant mortality and morbidity due to NET related symptoms.

3.1.3. Main clinical studies

The MAH has provided one Phase 3 study (CABINET) to support the current application. The CABINET study was designed as a randomised (2:1), double-blind, placebo-controlled trial. Subjects with epNET and subjects with pNET tumour types were evaluated separately and enrolled into two separate cohorts to independently evaluate the efficacy and safety of cabozantinib. Subjects in the study were required to have disease progression or be intolerant to at least one FDA-approved therapy except somatostatin analogues (SSAs). The treatment was cabozantinib 60 mg daily or matching placebo.

3.2. Favourable effects

epNET:

Primary endpoint: Median PFS by BIRC was 8.48 months (95% CI: 7.46, 12.45) in the cabozantinib arm compared with 3.98 months (95% CI: 3.02, 5.68) in the placebo arm; the difference was 4.5 months with a HR of 0.38; 95% CI 0.25, 0.58. Sensitivity analyses supported the primary analysis of PFS and showed consistent results with the BIRC assessment. Results of the subgroup analysis were consistent with the primary analysis of PFS with HRs below 1, including patients with different primary

tumour site at enrolment ('Midgut' with HR 0.33 (95% CI: 0.19, 0.57) vs 'Non-Midgut GI' with HR 0.57 (95% CI: 0.30, 1.06)).

pNET:

Primary endpoint: Median PFS by BIRC was 13.83 months (95% CI: 8.87, 16.95) in the cabozantinib arm compared with 4.47 months (95% CI: 3.02, 5.75) in the placebo arm; the difference between treatment arms was 9.4 months with a HR of 0.23; 95% CI: 0.12, 0.42. Sensitivity analyses supported the primary analysis of PFS and showed consistent results with the BIRC assessment. Results of the subgroup analysis were consistent with the primary analysis of PFS with HRs below 1, including the small subgroup of patients who have received prior sunitinib (HR 0.20; 95% CI: 0.06, 0.64).

3.3. Uncertainties and limitations about favourable effects

The clinical study report for the CABINET study is based on interim analyses which were originally planned for futility. Following DSMB recommendation, the Alliance stopped enrolment into the CABINET study on 07 August 2023 and the study was unblinded. The recommendation by the DSMB to stop the two cohorts based directly on the results without any pre specified interim analyses for efficacy has compromised the study integrity and there is formally no longer any control of the Type I error. The MAH has provided reliable information on the events leading up to the DSMB recommendation. Furthermore, the MAH has provided analyses of PFS HR over time which indicate that the study was not stopped at a random high.

Updated OS data show no clear difference between treatment arms in either cohort, with HRs close to 1 with wide confidence intervals. The interpretation of the OS data may be confounded by the proportion of cross-over to cabozantinib in the placebo-arms of both cohorts and further lines of therapy.

3.4. Unfavourable effects

Overall, the unfavourable effects of cabozantinib in the NET population are consistent with the known safety profile of cabozantinib, although some differences were observed.

All subjects in both treatment arms experienced at least one AE regardless of causality, and treatment related AEs were reported for 98% and 84% of subjects in the cabozantinib and placebo arm, respectively. Grade 3/4 AEs were reported for 69% vs 41 % of subjects.

The most frequently reported (>50%) AEs were fatigue, AST increased, ALT increased, diarrhoea, and hypertension. Embolism, flatulence, hypotension, and allergic rhinitis are new ADRs identified with frequency common (≥1/100 to <1/10).

"Venous and mixed thrombotic AEs" (ETM) were less frequently reported in epNET (cabozantinib: 5 subjects (3.8%), placebo: 1 subject (1.5%)) than in pNET (cabozantinib: 12 subjects (19%) vs placebo: 1 subject (3.2%)). For comparison, the incidence is 7.9 % in cabozantinib treated subjects in the pooled (previously reported) studies.

The ETM "QT prolongation" was more frequently reported in CABINET (8.2%) vs the pooled studies (4.1%), with the PT "Electrocardiogram QT prolonged" reported in 6 subjects (3.1%) vs 9 subjects (0.8%), respectively.

Treatment-related SAEs were frequently reported in both the cabozantinib (31.3%) and the placebo (20.4%) treatment arms of CABINET. Cardiac arrest, embolism and hypoxia were reported as SAEs in the cabozantinib arm.

In the cabozantinib arm, four (4) subjects experienced grade 5 AEs considered as possibly related to study drug by the Investigator; cardiac arrest, death, GI haemorrhage and sudden death.

Dose modifications (interruptions and reductions) due to an AE occurred at a high but comparable frequency in cabozantinib treated subjects in CABINET (86.7%) vs the pooled studies (85.8%). In CABINET, 24.6% of subjects experienced at least one AE that led to treatment discontinuation, compared to 30.9% in the pooled studies.

3.5. Uncertainties and limitations about unfavourable effects

Thromboembolic events are known risks of cabozantinib. The clinical relevance of the higher incidence of venous and mixed thrombotic events in epNET compared to pNET is uncertain. Nevertheless, this difference is reflected in section 4.4 of the SmPC.

Approximately 2/3 of the patients in the study experienced dose reductions due to AEs. The dose-exposure-response relationships are not investigated in the currently sought population. The MAH is reminded to further investigate dosing strategies as well as sources of variability in cabozantinib PK in future studies.

3.6. Effects Table

Table 80. Effects table for Cabometyx for the treatment of adult patients with progressive epNETs and pNETs after prior systemic therapy

Effect	Short description	Unit	Treatment Cabozantinib	Control Placebo	Uncertainties / Strength of evidence	N/A
Favourable Effects						
epNET cohort – ITT population (n=203)			N=134	N=69		
Primary endpoint **PFS** (DCO 24 Aug. 2023)	Progression-free survival by BIRC per RECIST v1.1	Median (95%CI) in months	8.48 (7.46, 12.45)	3.98 (3.02, 5.68)	Strengths: - Derived from randomised, double-blind Phase 3 study Uncertainties/Limitations: - Early unblinding of the study - Immature efficacy data	
			PFS HR=0.38 (95% CI: 0.25, 0.58)			
Secondary endpoint **Updated OS** (DCO 04 Sept. 2024)	Overall survival	Median (95%CI) in months	21.95 (17.64, 29.63)	22.47 (14.19, 30.03)		
			OS HR=1.04 (95% CI: 0.71, 1.52)			
pNET cohort – ITT population (n=95)			N=64	N=31		
Primary endpoint **PFS** (DCO 24 Aug. 2023)	Progression-free survival by BIRC per RECIST v1.1	Median (95%CI) in months	13.83 (8.87, 16.95)	4.47 (3.02, 5.75)	Strengths: - Derived from randomised, double-blind Phase 3 study Uncertainties/Limitations: - Early unblinding of the study - Immature efficacy data	
			PFS HR=0.23 (95% CI: 0.12, 0.42)			
Secondary endpoint	Overall survival	Median (95%CI) in months	40.08 (25.40, NE)	31.11 (22.18, NE)		

Effect	Short description	Unit	Treatment Cabozantinib	Control Placebo	Uncertainties / Strength of evidence	N/A
Updated OS (DCO 04 Sept. 2024)			OS HR= 1.11 (95% CI: 0.59, 2.09)			
Unfavourable Effects						
epNET cohort – Safety population (n=199)			N=132	N=67		
Grade 3-4 AEs	All causality (drug-related)	%	67 (59)	39 (27)	Strengths: - Derived from randomised, double-blind Phase 3 study Uncertainties/Limitations: - Impact of concurrent use of SSAs on safety assessment uncertain	
pNET cohort – Safety population (n=94)			N=63	N=31		
Grade 3-4 AEs	All causality (drug-related)	%	73 (65)	45 (23)	Strengths: - Derived from randomised, double-blind Phase 3 study Uncertainties/Limitations: - Impact of concurrent use of SSAs on safety assessment uncertain	

Abbreviations: AEs: adverse events; BIRC: blinded independent review committee; CI: confidence interval; DC: discontinuation; HR: hazard ratio; NE: not evaluable; pNET: pancreatic neuro-endocrine tumour; PPES: palmar-plantar erythrodysesthesia syndrome; RECIST v1.1: Response Evaluation Criteria In Solid Tumours version 1.1; SAEs: serious adverse events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

epNET cohort: For patients with epNET in the CABINET study, the comparison of cabozantinib vs placebo resulted in improved PFS. Prolonging time to progression by 4.5 months (HR 0.38; 95% CI 0.25, 0.58) is considered clinically relevant in this population of previously treated patients. While acknowledging the limitations of cross-study comparisons, it is noted that the effect size observed with cabozantinib is of similar magnitude as observed for everolimus in a relatively similar but less pretreated population in the RADIANT-4 study where everolimus was compared with placebo (HR 0.48; 95% CI 0.35, 0.67). The overall PFS observed with cabozantinib is supported by sensitivity analyses and reflected in the subgroups, including in patients previously treated with everolimus or Lu-177 dotatate. Although premature stopping of accrual to the study, the epNET cohort had nearly enrolled preplanned number of patients. There were concerns regarding the premature unblinding and termination of the study based on an interim analysis. However, these concerns have been mitigated by additional analyses and information provided during this procedure.

While there was a numeric trend in favour of cabozantinib in the original OS data, the updated OS results with one more year of follow-up show no clear difference between treatment arms with HR close to 1 with a wide confidence interval. However, with extensive crossover from the placebo arm to cabozantinib after progression/study unblinding, and access to other treatments for many patients, an OS benefit would be difficult to demonstrate. Furthermore, the study was not powered to show OS benefit.

pNET cohort: Improved PFS was observed in the pNET cohort for cabozantinib, with a gain of 9.4 months (HR of 0.23; 95% CI: 0.12, 0.42; p<0.0001) compared to placebo, which is clinically relevant

for the population of 2L+ pNET patients. The observed effect on PFS seems to be of a larger magnitude than shown for both everolimus (vs placebo HR 0.35; 95% CI 0.27, 0.45) in the RADIANT-3 study and sunitinib (vs placebo HR 0.43; 95% CI 0.27, 0.67) in the SUN 1111 study, in less pretreated patients, acknowledging the limitations of cross-study comparisons. The overall PFS observed with cabozantinib is reflected in the subgroups and supported by sensitivity analyses. Whether patients were previously treated with everolimus, sunitinib or Lu-177 dotatate, a relevant improvement of PFS with cabozantinib is noted. It cannot be ruled out that the overall improvement in PFS may be overestimated taking into consideration the early halting of accrual, and thereby the low number of events compared to planned, but a clinically relevant improvement in PFS is still expected.

As for the epNET cohort, there was a weak numerical trend in OS in favour of cabozantinib in the original OS data. The updated OS results with one more year of follow-up show no clear difference between treatment arms with HR close to 1 and a wide confidence interval. The interpretation of the OS data may be confounded by the proportion of cross-over to cabozantinib in the placebo-arms of both cohorts and further lines of therapy.

The toxicity of cabozantinib in CABINET was substantial, even including some drug related deaths. It was, however, overall consistent with the known safety profile of cabozantinib. The toxicity profile has already been reviewed for cabozantinib in the treatment of HCC, RCC and DTC, and is considered manageable. Flatulence, hypotension, allergic rhinitis and embolism have been included as ADRs in the SmPC. The incidences of some of the most frequent AEs in the cabozantinib-treated patients in CABINET were, however, higher than in the combined other pivotal studies. For these AEs the incidence in the placebo-treated patients in CABINET was also relatively high though, suggesting that the higher incidence of these AEs in CABINET could be due to the underlying condition/treated disease.

Safety data indicate that the 60 mg dose is poorly tolerated as approximately 2/3 of the patients experienced dose reductions due to AEs. At the time of the approval of the extension of indication for RCC (EMEA/H/C/004163/II/0017), the applicant was recommended to prospectively investigate lower dose levels for cabozantinib in future studies. The MAH is reminded to further investigate dosing strategies as well as sources of variability in cabozantinib PK in future studies.

3.7.2. Balance of benefits and risks

The primary endpoint PFS, reported sufficiently robust and clinically relevant delay in progression with cabozantinib compared to placebo in this pretreated population. Updated OS data showed no clear difference between treatment arms in either cohort with HRs close to 1 with wide confidence intervals, which prevents concluding on any potential detrimental effect. Delaying progression is considered to be of benefit for patients diagnosed with epNET/pNET as progressive disease may often be associated with new or worsening cancer-related symptoms, and the patient's performance status and tolerance to further therapy is expected to diminish with subsequent treatment lines. Although the toxicity of cabozantinib cannot be neglected, the safety data from the CABINET study indicate a similar toxicity profile as registered in other indications approved for Cabometyx, which is considered severe, but overall manageable. The observed improvement in PFS is therefore considered to outweigh the concerns regarding the toxicity, and it can be concluded that the B/R is positive in the finally agreed indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Cabometyx is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues for CABOMETYX based on final results from study CABINET (A021602). This is a multicenter, two-arm, randomised, double-blind, placebo-controlled phase 3 study investigating cabozantinib versus placebo in patients with advanced Neuroendocrine Tumors (NET). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.3 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cabometyx is not similar to Lutathera within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Cabomety-H-C-4163-II-0040’

Attachments

1. SmPC and Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 19 June 2025.

Appendix

1. CHMP AR on similarity dated 19 June 2025.