24 March2022
EMA/214682/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CABOMETYX

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/004163/II/0023

Note

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

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	Assessment Report
AST	aspartate aminotransferase
ATA	adequate tumor assessment
ATC	Anatomical Therapeutic Chemical
ATE	arterial thrombotic event
AUC	area under the plasma concentration-vs-time curve
BIRC	blinded independent radiology committee
BMI	body mass index
BOR	best overall response
BP	blood pressure
BSC	best supportive care
CAPN	chest, abdomen, pelvis, neck
CCO1	Clinical Cut-off 1 (19 August 2020)
CCO2	Clinical Cut-off 2 (08 February 2021)
CI	confidence interval
CMH	Cochran Mantel-Haenszel
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating DNA
CV%	coefficient of variation

CYP	cytochrome P450
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DOR	duration of response
DSR	disease stabilization rate
DTC	differentiated thyroid cancer
DVT	deep vein thrombosis
EBRT	external beam radiation therapy
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	emergency room
ESC	Executive Safety Committee
ETM	event to monitor
FSH	follicle stimulating hormone
FT4	free thyroxine
FTC	follicular thyroid cancer
FXa	factor Xa
GGT	γ-glutamyltransferase
GI	gastrointestinal
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IxRS	interactive voice/web response system
JNC	Joint National Committee
LDH	lactate dehydrogenase
LFT	liver function test
LMWH	low molecular weight heparin
LT4	levothyroxine
MAPK	MAP kinase
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MI	myocardial infarction
MID	minimal important differences
Min	Minimum
MKI	Multikinase inhibitor
MPA	Medicines Products Agency
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NE	not estimable
NPACT	nonprotocol anticancer therapy
NTRK	Neurotrophic receptor tyrosine kinase
OITT	overall response rate intent-to-treat

ORR	objective response rate
OS	overall survival
O-Safety	Overall response rate-Safety
PD	progressive disease or disease progression
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand 1
PEC	predicted environmental concentration
PFS	progression-free survival
PI	Prescribing Information
PK	pharmacokinetic(s)
Pow	octanol-water partition coefficient
PPE/PPES	palmar-plantar erythrodysesthesia syndrome
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
PTC	papillary thyroid cancer
PTT	partial thromboplastin time
qd	once daily
QTc	corrected QT interval
QTcF	corrected QT interval calculated by the Fridericia formula
RAI	radioiodine (radioactive iodine)
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RET	REarranged during Transfection
RPLS	reversible posterior leukoencephalopathy syndrome
RSI	request for supplementary information

RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SD	standard deviation
SE	standard error
SOC	system organ class
SoD	sum of target lesion diameters
Tg	thyroglobulin
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
UE	unable to evaluate
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VAS	visual analogue scale
VEGF(R)	vascular endothelial growth factor (receptor)
VTE	venous and mixed/unspecified thrombotic event
W#D#	Week # Day #
WHO	World Health Organization
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 27 July 2021 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 monotherapy treatment of adults and adolescent patients aged 12 years and older, 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 for CABOMETYX; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 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 P/0282/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0282/2021 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: <N/A>

Timetable	Actual dates
Submission date	27 July 2021
Start of procedure:	14 August 2021
CHMP Rapporteur Assessment Report	8 October 2021
PRAC Rapporteur Assessment Report	15 October 2021
PRAC Outcome	28 October 2021
CHMP members comments	29 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	4 November 2021
Request for supplementary information (RSI)	11 November 2021
CHMP Rapporteur Assessment Report	25 January 2022
PRAC Rapporteur Assessment Report	25 January 2022
PRAC members comments	02 February 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	10 February 2022
CHMP members comments	14 February 2022
Updated CHMP Rapporteur Assessment Report	18 February 2022
Request for Supplementary Information	24 February 2022
Joint Rapporteur's preliminary assessment report circulated on:	09 March 2022
Joint Rapporteur's updated assessment report circulated on:	17 March 2022
CHMP opinion:	24 March 2022

2. Scientific discussion

2.1. Introduction

Problem statement

This application concerns an extension of indication to include treatment of adult and adolescent patients aged 12 years and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) and who have progressed during or after systemic therapy.

Disease or condition

Differentiated thyroid cancer (DTC) includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC) and a rare type, Hürthle cell thyroid cancer.

According to ESMO (2019) DTC RAI-refractory disease[a] is defined as follows:

1. Absence of initial RAI uptake in metastases

2. Absence of RAI uptake in metastases after treatment with RAI

3. Presence of RAI uptake in some metastases, but absence in others

4. RECIST progression[b] despite RAI uptake in all metastases

[a]Other criteria, but controversial: high FDG uptake, aggressive histology, persistence of disease after several RAI treatment courses. [b]An increase of 20% in the sum of target lesions or the appearance of new lesions.

Risk factors for differentiated thyroid cancer include a diet low in iodine and environmental radiation exposure (Pellegriti et al 2013). Inherited conditions such as familial adenomatous polyposis and Cowden's disease have also been linked to thyroid cancers due to certain germline mutations, as well as a family history of the disease (Guilmette and Nose 2018). In most cases, the cause of thyroid cancer is unknown.

Epidemiology

Thyroid cancer is the most common endocrine neoplasm with an annual estimate in the United States of more than 44,000 newly diagnosed cases and over 2000 deaths; the US annual death rate is approximately 0.6% (American Cancer Society 2021). Over 87,000 new cases and over 6,000 deaths were reported in Europe each year (Globocan 2020); worldwide, there were over 586,000 cases and 43,000 deaths. Thyroid cancer is about 2.5 times more common in women than in men, and the incidence has almost tripled from the mid-1990s through 2014 (Roman et al 2017; Howlader et al 2017).

The most common type of thyroid cancer is differentiated thyroid cancer (> 90% of thyroid cancers). RAI refractoriness remains uncommon though, with an estimated incidence of 4-5 cases per million population (ESMO, 2019).

Thyroid cancer can occur at any age, but most tumours are diagnosed between the third and sixth decade of life. Thyroid cancer is rare in childhood, accounting for 1.5-3.0% of carcinomas in children and adolescents. Nevertheless, it is the most common malignant neoplasms of the endocrine system in this age group (Enemoto et al, 2012). The cases of thyroid cancer in children are increasing year by year, by an annual incidence of 1.1% per year, a trend observed throughout the world, especially in areas affected by radioactivity (Stefan et al 2020). This increase is real, mostly because of the different environmental factors and is not attributed to intense imagistic screening (Dekker et al 2018; Russo 2017; Drozd 2015; Piciu 2012; Niedziela 2004). According to the Surveillance, Epidemiology, and End Results (SEER) Program data, between 1975 and 1995, the annual percent change (APC) of paediatric thyroid carcinoma was +0.8%/year; with an accelerated +4.6%/year APC from 1996 to 2016 (Howlader 2019). Peak incidence is noted in children from 15-19 years of age (Rivkees et al 2011; Howlader 2020).

Biologic features, aetiology and pathogenesis

MET and vascular endothelial growth factor (VEGF) signalling have been implicated in tumour neo-angiogenesis, invasion, and dissemination, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumour types (Carmeliet and Jain 2011, Trusolino et al 2010, Aftab and McDonald 2011). Increased levels of VEGF have been documented in recurrent

thyroid cancer following surgery and in patients with metastatic disease (Zhou et al 2012, Klubo-Gwiezdzinska et al 2007). The angiogenic activity observed in DTC led to the development of anti-VEGF targeted therapies. Resistance to VEGF-targeted therapies may arise from the upregulation of alternative pro-angiogenic and pro-invasive signalling pathways, including the MET pathway (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). AXL is normally expressed at undetectable or very low levels in the thyroid (Axelrod et al 2014). AXL stimulation with its ligand GAS6 promoted survival of

thyroid cancer cell lines in culture. Enforced expression or activation of AXL in normal rat thyroid cells significantly reduced RAI uptake. These data indicate that AXL expression levels could be used as predictor of RAI refractoriness and as a possible novel therapeutic target of RAI-refractory DTCs (Collina et al 2019).

The MAP kinase pathway (MAPK) and the PI3K-AKT signalling pathways are the most common disrupted or upregulated pathways in the tumorigenesis of thyroid cancer. Activation of the MAPK pathway can result from BRAF and RAS mutations or RET and ALK rearrangements. RET is a proto-oncogene which encodes a receptor tyrosine kinase (RTK) that is involved in tumour cell survival and proliferation (Drosten 2004). Mutations that activate RET kinase activity are frequently found in patients with medullary thyroid cancer (MTC) (Elisei et al 2008, Moura et al 2009). About 10-20% of sporadic PTCs have chromosomal translocations involving the RET proto-oncogene (RET-PTC fusions). The prevalence of RET-PTCs fusions is higher after radiation exposure (50-80%) and in young adults with PTC (Ciampi and Nikiforov 2007). The most prevalent RET rearrangements are RET/PTC1 (CCD6-RET) representing approximately 60-70%, RET/PTC3 (NCOA4-RET) representing approximately 20-30%, and RET/PTC2 (PRKAR1A-RET) representing 5% (Nikiforov 2011, Bongarzone et al 1998, Tallini et al 1998). These rearrangements lead to constitutive activation of RET kinase and downstream signalling of the MAPK pathway. Targeting the RET RTK activity represents a treatment opportunity in MTC and PTC (Pierotti et al 1996, Prescott and Zeiger 2015). The presence of BRAF mutation (V600E) is associated with a more aggressive form of cancer and is highly prevalent in RAI-refractory PTC (Xing et al 2005). The PI3K-AKT signalling pathway is activated in a smaller fraction of patients with PTC and FTC and leads to increased cell proliferation (Ringel et al 2001).

Rearrangements involving the neurotrophic-tropomyosin receptor kinase (NTRK) gene family (NTRK1, NTRK2, and NTRK3) are well-known drivers in a wide diversity of human cancers. NTRK fusions with various partner genes induce oncogenesis by producing chimeric oncoproteins with a constitutively activated kinase function, and lead to downstream stimulation of cellular proliferation via the RAS/RAF/MAPK pathway. In the thyroid, NTRK-driven malignancies are rare (approx. 2%). In the special populations of paediatric papillary thyroid carcinomas (PTC) and post-Chernobyl reactor accident PTC, NTRK fusions seemed slightly more common, reported in 2–26% and 3–15%, respectively (Chu et al, 2020).

Given its predominance in the paediatric population, the most extensively studied paediatric thyroid cancer, in relation to molecular drivers, is PTC (little is known about the drivers of paediatric FTC at present). RET fusions are reported to be the most common observed alteration and appear to occur in approximately 25-30% of sporadic paediatric PTC (range 14-55%), a figure that further increases to nearly 45% (range: 14-87%) in patients exposed to radiation. Although less common than RET, other oncogenic fusions occur with increased frequency in sporadic paediatric PTC. Reported fusions include NTRK (1, 2 and 3), BRAF, and ALK. Although not comprehensively surveyed, these fusions have been identified in approximately 10% (range: 0-26%), 10% (range: 0-18%), and 5% (range: 0-21%) of paediatric PTC, respectively. BRAF point mutations are reported to be the second most common single oncogenic driver in sporadic paediatric PTC (25-30% of lesions, range: 0-63%). RAS mutations are

present in < 5% (range: 0-18) of sporadic PTC and are more frequent in benign thyroid nodules (15-40%) (Poulson et al, 2019).

Given the known oncogenic potential of the MET, AXL, and RET signalling pathways, targeting these oncoproteins in addition to VEGFRs may provide additional anticancer effects in DTC patients over more selective VEGFR inhibition strategies.

Clinical presentation, diagnosis and stage/prognosis

The majority of thyroid cancers are epithelial tumours that originate from thyroid follicular cells and can be classified on the basis of histology into differentiated thyroid cancers (DTC) including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), and undifferentiated, anaplastic thyroid carcinoma. Medullary thyroid cancer (MTC) is not a type of DTC but originates from the parafollicular C cells of the thyroid, (American Cancer Society 2019; Orphanet et al 2007; Ferlay 2019), see figure below.

Papillary thyroid carcinoma is characterised by its papillary growth pattern of follicular cells with distinct nuclei. Follicular thyroid carcinomas are solitary encapsulated tumours with invasion of follicular cells into the tumour capsule and/or vascular system. Hürthle cell carcinoma (HTC), also named oxyphilic or oncocytic cell carcinoma originate in thyroid follicles from follicular cells (hence they were initially grouped with follicular thyroid tumours) and are characterized by the presence of Hürthle cells, which are eosinophilic oxyphilic cells with round to oval nuclei. Hürthle cell thyroid cancer is now defined as a follicular thyroid cell "derived" cancer and not a variant of follicular cancer itself.

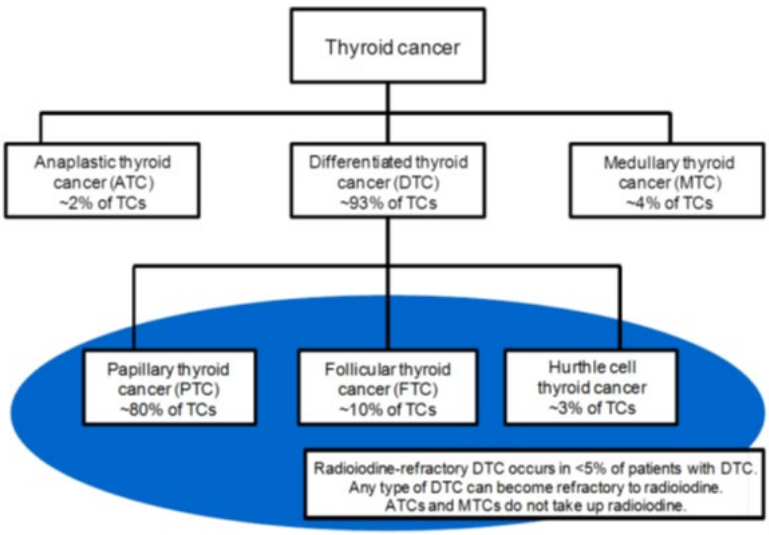


Figure 1. Classification of thyroid malignancies (Ancelle et al, 2012)

A common risk-stratification of DTC is based on The Union for International Cancer Control (UICC) tumour, node, metastasis (TNM) classification. The TNM classification depends on the size of primary tumour, the number and localisation of metastatic lymph nodes and number of distant metastases. The American Joint Committee on Cancer (AJCC) uses the combination of TNM Classification and an age of more than 55 years at diagnosis as risk factor. The differentiation of lymphatic invasion and angioinvasion is of high importance, because angioinvasion is associated with an intermediate risk of recurrence (Schmidbauer et al, 2017).

Thyroid cancer typically does not cause any signs or symptoms early in the disease. In most cases, a small growth or lump (nodule), discovered by the patient, health care provider, or incidentally on an imaging study (e.g., a CT or MRI scan), is the first sign of thyroid cancer. Symptoms that may be associated with thyroid cancer include hoarseness, difficulty breathing or swallowing, swollen lymph nodes especially in the neck, and pain in the throat or neck.

At initial diagnosis of DTC, about 10% of patients have local tumour invasion into surrounding tissues and/or distant metastases. Common sites of distant metastases are lung and bone (involved in 49% and 25% of all cases, respectively, and in 15% of cases both are affected), but other soft tissues and the central nervous system (CNS) can also be involved. The main predictors of outcome for patients with distant metastases are age, location of metastases, and uptake of RAI. Patients who develop RAI refractory DTC have a poor prognosis with an estimated median survival time of 2.5-3.5 years (Busaidy and Cabanillas 2012; Durante et al 2006; Schlumberger et al 2014). Patients who were initially treated with I-131 and achieved negative imaging studies after RAI therapy showed longer survival, with a 10-year survival rate of 92%. However, when the patients became refractory to RAI, the 10-year survival rate dropped to 10–29% (Durante et al, 2006).

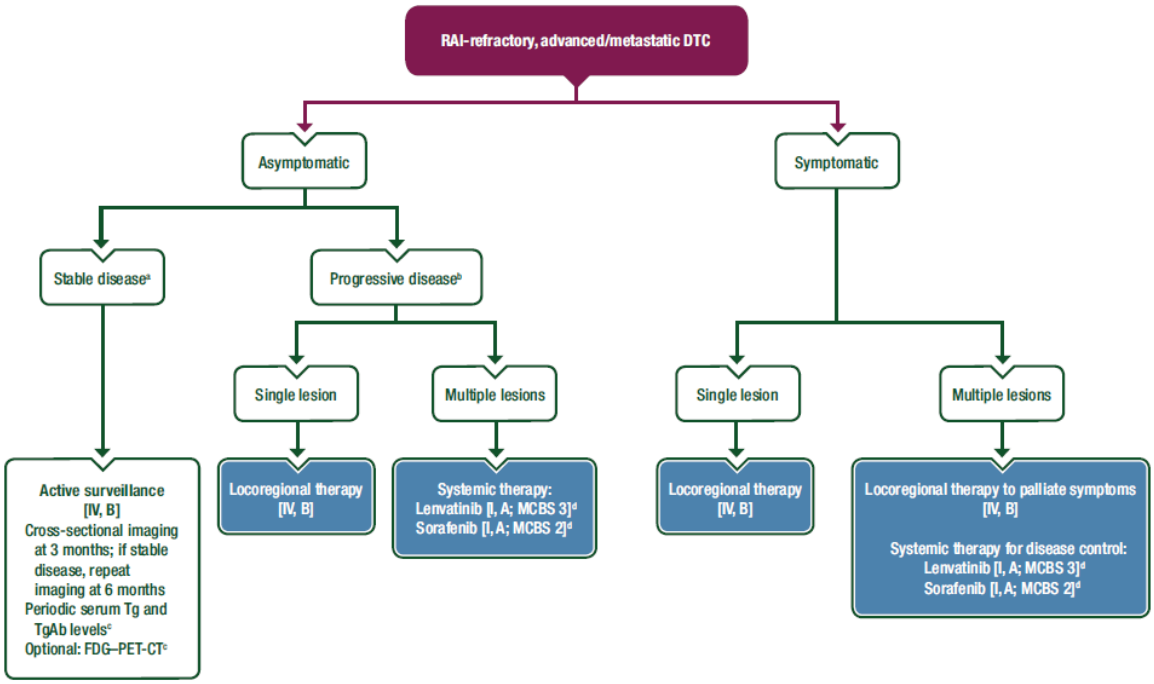
Management

Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC. Patients with a high risk of disease recurrence, incompletely resected cancer, or distant metastases, may receive RAI. After thyroidectomy, lifelong thyroid hormone replacement with levothyroxine (LT4) is indicated. LT4 replacement therapy lowers thyroid-stimulating hormone (TSH) levels by a negative feedback through the hypothalamic-pituitary axis and helps to prevent the growth of remaining thyroid cancer cells (Cooper et al 2009; National Comprehensive Cancer Network [NCCN] 2021).

Recent treatment advancements for patients with RAI-refractory DTC include tyrosine kinase inhibitors (TKIs) targeting the VEGFR which inhibits tumour angiogenesis and causes hypoxia in malignant tissue. Two available multikinase inhibitors (MKIs), sorafenib and lenvatinib are approved for the treatment of unresectable, radioiodine-refractory differentiated thyroid cancer, irrespective of the presence or absence of a RET mutation on the basis of significant improvement in PFS. According to European Society for Medical Oncology (ESMO) and NCCN guidelines, lenvatinib or sorafenib is recommended as the standard first-line systemic treatment of RAI refractory DTC (NCCN [Thyroid Carcinoma] 2021; Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; Filetti et al 2019). In the NCCN guidelines it is stated that lenvatinib is preferred.

Combined inhibition of the VEGF receptor (VEGFR) and MET represents a treatment opportunity which may enhance the efficacy over that achieved via inhibition of either pathway alone and overcome resistance (Sennino and McDonald 2012).

According to ESMO guideline (2019) not all patients with RAI-refractory disease require systemic MKI therapy immediately. The treatment strategy should be based on multiple factors, including symptoms, tumour burden, ECOG PS, lesion characteristics (e.g., paratracheal location or other features likely to cause symptoms) and disease progression [defined using RECIST v1.1 as a 20% increase in the sum of target lesions or the appearance of new lesion], see figure below. It is also stated that the optimal sequence of MKIs in RAI-refractory DTC cannot be determined based on currently available evidence.



[a]A large tumour burden may warrant either a locoregional or systemic therapy. [b]As assessed by the RECIST v1.1 [94]. [c]The trend overtime of serum Tg or TgAb levels and the uptake at FDG–PET may predict disease progression and outcome. [d]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMOMCBS Working Group and validated by the ESMO Guidelines Committee. DTC, differentiated thyroid cancer; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDG–PET, [18F]2-fluoro-2-deoxy-D-glucose—positron emission tomography; FDG–PET-CT, [18F]2-fluoro-2-deoxy-D-glucose—positron emission tomography–computed tomography; MCBS, ESMO-Magnitude of Clinical Benefit Scale; RAI, radioactive iodine; RECIST, Response Evaluation Criteria in Solid Tumours; Tg, thyroglobulin; TgAb, serum thyroglobulin antibody.

Figure 2. Recommendations for management of RAI-refractory, advanced/metastatic DTC patients (ESMO, 2019)

Although initial therapy with VEGFR-targeting TKIs provides clinical benefits by improving PFS and ORR, the majority of DTC patients will acquire resistance to therapy and develop progressive disease (PD). For DTC patients who develop resistance to TKI therapy, options are very limited and more effective therapies are needed.

Concerning thyroid cancer; in EU, selpercatinib, a selective RET inhibitor, received conditional approval in February 2021 as monotherapy for the treatment of adult patients with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib. Retsevmo is also indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant *medullary thyroid cancer* (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib (Retsevmo EU Product Information).

For the small number of thyroid cancers with changes in one of the NTRK genes, larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) are approved in the EU (in 2019 and 2020, respectively) as monotherapies for treatment of adult and paediatric patients (for Rozlytrek restricted to 12 years of age and older) with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options (for Rozlutrek the patient should also not have received a prior NTRK inhibitor).

In the paediatric population, response to sorafenib has been observed in progressive RAI refractory PTC, metastatic PTC not amenable to RAI, and when used as gap therapy when RAI could not be administered in a timely manner. Based on case reports, stable disease was reported in three paediatric patients with extensive bilateral metastatic pulmonary disease after treatment with lenvatinib (including in one patient previously treated with sorafenib). Studies evaluating lenvatinib in pediatric patients with refractory or relapsed solid tumours, including thyroid cancer, are ongoing (Paulson et al 2019).

2.1.1. About the product

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including the VEGF receptor (VEGFR), MET, AXL, and RET.

Cabometyx (cabozantinib tablets) are currently approved in the EU for the treatment of patients with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy (September 2016) and as first line treatment in adult patients with intermediate or poor risk (March 2018). Furthermore, the tablets are approved in patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib (September 2018). In February 2021 cabozantinib tablets were also approved for patients with advanced RCC, as a first-line treatment, in combination with nivolumab.

Cabozantinib capsules under the brand name Cometriq were conditionally approved in the EU for the treatment of adults with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC) (March 2014).

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

The MAH did not receive Scientific Advice from CHMP for the applied indication.

In Europe Exelixis (as the study Sponsor) received national scientific advice from the United Kingdom (MHRA) and Sweden (MPA) in 2018 concerning the design of and the regulatory strategy for the Phase 3 Study XL184-311. Progression Free Survival (PFS) was considered an acceptable primary endpoint, and placebo was considered an appropriate comparator due to the lack of available treatments in this patient population (particularly after the receipt of prior lenvatinib or sorafenib). It was pointed out that including subjects who have received prior lenvatinib would be of particular interest. The company was advised to narrow the patient population and conduct the trial in patients who had received only one prior VEGFR-targeted therapy as this was considered optimal for demonstration of a response to cabozantinib and subsequent data interpretation. The statistical design and approach were agreed. However, it was underlined by MHRA that ORR would not be acceptable as primary endpoint for this study and MPA remarked that PFS2 would be of interest to explore.

Cabozantinib studies in paediatric subjects:

A Phase 1 single arm study (study 4 of the Paediatric Investigational Plan (PIP), (EMA Decision P/0331/2019) was conducted in 41 children and adolescents with refractory solid tumours. Thirty-nine (39) patients received cabozantinib tablets. The study determined the recommended Phase 2 starting dose of cabozantinib in this population as 40 mg/m^2 (roughly equivalent to a 72 mg dose in adults with tablet). This study included 5 patients with thyroid cancer (however, this was medullary thyroid

cancers and not differentiated thyroid cancers), with 2 partial responses. The safety profile was concluded to be not substantially different from the safety profile in adults. An ongoing Phase 2 study (Study 7 of the PIP) is evaluating the safety and activity of the 40 mg/m^2 dose of cabozantinib tablets. This trial has included 109 patients, 7 of whom were < 9 years old at enrolment. Median age was 15.8 years (5.6- 27.1). One patient with DTC (RET fusion positive papillary thyroid cancer) was included and had a partial response.

2.1.3. General comments on compliance with GCP

The MAH confirms that the clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) and were conducted to meet the ethical requirement of European Directive 2001/20/EC. Furthermore, it is stated that the clinical trials carried out outside the European Union also meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

Cabozantinib is approved in Europe for adults. No new nonclinical pharmacology, pharmacokinetic, or toxicology studies have been conducted to support the extension of indication to include adults and adolescent patients aged 12 years and older, 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.

Data from juvenile toxicity studies were submitted and assessed as part of the initial MAA for Cabometyx. The studies are in accordance with the agreed PIP for cabozantinib (EMEA-001143-PIP01-11-M03). An updated assessment of these data, focussing on safety aspect related to use in the adolescent population (12-18 years) is provided below.

2.2.1. Pharmacology

No additional nonclinical pharmacology studies were submitted to support the current application which was considered acceptable by the Committee for Human Medicinal Products (CHMP).

2.2.2. Pharmacokinetics

No additional nonclinical pharmacokinetics studies were submitted to support the current procedure which was considered acceptable by the Committee for Human Medicinal Products (CHMP).

2.2.3. Toxicology

Juvenile toxicity studies were submitted and assessed as part of the initial MAA for Cabometyx. The studies are in accordance with the agreed PIP for cabozantinib (EMEA-001143-PIP01-11-M03). An updated assessment of these data, focussing on safety aspect related to use in the adolescent population (12-18 years) is provided below.

Summary of general toxicity profile for cabometyx:

In repeat-dose toxicity studies in rats for up to 6 months duration target organs for toxicity were GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, liver and kidney, with NOAEL at 1 mg/kg/day in a 2-week study, and 0.3 mg/kg/day in the 6-month study. In addition, lesions in bone (thickened physis in femur without significant effects on bone growth, 2-week study) and teeth (broken teeth, 6-month study) were observed. The adverse effects seen at doses ≥ 5 mg/kg/day were generally dose related, and reversible upon discontinuation. At the maximum dose of 1 mg/kg/day during the 6-month study, mild and mostly reversible effects were seen on liver and kidney.

In dogs, high doses (≥100 mg/kg/day) for 4-14 days caused hematopoietic- and hepatotoxicity, and dehydration. Additional targets for toxicity were GI-tract, lymphoid tissues, testes, bone (cessation of growth associated with atrophy of the primary spongiosa of the distal metaphysis), pancreas, gallbladder, eye and possibly CNS tissues, with NOAEL at 10 mg/kg/day. Lesions were reversible at 100 mg/kg /day. In a 6-month toxicity study in dogs dosed up to 5 mg/kg/day no signs of toxicity were evident, but some effects occurred in reproductive tissues at ≥1 mg/kg/day (decreased testes weights with correlative microscopic findings of bilateral testicular hypospermatogenesis and bilateral epididymal oligospermia, and decreased ovary weights correlated with instances of ovaries without corpora lutea), with hypospermatogenensis still present following 28 days recovery. An extra chronic study with 20 mg/kg showed some reversible hematopoietic- and hepatotoxicity, and effects on skin. Primary treatment-related findings in reproductive tissues were decreased testes weights, bilateral testicular hypospermatogenesis and epididymal oligospermia, and decreased ovary weights that correlated with ovaries without corpora lutea. Treatment-related findings were also present in mammary gland (reduced glandular tissue), uterus (fewer glands), and thymus (lymphoid depletion in males and females). Following recovery, reduced testes weight and hypospermatogenesis were not reversed, while ovarian effects were considered reversible. The histological appearance of testes, epididymis, ovaries, mammary glands, and uterus was similar to animals that have not attained complete sexual maturity, which was not the case in the control animals.

In both species, NOAELs were below human clinical exposure levels at intended therapeutic dose.

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. In a 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low. Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

In a dose-finding 4-week study in rash-mice, dose-related decreases in testes and ovarian weights accompanied by correlative histopathologic findings (degeneration/atrophy of the seminiferous tubules and ovarian hypoplasia) was observed at all dose levels (≥5 mg/kg/day). Cabozantinib-related effects on male and female reproductive organs were also observed in a fertility study in rats at exposure levels at or below human exposure, leading to reduced fertility at ≥1 mg/kg/day for females and ≥2.5 mg/kg/day for males. Weights of testes, epididymis, prostate and seminal vesicles decreased, and reductions occurred in sperm count and concentration from 2.5 mg/kg, with no fertile males were present at ≥2.5 mg/kg. A dose-related prolongation of diestrus showed at 2.5 mg/kg. Although the majority of females had confirmed matings, there were no pregnancies in either group. Female fertility and embryo/foetal viability were reduced at 1 mg/kg. The reversibility of the effects on male and female fertility is not known.

Embryo/foetal viability and development were adversely affected at exposure levels well below human exposure

Toxicity studies in juvenile rats

- Dose range-finding repeat-dose toxicity and toxicokinetic study in juvenile Wistar rats (XL184-NC-031, non-GLP)

Juvenile Wistar rats (9/sex/group) were administered XL184 at 0, 0.3, 1 or 3 mg/kg/day by gavage at post-natal days (PND) 12-35. Plasma samples for TK analysis were collected from satellite animals (5/sex/group).

Toxicokinetic data are presented in Table 1. Due to suspected test article-related unscheduled deaths in the high-dose group from PND18, the dose level was lowered from 3 to 2 mg/kg/day on PND20. A reduction to 2 mg/kg/day for this group was not associated with any clinical findings indicative of toxicity. The 1 mg/kg/day dose level showed decreased body weights and teeth changes, and the NOAEL was determined to be at 0.3 mg/kg/day. Based on test article-associated mortality observed at clinically-relevant exposures in PND 12-aged juvenile rats, a definitive juveniletoxicity study was conducted with dosing beginning at PND 21 (ie, age equivalent to > 2 year old human infant) in order to minimize risk of morbidity and unscheduled deaths.

- Repeat-dose toxicity and toxicokinetic study in juvenile Wistar rats (XL184-NC-032, GLP)

Juvenile Wistar rats (10/sex/group) were administered XL184 via oral gavage at 0 (vehicle control), 0.3, 1 and 2 mg/kg/day from PND21 to 35 [cohort 1] or PND21 to 70 [cohort 2]. Additional groups of rats (10/sex/group) in Cohorts 1 and 2 received vehicle only or XL184 at 2 mg/kg/day and were then provided a 4-week recovery period. Blood samples were taken for toxicokinetic analysis on PND21, 35 or 70 (9/sex/group). Evaluations included body weight and food consumption, ophthalmoscopy, sexual maturation, clinical chemistry, haematology, necropsy and histopathology. Toxicokinetic data are presented in Table 1.

Test article related effects included a higher incidence of teeth abnormalities, slightly reduced body weight gain and food consumption at 2 mg/kg/day, primarily in the Cohort 2 animals. Clinical pathology findings at ≥1 mg/kg/day (both cohorts) included slightly higher red cell indices, occasionally higher leukocytes, modified calcium, enzyme activity (ALT and ALP), globulin concentration, marginally lower clotting times, albumin and albumin to globulin ratio. Increased numbers of peripheral T and B lymphocytes and NK cells were observed in Cohort 1 (PND36) at ≥1 mg/kg/day. In Cohort 2 (PND71), cell counts were in general comparable with those observed in control groups, with the exception of a moderate increase in cytotoxic T cells and a marked increase in B lymphocytes in males, and a moderate increase in NK-cells in females, both at ≥1 mg/kg/day.

Reduced organ weights (spleen, thymus, kidney, liver, heart, ovaries) were seen in Cohort 1 animals at ≥1 mg/kg/day. Reduced bone mineral density were seen in both cohorts at 2 mg/kg/day, and were only reversible in Cohort 1. Microscopically in Cohort 1, test article-related findings were present in the spleen (decreased haematopoiesis) of males dosed ≥1.0 mg/kg/day and females dosed at ≥0.3 mg/kg/day, and in the ovary (pubescent) and uterus (immature, increased mucus cells) of females dosed at ≥1 mg/kg/day. The findings in spleen, ovary and uterus were reversible following 4 weeks recovery. Macroscopic findings present in occasional Cohort 2 animals dosed at 2 mg/kg/day included pale, chipped and/or broken teeth observed at the terminal sacrifice or at the end of the 4-week recovery period. Microscopically, test article-related findings in Cohort 2 females were present in spleen (increased haemopoiesis, ≥0.3 mg/kg/day), liver (increased pigment, ≥1 mg/kg/day), and mandibular lymph node (lymphoid hyperplasia, 2 mg/kg/day). Following recovery, the increased haematopoiesis was reduced, but the liver and mandibular lymph node findings was not reversed.

As the microscopic changes present in spleen were considered non-adverse, NOAEL was determined to 0.3 mg/kg/day for both cohorts. At NOAEL, XL184 AUC levels are estimated to be approximately 0.1-fold human exposure at steady-state.

- Oral gavage study for effects on pre- and postnatal development in rats, including maternal function and juvenile arm (XL184-NC-040, GLP)

In the juvenile arm of the study, juvenile SD rats (15/sex/group) were administered XL184 at 0 (vehicle control), 1 and 2 mg/kg/day from PND12 to 35 [cohort 1] or PND12 to 70 [cohort 2]. Terminal sacrifice occurred either at the end of the dosing phase or following a 4-week non-treatment recovery period (approximately PND70 and PND98 for cohorts 1 and 2, respectively). Due to mortalities in both cohorts at 2 mg/kg/day, recovery was only assessed for the 1 mg/kg/day animals. Evaluations included clinical observations, body weight and food consumption, land mark and behavioural assessments (locomotor activity, pupillary reflex, Morris water maze, auditory startle), macroscopic observations at necropsy, terminal body and organ weights, bone density determinations, and microscopic evaluation of protocol-specified tissues. A single plasma sample was taken for XL184 concentration measurements from each juvenile rat prior to terminal sacrifice at the end of the dosing phase.

Cohort 1

There was test article related mortalities (7 of 15 males and 6 of 15 females), and macroscopic and microscopic findings, including thickened wall of the duodenum, and alopecia of the skin, at 2 mg/kg/day. XL184-related clinical findings at both dose levels included significantly decreased body weight, reduced food consumption, decreased mean terminal body weights, organ weight changes in the spleen, uterus, ovary, and testes (2 mg/kg/day). Microscopic findings considered test article-related were present in lymphatic tissues, GI tract, bone marrow, skin and female reproductive tissues (delayed maturation) at ⩾1 mg/kg/day, and in adrenal, bone (physeal hypertrophy), pancreas and testes (delayed maturation) at 2 mg/kg/day. Decreased bone mineral density (BMD) was observed at doses ≥1 mg/kg/day.

Cohort 2

Adverse effects in juveniles administered XL184 from LD12 to LD70 paralleled those administered XL184 from LD12 to LD35 and resulted in test article-related mortalities (6 of 15 males and 2 of 15 females) and macroscopic and microscopic findings at 2 mg/kg/day. Test article-related clinical findings, significant decreased body weight, reduced food consumption, reduced locomotor activity, and decreased BMD were observed at doses ≥1 mg/kg/day. No effects on organ weights were evident. Test article-related microscopic findings in addition to those seen in cohort 1 animals were present in liver (pigment in hepatocyte), testes (degeneration and/or atrophy of seminiferous tubules) and epididymis (reduced luminal sperm) at 2 mg/k/day, and in kidney (glomerulonephritis and chronic progressive nephropathy) at ⩾ 1 mg/kg. As in cohort 1, there was a significant and dose-related decrease in bone mineral density (BMD) at ⩾ 1 mg/kg.

Taken together, there were adverse XL184-related effects at all doses (1 and 2 mg/kg/day), and a NOAEL could therefore not be determined. Findings on male reproductive organs were seen at 2 mg/kg/day, with more severe findings in cohort 2 than cohort 1. Single plasma PK samples were taken at approximately 24 hours post final dose. At 1 mg/kg/day, plasma concentrations are estimated to be ≤0.2-fold steady state in patients at therapeutic dosing.

Toxicokinetic data

In a definitive 7-week repeat dose toxicity study of XL184 in juvenile rats (Study Report XL184-NC-032), toxicokinetic cohorts of Cr1:WI (Han) juvenile rats (9/sex/dose level) received once daily oral doses of control vehicle formulation only (EtOH:PEG 400: RO water [5:45:50]) or XL184 (malate salt) at 0.3, 1 and 2 mg/kg from postnatal day (PND) 21 to 70. A summary of the mean toxicokinetic results is presented in Table 1

Table 1. Toxicokinetic Summary of XL184 Following Repeat-Oral Dosing in Juvenile Rats: Accumulation and Dose-Proportionality (Study Reports XL184-NC-031 and XL184-NC-032)

					Males[a]			Females[a]		
Study Report	Species	Duration	Dose (mg/kg/d)	Dosing Day[b]	AUC_{0-24} (ng•h/mL)	AF	DP	AUC_{0-24} (ng•h/mL)	AF	DP
XL184-NC-032	Rat	49 Days	0.3	PND 21	6,000	—	1.0	6,880	—	1.0
				PND 35	5,490	0.92	—	7,800	1.13	—
				PND 70	7,680	1.28	—	10,100	1.47	—
			1.0	PND 21	20,000	—	3.3	20,200	—	2.9
				PND 35	15,900	0.80	—	20,500	1.01	—
				PND 70	22,900	1.15	—	31,300	1.55	—
			2.0	PND 21	37,300	—	6.2	46,400	—	6.7
				PND 35	31,500	0.84	—	41,700	0.90	—
				PND 70	40,200	1.08	—	53,000	1.14	—
XL184-NC-031	Rat	23 Days	0.3	PND 12	7,190	—	1.0	7,510	—	1.0
				PND 35	7,500	1.04	—	8,600	1.20	—
			1.0	PND 12	22,500	—	3.3	20,600	—	2.7
				PND 35	18,100	0.80	—	23,900	1.16	—
			3.0	PND 12	66,600	—	9.3	64,100	—	8.5
			2.0[c]	PND 35	18,200	NC	—	20,900	NC	—

AF, accumulation factor (ratio AUC_{0-24} Day X/AUC_{0-24} Day 1); AUC_{0-24}, area under the plasma concentration-time curve over 24 hours; DP, dose proportionality (ratio AUC_{0-24} dose X/AUC_{0-24} of lowest administered dose on PND 12 [XL184-NC-032] or PND 21 [XL184-NC-031]); NC, not calculated; PND, post-natal day. [a] Group mean values; [b] Dosing Day 1 was PND 21 (XL184-NC-032) or PND 12 (XL184-NC-031); [c] Dose was reduced to 2 mg/kg from 3 mg/kg after 9 doses starting on PND 20.

2.2.4. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Cabometyx			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Test protocol unknown	pH 7.4: 5.15	Potential PBT: Yes

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	At pH 7.4: 5.15	B
	BCF	whole fish, low treatment group: 719 whole fish, high treatment group: 745	not B
Persistence	DT50 or ready biodegradability	Not necessary since not B	P/not P
Toxicity	NOEC or CMR	Not necessary since not B	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.007	mg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No

2.2.5. Discussion and conclusion on non-clinical aspects

Toxicity

Findings in adult animals of potential relevance for the adolescent patient population

In repeat-dose toxicity studies for up to 6 months in rats and dogs, target organs of toxicity were GI tract, bone marrow, lymphoid tissues, kidney, adrenal, teeth (rats), and reproductive tract tissues, without safety margins. Generally, the findings were reversible upon cessation of dosing.

Thickened physis in femur was observed in a short-term study in rats (5 mg/kg/day for 2-weeks). In young dogs, cessation of bone growth associated with atrophy of the primary spongiosa of the distal metaphysis was observed at high doses in a short-term study in dogs (100 mg/kg/day for 5 days), likely related to anorexia, dehydration and/or stress. No effects on bone growth were, however, observed in 6-month studies in rats (up to 1 mg/kg/day) or dogs (up to 20 mg/kg/day).

In rats, effects on reproductive organs in males (decreased weights of testes, epididymis, prostate and seminal vesicles, decreased sperm count and concentration) and females (prolonged diestrus) were observed at exposure levels at or below human exposure, leading to reduced fertility at ≥1 mg/kg/day for females and ≥2.5 mg/kg/day for males. Potential reversibility of effects on fertility is unknown.

In dogs, findings in male and female reproductive tissues comprises reduced organ weights (testes, epididymides, prostate, ovaries) and histopathological findings (testicular hypospermatogenesis and

epididymal oligospermia, ovaries without corpora lutea, reduced glandular tissue in mammary gland and uterus). The findings were considered reversible in females, while the findings were only partially reversible in males.

Studies in juvenile animals

In study XL184-NC-032, animals have been dosed at up to 2 mg/kg/day from PND21-35 and 21-70. This is not in accordance with the agreed PIP where dosing from PND12 is outlined (EMEA-001143-PIP01-11-M03), but since the intended patient population for DTC includes adolescents (aged 12 years and older), dosing from PND21 is considered acceptable. Findings included increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), tooth abnormalities, reduced bone mineral content and density, liver pigmentation and lymph node lymphoid hyperplasia. Except for bone and liver findings, other findings were reversible. No effect was seen in male reproductive organs in juvenile animals dosed from PND21-35/70.

However, considering observed effects on male reproductive organs in adult rats at exposure levels higher than achieved in juvenile animals but below human exposure, effects on sexual development cannot be excluded.

A juvenile arm with dosing from PND12 to PND35/70 was included as part of PPND study XL184-NC-040. Here, findings included unscheduled deaths (2 mg/kg), decreased body weights, food consumption, organ weights (spleen, uterus, ovary, testes), and microscopic changes in multiple tissues (including bone (physeal hypertrophy, reduced mineral density), lymphoid tissues, GI tract, ovary, testes, uterus). Findings on male reproductive organs were seen at 2 mg/kg/day, being more severe following treatment up to PND70 than PND35. While findings at 1 mg/kg/day were reversible, reversibility at 2 mg/kg was not assessed due to the unscheduled deaths.

Generally, the results indicate that the younger rats (dosed from PND12, corresponding to paediatric age ≤2 years) are more sensitive to cabozantinib-related toxicity, including testicular toxicity, than rats dosed from PND21.

Existing non-clinical data have not revealed significant effect on bone growth. However, reduced bone mineral density and content was observed at exposure levels well below human exposure in the two definitive juvenile toxicity studies. In animals dosed from PND21-70 the finding was not reversed within 4 weeks recovery. Thus, potential effects on bone development cannot be excluded.

The intended patient population for the DTC-indication comprises adults and adolescents from 12 years of age. No new non-clinical studies have been provided to support the variation application, and no further studies are requested. Previously conducted studies in adult and juvenile animals indicate similar target organs for toxicity (GI tract, bone, bone marrow, lymphoid tissues, kidney, adrenal and reproductive tract tissues). No effect was seen in male reproductive organs in juvenile animals dosed from PND21-35/70. When dosed from PND12, however, findings on testes (degeneration and/or atrophy of seminiferous tubules) and epididymis (reduced luminal sperm) were seen at 2 mg/kg/day, being more severe following treatment up to PND70 than PND35.

Histopathological findings of potential relevance for the intended patient population includes reduced bone mineralisation and findings in male and female reproductive organs, without safety margins. While recovery data indicate reversibility of effects in female reproductive organs, reversibility has not been demonstrated for cabozantinib-related effects om bone mineralisation and male reproductive organs. In view of the severity of the disease to be treated, the potential risk of effects on bone mineralisation and delay in sexual maturation is considered acceptable from a non-clinical point of view.

The non-clinical findings are adequately reflected in the proposed SmPC.

Environmental Risk Assessment

Cabozantinib is not a PBT substance. The extension of indication to include patients with locally advanced or metastatic DTC refractory or not eligible to radioactive iodine 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 however, see also "General comments on compliance with GCP", further above.

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

Table 2. Summary of clinical efficacy studies of cabozantinib included in the efficacy analysis set

Study (Region)	Phase	Study Design	Cabozantinib (XL184) Doses[a]	Study Population	No. Subjects Treated	No. Subjects in the Safety Analysis Set	Study Status; Type of Report
XL184-311 CSR (NAM, EU, APAC)	3	Double-blind, randomized, controlled	treatment: 60 mg tablet control: matched placebo	advanced DTC (post-sorafenib or lenvatinib)	125 cabo 62 pbo	125 cabo 62 pbo	Active; CSR
XL184-311 CSR Addendum 1	3	Double-blind, randomized, controlled	treatment: 60 mg tablet control: matched placebo	advanced DTC (post-sorafenib or lenvatinib)	170 cabo 88 pbo	N/A	Active; CSR Addendum

APAC, Asia-Pacific; CSR, clinical study report; EU, European Union; DTC, differentiated thyroid cancer; N/A, not applicable; NAM, North America; pbo, placebo.

2.3.2. Pharmacokinetics

In support of the current variation towards an extension of indication, the MAH submitted the bioanalytical report for Phase 3 study XL184-311 (A1805046.21.INT), the clinical pharmacokinetics analysis report Phase 3 study XL184-311 (XL184-311.PK.001), as well as the population PK Analysis Report (XL184 311.PopPK.001). Results from the clinical pharmacology studies that were included in the original cabozantinib marketing application are not discussed further in this AR.

Bioanalysis

Concentrations of cabozantinib in plasma were analysed using a validated liquid chromatography-tandem mass (LC-MS/MS) method at Alliance Pharma (Malvern, PA, USA).

Pharmacokinetic analysis in Study XL184-311

Cabozantinib plasma concentrations were measured in both the cabozantinib and placebo treatment arms in the pivotal Study XL184-311. PK samples were collected at predose, on Week 3 Day 1 (W3D1), W5D1, and W9D1. All available PK data from enrolled subjects of the 19 August 2020 data cutoff date were included in the PK analysis. The eligible records from a total of 58 placebo subjects were all below the limit of quantification.

A total of 115 subjects in the cabozantinib treatment arm had PK concentrations data, with 293 eligible records in the analysis dataset and were included in the PK analysis. Summary statistics for the observed cabozantinib concentrations collected at planned visit are presented below (**Error! Reference source not found.**).

Table 3. Summary table of cabozantinib plasma PK concentrations by visit for subjects in the cabozantinib arm (Subjects with analysis eligible records[a], Study XL184-311)

Nominal Dose (mg)	Statistics	Concentration (ng/mL) at Scheduled Visit		
		Week 3 Day 1	Week 5 Day 1	Week 9 Day 1
60	N	107	100	86
	Mean	1450	1220	869
	SD	624	671	574
	CV%	43.0	55.1	66.0
	Min	0	0	4.27
	Median	1370	1120	859
	Max	3200	3160	2790

CV%, coefficient of variation; Max, maximum; Min, minimum; PK, pharmacokinetic; SD, standard deviation.

[a] A concentration record had to meet specific requirements to be considered analysis eligible, which included the following: 1) The sample met stability requirements, 2) The PK concentration was not missing, and 3) The PK plasma sample was associated with a planned visit (ie, was not unscheduled or taken during screening).

Mean plasma concentrations for cabozantinib decreased from W3D1 to W9D1. In case PK data were filtered to select analysis eligible records prior to any dose modification from the initial cohort-assigned cabozantinib dose, mean plasma concentrations at W3D1, W5D1 and W9D1 were 1460 ng/mL with CV% of 42.6% [n=94], 1340 ng/mL with CV% of 48.2% [n=66]), and 1190 ng/ml, with CV% of 49.2% [n=28]. Although the arithmetic mean value at W9D1 still appeared lower than that at W3D1the difference was within their respective CV%.

Population PK model

A population pharmacokinetic (PopPK) model of cabozantinib was developed (Study XL184 311.PopPK.001) using nonlinear mixed effects modelling methodology and implemented in the NONMEM software system. The PopPK model of cabozantinib was previously developed using cabozantinib concentration time data from 11 studies in healthy subjects and subjects with different types of malignancies (hepatocellular carcinoma [HCC], renal cell carcinoma [RCC], castration-resistant prostate cancer [CRPC], medullary thyroid cancer [MTC]) to support the submission for cabozantinib in combination with nivolumab in previously untreated (first line) advanced or metastatic RCC (XL184-CA2099ER.PopPK.001).

In the previous PopPK model, cabozantinib concentration-time data following the administration of both cabozantinib capsule and tablet formulations were described by different absorption kinetics and bioavailability between capsule and tablet formulations. For the current submission, the previous cabozantinib PopPK model was updated using cabozantinib PK data from Study XL184-311 combined with PK data from previous cabozantinib studies with the tablet formulation only. In addition, PK data from capsule formulation were not included because they are only relevant to MTC and have different absorption kinetics and bioavailability relative to tablets. Thus, the analysis included 4746 quantifiable PK samples obtained from 1745 subjects from one Phase 1 and six Phase 3 clinical studies with the cabozantinib tablet formulation up to a 60 mg dose (**Table 4**).

Table 4. Studies and number of subjects included in the integrated popPK analysis (Study XL184 311.PopPK.001)

Study Phase	Study No.	Population	Number (%) of Subjects[a]
1	XL184-020[a]	Healthy	63 (3.6)
3	XL184-306	CRPC	41 (2.4)
3	XL184-307	CRPC	498 (28.5)
3	XL184-308	RCC	282 (16.2)
3	XL184-309	HCC	452 (25.9)
3	XL184-311	DTC	101 (5.8)
3	CA2099ER	RCC	308 (17.7)
	Total		1745 (100)

CRPC, castration-resistant prostate cancer; DTC, differentiated thyroid cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

[a] XL184-020 was the only study to have morning dosing and serial PK sampling; other studies had evening dosing and sparse PK sampling.

[b] Includes subjects with at least one quantifiable concentration

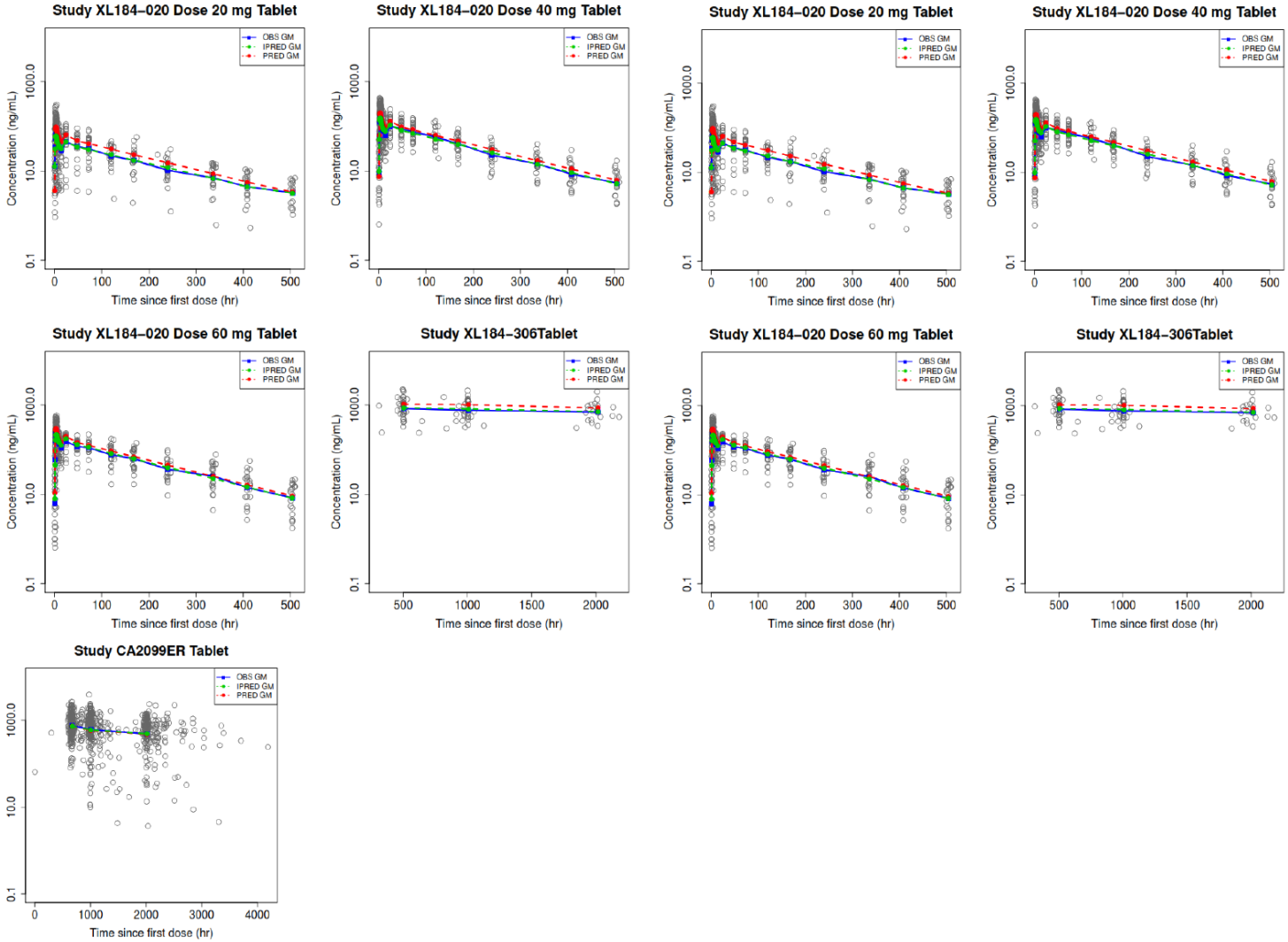
A 2-compartment disposition model with first-order elimination and two parallel absorptions process was used to describe the PK data. The absorption process was described by 1) a slow absorption phase which was described by four transit absorption compartments and 2) a delayed absorption process characterized by a lag time to describe the increase in cabozantinib exposure which was observed approximately 24 hours after the first dose in Phase 1 Study XL184-020.

Base model ETA plots were examined to identify covariate-parameter relationships for inclusion in the full PK model. The covariates body weight on apparent clearance (CL/F) and apparent volume (Vc/F) and sex on CL/F were selected for inclusion into the full model.

Goodness of fit plots for the final (full) model are provided in Figure 3. According to the Applicant, inspection of the figures suggested good agreement between geometric mean observed data and model predicted typical individual and individual values.

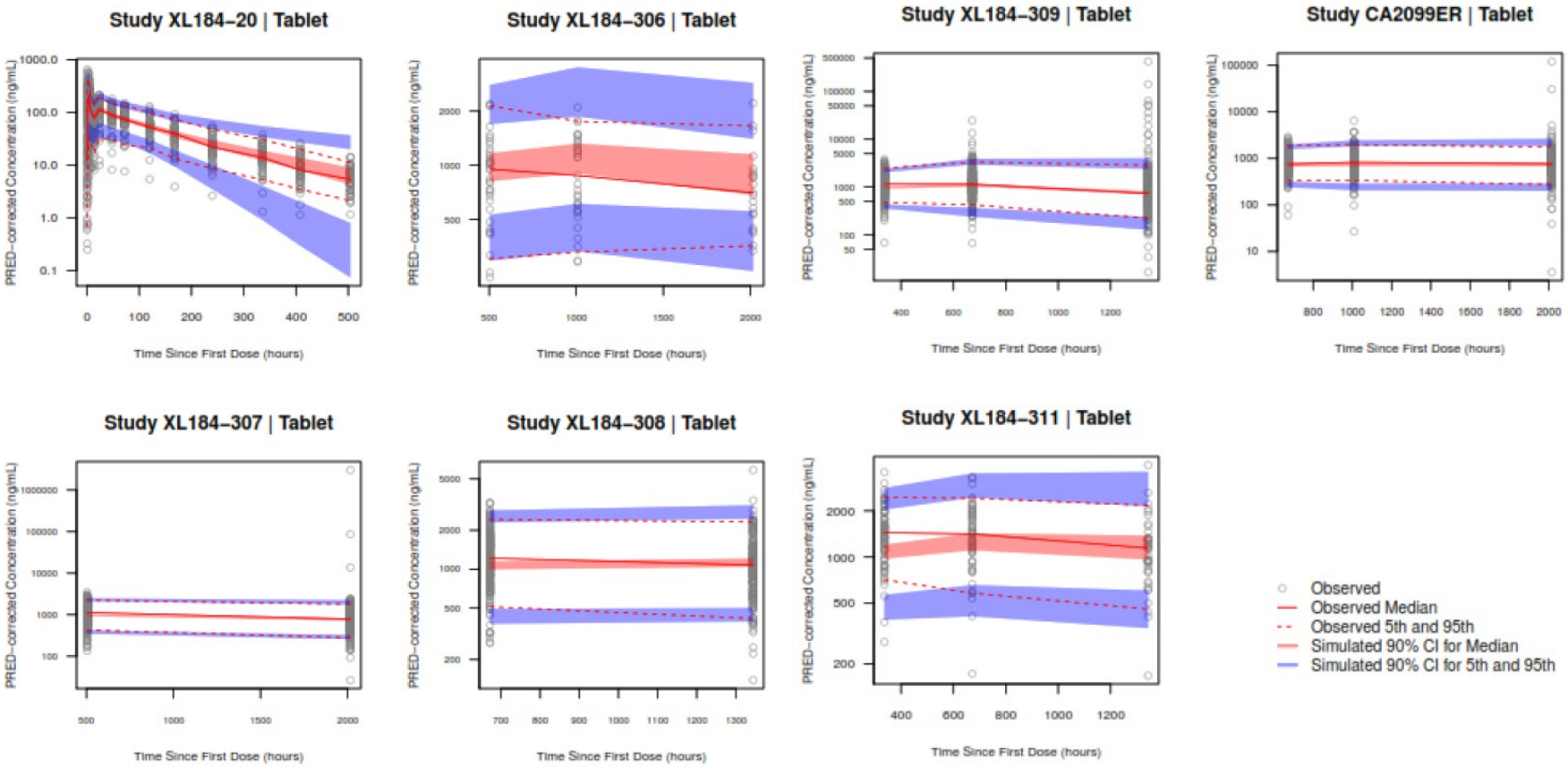
The predictive performance of the final (full) model was evaluated using internal pcVPCs. Prediction-corrected simulated and observed cabozantinib concentration data were used to compute the statistical intervals. According to the Applicant, the results of the internal pcVPCs (Figure 4) showed that the

model was able to adequately predict the 5th percentile, median, and 95th percentile cabozantinib concentration-time profiles for healthy subjects and subjects with various cancer types.



Caption: Black open circles are individual PK observations; blue solid squares and solid blue line are the geometric means of the observations; green solid circle and green dashed line are the geometric mean individual predictions; and red solid circle and red dashed lines are the geometric mean typical individual predictions.

Figure 3. Goodness of Fit plots for the final (full) model by individual clinical study (popPK Study XL184-311.PopPK.001)



Caption: Gray open circles are individual prediction (PRED) corrected PK observations; Lower, middle and upper shaded areas correspond to 90% confidence intervals for the 5th, 50th and 95th percentiles, respectively. Red dashed lines correspond to the observed 5th and 95th percentiles and solid red line corresponds to median of observed data.

Figure 4. Internal prediction-corrected visual predictive check by individual clinical study (popPK Study XL184-311.PopPK.001)

Parameter estimates for the full model are provided in **Table 5.** Separate residual error terms were estimated for healthy subjects and subjects with various cancer types and the residual error estimates were higher for subjects with cancer (36%) compared to healthy subjects (27%). Approximately 74% of the dose was absorbed by the transit absorption pathway and approximately 26% of the dose was absorbed prior to the 24 hour post dose PK sample with a lag time of approximately 19 hours.

Table 5. Full model parameter estimates (Study XL184-311.PopPK.001)

Parameter	Estimate	ASE	RSE	95%CI	Units
CL/F	2.05	0.0323	1.6	(1.98, 2.11)	L/hr
Vc/F	98.8	7.69	7.8	(83.8, 114)	L
Ka	3.39	0.175	5.2	(3.04, 3.73)	hr^{-1}
V3/F	178	4.32	2.4	(170, 187)	L
Q /F	15.5	0.976	6.3	(13.6, 17.4)	L/hr
F1	0.735	0.017	2.3	(0.702, 0.769)	
ALAG4	19.1	0.0404	0.2	(19.1, 19.2)	hr
Weight on CL/F	0.144	0.0614	42.5	(0.0241, 0.265)	
Weight on Vc/F	2.03	0.27	13.3	(1.50, 2.55)	
Female on CL/F	-0.214	0.0268	-12.5	(-0.266, -0.161)	
Residual Variability					
Healthy subjects	26.6	0.598	2.3	(25.4, 27.7)	%
Subjects[a]	36.3	0.615	1.7	(35.1, 37.5)	%
IIV					
CL/F	43.1[b]			(41.0, 45.0)	%CV
Vc/F	100[c]			(88.7, 111)	%CV
Ka	39.3[d]			(31, 46.1)	%CV
OFV	-2290.11				

ASE = asymptotic standard error; RSE = relative standard error; CI = confidence interval; CL/F = apparent clearance; Vc/F = apparent volume of the central compartment; Ka = absorption rate constant; V3/F = apparent volume of distribution of the peripheral compartment; Q/F = apparent flow parameter between compartments; F1 = fraction of dose absorbed from the first absorption depot; ALAG = absorption lag time; IIV = interindividual variability; OFV = objective function value; CV = coefficient of variation

[a] pooled subjects with various cancer types
[b] shrinkage is 19.6%
[c] shrinkage is 66.1%
[d] shrinkage is 82.0%

Typical PK parameters estimated from the final population PK model for a White male, DTC subject with a body weight of 70 kg were as follows: CL/F of 2.05 L/h, Vc/F of 98.8 L, Q/F of 15.5.0 L/h, and Vp/F of 178 L. The inter-subject variability was 43% for CL/F and 100% for Vc/F.

Special populations

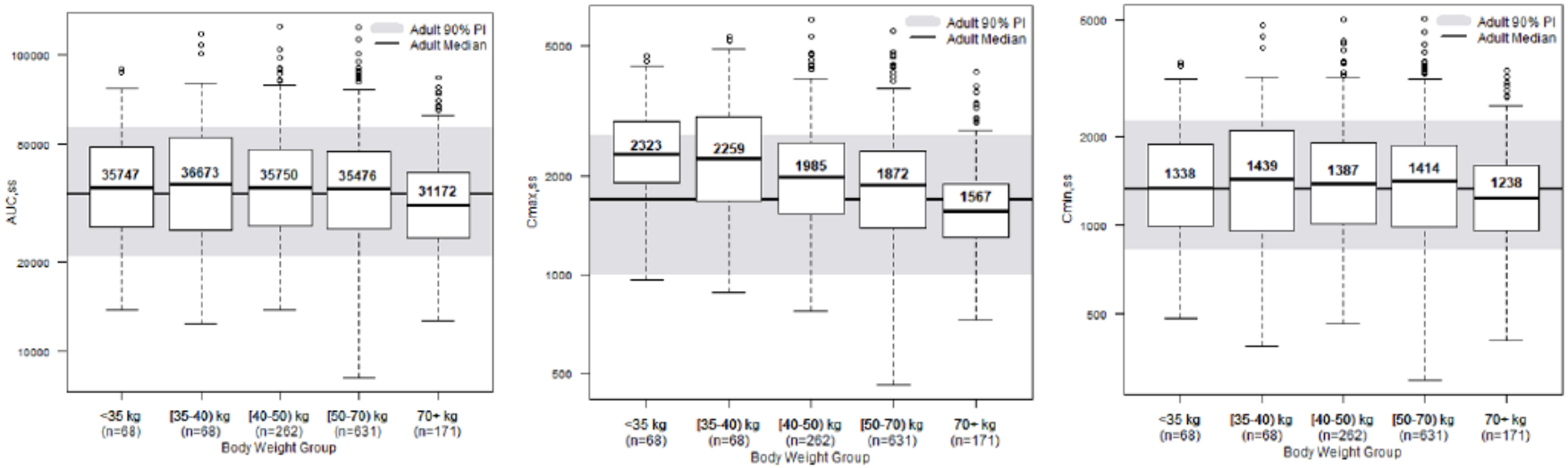
In the popPK model, the impact of covariates was assessed on the steady state area under the concentration-time profile during one dosing interval (AUC(0-24,ss)), the steady state maximum concentrations (Cmax,ss) and the pre-dose plasma concentrations at steady state (Cmin,ss) for specified covariate values (i.e., test conditions) relative to a reference set of covariate values. Specifically, the reference condition was defined as a male subject with DTC and a body weight of 70 kg receiving a 60 mg cabozantinib tablet once daily. The test condition differs from the reference by changing a specific covariate value. All other covariate values were identical to the reference.

- **Adolescents**

There were no adolescent subjects enrolled in Phase 3 Study XL184-311. Therefore, the expected adolescent cabozantinib exposures were extrapolated using the population PK model developed based on the adult data. Two approaches were utilized to estimate the anticipated range of body weight effect on cabozantinib exposures: 1) weight effect based on model estimates and 2) weight effect based on allometric scaling. A total of 1200 adolescents were simulated, with fifty subjects per half-year of age from 12 to 17.5 years (total of 12 age categories) sampled from a normal distribution of body weight for each age and sex based on the CDC growth chart (Kuczmarski et al 2002). Steady-state simulations were performed for the 1200 adolescent subjects using the parameter estimates from the final (full) PK model based on a daily dose of 40 or 60 mg. AUC(0-24,ss), $C_{max,ss}$ and $C_{min,ss}$ exposure metrics were computed and mean values and SD were generated in addition to boxplots. The steady state exposure metrics were summarized by weight groups (i.e., < 35, > 35 to < 40, < 40, ≥ 40 to < 50, ≥ 50 to < 70 kg) for the plots.

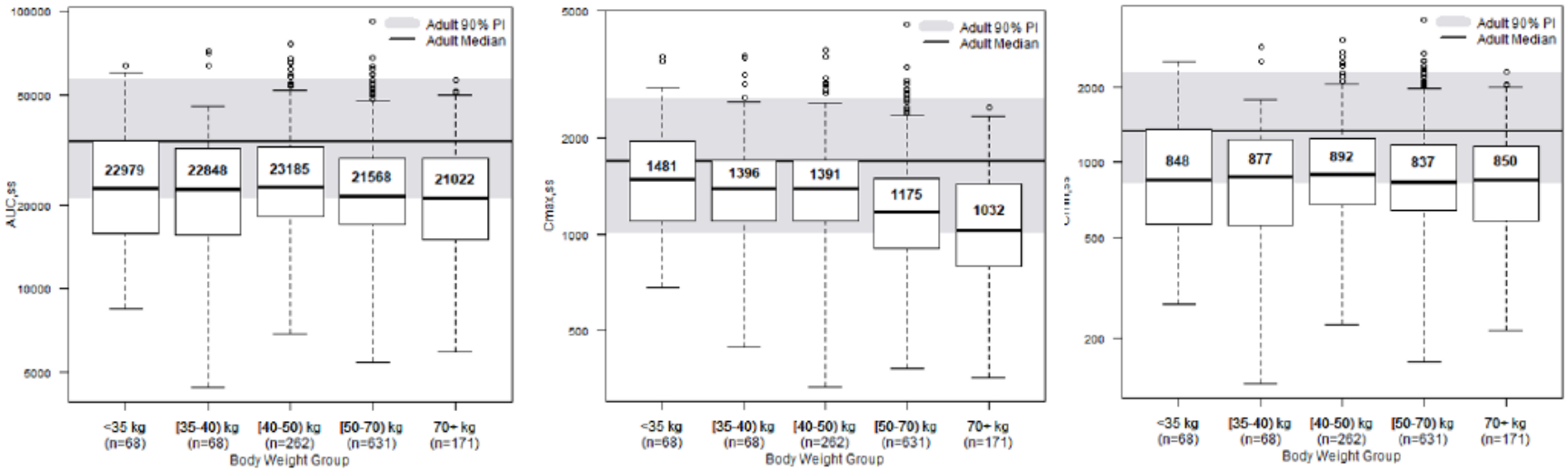
Results of the predicted steady-state exposure in adults and adolescents or various weight receiving a 60 mg or 40 mg dose, using model estimated for the effect of weight is shown in **Figure 5 and Figure 6**.

Results of the predicted steady-state exposure in adults and adolescents or various weight, receiving a 60 mg or 40 mg dose, using allometric scaling, is shown in **Figure 7 and Figure 8**



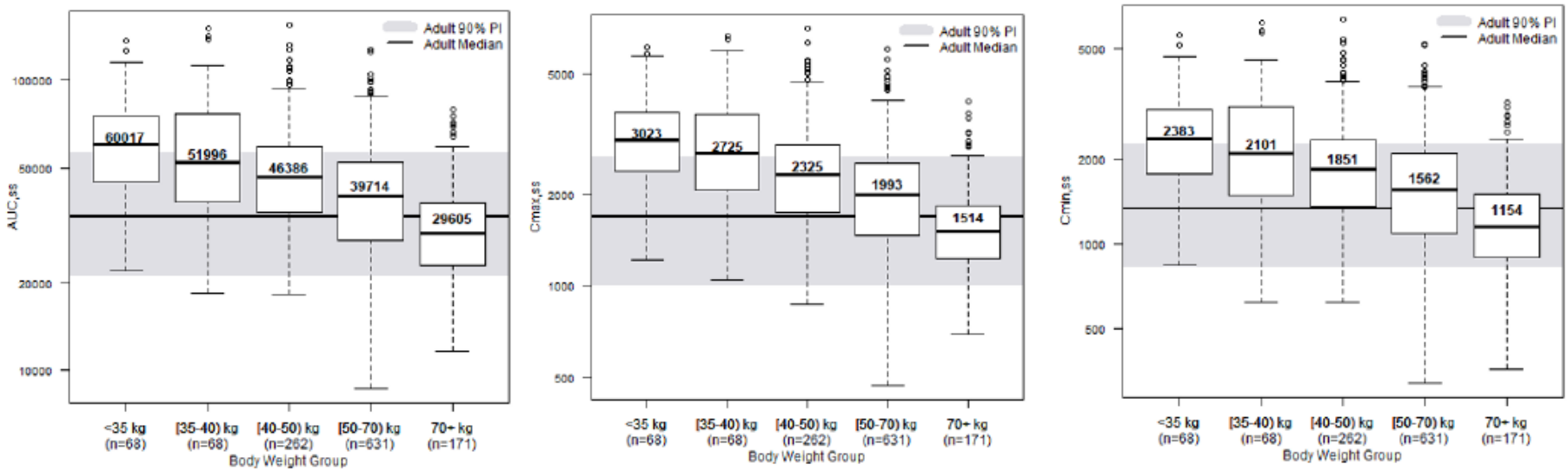
Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box and labeled as the value inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3); the gray shaded region represents the 90% prediction interval of adult reference; solid line through the gray region is the predicted median adult reference.

Figure 5. Predicted steady-state adult and adolescent exposure using the final (full) model (60 mg dose) $AUC_{(0\text{-}24,ss)}$, left, $C_{max,ss}$, mid and $C_{min,ss}$, right (popPK Study XL184-311.PopPK.001)



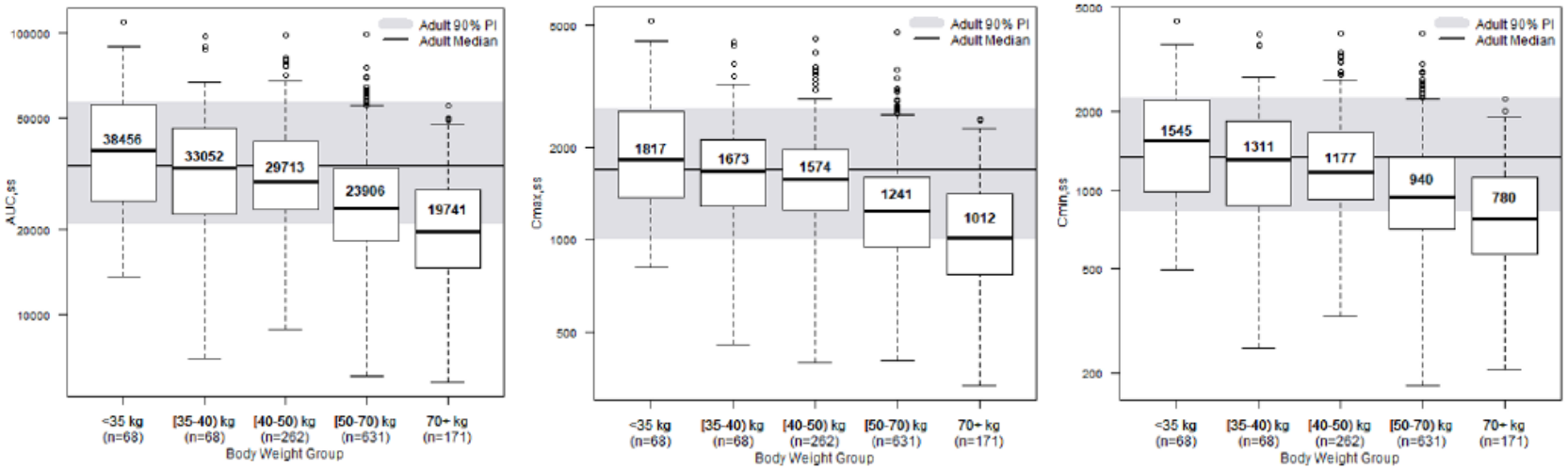
Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box and labeled as the value inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3); the gray shaded region represents the 90% prediction interval of adult reference; solid line through the gray region is the predicted median adult reference.

Figure 6. Predicted steady-state adult and adolescent exposure using the final (full) model (<u>40 mg Dose</u>) $AUC_{(0\text{-}24,ss)}$, left, $C_{max,ss}$, mid and $C_{min,ss}$, right (popPK Study XL184-311.PopPK.001)



Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box and labeled as the value inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3); the gray shaded region represents the 90% prediction interval of adult reference; solid line through the gray region is the predicted median adult reference.

Figure 7. Predicted steady-state adult and adolescent exposure using the final (full) model and allometric scaling (60 mg Dose) $AUC_{(0\text{-}24,ss)}$, left, $C_{max,ss}$, mid and $C_{min,ss}$, right (popPK Study XL184-311.PopPK.001)



Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box and labeled as the value inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3); the gray shaded region represents the 90% prediction interval of adult reference; solid line through the gray region is the predicted median adult reference.

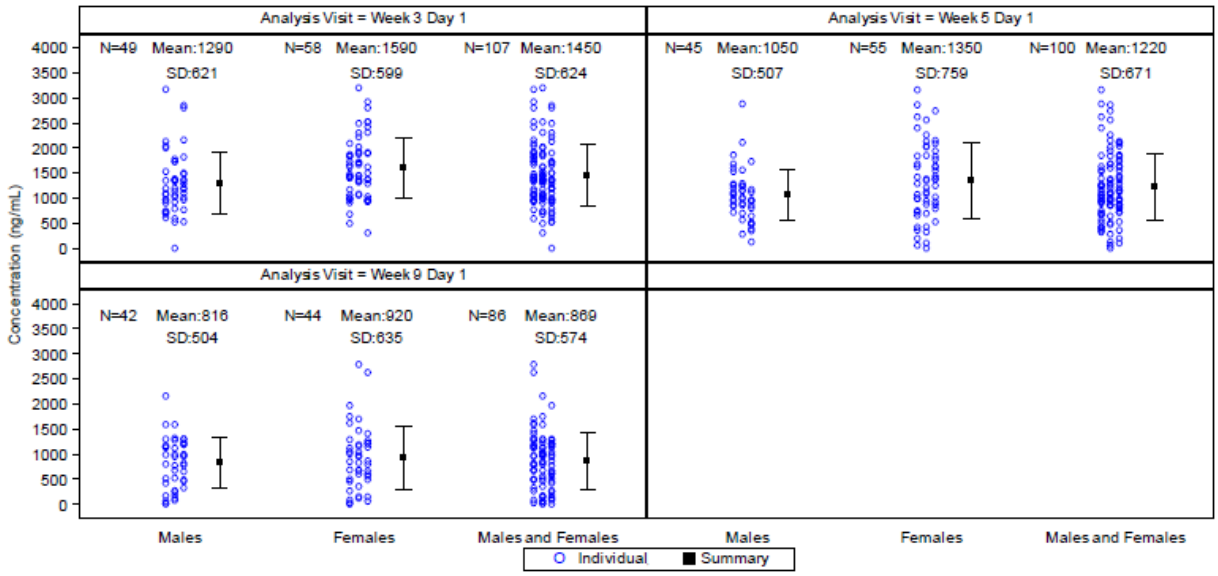
Figure 8. Predicted steady-state adult and adolescent exposure using the final (full) model and <u>allometric scaling</u> (<u>40 mg Dose</u>) $AUC_{(0\text{-}24,ss)}$, left, $C_{max,ss}$, mid and $C_{min,ss}$, right (popPK Study XL184-311.PopPK.001)

Adolescent simulations using the final (full) model parameter estimates predicted similar AUC(0 24,ss) and Cminss but 37% higher Cmaxss in adolescent with body weight < 40 kg receiving 60 mg qd compared to adult subjects receiving the same dose. As expected, the predicted steady state AUC(0-24ss), Cmax,ss and Cmin,ss exposure for adolescent subjects receiving 40 mg qd tended to be on the low side of the range relative to adult subjects receiving 60 mg qd (i.e., the mean of each weight group was lower than for adults); however, Cmaxss for adolescent subjects receiving 40 mg qd and weighing < 40 kg had exposure within the 90% prediction interval of the adult subjects receiving 60 mg qd.

Simulations generated using allometric scaling predicted to have approximately 1.7-fold higher cabozantinib mean exposure (AUC(0-24,ss), Cmaxss and Cminss) in adolescent subjects with body weights < 40 kg and receiving 60 mg qd relative to adult subjects with DTC receiving the same daily dose. The predicted exposure for adolescent subjects < 40 kg receiving 40 mg qd was comparable (within 10% in mean exposures) to that of adult subjects with DTC receiving 60 mg qd. According to the Applicant, extrapolating adolescent exposure using allometric scaling is a conservative representation of the maximum anticipated body weight effect on cabozantinib exposure and could overestimate the effect of body weight on PK.

- **Weight, gender**

In general, in Phase 3 Study XL184-311, the mean cabozantinib plasma concentration values were 1.23-fold, 1.29-fold, and 1.13-fold higher in females than in males at W3D1, W5D1, and W9D1, respectively, though the spread of the standard deviations between males and females overlapped **(Figure 9).**

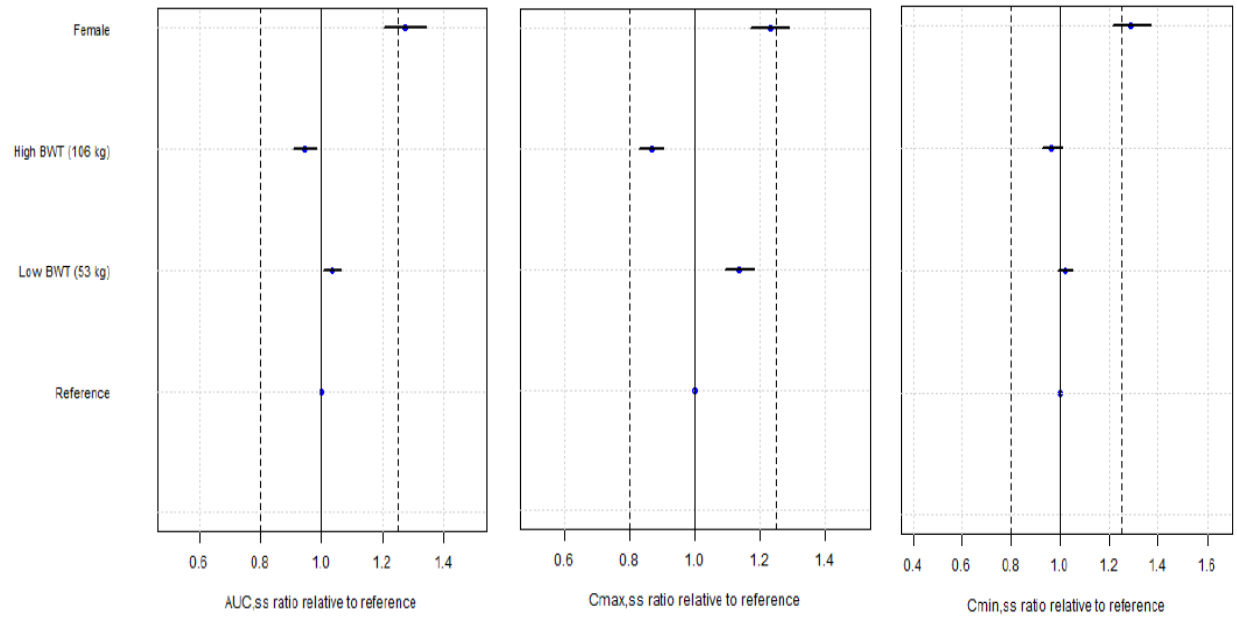


DTC, differentiated thyroid cancer; PK, pharmacokinetic; SD, standard deviation
Closed squares represent arithmetic mean. Error bars represent the SD.
A small offset was added to x-axis values to prevent overplotting of datapoints.
Note: PK samples were to be taken approximately 8 hours or more after the previous dose of cabozantinib. Accurate timing of the sample collection was not deemed critical to the steady-state PK evaluation given the long half-life and low fluctuation of steady-state cabozantinib concentrations.

[a] A concentration record had to meet specific requirements to be considered analysis eligible, which included the following: 1) The sample met stability requirements, 2) The PK concentration was not missing, and 3) The PK plasma sample was associated with a planned visit (ie, was not unscheduled or taken during screening).

Figure 9. Individual and summary (mean ± SD) plasma cabozantinib concentrations plotted versus nominal visit for DTC subjects in the cabozantinib arm (filtered to select analysis eligible records[a]) (Study XL184-311)

In the popPK analysis, for continuous covariates, such as body weight, 5th and 95th percentiles in the integrated analysis dataset (weight: 53 and 106 kg) were used to represent extreme covariate values. The covariate effects on AUC(0-24,ss), Cmax,ss and Cmin,ss, are illustrated as forest plots in **Figure 10,** respectively. Body weight had minimal impact (<14% change) cabozantinib exposure based on predicted AUC(0-24,ss), Cmax,ss, and Cmin,ss values. Only sex showed a slight impact on cabozantinib exposure with approximately 23-29% higher AUC(0-24,ss), Cmax,ss and Cmin,ss values for females.



Note: A reference subject (Reference) is defined as a male subject with DTC and a body weight of 70 kg. Other test conditions are defined as follows: Low BWT: a subject with body weight of 53 kg; High BWT: a subject with body weight of 106 kg.

Blue solid circles show the ratio of the typical parameter value under the test conditions compared to the reference subject, and the line segments represent the corresponding 90% confidence interval. Vertical dashed lines indicate the interval between ratios of 0.8 to 1.25.

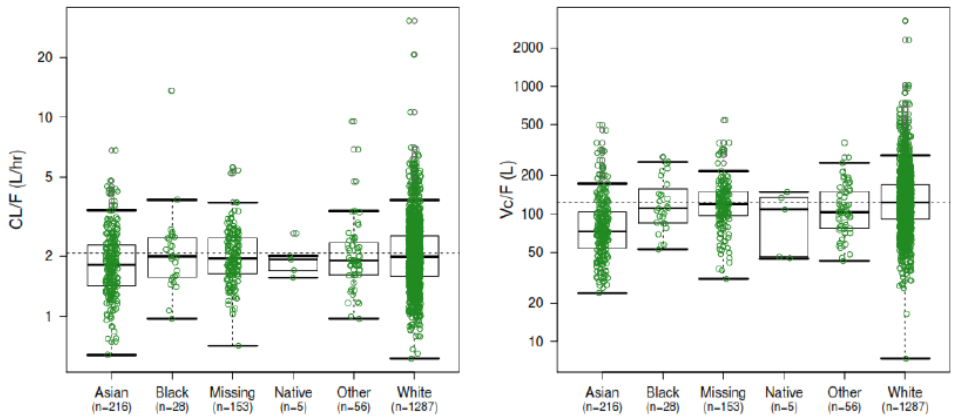
Figure 10. Impact of covariates on AUC(0-24,ss) (left) and $C_{max,ss}$ (mid) and $C_{min,ss}$ (right) (popPK Study XL184-311.PopPK.001)

In the final popPK model, females had 21% lower CL/F than males, which resulted in > 20% higher exposure.

The popPK estimated exponent of body weight effect on CL/F was 0.144, which resulted in minimal impact on predicted steady state cabozantinib exposure.

- **Race**

In the popPK analysis, although the Asian population had lower CL/F and V/F compared with other races based on a post-hoc analysis, the overall range of cabozantinib PK in Asian subjects was overlapping with White subjects (Figure 11). The DTC population, as investigated in Phase 3 Study XL184-311 had similar CL/F and V/F to other cancer types and healthy subjects, suggesting the exposure at steady state were comparable among patients with different tumour types.



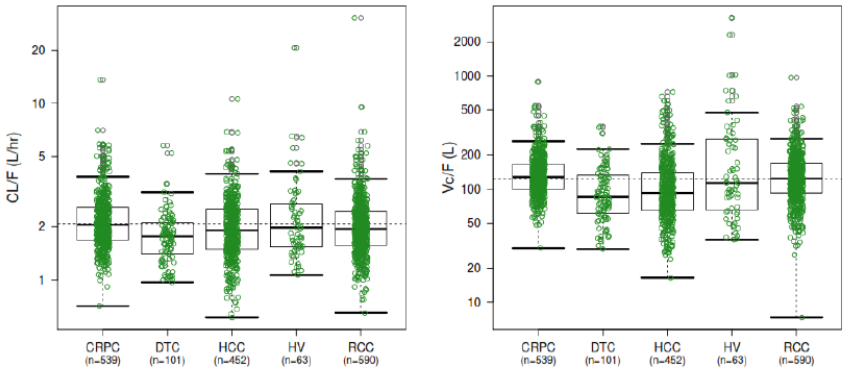
Vc/F = apparent volume; CL/F = apparent clearance; n= number of subjects

Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3) and open green circles represent the predicted values for individual subjects; dashed line represents model estimate for a 78 kg male subject.

Figure 11. Post hoc Estimate of CL/F and Vc/F by Race (popPK Study XL184-311.PopPK.001)

- **Cancer type**

The observed cabozantinib PK exposures in subjects with DTC in study XL184-311 are consistent with those obtained in subjects with HCC and RCC. This is confirmed in the popPK study, where subjects with different cancer types have a slightly lower CL/F and Vc/F relative to healthy subjects. However, the range of cabozantinib PK in DTC was overlapping with subjects with other cancer types **(Figure 12).**



Vc/F = apparent volume; CL/F = apparent clearance; n = number of subjects; CRPC = castration-resistant prostate cancer; DTC = differentiated thyroid cancer; HCC = hepatocellular carcinoma; HV = healthy volunteers; RCC = renal cell carcinoma

Note: Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively; median is shown as a line inside the box; whiskers represent minimum and maximum values that are within 1.5x the inter-quartile range (IQR) below Q1 and above Q3, respectively; black circles represent outliers (values >1.5x IQR below Q1 or above Q3) and open green circles represent the predicted values for individual subjects; dashed line represents model estimate for a 78 kg male subject.

Figure 12. Post hoc estimate of CL/F and Vc/F by cancer type (popPK Study XL184-311.PopPK.001)

Pharmacokinetic interaction studies

No additional drug-drug interaction studies were conducted for this application.

2.3.3. Pharmacodynamics

Mechanism of action

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including the VEGF receptor (VEGFR), MET, AXL, and RET.

Primary and secondary pharmacology

No new clinical pharmacology studies were conducted for this application. Exposure-response analyses were conducted and are presented below.

2.3.4. PK/PD modelling

- **Exposure-effect analysis**

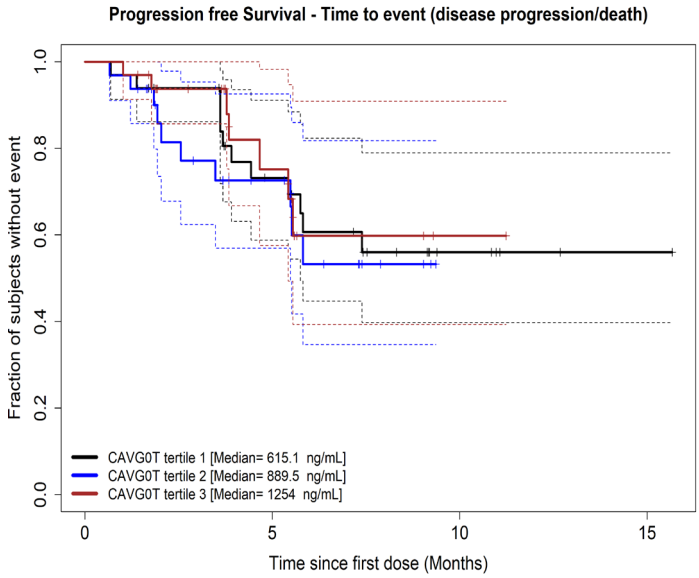
Kaplan-Meier (KM) analysis by cabozantinib exposure tertile was used to investigate the exposure-response (ER) relationship between cabozantinib exposure and clinical efficacy and safety endpoints, and a log-rank test was used to compare the cabozantinib exposure subgroups for each endpoint in DTC subjects from Study XL184-311 (XL184-311.ER.001). The endpoints evaluated were PFS, cabozantinib dose modification, palmar-plantar erythrodysesthesia (PPE), diarrhoea, hypertension, oral mucositis/stomatitis, fatigue/asthenia, and alanine/aspartate aminotransferase (ALT/AST) elevation.

For ALT/AST, the event was derived using clinical laboratory data. The analysis included cabozantinib-treated subjects who received at least one dose of cabozantinib and had at least one measurable cabozantinib concentration available. Of those 125 cabozantinib-treated subjects, 115 subjects had at least one measurable PK concentration. Fourteen out of 115 subjects were excluded from popPK analysis due missed information but were included in the ER analysis and typical PK parameters were used. Cabozantinib exposure was defined as the overall average concentration calculated from time 0 to the time of event or censoring (CAVG0T), which is a time-invariant exposure measure. For the cabozantinib dose modification endpoint, the average concentration over the first week of treatment (CAVG1W) was used to represent cabozantinib exposure to avoid possible correlation between CAVG0T and time of cabozantinib dose modification.

Cabozantinib Exposure Response for efficacy in DTC

For the assessment of PFS, a combined total of 29 subjects had events of disease progression or death out of 98 subjects with at least one quantifiable cabozantinib concentration, a valid baseline tumour assessment and at least one evaluable post-baseline tumour assessment.

KM plots showed no clear relationship observed between the fraction of subjects with progressive disease or death and the different cabozantinib exposure tertiles, as shown in Figure 13. There was no statistically significant difference across the cabozantinib exposure tertiles as shown by log-rank test in **Table *6***.



CAVG0T, predicted average cabozantinib concentration from time zero to the event or censoring time.
Note: Dashed lines represent 95% confidence intervals for each exposure tertile.

Figure 13. Study XL184-311: Predicted survival curves for progression free survival by cabozantinib exposure tertiles

Table 6. Log-rank test for PFS exposure tertiles

Tertile	N	Events Observed	Events Expected	Chi-Square Test	P-Value
1	33	12	12.4	0.542	0.763
2	32	10	8.34		
3	33	7	8.25		

PFS, progression-free survival; N, number of subjects; Event, disease progression or death.

Cabozantinib Exposure Response for safety in DTC

A total of 92 subjects (with at least one quantifiable cabozantinib concentration) had a cabozantinib dose modification out of 114 subjects (80.7%). For the evaluation of dose modification, the cabozantinib exposure over the first week of treatment (CAVG1W) was used. The KM plot showed no clear relationship of the rate of dose modification and cabozantinib exposure tertiles. The log-rank tests also indicated that there was no statistically significant difference across the cabozantinib exposure tertiles.

A total of 55 subjects had an event of PPE (Grade >1) out of 115 subjects. Although the KM plot showed a trend of an increasing frequency of PPE as cabozantinib exposure increase, a log-rank test indicated that there was no statistically significant difference across the cabozantinib exposure tertiles.

A total of 24 subjects (blood pressure data) and 11 subjects (MedDRA) had an event of hypertension (Grade ≥ 3) out of 115 subjects with at least one quantifiable cabozantinib concentration. KM plots showed that a smaller fraction of subjects experienced hypertension (Grade >3, based on blood pressure data) in the lowest cabozantinib tertile compared to the highest exposure tertiles. The log-rank test for hypertension (vital sign data) indicated that there was a statistically significant relationship of cabozantinib exposure with the event rate. The results based on the MedDRA terms indicated that there was no relationship between hypertension and cabozantinib exposure; however, the number of events was too low for a meaningful ER analysis.

Event rates were lower for fatigue/ asthenia (Grade ≥ 3), oral mucositis/ stomatitis (Grade ≥ 3), diarrhea (Grade ≥ 3), nausea/vomiting (Grade >3), and ALT/AST elevation (Grade >3). The KM plot for fatigue/asthenia (Grade ≥ 3) showed that a smaller fraction of subjects experienced fatigue/ asthenia in the lowest cabozantinib tertile compared to the highest exposure tertiles. The log-rank test indicated that there was a statistically significant relationship of cabozantinib exposure with the event rate. Similarly, the rate of oral mucositis/stomatitis (Grade ≥ 3) and diarrhea (Grade ≥ 3) tended to be higher in the higher cabozantinib exposure tertiles; however, no significant relationship with cabozantinib exposure was observed and based on a log-rank test there was no statistically significant difference in the exposure tertiles. KM plots and log-rank tests indicated that there were no statistically significant relationships of cabozantinib exposure with the event rates of nausea/vomiting (Grade >3) or ALT/ AST elevation (Grade >3).

2.3.5. Discussion on clinical pharmacology

Bioanalytical methods. Plasma samples from Phase 3 Study XL184-311 were analysed for cabozantinib using a sufficiently validated LC-MS/MS assay within the previously determined stability period. ISR was conducted and the outcome was compliant with requirements. Further, based on the provided summary of the method validation, QC coverage of the calibration range for the measurement of cabozantinib in human plasma is not aligned to EMA bioanalytical guidance. QCs were applied at 7.5% and 75% of the calibration curve, and a QC sample covering the middle 30-50% portion of the calibration range was missing. However, assay performance at the mid-range was sufficiently demonstrated based on the observed linearity of the calibration curve, as well as accuracy and precision at the 400 mg calibration curve standard and ISR of samples at concentrations around 50% of the calibration curve (0.5-1000 ng/ml).

PopPK model. A popPK model was used to describe the cabozantinib PK in different populations and for covariate analysis. The popPK model included only PK data obtained with the cabozantinib tablet formulation. PK data from capsule formulation were not included because they are only relevant to

medullary thyroid cancer (MTC) and have different absorption kinetics and bioavailability relative to tablets.

The popPK model appears validated to a sufficient extent and provides an adequate description of the cabozantinib PK data following administration of the tablet formulation. The shown GOF plots are somewhat atypical, with only DV-PRED and DV-IPRED plots in the appendix of the popPK study report, but e.g., no PWRES nor IWRES vs time plots. Still, GOF plots indicated that the final model described the observed data adequately in the various treatment scenarios. Further, the visual predictive checks showed that the final model captured both the central tendency and the interindividual variability of cabozantinib PK plasma reasonably well.

In the popPK model, body weight was included as covariate of both CL/F and Vc/F, as power models with estimated exponents. The estimated exponents were far off from the theoretical exponents of allometric scaling, probably due to the fact that larger body weights in the dataset are associated with overweight and obesity and hence not correlated with larger organ sizes.

PK in Phase 3 Study. The observed cabozantinib PK exposures after 3, 5 and 9 weeks of OD dosing of subjects with DTC in Phase 3 study XL184-311 appeared to decrease slightly over time going from Week 3 to Week 9. This decrease is expectedly for a major part caused by dose reduction or interruptions over time.

Adolescents. There were no adolescent subjects enrolled in Phase 3 Study XL184-311. The appropriate dosing regimen for adolescents with different body weights was investigated using popPK. For this purpose, two approaches were utilized to estimate the anticipated range of body weight effect on cabozantinib exposures: 1) weight effect based on model estimates and 2) weight effect based on allometric scaling. A total of 1200 adolescents were simulated, with fifty subjects per half-year of age from 12 to 17.5 years (total of 12 age categories). Steady-state simulations were performed for the 1200 adolescent subjects using the parameter estimates from the final (full) PK model based on a daily dose of 40 or 60 mg. AUC(0-24,ss), Cmax,ss and Cmin,ss exposure metrics were computed and mean values and SD were generated in addition to boxplots. The steady state exposure metrics were summarized by weight groups (i.e., < 35, > 35 to < 40, < 40, ≥ 40 to < 50, ≥ 50 to < 70 kg) for the plots.

In general, based on the currently provided simulations, most of the interquartile weight ranges of predicted cabozantinib exposures for adolescent subjects receiving 60 mg qd dosing regimens fell within the simulated adult exposure associated with a daily dose of 60 mg. However, $C_{max,ss}$ for adolescent subjects weighing <40 kg was slightly higher than adult subjects (median $C_{max,ss}$ was 36% higher) with DTC receiving 60 mg qd. The predicted steady state AUC(0-24,ss), $C_{max,ss}$ and $C_{min,ss}$ exposure for adolescent subjects receiving 40 mg qd tended to be on the low side of the range relative to adult subjects with DTC receiving 60 mg qd; the predicted median exposure in adolescents was 32, 14, and 35% lower than adult for AUC(0-24,ss), $C_{max,ss}$ and $C_{min,ss}$, respectively. However, $C_{max,ss}$ for adolescent subjects receiving 40 mg qd and weighing <40 kg had exposure within the 90% prediction interval of the adult subjects receiving 60 mg qd.

The popPK model with estimated exponents fits the current dataset better than the model with fixed exponents; however, the model with the lowest OFV is not necessarily the best model to use for extrapolation. Allometric scaling with fixed exponents is considered the "best guess" when the model should be used to extrapolate exposure from adults to adolescents. Indeed, this is in line with the approach taken by the Applicant. However, with respect to these simulations with fixed allometric exponents, it appears that the model with fixed components initially used was not fitted to the data. Instead, only the magnitude of the covariate effect of body weight on CL/F and Vc/F was altered, while keeping all other parameter estimates the same. Therefore, in order to assess which model is best

suited for extrapolation, t four different models were compared: Model 1 (current final model), with body weight effect on CL/F and Vc/F and the sec effect on CL/F estimated, Model 2: Model 1 without the effect of sex on CL/F, Model 3: Model 1 but the effect of body weight on CL/F and Vc/F fixed to theoretical exponents of allometric scaling and Model 4: Model 2 but the effect of body weight on CL/F and Vc/F fixed to theoretical exponents of allometric scaling..

These models were evaluated with a focus on how well they describe the PK of subjects in the lower body weight range (e.g., <60 kg). The pcVPCs stratified on study were complemented with pcVPCs stratified on body weight (e.g., <60 kg and ≥60 kg). Overall, the parameter estimation of the four models appears comparable to a reasonable extent, with CL/F within 10% difference. GOF and VPC plots for the new models 2-4 in the lowest weight range <60 kg do not indicate improved fit of the data as compared to the original Model 1. With the limited differences between the fit of the models, simulations with either model is indicated to yield comparable outcome as the original full model. Simulations with the full Model 1, predict that the proposed dose-advice for patients <40 kg and >40 kg yields comparable $C_{max,ss}$ in adolescents to that predicted in adult patients, whereas the $AUC_{0-24,ss}$ and $C_{min,ss}$ in adolescent patients <40 kg are in the lower part of the range predicted in adult patients.

The proposed dose advice based on modelling and simulation with the original full Model 1 is considered sufficiently robust, the dose advice for adolescent patients <40 kg based on this M&S approach is considered acceptable from a PK point of view. The currently proposed dose recommendation in adolescents is based on PK modelling and simulation. Further, the fact that no exposure-efficacy relationship for PFS was observed in adults with DTC, whereas a trend of increased AE rates for some safety endpoints was observed at higher cabozantinib concentrations, was taken into account. A PK modelling and simulation approach in principle may support a different cabozantinib starting dose for adolescents dependent on body weight, based on the aim to obtain comparable exposure. However, in this consideration it is assumed that no relevant differences exist between adolescents and adults with respect to pathophysiology and disease characteristics are present. With respect to PK, no such differences are expected. The situation with respect to expected efficacy and safety is discussed in further sections.

In the SmPC section 5.2, factual information was provided on the predicted cabozantinib plasma concentrations in patients <40 kg at a 40 mg dose and in patients >40 kg at a 60 mg dose, as compared to plasma concentrations in adult patients at a 60 mg dose.

Other special patient populations. *Gender and weight*. In general, in Phase 3 Study XL184-311, the mean cabozantinib plasma concentration values were 1.23-fold, 1.29-fold, and 1.13-fold higher in females than in males at W3D1, W5D1, and W9D1, respectively, though the spread of the standard deviations between males and females overlapped. The popPK estimated exponent of body weight effect on CL/F was 0.144, which resulted in minimal impact on predicted steady state cabozantinib exposure. Therefore, the effect of gender cannot completely be explained by a lower body weight of females. The observed difference in exposure between male and female is comparable to the difference observed for the other cabozantinib indications, and is considered to lack clinical relevance.

Cancer type. The observed cabozantinib PK exposures in subjects with DTC in study XL184-311 are consistent with those subjects with HCC and RCC, and this observation was confirmed by population PK where there were no differences in cabozantinib PK among multiple cancer types. In addition, in adults, there were no clinically relevant effects of body weight, sex, and race on the PK of cabozantinib.

Exposure-effect analyses. Kaplan-Meier (KM) analysis by cabozantinib exposure tertile was used to investigate the exposure-response (ER) relationship between cabozantinib exposure and clinical

efficacy and safety endpoints, and a log-rank test was used to compare the cabozantinib exposure subgroups for each endpoint in DTC subjects.

No ER relationship between average cabozantinib concentration and PFS was observed.

There was a trend of an increase in frequency of PPE (Grade $\geq$ 1) as cabozantinib exposure increased, although not statistically significant. Further, though exposure-safety relationships were inconclusive due to the small number of events for these safety endpoints, higher event rate was observed in higher cabozantinib exposure for these endpoints for Grade $\geq$ 3 fatigue/asthenia, Grade $\geq$ 3 oral mucositis/ stomatitis, and Grade $\geq$ 3 diarrhoea. According to the Applicant, adverse events were manageable by dose modifications.

2.3.6. Conclusions on clinical pharmacology

The cabozantinib pharmacokinetics in support of the requested extension of indication to include patients with DTC has been investigated to a sufficient extent. Cabozantinib PK in DTC patients are comparable to that in other cancer patient populations investigated earlier. Within the present procedure, the MAH submitted modelling and simulation PK data for the age group ≥12- <18 years that indicated that the exposures of cabozantinib between adults and adolescents, using a weight-based cut-off dosing approach, can be considered comparable. These data are included in the SmPC section 5.2.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies were conducted for this variation. The cabozantinib dose of 60 mg qd tablet has received approval for patients with advanced RCC and HCC. Cabozantinib 60 mg qd (as tablets) has also shown preliminary efficacy in an Investigator-sponsored study (ISS) in subjects with DTC. Thus, the initial cabozantinib dose for Phase 3 study XL184-311 was 60 mg qd (tablet formulation).

In Phase 3 Study XL184-311, no ER relationship between PFS and average cabozantinib concentration was observed in DTC subjects supporting a dose of 60 mg QD with or without dose modification (i.e., 40 mg or 20 mg).

No adolescents with DTC were enrolled in Study XL184-311. The PopPK model based on adult data was used to extrapolate the adolescent cabozantinib exposure and provided a rationale for dose selection for the adolescent population with low body weight < 40 kg (see section 'Adolescents' under 'Special patient population' in the PK assessment part of this AR). Based on popPK simulations the chosen dose for an adolescent with body weight < 40 kg is 40 mg QD. The dose of 60 mg QD was chosen for an adolescent with body weight ≥ 40 kg as the predicted exposure for this body weight group is similar to an adult population.

Main study

Title of Study

Study XL184-311 (COSMIC-311)

A Phase 3, randomised, double-blind, placebo-controlled study of cabozantinib (XL184) in subjects with radioiodine-refractory Differentiated Thyroid Cancer (DTC) who have progressed after prior VEGFR-targeted therapy, see study design in Figure 14 below.

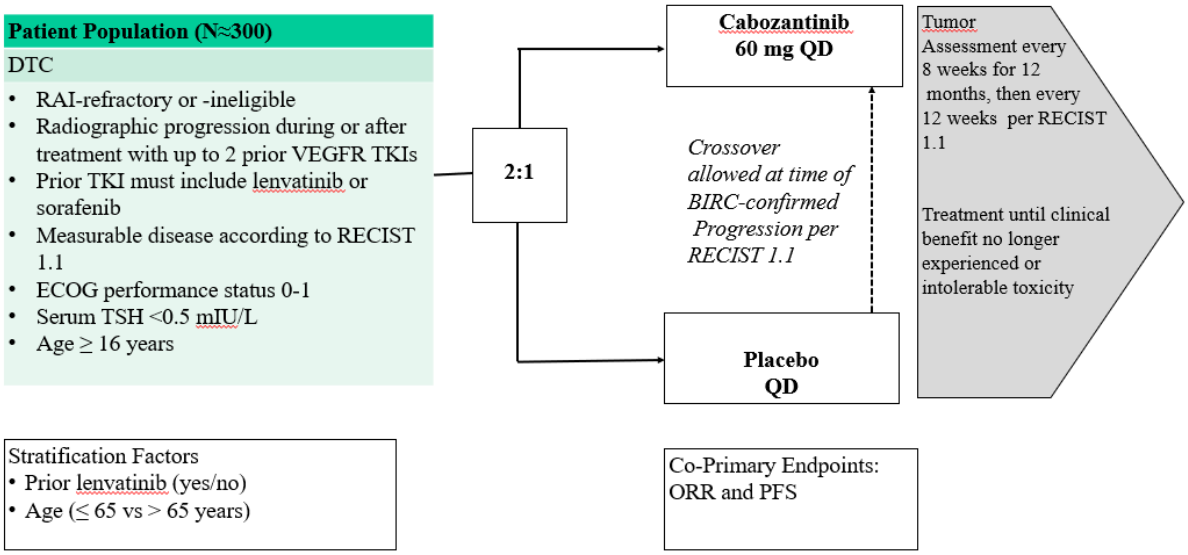


Figure 14. Study design of Study XL184-311

Abbreviations: BIRC=blinded independent radiology committee; DTC=differentiated thyroid cancer; ECOG=Eastern Cooperative Oncology Group; QD=once daily; ORR=objective response rate; PFS=progression-free survival; RAI=radioiodine (radioactive iodine); RECIST=Response Evaluation Criteria in Solid Tumors; TKI=tyrosine kinase inhibitor; TSH=thyroid stimulating hormone; VEGFR=vascular endothelial growth factor receptor

*Of note, it is stated in the figure that ORR and PFS are co-primary endpoints, however, it is more correct to denominate them as multiple primary endpoints.

Methods

Study participants

Inclusion criteria:

1. Histologically or cytologically confirmed diagnosis of DTC,

2. Measurable disease according to RECIST 1.1 on CT/MRI performed within 28 days prior to randomization

3. Must have been previously treated with or deemed ineligible for treatment with Iodine-131 for DTC

4. Must have been previously treated with at least one of the following VEGFR-targeting TKI agents for DTC: lenvatinib or sorafenib (up to two prior VEGFR-targeting TKI agents were allowed including, but not limited to, lenvatinib and sorafenib)

5. Must have experienced documented radiographic progression per RECIST 1.1 per the Investigator during or following treatment with a VEGFR-targeting TKI prior to starting the next anticancer therapy (which may have been treatment in this study)

6. Recovery to baseline or ≤ Grade 1 (Common Terminology Criteria for Adverse Events Version 5 [CTCAE v5]) from toxicities related to any prior treatments, unless AE(s) were clinically non-significant and/or stable on supportive therapy

7. Age ≥ 16 years old on the day of consent

8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1

9. Adequate organ and marrow function

10. Must have received thyroxine suppression therapy, and TSH must have been below the lower cut-off of the reference range or less than 0.50 mIU/L (< 0.50 µIU/mL), whichever was lower, within 28 days before randomization (if hormone replacement therapy was tolerated a TSH level of ≤ 0.1 mIU/L was targeted)

11. Capable of understanding and complying with the protocol requirements and signed informed consent (or informed assent and parental/guardian consent for subjects < 18 years of age)

12. Sexually active fertile subjects and their partners must have agreed to use highly effective methods of contraception.

13. Female subjects of childbearing potential must not have been pregnant at screening.

Exclusion Criteria

1. Prior treatment with any of the following: Cabozantinib; Selective small-molecule v-raf murine sarcoma viral oncogene homolog B1 (BRAF) kinase inhibitor; More than 2 VEGFR-targeting TKI agents; More than 1 immune checkpoint inhibitor therapy; 1 systemic chemotherapy regimen (given as single agent or in combination with another chemotherapy agent)

2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever was longer, before randomization

3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization

4. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization.

5. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before randomization.

6. Concomitant anticoagulation with oral anticoagulants or platelet inhibitors

7. The subject had uncontrolled, significant intercurrent or recent illness

8. Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Complete wound healing from major surgery must have occurred 4 weeks before randomization and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before randomization. Subjects with clinically relevant ongoing complications from prior surgery were not eligible.

9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization. If a single ECG showed a QTcF with an absolute value > 500 ms, two additional ECGs

at intervals of approximately 3 min were performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF were used to determine eligibility.

10. Pregnant or lactating females

11. Inability to swallow tablets

12. Previously identified allergy or hypersensitivity to components of the study treatment formulations

13. Diagnosis of another malignancy within 3 years before randomization, except for superficial skin cancers, or localized, low-grade tumours deemed cured and not treated with systemic therapy

Treatments

Subjects received blinded study drug once daily, orally at bedtime. Study drug consisted of tablets containing 60 mg of cabozantinib or matched placebo. Cabozantinib/placebo was given in clinic on W1D1 and taken once daily at home thereafter until study treatment was discontinued.

Two dose reductions, in decrements of 20 mg cabozantinib or matched placebo, were permitted to manage or prevent worsening of an AE or toxicity. Subjects could be re-escalated to the previous dose (but not higher than 60 mg/day) at the discretion of the Investigator and agreement of the Sponsor for AEs resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose interruptions of study treatment for any reason were allowed for up to 8 weeks. Restarting treatment after interruptions longer than 8 weeks was permitted with approval of the Sponsor. All study treatment had to be discontinued if a once daily dose of 20 mg cabozantinib/matched placebo (minimum dose) was not tolerated.

Antiemetics and antidiarrheal. Granulocyte colony-stimulating factors (G-CSF or GM-CSF) were allowed if used per clinical guidelines (e.g., ASCO or ESMO guidelines). Bisphosphonates or denosumab. Transfusions and hormone replacement (including TSH-suppressive thyroid hormone therapy). Individualised anticoagulation therapy with low dose LMWH was allowed if clinically indicated for supportive treatment and the benefit outweighed the risk per the Investigator’s discretion.

Erythropoietic-stimulating agents (e.g., epoetin alfa and darbepoetin alfa) were not to be used. Co-administration of strong CYP3A4 inducers or inhibitors was to be avoided, per the current SmPC. Any systemic NPACT (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of DTC) were prohibited. Therapeutic doses of oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) were also not allowed.

Objectives

The objective of this study was to evaluate the effect of cabozantinib compared with placebo on progression-free survival (PFS) and objective response rate (ORR).

Outcomes/endpoints

Primary endpoints:

- PFS per RECIST 1.1 by BIRC

Defined as time from randomisation to the earlier of either Progression Disease (PD) per BIRC per RECIST 1.1 or death from any cause in the ITT population.

- ORR per RECIST 1.1 by BIRC

Defined as the proportion of subjects with a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1. by BIRC. The confirmation must have occurred at least 28 days after the response of CR or PR was observed. The primary analysis of ORR was limited to the first 100 randomised subjects (OITT population).

Secondary endpoints:

- Overall survival (OS) - defined as the time from randomisation to death due to any cause.
- Duration of objective tumour response - defined as the time from the first documentation of objective response by BIRC or by the Investigator (subsequently confirmed at a visit ≥ 28 days later) to disease progression or death due to any cause.
- Safety and tolerability
- Pharmacokinetics (PK) of cabozantinib
- Relationship of baseline and post-baseline changes in serum thyroglobulin (Tg)
- Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

Radiographic response and radiographic PD were determined using RECIST 1.1. For the purpose of determining the study endpoints of PFS, response rates, and duration of response (DOR), central review of radiographic images were conducted by a BIRC. The BIRC comprised board-certified radiologists who determined radiographic responses and progression following randomisation. Two primary readers were to assess independently each case in a dual read. The Primary Readers were responsible for all aspects of the read of a case, including target and non-target lesion selection and lesion contours and measurements. If the dual primary independent assessments were discordant a third radiologist were to serve as adjudicator to determine which of the reads was to be accepted. To minimize the potential introduction of bias, these individuals did not have any direct contact with the study site personnel or subjects. All radiographic tumour assessments (both scheduled and unscheduled) were sent to the BIRC, which also reviewed prior radiation history data for the purpose of selection of target lesions. To ensure image consistency, the same imaging modalities used at screening were used for subsequent tumour assessments after randomisation.

Clinical deterioration or radiographic progression determined by the Investigator were not to be considered as events for the primary analysis. The recorded date of radiographic progression was the date of the tumour assessment visit at which progression was declared. If multiple scan dates were associated with a tumour assessment visit, the earliest assessment date within the set was chosen as the progression date. Only adequate tumour assessments (ATAs) were considered in the determination of radiographic progression and censoring dates. An ATA was defined as one that resulted in a time point assignment of response (CR or PR), stable disease (non-CR/non-PD), or progression. For PFS, ATA was based on soft tissue evaluation by CT/MRI.

Radiographic tumour assessments included computed tomography (CT) or magnetic resonance imaging (MRI) scans and bone scans. CT/MRI scans of the chest, abdomen, pelvis, and neck (CAPN) were assessed at screening and every 8 weeks (± 7 days) after randomisation during the first 12 months on study, then every 12 weeks (±14 days) thereafter. An MRI (or CT) of the brain was performed in all subjects at screening. After randomisation, scans of the brain were only required in subjects with known brain metastasis following the same post-baseline frequency as the imaging for CAPN. Whole body bone scans were acquired for all subjects at screening using a technetium-99 (99Tc) bone seeking radiopharmaceutical; follow-up scans were performed every 24 weeks (± 14 days) thereafter only for subjects who had documented bone metastases.

Radiographic tumour assessments were acquired according to the protocol-defined schedule irrespective of whether study treatment was given, reduced, held, or discontinued including for subjects randomised to placebo who crossed over to receive cabozantinib. Tumour assessments continued until the later of Investigator-assessed radiographic disease progression per RECIST 1.1 that was confirmed by BIRC or the date of the decision to permanently discontinue study treatment. Bone scan findings alone were not used for the determination of progression or response per RECIST 1.1 and required corroboration by CT or MRI.

Sample size

The study was designed to provide adequate power for both primary endpoints of ORR and PFS, employing a modified Bonferroni procedure (see section below on Interim analyses/Multiplicity). It was estimated that 100 subjects would be adequate to evaluate the co-primary endpoint of ORR alone, and 300 subjects would be needed to evaluate the primary endpoint of PFS. To allow for an earlier evaluation of ORR, this study employed a "trial within a trial design", where the primary analysis of ORR was limited to the first 100 subjects randomized to the study, defined as the OITT population. Analysis of ORR was expected to occur 6 months after the last subject was enrolled in this population. The study was to proceed to full enrolment of 300 subjects irrespective of the results of the ORR analysis in the OITT population.

For ORR, it was calculated that 100 subjects would provide more than 90% power to reject the null hypothesis of no difference in ORR, assuming a true ORR of 2% in the placebo arm and 35% in the cabozantinib, a 2:1 allocation ratio, and a 2-sided alpha of 0.01, using a test of difference in proportions with a pooled variance estimate.

For PFS, assuming exponential distribution, proportional hazards, and a 2:1 treatment allocation ratio (cabozantinib:placebo), it was calculated that 193 events would be required to provide 90% power to detect an HR of 0.61 using the log-rank test and a 2-sided significance level of 0.04. This corresponds to a 36% reduction in the risk of progression or death, or a 64% improvement in median PFS from 5.5 months to 9.0 months. With a constant accrual rate of 20 subjects per month, a total of 300 subjects (200 in the cabozantinib arm, 100 in the placebo arm) was estimated to be needed to observe the required number of PFS events within the planned study duration (15 months accrual; approximately 20 months to observe the required events).

Under this design and with the application of the fallback method the minimum observed effects that would result in statistical significance for PFS tested at the 5% or 4% level are presented below:

Alpha-level	Analysis	Information Fraction	p-value	HR	Median PFS (months)	
					Placebo	Cabozantinib

5%	Interim	43%	0.0013	0.474	5.5	11.6
	Final	100%	0.0496	0.742	5.5	7.4
4%	Interim	43%	0.0008	0.469	5.5	11.7
	Final	100%	0.0397	0.738	5.5	7.5

Randomisation

Subjects who met all study eligibility criteria were randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd)
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomisation was stratified by:

- Receipt of prior lenvatinib (yes vs no)
- Age at informed consent (≤ 65 years vs > 65 years)

Blinding (masking)

This was a double-blind study. For the crossover phase the Investigator could un-blind individual subjects with BIRC-confirmed radiographic PD via the IRT system.

Statistical methods

The following analysis sets were used for the analyses:

- The Intent-To-Treat (ITT) population was defined as all randomised subjects regardless of whether any study treatment or the correct study treatment was received. The Overall Response Rate Intent-To-Treat (OITT) population was defined as the first 100 ITT subjects.
- The Safety population was to include all randomised subjects who received any amount of study treatment (either cabozantinib or cabozantinib-matched placebo). Analyses based on the Safety population was to be performed according to the actual treatment received. Subjects who received both treatments in error was to be summarised in the cabozantinib group.
- The Overall response rate Safety (O-Safety) population was to include the subjects included in the OITT population receiving any amount of study treatment (either cabozantinib or cabozantinib-matched placebo).

Primary efficacy analyses

The multiple primary efficacy endpoints for this study were PFS in the ITT population and ORR in the OITT population, both per BIRC. Formal hypothesis tests were planned for these endpoints and the primary objectives of the study was to be declared as met if at least one hypothesis was rejected at its respective alpha level. All other statistical evaluations of efficacy were to be considered exploratory. An interim analysis for PFS was planned at the time of the primary analysis of ORR.

ORR: The difference in proportions between treatment conditions in subjects in ORR (best overall response of confirmed complete or partial response) per RECIST 1.1 in the targeted patient population was defined by the primary estimand with the attributes summarised in **Table 7**.

Table 7. Primary Estimand Attribute for ORR

Estimand attribute [1]	**Primary definition for study**	
Population	Subjects randomized into the study intended to include patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeted therapy.	
Endpoint	Radiographic response per RECIST 1.1	
Intercurrent events	**Event**	**Strategy**
	Receipt of assigned study treatment	Treatment policy
	Receipt of local radiation to bone	Treatment policy
	Surgical resection of non-target tumor lesions	Treatment policy
	Death	Treatment policy
	Loss to radiographic follow up	Treatment policy
	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy
	Surgical resection of target tumor lesions	While on treatment*
	Receipt of systemic non-protocol anti-cancer medications	While on treatment*
	Receipt of local non-protocol anti-cancer medications for disease under study	While on treatment*
	Receipt of local radiation to soft tissue for disease under study	While on treatment*
Population summary	Difference in proportions of subjects with a best overall response of confirmed complete response or confirmed partial response per RECIST 1.1 between treatment conditions.	
Estimator	Fisher's exact test	

* A modified version of the "while on treatment" strategy is employed for these intercurrent events. Only data prior to the occurrence of these intercurrent events is of interest, but under the ITT principle, receipt of study treatment itself is not considered.

The primary analysis of ORR was based on tumour assessments per BIRC and included all subjects in the OITT population. Hypothesis testing for ORR was to be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance. If the p-value for the test was less than the set alpha level, and the point estimate for ORR in the cabozantinib arm was higher than that in the placebo arm, the null hypothesis of no difference in ORR was to be rejected. If a sufficient number of responders were observed, analysis using the Cochran-Mantel-Haenszel (CMH) method to adjust for stratification factors per IRT could also be conducted. Point estimates of ORR for each treatment arm, the difference in ORR between the two treatment arms, and associated confidence intervals, the odds ratio and its confidence intervals, were to be provided. The 2-sided 95% and 99% CIs for the point estimates, corresponding to the alpha level used for hypothesis testing, were to be calculated using exact methods. Likewisse the 2-sided 95% and 99% CIs for the difference in ORR between the two treatment arms and for the odds ratio were to be calculated by asymptotic methods.

Sensitivity analyses for ORR planned to be performed included ORR based on tumour assessments per RECIST 1.1 per investigator, and concordance in ORR assessment between BIRC and investigator was to be summarised for the OITT population. In addition, ORR was also to be analysed descriptively for the ITT population at the time of final PFS analysis, and Waterfall plots displaying maximum percent tumour reduction since baseline in target lesions generated, for tumour assessment data on or before the progression/censoring date of the respective PFS analyses, per BIRC and per investigator.

The disease stabilisation rate (DSR) defined as the sum of ORR and proportion of subjects with stable disease for at least 15 weeks was also to be summarised for the ITT population, and the odds ratio provided with corresponding 95% confidence interval. The ORR may also be summarised for crossover

subjects during their course of treatment with open-label cabozantinib for the ITT population upon observance of sufficient responses.

PFS: For Progression-Free Survival (PFS), the primary efficacy analysis was to include all subjects in the ITT population. The recorded date of radiographic progression was the earliest assessment date associated with the tumour assessment visit at which progression was declared. Only adequate tumour assessments (ATAs) were to be considered in the determination of radiographic progression and censoring dates. An ATA was defined as one that resulted in a time point assignment of: response (complete or partial), stable disease/(non-CR, non-PD), or progression. For PFS, ATA was based on soft tissue evaluation by CT/MRI.

The primary estimand for PFS was the difference in survival functions between treatment conditions in the duration of radiographic progression-free survival in the targeted population, with the attributes summarised in **Table 8** .

Table 8. Primary Estimand Attribute for PFS

Estimand attribute [1]	**Primary definition**	
Population	Subjects randomized into the study intended to include patients with radioiodine-refractory DTC who have progressed after prior VEGFR-targeted therapy.	
Endpoint	Duration of radiographic progression-free survival	
Intercurrent events	**Event**	**Strategy**
	Receipt of assigned study treatment	Treatment policy
	Clinical deterioration	Treatment policy
	Receipt of local radiation to bone	Treatment policy
	Surgical resection of non-target tumor lesions	Treatment policy
	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy
	Surgical resection of target tumor lesions	Hypothetical
	Receipt of systemic non-protocol anti-cancer medications	Hypothetical
	Receipt of local non-protocol anti-cancer medications for disease under study	Hypothetical
	Receipt of local radiation to soft tissue for disease under study	Hypothetical
Population summary	Difference in survival functions between treatment conditions.	

Two alternative estimands for PFS were defined, arising from changes in strategy for handling some intercurrent events:

Alternative estimand 1 changed the strategy for the intercurrent events; *Surgical resection of target tumour lesions, Receipt of systemic non- protocol anti-cancer medications, Receipt of local non-protocol anti-cancer medications for disease under study*, and *Receipt of local radiation to soft tissue for disease under study*, to "composite" where they count as events instead of leading to censoring, resulting in an endpoint that comprises radiographic and clinical progression (as well as death).

Alternative estimand 2 changes the strategy to "composite" only for *systemic non- protocol anti-cancer medications*, yielding an endpoint that comprises radiographic progression, death, or initiation of systemic NPACT.

The primary analysis of PFS (designated PFS-EP-1) was event-based and was to be conducted after at least 193 events had been observed in the ITT population (progression per RECIST 1.1 per BIRC or deaths), with actual critical values will depend upon the true number of events observed at each analysis, at either a 2-sided α=0.04 or 0.05 level of significance as per the testing strategy. The hypothesis testing between the two treatment arms was to be performed using a log-rank test with stratification factors as in the randomisation; Receipt of prior lenvatinib (yes or no), and Age at informed consent (≤ 65 years vs. > 65 years), as recorded in the IRT. If the p-value for the stratified

log-rank test was less than the critical value and the hazard ratio was less than one, the null hypothesis was to be rejected and PFS inferred to be superior in the cabozantinib arm compared to the placebo arm. The median duration of PFS and the associated 96% or 95% confidence interval (CI) for each treatment arm was to be estimated using the Kaplan-Meier method. The stratified hazard ratio (HR) and its 96% or 95% CI was to be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomisation stratification factors as were used for the log-rank test. The above analysis will also be provided for the OITT population.

PFS sensitivity analyses: Sensitivity analyses were planned to evaluate the impact of different assumptions or conditions that potentially influence the estimate of the primary estimand (PFS-EP-1).
PFS-EP-2 evaluated the influence of potentially inconsistent tumour assessment intervals between arms, by assigning the date of the scheduled visit as the event date, rather than the date of recorded progression.
PFS-EP-3 evaluated the influence of the assessor of radiographic progression, and was based on RECIST 1.1 evaluations by the investigator rather than the BIRC.
PFS-EP-4 evaluated the influence of the missing tumour assessments, by classifying subjects who experience ≥ 2 consecutive missing scheduled ATA immediately prior to documented radiographic progression as having an event at the date of the last ATA prior to the missing visits, rather than being censored.

Three supplemental analyses directed at the two alternative estimands for PFS were to be carried out; the primary analysis of alternative estimand 1, and 2, respectively (PFS-EA1-1, PFS-EA2-1), and a sensitivity analysis of alternative estimand 2, similar to PFS-EP-4 defined above (PFS-EA2-2).

Four additional "differential" sensitivity analyses based on the primary analysis (PFS- EP-1) were to be conducted to evaluate the impact of potentially informative censoring, with selected censored subjects re-classified as events, differentially by treatment arm. In all of these (PFS-EP-11, PFS-EP-12, PFS-EP-13, PFS-EP-14), rPD by Investigator but not BIRC, was assigned as an event at date of first rPD in the experimental arm, and in one also in the control arm (PFS-EP-13). Discontinuation of radiographic assessment for reason other than rPD and without systemic non-protocol anti-cancer therapy, was as an event at last ATA (PFS-EP-11, PFS-EP-12, PFS-EP-13, PFS-EP-14). Systemic non-protocol anti-cancer therapy (sNPACT) prior to rPD (INV or BIRC), was assigned as an event at first sNPACT in Experimental and Control arm (PFS-EP-12), or only control arm (PFS-EP-14).

All sensitivity and supplemental analyses were to include all subjects in the ITT population. Tabulated summaries of survival times, hazard ratios, and log rank test statistics as well as graphs of survival functions was to be presented.

The concordance in assessment of radiographic progression and the date between BIRC and investigator was to be summarised for the ITT population.

Secondary efficacy analyses

Overall survival: OS was defined as the time from randomisation to death due to any cause. Subjects who were lost to follow-up, withdrew consent from survival follow-up or were alive on or after the data cutoff were to be right censored. The analysis of OS was to include all subjects in the OITT and ITT populations and summaries (median and 95% CI for median, stratified and unstratified HRs and their 95% CI) and graphs as described for primary analysis of PFS were to be generated. Log-rank p- values were to be calculated for descriptive purposes (formal inferences not drawn). If the null hypothesis for ORR was rejected an administrative interim analysis of OS was to be performed with the primary purpose of evaluating the potential for detriment to survival with cabozantinib treatment.

A sensitivity analysis for OS in the ITT population was to be conducted, censoring for receipt of any subsequent anti-cancer therapy. An exploratory OS analysis for the ITT population was to be conducted adjusting for crossover of placebo subjects to cabozantinib as a time-dependent covariate. Additional exploratory OS analysis may also be conducted to adjust for the crossover to cabozantinib utilizing the inverse probability of censoring weights (IPCW) or rank preserving structural failure time model (RPSFTM), if feasible.

Duration of objective response was to be analysed similar to PFS for OITT and ITT populations.

Time to objective response was defined as the time from randomisation to the first documentation of objective response that is subsequently confirmed at a visit that is $\geq$ 28 days later to disease progression or death due to any cause, was to be analyses using arithmetic (not Kaplan-Meier) methods.

The time to second disease progression or death (PFS2), defined as the time from randomisation to the date of the earliest of the following events: start of second subsequent non-radiation anti-cancer therapy, second objective disease progression, or death. For placebo subjects who have crossed over to receive cabozantinib, cabozantinib was to be considered as the first subsequent therapy. For subjects randomised to cabozantinib who continued on study treatment after their first disease progression, the start date of their first subsequent therapy was to be considered to be a potential event date. Subjects alive and for whom a PFS2 event has not been observed was to be censored at the last time known to be alive. The summaries (median and 95% CI for median, stratified and unstratified HRs and their 95% CI) and graphs as described for primary analysis of PFS were to be generated for PFS2. Log-rank p-values were to be calculated and presented for descriptive purposes (formal inferences not to be drawn).

Baseline and changes from baseline for the biomarker thyroglobulin was to be summarised by descriptive statistics (mean, standard deviation and median) by treatment group using all available data from protocol-defined time-points (baseline, W5D1, and W9D1), and a waterfall plot of best percentage decrease from baseline presented for each treatment group (in OITT and ITT populations).

Health-related quality of life (HRQOL), assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L) was to be summarised at each time point for each of the 6 questions by, within each treatment arm; descriptive statistics, Rate of completion, Mean change from baseline (95% CI=, p-value from one-sample t-test, Effect size, Shift in the severity scale since baseline, and between treatment arms by difference in; the effect sizes, mean change from baseline (t-test). Plots for mean±standard error and the corresponding mean for change from baseline over time, Percentage of subjects in Level 1 (no problem) vs. Levels 2-5 (any problems) over time, Percentage of subjects with any problems (Level 2-5) were to be presented. Repeated-measures mixed-effects models were to be used to explore treatment differences over time for the blinded phase of the study only. These analyses were to include the outcome variable of QOL score change from baseline. The predictors (fixed effects) were to be the baseline scores, treatment arms, visit, and randomisation strata. The individual subject nested within the planned treatment arm was to be the random effect. All available data were to be included for the analysis, and the estimated least squares means for the two treatment arms and their difference, the p-values comparing the 2 treatment arms, and the effect size presented. No adjustments were to be made for multiple comparisons. An effect size of differences in the $\geq$ 0.3 range was to be considered potentially clinically meaningful. All summaries were to be provided for the OITT and ITT populations.

Subgroup analyses

Subgroups based on baseline characteristics and stratification factors were to be explored for the primary efficacy endpoints and Overall Survival.

Interim analyses / Multiplicity

The multiplicity issue resulting from analysis of two primary endpoints (PFS and ORR) was addressed by applying a modified Bonferroni procedure (dividing the alpha between the two primary endpoints).

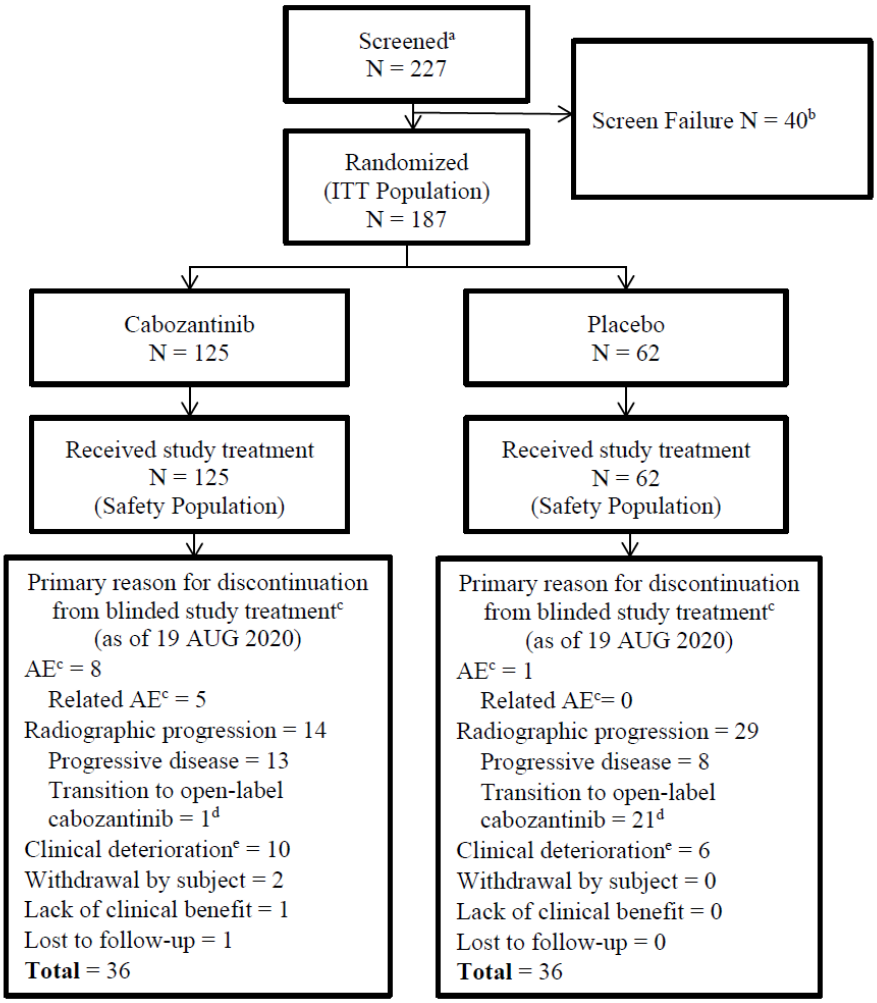
ORR was tested at the 2-sided 1% alpha significance level and PFS tested at the 2-sided 4% alpha significance level. Additionally, the fallback method for alpha allocation was to be implemented as follows:

- If the null hypothesis was rejected for ORR, its alpha allocation of 1% would be passed to PFS which would then be tested at the 5% level.
- If the null hypothesis was not rejected for ORR, then PFS was to be tested at its original alpha allocation of 4%.

An interim analysis was planned for the second primary endpoint of PFS at the time of the primary ORR analysis when approximately 43% of the planned total PFS events were expected to have been observed. Inflation of Type 1 error arising from repeated analyses of PFS was to be controlled by a Lan-DeMets O'Brien Fleming alpha spending function, using the actual information fraction at the interim analysis (see table under Sample size section). Rejection of the null hypothesis for PFS at the interim analysis was not expected; it was intended to allow evaluation of PFS at the time of the primary analysis of ORR. The interim analysis was conducted under supervision of the IDMC, which operated independently from the sponsor and the clinical investigators.

Results

Participant flow



AE, adverse event; BIRC, blinded independent radiology committee; ITT, intent-to-treat; SAE, serious adverse event.
Note: reasons for study treatment discontinuation were defined on the case report form.
[a] A total of 25 subjects were in screening with eligibility determination still pending at the time of the 19 August 2020 database cutoff date.

[c] Excluding AEs due to disease progression.
[d] Transition to open-label study treatment required subjects to have BIRC-confirmed progressive disease.
[e] Clinical deterioration comprises AEs or SAEs related to disease progression.

Figure 15. Flow chart of subject disposition as of CCO1 (ITT population)

Subjects' trial participation consisted of the following periods:

Pre-treatment period: Potential subjects were screened to determine if they met the required eligibility criteria. Qualifying screening assessments were performed within 28 days before randomization unless otherwise specified.

Treatment period: Subjects who met all study eligibility criteria were randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd)
- Placebo arm: Oral cabozantinib-matched placebo qd

Crossover phase: Subjects randomised to the placebo arm were permitted to crossover to receive cabozantinib upon experiencing radiographic disease progression (PD) as determined by the Investigator per RECIST 1.1 and confirmed by the BIRC. A real-time, dual reader adjudicated BIRC review of radiographic images per RECIST 1.1 was employed to document objective radiographic progression contemporaneously with subject study participation. At the time of Investigator-determined radiographic progression per RECIST 1.1, the Investigator could request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD and un-blind those subjects with BIRC-determined radiographic PD via the Interactive Response Technology (IRT) system.

Subjects randomised to placebo who crossed over to receive cabozantinib had baseline re-established and restarted the tumour assessment schedule. The new baseline was to be based upon the most recent set of scans performed prior to un-blinding for crossover. If these scans were performed > 8 weeks prior to the first crossover dose, new scans were required to establish the crossover baseline.

Un-blinded subjects randomised to placebo had the opportunity, if eligible, to enter the crossover phase to receive cabozantinib and undergo study assessments. These subjects were to continue on study treatment if the Investigator believed the subject was still deriving clinical benefit. Subjects who were ineligible or opted not to crossover to receive cabozantinib had study treatment discontinued and proceeded with post-treatment assessments.

In the crossover phase, safety assessments and radiographic tumour assessments continued per protocol, although scans were not submitted to BIRC. PK, biomarker, and HRQOL assessments were discontinued.

End of study treatment: Subjects received blinded study treatment or un-blinded treatment with cabozantinib as long as they continued to experience clinical benefit in the opinion of the Investigator or until there was unacceptable toxicity or the need for systemic NPACT. Treatment could continue after radiographic PD per RECIST 1.1 in the absence of systemic NPACT as long as the Investigator believed that the subject was still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighed potential risk.

Post-treatment period: A post-treatment follow-up visit occurred 30 (+14) days after the date of the decision to discontinue study treatment. Subjects were contacted every 12 weeks (± 7 days) after the post-treatment follow-up visits to assess survival status and document receipt of NPACT and subsequent progression status. This continued until the subject expired or the Sponsor decided to discontinue collection of these data in the study.

An Independent Data Monitoring Committee (IDMC) monitored unblinded results of the study on a regular basis. The objectives of the IDMC were to evaluate interim data to protect subject welfare and to provide recommendations regarding study conduct to the Sponsor. Formal futility analyses were not planned. The committee operated independently from the Sponsor and the clinical Investigators. To minimize the potential introduction of bias, IDMC members did not have any direct contact with the study site personnel or subjects. The IDMC members were selected for their expertise in oncology and/or biostatistics.

Reasons for screen failures

A total of 40 subjects failed screening as of **CCO1** (i.e., the data cut off at 19 August 2020). There was a total of 59 reasons for screen failure (data not shown). An additional 25 subjects were in screening with eligibility still pending at the data cut-off date.

The most common reasons for screen failure were 7 subjects not fulfilling the exclusion criterion "Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 4 weeks before randomization", 6 subjects not fulfilling the inclusion criterion of "Histologically or cytologically confirmed diagnosis of DTC including FTC and its variants" and 5 subjects each not fulfilling the exclusion criterion "Other clinically significant disorders as specified in the protocol" and the inclusion criterion "UPCR ≤ 1 mg/mg (≤ 113.2 mg/mmol)".

Recruitment

Study period: 27 February 2019 (first subject randomised) – 19 August 2020 (data cut-off date; minimum of 6 months' follow-up for the first 100 subjects).

A total of 161 unique sites headed by 174 principal investigators in 25 countries were activated for this study: of these sites, 89 enrolled 187 subjects for this study as of the 19 August 2020 data cut-off date.

Conduct of the study

Protocol amendments

There were no global amendments to the original protocol (dated 30 April 2018).

The original protocol had four country-specific amendments and one country-specific addendum: two amendments for Germany (amendment 0.1.1 dated 01 May 2019 and amendment 0.1.1.1.1 dated 03 August 2020, respectively), one amendment for Canada (amendment 0.2 dated 28 February 2019), one amendment for France (appendix 0.3 dated 22 April 2019) and one addendum for UK (dated 25 March 2019). These amendments mainly concerned revisions of definitions, addition of language in order to make clarifications/specifications/modifications. This pertained for instance to some of the inclusion and exclusion criteria (e.g., specification of contraception recommendations, revision of the definition of hypertension, lowering of the exclusionary QTcF threshold, correction of the timeframe for ECG testing) For Germany further consolidated guidance was also given in an appendix for investigators in light of the COVID-19 pandemic. The addendum for UK was prepared to clarify the definition of the end of the trial.

Some special accommodations were also performed in regards to the global COVID-19 pandemic. This included e.g., that safety assessment visits, including laboratory test visits, were allowed to be performed remotely as appropriate, tumour assessments were allowed to be performed at a local radiology facility on an individual basis depending on local circumstances. Safety and imaging results obtained remotely were documented, as for data obtained on site. Tumour images obtained at local radiology facilities were sent to BIRC. An interviewer-administered validated phone version of quality of life questionnaires was allowed to be used as an alternative as appropriate. Use of the phone format questionnaire was to be documented as a COVID-19 related protocol deviation in the source document. Telehealth visits were performed in 21 subjects (11%) due to the COVID-19 pandemic and resulted in a missed or incomplete assessment since procedures such as vitals, physical exam and ECG could not be performed.

Protocol deviations

Subject-specific protocol deviations

- *Eligibility deviations*

A total of 7 subjects (5.6%) in the cabozantinib arm and 2 subjects (3.2%) in the placebo arm failed to meet at least one eligibility criterion. A total of 5 subjects (4.0%) in the cabozantinib arm vs. 1 subject (1.6%) in the placebo arm failed at least one inclusion criteria. The most common inclusion criteria deviation was not meeting the required screening laboratory values of TSH within the required time period while receiving thyroxine suppression therapy (3 subjects [2.4%] in the cabozantinib arm vs. none in the placebo arm). A total of 2 subjects (1.6%) in the cabozantinib arm and 1 subject (1.6%) in the placebo arm failed at least one exclusion criterion. All reported exclusion criteria deviations occurred in one subject each.

- *Important on-study protocol deviations (i.e., other than eligibility criteria deviations)*

Table 9. Summary of subjects with any important protocol deviations (ITT population)

Deviation	Cabozantinib (N = 125) n (%)	Placebo (N = 62) n (%)
Subjects with at least one important protocol deviation	10 (8.0)	6 (9.7)
Missed/incomplete assessment[a]	5 (4.0)	2 (3.2)
Prohibited medication[b]	3 (2.4)	1 (1.6)
Randomization irregularity	2 (1.6)	1 (1.6)
Informed consent	1 (0.8)	1 (1.6)
Personal identifier breach[c]	0	1 (1.6)

CT, computed tomography; ECG, electrocardiogram; IRB, Institutional Review Board; ITT, intent-to-treat.
Subjects were counted only once within each category and in the total but could be counted in multiple categories.
[a] Deviations reported in this category comprised missed safety labs, missed CT scan of neck at screening, and ECGs not obtained per protocol.
[b] The most frequently received protocol prohibited medications were anticoagulant agents.
[c] The medical record number and full name for Subject 9403-3146 in the placebo arm was found in the screen capture sent to the imaging vendor. A report of the deviation was sent to the IRB.

Three important deviations categorized as randomization irregularities were reported and were related to accidental un-blinding at the site. In this study, Investigators were able to submit crossover requests or complete immediate emergency safety un-blinding via the IxRS.

Site-specific protocol deviations

Table 10. Summary of important site-specific deviations

Category Deviation	n
Safety Assessment Related	
Failure to report SAEs within the required time period[a]	8
Study Drug Related	
Dispensation of IP with known temperature excursion	1
Other	
Fabrication of source documentation	1

IP, investigational product; ITT, intent-to-treat; SAE, serious adverse event.
[a] Late SAE reporting was defined as reporting fatal, or life threatening, related SAEs > 4 days late and reporting all other SAEs ≥ 14 days late.

Baseline data

The data for baseline demographic characteristics, baseline disease history, prior radioiodine therapy for DTC, prior non-radiation anticancer therapy for DTC and prior radiation therapy were generally similar between subjects randomised as of CCO1 (ITT population where the primary endpoint was met) and CCO2 (Full ITT population). The majority of the differences between the two data sets for all the various baseline characteristics were in the range of 1-4%; consequently, only data for CCO1 are shown in the Assessment Report.

Table 11. Baseline demographic characteristics as of CCO1 (ITT and OITT populations)

Subject Characteristic	ITT Population		OITT Population	
	Cabozantinib (N = 125)	Placebo (N = 62)	Cabozantinib (N = 67)	Placebo (N = 33)
Age (years)				
Median (range)	65.0 (32, 85)	66.0 (37, 81)	62.0 (32, 82)	63.0 (47, 81)
Age category (years)				
16 to ≤ 17, n (%)	0	0	0	0
≥ 18, n (%)	125 (100)	62 (100)	67 (100)	33 (100)
< 65, n (%)	62 (50)	29 (47)	35 (52)	17 (52)
≥ 65, n (%)	63 (50)	33 (53)	32 (48)	16 (48)
65 to < 75, n (%)	48 (38)	23 (37)	26 (39)	13 (39)
75 to < 85, n (%)	14 (11)	10 (16)	6 (9.0)	3 (9.1)
≥ 85, n (%)	1 (0.8)	0	0	0
Sex, n (%)[a]				
Male	57 (46)	28 (45)	32 (48)	12 (36)
Female	68 (54)	34 (55)	35 (52)	21 (64)
Race, n (%) [b]				
American Indian/Alaska Native	3 (2.4)	0	1 (1.5)	0
Asian	20 (16)	14 (23)	10 (15)	9 (27)
Black/African American	1 (0.8)	2 (3.2)	1 (1.5)	1 (3.0)
Native Hawaiian/Other Pacific Islander	0	0	0	0
White	90 (72)	41 (66)	47 (70)	20 (61)
Multiple	0	0	0	0
Other	2 (1.6)	1 (1.6)	2 (3.0)	0
Not Reported	8 (6.4)	4 (6.5)	6 (9.0)	3 (9.1)
Missing	1 (0.8)	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	21 (17)	6 (9.7)	12 (18)	2 (6.1)
Not Hispanic or Latino	95 (76)	53 (85)	51 (76)	29 (88)
Not reported	9 (7.2)	3 (4.8)	4 (6.0)	2 (6.1)
Geographic region, n (%)				
Asia	16 (13)	13 (21)	6 (9.0)	8 (24)
North America (USA/Canada)	13 (10)	9 (15)	8 (12)	6 (18)
Europe	65 (52)	32 (52)	35 (52)	14 (42)
Rest of the world	31 (25)	8 (13)	18 (27)	5 (15)
Receipt of prior lenvatinib (stratification factor per CRF), n (%)				
Yes	79 (63)	39 (63)	41 (61)	21 (64)
No	46 (37)	23 (37)	26 (39)	12 (36)
Receipt of prior lenvatinib (stratification factor per IxRS), n (%)				
Yes	79 (63)	39 (63)	41 (61)	21 (64)
No	46 (37)	23 (37)	26 (39)	12 (36)

Age at informed consent (stratification factor per CRF), n (%)				
≤ 65 years	63 (50)	30 (48)	35 (52)	17 (52)
> 65 years	62 (50)	32 (52)	32 (48)	16 (48)
Age at informed consent (stratification factor per IxRS), n (%)				
≤ 65 years	63 (50)	30 (48)	35 (52)	17 (52)
> 65 years	62 (50)	32 (52)	32 (48)	16 (48)
ECOG PS, n (%)				
0	59 (47)	30 (48)	33 (49)	17 (52)
1	66 (53)	32 (52)	34 (51)	16 (48)
Smoking history, n (%)				
Current	2 (1.6)	2 (3.2)	0	0
Former	40 (32)	19 (31)	24 (36)	9 (27)
Never	83 (66)	41 (66)	43 (64)	24 (73)
Weight, median (range) (kg)	69.50 (40.3, 117.0)	64.80 (43.0, 135.5)	69.80 (44.0, 117.0)	68.15 (43.6, 135.5)
BMI, median (range) (kg/m^2) [c]	24.94 (15.5, 43.5)	23.69 (17.3, 46.3)	26.51 (15.5, 43.5)	24.96 (17.7, 46.3)

BMI, body mass index; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; IxRS, interactive voice/web response system; OITT, overall response rate intent-to-treat.

[b] More than one category could be reported for each subject.

[c] BMI is defined as weight (kg)/[height (m)]^2.

Table 12. Baseline disease history as of CCO1 (ITT and OITT populations)

Subject Characteristic	ITT Population		OITT Population	
	Cabozantinib (N = 125)	Placebo (N = 62)	Cabozantinib (N = 67)	Placebo (N = 33)
Diagnosis of DTC by histology or cytology (Yes), n (%)	125 (100)	62 (100)	67 (100)	33 (100)
DTC subtypes (per CRF), n (%)[a, b]				
Papillary thyroid carcinoma	67 (54)	35 (56)	39 (58)	20 (61)
Follicular thyroid carcinoma	62 (50)	28 (45)	30 (45)	13 (39)
Time to randomization since initial histological/cytological diagnosis of DTC (years)				
n	125	61	67	32
median (range)	7.63 (0.1, 33.0)	8.08 (1.0, 29.5)	7.83 (2.0, 26.8)	6.20 (1.0, 29.5)
Metastatic disease (per CRF), n (%)	117 (94)	60 (97)	63 (94)	32 (97)
Measurable disease per Investigator, n (%)	125 (100)	62 (100)	67 (100)	33 (100)
Measurable disease per BIRC, n (%)	119 (95)	60 (97)	62 (93)	31 (94)
Extent of baseline disease per tumor assessment, per BIRC, n (%)				
Bone	40 (32)	14 (23)	20 (30)	10 (30)
Important visceral sites	92 (74)	43 (69)	51 (76)	25 (76)
Lung	86 (69)	41 (66)	48 (72)	24 (73)
Liver	20 (16)	8 (13)	11 (16)	7 (21)
All other sites[c]	94 (75)	52 (84)	52 (78)	26 (79)
Lymph node[d]	80 (64)	46 (74)	46 (69)	21 (64)
Pleural cavity	17 (14)	17 (27)	5 (7.5)	9 (27)
Number of target lesions per BIRC, n (%)				
1	68 (54)	30 (48)	37 (55)	20 (61)
2	34 (27)	22 (35)	16 (24)	4 (12)
≥ 3	17 (14)	8 (13)	9 (13)	7 (21)
Number of non-target anatomic sites per BIRC, n (%)				
1	41 (33)	22 (35)	23 (34)	10 (30)
2	35 (28)	11 (18)	25 (37)	6 (18)
≥ 3	25 (20)	17 (27)	13 (19)	13 (39)

BIRC, blinded independent radiology committee; CRF, case report form; CT, computed tomography; DTC, differentiated thyroid cancer; ITT, intent-to-treat; MRI, magnetic resonance imaging; OITT, overall response rate intent-to-treat

[a] Subjects may be counted in more than one category.

[b] Five subjects (4 subjects in the cabozantinib arm and 1 subject in the placebo arm) in the ITT population were noted as having both papillary and follicular histologic subtypes.

[c] All other sites shown are those with ≥ 25% incidence in either arm.

[d] Lymph nodes are considered as one organ and only counted once.

Prior radioiodine therapy

Table 13. Prior radioiodine therapy for DTC as of CCO1 (ITT and OITT populations)

Subject Characteristic	ITT Population		OITT Population	
	Cabo (N = 125)	Placebo (N = 62)	Cabo (N = 67)	Placebo (N = 33)
Refractory to RAI therapy for DTC, n (%)	121 (97)	62 (100)	65 (97)	33 (100)
Ineligible for RAI therapy for DTC, n (%)[a]	5 (4.0)	0	3 (4.5)	0
Reason refractory to or ineligible for RAI therapy for DTC[b], n (%)				
Did not demonstrate RAI uptake	35 (28)	14 (23)	17 (25)	8 (24)
Disease progression despite RAI avidity	78 (62)	41 (66)	44 (66)	22 (67)
Extensive cumulative RAI exposure	5 (4.0)	2 (3.2)	2 (3.0)	1 (3.0)
Unknown	2 (1.6)	5 (8.1)	1 (1.5)	2 (6.1)
Other	5 (4.0)	0	3 (4.5)	0
Received prior RAI therapy for DTC, n (%)[c]	113 (90)	61 (98)	60 (90)	33 (100)
Median (range) time from end of last prior RAI therapy to randomization, months	48.2 (3, 204)	43.8 (2, 225)	49.0 (4, 152)	39.8 (2, 225)
Median (range) time from when subject was deemed RAI-refractory or RAI-ineligible to randomization, months	38.8 (-2[d], 224)	34.6 (0, 144)	38.4 (-2[d], 143)	29.2 (0, 118)

Cabo, cabozantinib; DTC, differentiated thyroid cancer; ITT, intent-to-treat; OITT, overall response rate intent-to-treat; RAI, radioiodine.
Prior therapies were defined as having a start date prior to first dose of study treatment.
[a] One subject in the cabozantinib arm received one dose of RAI and was then deemed ineligible.
[b] Subjects may be counted in more than one category.
[c] In the ITT population, 8 subjects in the cabozantinib arm and 1 subject in the placebo arm had their prior RAI entered after the data cutoff date.

The most common reason subjects were refractory to RAI therapy was disease progression despite RAI avidity. A total of 5 subjects in the cabozantinib arm were ineligible for RAI therapy for DTC (1 subject received one dose of RAI and was then deemed ineligible); reasons included iodine allergy and intact thyroid gland. All subjects who were refractory to prior RAI received prior RAI. However, for 8 subjects in the cabozantinib arm and 1 subject in the placebo arm, the prior RAI treatment information was entered after the data cut-off date; therefore, these subjects are not summarised as having received prior RAI in the table above.

Prior non-radiation anticancer therapies

Table 14. Prior non-radiation anticancer therapy for DTC as of CCO1 (ITT and OITT populations)

Subject Characteristic	ITT Population		OITT Population	
	Cabozantinib (N = 125)	Placebo (N = 62)	Cabozantinib (N = 67)	Placebo (N = 33)
Indication, n (%)				
DTC	125 (100)	62 (100)	67 (100)	33 (100)
Other	1 (0.8)	1 (1.6)	0	0
Therapy type for DTC, n (%)[a]				
Systemic	123 (98)	60 (97)	66 (99)	32 (97)
Local	11 (8.8)	8 (13)	8 (12)	5 (15)
Unknown	6 (4.8)	2 (3.2)	4 (6.0)	1 (3.0)
Other	1 (0.8)	1 (1.6)	1 (1.5)	1 (3.0)
Context of therapy, n (%)				
Neoadjuvant	3 (2.4)	3 (4.8)	2 (3.0)	1 (3.0)
Adjuvant	64 (51)	30 (48)	35 (52)	10 (30)
Locally advanced or metastatic setting	116 (93)	54 (87)	61 (91)	33 (100)
Number of prior systemic nonradiation anticancer regimens for DTC per subject, n (%)				
0[b]	2 (1.6)	2 (3.2)	1 (1.5)	1 (3.0)
1	12 (9.6)	9 (15)	9 (13)	4 (12)
≥ 2	111 (89)	51 (82)	57 (85)	28 (85)
Median (range)	2.0 (0, 5)	2.0 (0, 5)	2.0 (0, 5)	2.0 (0, 5)
Number of prior VEGFR-TKI agents for DTC per subject, n (%)				
0	0	1 (1.6)[c]	0	0
1	91 (73)	47 (76)	46 (69)	24 (73)
≥ 2	34 (27)	14 (23)	21 (31)	9 (27)
Median (range)	1.0 (1, 2)	1.0 (0, 2)	1.0 (1, 2)	1.0 (1, 2)
Number of prior PD-1/PD-L1 agents per subject for DTC, n (%)				
0	119 (95)	58 (94)	63 (94)	30 (91)
1	6 (4.8)	4 (6.5)	4 (6.0)	3 (9.1)
≥2	0	0	0	0
Median (range)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Received prior sorafenib for DTC, n (%)				
Yes	77 (62)	35 (56)[c]	45 (67)	20 (61)
No	48 (38)	27 (44)	22 (33)	13 (39)
Received prior lenvatinib for DTC, n (%)				
Yes	79 (63)	39 (63)	41 (61)	21 (64)
No	46 (37)	23 (37)	26 (39)	12 (36)
Received prior sorafenib but no lenvatinib for DTC, n (%)	46 (37)	22 (35)	26 (39)	12 (36)
Received prior lenvatinib but no sorafenib for DTC, n (%)	48 (38)	26 (42)	22 (33)	13 (39)

Received prior sorafenib and lenvatinib for DTC, n (%)	31 (24.8)	13 (21.0)	19 (28.4)	8 (24.2)
Received sorafenib before receiving lenvatinib, n (%)	24 (19)	9 (15)	12 (18)	5 (15)
Received lenvatinib before receiving sorafenib, n (%)	7 (5.6)	4 (6.5)	7 (10)	3 (9.1)
Median (range) time from progression on most recent prior nonradiation systemic anticancer regimen for DTC to randomization, months	1.40 (0.4, 76.2)	1.68 (0.5, 75.6)	1.31 (0.4, 38.9)	1.76 (0.5, 33.3)
Median (range) time from end of most recent prior nonradiation systemic anticancer regimen for DTC to randomization, months	1.45 (0.4, 47.3)	1.76 (0.5, 134.6)	1.45 (0.4, 19.6)	1.97 (0.5, 58.0)
Progression on most recent prior VEGFR-TKI therapy for DTC, n (%)	97 (78)	46 (74)	55 (82)	24 (73)
Median (range) time on most recent prior VEGFR-TKI therapy for DTC, months	18.20 (0.2, 94.9)	14.88 (0.9, 81.8)	13.83 (0.2, 94.9)	14.65 (2.2, 73.6)
Median (range) time from progression on most recent prior VEGFR-TKI therapy for DTC to randomization, months	1.45 (0.4, 36.1)	1.58 (0.5, 39.8)	1.51 (0.4, 32.9)	1.68 (0.5, 33.3)
Median (range) time from end of most recent prior VEGFR-TKI therapy for DTC to randomization, months	1.51 (0.4, 47.3)	1.84 (0.5, 58.0)	1.51 (0.4, 32.9)	1.97 (0.5, 58.0)
Progression while receiving sorafenib or lenvatinib for DTC at any time, n (%)	111 (89)	51 (82)	61 (91)	27 (82)
Progression while receiving sorafenib or lenvatinib for DTC as most recent prior systemic nonradiation anticancer agent for DTC, n (%)	96 (77)	46 (74)	54 (81)	24 (73)
Median (range) time from progression on sorafenib or lenvatinib as the most recent prior systemic nonradiation anticancer agent for DTC to randomization (among subjects who received sorafenib or lenvatinib as most recent prior systemic agent), months	1.15 (0.4, 13.1)	1.31 (0.5, 39.8)	1.17 (0.4, 7.5)	1.49 (0.5, 14.1)
Median (range) duration of prior sorafenib for DTC, months	11.60 (0.2, 90.8)	14.72 (2.4, 61.5)	10.97 (0.2, 90.8)	14.80 (2.4, 48.4)
Total duration of treatment on prior sorafenib (months) for DTC, n (%)				
< 1 month	2 (1.6)	0	2 (3.0)	0
≥ 1 to < 3 months	5 (4.0)	3 (4.8)	2 (3.0)	3 (9.1)
≥ 3 to < 6 months	14 (11)	2 (3.2)	12 (18)	2 (6.1)
≥ 6 months	56 (45)	30 (48)	29 (43)	15 (45)
Median (range) duration of prior lenvatinib for DTC, months	18.73 (1.0, 94.9)	16.23 (0.9, 81.8)	13.90 (1.0, 94.9)	14.00 (2.2, 73.6)
Total duration of treatment on prior lenvatinib (months) for DTC, n (%)				
< 1 month	2 (1.6)	1 (1.6)	1 (1.5)	0
≥ 1 to < 3 months	2 (1.6)	2 (3.2)	1 (1.5)	2 (6.1)
≥ 3 to < 6 months	6 (4.8)	6 (9.7)	3 (4.5)	5 (15)
≥ 6 months	69 (55)	30 (48)	36 (54)	14 (42)

Best response on the most recent regimen for DTC, n (%)				
Complete response	3 (2.4)	1 (1.6)	2 (3.0)	0
Partial response	20 (16)	15 (24)	10 (15)	8 (24)
Stable disease	45 (36)	19 (31)	20 (30)	9 (27)
Progressive disease	39 (31)	20 (32)	27 (40)	13 (39)
Not evaluable	2 (1.6)	0	1 (1.5)	0
Unknown	16 (13)	7 (11)	7 (10)	3 (9.1)
Reason for stopping most recent prior nonradiation anticancer agent for DTC, n (%)				
Progression	107 (86)	48 (77)	59 (88)	25 (76)
Toxicity	12 (9.6)	10 (16)	6 (9.0)	7 (21)
Completion	4 (3.2)	4 (6.5)	1 (1.5)	1 (3.0)
Other	2 (1.6)	0	1 (1.5)	0
Selected prior nonradiation systemic anticancer agents for DTC of interest, n (%)[a, d]				
Protein Kinase Inhibitors (other than sorafenib and lenvatinib)				
Everolimus	4 (3.2)	0	3 (4.5)	0
Nintedanib	1 (0.8)	0	1 (1.5)	0
Pazopanib	1 (0.8)	1 (1.6)	0	1 (3.0)
Selumetinib	0	1 (1.6)	0	0
Trametinib	0	1 (1.6)	0	0
Vandetanib	1 (0.8)	0	1 (1.5)	0
Immunotherapies (PD-1/PD-L1/CTLA4/other)				
Ipilimumab	1 (0.8)	2 (3.2)	1 (1.5)	1 (3.0)
Other				
Anthracyclines	2 (1.6)	0	0	0
Antineoplastic agents	11 (8.8)	4 (6.5)	5 (7.5)	3 (9.1)
Cisplatin and doxorubicin (combination)	1 (0.8)	0	1 (1.5)	0
Investigational drug	0	1 (1.6)	0	1 (3.0)

CTLA4, cytotoxic T-lymphocyte-associated protein 4; DTC, differentiated thyroid cancer; ITT, intent-to-treat; OITT, overall response rate intent-to-treat; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.
Prior therapies were defined as having a start date prior to first dose of study treatment.
Therapy count excludes radioiodine therapy.
[a] Prior therapies could be taken together but are summarized separately. Subjects may be counted in more than one category.

Prior radiation therapy

Table 15. Prior radiation therapy for DTC as of CCO1 (ITT and OITT populations)

	ITT Population		OITT Population	
	Cabo (N = 125)	Placebo (N = 62)	Cabo (N = 67)	Placebo (N = 33)
Incidence of prior radiation therapy by indication, n (%)				
DTC	67 (54)	30 (48)	36 (54)	18 (55)
Other	1 (0.8)	1 (1.6)	1 (1.5)	0
Number of prior radiation therapies for DTC per subject, n (%)				
1	32 (26)	14 (23)	15 (22)	9 (27)
2	16 (13)	9 (15)	11 (16)	4 (12)
≥ 3	19 (15)	7 (11)	10 (15)	5 (15)
Median (range)[a]	2.0 (1, 11)	2.0 (1, 8)	2.0 (1, 11)	1.5 (1, 8)
Type of prior radiation therapy for DTC[b], n (%)				
External beam radiation therapy	59 (47)	28 (45)	31 (46)	17 (52)
Internal radiation therapy (brachytherapy)	5 (4.0)	0	2 (3.0)	0
Radiofrequency ablation	11 (8.8)	1 (1.6)	9 (13)	0
Radioembolization	1 (0.8)	0	0	0
Other	6 (4.8)	1 (1.6)	3 (4.5)	1 (3.0)
Median (range) time from end of most recent radiation therapy for DTC to randomization, months	17.2 (1, 129)	16.0 (0, 174)	17.6 (1, 129)	16.0 (1, 174)

Cabo, cabozantinib; DTC, differentiated thyroid cancer; ITT, intent-to-treat; OITT, overall response rate intent-to-treat.
Prior therapies were defined as having a start date prior to first dose of study treatment.
[a] Only subjects who received prior radiation therapy for DTC were included.
[b] Subjects may be counted in more than one category.

In order to be eligible for this study, subjects were required to have a TSH value below the normal range. The majority of subjects (approximately 84%) had a baseline TSH value of ≤ 0.1 mIU/L. Median baseline thyroglobulin values were 2027.83 ng/mL in the cabozantinib arm and 1746.30 ng/mL in the placebo arm (ITT population).

Concomitant medications

Concomitant medications that had a ≥ 10% higher incidence in the cabozantinib only arm compared with the placebo arm by decreasing frequency of between-arm difference were loperamide, amlodipine, urea, calcium, paracetamol (acetaminophen), and clobetasol (safety population). In the cabozantinib arm 9/125 (7.2%) vs. 10/62 (16%) in the placebo arm used dexamethasone.

Treatment compliance

A total of 12 subjects (9.6%) in the cabozantinib only arm and 3 subjects (4.8%) in the placebo arm had their dose interrupted due to subject non-compliance for reasons other than an AE.

Crossover subjects: baseline characteristics prior to crossover (ITT population)

For the 19 subjects in the ITT population who were randomised to placebo then crossed over to receive cabozantinib upon BIRC-confirmed radiographic progression, selected demographic and baseline characteristics were re-established immediately prior to crossover. The median age of subjects in the placebo crossover arm was 66 years, consistent with that in the cabozantinib arm (ITT population). A

higher proportion of subjects in the placebo crossover arm had a baseline ECOG PS of 1 immediately prior to crossover compared with the cabozantinib arm (74% vs 53%, respectively). The median time to progression while on placebo per BIRC was 1.77 months (range: 0.6 -7.1 months) in the placebo crossover arm. Number of target lesion locations prior to crossover was 1 for 32% of the patients and 2 for 42% of the patients.

Numbers analysed

Table 16. Analysis populations

	Cabozantinib n (%)	Placebo n (%)
ITT population[a]	125 (100)	62 (100)
OITT population[a,b]	67 (100)	33 (100)
Safety population[c]	125 (100)	62 (100)
O-Safety population[d]	67 (100)	33 (100)
Placebo crossover subjects[e]	-	19
Pharmacokinetic population[f]	107	54

BIRC, blinded independent radiology committee; ITT, intent-to-treat; O-Safety, overall response rate safety population; OITT, overall response rate intent-to-treat; PD, disease progression; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Includes all randomized subjects in the respective population (ITT or OITT).
[b] OITT population consisted of the first 100 subjects who were randomized to receive study treatment.
[c] Safety population comprised all subjects who received any amount of study treatment.
[d] O-Safety population comprised all subjects in the OITT population who received any amount of study treatment.
[e] Placebo crossover subjects consisted of eligible subjects in the ITT population who were randomized to placebo then crossed over to receive cabozantinib upon experiencing BIRC-confirmed radiographic PD per RECIST 1.1.
[f] The PK population consisted of all subjects with available PK data.

Table 17. Subject disposition as of CCO1 (ITT and OITT populations)

	ITT [a]		OITT	
	Cabo (N = 125) n (%)	Placebo (N = 62) n (%)	Cabo (N = 67) n (%)	Placebo (N = 33) n (%)
Received study treatment	125 (100)	62 (100)	67 (100)	33 (100)
Discontinued blinded study treatment	36 (29)	36 (58)	30 (45)	24 (73)
Primary reason for discontinuation from blinded study treatment:				
AE or SAE unrelated to progression of disease under study	8 (6.4)	1 (1.6)	6 (9.0)	1 (3.0)
Related to study treatment	5 (4.0)	0	5 (7.5)	0
Not related to study treatment	3 (2.4)	1 (1.6)	1 (1.5)	1 (3.0)
Radiographic progression	14 (11)	29 (47)	13 (19)	19 (58)
Progressive disease	13 (10)	8 (13)	12 (18)	7 (21)
Transition to Open-Label[b]	1 (0.8)	21 (34)	1 (1.5)	12 (36)
Clinical deterioration[c]	10 (8.0)	6 (9.7)	8 (12)	4 (12)
Withdrawal by subject	2 (1.6)	0	1 (1.5)	0
Lack of clinical benefit	1 (0.8)	0	1 (1.5)	0
Lost to follow-up	1 (0.8)	0	1 (1.5)	0
Discontinued radiographic follow-up	38 (30)	22 (35)	30 (45)	15 (45)
Primary reason for discontinuation from radiographic follow-up:				
Death	11 (8.8)	10 (16)	10 (15)	5 (15)
Lost to follow-up	1 (0.8)	0	0	0
Completed	10 (8.0)	7 (11)	9 (13)	6 (18)
Clinical deterioration	6 (4.8)	1 (1.6)	3 (4.5)	1 (3.0)
Withdrawal by subject	3 (2.4)	1 (1.6)	3 (4.5)	1 (3.0)
Other	7 (5.6)	3 (4.8)	5 (7.5)	2 (6.1)

Discontinued survival follow-up	28 (22)	17 (27)	21 (31)	10 (30)
Primary reason for discontinuation from survival follow-up				
Death	23 (18)	17 (27)	17 (25)	10 (30)
Withdrew full consent from all study interventions and non-interventional study assessments	3 (2.4)	0	2 (3.0)	0
Lost to follow-up	2 (1.6)	0	2 (3.0)	0

AE, adverse event; BIRC, blinded independent radiology committee; Cabo, cabozantinib; ITT, intent-to-treat; OITT, overall response rate intent-to-treat; SAE, serious adverse event.
Note: reasons for study treatment discontinuation were defined on the case report form.
[a] In this study, the ITT and Safety populations are the same.
[b] Transition to open-label study treatment required subjects to have BIRC-confirmed progressive disease.
[c] Clinical deterioration comprises AEs or SAEs related to disease progression.

As of the data cut-off date, a total of 21 subjects randomised to placebo were approved for crossover; however, two of these subjects did not begin open-label cabozantinib until after the data cut-off date and were not included in summaries of subjects who crossed over. Of the 19 subjects who crossed over, 5 discontinued cabozantinib after crossing over. The most common reason for treatment discontinuation was clinical deterioration (3 subjects). Two subjects who were randomised to cabozantinib transitioned to open-label cabozantinib (1 subject was recorded as discontinuing blinded study treatment due to PD). One of these subjects discontinued open-label study treatment after the transition due to clinical deterioration.

Outcomes and estimation

Primary efficacy analyses of cabozantinib were based on the pre-specified primary endpoint analysis of ORR in the first 100 randomized subjects and an interim primary endpoint analysis of PFS from the 187 subjects (125 cabozantinib, 62 placebo) randomized as of CCO1 on 19 August 2020. CCO1 was set 6 months after the 100th subject randomised. After the 19 August 2020 cut-off date, subjects continued to enrol in the study and receive blinded study treatment.

Table 18. Primary efficacy endpoints and OS endpoint analyses in Study XL184-311

Data Cutoff	Description	Population	Number of Subjects	Median Follow-up
Clinical Cutoff 1 (19 August 2020; XL184-311 CSR)	PFS per RECIST 1.1 by BIRC	ITT Population	187	6.24 months
	ORR by BIRC per RECIST 1.1[a]	OITT Population	100	8.85 months
	ORR by BIRC per RECIST 1.1[a]	ITT Population	187	6.24 months
	OS	ITT Population	187	6.24 months
	Tg Change from Baseline	ITT Population	187	6.24 months
	Health-Related Quality of Life	ITT Population	187	6.24 months
Clinical Cutoff 2 (08 February 2021; XL184-311 CSR Addendum 1)	PFS per RECIST 1.1 by BIRC	Full ITT Population	258	10.1 months
	PFS per RECIST 1.1 by BIRC	Primary Analysis Subset[b] (ITT Population)	187	11.9 months
	ORR by BIRC per RECIST 1.1[a]	Full ITT Population	258	10.1 months
	ORR by BIRC per RECIST 1.1[a]	Primary Analysis Subset[b] (ITT Population)	187	11.9 months
	OS	Full ITT Population	258	10.1 months
	OS	Primary Analysis Subset[b] (ITT Population)	187	11.9 months

BIRC, blinded independent radiology committee; DOR, duration of objective response; ITT, intent-to-treat; OITT, overall response rate intent-to-treat; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; Tg, serum thyroglobulin.

[a] In addition, duration of response was an additional endpoint.

[b] The Primary Analysis subset is comprised of the 187 subjects randomized as of Clinical Cutoff 1 on 19 August 2020. At Clinical Cutoff 2 on 08 February 2021, PFS by BIRC, ORR by BIRC, and OS analyses were repeated using the Primary Analysis subset (N = 187) with approximately 6 months of additional follow-up.

Multiple primary endpoint

PFS (clinical cut-off date 19 August 2020)

Table 19. Progression-free survival per BIRC as of CCO1 (ITT population)

	Cabozantinib (N = 125)	Placebo (N = 62)
Number (%) of subjects		
Censored	94 (75)	19 (31)
Receipt of local radiation to soft tissue for DTC	1 (0.8)	1 (1.6)
No post-baseline ATA[a]	23 (18)	8 (13)
No event by last ATA	67 (54)	10 (16)
2 or more missed ATA prior to event	3 (2.4)	0
Event	31 (25)	43 (69)
Death	6 (4.8)	2 (3.2)
Progressive disease	25 (20)	41 (66)
Duration of progression-free survival (months)		
Median (96% CI)	NE (5.7, NE)	1.9 (1.8, 3.6)
25th percentile, 75th percentile[b]	4.4, NE	1.6, 5.4
Range	0.03+, 15.67+	0.03+, 9.26+
Observed p-value (stratified log-rank test)[c]	< 0.0001	
Hazard ratio (96% CI; stratified)[d]	0.22 (0.13, 0.36)	
Observed p-value (unstratified log-rank test)	< 0.0001	
Hazard ratio (96% CI; unstratified)[d]	0.23 (0.14, 0.37)	
K-M landmark estimates (% of subjects event-free) at		
3 months	88.2	42.4
6 months	56.9	16.9
9 months	54.3	6.3
12 months	54.3	NE

ATA, adequate tumor assessments; BIRC, blinded independent radiology committee; CI, confidence interval; DTC, differentiated thyroid cancer; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; K-M, Kaplan-Meier; NE, not estimable.

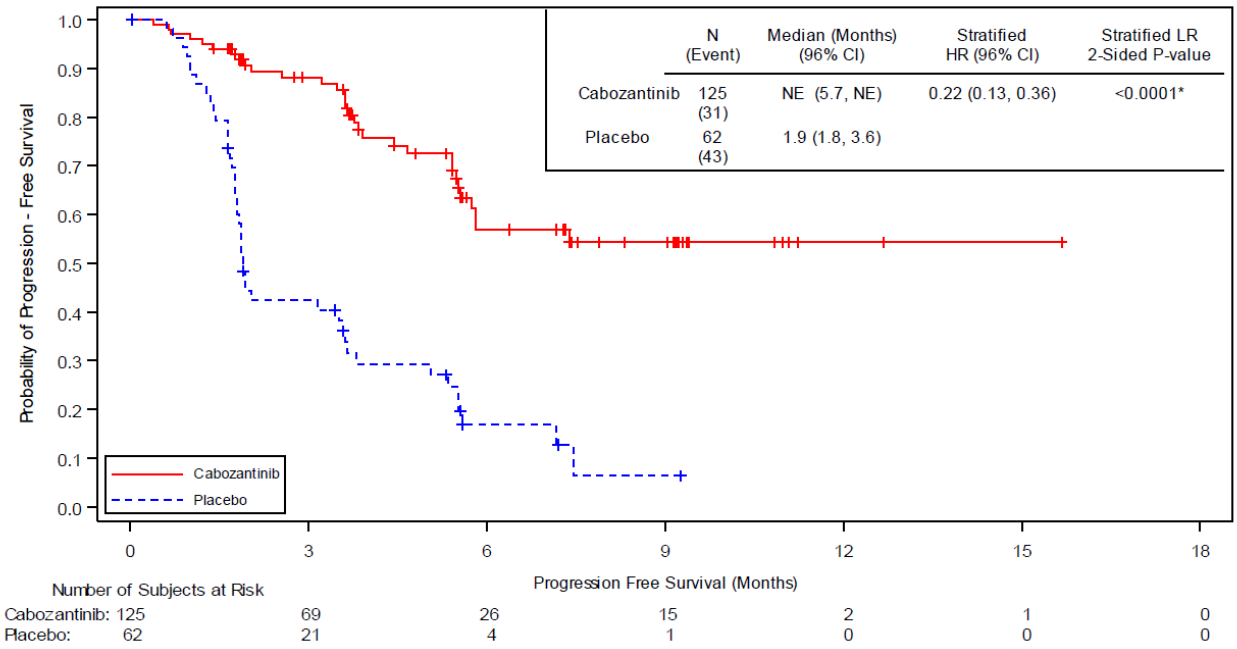
+ indicates a censored observation (please see PFS censoring rules in XL184-311 CSR, Section 9.7.1.2.2

[a] Two subjects in the cabozantinib arm (1807-3002 and 3808-3111) died before their first post-baseline scan. These subjects are summarized under the events (death) category and not under the censored (no post-baseline ATA) category for PFS but were considered censored for having no post-baseline scan in the ORR analysis. Of note, 20 cabozantinib and 8 placebo subjects were enrolled too close to the data cut cutoff date to have had a post-baseline tumor assessment.

[b] Percentiles were based on Kaplan-Meier estimates.

[c] Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

[d] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable). HR < 1 indicated PFS in favor of cabozantinib.



BIRC, blinded independent radiology committee; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test; NE, not estimable.
+ indicates a censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

Figure 16. Kaplan-Meier plot of PFS per BIRC as of CCO1 (ITT population)

Sensitivity and supplementary analyses: PFS (primary analysis: CCO1).

Overall, the BIRC and Investigator agreed on subjects' radiographic PD status 91% of the time for the cabozantinib arm and 79% of the time for the placebo arm, see table below.

Table 20. Concordance between BIRC and Investigator read in progressive disease status for tumor assessment[a] as of CCO1 (ITT population)

	Cabozantinib (N = 97) n (%)	Placebo (N = 53) n (%)	Total (N = 150) n (%)
Number of discordance			
Investigator progressed / BIRC not progressed	4 (4.1)	3 (5.7)	7 (4.7)
Investigator not progressed / BIRC progressed	5 (5.2)	8 (15)	13 (8.7)
Total discordance	9 (9.3)	11 (21)	20 (13)
Number of concordance			
Progressive disease	21 (22)	33 (62)	54 (36)
Not progressive disease	67 (69)	9 (17)	76 (51)
Total concordance	88 (91)	42 (79)	130 (87)

BIRC, blinded independent radiology committee; ITT, intent-to-treat .
[a] In subjects having at least one adequate post-baseline tumor assessment by both BIRC and Investigator.

When both the BIRC and Investigator agreed PD had occurred, the BIRC and Investigator agreed on the dates of PD 76% of the time for the cabozantinib arm and 79% of the time for the placebo arm, see table below.

Table 21. Concordance between BIRC and Investigator read in date of progressive disease for tumour assessments among subjects who progressed[a] as of CCO1 (ITT population)

	Cabozantinib (N = 21) n (%)	Placebo (N = 33) n (%)	Total (N = 54) n (%)
Concordant	16 (76)	26 (79)	42 (78)
Discordant	5 (24)	7 (21)	12 (22)

BIRC, blinded independent radiology committee; ITT, intent-to-treat.
[a] Subjects who progressed according to both the BIRC and Investigator.

Other sensitivity and supplementary analyses: PFS as of CCO1 (ITT population)

The table below provides point estimates and 95% CIs of stratified HRs for the primary PFS (PFS-EP-1) analysis described above and for pre-specified sensitivity (PFS-EP-2, PFS-EP-3, PFS-EP-4, PFS-EP-11, PFS-EP-12, PFS-EP-13, PFS-EP-14) and supplementary (PFS-EA1-1, PFS-EA2-1, PFS-EA2-2) analyses, in which additional or alternative clinical outcomes were considered to be events (see under "Statistical methods" for more details).

Table 22. Sensitivity and supplementary analyses of PFS as of CCO1 (ITT population)

PFS Analysis	No. of Events/Subjects (%) Median Duration (mo)		Stratified Hazard Ratio	95% CI	Stratified Log-rank p-value
	Cabozantinib	Placebo			
Primary analysis, PFS1-EP-1[a]	31/125 (25) NE	43/62 (69) 1.9	0.22	0.13, 0.36*	<0.0001
PFS-EP-2[b]	29/125 (23) NE	41/62 (66) 1.9	0.21	0.13, 0.34	<0.0001
PFS-EP-3[c]	31/125 (25) NE	40/62 (65) 1.9	0.27	0.17, 0.44	<0.0001
PFS-EP-4[d]	34/125 (27) NE	43/62 (69) 1.9	0.25	0.15, 0.39	<0.0001
PFS-EA1-1[e]	35/125 (28) 9.2	40/62 (65) 1.9	0.29	0.18, 0.47	<0.0001
PFS-EA2-1[f]	31/125 (25) NE	43/62 (69%) 1.9	0.22	0.14, 0.35	<0.0001
PFS-EA2-2[g]	34/125 (27) NE	43/62 (69) 1.9	0.25	0.15, 0.39	<0.0001
PFS-EP-11[h]	38/125 (30) 7.2	43/62 (69) 1.9	0.26	0.17, 0.42	<0.0001
PFS-EP-12[h]	38/125 (30) 7.2	43/62 (69) 1.9	0.26	0.17, 0.42	<0.0001
PFS-EP-13[h]	38/125 (30) 7.2	46/62 (74) 1.9	0.25	0.16, 0.39	<0.0001
PFS-EP-14[h]	38/125 (30) 7.2	43/62 (69) 1.9	0.26	0.17, 0.42	<0.0001

ATA, adequate tumor assessments; BIRC, blinded independent radiology committee; CI, confidence interval; ITT, intent-to-treat; NE, not estimable; NPACT, nonprotocol anticancer therapy; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

*96% CI is presented for the primary analysis of PFS (PFS1-EP-1), as PFS1-EP-1 was tested at 4% alpha.

[a] PFS-EP-1: Primary analysis of PFS.

[b] PFS-EP-2: Date of radiographic progression was based on the date of the scheduled visit, rather than the date of recorded progression.

[c] PFS-EP-3: Radiographic progression was based upon RECIST 1.1 evaluations by the Investigator rather than the BIRC.

[d] PFS-EP-4: Rather than being censored, subjects who experienced ≥ 2 consecutive missing scheduled ATA immediately prior to documented radiographic progression were classified as having an event at the date of the last ATA prior to the missing visits.

[e] PFS-EA1-1: Selected clinical intercurrent events to were changed to "composite," resulting in an endpoint that comprised radiographic and clinical progression, as well as death.

[f] PFS-EA2-1: Receipt of systemic NPACT was changed to "composite," resulting in an endpoint that comprised radiographic progression, death, or initiation of systemic NPACT.

[g] PFS-EA2-2: Sensitivity analysis of PFS-EA2-1 similar to PFS-EP-4 (footnote "d" above).

[h] PFS-EP-11 to PFS-EP-14: Selected censored subjects were re-classified as events, differentially by treatment arm, to evaluate the impact of potentially informative censoring based on PFS-EP-1. These were highly conservative definitions intended to evaluate potential bias.

Objective response rate (ORR)

Objective Response Rate per RECIST 1.1 by BIRC as of CCO1 (OITT and ITT Population).

Table 23. ORR per BIRC as of CCO1 (OITT and ITT population)

	OITT Population		ITT Population	
	Cabozantinib (N = 67)	Placebo (N = 33)	Cabozantinib (N = 125)	Placebo (N = 62)
Best overall response, n (%)[a]				
Confirmed complete response (CR)	0 (0)	0 (0)	0	0
Confirmed partial response (PR)	10 (15)	0 (0)	11 (8.8)	0
Stable disease (SD)	46 (69)	14 (42)	76 (61)	21 (34)
Unconfirmed CR (uCR)	0	0	0	0
Unconfirmed PR (uPR)	5 (7.5)	0	8 (6.4)	0
Progressive disease (PD)	4 (6.0)	18 (55)	8 (6.4)	31 (50)
No disease (NA)	1 (1.5)	0	1 (0.8)	0
Unable to evaluate (UE)	1 (1.5)	1 (3.0)	2 (1.6)	1 (1.6)
Missing	5 (7.5)	0	27 (22)	9 (15)
No baseline assessments	0	0	0	0
No post-baseline assessments	4 (6.0)	0	25 (20)	8 (13)
No qualifying post-baseline assessment on or before the primary PFS analysis censoring or event date	4 (6.0)	0	25 (20)	8 (13)
SD not meeting minimum criteria from randomization	1 (1.5)	0	2 (1.6)	1 (1.6)
Objective response rate (CR+PR), n (%)	10 (15)	0	11 (8.8)	0
Treatment difference (cabozantinib – placebo) (95% CI)[b]	21 (11.2, 30.6)		8.8 (3.8, 13.8)	
Observed stratified CMH test p-value per IxRS[c]	0.0057		0.0163	
Observed unstratified Fisher exact test p-value	0.0040		0.0171	
Disease stabilization rate (ORR+SD ≥ 16 weeks), n (%)	42 (63)	11 (33)	54 (43)	10 (16)
95% CI	(50.0, 74.2)	(18.0, 51.8)	(34.4, 52.4)	(8.0, 27.7)
DOR per BIRC (K-M), median (range), months	NE (1.94+, 7.33+)	NA	NE (1.87+, 7.33+)	NA
Time to Objective Response per BIRC (Arithmetic), median (range) time from randomization, months	2.5 (1.74, 3.94)	NA	1.9 (1.74, 3.94)	NA

BIRC, blinded independent radiology committee; CI, confidence interval; CMH, Cochran Mantel-Haenszel; OITT, overall response rate intent-to-treat; IxRS, interactive voice/web response system; RECIST, Response Evaluation Criteria in Solid Tumors.

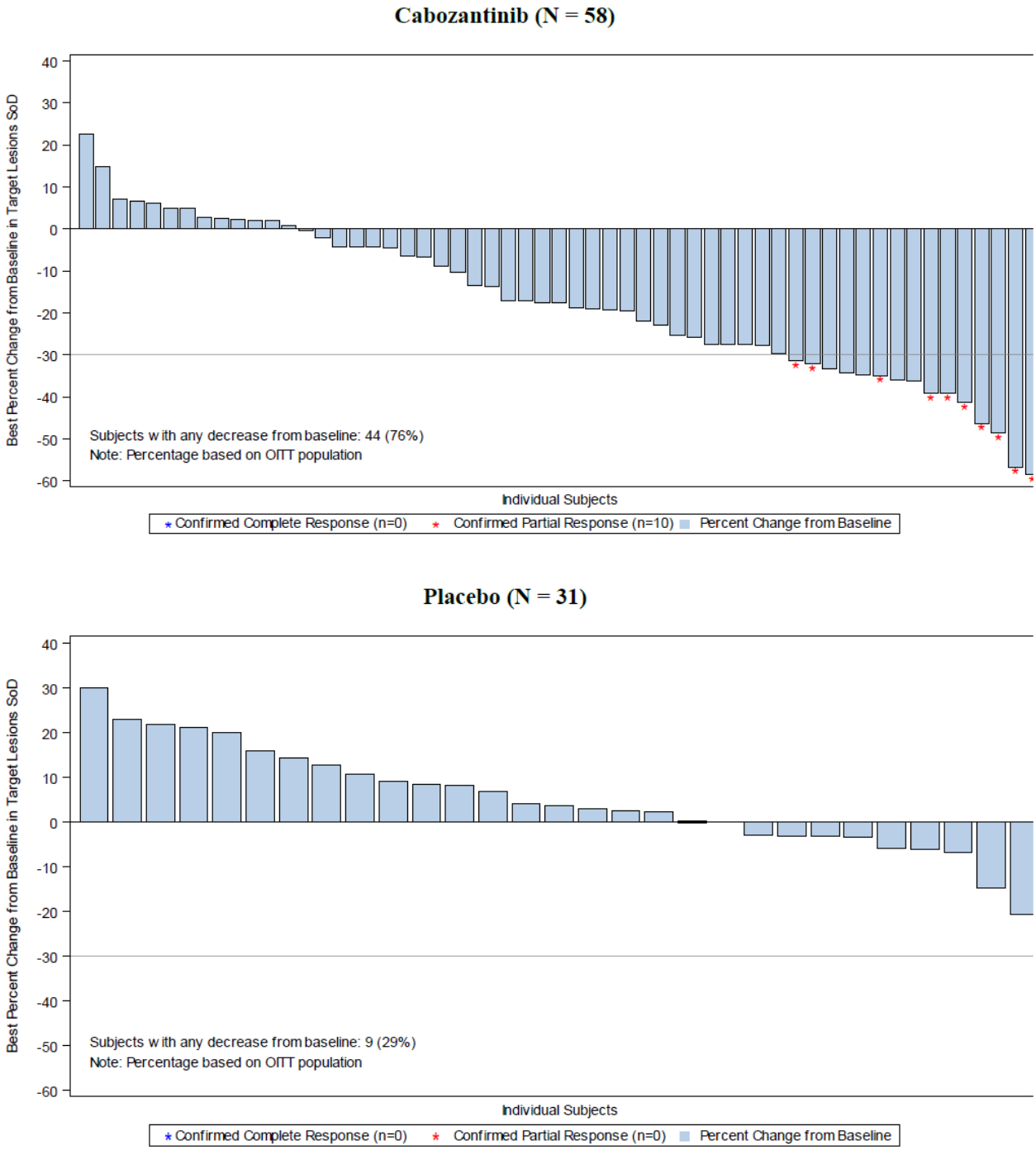
[a] Best overall response was assessed based on RECIST 1.1 criteria and was calculated based on subjects in the OITT population. Note that a CR or PR was not considered as an objective response if a subject progressed or received subsequent anticancer therapy prior to the first CR or PR. To be classified as a CR or PR, confirmation of response must have occurred > 28 days after the response was first observed.

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

[c] Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

The best percentage change from baseline in tumour target lesion size in the OITT population as determined by BIRC per RECIST 1.1 is depicted in the figure below.

Among subjects in the OITT population with at least one baseline and at least one post-baseline target lesion assessment, 44/58 (76%) in the cabozantinib arm and 9/31 (29%) in the placebo arm had a post-baseline reduction in the sum of target lesion diameters (SoD).



BIRC, blinded independent radiology committee; OITT, overall response rate intent-to-treat; PFS, progression-free survival; SoD, sum of target lesion diameters.
Subjects are not represented due to lack of evaluable post-baseline assessment, censoring (per PFS rules) before first evaluable post-baseline assessment, lack of target lesions, and/or incomplete or unevaluable target lesion assessment.
Data from time points after the first date of any of the censoring events defined for the primary PFS analysis (in XL184-

Figure 17. Waterfall plot of best percentage change in tumour target lesion size from baseline per BIRC as of CCO1 (OITT population, subjects with at least one baseline and post-baseline target lesion assessment)

A sensitivity analysis of ORR per RECIST 1.1 as determined by the Investigator was conducted in the OITT population using the data cut-off date as of CCO1. The ORR per Investigator for the OITT population was 21% (95% CI: 11.9, 32.6) in the cabozantinib arm and 0% (95% CI: 0.0, 10.6) in the placebo arm (unstratified p-value of 0.0040). Results were similar to those determined by BIRC.

However, the proportion of patients with SD was equal in this population (58% in each arm). For the OITT population, the median (range) time from randomization to the first objective response was 1.9 (1.38, 7.29) months per Investigator in the cabozantinib arm.

Among subjects in the OITT population with at least one baseline and at least one post-baseline target lesion assessment, 51/61 (84%) in the cabozantinib arm and 8/32 (25%) in the placebo arm had a post-baseline reduction in the SoD.

Comparison of BIRC-determined and Investigator-determined Overall Response Rate as of CCO1 (OITT Population)

The table below provides a summary of concordance and discordance between the BIRC- and Investigator-determined assessments of tumour response status in subjects having at least one adequate post-baseline tumour assessment by both BIRC and Investigator. Overall, the BIRC and Investigator agreed on subjects' response status 80% of the time for the cabozantinib arm and 100% of the time for the placebo arm.

Table 24. Concordance between BIRC-determined and Investigator-determined tumour response status[a] as of CCO1 (OITT population)

	Cabozantinib (N = 61) n (%)	Placebo (N = 33) n (%)	Total (N = 94) n (%)
Number of discordance			
Investigator response / BIRC no response	8 (13)	0	8 (8.5)
Investigator no response / BIRC response	4 (6.6)	0	4 (4.3)
Total discordance	12 (20)	0	12 (13)
Number of concordance			
Response	6 (9.8)	0	6 (6.4)
No response	43 (70)	33 (100)	76 (81)
Total concordance	49 (80)	33 (100)	82 (87)

BIRC, blinded independent radiology committee; OITT, overall response rate intent-to-treat.
[a] In subjects having at least one adequate post baseline tumor assessment by both BIRC and Investigator.

Secondary endpoints

Overall survival

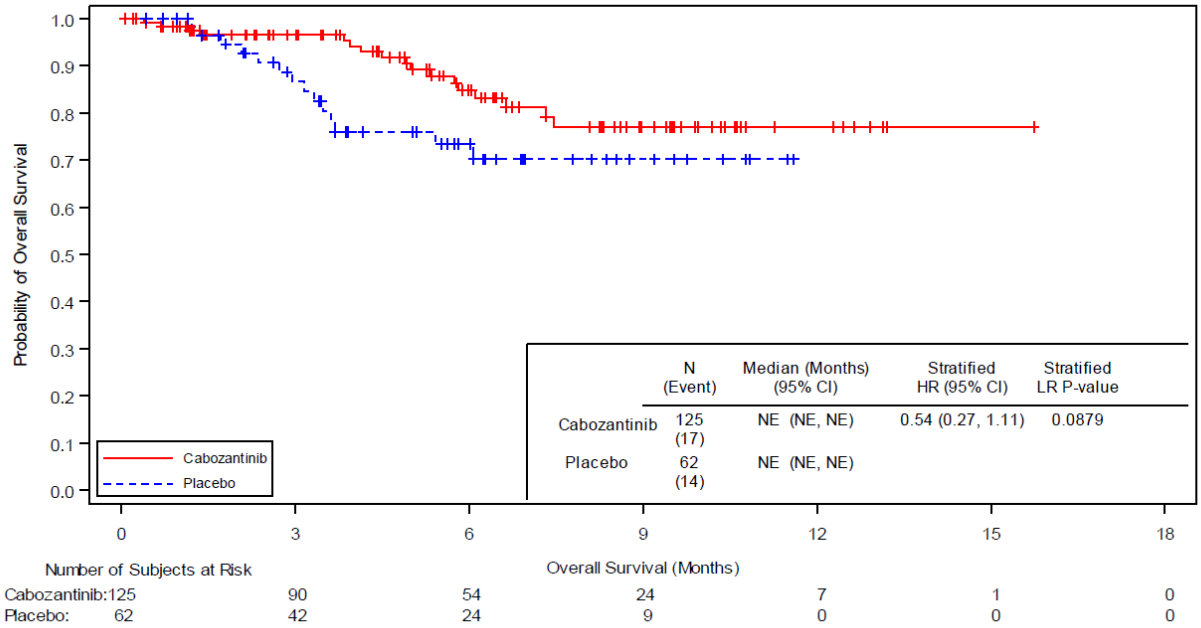
The analysis of the OS endpoint was performed using the ITT population. As of CCO1, a total of 31 deaths (17 cabozantinib, 14 placebo) were reported by this date. A total of 2 subjects (in the cabozantinib arm) withdrew full consent including for survival follow-up. All subjects were censored at their last known alive date. Subjects who were known to have died after the data cut-off date of 19 August 2020 were censored on that date. The median time of follow-up through 19 August 2020 was 6.24 months in the ITT population. Of note, the placebo arm included 19 subjects who subsequently crossed over to receive cabozantinib; these subjects were not censored at the time of crossover and were analysed under the randomised placebo arm for OS analysis under intent-to-treat principles.

Table 25. Overall Survival as of CCO1 (ITT population)

	Cabozantinib (N = 125)	Placebo (N = 62)
Number (%) of subjects		
Censored	108 (86)	48 (77)
Death	17 (14)	14 (23)
Duration of overall survival (months) [a]		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
25th percentile	NE	5.4
75th percentile	NE	NE
Range	0.07+, 15.74+	0.43+, 11.60+
Observed p-value (stratified log-rank test)[b, d]	0.0879	
Hazard ratio (95% CI; stratified)[b,c]	0.54 (0.27, 1.11)	
Observed p-value (unstratified log-rank test)[d]	0.0927	
Hazard ratio (95% CI; unstratified)	0.55 (0.27, 1.12)	
K-M landmark estimates (% of subjects event-free) at:		
3 months	96.5	86.6
6 months	84.8	73.4
9 months	77.0	70.2
12 months	77.0	NE

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; K-M, Kaplan-Meier; NE, not estimable; OS, overall survival.
+ indicates a censored observation (please see OS censoring rules in XL184-311 CSR, Section 9.7.1.4.1).
[a] Percentiles were based on Kaplan-Meier estimates.
[b] Stratification factors based on IxRS were receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
[c] p-value is non-inferential as OS is not a controlled endpoint.
[d] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable). HR < 1 indicated OS in favor of cabozantinib.
Source: XL184-311 CSR, Table 14.2.7.1

A total of 86% in the cabozantinib arm was censored compared to 77% in the placebo arm. Reasons for censoring were "alive" (82% in the cabozantinib arm vs. 73% in the placebo arm) and "death after data cut-off date" (4.8% in both arms).



CI, confidence; HR, hazard ratio, ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test, NE, not estimable.
+ Indicates censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

Figure 18. Kaplan-Meier plot of Overall Survival as of CCO1 (ITT population)

OS in the OITT population: The OS analysis was performed for the OITT population using the same analysis methods as for the ITT population. The median time of follow-up through 19 August 2020 was 8.85 months in the OITT population. Results were consistent with those of the OS analysis in the ITT population: the HR, adjusted for stratification factors (per IxRS), was 0.56 (95% CI: 0.25, 1.28). The Kaplan-Meier estimates for median duration of OS were not estimable in both arms.

Extent of non-protocol anticancer therapies (ITT and OITT populations)

The incidence of subsequent systemic non-radiation NPACT for each treatment arm in the ITT and OITT populations are summarised in the table below.

Table 26. Summary of non-protocol systemic non-radiation anticancer therapies (ITT and OITT populations)

Anticancer Therapies	ITT Population		OITT Population	
	Cabozantinib (N = 125) n (%)	Placebo (N = 62) n (%)	Cabozantinib (N = 67) n (%)	Placebo (N = 33) n (%)
Systemic nonradiation anticancer therapy	3 (2.4)	4 (6.5)	3 (4.5)	4 (12)
Protein Kinase Inhibitors (TKI)	3 (2.4)	4 (6.5)	3 (4.5)	4 (12)
Axitinib	1 (0.8)	0	1 (1.5)	0
Cabozantinib (commercial)[a]	0	2 (3.2)	0	2 (6.1)
Dabrafenib	0	1 (1.6)	0	1 (3.0)
Lenvatinib	2 (1.6)	1 (1.6)	2 (3.0)	1 (3.0)
Trametinib	0	1 (1.6)	0	1 (3.0)
Antineoplastic Agents	0	1 (1.6)	0	1 (3.0)

ITT, intent-to-treat; OITT, overall response rate intent-to-treat; TKI, tyrosine kinase inhibitor.
Subjects may be counted in more than one category; at each level of summarization, a subject was counted only once if the subject reported one or more therapies.
[a] Subjects 1193-3076 and 1368-3053 in the placebo arm were treated with commercially-available cabozantinib after being discontinued from the study.
Source: Table 14.3.1.3.1 and Table 14.3.1.3.3

Censoring for receipt of subsequent non-protocol anticancer therapy (NPACT); ITT population:

The OS analysis was repeated censoring survival times for subjects who received subsequent NPACT after randomization at the date of first receipt of such therapy; per protocol, subjects receiving these therapies had to discontinue study treatment. Results were consistent with those of the OS analysis for the ITT population: for the sensitivity analysis the HR, adjusted for stratification factors (per IxRS), was 0.52 (95% CI: 0.25, 1.10). The Kaplan-Meier estimates for median duration of OS were not estimable in either treatment arm.

Thyroglobulin (Tg) change from baseline as of CCO1 (ITT population)

Serum Tg, a tumour marker for DTC, was assessed at baseline, W5D1, W9D1, and every 8 weeks thereafter.

Median Tg levels at baseline were 2027.83 ng/mL in the cabozantinib arm and 1746.30 ng/mL in the placebo arm. The best change from baseline was defined as the largest decrease (or smallest increase if no decrease) from baseline. The worst change from baseline was defined as the largest increase (or smallest decrease if no increase) from baseline.

Table 27. Changes in thyroglobulin compared with baseline as of CCO1 (ITT population)

	Cabozantinib (N = 125)					Placebo (N = 62)				
	Baseline (n = 125)	Week 5 (n = 106)	Week 9 (n = 87)	Best Change[a] (n = 108)	Worst Change[a] (n = 108)	Baseline (n = 62)	Week 5 (n = 52)	Week 9 (n = 34)	Best Change[a] (n = 52)	Worst Change[a] (n = 52)
% median change from baseline	–	-27.63	-27.61	-46.47	0.00	–	14.31	34.69	14.31	56.80

ITT, intent-to-treat.
[a] Best change is the largest decrease (or smallest increase if no decrease) from baseline; worst change from baseline is the largest increase (or smallest decrease if no increase) from baseline.
Source: XL184-311 CSR, Table 14.2.12.1

Health-Related Quality of Life as of CCO1 (ITT population)

Patient Reported Outcomes (PROs) were assessed using the EQ-5D-5L, a validated questionnaire measuring general health outcomes. The EQ-5D-5L includes a descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system comprises five dimensions: mobility, self-care, usual

activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels of increasing severity, from 1 (no problem) to 5 (extreme problems). The descriptive system is used to obtain the EQ-Index. The EQ VAS records the patient's self-rated health on a vertical VAS, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

Subjects completed a baseline questionnaire, and post-baseline assessments were collected every 4 weeks (W5D1, W9D1, etc) until W25D1 followed by every 8 weeks. Assessments continued regardless of whether study treatment was given, reduced, interrupted, or discontinued until the later of investigator-assessed radiographic disease progression per RECIST 1.1 that was confirmed per real-time BIRC review or the date of the decision to permanently discontinue study treatment. Subjects, who were blinded to treatment completed the questionnaire on the day of the visit prior to seeing study site personnel. Subjects were not to receive medical results prior to completing the questionnaire. HRQOL assessments were not collected for the 40 subjects who transitioned to the crossover phase or if the study transitioned to the maintenance phase.

The EQ-5D-5L questionnaire completion rate (number of subjects who completed all questions/number of expected subjects still on study at each visit) at baseline was 98% in the cabozantinib arm and 100% in the placebo arm and remained above 80% in each treatment arm through Week 33. Beyond W33D1, there were fewer than 5 subjects in the placebo arm, too few to allow for any conclusion. Questionnaires were predominantly collected in subjects who were on study treatment (duration of study treatment was longer in the cabozantinib arm) and before progression.

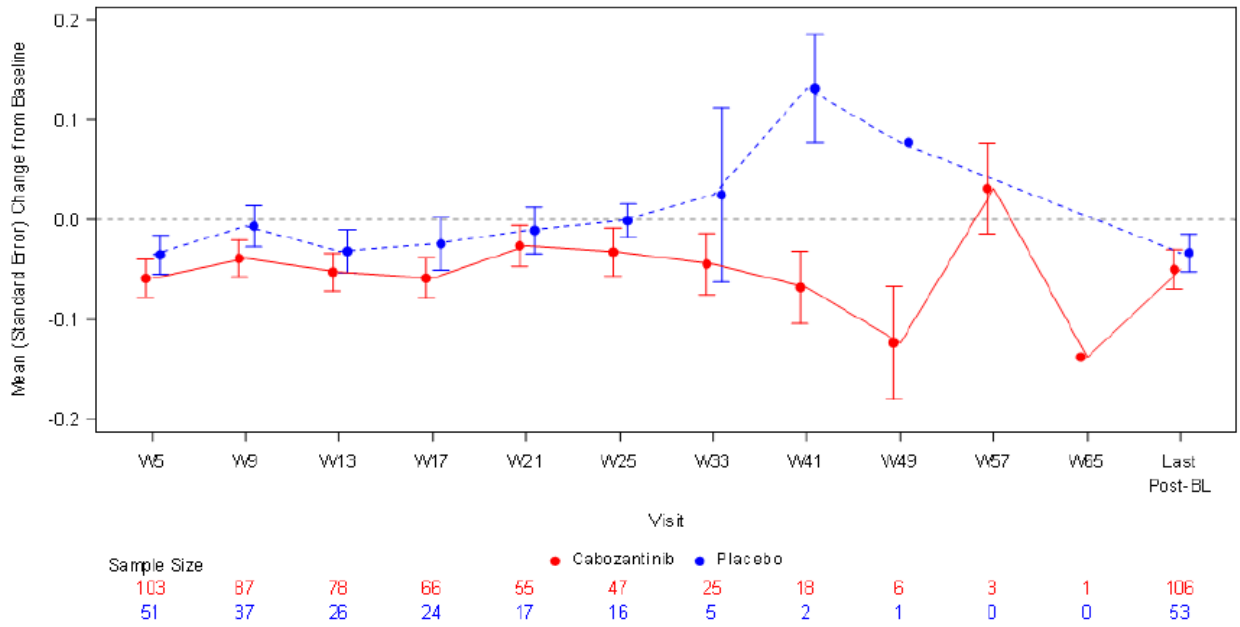
The minimal important differences (MID) for the EQ-5D-5L in cancer patients were previously established as 0.06 - 0.08 for EQ-5D Index, and 7 for EQ-VAS (Pickard et al 2007). In addition, for the EQ-Index and the EQ-VAS, the effect size for change from baseline was calculated as mean of change in score/pooled SD for baseline scores. An effect size ≥ 0.3 was considered potentially clinically meaningful (Sloan et al 2005; Yost and Eton 2005).

EQ-Index

Patient's health state described by dimensions' values was converted into a single index value normalised across 10 countries in which the value set has been validated. EQ-Index values were anchored by 0 (dead) and 1 (full health), i.e., a higher index score indicated better health.

At baseline, mean EQ-Index scores were 0.751 in the cabozantinib arm and 0.729 in the placebo arm. All treatment differences in mean change from baseline EQ-Index values were < 0.06 through W33D1 (MID = 0.06 – 0.08; see figure below). Beyond this time point there were fewer than 5 subjects in the placebo arm and results cannot be interpreted.

QoL remained stable throughout the duration of the treatment up to time points with less than 5 subjects by arm.



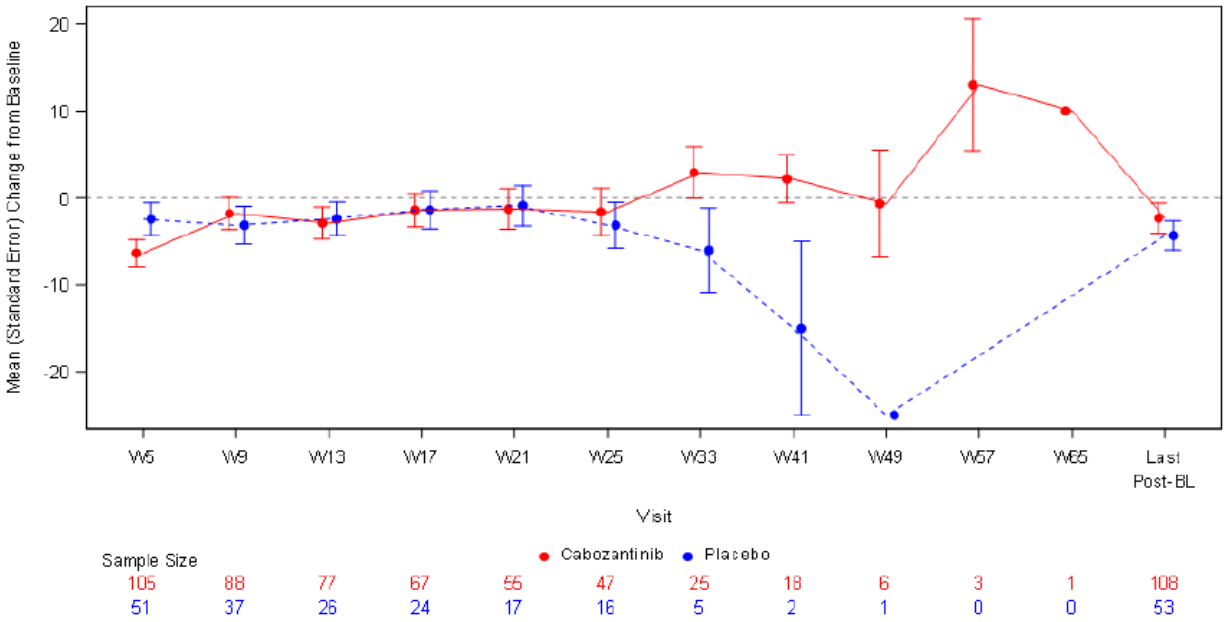
ITT, intent-to-treat; Post-BL, post-baseline; SE, standard error; W, week
Higher index scores indicate better quality of life: index is scored from 0 (death) to1 (full health)
The number of subjects at baseline with EQ-Index scores was 122 in the cabozantinib and 62 in the placebo arm.

Figure 19. Mean (±SE) change from baseline of EQ-Index score as of CCO1 (ITT population; countries in which EQ-Index is validated)

EQ-VAS

At baseline, mean EQ-VAS scores for the ITT population were 69.4 in the cabozantinib arm and 67.8 in the placebo arm. All treatment differences in mean change from baseline EQ-VAS values were < 7 through W33D1 (MID = 7; see figure below). Beyond this time point, there were fewer than 5 subjects in the placebo arm, so results cannot be interpreted.

QoL remained stable throughout the duration of the treatment up to time points with fewer than 5 subjects by arm.



ITT, intent-to-treat; Post-BL, post-baseline; SE, standard error; VAS, visual analogue scale; W, week.
Higher EQ-VAS scores indicate better quality of life: EQ-VAS is scored from 0 (worst health you can imagine) to 100 (best health you can imagine).
The number of subjects at baseline with EQ-VAS scores was 122 in the cabozantinib and 62 in the placebo arm.

Figure 20. Mean (±SE) change from baseline of EQ-VAS score as of CCO1 (ITT population)

Results from a repeated measures analysis is shown below:

Table 28. EQ-VAS and EQ-Index scores: change from baseline, repeated-measures analysis (ITT population, countries in which index is validated [index]; ITT population [VAS])

	Cabozantinib (N = 125) n LSMeans (SE)	Placebo (N = 62) n LSMeans (SE)	Difference in Mean Change[a]	Pooled SD	P-value[a]	Effect Size[b]
EQ-Index	106 -0.0479 (0.0180)	53 -0.0387 (0.0229)	-0.0092	0.1580	0.6797	-0.0581
EQ-VAS	108 -3.0415 (1.6746)	53 -2.6727 (2.1078)	-0.3689	15.3759	0.8510	-0.0240

ITT, intent-to-treat; LSMean, least squares means; SD, standard deviation; SE, standard error; VAS, visual analogue scale.
A higher score indicates better health-related quality of life.

[a] Derived from the prespecified repeated-measures mixed-effects model analysis of covariance. Predictors (fixed effects) were baseline scores, treatment, visit, and randomization strata. Individual subject nested within the planned treatment arm was the random effect. No adjustment was made for multiple comparisons.

[b] Effect size = (mean of change in score)/(pooled SD for both groups for baseline values). Effect size differences ≥ 0.3 were regarded as likely to be clinically relevant (Sloan et al 2005, Yost and Eton 2005).

Ancillary analyses

Supportive analyses of PFS by BIRC was conducted on the Full ITT population (258 subjects) and the Primary Analysis subset (187 subjects) at CCO2 (08 February 2021) and included radiographic progression events as determined by the BIRC per RECIST 1.1 or death due to any cause.

Table 29. PFS per RECIST 1.1. by BIRC as of CCO2 (Full ITT population and Primary Analysis Subset)

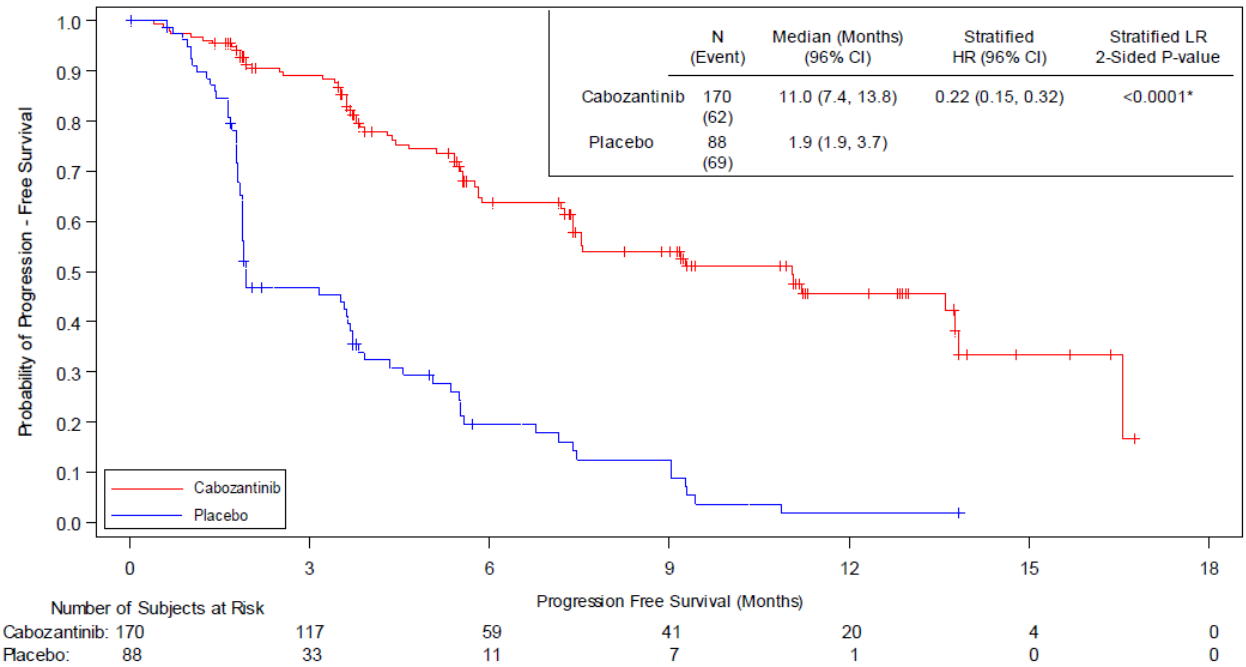
	Full ITT Population (N = 258)		Primary Analysis Subset (N = 187)	
	Cabozantinib (N = 170)	Placebo (N = 88)	Cabozantinib (N = 125)	Placebo (N = 62)
Number (%) of subjects				
Censored	108 (64)	19 (22)	69 (55)	4 (6.5)
Receipt of local radiation to soft tissue for DTC	2 (1.2)	1 (1.1)	2 (1.6)	1 (1.6)
No post-baseline ATA[a]	15 (8.8)	8 (9.1)	3 (2.4)[b]	0
No event by last ATA	81 (48)	8 (9.1)	55 (44)	3 (4.8)
2 or more missed ATA prior to event	4 (2.4)	0	4 (3.2)	0
Systemic NPACT	6 (3.5)	2 (2.3)	5 (4.0)	0
Event	62 (36)	69 (78)	56 (45)	58 (94)
Death	12 (7.1)	4 (4.5)	9 (7.2)	3 (4.8)
Progressive disease	50 (29)	65 (74)	47 (38)	55 (89)
Duration of PFS (months)				
Median (96% CI)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)	11.1 (7.4, 13.8)	1.9 (1.8, 3.8)
25th percentile, 75th percentile[c]	4.7, 16.6	1.8, 5.5	5.1, 16.6	1.7, 5.5
Range	0.03+, 16.76+	0.03+, 13.83+	0.03+, 16.76+	0.03+, 13.83+
Observed p-value (stratified log-rank test)[d]	<0.0001		<0.0001	
Hazard ratio (95% CI; stratified)[d,e]	0.22 (0.15, 0.31)		0.22 (0.15, 0.32)	
Hazard ratio (96% CI; stratified)[d,e]	0.22 (0.15, 0.32)		0.22 (0.14, 0.33)	
Observed p-value (unstratified log-rank test)	<0.0001		<0.0001	
Hazard ratio (95% CI; unstratified)[e]	0.23 (0.16, 0.33)		0.23 (0.16, 0.34)	
Hazard ratio (96% CI; unstratified)[e]	0.23 (0.16, 0.33)		0.23 (0.16, 0.34)	
K-M landmark estimates (% of subjects event-free) at:				
3 months	89.1	46.8	89.0	45.9
6 months	63.7	19.5	64.7	20.8
9 months	54.0	12.4	54.9	13.2
12 months	45.6	1.8	46.3	1.9

ATA, adequate tumor assessment; BIRC, blinded independent radiology committee; CI, confidence interval; DTC, differentiated thyroid cancer; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; K-M, Kaplan-Meier; NPACT, nonprotocol anticancer therapy; PFS, progression-free survival.

+ indicates a censored observation (please see PFS censoring rules in XL184 CSR Section 9.7.1.2.2)

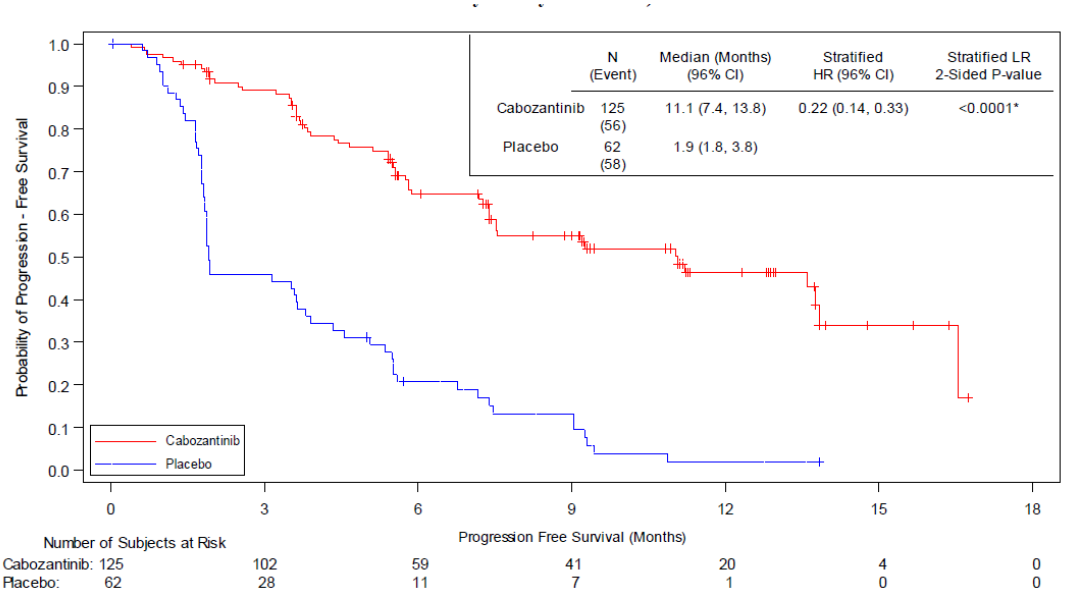
[a] In the Full ITT population, 11 cabozantinib and 8 placebo subjects were enrolled too close to the data cut cutoff date to have had a post-baseline tumor assessment. Four cabozantinib subjects decided to withdraw from treatment before any post-baseline tumor assessment. In addition, 3 subjects in the cabozantinib arm (1807-3002, 3808-3111, and 3907-3338) and 1 subject in the placebo arm (3905-3275) died before their first post-baseline scan. These subjects are summarized under the events (death) category and not under the censored (no post-baseline ATA) category for PFS but were considered censored for having no post-baseline scan in the ORR analysis (Table 22).

[b] The Primary Analysis subset includes approximately 6 months additional follow-up for all subjects from the prespecified interim PFS analysis. As a result, there are fewer subjects without a post-baseline assessment in this analysis compared with the Full ITT Population analysis.
[c] Percentiles were based on K-M estimates.
[d] Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
[e] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable). HR < 1 indicated PFS in favor of cabozantinib.



BIRC, blinded independent radiology committee; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test.
+ indicates value from censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

Figure 21. Kaplan-Meier plot of PFS per BIRC as of CCO2 (Full ITT population)



BIRC, blinded independent radiology committee; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test.
+ indicates value from censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).

Figure 22. Kaplan-Meier plot of PFS per BIRC as of CCO2 (ITT population, Primary Analysis Subset)

Sensitivity and supplementary analyses: Progression-Free Survival (supportive analysis: CCO2)

Sensitivity and supplementary analyses of PFS as of CCO2 are limited to BIRC-related analyses.

For the Full ITT Population (N = 258) and Primary Analysis subset (N = 187), the table below provides point estimates and 95% CIs of stratified HRs for the primary PFS (PFS-EP-1) analysis described above and for pre-specified sensitivity (PFS-EP-2 and PFS-EP-4) and supplementary (PFS-EA2-1 and PFS-EA2-2) analyses, in which additional or alternative clinical outcomes were considered to be events.

Table 30. Sensitivity and supplementary analyses of PFS as of CCO2 (Full ITT population and Primary Analysis Subset)

PFS Analysis	No. of Events/Subjects (%) Median Duration (mo)		Stratified Hazard Ratio	95% CI	Stratified Log-rank p-value
	Cabozantinib	Placebo			
Full ITT Population (N = 258)					
PFS-EP-1[a]	62 (36) 11.0	69 (78) 1.9	0.22	0.15, 0.31	<0.0001
PFS-EP-2[b]	61 (36) 11.0	68 (77) 1.9	0.22	0.15, 0.31	<0.0001
PFS-EP-4[c]	66 (39) 9.3	69 (78) 1.9	0.24	0.17, 0.34	<0.0001
PFS-EA2-1[d]	68 (40) 9.2	71 (81) 1.9	0.22	0.16, 0.32	<0.0001
PFS-EA2-2[e]	72 (42) 8.9	71 (81) 1.9	0.24	0.17, 0.34	<0.0001
Primary Analysis Subset (N = 187)					
PFS-EP-1[a]	56 (45) 11.1	58 (94) 1.9	0.22	0.15, 0.32	<0.0001
PFS-EP-2[b]	55 (44) 11.1	57 (92) 1.9	0.22	0.15, 0.32	<0.0001
PFS-EP-4[c]	60 (48) 11.0	58 (94) 1.9	0.24	0.16, 0.35	<0.0001
PFS-EA2-1[d]	61 (49) 9.3	58 (94) 1.9	0.22	0.15, 0.33	<0.0001
PFS-EA2-2[e]	65 (52) 9.2	58 (94) 1.9	0.25	0.17, 0.36	<0.0001

ATA, adequate tumor assessments; CCO2, Clinical Cutoff 2; CI, confidence interval; ITT, intent-to-treat; mo, months; No, number; NPACT, nonprotocol anticancer therapy; PFS, progression-free survival.

[a] PFS-EP-1: PFS analysis as of CCO2 (data cutoff of 08 February 2021).

[b] PFS-EP-2: Date of radiographic progression was based on the date of the scheduled visit, rather than the date of recorded progression.

[c] PFS-EP-4: Rather than being censored, subjects who experienced ≥ 2 consecutive missing scheduled ATA immediately prior to documented radiographic progression were classified as having an event at the date of the last ATA prior to the missing visits.

[d] PFS-EA2-1: Receipt of systemic NPACT was changed to "composite," resulting in an endpoint that comprised radiographic progression, death, or initiation of systemic NPACT (XL184-311 CSR, Section 9.7.1.2.2.2).

[e] PFS-EA2-2: Sensitivity analysis of PFS-EA2-1 similar to PFS-EP-4 (footnote "c" above).

Objective Response Rate per RECIST 1.1 by BIRC as of CCO2 (ITT Population)

- A supportive analysis of ORR per RECIST 1.1 as determined by BIRC was performed as of CCO2. This supportive analysis was performed using the 258 subjects in the Full ITT Population.
- Separately, a supportive analysis of ORR per RECIST 1.1 as determined by BIRC was performed on the 187 subjects in the Primary Analysis subset as of CCO2.

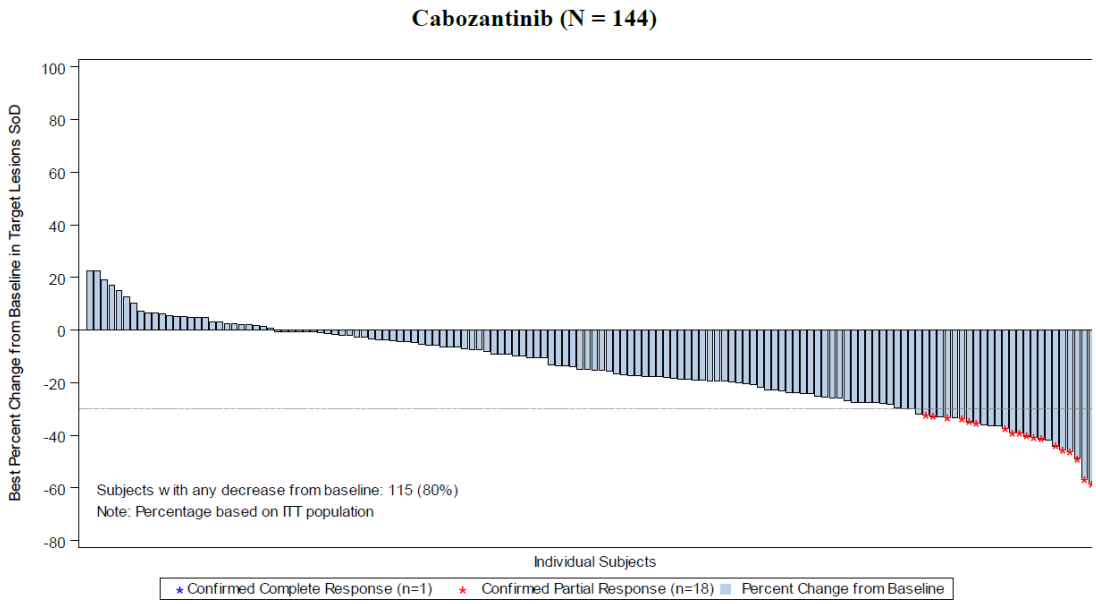
Table 31. ORR per BIRC as of CCO2 (Full ITT population and Primary Analysis Subset)

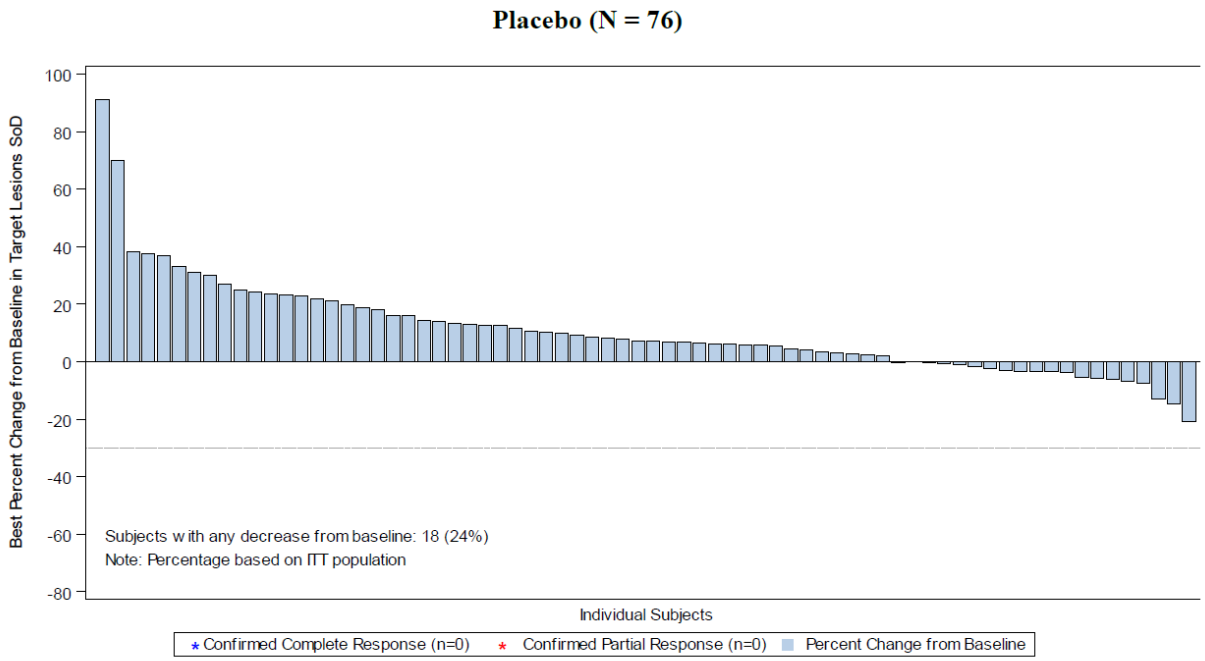
	Full ITT Population (N = 258)		Primary Analysis Subset (N = 187)	
	Cabozantinib (N = 170)	Placebo (N = 88)	Cabozantinib (N = 125)	Placebo (N = 62)
Best overall response, n (%)[a]				
Confirmed complete response (CR)	1 (0.6)	0	1 (0.8)	0
Confirmed partial response (PR)	18 (10.6)	0	18 (14.4)	0
Stable disease (SD)	117 (68.8)	34 (38.6)	87 (69.6)	26 (41.9)
Unconfirmed CR (uCR)	0	0	0	0
Unconfirmed PR (uPR)	8 (4.7)	0	8 (6.4)	0
Progressive disease (PD)	11 (6.5)	42 (47.7)	9 (7.2)	34 (54.8)
No disease (NA)	1 (0.6)	0	1 (0.8)	0
Unable to evaluate (UE)	3 (1.8)	1 (1.1)	3 (2.4)	1 (1.6)
Missing	19 (11.2)	11 (12.5)	6 (4.8)	1 (1.6)
No baseline assessments	0	0	0	0
No post-baseline assessments	18 (10.6)	9 (10.2)	5 (4.0)	0
No qualifying post-baseline assessments on or before PFS censoring or event date	18 (10.6)	9 (10.2)	5 (4.0)	0
SD not meeting minimum criteria from randomization	1 (0.6)	2 (2.3)	1 (0.8)	1 (1.6)
Objective response rate (CR+PR), n (%)	19 (11)	0	19 (15)	0
95% CI	6.9, 16.9	0.0, 4.1	9.4, 22.7	0.0, 5.8
Treatment difference (cabozantinib – placebo) (95% CI)[b]	11 (6.4, 15.9)		15 (8.9, 21.5)	
Observed stratified CMH test p-value per IxRS[c]	0.0009		0.0010	
Observed unstratified Fisher exact test p-value	0.0003		0.0005	
Disease stabilization rate (ORR+SD ≥ 16 weeks), n (%)	90 (52.9)	17 (19.3)	81 (64.8)	15 (24.2)
95% CI	45.1, 60.6	11.7, 29.1	55.8, 73.1	14.2, 36.7
DOR per BIRC (K-M), median (range), months	10.2 (1.87+, 12.85+)	NA	10.2 (1.87+, 12.85+)	NA
Time to Objective Response per BIRC, median (range) time from randomization, months[d]	3.581 (1.74, 7.52)	NA	3.581 (1.74, 7.52)	NA

BIRC, blinded independent radiology committee; CI, confidence interval; CMH, Cochran Mantel-Haenszel; CR, complete response; ITT, intent-to-treat; IxRS, interactive voice/web response system; K-M, Kaplan-Meier; NA, not applicable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
+ Indicates value from censored observation.
[a] Best overall response was assessed based on RECIST 1.1 criteria and was calculated based on subjects in the ITT population. Note that a CR or PR was not considered as an objective response if a subject progressed or received subsequent anticancer therapy prior to the first CR or PR. To be classified as a CR or PR, confirmation of response must have occurred > 28 days after the response was first observed.
[b] Using asymptotic confidence limits based on large number theorem.
[c] Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
[d] Time to objective response is an arithmetic summary amongst those with an objective response and is defined as time from randomization to the first CR or PR that is subsequently confirmed.

The best percentage change from baseline in tumour target lesion size in the Full ITT population as determined by BIRC per RECIST 1.1 is depicted in the figure below.

Among subjects in the Full ITT population with at least one baseline and at least one post-baseline target lesion assessment, 115/144 (80%) in the cabozantinib arm and 18/76 (24%) in the placebo arm had a post-baseline reduction in the sum of target lesion diameters (SoD).





BIRC, blinded independent radiology committee; ITT, intent-to-treat; PFS, progression-free survival; SoD, sum of target lesion diameters.
Subjects are not represented due to lack of evaluable post-baseline assessment, censoring (per PFS rules) before first evaluable post-baseline assessment, lack of target lesions, and/or incomplete or unevaluable target lesion assessment.
Data from time points after the first date of any of the censoring events defined for the primary PFS analysis (in XL184-311 CSR, Section 9.7.1.2.2) were excluded.

Figure 23. Waterfall plot of best percentage change in tumour target lesion size from baseline per BIRC as of CCO2 (Full ITT population; subjects with at least one baseline and at least one post-baseline target lesion assessment)

The best percentage change from baseline in tumour target lesion size in the Primary Analysis subset as determined by BIRC per RECIST 1.1 is depicted in the figure below. Among subjects in the Primary Analysis subset with at least one baseline and at least one post-baseline target lesion assessment, 90/114 (79%) in the cabozantinib arm and 16/60 (27%) in the placebo arm had a post-baseline reduction in the SoD.

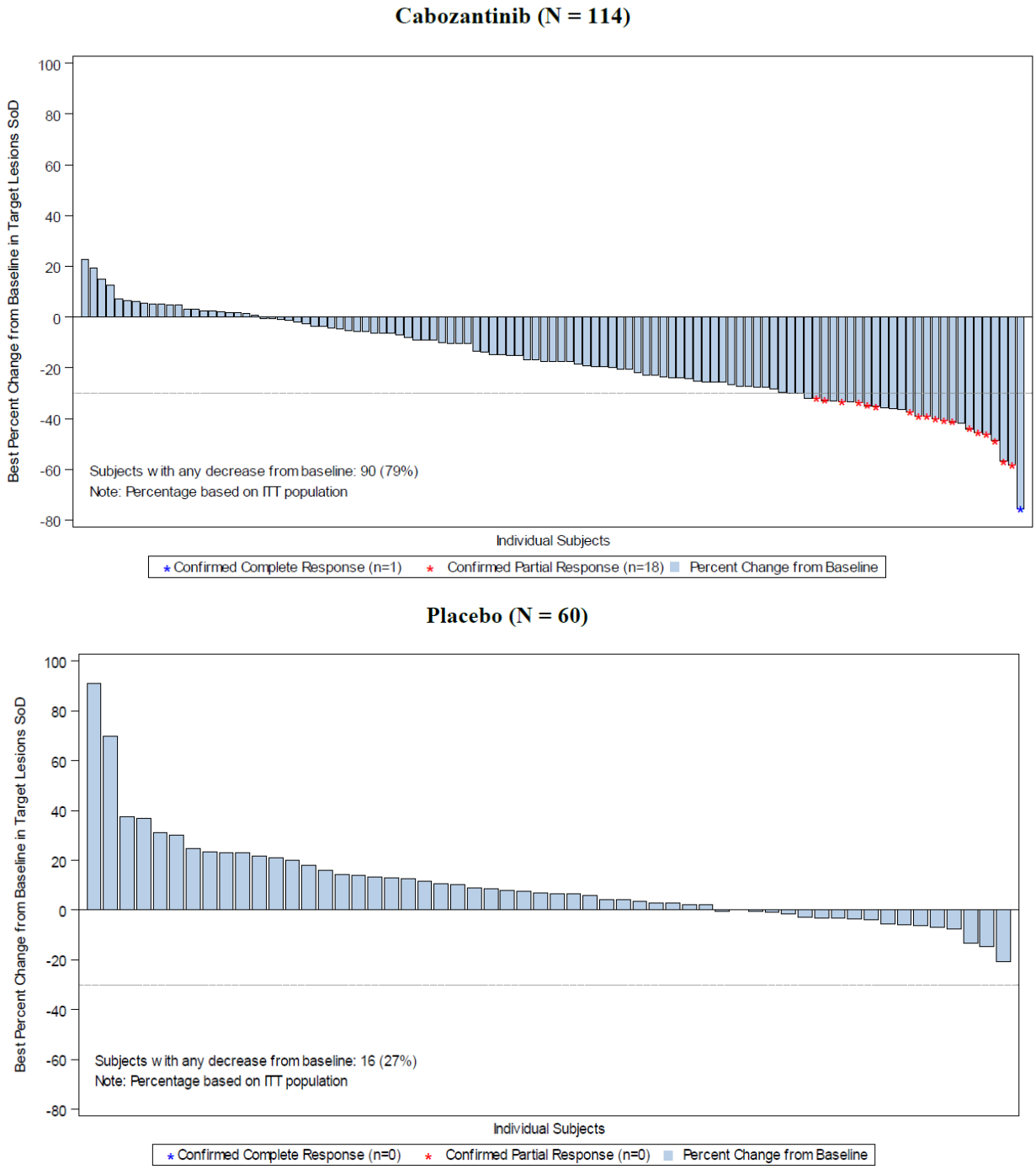


Figure 24. Waterfall plot of best percentage change in tumour target lesion size from baseline per BIRC as of CCO2 (ITT population, Primary Analysis Subset; subjects with at least one baseline and at least one post-baseline target lesion assessment)

BIRC, blinded independent radiology committee; ITT, intent-to-treat; PFS, progression-free survival; SoD, sum of target lesion diameters.
Subjects are not represented due to lack of evaluable post-baseline assessment, censoring (per PFS rules) before first evaluable post-baseline assessment, lack of target lesions, and/or incomplete or unevaluable target lesion assessment. Data from time points after the first date of any of the censoring events defined for the primary PFS analysis (in XL184-311 CSR, Section 9.7.1.2.2) were excluded.

Overall Survival as of CCO2 (Full ITT population and Primary Analysis Subset)

The supportive analysis of the OS endpoint was performed using the Full ITT population and Primary Analysis subset as of CCO2. In the Full ITT population, a total of 58 deaths (37 cabozantinib, 21 placebo) were reported at CCO2 (see table below), compared with 31 deaths reported at CCO1. Survival status as of the data cut-off date was determined for all 258 randomized subjects. Of note, 133 subjects (78%) in the cabozantinib arm and 67 subjects (76%) in the placebo arm were censored at their last known alive dates including 2 cabozantinib subjects who died after data cut-off.

Table 32. Overall Survival as of CCO2 (Full ITT population and Primary Analysis Subset)

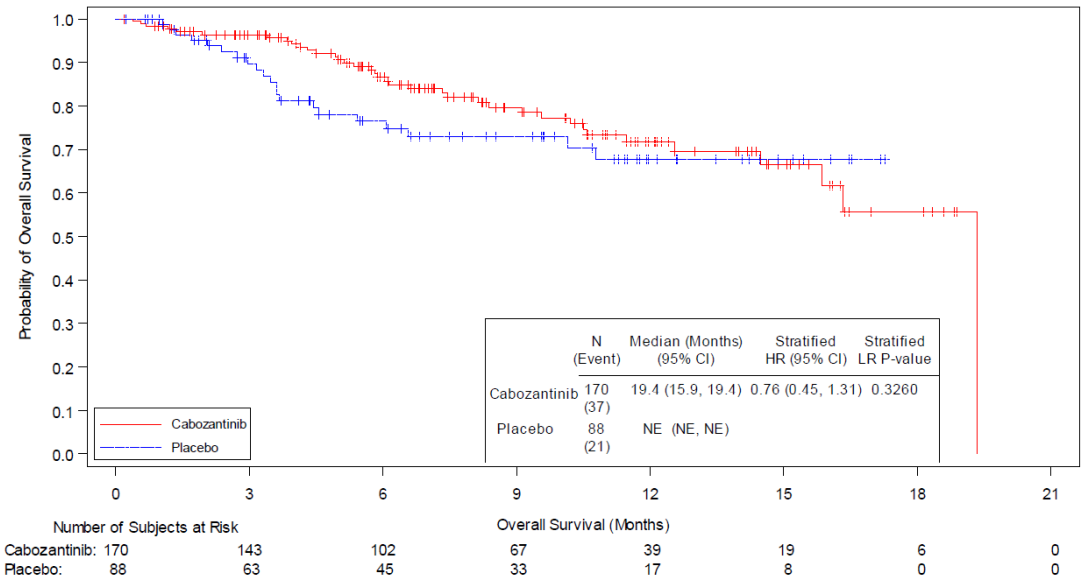
	Full ITT Population (N = 258)		Primary Analysis Subset (N = 187)	
	Cabozantinib (N = 170)	Placebo (N = 88)	Cabozantinib (N = 125)	Placebo (N = 62)
Number (%) of subjects				
Censored	133 (78)	67 (76)	91 (73)	42 (68)
Alive	131 (77)	67 (76)	89 (71)	42 (68)
Death after data cutoff date	2 (1.2)	0	2 (1.6)	0
Death	37 (22)	21 (24)	34 (27)	20 (32)
Duration of overall survival (months) [a]				
Median (95% CI)	19.4 (15.9, NE)	NE (NE, NE)	19.4 (15.9, NE)	NE (NE, NE)
25th percentile	10.5	6.1	10.5	5.4
75th percentile	19.4	NE	19.4	NE
Range	0.20+, 19.35	0.23+, 17.28+	0.39, 19.35	0.99+, 17.28+
Observed p-value (stratified log-rank test)[b]	0.3260		0.2774	
Hazard ratio (95% CI; stratified)[b, c]	0.76 (0.45, 1.31)		0.74 (0.42, 1.28)	
Observed p-value (unstratified log-rank test)	0.3567		0.2997	
Hazard ratio (95% CI; unstratified)[c]	0.78 (0.45, 1.33)		0.75 (0.43, 1.30)	
K-M landmark estimates (% of subjects event-free) at:				
3 months	96.4	89.7	96.0	88.5
6 months	86.6	76.5	86.9	73.8
9 months	79.7	73.0	80.0	70.4
12 months	71.7	67.7	72.0	65.3
18 months	55.6	NE[d]	55.8	NE[d]

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; K-M, Kaplan-Meier; NE, not estimable; OS, overall survival.
+ indicates a censored observation (please see OS censoring rules in XL184-311 CSR Section 9.7.1.4.1).
[a] Percentiles were based on K-M estimates.
[b] Stratification factors based on IxRS were receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
[c] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable). HR < 1 indicated OS in favor of cabozantinib.
[d] In the Full ITT population and Primary Analysis subset, maximum duration of OS in the placebo arm was 17.28 months at CCO2.

As can be seen from the table above, the K-M estimate in the full ITT population for median duration of OS was 19.4 months (95% CI: 15.9, NE) in the cabozantinib arm and NE in the placebo arm, HR was 0.76 (95% CI stratified: 0.45, 1.31). However, due to the immaturity of the data, this estimate is not reliable at present.

Of note, the tail of the K-M curve for the full ITT population (see below) and median estimate for OS are unstable due to the low number of subjects at risk with the longest follow up times and an event experienced by the subject with the longest follow-up. The placebo arm of the full ITT population included 40 subjects who crossed over to receive cabozantinib, 8 of whom had an event. The other 32

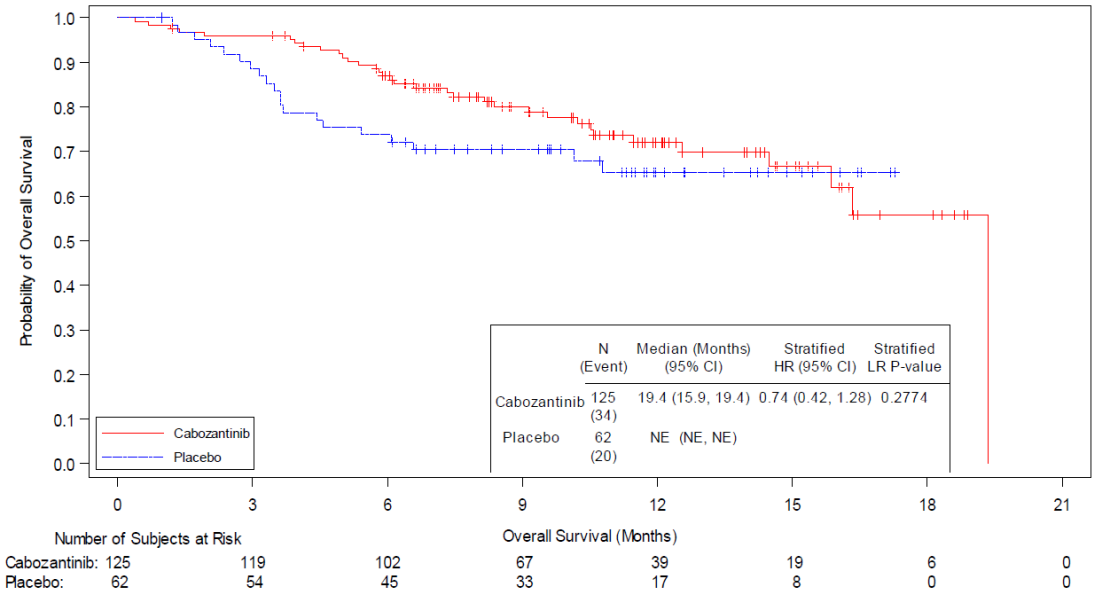
subjects were censored; of these subjects, 12 had at least 6 months of post-crossover survival and 2 were still on open-label cabozantinib as of CCO2. The placebo crossover subjects were not censored at the time of crossover and were analysed under the randomised placebo arm for OS analysis under ITT principles.



CI, confidence; HR, hazard ratio, ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test, NE, not estimable; OS, overall survival.
+ Indicates censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
The upper limit of the 95% CI for median OS should be interpreted as NE.
The last remaining subject in the cabozantinib arm had an event leading the survival probability to 0% as no subject remained at risk anymore.

Figure 25. Kaplan-Meier plot of Overall Survival as of CCO2 (Full ITT population, N = 258)

Of note, in the Primary Analysis Subset, the placebo arm included 35 subjects who crossed over to receive cabozantinib



CI, confidence; HR, hazard ratio, ITT, intent-to-treat; IxRS, interactive voice/web response system; LR, log-rank test, NE, not estimable; OS, overall survival.
+ Indicates censored observation
Stratification factors (per IxRS) comprise receipt of prior lenvatinib (yes vs no) and age at informed consent (≤ 65 years vs > 65 years).
The upper limit of the 95% CI for median OS should be interpreted as NE.
The last remaining subject in the cabozantinib arm had an event leading the survival probability to 0% as no subject remained at risk anymore.

Figure 26. Kaplan-Meier plot of Overall Survival as of CCO2 (ITT population, Primary Analysis Subset, N = 187)

Extent of non-protocol anticancer therapies (Full ITT population and Primary Analysis Subset)

The incidence of subsequent systemic non-radiation non-protocol anticancer therapy (NPACT) received by ≥2 subjects in either treatment arm as of CCO2 are summarized in the table below for the Full ITT population and the Primary Analysis subset.

Table 33. Summary of non-protocol systemic non-radiation anticancer therapies (≥ 2 subjects in either treatment arm; Full ITT population and Primary Analysis Subset)

Anticancer Therapies	Full ITT Population (N = 258)		Primary Analysis Subset (N = 187)	
	Cabozantinib (N = 170) n (%)	Placebo (N = 88) n (%)	Cabozantinib (N = 125) n (%)	Placebo (N = 62) n (%)
Systemic nonradiation anticancer therapy	19 (11)	10 (11)	18 (14)	7 (11)
Protein Kinase Inhibitors (TKI)[a]	16 (9.4)	9 (10)	15 (12)	6 (9.7)
Cabozantinib (commercial)	2 (1.2)	3 (3.4)	2 (1.6)	2 (3.2)
Dabrafenib	2 (1.2)	1 (1.1)	2 (1.6)	1 (1.6)
Lenvatinib	7 (4.1)	4 (4.5)	6 (4.8)	2 (3.2)
Sunitinib	2 (1.2)	0	2 (1.6)	0
Trametinib	2 (1.2)	1 (1.1)	2 (1.6)	1 (1.6)

ITT, intent-to-treat; NPACT, nonprotocol anticancer therapy; TKI, tyrosine kinase inhibitor.
Subjects may be counted in more than one category; at each level of summarization, a subject was counted only once if the subject reported one or more therapies.
Receipt of open-label cabozantinib is not considered receipt of NPACT. Therefore, the 40 and 35 subjects randomized to the placebo arm in the Full ITT population and Primary Analysis subset, respectively, who crossed over to receive open-label cabozantinib were not summarized as having received NPACT (Section 3.2.1.1).
[a] Therapies listed are those used by > 2 subjects in either treatment arm.

Overall Survival: censoring for receipt of subsequent non-protocol anticancer therapy (Full ITT population and Primary Analysis Subset)

As a sensitivity analysis, the OS analysis was repeated censoring survival times for subjects who received subsequent NPACT after randomization at the date of first receipt of such therapy; per protocol, subjects receiving these therapies had to discontinue study treatment. Placebo subjects receiving open-label cabozantinib upon crossover were analysed under the randomized placebo arm for OS based on ITT principles. Receipt of open-label cabozantinib is not considered receipt of NPACT. Therefore the 40 and 35 subjects randomized to the placebo arm in the Full ITT population and Primary Analysis subset, respectively, who crossed over to receive open-label cabozantinib were not censored for having received NPACT in the sensitivity analysis for OS.

The results for the OS sensitivity analysis for receipt of subsequent NPACT were consistent with the corresponding OS analyses for the Full ITT population and for the Primary Analysis subset. HR for Full ITT population (both stratified and unstratified) of 0.67 (95% CI stratified: 0.38, 1.17 and unstratified: 0.38, 1.18). For the Primary Analysis Subset HR (both stratified and unstratified) was 0.64 (95% CI stratified: 0.35, 1.14 and unstratified: 0.36, 1.14).

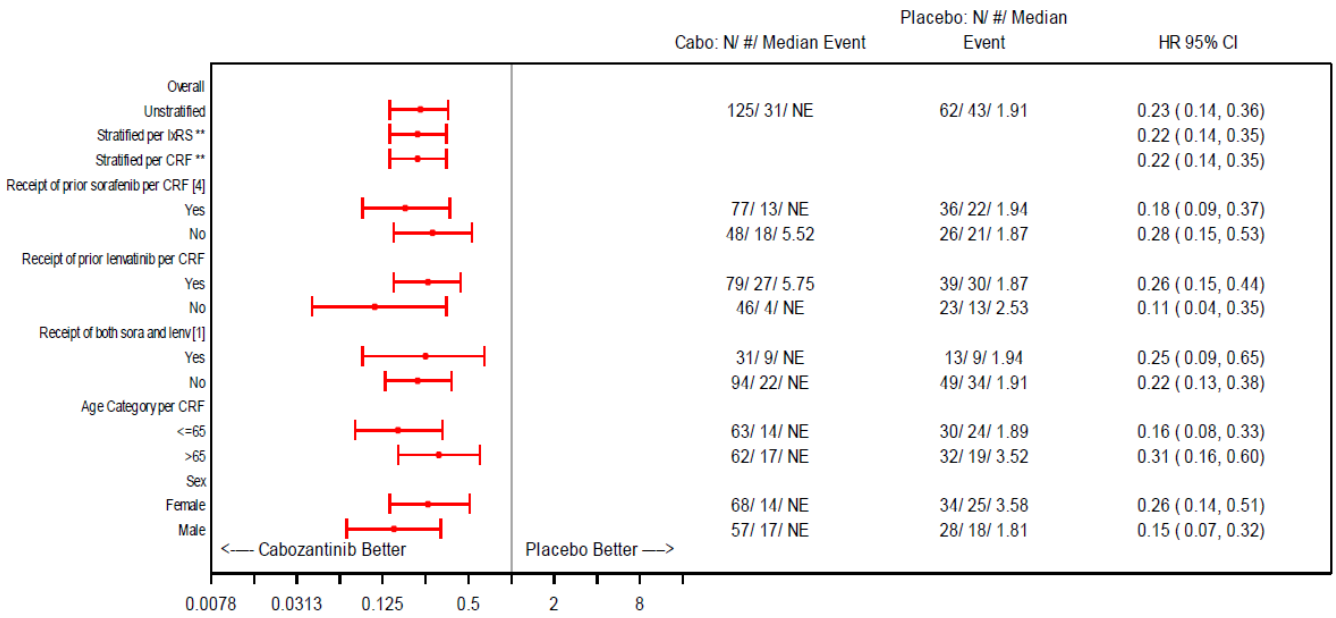
Pharmacogenetics and biomarkers

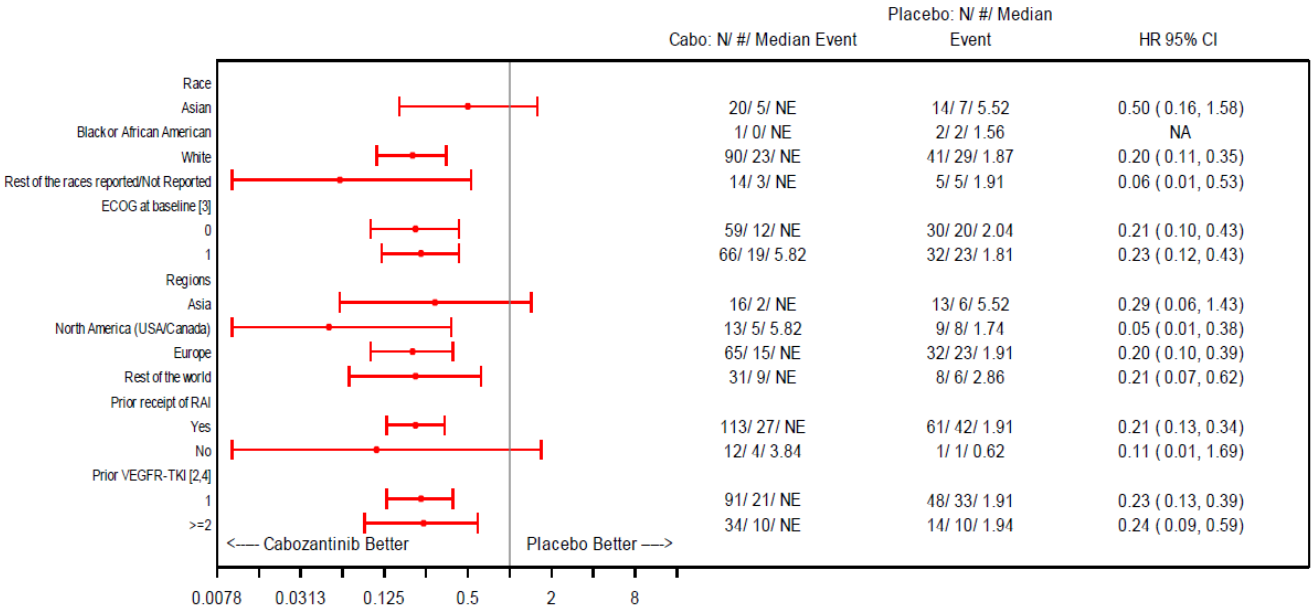
Unless prohibited by local regulations, failure to grant informed consent for this purpose, or Sponsor decision, a blood sample was collected pre-dose on W1D1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment. Blood samples were also collected to evaluate plasma and/or serum biomarkers pre-dose on W1D1, W5D1, and W9D1 (each ± 3 days). Of note though, pharmacogenetic and biomarker samples were not analysed for this CSR.

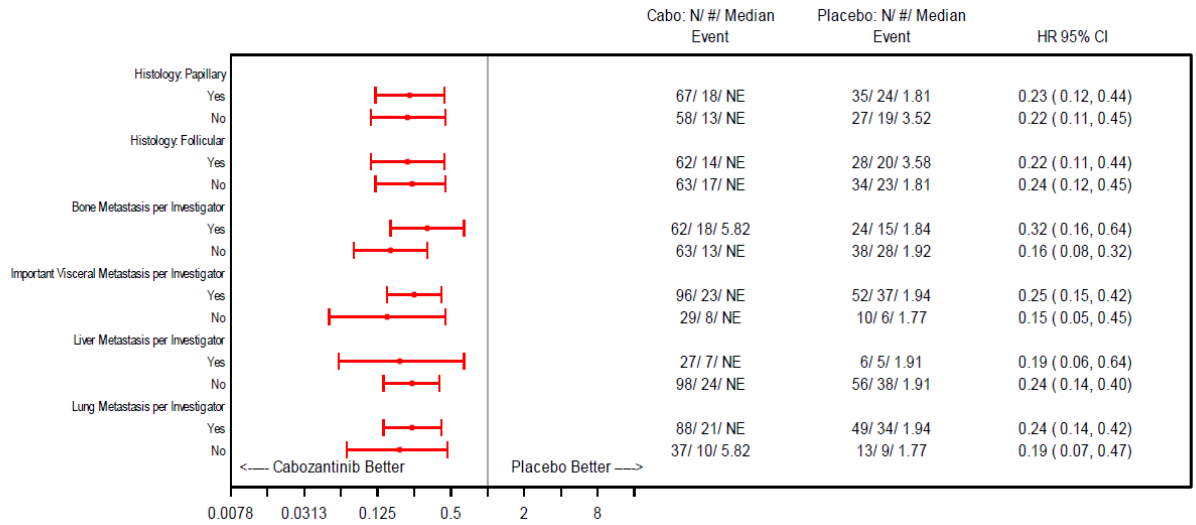
Subgroup analyses

Progression-Free Survival by subgroup as of CCO1 (ITT population)

Subgroup analyses of the primary PFS analysis is summarised in the Forest plot shown in the figure below. The analyses showed a consistently favourable effect of cabozantinib on PFS: all estimable HRs were < 1.







BIRC, blinded independent radiology committee; Cabo, cabozantinib; CI, confidence interval; CRF, case report form; DTC, differentiated thyroid cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; NA, not applicable; NE, not estimable; PFS, progression-free survival; RAI, radioactive iodine; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
**Stratification factors are receipt of prior lenvatinib (yes, no) and age at informed consent (≤ 65 years vs > 65 years).
[1] Receipt of prior sorafenib and lenvatinib per CRF
[2] Prior VEGFR-TKI anticancer therapy agents for DTC per subject per history of non-radiation anticancer therapy
[3] ECOG PS at baseline

Figure 27. Forest plot of subgroup analyses for PFS per BIRC as of CCO1 (unstratified Hazard Ratios, ITT population)

Progression-Free Survival by subgroup as of CCO2 (Full ITT population and Primary Analysis Subset)

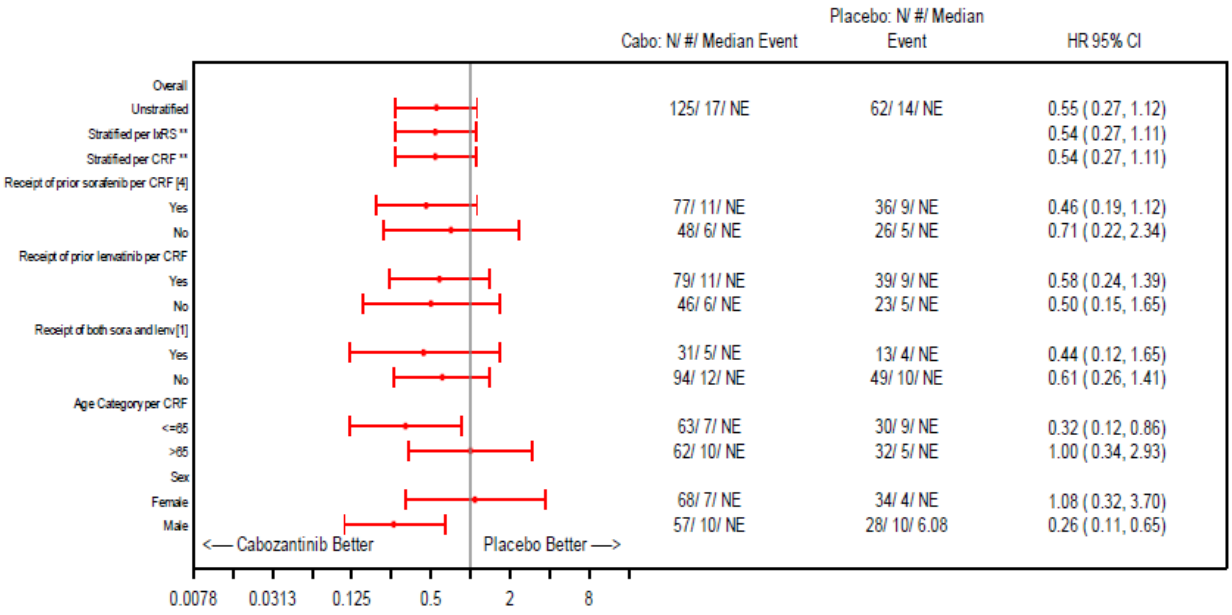
In the Full ITT Population (N = 258), subgroup analyses continued to show a consistently favourable effect of cabozantinib on PFS: almost all estimable HRs were < 1 and almost all upper limits of 95% CIs were < 1 (exception was for the subgroup of Black or African American who comprised a very low number of subjects; 2 patients in each of the treatment arms. For the subgroups that had upper limit

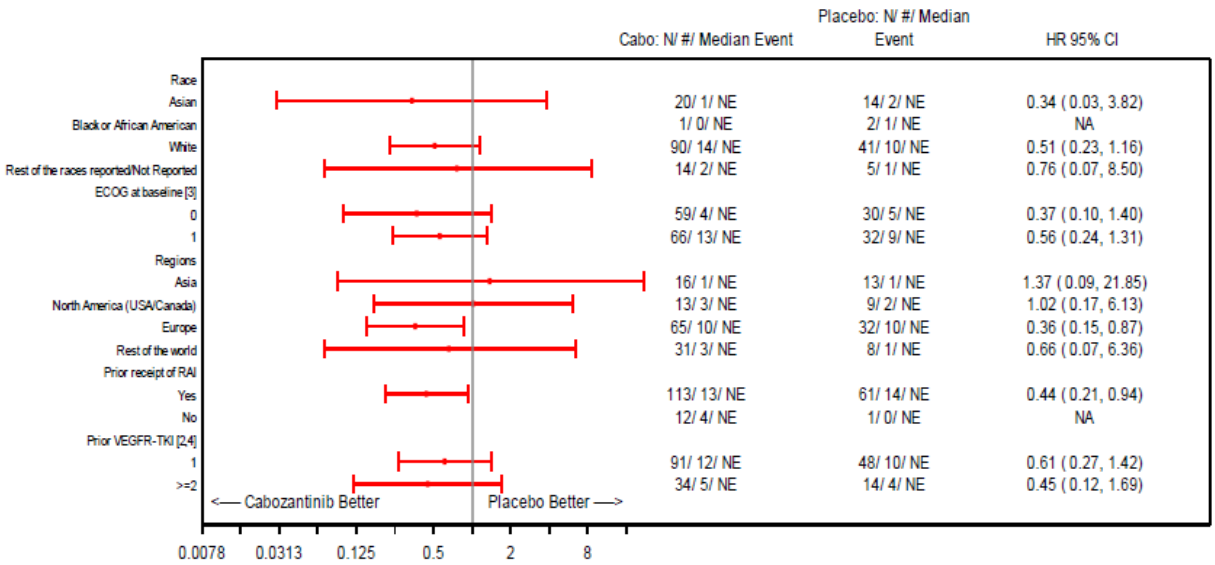
of 95% CI > 1 in the ITT population, race Asian and region Asia, these limits were now <1 while the subgroup "no prior receipt of RAI" were NA, for both the Full ITT Population and the Primary Analysis subset).

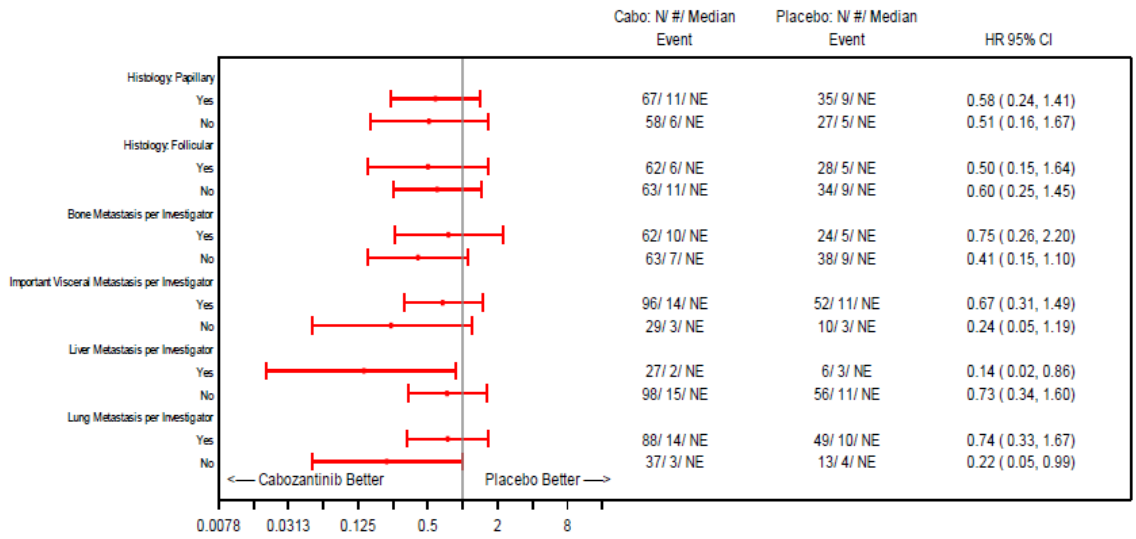
In the Primary Analysis Subset (N = 187), subgroup analyses showed a consistently favourable effect of cabozantinib on PFS: almost all estimable HRs were < 1 and all upper limits of 95% CIs were < 1.

Overall survival

Analyses of OS by subgroup conducted in the ITT population are shown in the forest plot below. Of note, since the majority of subjects were alive as of the data cut-off date, there are not enough events to make meaningful conclusions for OS subgroups.







Cabo, cabozantinib; CI, confidence interval; CRF, case report form; DTC, differentiated thyroid cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; NA, not applicable, NE, not estimable; OS, overall survival; RAI, radioactive iodine; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
**Stratification factors are receipt of prior lenvatinib (yes, no) and age at informed consent ≤ 65 years vs > 65 years).
[1] Receipt of prior sorafenib and lenvatinib per CRF
[2] Prior VEGFR-TKI anticancer therapy agents for DTC per subject per history of non-radiation anticancer therapy
[3] ECOG PS at baseline

Figure 28. Forest plot of subgroup analyses for OS (unstratified Hazard Ratios, ITT population)

Analyses of OS by subgroup conducted in the Full ITT population and for the Primary Analysis subset showed only small differences from the analyses of OS for subgroup for the ITT population (*data not shown*). Also, for these two populations, there were too few events to interpret OS subgroup analyses as most of the subjects were alive as of CCO2.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). Presented in the table below is the results from the prespecified primary interim PFS analysis with clinical cut-off date 19 August 2020.

Table 34 . Summary of efficacy for trial XL184-311

Title: A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy	
Study Identifier	**XL184-311**
Design	Study XL184-311 was a Phase 3 multicenter, randomised, double-blind, placebo-controlled study of cabozantinib in subjects with Radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) who had progressed during or after prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy, with objective response rate (ORR) and progression-free survival (PFS) as the multiple primary efficacy endpoints.

	Approximately 300 eligible subjects who met all study eligibility criteria were randomised in a 2:1 ratio to receive either cabozantinib or cabozantinib-matched placebo, as follows: Cabozantinib arm - Oral cabozantinib (60 mg) qd, and Placebo arm - Oral cabozantinib-matched placebo qd. Randomisation was stratified by receipt of prior lenvatinib and age at informed consent (≤ 65 years vs > 65 years). All subjects received best supportive care (BSC) in addition to the randomised study treatment.	
	Study Period: 27 February 2019 (first subject randomised) - 19 August 2020 (data cutoff date; minimum of 6 months' follow-up for the first 100 subjects)	
Hypothesis	Cabozantinib will improve ORR or PFS as compared to placebo in RAI-refractory DTC that has progressed after prior VEGFR-targeted therapy.	
Treatment Groups	**Cabozantinib only arm**: Subjects randomised to and receiving cabozantinib. **Placebo arm**: Subjects randomised to and receiving placebo **Placebo crossover arm**: Subjects randomised to placebo but receiving cabozantinib after crossover. **All cabozantinib arm**: All subjects receiving cabozantinib including crossover subjects.	
ENDPOINTS AND ANALYSES		
Primary Endpoints To evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.	PFS per RECIST 1.1 by BIRC	PFS was defined as the time from randomisation to the earlier of either the date of radiographic progression per blinded independent radiology committee (BIRC) or the date of death due to any cause. PFS was summarised descriptively using the Kaplan-Meier method.
	ORR* per RECIST 1.1 by BIRC	ORR was defined as the proportion of subjects with measurable disease at baseline who experienced a best overall response (BOR) of complete response (CR) or partial response (PR) which was confirmed at a subsequent visit ≥ 28 days later. ORR was summarised descriptively, and inference testing conducted with Fisher's exact test. The primary analysis of ORR was limited to the first 100 subjects randomised to the study and defined as the overall response rate intent-to-treat (OITT) population. The data cutoff for the prespecified primary endpoint analysis of ORR on the

		OITT population occurred 6 months after the last subject enrolled in the OITT population.
Secondary Endpoints		• Overall survival (OS): Duration of OS was defined as the time from randomisation to death due to any cause. Analysis of the additional endpoint OS was descriptive and non-inferential as OS was not a controlled endpoint for the study. • Duration of objective tumor response. • Relationship of baseline and post-baseline changes in serum thyroglobulin (Tg). • Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ5D-5L).
Data Cutoff Date	The data cutoff date for the primary analysis of ORR and the prespecified interim primary endpoint analysis of PFS was 19 August 2020 (=CCO1).	
Analysis Population	187 subjects were randomised in a 2:1 ratio (ITT population): 125 subjects in the cabozantinib arm and 62 subjects in the placebo arm.	

RESULTS AND ANALYSES

Efficacy Parameters (CCO1)	**Efficacy in ITT Population**	
	Cabozantinib (N = 125)	**Placebo (N = 62)**
PFS per RECIST 1.1 by BIRC		
Event	31 (25)	43 (69)
Median (96% CI)	NE (5.7, NE)	1.9 (1.8, 3.6)
Hazard ratio (96% CI; stratified)[a]	0.22 (0.13, 0.36)	
Observed p-value (stratified log-rank test)[b]	< 0.0001	
K-M landmark estimates (% of subjects event-free) at		
6 months	56.9	16.9
9 months	54.3	6.3
Overall Survival (OS)		
Number (%) of subjects		
Censored	108 (86)	48 (77)
Death	17 (14)	14 (23)
Duration of overall survival (months)[c]		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

Hazard ratio (95% CI; stratified)[b] [d]	0.54 (0.27, 1.11)	
Observed p-value (stratified log-rank test)[a][b]	0.0879	
K-M landmark estimates (% of subjects event-free) at:		
6 months	84.8	73.4
9 months	77.0	70.2

Abbreviations: BIRC, blinded independent radiology committee; CCO1, Clinical Cut-off 1 (19 August 2020); CI, confidence interval; CR, complete response; ITT, intent-to-treat; K-M, Kaplan-Meier; LS Mean, least squares means; NE, not estimable; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation; SE, standard error; VAS, visual analogue scale

aEstimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable). HR < 1 indicated PFS in favor of cabozantinib. bStratification factors based on IxRS were receipt of prior lenvatinib (yes vs no) and age at informed consent (⩽ 65 years vs > 65 years).cPercentiles were based on Kaplan-Meier estimates.dp-value is non-inferential as OS is not a controlled endpoint.*Of note, the study did not meet the multiple primary endpoint of ORR in the OITT population as the study failed to reject the null hypothesis of ORR at the pre-specified alpha of 1%. Therefore, results are not displayed for ORR in the table above.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive studies

In patients with RAI-refractory DTC, preliminary clinical activity of cabozantinib has been demonstrated in two clinical trials. Short summaries of the main results from these two trials are given below.

- Single-arm Phase 1 study (XL184-00; drug-drug interaction study), 15 subjects with advanced, metastatic DTC refractory to standard therapy with RAI were enrolled (Cabanillas et al 2014). Most patients (11/15) in the DTC cohort had received at least one VEGFR-targeted therapy, whereof 10/15 patients had received prior sorafenib. All patients had progressed during or after their most recent systemic therapy prior to study entry. The initial dose in this study was 140 mg cabozantinib (Cometriq, capsule formulation) per day. Subjects in the DTC cohort received a median average daily dose of 62 mg cabozantinib. The ORR (exploratory endpoint) for DTC subjects in this study was 53%, and 40% of DTC subjects achieved stable disease as best response. Of the 11 patients pre-treated with a VEGFR inhibitor, 5 had a confirmed PR – 4 of whom had prior sorafenib therapy. All 14 evaluable patients had tumour regression. Duration of response ranged from 2.0 to 14.5+ months. Median PFS and OS were not reached (median follow-up was 12 months and 26 months, respectively).
- A Phase 2, single-arm Investigator-sponsored study (NCT01811212) enrolled 25 subjects with RAI-refractory DTC who had progressed after one or two prior VEGFR-targeted therapies (Cabanillas et al 2017). Twenty-one patients had received only one prior VEGFR-targeted therapy (12/25 sorafenib, 5/25 pazopanib, or 4/25 cediranib), and four patients had received two such therapies. Of note, 1 patient had used lenvatinib and pazopanid in combination while 1 patient had used a combination of sorafenib + pazopanib and 1 patient had used a

combination of sorafenib + cediranib. The initial dose in this study was 60 mg cabozantinib (tablet formulation) per day. The ORR was 40%, and 52% of subjects had stable disease as best response. The number of prior VEGFR therapies was associated with response: PR was achieved in 10 of 21 patients (48%) with only one prior VEGFR-targeted therapy, whereas zero of four responses (0%) were seen in patients who received two prior VEGFR-targeted therapies. However, variable degrees of tumour reduction (6%, 19%, and 30%) were seen in three evaluable patients who received two prior VEGFR-targeted therapies. The authors concluded (among other things) that one (as opposed to two) prior VEGFR-targeted treatment was associated with a better response rate. Median duration of response was 11 months. The median PFS was 13 months (95% confidence interval [CI]: 11, 35), and the median OS was 35 months (95% CI: 18, not reached). Dose reductions to 40 mg occurred in 56% of subjects, and further reductions to 20 mg occurred in 32% of subjects.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The main evidence of efficacy submitted to support the claimed indication is **.** Study XL184-311 a Phase 3, double-blind, randomised, placebo-controlled, multicentre, global clinical trial which primary objective was to evaluate efficacy and safety of cabozantinib as monotherapy in patients with locally advanced or metastatic differentiated thyroid cancer (DTC) and who are refractory or not eligible to radioactive iodine (RAI) and have progressed during or after prior VEGFR-targeted therapy. Subjects were randomised to receive either cabozantinib or placebo and stratified by age (≤65 years vs. > 65 years) and receipt of prior lenvatinib (yes or no). Considering that age is an important prognostic factor in DTC, with better survival observed in younger patients, it is reasonable to stratify for this factor. "AJCC/TNM 2016 8th edition criteria" operates with a cut-off for patients with a lower age cut-off < and > 55 years but considering that most subjects included in the study were diagnosed with DTC several years before being enrolled into the study and other factors than age might be of higher prognostic factor (such as e.g., tumor size, node metastasis, extranodal tumor extension and degree of distant metastasis) the age data cut-off chosen can be agreed.

Currently, any experience of potential activity of cabozantinib in patients who have previously used lenvatinib is limited. When taking into account that there might be differential efficacy in lenvatinib-exposed and unexposed patients, it is reasonable to secure a balance in the study between these two patient groups. No biomarkers have been validated to successfully determine who will respond best to lenvatinib or sorafenib (Gild et al, 2017).

The randomisation was 2:1, thereby allowing more subjects the chance to receive active treatment.

The use of a blinded and independent radiological assessment of PFS in order to reduce possible investigator bias is endorsed. Crossover to cabozantinib was optional for subjects initially randomised to placebo upon experiencing radiographic disease progression) as confirmed by BIRC.

The design of the study is in general acceptable.

Study population. Generally, the inclusion and exclusion criteria for Study XL184-311 appears to largely reflect the target population of the indication sought. This population ought to be refractory or not eligible to RAI. The patients had to have received either lenvatinib or sorafenib previously before inclusion, and thus being refractory towards RAI is a requirement. Hence, it is assumed that the RAI refractoriness of each patient has already been evaluated before any of the two TKIs were given. In regards to patients being "non-eligible", the enrolment aimed to include subjects who had an intact

thyroid gland as this would normally preclude treatment with RAI. Five patients in the study were deemed ineligible for RAI treatment, and it seems that all these patients had either a complete or partial thyroid gland.

Only patients with ECOG 0 or 1 were eligible, implying a quite fit population.

Patients had to have previously been treated with at least one of the two VEGFR-targeting TKIs lenvatinib or sorafenib. However, up to two VEGFR-targeting TKI agents were allowed (this had to include lenvatinib or sorafenib but were not limited to those). Furthermore, patients were not excluded if they previously had received maximum 1 immune checkpoint inhibitor or 1 systemic chemotherapy regimen. These broad entry criteria could lead to a rather heterogenous population potentially making it challenging to demonstrate the optimal use of cabozantinib in this setting. Patients had to have experienced documented radiographic progression per RECIST per the investigator.

Comparator. The study is placebo-controlled. Considering that there are no consensus/approved drugs/combination therapies for patients with RAI-refractory DTC who have progressed during or after prior VEGFR-targeted therapy, the use of placebo as control is viewed as acceptable.

Endpoints. The multiple primary objectives of the study were to compare PFS and ORR per RECIST 1.1 by BIRC in patients treated with cabozantinib vs. placebo. The use of PFS as a primary endpoint is acceptable. However, using solely ORR as a primary endpoint would not have been considered acceptable for this study. Among endpoints listed as additional were OS, DoR, safety and PRO-data.

The inclusion of cross-over data makes the analysis of OS less clear-cut and limits the interpretation of these results. Only evaluation of a potential detriment to survival with the cabozantinib treatment will therefore be possible to extract from these OS analyses. Notwithstanding this, considered the lack of treatment alternatives for this patient group, it would be unethical not to offer placebo patients the opportunity to cross over to a potentially beneficial treatment.

Statistical analysis. The statistical methods used for analysis, including sensitivity analyses, handling of missing values, methods for controlling the Type-I error and sample size calculations, are in general acceptable. The use of an ITT population for hypothesis testing and estimation is endorsed. PFS and ORR were defined as multiple primary endpoints, and study success was to be declared if at least one null hypothesis was rejected. A modified Bonferroni procedure was used to control the Type-I error, dividing the alpha between them. While from a statistical point of view rejecting only one of the null hypotheses for ORR or PFS could be acceptable, the outcome could have been problematic, since, in line with the above, rejecting solely the ORR null hypothesis would not have been sufficient for this study. The primary analysis for ORR was performed by Fisher's exact test. According to guidelines it should have been planned to include stratification factors used in the randomisation in the analysis of the primary endpoints, and therefore to also ensure enough subjects in important strata were included. However, the MAH has provided supplementary analyses that were stratified according to stratification factors used in randomisation, showing consistent results. Likewise, being a multi-center study, the analysis should have been stratified by center, or region. Also, in this case sensitivity analyses by region have been submitted, showing consistent results. Censoring subjects with progression after two or more missed assessments, or receiving subsequent or additional anti-cancer therapy, for the primary PFS analysis is not in agreement with the preferred analysis recommended by the guidelines. However, this applies to only a few patients, and sensitivity analyses that assign these as events instead of censoring are consistent with the primary analysis, and therefore this has not had a significant impact on the results.

The final analysis showed that the ORR null hypothesis could not be rejected, while PFS demonstrated statistically significant results. Consequently, PFS became the only primary endpoint demonstrating the benefit of cabozantinib over placebo.

Cabozantinib dose. The recommended adult dose is 60 mg cabozantinib once daily. This dose has already received approval for patients with advanced RCC and HCC. Cabozantinib 60 mg qd (as tablets) has also shown preliminary efficacy in an Investigator-sponsored study (ISS) in subjects with DTC. In Study XL184-311, no ER relationship between PFS and average cabozantinib concentration was observed in DTC subjects supporting a dose of 60 mg QD in adults with or without dose modification (i.e., 40 mg or 20 mg). With regard to adolescents, PK modelling and simulation is used by the MAH in an effort to support a cabozantinib starting dose of 60 mg qd for adolescents with body weight ≥ 40 kg and a starting dose of 40 mg qd for adolescents with body weight < 40 kg, based on the aim to obtain comparable exposure. Further optimisation of the popPK model was requested in order to be able to make a final conclusion on the appropriate dose for this age group. The MAH has performed additional modelling and simulation (M&S) exercises testing several models, essentially yielding a comparable predicted exposure. The proposed dose advice based on M&S with the original full popPK Model 1 is considered sufficiently robust. Consequently, the dose advice for patients <40 kg based on this M&S approach is considered acceptable from a PK point of view.

Study conduct. No global amendments were made to the original protocol, only 4 country-specific amendments and one country-specific addendum (in Germany, Canada, France, and UK, respectively). These amendments mainly concerned addition of various clarifications and modifications (including for some of the inclusion and exclusion criteria). Certain special accommodations were also performed in regards to the global COVID-19 pandemic but were implemented for only a few countries and not globally. As none of the amendments were deemed to affect the study population, schedule of assessment or the endpoints of the study, it was deemed unnecessary to implement them globally. This is acknowledged. No specific GCP-related issues were revealed during the assessment. The MAH has informed that no EU (or alternatively non-EU) inspections of study sites and/or CROs have been conducted

Efficacy data and additional analyses

Primary efficacy analyses of cabozantinib were based on the pre-specified primary endpoint analysis of ORR in the first 100 randomised subjects (i.e., 67 subjects in the cabozantinib arm and 33 subjects in the placebo arm; called the OITT population). In addition, a pre-specified interim primary endpoint analysis of PFS from the 187 subjects (i.e., 125 cabozantinib, 62 placebo, called the ITT population) randomised as of clinical cut-off 1 (CCO1) on 19 August 2020 was provided. CCO1 was set 6 months after the first 100th subject randomised, resulting in a median duration of follow-up of 6.24 months and 8.85 months for the PFS and ORR analysis, respectively. After the 19 August 2020 cut-off, subjects continued to enrol in the study and receive blinded study treatment.

The PFS analysis was regularly reviewed by an independent data monitoring committee, and based on the significant results, the committee recommended to stop enrolment. Thus, the last subject was randomised on 02 February 2021. From August 2020 to February 2021 a total of 71 additional patients were enrolled (45 more in the cabozantinib arm and 26 more in the placebo arm), giving a total of 258 subjects (i.e., 170 subjects in the cabozantinib arm and 88 subjects in the placebo arm). This population was called the Full ITT population. A second clinical cut-off of 08 February 2021 (CCO2) was then used to provide efficacy data of the Full ITT population and longer follow-up of the Primary Analysis Subset (i.e., the ITT population consisting of the initially 187 subjects). The corresponding supportive analysis was focused on updated efficacy analyses by BIRC of PFS, ORR, and OS. There were two dates for database lock, i.e., 19 August 2020 and 08 February 2021. In general, subjects with BIRC-determined radiographic PD via the Interactive Response Technology (IRT) system could be unblinded during the study, and those subjects belonging to the placebo group had the option to cross

over to the cabozantinib group. On 16 April 2021 all sites were ultimately unblinded (i.e., after the efficacy analyses were finalised).

Baseline and disease characteristics. In general, the baseline patient demographic and disease/tumour characteristics were well balanced between the two treatment arms in the ITT population (N=187). In both arms subjects were predominantly white with median age around 65 years, ~ 55% were females and 52% were enrolled in Europe. The proportion of Asian subjects was 16% in cabozantinib group vs. 23% in the placebo group. Around 50% in each arm was < 65 years or ≥ 65 years and 63% in each arm had previously received lenvatinib (stratification factors).

Overall, the baseline disease history of the enrolled patients reflected the population intended for treatment and was mainly equally distributed between the two arms. The included patients had either the papillary subtype of DTC (~ 55%) or follicular subtype (45-50%). Of the patients with follicular subtype, 17% had Hürthle cell thyroid cancer. Approximately 95% of patients in both arms had metastatic disease and measurable disease. It is noted that no patients were stated to have locally advanced disease while the proposed indication includes also "locally advanced". Considering that patients with locally advanced disease will receive the same treatment as patients with metastatic disease and efficacy in locally advanced therapy can be assumed, this is acceptable. This is also in alignment with the other TKis for differentiated thyroid cancer, sorafenib and lenvatinib

Almost all patients in both arms were stated to be refractory to prior RAI therapy. The most common reason for refractoriness was "disease progression despite RAI avidity" (> 60% in both arms) and no demonstration of RAI uptake (> 20% in both arms).

Approximately a total of 52% of subjects had received prior radiation therapy for DTC (most commonly was external beam radiation therapy with ~ 45% in each arm).

The protocol allowed inclusion of patients who had received a maximum of two previous VEGFR-TKI agents for DTC. However, > 70% of the patients in both arms received only one prior VEGFR-TKI. Of these, 63% in each arm had received prior treatment with lenvatinib. Sorafenib had been used previously by 62% in the cabozantinib vs. 56% in the placebo arm. This quite equal proportion of patients receiving prior sorafenib and prior lenvatinib might reflect that the availability of lenvatinib is limited in some countries and regions. Around 25% in the cabozantinib arm vs. 21% in the placebo arm had received prior treatment with both lenvatinib and sorafenib. For around 50% of the patients in each treatment arm the "context of therapy" were stated to be "adjuvant therapy" where "adjuvant therapy" mainly comprised radioactive iodine. In the remaining cases, the therapy was a systemic treatment such as lenvatinib, sorafenib and/or another therapy.

Multiple primary endpoints

PFS

Results from the prespecified primary interim analysis of the ITT population (N=187; 125 in the cabozantinib arm and 62 in the placebo arm), clinical cut-off 19 August 2020, median follow-up 6.24 months:

A statistically significant benefit in PFS were observed for cabozantinib over placebo (HR = 0.22, 96% CI [stratified]: 0.13, 0.36; stratified log-rank test p-value <0.0001). The PFS data were rather immature for the cabozantinib arm (25% events vs. 69% in the placebo arm, respectively). Median PFS in the cabozantinib arm was not reached (96% CI: 5.7, NE) vs. 1.9 (96% CI: 1.8, 3.6) months in the placebo arm. The main reasons for censoring were no event by last adequate tumour assessment (ATA) (54% in the cabozantinib arm vs. 16% in the placebo arm) and no post-baseline ATA (18% in

the cabozantinib arm vs. 13% in the placebo arm). Very few patients were censored due to 2 or more missed ATA prior to event (2.4% in the cabozantinib arm vs. 0 in the placebo arm) and receipt of local radiation to soft tissue for DTC (0.8% for the cabozantinib arm and 1.6% in the placebo arm). No patients were censored due to subsequent NPACT. This low number of censoring due to missed ATA is reassuring in regards to the size of the effect of informative censoring. Separation of the Kaplan-Meier (K-M) curves favouring cabozantinib occurred early (around 1 month), and with no crossing of the curves. The curve for the placebo arm shows an early steep fall (at around 2 months). This time point coincides with the median time to progression of ~ 1.8 months (range 0.6-7.1) for the placebo arm, and at that time point placebo patients could cross over to the cabozantinib arm.

Results of the sensitivity analyses and other supplementary analyses (including the analysis using PFS as assessed by the Investigator) were consistent with the primary efficacy results supporting the robustness of the primary analysis.

The updated PFS analyses performed at clinical cut-off 08 February 2021 in the Full ITT population (N=258; 170 in the cabozantinib arm and 88 in the placebo arm) and with a median follow-up of 10.1 months, were in support of the primary PFS analysis. The median PFS (cabozantinib vs. placebo) was stated to be 11.0 (96% CI: 7.4, 13.8) vs. 1.9 (96% CI: 1.9, 3.7) months. A gain in PFS of around 9 months is considered clinically relevant in a setting where the therapeutic alternatives are limited. The results for the Primary Analysis Subset (median follow-up: 11.9 months) were in line with the results observed for the Full ITT population.

The median PFS in the placebo arm was short (1.9 months in all analyses) indicating a patient population with rapidly progressing disease. The updated analyses continued to demonstrate separation of the Kaplan-Meier (K-M) curves favouring cabozantinib, with no crossing of the curves. The PFS outcome is considered clinically relevant in a disease setting with few alternative treatment options.

ORR

For ORR a pre-specified primary endpoint analysis of the OITT population (N=100; 67 in the cabozantinib arm and 33 in the placebo arm), median follow-up 8.85 months, was performed at clinical cut-off 19 August 2020. However, this primary endpoint was not met as the study failed to reject the null hypothesis of ORR at the pre-specified alpha of 1%. There is therefore not sufficient sample evidence to support the claim that there is a difference in ORR between cabozantinib and placebo. Consequently, ORR cannot confirm the primary PFS endpoint.

The observed ORR in the cabozantinib arm was rather modest; 15% (99% CI: 5.8, 29.3) vs. 0% (99% CI: 0.0, 14.8) in the placebo arm (unstratified p-value of 0.0281 using Fisher's Exact Test). All objective responses in the cabozantinib arm were partial (10/67) vs. none in the placebo arm. The rate of stable disease in the cabozantinib arm relative to placebo was higher (69% vs. 42%, respectively). This could imply that the PFS effect of cabozantinib primarily might be caused by disease stabilisation, rather than a decrease in tumour burden. Conversely, more subjects in the placebo arm had progressive disease (55% vs. 6% in the cabozantinib arm). The disease stabilisation rate (DSR; ORR+SD ≥ 16 weeks) were 60% vs. 27% in the cabozantinib arm and placebo arm, respectively.

It is noticed that higher ORR values were observed for cabozantinib in the phase 1 (XL184-00) and 2 (NCT01811212) studies (53% and 40%, respectively), while the ORR value used for planning the pivotal study was 35%. However, the phase 1 and 2 trials were small and single armed, and in the Phase 1 study a higher dose of cabozantinib was used (140 mg qd in the form of a capsule which is not bioequivalent with the tablet formulation), thus direct comparisons would not be entirely valid. Although cross trial comparisons of ORR have its obvious limitations and encumbered with a high degree of uncertainty, it is still noted that low response rates have also been previously reported in

studies for other indications for cabozantinib (EPAR, EMEA/H/C/004163/II/0005, EPAR, EMEA/H/C/004163/0000).

In the cabozantinib arm the median (range) time from randomisation to the first objective response per BIRC was 2.5 months (1.74, 3.94) in the OITT population. The median duration of response (DoR) per BIRC was not evaluable (median not reached) at CCO1.

Updated data for the Full ITT population, per clinical cut-off 08 February 2021, were in agreement with the results reported at CCO1 (ORR was 11% [95% CI: 6.9, 16.9] and 0% [95% CI: 0.0, 4.1] in the cabozantinib arm vs. the placebo arm, respectively). Median DoR per BIRC was 10.2 months and median time to objective response per BIRC was 3.58 months (1.74, 7.52) in the cabozantinib arm.

Secondary endpoints

OS. The analysis of OS in the ITT population at clinical cut-off 19 August 2020 were immature (86% and 77% of the patients being censored in the cabozantinib arm and placebo arm, respectively). The median was not reached in either study arm. HR was 0.54 (95% CI [stratified]: 0.27, 1.11) with an observed p-value (stratified log-rank test) of 0.0879. The K-M plot is characterised by a lot of censoring in both arms.

Of note, the placebo arm included 19 subjects who subsequently crossed over to receive cabozantinib, constituting around 29% (19/62) of the total number of placebo patients. For these patients, selected demographic and baseline characteristics were re-established immediately prior to crossover. The median age was consistent with that in the cabozantinib arm (ITT population). However, a higher proportion of subjects in the placebo crossover arm had a baseline ECOG PS of 1 immediately prior to crossover compared with the cabozantinib arm (74% vs. 53%, respectively). The median time to progression while on placebo per BIRC was 1.77 months (range: 0.6 -7.1 months) in the placebo crossover arm.

These subjects were not censored at the time of crossover as receipt of open-label cabozantinib was not considered receipt of NPACT. Thus, these subjects were analysed under the randomised placebo arm for OS analysis under intent-to-treat principles. Due to the inclusion of placebo patients receiving cabozantinib in the placebo arm, this arm performs better than would otherwise be expected.

Overall, there was a low number of patients in the ITT population who received subsequent NPACT in the study (2.4% in the cabozantinib arm vs. 6.5% in the placebo arm; the majority of these NPACTs were TKIs). The relatively infrequent use of subsequent NPACT probably reflects the lack of alternative therapies in this setting. Results for the OS sensitivity analysis for receipt of subsequent NPACT were consistent with the corresponding main OS analysis.

In the updated analysis for the Full ITT population, per clinical cut-off 08 February 2021, the number of patients crossing over from the placebo arm to the cabozantinib arm had increased from 19 to 40. Eight of these 40 patients had an event. The other 32 subjects were censored; of these subjects, 12 had at least 6 months of post-crossover survival and 2 were still on open label cabozantinib as of 08 February 2021. As a consequence of this, OS of the cabozantinib arm will be more heavily confounded. In the Full ITT population, HR for OS was 0.76 (95% CI [stratified]: 0.45, 1.31). The data are still immature, and the follow-up is not long enough to provide a reliable estimate of the median, nevertheless no apparent detrimental effect on survival in the cabozantinib arm is currently observed.

The analysis for the Primary Analysis Subset (in this subset 35 placebo patients had crossed over) was in line with the analysis for the Full ITT population (HR=0.74, 95% CI [stratified]: 0.42, 1.28). As for the PFS analyses (see above) no further updated OS analyses are available or planned. It is acknowledged that due to crossover, OS would be difficult to interpret.

HRQoL. The PROs were captured through the use of the validated questionnaire EQ-5D-5L (which includes EQ-Index and EQ-VAS). At the various time points for completion of the questionnaires, the majority of the 95% CIs were overlapping between the cabozantinib and placebo arms for the measured dimensions in the EQ-5D-5L questionnaire. The HRQoL results are considered to be of a descriptive, hypothesis-generating nature and the number of patients is limited. Considering that the placebo patients had a rather short time to progression (median around 1.8 months), and would then cross over to the cabozantinib arm, the time period where there would be an actual comparison in QoL between placebo and cabozantinib is quite short. Furthermore, it is not considered that these data would lead to any difference in clinical management or inform treatment decisions. In conclusion, the data are not regarded adequate to include in section 5.1 of the SmPC.

Subgroups. Many subgroups were analysed and the size and number of events in each subgroup varied. Subgroup analyses were not powered to detect a treatment difference. Notwithstanding this, it is noted that a benefit in PFS in favour of the cabozantinib arm was seen across all subgroups for the ITT population (cut-off 19 August 2020) with HRs being < 1. Almost all upper limits of 95% CIs were also < 1 (exceptions occurred in subgroups with a very low number of subjects).

Assessment of paediatric data on clinical efficacy

No patients < 18 years were included in the pivotal study. The MAH presented PK data to demonstrate comparable exposure of cabozantinib between adolescents and adults implying that extrapolation of efficacy from adult to adolescents could be adequate. Moreover , the MAH stated that there is biological similarity of the diseases in adolescents and adult subjects.

However, some important differences between paediatric and adult DTC are reported in the literature. Zanella et al (2021) refers to that DTC in paediatric patients is characterised as a distinct disease from that observed in adults, with particularities in the pathophysiology, clinical presentation, and long-term outcomes. Differences in the molecular pathology of the tumour between adult and paediatric DTC have been reported. Paediatric patents more often than adults present with aggressive, advanced stage disease, but still the prognosis is better compared to older adults. Galuppini et al (2019) suggests, as it seems that younger paediatric patients have a more aggressive tumour at diagnosis in terms of extent, lymph node involvement and distant metastases than older patients, and that DTC in childhood is locally more aggressive, that it should be considered as a distinct clinical entity also from DTC in adolescence..

The American Thyroid Association (ATA), accounting for the differences observed in paediatric vs. adult DTC, has published specific guidelines for thyroid nodule and DTC for children (Francis et al, 2015). In these guidelines (it is stated that although more studies are required regarding the use of agents like sorafenib (and lenvatinib) in children, particularly with respect to dosing and toxicity, the use of molecularly targeted therapies may be contemplated in the rare situation in which a child warrants systemic treatment. However, it is pointed out that it is difficult to define iodine-refractory disease in paediatric DTC, and iodine-refractory DTC can remain stable over years of follow-up. For that reason, all children being considered for anti-neoplastic therapy should be referred to centers familiar with the use of these therapeutic agents in thyroid cancer.

In the EU no medicinal products are currently approved for treatment of specifically DTC in patients < 18 years.

From literature submitted by the MAH, Sapuppo et al (2021) and Galuppini et al 2019 it seems that paediatric DTC patients are mainly treated with the same modalities as adult DTC patients., However, it appear like there are some differences concerning when to start further treatment. External beam radiotherapy might be relevant for selected patients. Given the longer life span of paediatric patients

compared to adults, the risk of secondary cancer will be higher, and a more conservative approach is generally taken towards using adjuvant RAI in paediatric DTC patients and external radiation in paediatric DTC patients who have become refractory to RAI. For adult DTC patients who become RAI-refractory and have exhausted local treatment options, the next step in the treatment hierarchy is usually the TKis lenvatinib and/or sorafenib. None of these 2 agents are currently approved for treatment of patients < 18 years of age. As RET mutations seem to be more prevalent in paediatric DTC patients, treatment with specific RET inhibitors would be of interest. In the EU praseltinib (Gavreto) is not approved for thyroid cancer while selpercatinib (brand name Retsevmo in Europe) is approved (among other indications) for advanced RET fusion positive thyroid cancer (after prior treatment with sorafenib and/or lenvatinib), although only for adults.

Although an increase in incidences of paediatric thyroid carcinoma is reported (Howlader 2019), it is acknowledged that the number of these specific paediatric patients with RAI refractory DTC is extremely limited. An incidence of paediatric DTC of 0.2 to 3 cases/million children/year has been reported (Lebbink et al., 2020). Klein Hesselink et al (2016) reported age-standardised incidence rates for DTC for children 0–4 years of age of 0.4 per 100 000, and up to 1.5 per 100 000 for adolescents aged 15–19 years. Considering the normally high cure rates and good prognosis for children with DTC, a condition of relapsed/refractory DTC in paediatric patients would be even rarer and only make up a small subset. Consequently, it seems unfeasible to conduct randomised controlled trials in this patient group.

At present, cabozantinib is not approved in paediatric patients for any indication, hence the experience with cabozantinib and knowledge of its potential efficacy in paediatric patients is sparse. The MAH summarised any efficacy data available from use of cabozantinib in paediatric patients presenting the following studies:

- Study 4 of the PIP, called XL184-011 or ADVL1211. This is a completed phase 1 study which evaluated the starting dose of cabozantinib in 39 children and adolescents (age ≥ 2 - ≤18 years) with refractory solid tumours. Five patients had MTC (none with DTC), 2 partial responses and 2 stable disease were reported (the study had no primary efficacy endpoint). In addition, one patient with Wilms tumor and one patient with clear cell sarcoma both reported partial responses. A dose of 40 mg/m^2 was recommended for further evaluation in a phase 2 study.
- Study 7 of the PIP, XL189 or also called ADVL1622 is performed by the Children's Oncology Group (COG). It is an ongoing open-label trial evaluating the safety and activity of the 40 mg/m^2 dose of cabozantinib in children aged 2 years to < 18 years (and young adults) with a relapsed or refractory solid malignant tumour. The final clinical study report is expected by April 2022 Patients with various sarcomas were enrolled in addition to a cohort consisting of "rare tumours". In the latter group there was one patient with "RET fusion positive PTC" who had a partial response. Overall, it was concluded that cabozantinib is active in patients with relapsed refractory osteosarcoma (10/29 patients) and deserved to be further studied. However, the age of these specific patients is not mentioned by Akshintala et al (2021). Clinical activity of cabozantinib was limited in other sarcomas (Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma) and Wilms tumour. In addition, a randomised, double-blind, controlled, parallel-group safety and efficacy clinical trial of cabozantinib in patients aged from birth to less than 18 years with a malignant solid tumour(s) is reportedly planned
- The MAH also referred to a phase 2 single-arm trial called study CABONE (French Sarcoma Group; Italiano et al, 2020). Paediatric patients < 16 years were to receive a dose of 40 mg/m^2. Cabozantinib showed antitumor activity (partial responses) in 10 and 5 patients with

Ewing sarcoma (EWS) and osteosarcoma (OST), respectively. Information regarding the age of these specific patients could not be found. However, it has to be taken into account that only a total of 8/90 patients (2 with EWS and 6 with OST) < 18 years were included in the study.

Efficacy data available from use of cabozantinib in paediatric patients, is very limited and for DTC virtually non-existing. Apart from one patient (in Study ADVL1622) reported to have "RET fusion positive PTC", none of the studies included paediatric patients with RAI-refractory DTC.

The MAH presented an extrapolation approach to support the indication for adolescent 12-18 years of age.

In order to accept an efficacy assessment solely based on the concept of extrapolation, a reasonable degree of certainty, that the disease, progression of disease, treatment and prognosis are similar for adolescents and adults is a prerequisite. In addition, the proposed doses should lead to comparable exposures and a similar PK/response relation. The original full popPK model is sufficiently robust to support the recommended dose for patients ≥12-<18 years therefore from a PK point of view, it is considered acceptable, to extrapolate from adults to adolescents. These data are included in the SmPC section 5.2. No ER relationship between average cabozantinib concentration and PFS was observed.

As previously mentioned, biological, molecular/genetic and clinicopathological disparities exist between paediatric and adult DTC.

Overall efficacy data from use of cabozantinib in paediatric patients, and for DTC it is virtually non-existing (one adolescent patient with "RET fusion positive PTC", has been identified). According to the sought indication, cabozantinib is intended to be used in a late treatment line, i.e., after prior systemic therapy has failed. Consequently, the anticipated effect of cabozantinib will not only be depended on the basic treatment of surgery and RAI, but also on the type of systemic therapy the adolescent patient has previously failed on. This adds to the uncertainty of whether it can be assumed that the efficacy between adults and adolescents will be sufficiently comparable and consequently allow for an extrapolation between the two patient populations.

Due to a very low incidence of paediatric patients with DTC and an even lower incidence with RAI-refractory DTC, obtaining further clinical study data for this group of patients seem to be unfeasible. It is acknowledged that there is an unmet medical need for the few paediatric patients that would require further treatment beyond RAI and other systemic therapy. For these patients, cabozantinib might be an option. Notwithstanding this, it is still unclear whether the disease histology, genetic background, treatment and prognosis are sufficiently comparable between adults and adolescents making it justified to extrapolate the efficacy of cabozantinib from adult patients to adolescent patients.

2.4.3. Conclusions on the clinical efficacy

In the single pivotal study XL184-311, cabozantinib demonstrated a clinically relevant and statistically significant improvement in PFS per BIRC compared with placebo in adult patients. This result is encouraging in a patient group with few alternative treatment options. The OS data are still immature,and no further updates of the OS analysis will be available due to the influence of crossover. It is noted however, that despite crossover of patients from the placebo arm, no apparent detrimental effect on survival in the cabozantinib arm is currently observed.

With regards to patients ≥12 -<18 years, the assessment of cabozantinib's efficacy in this patient group would mainly depend on the adequacy of extrapolating the efficacy data from adults. At present,

it is not considered that the available data are convincingly enough to unequivocally conclude that the disease histology, genetic background, treatment and prognosis are sufficiently comparable between adults and adolescents allowing for an extrapolation of efficacy data from adults to adolescents. The efficacy of cabozantinib in the intended later treatment line might be influenced by the type of prior systemic therapy used in RAI refractory adolescents.

The final agreed indication is as follows (~~strike-through~~: text deleted):

"CABOMETYX is indicated as monotherapy for the treatment of adult ~~and adolescent~~ patients ~~aged 12 years and older~~ 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."

2.5. Clinical safety

Introduction

The safety data for the claimed indication is derived from the Phase III, randomized, double-blind, placebo-controlled pivotal Study XL184-311. The safety population included subjects that received at least one dose of study treatment. In addition, pooled safety data is also provided from previously reported studies (Studies XL184-309, XL184-308, and A031203) to set observations in Study XL184-311 in context with prior cabozantinib safety experience.
As described in the current Cabometyx SmPC, the most frequent adverse reactions of any grade (experienced by at least 25% of patients) during treatment of currently approved indications (renal cell carcinoma (RCC) and hepatic cell carcinoma (HCC)) included diarrhoea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysaesthesia syndrome (PPES), hypertension, weight decreased, vomiting, dysgeusia, constipation, and aspartate aminotransferase (AST) increased.
The most common serious adverse drug reactions in the RCC population (≥1% incidence) are abdominal pain, diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and palmar-plantar erythrodysaesthesia syndrome (PPES).

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, asthenia, fatigue, PPES, diarrhoea, hyponatraemia, vomiting, abdominal pain, and thrombocytopenia.

Table 35. Summary of Safety Concerns (from RMP)

Summary of safety concerns	
Important identified risks	• Gastrointestinal perforation • Gastrointestinal and non-gastrointestinal 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

Safety data presented in this report are mainly derived from study XL184-311, a randomized, placebo-controlled, Phase 3 Study evaluating the safety and efficacy of cabozantinib 60 mg (tablet formulation) in subjects with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) and who have progressed following vascular endothelial growth factor receptor (VEGFR)-targeted therapy.

The Safety Data Analysis Set in study XL184-311 was defined for subjects that received at least one dose of study treatment. All randomized subjects received their assigned study treatment; therefore, the ITT population and Safety population in this study are the same. There were 125 subjects in the XL184-311 cabozantinib arm at the assigned 60 mg qd dose as of the 19 August 2020 cutoff date, and for comparison, 62 subjects in the placebo arm. No additional safety data was submitted with the updated analysis of PFS and OS (median follow up 10.1 months, n= 258). The MAH includes children ≥12 years in the indication, but only adult patients (≥18 years) were included in the pivotal study.

Study XL184-311 is the focus of this submission. However, in addition, pooled safety data is also provided from previously reported studies so that the observations in Study XL184-311 will be set in context with prior cabozantinib safety experience.

Patient exposure

In Study XL184-311, a total of 187 subjects received study treatment: 125 subjects in the cabozantinib arm and 62 subjects in the placebo arm. 19 subjects crossed over from the placebo arm to receive cabozantinib in the crossover phase (data from the crossover period is summarized independently).

Median duration of exposure (including dose interruptions) was almost twice as long in the cabozantinib arm (60 mg) compared with the placebo arm (4.4 months vs 2.3 months). Median dose intensity of cabozantinib was 70%, corresponding to a median daily dose of 42 mg. In the placebo

group, the median dose intensity was 90 %, and the median daily dose was 60 mg. Drug exposure is summarized in **Table *36***.

Table 36. Study XL184-311: Study Treatment Exposure (Safety Population)

	Cabozantinib (N = 125)	**Placebo (N = 62)**
Duration of exposure (including dose holds) (months)[a]		
Mean (SD)	5.03 (3.520)	3.49 (2.544)
Median (range)	4.44 (0.0, 15.7)	2.33 (0.3, 11.6)
Average daily dose of cabozantinib/matched placebo (mg/day)[b]		
Mean (SD)	41.83 (13.461)	54.13 (10.856)
Median (range)	42.01 (9.5, 60.0)	60.00 (18.4, 68.3)[c]
Percent dose intensity of cabozantinib/matched placebo (%)[d]		
Mean (SD)	69.71 (22.435)	90.22 (18.094)
Median (range)	70.02 (15.8, 100.0)	100.00 (30.6, 113.8)[c]
Duration of exposure (excluding dose holds) (months)[e]		
Mean (SD)	4.21 (3.180)	3.26 (2.595)
Median (range)	3.75 (0.0, 13.5)	2.17 (0.3, 11.6)

SD, standard deviation.

Duration of exposure = (date of decision to discontinue study treatment – date of first dose + 1)/30.4375. For subjects still on study, the data cutoff date was used to calculate the exposure.

Average daily dose of cabozantinib (placebo) = total doses received (mg)/duration of exposure (days).

An average dose > 60 mg was recorded for two placebo subjects (7028-3081 and 9503-3034) who crossed over to receive open-label study treatment due to inconsistencies in recording dates of end of blinded treatment and start of open-label treatment. In each case subjects received a maximum dose of 60 mg.

Percent dose intensity of cabozantinib (placebo) = 100 × (average daily dose mg/day)/(60 mg/day).

Duration of treatment = (date of decision to discontinue study treatment - date of first dose - total duration of dose interruptions + 1)/30.4375.

A total of 72 subjects in the Safety population discontinued blinded study treatment as of the data cutoff date: 36 subjects (29%) in the cabozantinib arm and 36 subjects (58%) in the placebo arm. There was a low rate of treatment discontinuation due to AEs related to study treatment in each treatment arm (cabozantinib 4%, placebo 0%). This is further discussed below.

Dose modifications

In Study XL184-311, if a subject experienced an unacceptable study treatment-related AE, it was managed with supportive care at the earliest signs of toxicity. If this proved ineffective, dose reductions or interruptions were to be considered to prevent worsening of toxicity. Following a dose

interruption, the subject could resume treatment if the AE resolved to ≤ Grade 1 or to baseline values within 8 weeks. Study treatment could be started at a reduced dose to avoid worsening AEs, if the AE was related to treatment, or dose reduction was otherwise deemed clinically necessary. Study-permitted dose levels for cabozantinib and cabozantinib-matched placebo are defined in **Table *37***.

Dose re-escalation was not permitted for a drug-related dose reduction triggered by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal). Subjects unable to tolerate a dose of 20 mg had study treatment discontinued.

Table 37. Study XL184-311: Dose Reductions of Cabozantinib and Cabozantinib-Matched Placebo (Safety Population)

Starting dose	First Dose Level Reduction	Second Dose Level Reduction	Third Dose Level Reduction
60 mg of cabozantinib (or matched placebo)	40 mg of cabozantinib (or matched placebo)	20 mg of cabozantinib (or matched placebo)[a]	Not allowed

Study treatment was discontinued if a qd dose of 20 mg cabozantinib/matched placebo (minimum dose) was not tolerated.

A summary of dose modifications (interruptions and reductions) due to AEs is presented in **Table *38***

Table 38. Study XL184-311: Drug Interruptions (Holds) and Dose Reductions due to Adverse Events (Safety Population)

	Cabozantinib (N = 125)	Placebo (N = 62)
Dose interruptions:		
Subjects with any dose interruption due to AE, n (%)	90 (72)	17 (27)
Median (range) time to first dose interruption due to AE (days)[a]	30.0 (4, 378)	29.0 (3, 225)
Dose reductions:		
Subjects with any dose reduction, n (%)	70 (56)	3 (4.8)
First dose level reduction (40 mg)[b]	69 (55)	2 (3.2)
Median (range) time to first dose reduction due to AE (days)[b,d]	57.0 (15, 386)	85.0 (30, 153)
Second dose level reduction (20 mg)	28 (22)	1 (1.6)[c]
Median (range) time to second dose reduction due to AE (days)[b,e]	113.0 (29, 370)	NA
Dose modifications (reduction or interruption):		
Subjects with any dose modification due to AE, n (%)[f]	97 (78)	17 (27)
Median (range) time to first dose modification (days)[f]	30.0 (4, 378)	29.0 (3, 225)

	Cabozantinib (N = 125)	Placebo (N = 62)
Median (range) time to second dose modification (days)[g]	75.0 (26, 242)	43.0 (23, 62)

Adverse events

In Study XL184-311, a treatment-emergent adverse event (TEAE) was defined as any event that began or worsened on or after date of first dose of study treatment. For brevity, "TEAE" is hereafter referred to as "AE." For the purpose of data collection, all AEs that occurred after informed consent through the end of the study observation period or until a subject was determined to be a screening failure, were to be recorded by the investigational site. This requirement included AEs from unscheduled as well as scheduled visits. AEs reported in the placebo arm occurred during the blinded study period. Abnormal laboratory values, ECG findings, or vital signs that were considered clinically significant by the Investigator were to be recorded as AEs.

The safety observation period for subjects randomized to and receiving any cabozantinib was defined as the time between the date of first dose of cabozantinib to the earlier of the date of last dose of cabozantinib +30 days, date of withdrawal of consent by subject, date of death, or date of data cutoff.

Clinic visits occurred at minimum every 2 weeks after treatment was initiated through Week 9, and then every 4 weeks through a 30-day post-treatment follow-up visit with contact every 12 weeks thereafter to assess survival status and to document receipt of subsequent anticancer therapy.

Adverse events were coded per the MedDRA version 23.0. Adverse events were graded by the Investigator per CTCAE v5. For the purposes of this report, treatment-related AEs were defined as those assigned as "related" to study treatment by the Investigator.

The safety population of cabozantinib excludes subjects in the placebo arm who crossed over to receive cabozantinib. For subjects who crossed over from placebo to cabozantinib, only the safety data from the time on placebo is summarized in the safety population data. Safety data from the crossover population is discussed in a separate section below.

Table 39 Study XL184-311: Overview of treatment-emergent adverse events (Safety Population)

	Cabozantinib (N = 125) n (%)	Placebo (N = 62) n (%)
Any AE	117 (94)	52 (84)
Treatment-related AE	112 (90)	32 (52)
Grade 3 or 4 AE	71 (57)	16 (26)
Grade 4 AE	7 (5.6)	2 (3.2)
Treatment-related Grade 4 AE	5 (4.0)	0
SAE	43 (34)	18 (29)
Treatment-related SAE	20 (16)	1 (1.6)

	Cabozantinib (N = 125) n (%)	**Placebo (N = 62) n (%)**
Grade 5 AE ≤ 30 days after last dose	9 (7.2)	7 (11)
Treatment-related Grade 5 AE ≤ 30 days after last dose	0	0
Treatment-related Grade 5 AE at any time	0	0
AE leading to treatment discontinuation (not related to disease under study)	6 (4.8)	0
Related to study treatment	5 (4.0)	0
AE leading to dose modification (reduction or interruption)	94 (75)	17 (27)
AE leading to dose reduction	71 (57)	3 (4.8)
AE leading to dose interruption	86 (69)	15 (24)

AE, adverse event (only treatment-emergent events are summarized); CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

Subjects are counted only once in each category but may be counted in multiple categories.

Events are recorded with onset date through the end of the safety observation period unless otherwise stated (ie, "at any time").

For each treatment arm the frequency and percentage of subjects with AEs were tabulated by worst CTCAE grade for overall incidence by system organ class (SOC) and preferred term (PT) or only by PT.

Adverse events that occurred at a ≥ 10% higher incidence in the cabozantinib arm compared with the placebo arm by decreasing frequency were diarrhoea, PPE, hypertension, ALT increased, nausea, AST increased, hypocalcaemia, fatigue, mucosal inflammation, weight decreased, and proteinuria. Adverse events reported for ≥20% of subjects in the cabozantinib arm were diarrhoea, PPE, hypertension, fatigue, ALT increased, nausea, AST increased, decreased appetite, and hypocalcaemia **Table *40***

Table 40. Study XL184-311: Summary of Frequent Adverse Events (≥ 10% Incidence in Either Treatment Arm; Safety Population)

	Cabozantinib (N=125) n (%)		**Placebo (N=62) n (%)**	
Preferred Term	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Number of subjects with at least one AE	117 (94)	71 (57)	52 (84)	16 (26)
Diarrhoea	64 (51)	9 (7.2)	2 (3.2)	0
PPE	57 (46)	13 (10)	0	0
Hypertension	35 (28)	11 (8.8)	3 (4.8)	2 (3.2)

Preferred Term	Cabozantinib (N=125) n (%)		Placebo (N=62) n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue	34 (27)	10 (8.0)	5 (8.1)	0
Alanine aminotransferase increased	30 (24)	1 (0.8)	1 (1.6)	0
Nausea	30 (24)	4 (3.2)	1 (1.6)	0
Aspartate aminotransferase increased	29 (23)	0	1 (1.6)	0
Decreased appetite	29 (23)	4 (3.2)	10 (16)	0
Hypocalcaemia	29 (23)	9 (7.2)	1 (1.6)	1 (1.6)
Weight decreased	23 (18)	1 (0.8)	3 (4.8)	0
Asthenia	19 (15)	3 (2.4)	9 (15)	0
Dyspnoea	19 (15)	4 (3.2)	11 (18)	2 (3.2)
Proteinuria	19 (15)	1 (0.8)	2 (3.2)	0
Vomiting	18 (14)	1 (0.8)	5 (8.1)	0
Mucosal inflammation	17 (14)	3 (2.4)	0	0
Stomatitis	16 (13)	3 (2.4)	2 (3.2)	0
Hypomagnesaemia	15 (12)	1 (0.8)	3 (4.8)	0
Constipation	13 (10)	0	5 (8.1)	0
Dysphonia	13 (10)	0	1 (1.6)	0
Anaemia	7 (5.6)	2 (1.6)	8 (13)	0
Cough	6 (4.8)	0	12 (19)	0

AE, adverse event; PPE, palmar-plantar erythrodysaesthesia syndrome.

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

Denominators for percentages are N, the total number of subjects in each treatment arm.

Overall, AEs with severity Grade 3/4 were reported for 57% of subjects in the cabozantinib arm and for 26% of the placebo subjects. The most frequent Grade 3/4 AEs (≥ 5% incidence) reported for subjects in the cabozantinib arm in descending order of incidence were PPE, hypertension, fatigue, diarrhoea, and hypocalcaemia. There were no Grade 3 or 4 AEs with a ≥ 5% incidence reported in the placebo arm **Table *41***.

Table 41. Study XL184-311: Summary of Adverse Events with a Difference of ≥ 5% (All Grades) or ≥ 2% (Grade 3/4) Between Treatment Arms (Safety Population)

	Cabozantinib (N=125) n (%)		Placebo (N=62) n (%)	
Preferred Term	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade ¾**
Number of subjects with at least one AE	117 (94)	71 (57)	52 (84)	16 (26)
Diarrhoea	64 (51)	9 (7.2)	2 (3.2)	0
PPE	57 (46)	13 (10)	0	0
Hypertension	35 (28)	11 (8.8)	3 (4.8)	2 (3.2)
Alanine aminotransferase increased	30 (24)	1 (0.8)	1 (1.6)	0
Nausea	30 (24)	4 (3.2)	1 (1.6)	0
Aspartate aminotransferase increased	29 (23)	0	1 (1.6)	0
Hypocalcaemia	29 (23)	9 (7.2)	1 (1.6)	1 (1.6)
Fatigue	34 (27)	10 (8.0)	5 (8.1)	0
Weight decreased	23 (18)	1 (0.8)	3 (4.8)	0
Mucosal inflammation	17 (14)	3 (2.4)	0	0
Proteinuria	19 (15)	1 (0.8)	2 (3.2)	0
Stomatitis	16 (13)	3 (2.4)	2 (3.2)	0
Blood lactate dehydrogenase increased	12 (9.6)	0	0	0
Dysgeusia	12 (9.6)	0	0	0
Dysphonia	13 (10)	0	1 (1.6)	0
Dry mouth	12 (9.6)	1 (0.8)	1 (1.6)	0
Headache	12 (9.6)	2 (1.6)	1 (1.6)	0
Thrombocytopenia	9 (7.2)	0	0	0
Hypokalaemia	11 (8.8)	1 (0.8)	1 (1.6)	0
Hypomagnesaemia	15 (12)	1 (0.8)	3 (4.8)	0
Decreased appetite	29 (23)	4 (3.2)	10 (16)	0
Vomiting	18 (14)	1 (0.8)	5 (8.1)	0
Pulmonary embolism	6 (4.8)	3 (2.4)	0	0
Asthenia	19 (15)	3 (2.4)	9 (15)	0
Cough	6 (4.8)	0	12 (19)	0

Preferred Term	Cabozantinib (N=125) n (%)		Placebo (N=62) n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade ¾
Anaemia	7 (5.6)	2 (1.6)	8 (13)	0
Hypercalcaemia	1 (0.8)	1 (0.8)	4 (6.5)	2 (3.2)

AE, adverse event; PPE, palmar-plantar erythrodysaesthesia syndrome.

Denominators for percentages are N, the total number of subjects in each treatment arm.

Grade 3/4 AEs that had a ≥ 2% higher per-subject incidence in the cabozantinib arm compared with placebo by decreasing frequency of between-arm difference were PPE, fatigue, diarrhoea, hypertension, hypocalcaemia, decreased appetite, nausea, asthenia, mucosal inflammation, pulmonary embolism, and stomatitis **Table *42***

Table 42. Study XL184-311: Summary of Frequent Grade 3 or 4 Adverse Events Regardless of Causality (≥ 2% Incidence in the Either Treatment Arm; Safety Population)

Preferred Term	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
Number of subjects with at least one Grade 3 or 4 AE	71 (57)	16 (26)
PPE	13 (10)	0
Hypertension	11 (8.8)	2 (3.2)
Fatigue	10 (8.0)	0
Diarrhoea	9 (7.2)	0
Hypocalcaemia	9 (7.2)	1 (1.6)
Decreased appetite	4 (3.2)	0
Dyspnoea	4 (3.2)	2 (3.2)
Nausea	4 (3.2)	0
Pleural effusion	4 (3.2)	2 (3.2)
Asthenia	3 (2.4)	0
Mucosal inflammation	3 (2.4)	0
Pulmonary embolism	3 (2.4)	0

Stomatitis	3 (2.4)	0
Hypercalcaemia	1 (0.8)	2 (3.2)

AE, adverse event; PPE, palmar-plantar erythrodysaesthesia syndrome.

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

Denominators for percentages are N, the total number of subjects in each treatment arm.

Table 43. Study XL184-311: Frequent Adverse Events Leading to Dose Modification (≥ 5% Incidence in Either Treatment Arm; Safety Population)

Preferred Term	***Cabozantinib (N=125)*** ***n (%)***	***Placebo (N=62)*** ***n (%)***
Subjects with at least one AE that led to dose modifications	***94 (75)***	***17 (27)***
PPE	*28 (22)*	*0*
Diarrhoea	*22 (18)*	*0*
Decreased appetite	*11 (8.8)*	*1 (1.6)*
Fatigue	*11 (8.8)*	*2 (3.2)*
Hypertension	*10 (8.0)*	*0*
Asthenia	*9 (7.2)*	*0*
Dyspnoea	*9 (7.2)*	*3 (4.8)*
Nausea	*8 (6.4)*	*0*
Proteinuria	*8 (6.4)*	*0*
Alanine aminotransferase increased	*7 (5.6)*	*0*
Hypocalcaemia	*7 (5.6)*	*0*
Mucosal inflammation	*7 (5.6)*	*0*

AE, adverse event; PPE, palmar-plantar erythrodysaesthesia syndrome.

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

Denominators for percentages are N, the total number of subjects in each treatment arm.

Safety Observations in the Crossover Phase of Study XL184-311

Subjects randomized to the placebo arm were permitted to crossover to receive cabozantinib upon experiencing radiographic progressive disease, as determined by the Investigator per RECIST 1.1 and confirmed by BIRC. As of the data cutoff, 19 subjects crossed over from the placebo arm to receive cabozantinib in the crossover phase of Study. Two placebo subjects did not begin open-label cabozantinib until after the data cutoff date. Safety observations in the crossover phase of Study XL184-311 were similar to the cabozantinib-only arm and are summarized below.

The median duration of cabozantinib exposure (including dose holds) in the crossover phase was 2.3 (range 0.1 - 6.0) months. The median daily dose was 38.5 mg cabozantinib, and the corresponding median dose intensity was 64.2%. Safety observations in the crossover phase of Study XL184-311 were similar to the cabozantinib-only arm (**Table *44***).

A total of 4 crossover subjects (21%) died as of the 19 August 2020 data cutoff date. All deaths occurred ≤ 30 days after last dose of study treatment. Three deaths were assessed by the Investigator as causally associated with DTC. One subject had a death reported by the Investigator as other than causally associated with DTC; the associated Grade 5 AE PT was suspected COVID-19.

Table 44. Study XL184-311: Overview of Treatment Emergent Adverse Events and Deaths – cabozantinib placebo crossover

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Table 14.3.1.5.1.1
Overview of Treatment Emergent Adverse Events and Deaths
Population: Safety

Subjects experiencing a/an:	Cabozantinib Only (N=125)	Cabozantinib Placebo Crossover (N=19)	All Cabozantinib (N=144)	Placebo (N=62)
TEAE [1]	117 (94%)	18 (95%)	135 (94%)	52 (84%)
Related TEAE [1]	112 (90%)	17 (89%)	129 (90%)	32 (52%)
Serious TEAE [1]	43 (34%)	7 (37%)	50 (35%)	18 (29%)
Serious related TEAE [1]	20 (16%)	0	20 (14%)	1 (1.6%)
Serious related TEAE at any time	20 (16%)	0	20 (14%)	1 (1.6%)
Worst Grade 3 or 4 TEAE [1]	71 (57%)	5 (26%)	76 (53%)	16 (26%)
Worst Grade 3 or 4 related TEAE [1]	59 (47%)	3 (16%)	62 (43%)	4 (6.5%)
Worst Grade 4 TEAE [1]	7 (5.6%)	1 (5.3%)	8 (5.6%)	2 (3.2%)
Worst Grade 4 related TEAE [1]	5 (4.0%)	0	5 (3.5%)	0
Grade 5 TEAE <= 30 days after last dose of study treatment	9 (7.2%)	4 (21%)	13 (9.0%)	7 (11%)
Grade 5 TEAE judged not to be causally related to the disease <= 30 days of last dose of study treatment	2 (1.6%)	1 (5.3%)	3 (2.1%)	2 (3.2%)

Subjects experiencing a/an:	Cabozantinib Only (N=125)	Cabozantinib Placebo Crossover (N=19)	All Cabozantinib (N=144)	Placebo (N=62)
Grade 5 Related TEAE at anytime	0	0	0	0
Grade 5 Related TEAE <= 30 days after last dose of study treatment	0	0	0	0
TEAE leading to dose modification (reduction or hold) [1]	94 (75%)	13 (68%)	107 (74%)	17 (27%)
TEAE leading to dose reduction [1]	71 (57%)	10 (53%)	81 (56%)	3 (4.8%)
TEAE leading to dose hold [1]	86 (69%)	11 (58%)	97 (67%)	15 (24%)
TEAE leading to treatment discontinuation [1]	16 (13%)	5 (26%)	21 (15%)	3 (4.8%)
TEAEs not causally related to disase under Study [1]	6 (4.8%)	1 (5.3%)	7 (4.9%)	0
TEAEs not related to study treatment [1]	2 (1.6%)	1 (5.3%)	3 (2.1%)	0
TEAEs related to study treatment [1]	5 (4.0%)	0	5 (3.5%)	0
TEAEs causally related to disease under Study [1]	10 (8.0%)	3 (16%)	13 (9.0%)	3 (4.8%)
TEAEs related to study treatment [1]	0	0	0	0

Comparison of Safety in Study XL184-311 with Pooled Studies (Studies XL184-309, XL184-308, and A031203)

Safety results from the 60-mg cabozantinib arm of Study XL184-311, pooled studies (cabozantinib 60-mg treatment arms of Studies XL184-309, XL184-308, and A031203), and the 140-mg cabozantinib capsules arm of Study XL184-301 are provided to present the observations in the DTC population

(XL184-311) in context with respect to the broader cabozantinib safety experience. These studies were chosen on the basis that they led to the approval of cabozantinib for the treatment of RCC (Studies XL184-308 and A031203), HCC (Study XL184-309), and MTC (Study XL184-301).

Cross-study comparison is limited due to differences in the study population, study design, intended dose and formulation, 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. Overall, there were no additional safety concerns for Study XL184-311 compared with the other studies. The incidence of frequent AEs in Study XL184-311 was generally consistent with the other studies.

A summary of frequent AEs (≥ 10% in the cabozantinib arm) of any grade in Study XL184 311, compared with the pooled studies and Study XL184-301, is presented in **Table *45***.

Table 45. Study XL184-311, Pooled Studies (Studies XL184-309, XL184-308, and A031203), and Study XL184-301: Summary of Frequent Adverse Events (≥ 10% Incidence in the Cabozantinib Arm of Study XL184-311; Safety Population)

Preferred Term	**Study XL184-311 (60 mg cabozantinib) (N=125) n (%)**	**Pooled Studies (60 mg cabozantinib) (N=876) n (%)**	**Study XL184-301 (140 mg cabozantinib) (N=214) n (%)**
Number of subjects with at least one AE	117 (94)	866 (99)	214 (100)
Diarrhoea	64 (51)	553 (63)	135 (63)
PPE	57 (46)	389 (44)	107 (50)
Hypertension	35 (28)	311 (36)	63 (29)
Fatigue	34 (27)	448 (51)	87 (41)
Alanine aminotransferase increased	30 (24)	176 (20)	46 (22)
Nausea	30 (24)	338 (39)	92 (43)
Aspartate aminotransferase increased	29 (23)	210 (24)	46 (22)
Decreased appetite	29 (23)	414 (47)	98 (46)
Hypocalcaemia	29 (23)	50 (6)	45 (21)
Weight decreased	23 (18)	210 (24)	102 (48)
Asthenia	19 (15)	164 (19)	45 (21)
Dyspnoea	19 (15)	134 (15)	29 (14)
Proteinuria	19 (15)	63 (7)	4 (2)
Vomiting	18 (14)	245 (28)	52 (24)
Mucosal inflammation	17 (14)	129 (15)	50 (23)
Stomatitis	16 (13)	166 (19)	62 (29)

Preferred Term	Study XL184-311 (60 mg cabozantinib) (N=125) n (%)	Pooled Studies (60 mg cabozantinib) (N=876) n (%)	Study XL184-301 (140 mg cabozantinib) (N=214) n (%)
Hypomagnesaemia	15 (12)	98 (11)	41 (19)[a]
Constipation	13 (10)	184 (21)	57 (27)
Dysphonia	13 (10)	173 (20)	43 (20)

AE, adverse event; PPE, palmar-plantar erythrodysaesthesia syndrome.

Denominators for percentages are N, the total number of subjects in each treatment arm.

[a] These events were recorded as magnesium decreased in Study XL184-301.

Serious adverse event/deaths/other significant events

Serious adverse events

The overall incidence of SAEs are show in **Table *46***

Table 46. Study XL184-311: Summary of Serious Adverse Events (≥ 1% Incidence in Either Treatment Arm; Safety Population)

Preferred Term	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
Subjects with at least one SAE of any grade	43 (34)	18 (29)
Diarrhoea	4 (3.2)	0
Pleural effusion	4 (3.2)	3 (4.8)
Pulmonary embolism	4 (3.2)	0
Dyspnoea	3 (2.4)	4 (6.5)
Deep vein thrombosis	2 (1.6)	0
Disease progression	2 (1.6)	0
General physical health deterioration	2 (1.6)	0
Hypertension	2 (1.6)	0
Hypocalcaemia	2 (1.6)	0
Pneumonia	2 (1.6)	1 (1.6)
COVID-19a	1 (0.8)	1 (1.6)

Cardiac arrest	1 (0.8)	1 (1.6)
Hypercalcaemia	1 (0.8)	1 (1.6)
Pain	1 (0.8)	1 (1.6)
Carotid artery stenosis	0	1 (1.6)
Fall	0	1 (1.6)
Hydrothorax	0	1 (1.6)
Hyponatraemia	0	1 (1.6)
Influenza	0	1 (1.6)
Lower respiratory tract infection	0	1 (1.6)
Oedema peripheral	0	1 (1.6)
Pain in jaw	0	1 (1.6)
Pruritus	0	1 (1.6)
Spinal fracture	0	1 (1.6)
Tumour pain	0	1 (1.6)

SAE, serious adverse event.

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

Denominators for percentages are N, the total number of subjects in each treatment arm.

Two confirmed cases of COVID-19 infections were reported. Subject 8630-3165 in the cabozantinib arm was hospitalized due to Grade 3 COVID-19 and died ≥ 30 days after last dose of study treatment due to respiratory failure (cause of death was reported as COVID-19 infection). The subject presented with dyspnoea and was found to have ground glass opacities on CT scan. Subject 3401-3137 in the placebo arm had Grade 2 COVID-19 with symptoms of fever and cough. This subject recovered.

Table 47. Study XL184-311: Summary of Frequent Treatment-Related Serious Adverse Events (≥ 1% Incidence in Either Treatment Arm; Safety Population)

Preferred Term	**Cabozantinib (N=125) n (%)**	**Placebo (N=62) n (%)**
Subjects with at least one related SAE	20 (16)	1 (1.6)
Diarrhoea	4 (3.2)	0
Deep vein thrombosis	2 (1.6)	0
Hypertension	2 (1.6)	0
Pulmonary embolism	2 (1.6)	0
Pruritus	0	1 (1.6)

SAE, serious adverse event.

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

Denominators for percentages are N, the total number of subjects in each treatment arm.

Table 48. Study XL184-311, Pooled Studies (Studies XL184-309, XL184-308, and A031203), and Study XL184-301: Summary of Serious Adverse Events (≥ 2% Incidence in the Cabozantinib Arm of Study XL184 311; Safety Population).

Preferred Term	Study XL184-311 (60 mg cabozantinib) (N=125) n (%)	Pooled Studies (60 mg cabozantinib) (N=876) n (%)	Study XL184-301 (140 mg cabozantinib) (N=214) n (%)
Subjects with at least one SAE, (any grade)	43 (34)	401 (46)	90 (42.1)
Diarrhoea	4 (3.2)	16 (1.8)	3 (1.4)
Pleural effusion	4 (3.2)	12 (1.4)	0
Pulmonary embolism	4 (3.2)	9 (1.0)	5 (2.3)
Dyspnoea	3 (2.4)	16 (1.8)	2 (0.9)

SAE, serious adverse event. Denominators for percentages are N, the total number of subjects in each treatment arm.

Deaths

The incidence of deaths is summarized in **Table 49** Survival information was collected on subjects during the safety observation period and at 12-week intervals thereafter until death (the precise date of death was recorded on the CRF).

A total of 31 deaths were reported as of the cutoff date of 19 August 2020: 17 (14%) in the cabozantinib arm, 10 (16%) in the placebo arm, and 4 additional deaths in the placebo crossover arm. None of the deaths were considered related to study treatment, per Investigator.

Table 49. Summary of Deaths (Safety Population)

	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
All deaths	17 (14)	10 (16)a
Deaths ≤ 30 days after last dose	9 (7.2)	7 (11)

	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
Deaths > 30 days after last dose	8 (6.4)	3 (4.8)

Four additional subjects in the placebo crossover arm expired as of the data cutoff date and are excluded from the total number of deaths in the placebo arm in the Safety Population

Every death through 30 days after the last dose of study treatment that occurred within the safety observation period had an associated Grade 5 AE, summarized in **Table *50*.** None of these Grade 5 events were considered related to study treatment, per Investigator.

Table 50 Grade 5 Events through 30 Days after Last Dose of Study Treatment (Safety Population)

Preferred Term	Cabozantinib (N = 125) n (%)	Placebo (N = 62) n (%)
Number of subjects with a Grade 5 AE	9 (7.2)	7 (11)
Disease progression	2 (1.6)	2 (3.2)
Arterial haemorrhage	1 (0.8)a	0
Cardiac arrest	1 (0.8)a	1 (1.6)
Cardio-respiratory arrest	1 (0.8)a	0
Pneumonia	1 (0.8)a	0
Pulmonary embolism	1 (0.8)a	0
Thyroid cancer	1 (0.8)	1 (1.6)
Thyroid cancer metastatic	1 (0.8)	0
Cerebrovascular accident	0	1 (1.6)
General physical health deterioration	0	1 (1.6)
Poorly differentiated thyroid carcinoma	0	1 (1.6)

AE, adverse event. At each level of subject summarization, a subject was counted once for the most severe event if the subject reported one or more events. Denominators for percentages are N, the total number of subjects in each Treatment arm. a Abbreviated narrative provided.

Deaths after 30 days from the last dose of study drug in Study XL184-311 are summarized in **Table *51***. A total of 11 deaths occurred more than 30 days after the last dose of study treatment: 8 (6.4%) in the cabozantinib arm and 3 (4.8%) in the placebo arm. Of the 8 deaths in the cabozantinib arm, 6 were events of thyroid cancer or disease progression. Of the 2 other deaths, one was an event of

respiratory failure, and one was an event of unknown cause (considered related to DTC per Investigator). All deaths were considered unrelated to study treatment, per Investigator.

Table 51 Study XL184-311: Summary of Deaths More Than 30 Days after Last Dose of Study Treatment (Safety Population)

	Cabozantinib N=125 **n (%)**	**Placebo N=62** **n (%)**
Deaths > 30 days after last dose	8 (6.4)	3 (4.8)
Primary death reason		
Death[a]	1 (0.8)	0
Disease progression	5 (4.0)	0
Euthanasia	0	1 (1.6)
Respiratory failure	1 (0.8)	0
Sepsis	0	1 (1.6)
Thyroid cancer	0	1 (1.6)
Thyroid cancer metastatic	1 (0.8)	0

[a]Investigator considered death related to DTC

(a) Events to monitor (ETMs)

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 characterizing the safety profile of cabozantinib. Incidence of ETMs is listed in **Table *52*** below.

It is important to note that some ETMs contain a broad list of MedDRA PTs, and that the overall ETM incidences therefor should be interpreted with caution (eg, the ETM of QT prolongation contains many PTs, which medically could possibly be linked to QT prolongation but may not have been associated with a documented QT-prolongation).

The most frequently observed ETMs (≥ 10% in cabozantinib arm) were diarrhoea, PPE, hypertension, proteinuria and VTEs. Among them, the more frequently (≥ 5% in cabozantinib) observed ETMs with Grade 3 events were PPE, hypertension, and diarrhoea. ETMs with Grade 3 or higher events occurring at rates between 2 and 5% (in any treatment arm) were VTEs, haemorrhage, and events possibly linked to QT prolongation.

A total of 2 subjects (1.6%) in the cabozantinib arm experienced a PT of QT prolongation on study. Both events were Grade ≤ 2 and neither QTcF was > 500 ms (one subject had post baseline ECG assessments that showed prolonged QTcF interval (QTcF > 500 ms) per Investigator evaluation. The case was submitted for central review, and the QTcF elevation > 500 ms was not confirmed). No PT of QT prolonged was reported in the placebo arm. There were no events of torsades de pointes and no events of sudden death on either treatment arm.

Grade 5 ETMs had low rates across treatment arms and consisted of different isolated events within each treatment arm. In the cabozantinib arm, four Grade 5 events were reported: arterial haemorrhage, pulmonary embolism, cardiac arrest, and cardio-respiratory arrest (1 subject each). All were assessed as not related to study drug by the Investigator.

Table 52. Study XL184-311: Incidence of Adverse Events to Monitor (Safety Population)

ETM **Preferred Term**	**Cabozantinib (N=125)** **n (%)** **Grade**			**Placebo (N=62)** **n (%)** **Grade**		
	Any	**3/4**	**5**	**Any**	**3/4**	**5**
GI perforation	1 (0.8)	1 (0.8)	0	0	0	0
Large intestine perforation	1 (0.8)	1 (0.8)	0	0	0	0
Fistula	0	0	0	0	0	0
Abscess—all	3 (2.4)	2 (1.6)	0	0	0	0
Anal abscess	1 (0.8)	1 (0.8)	0	0	0	0
Rectal abscess	1 (0.8)	1 (0.8)	0	0	0	0
Tooth abscess	1 (0.8)	0	0	0	0	0
Intra-abdominal and pelvic abscess	2 (1.6)	2 (1.6)	0	0	0	0
Anal abscess	1 (0.8)	1 (0.8)	0	0	0	0
Rectal abscess	1 (0.8)	1 (0.8)	0	0	0	0
Haemorrhage (≥ Grade 3)	3 (2.4)	2 (1.6)	1 (0.8)	0	0	0
Arterial haemorrhage	1 (0.8)	0	1 (0.8)	0	0	0
Haematoma	1 (0.8)	1 (0.8)	0	0	0	0
Haemoptysis	1 (0.8)	1 (0.8)	0	0	0	0
Muscle haemorrhage	1 (0.8)	1 (0.8)	0	0	0	0
Arterial thrombotic events	1 (0.8)	0	0	0	0	0
Aortic thrombosis	1 (0.8)	0	0	0	0	0
Venous and mixed/unspecified thrombotic events	12 (9.6)	4 (3.2)	1 (0.8)	0	0	0
Pulmonary embolism	6 (4.8)	3 (2.4)	1 (0.8)	0	0	0
Deep vein thrombosis	3 (2.4)	1 (0.8)	0	0	0	0
Pelvic venous thrombosis	1 (0.8)	0	0	0	0	0

ETM Preferred Term	Cabozantinib (N=125) n (%) Grade			Placebo (N=62) n (%) Grade		
Superior vena cava syndrome[a]	1 (0.8)	0	0	0	0	0
Thrombosis[b]	1 (0.8)	0	0	0	0	0
Wound complications	2 (1.6)	2 (1.6)	0	0	0	0
Wound dehiscence	1 (0.8)	1 (0.8)	0	0	0	0
Wound infection	1 (0.8)	1 (0.8)	0	0	0	0
Hypertension	37 (30)	12 (9.6)	0	3 (4.8)	2 (3.2)	0
Hypertension	35 (28)	11 (8.8)	0	3 (4.8)	2 (3.2)	0
Blood pressure increased	1 (0.8)	0	0	0	0	0
Hypertensive crisis	1 (0.8)	1 (0.8)	0	0	0	0
Osteonecrosis	3 (2.4)	1 (0.8)	0	3 (4.8)	1 (1.6)	0
Osteonecrosis of jaw	1 (0.8)	1 (0.8)	0	1 (1.6)	0	0
Tooth abscess	1 (0.8)	0	0	0	0	0
Tooth infection	1 (0.8)	0	0	0	0	0
Pain in jaw	0	0	0	2 (3.2)	1 (1.6)	0
PPE[c]	57 (46)	13 (10)	0	0	0	0
Proteinuria[d]	20 (16)	1 (0.8)	0	2 (3.2)	0	0
Proteinuria	19 (15)	1 (0.8)	0	2 (3.2)	0	0
Urine protein/creatinine ratio increased	1 (0.8)	0	0	0	0	0
PRES (RPLS)[e]	0	0	0	0	0	0
Diarrhoea	64 (51)	9 (7.2)	0	2 (3.2)	0	0
QT prolongation[f]	5 (4.0)	1 (0.8)	2 (1.6)	1 (1.6)	0	1 (1.6)
Electrocardiogram QT prolonged	2 (1.6)	0	0	0	0	0
Cardiac arrest	1 (0.8)[g]	0	1 (0.8)[g]	1 (1.6)	0	1 (1.6)
Cardio-respiratory arrest	1 (0.8)[h]	0	1 (0.8)[h]	0	0	0
Syncope	1 (0.8)[i]	1 (0.8)[i]	0	0	0	0

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ETM, event to monitor; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; PPE, palmar-plantar erythrodysaesthesia syndrome; PRES, posterior reversible encephalopathy syndrome (RPLS, reversible

ETM	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
Preferred Term	**Grade**	**Grade**

posterior leukoencephalopathy syndrome); SMQ, Standard MedDRA Query. Adverse events were graded per CTCAE v5. Reported AEs were coded using MedDRA v23.0. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events [a]Subject 6110-3163 experienced a Grade 2 AE of superior vena cava syndrome (concurrent with Grade 3 progression of disease under study) and was assessed as causally related to DTC and not related to study treatment per Investigator.

[b]Verbatim term: thrombosis left leg. [c]Per CTCAE v5, there are no events of PPE with severity > Grade 3.

[d]Per CTCAE v5, there are no events of proteinuria with severity > Grade 3. [e]One subject (3103-3101) in the cabozantinib arm who was counted under the hypertension ETM was also assessed as having PRES (RPLS) by the Investigator. [f]Based on 20 preferred terms in the search criteria Torsade de pointes/QT prolongation SMQ (broad).

[g]QTcF values at screening and Weeks 1, 5, 9, and 21 did not show evidence of QTcF prolongation (eg, values were < 500 ms) for this subject. The Week 21 ECG was performed approximately 1 month prior to the Grade 5 event.

[h]QTcF values at screening and Week 5 did not show evidence of QTcF prolongation for this subject. The Week 5 ECG was performed approximately 2 weeks prior to the Grade 5 event.

[i]QTcF values at screening and Weeks 1, 5, and 9 did not show evidence of QTcF prolongation for this subject. The Week 9 ECG was performed 1 day after the event of syncope.

The ETMs in Study XL184-311 are compared with the pooled studies and Study XL184-301 in **Table *53***. It is important to note, that over time, the ETM category definitions were refined, with more broad criteria implemented for Study XL184-311. Hence, cross-study comparison must be done with caution.

There was a higher incidence of proteinuria in Study XL184-311 compared to the pooled studies and Study XL184-301. Of the cases of proteinuria, all but one of the subjects had proteinuria of Grade 1 or 2 severity, and all events were non-serious. There was also a slightly higher incidence of venous and mixed/unspecified thrombotic events in Study XL184-311 compared to the pooled studies and Study XL184-301. Of the 12 subjects in the cabozantinib arm who experienced an ETM of VTE, 7 subjects had events that were Grade 1 or 2 of severity including 2 subjects with pulmonary embolism that was considered an incidental finding and was assigned a Grade < 3 by the Investigator. 1 subject experienced a Grade 5 suspected pulmonary embolism 1 day after discontinuing study treatment.

Table 53. Study XL184-311, Pooled Studies (Studies XL184-309, XL184-308, and A031203), and Study XL184-301: Incidence of Adverse Events to Monitor (Safety Population).

	Study XL184-311[a] (60 mg cabozantinib) (N=125) n (%)			Pooled Studies[b] (60 mg cabozantinib) (N=876) n (%)			Study XL184-301[c] (140 mg cabozantinib) (N=214) n (%)	
	Grade			Grade			Grade	
ETM	**Any**	**3/4**	**5**	**Any**	**3/4**	**5**	**Any**	**≥ 3**
GI perforation	1 (0.8)	1 (0.8)	0	9 (1.0)	7 (0.8)	1 (0.1)	7 (3.3)	7 (3.3)
Fistula	0	0	0	11 (1.3)	3 (0.3)	1 (0.1)	10 (4.6)[c]	5 (2.3) 3 Grade 5 AEs
Abscess—all	3 (2.4)	2 (1.6)	0	25 (2.9)	13 (1.5)	0	NA	NA
Intra-abdominal and pelvic abscess	2 (1.6)	2 (1.6)	0	9 (1.0)	7 (0.8)	0	5 (2.3)	1 (0.5)
Haemorrhage (≥ Grade 3)	3 (2.4)	2 (1.6)	1 (0.8)	45 (5.1)	38 (4.3)	7 (0.8)	NA	7 (3.3) 2 Grade 5 AEs
Arterial thrombotic events	1 (0.8)	0	0	20 (2.3)	12 (1.4)	3 (0.3)	5 (2.3)	2 (0.9)
Venous and mixed/unspecified thrombotic events[d]	12 (9.6)	4 (3.2)	1 (0.8)	58 (6.6)	36 (4.1)	2 (0.2)	12 (5.6)	10 (4.7)
Wound complication	2 (1.6)	2 (1.6)	0	12 (1.4)	2 (0.2)	0	4 (1.9)	2 (0.9)
Hypertension	37 (30)	12 (9.6)	0	318 (36)	149 (17)	0	70 (33)	18 (8.4)
Osteonecrosis	3 (2.4)	1 (0.8)	0	2 (0.2)	1 (0.1)	0	3 (1.4)	1 (0.5)
PPE[e]	57 (46)	13 (10)	0	389 (44)	112 (13)	0	107 (50)	27 (13)
Proteinuria[e, f]	20 (16)	1 (0.8)	0	63 (7.2)	17 (1.9)	0	4 (1.9)	2 (0.9)
PRES (RPLS)[g]	0	0	0	0	0	0	1 (0.5)	1 (0.5)
Diarrhoea	64 (51)	9 (7.2)	0	553 (63)	92 (11)	0	135 (65)	34 (16)
QT prolongation[h]	5 (4.0)	1 (0.8)	2 (1.6)	7 (0.8)	1 (0.1)	0	5 (2.3)[i]	1 (0.5)

CTCAE, Common Terminology Criteria for Adverse Events; ETM, event to monitor; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; NA, not applicable; PPE, palmar-plantar erythrodysaesthesia syndrome; RPLS, reversible posterior leukoencephalopathy syndrome (preferred term: posterior reversible encephalopathy syndrome [PRES]); SMQ, Standard MedDRA Query. [a] Adverse events were graded per CTCAE v5. [b] Adverse events were graded per CTCAE v4. [c] In Study XL184-301, GI fistulas and non-GI fistulas were considered separately, and the majority of fistulas were non-GI (incidences: non-GI 3.7%, GI 0.9%).

[d] This ETM was based on a customized set of 91 PTs for Study XL184-301, based on the single SMQ (venous and mixed thromboembolic events) for the pooled studies, and two SMQs (thromboembolic venous events and mixed thromboembolic events) for Study XL184-311. [e] Per CTCAE v4 and v5, there are no events of PPE or proteinuria with severity > Grade 3. [f] This ETM was based on a set of 5 PTs for Study XL184-301, a customized set of 5 PTs for the pooled studies, and the proteinuria SMQ (narrow) for Study XL184-311. [g] One subject (3103-3101) in the cabozantinib arm who was counted under the hypertension ETM was also assessed as having PRES (RPLS) by the Investigator. [h] This ETM was based on a set of 4 PTs for Study XL184-301 and the pooled studies, and based on the Torsade de pointes/QT prolongation SMQ (broad) for Study XL184-311. for PTs under this ETM in Study XL184-311. [i] In Study XL184-301, a mean increase in QTc correction by the Fridericia's formula (QTcF) of 10-15 ms relative to placebo was observed after 4 weeks following initiation of cabozantinib treatment (ie, steady-state).

Median time to each ETM in Study XL184-311 is summarized in **Table *54***.

Table 54. Study XL184-311: Time to First Occurrence of Event to Monitor (Safety Population)

	Cabozantinib (N=125)	**Placebo (N=62)**
ETM	**Time to First Occurrence of ETM Median (25th, 75th Percentiles), days**	
GI perforation	97.0 (97.0, 97.0)	NA
Fistula	NA	NA
Abscess—all	267.0 (146.0, 330.0)	NA
Intra-abdominal and pelvic abscess	298.5 (267.0, 330.0)	NA
Haemorrhage (≥ Grade 3)	98.0 (62.0, 117.0)	NA
Arterial thrombotic events	113.0 (113.0, 113.0)	NA
Venous and mixed/unspecified thrombotic events	50.0 (20.5, 57.0)	NA
Wound complications	41.0 (15.0, 67.0)	NA
Hypertension	15.0 (15.0, 28.0)	15.0 (14.0, 58.0)
Osteonecrosis	126.0 (24.0, 146.0)	84.0 (15.0, 277.0)
PPE[a]	28.0 (15.0, 43.0)	NA
Proteinuria[b]	21.0 (15.0, 30.5)	64.0 (15.0, 113.0)
PRES (RPLS)	NA	NA
QTc prolongation[c]	54.0 (31.0, 84.0)	27.0 (27.0, 27.0)

	Cabozantinib (N=125)	Placebo (N=62)
ETM	**Time to First Occurrence of ETM Median (25th, 75th Percentiles), days**	

ETM, event to monitor; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; NA, not applicable; PPE, palmar-plantar erythrodysaesthesia syndrome; PRES, posterior reversible encephalopathy syndrome (RPLS, reversible posterior leukoencephalopathy syndrome); SMQ, Standard MedDRA Query.

Adverse events were graded per CTCAe v5. Reported AEs were coded using MedDRA v23.0.

Time to first occurrence was defined as (date of onset of first occurrence of ETM – first dose date +1).

Per CTCAE v5, there are no events of PPE with severity > Grade 3.

Per CTCAE v5, there are no events of proteinuria with severity > Grade 3.

Based on 20 preferred terms in the search criteria Torsade de pointes/QT prolongation SMQ (broad).

Laboratory findings

Cabozantinib has previously been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, and hyponatremia).

In Study XL184-311, laboratory parameters were assessed at the following time points: Screening; Treatment Period: Day 1 of Weeks 1, 3, 5, 7, and 9; every 4 weeks thereafter through discontinuation; Post Treatment Assessment: 30 days after the decision to discontinue study treatment. In **Table *55*** laboratory parameters evaluated are summarized.

Table 55. Laboratory parameters evaluated in Study XL184-311

Serum Chemistry	Alkaline phosphatase, ALT, AST, calcium, creatinine, glucose, magnesium, phosphorus, potassium, sodium, total bilirubin, lipase, amylase
Haematology	White blood cell count, neutrophils, lymphocytes, haemoglobin, platelet count, haematocrit
Urine/LDH	Urine protein/urine creatinine ratio and LDH
Other	TSH, Free T4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; T4, thyroxine; TSH, thyroid-stimulating hormone.

Complete lists of laboratory results are provided in XL184-311 CSR, Section 12.4.

Quantitative laboratory parameters included in CTCAE v5 were graded per those criteria programmatically. Criteria for UPCR and LDH, which are not included in CTCAE v5, were defined by the Sponsor as described in **Table *56***.

Table 56. Study XL184-311: Grading of UPCR and LDH

UPCR[a]	• Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥0.15 to ≤1.0 mg/mg) • Grade 2 if > 121.0 to ≤ 396.0 mg/mmol (>1.0 to <3.5 mg/mg) • Grade 3 if > 396.0 mg/mmol (>3.5 mg/mg)
LDH	• Grade 1 if > ULN to ≤ 2 × ULN • Grade 2 if > 2 × ULN to ≤ 3 × ULN • Grade 3 if > 3 × ULN

LDH, lactate dehydrogenase; ULN, upper limit of normal; UPCR, urine protein/creatinine ratio.

Subjects were eligible for enrolment in Study XL184-311 with UPCR laboratory results of ≤ 1.0 mg/mg (≤ 113.2 mg/mmol).

Serum Chemistry

Treatment-emergent abnormalities of selected serum chemistry parameters in Study XL184-311 are summarized in **Table *57***. Most of the treatment-emergent chemistry abnormalities were of Grade 1 or 2 severity in both treatment arms.

Serum chemistry abnormalities (all grades) that had a ≥ 5% higher per-subject incidence in the cabozantinib arm compared with placebo by decreasing frequency were AST increased, LDH increased, ALT increased, calcium corrected decreased, magnesium decreased, ALP increased, potassium decreased, albumin decreased, total bilirubin increased, potassium increased, glucose decreased, sodium decreased, and GGT increased.

The serum chemistry parameters with the highest incidence (≥ 10%) of shifts from baseline of at least 2 grades (worsening) in the cabozantinib arm comprised calcium corrected decreased (and LDH increased There were no parameters in the placebo arm that met the same criteria.

Table 57. Study XL184-311: Summary of Selected Serum Chemistry Abnormalities (Safety Population)

	Cabozantinib (N=125) n (%)		**Placebo (N=62) n (%)**	
Abnormality	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
ALP increased	43 (34)	0	9 (15)	0
ALT increased	82 (66)	2 (1.6)	7 (11)	0
AST increased	96 (77)	1 (0.8)	11 (18)	0
Albumin decreased	24 (19)	1 (0.8)	4 (6.5)	0
Amylase increased	10 (8.0)	0	6 (9.7)	3 (4.8)
Calcium, corr decreased	45 (36)	11 (8.8)	6 (9.7)	1 (1.6)

	Cabozantinib (N=125) n (%)		Placebo (N=62) n (%)	
Abnormality	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Calcium, corr increased	2 (1.6)	1 (0.8)	8 (13)	3 (4.8)
Creatinine increased	19 (15)	2 (1.6)	8 (13)	0
GGT increased	32 (26)	3 (2.4)	13 (21)	1 (1.6)
Glucose decreased	9 (7.2)	0	1 (1.6)	0
Glucose increased	75 (60)	1 (0.8)	45 (73)	2 (3.2)
LDH increased	112 (90)	13 (10)	20 (32)	2 (3.2)
Lipase increased	10 (8.0)	2 (1.6)	2 (3.2)	1 (1.6)
Magnesium decreased	31 (25)	3 (2.4)	3 (4.8)	0
Magnesium increased	11 (8.8)	0	8 (13)	1 (1.6)
Potassium decreased	22 (18)	1 (0.8)	2 (3.2)	0
Potassium increased	12 (9.6)	1 (0.8)	2 (3.2)	0
Sodium decreased	19 (15)	0	6 (9.7)	1 (1.6)
Sodium increased	10 (8.0)	0	5 (8.1)	0
Total bilirubin increased	15 (12)	0	3 (4.8)	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; corr, corrected; GGT, γ-glutamyltransferase; LDH, lactate dehydrogenase.

For each laboratory abnormality, subjects were summarized at the worst value reported after first dose. Laboratory results from both central and local laboratories were included.

Sponsor-defined grades for LDH were as follows: Grade 1 (> ULN to ≤ 2 × ULN), Grade 2 (> 2 × ULN to ≤ 3 × ULN), Grade 3 (> 3 × ULN)

Screening for Potential Drug-Induced Liver Injury

In Study XL184-311, blinded laboratory data listings were screened and reviewed by the Sponsor quarterly for potential cases of drug-induced liver injury (DILI) as identified by ALT, AST, and bilirubin levels meeting Hy's Law criteria (FDA Drug-Induced Liver Injury 2009).

There were no cases of potential DILI based on the laboratory parameters described above reported in this study.

Screening for Renal Dysfunction

In Study XL184-311, the potential for study treatment to induce renal failure was assessed by the routine evaluation of subjects who met sponsor-defined laboratory screening criteria indicating risk of

renal dysfunction, and by the incidence of AEs and SAEs related to renal failure. Subjects were screened for possible treatment-emergent renal toxicity due to study treatment using three criteria:

(1) Serum creatinine ≥ 3 × ULN and ≥ 2 × baseline value, OR

(2) Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 AND ≥ 25% reduction from baseline, OR

(3) eGFR ≤ 50% baseline value

A total of 2 subjects (1.6%) in the cabozantinib arm met the screening criteria for potential drug related renal dysfunction compared with none in the placebo arm. Of the 2 subjects in the cabozantinib arm who met at least one of these qualifying criteria, none were determined to have cabozantinib induced renal toxicity.

Haematology

Treatment-emergent abnormalities of selected haematology parameters in Study XL184-311 are summarized in **Table *58***. Most of the treatment-emergent haematology abnormalities were of Grade 1 or 2 severity in both treatment arms.

Table 58. Study XL184-311: Summary of Haematology Abnormalities (Safety Population)

	Cabozantinib (N=125) n (%)		**Placebo (N=62) n (%)**	
Abnormality	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Haemoglobin decreased	59 (47)	3 (2.4)	33 (53)	1 (1.6)
Haemoglobin increased	4 (3.2)	0	0	0
Leukocytes decreased	47 (38)	3 (2.4)	4 (6.5)	1 (1.6)
Lymphocytes decreased	40 (32)	9 (7.2)	20 (32)	3 (4.8)
Lymphocytes increased	1 (0.8)	0	0	0
Neutrophils decreased [a]	39 (31)	3 (2.4)	3 (4.8)	1 (1.6)
Platelets decreased	33 (26)	0	3 (4.8)	0

Considers worst value after first dose for each abnormality per subject. Laboratory results from both central and local laboratories are included.

[a] absolute neutrophil count

Urinalysis Parameters

Treatment-emergent assessments of UPCR increased in Study XL184-311 are summarized in **Table *59*** and include laboratory abnormalities and laboratory abnormalities reported as AEs.

Table 59. Study XL184-311: Summary of Haematology Abnormalities (Safety Population)

Assessment	Cabozantinib (N=125) n (%)	Placebo (N=62) n (%)
UPCR increased	68 (54)	24 (39)
Laboratory abnormality:		
Any Grade	68 (54)	24 (39)
Grade 3 or 4	2 (2)	0
Reported as AE (urine protein/creatinine ratio increased)	1 (0.8)	0
Grade 3 or 4	0	0

AE, adverse event; UPCR, urine protein/creatinine ratio.

Laboratory results were graded per sponsor-defined criteria (see Section 2.7.4.**Error! Reference source not found.** for further details).

For each laboratory abnormality, subjects are summarized at the worst value reported after first dose. Laboratory results from both central and local laboratories are included.
Denominators for percentages are N, the total number of subjects in each treatment arm.

Thyroid Function

For inclusion in Study XL184-311, subjects were required to be receiving thyroid replacement therapy and have TSH levels below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 µIU/mL), whichever was lower. Therefore, it is difficult to interpret the impact of cabozantinib treatment on thyroid function parameters.

Hypothyroidism was reported as an AE for 2.4% of subjects in the cabozantinib arm and 0% of subjects in the placebo arm. All events in the cabozantinib arm were Grade 1 or 2.

Safety in special populations

Paediatric population

The safety of cabozantinib in children and adolescents aged < 18 years has not yet been established. No data are available in the intended population.

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, knowledge to date is adequately reflected in the SmPC.

Discontinuation due to adverse events

A total of 18 subjects (14.4%) in the cabozantinib arm and 7 subjects (5.6%) in the placebo arm discontinued blinded treatment due to an AE, whatever the causal relationship and including those reported as related to disease progression or clinical deterioration. The rate of treatment discontinuation due to AEs related to study treatment was 4 % for the cabozantinib arm and 0% for the placebo arm. The overall incidence of study treatment discontinuation due to an AE regardless of causality (excluding AEs related to disease under study) was 6 subjects (4.8%) in the cabozantinib arm and none in the placebo arm. The only AE that led to study treatment discontinuation (not related to disease under study) in ≥ 1% of subjects in the cabozantinib arm was fatigue (1.6% of subjects).

Post marketing experience

Cabozantinib capsules (Cometriq) were approved for the treatment of patients with progressive, metastatic MTC at a dose of 140 mg qd and for the treatment of adults with progressive, unresectable locally advanced or metastatic MTC. Cabozantinib tablets (Cabometyx) have also been approved for the treatment of adult patients with advanced RCC and adult patients with HCC. Cabozantinib tablets are also approved in the US and EU for adult patients with advanced RCC. Through 28 November 2020, the estimated number of patients treated with cabozantinib exceeds 60,000 patients in the post marketing setting, including approximately 3,800 treated with Cometriq.

Cumulative data from a combined 96 paediatric patients exposed to cabozantinib in the post marketing setting suggest that the safety profile in the paediatric population does not differ significantly from that observed with adults.

2.5.1. Discussion on clinical safety

The safety data for the claimed indication is derived from the Phase III, randomized, double-blind, placebo-controlled pivotal Study XL184-311. The safety population included subjects that received at least one dose of study treatment. In addition, pooled safety data is also provided from previously reported studies (Studies XL184-309, XL184-308, and A031203) to set observations in Study XL184-311 in the context of prior cabozantinib safety experience.

Patient Exposure
At total of 187 subjects were included in the safety population, 125 in the cabozantinib arm, and 62 in the placebo arm. The size of the defined safety population is sufficient to detect common AEs. However, the safety population size is not sufficient to detect potential rare adverse events. Median duration of exposure was 4.4 months in the cabozantinib arm and 2.3 months in the placebo arm. 4.4 months is a limited amount of time, which does not enable detection of potential long-term adverse events or AEs with a long lag time. Dose modifications (reductions and interruptions) due to an AE occurred at a higher frequency in the cabozantinib arm compared to placebo (78% vs 27%), but to a similar extent as in previous studies of RCC and HCC. Median daily dose of cabozantinib was 42 mg, which is comparable to the median daily dose in the studies of RCC and HCC.

No paediatric patients were exposed to the drug in the pivotal study.

Adverse Events
Overall, the types of AEs reported are consistent with previous observations for cabozantinib and there

were no new safety signals identified. The overall incidence of AEs in the cabozantinib arm and the placebo arm was 94% vs 84%, respectively. The incidence of treatment-related AEs was higher in the cabozantinib arm (90%) compared to the placebo arm (52%). The most frequent AEs (reported for ⩾ 20% of subjects) in the cabozantinib arm were diarrhoea, PPE, hypertension, fatigue, ALT increased, nausea, AST increased, decreased appetite, and hypocalcaemia. These AEs were also reported at ⩾ 20% incidence in the pooled studies, except for hypocalcaemia (23% in Study XL184-311 vs 6% in the pooled studies). Another AE which was more frequently reported in the DTC population, cabozantinib arm, was proteinuria (15% in Study XL184-311 vs 7% in the pooled studies). The most frequently reported AEs leading to dose reduction corresponded to the frequently reported AEs overall.

Hypocalcaemia is a known frequent complication in patients undergoing thyroid surgery and was hence expected to occur at a higher incidence in DTC and MTC, than in the pooled studies in patients with RCC and HCC. However, it should be noted that the incidence was markedly higher in the cabozantinib arm compared to the placebo arm (23% vs 1.6%) in the DTC population, indicating a potential relation to treatment. No case of hypocalcaemia led to severe clinical consequences, and they were managed with calcium supplementation and/or cabozantinib dose modification. Hypocalcaemia is mentioned in the SmPC section 4.4 among biochemical parameters to monitor during cabozantinib treatment.

Of the proteinuria events, all but one of the subjects had proteinuria of Grade 1 or 2 severity, and all events were non-serious. Proteinuria is listed as an ETM, regular monitoring of urine protein is recommended in the Cabometyx SmPC section 4.4, and proteinuria is listed as a common AE. Blockage of the VEGF pathway is known to contribute to proteinuria. However, there is no explanation for the difference in frequency of proteinuria in study XL184-311, compared to previous studies. The MAH discussed several plausible reasons for the differences in hypocalcaemia, which are acknowledged. An update to the existing warning in the EU SmPC regarding electrolytes with the proposed additional wording: "Hypocalcaemia has been observed with cabozantinib at a higher frequency and/or increased severity (including grade 3 and 4) in patients with thyroid cancer compared to patients with other cancers" is granted.

Grade 3/4 events were reported for 57% of subjects in the cabozantinib arm and 26% in the placebo arm. Grade 3/4 AEs that had a ≥ 2% higher per-subject incidence in the cabozantinib arm compared with placebo by decreasing frequency of between-arm difference were PPE, fatigue, diarrhoea, hypertension, hypocalcaemia, decreased appetite, nausea, asthenia, mucosal inflammation, pulmonary embolism, and stomatitis.

SAEs
The overall incidence of SAEs was 34% in the cabozantinib arm and 29% in the placebo arm (16% vs 1.6% related to study treatment, respectively). SAEs reported for ≥ 2% of subjects in the cabozantinib arm were diarrhoea, pulmonary embolism, pleural effusion, and dyspnoea. Pleural effusion and dyspnoea were also reported for ≥ 2% of subjects in the placebo arm. Treatment related SAEs with a ⩾ 1% incidence in the cabozantinib arm were deep vein thrombosis, hypertension, and pulmonary embolism; all included in the ETMs.
There were no new SAEs in Study XL184-311, compared to previous studies in other indications.

Deaths
A total of 31 deaths were reported in the study, 14% in the cabozantinib arm and 16% in the placebo arm. None of the deaths were considered related to study treatment, per Investigator.
Through 30 days after last dose of study treatment, 4 of 9 subjects in the cabozantinib arm experienced a Grade 5 AE of disease progression or thyroid cancer. The other Grade 5 AEs reported

were arterial haemorrhage, cardiac arrest, cardio-respiratory arrest, pulmonary embolism, and pneumonia (1 subject each).

Events to Monitor
Most ETMs occurred at a higher incidence in the cabozantinib arm compared to the placebo arm. As discussed above, there was a higher incidence of proteinuria in study XL184-311, compared to previous studies. However, when looking at individual studies the incidence of proteinuria was not higher in DTC compared to other indications and there is hence no further concern. The incidence of VTEs was slightly higher than in previous studies. This might be explained by the fact that the ETM of VTE was based on different PTs in the different studies. Thrombosis is mentioned in the SmPC section 4.4. The time to first occurrence varies among the ETMs (range from 15-330 days). Hence, the exposure time (4.4 months (range 0.0, 15.7) might not enable detection of ETMs appearing with a long lag time.

Laboratory findings
Serum chemistry abnormalities (all grades) that had a ≥ 5% higher incidence in the cabozantinib arm compared with the placebo arm were AST increased, LDH increased, ALT increased, calcium corrected decreased, magnesium decreased, ALP increased, potassium decreased, albumin decreased, total bilirubin increased, potassium increased, glucose decreased, sodium decreased, and GGT increased. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment, as stated in SmPC section 4.4.
LDH increased 90% in the cabozantinib arm vs 32% in the placebo arm. LDH increase adverse events (AEs) have been consistently reported across cabozantinib monotherapy studies, with a similar frequency in thyroid cancer studies (6.7% in the XL184-311DTC study and 8.9% in the XL184-401 MTC study) and a non-thyroid cancer study (7.3% in the XL184-308 RCC study). When considering laboratory data, LDH increase abnormalities were consistently and similarly increased across cabozantinib 60 mg monotherapy studies (90% in XL184-311, 88% in XL184-401 and 84% in XL184-309). LDH increase in cabozantinib studies is not evocative of an increased frequency in DTC compared to other cancersand hence no need for adding LDH as an ADR.
No subjects in the study met Hy's Law screening criteria or additional screening criteria for potential DILI. A total of 2 subjects in the cabozantinib arm and none in the placebo arm met the screening criteria for potential drug-related renal dysfunction. Haematology abnormalities (all grades) that had a ≥ 5% higher per-subject incidence in the cabozantinib arm compared with placebo were leukocytes decreased, neutrophils decreased, and platelets decreased.

Assessment of paediatric data on clinical safety

No paediatric patients were included in the pivotal study. A summary of clinical paediatric data and post-marketing paediatric data were provided. Available paediatric safety data come from three clinical trials (Study ADVL1211, Study ADVL1622, The CABONE study) and from post-marketing safety data from the global cabozantinib database. The robustness of the submitted data does not allow for a proper assessment, since the clinical data comprises (a) a phase I study with 39 paediatric patients (previously assessed for Cometriq), (b) an ongoing phase II study with 71 paediatric patients, CSR expected in Q2 2022, and (c) a phase II study with 8 paediatric patients, and the post-marketing data includes around 100 patients, of which 11 with thyroid cancer (type not specified).
Hence, the possibility of new safety concerns cannot be ruled out. TKIs have been shown to impact growth in paediatric patients and the effect of cabozantinib on longitudinal growth is still under investigation. It is also of note that the provided paediatric data mostly includes patients with other

tumour types than thyroid cancer (n=7 with MTC in the three above mentioned clinical trials), and the relevance of these data for assessment of cabozantinib in DTC remains uncertain.

Post marketing data for cabozantinib are subject to continued pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, individually as expedited reports as well as periodically in aggregate reports to global health authorities. Through 28 November 2020, the reviewed post marketing safety data are consistent with the known safety profile of cabozantinib and confirms the clinical trial safety data for cabozantinib. The safety profile of cabozantinib in the post marketing setting remains favourable and similar to the profile established during clinical trials
The MAH confirmed that the safety profile in the paediatric population will be closely monitored and discussed in the PSUSA.

2.5.2. Conclusions on clinical safety

In conclusion, the safety of cabozantinib in DTC in adults is generally consistent with the known safety profile. Overall, the safety profile of cabozantinib in DTC appears manageable with dose modifications, and no major safety concerns are raised for the adult population.

Regarding the safety profile in the paediatric population, the robustness of the submitted data does not allow a proper assessment and thus, the possibility of new safety concerns cannot be ruled out. In addition, the provided paediatric data mostly includes patients with other tumour types than thyroid cancer and the relevance of these data for assessment of cabozantinib in DTC remains uncertain. Thus, in conclusion, it is still unclear whether the safety profile of cabozantinib in adolescents is similar to that in adults with DTC.

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.

2.5.4. Direct Healthcare Professional Communication

Not Applicable

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 6.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.1 with the following content:

Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal perforation • Gastrointestinal and non-gastrointestinal 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

Ongoing and Planned Additional Pharmacovigilance Activities in the Pharmacovigilance Plan

Category 3- Study				
Study/status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy/ongoing (CASSIOPE)	**Primary:** • To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy. **Secondary:** • To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings • To describe all treatment-emergent nonserious and serious AEs • To describe the effectiveness of cabozantinib in RCC in real-life in terms of progression-free survival and best overall response • To describe the health care resource utilisation associated with the management of treatment-related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays; concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).	To assess the risk-benefit profile of Cabometyx with respect to identified and potential risks	1. Protocol submission 2. Protocol approval 3. Study start 4. Study finish 5. Progress report submission 6. Interim report 7. Final report	1. Submitted 24 April 2017 2. 12 October 2017 3. 24 April 2018 4. Planned June 2022 (LPO) 5. 25 October 2019 6. Submitted 01 December 2020 7. Planned March 2023

AE=adverse event; LPO=last patient out; PRAC=Pharmacovigilance Risk Assessment Committee; RCC=renal cell carcinoma.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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: PASS.
Gastrointestinal and non-gastrointestinal fistulas	**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: PASS.
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: PASS.
Haemorrhage	**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: PASS.
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: PASS.
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
Osteonecrosis	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
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: PASS.
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: PASS.
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: PASS.
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.

ATE=arterial thromboembolic event; PL= 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, 5.1 and 5.2 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:

The design, layout and format of the package leaflet is continued. There are minor changes in relate the safety profile to include the safety profile in DTC. However, the current writing style has been respected. The evidence from user testing previously performed on the CABOMETYX leaflet is considered relevant and applicable to this application.

2.7.2. Additional monitoring

At this stage, no additional pharmacovigilance measures have been proposed. No additional monitoring is requested.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final approved indication is "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."

3.1.2. Available therapies and unmet medical need

Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment. TSH suppression is recommended for all patients with persistent structural disease in the absence of specific contraindications. DTC is usually a slow-growing disease, even if the patients develop distant metastasis. Radioactive iodine (I-131) (RAI) is the standard initial therapy for recurrent or metastatic DTC. For patients becoming refractory to RAI, the tyrosine kinase inhibitors (TKIs) sorafenib and lenvatinib is a standard option when local treatments (e.g., palliative surgery, radiofrequency ablation, external beam radiation therapy) have been exhausted and the disease is progressive or symptomatic.

Treatment options are very limited for patients developing resistance to TKI therapy. For adult patients diagnosed with advanced RET fusion-positive thyroid cancer the RET inhibitor selpercatinib is recently approved in the EU. In addition, for patients with solid tumours expressing NTRK gene fusion, larotrectinib and entrectinib might be an option (approved in the EU for adults in addition to paediatric patients and in patients from the age of 12, respectively). However, these new drugs cover only specific molecular subtypes of DTCs and, overall, more effective therapies for RAI refractory DTC are thus still needed.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicentre, randomised (2:1), double-blind, placebo-controlled study comparing cabozantinib in adult patients with metastatic DTC who were refractory to or deemed ineligible for treatment with Iodine-131, had previously received up to maximum two regimens of VEGFR-targeted therapy, whereof one of them had to be either sorafenib or lenvatinib, and had demonstrated disease progression (documented radiographic PD per Investigator per RECIST 1.1) on the last therapy. Randomisation was stratified by age (≤65 years vs. > 65 years) and prior receipt of lenvatinib (yes or no). Multiple primary endpoints in the XL184-311 study were PFS and ORR. Crossover to cabozantinib was optional for subjects initially randomised to placebo upon experiencing radiographic disease progression as confirmed by BIRC.

3.2. Favourable effects

The prespecified primary interim PFS analysis (data cut-off 19 August 2020) for the ITT population (N=187, whereof 125 in the cabozantinib arm and 62 in the placebo arm, median follow-up 6.24

months) showed a statistically significant benefit in PFS for cabozantinib over placebo (HR = 0.22, 96% CI [stratified]: 0.13, 0.36; observed p-value [stratified log-rank test] <0.0001). Median PFS in the cabozantinib arm was not reached (96% CI: 5.7, NE) vs. 1.9 (96% CI: 1.8, 3.6) months in the placebo arm in this analysis.

The updated PFS analysis, (data cut-off 08 February 2021) for the Full ITT population, (N=258, whereof 170 in the cabozantinib arm and 88 in the placebo arm, median follow-up 10.1 months) showed a HR of 0.22, 96% CI (stratified): 0.15, 0.32; observed p-value (stratified log-rank test) <0.0001. The median PFS (cabozantinib vs. placebo) was 11.0 (96% CI: 7.4, 13.8) vs. 1.9 (96% CI: 1.9, 3.7) months.

The results for the Primary Analysis Subset (i.e., the ITT population, but with a longer median follow-up of 11.9 months) were in support of the results observed for the Full ITT population.

Cabozantinib showed efficacy in PFS (HR<1 and 95% CI excluding 1) in the majority of subgroups, this includes the subgroups "receipt of prior lenvatinib or not", "receipt of prior sorafenib or not" and "receipt of prior sorafenib and lenvatinib or not" (data cut-off 19 August 2020). The updated subgroup analyses (data cut-off 08 February 2021) were consistent with the analyses at the first cut-off date.

3.3. Uncertainties and limitations about favourable effects

PFS and ORR were defined as multiple primary endpoints, and study success was to be declared if at least one null hypothesis was rejected. ORR was 15% (99% CI: 5.8, 29.3) in the cabozantinib arm vs. 0% (99% CI: 0.0, 14.8) in the placebo arm, however, ORR was not met as Study XL184-311 failed to reject the null hypothesis of ORR at the pre-specified alpha of 1% (observed unstratified Fisher exact test p-value= 0.0281).

OS was not a controlled endpoint and at the time of progression patients in the placebo arm could cross over to the cabozantinib arm. Furthermore, OS data were immature with > 75% of events censored at the latest clinical cut-off (08 February 2021). No further updates of the OS analysis are available or planned. Use of subsequent anticancer therapy post study will also be a confounding factor. However, it is noted, that despite crossover of patients from the placebo arm, no apparent detrimental effect on survival in the cabozantinib arm is currently observed.

3.4. Unfavourable effects

Overall, the unfavourable effects of cabozantinib in the adult DTC trial population are consistent with the known safety profile of cabozantinib, although some differences were observed. The frequency of adverse events regardless of causality was 94% in the cabozantinib arm and 84% in the placebo arm. 90% of the AEs in the cabozantinib arm were assessed as treatment-related, vs 52% in the placebo arm.

The most frequent AEs (≥ 20% of subjects, all grades) were diarrhoea, PPE, hypertension, fatigue, ALT increased, nausea, AST increased, decreased appetite, and hypocalcaemia. In the cabozantinib arm, there was a higher incidence of hypocalcaemia compared to the pooled studies (23% vs 6%), and a higher incidence of proteinuria (15%), compared to the pooled studies (7%) and Study XL184-301 (2%). The proportion of patients experiencing at least one grade 3/4 AEs was 57% in the cabozantinib arm, and 26% in the placebo arm.

The incidence of treatment-related SAEs in the cabozantinib arm (16%) was generally consistent with previous studies. The most frequent treatment-related SAEs (≥ 1% incidence) in the cabozantinib arm

of Study XL184-311 were diarrhoea (3.2% of subjects), deep vein thrombosis (DVT) (1.6%), hypertension (1.6%), and pulmonary embolism (1.6%)

None of the deaths reported (n=31) were considered related to study treatment, per Investigator.

Dose modifications (interruptions and reductions) due to an AE occurred at a higher frequency in the cabozantinib arm compared to placebo (78% vs 27%), but to a similar extent as in previous studies. The incidence of AEs leading to treatment discontinuation (not related to disease under study) was higher in the cabozantinib arm (4.8%) than in the placebo arm (0%).

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 60. Effects Table for Cabometyx, as monotherapy for 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

Effect	Short description	Unit	Treatment Cabozantinib N=125	Control Placebo N=62	Uncertainties / Strength of evidence	References
Favourable Effects Data cut-off: **19 August 2020**						
PFS	Progression Free Survival (ITT population, N=187)	Median in months	NE (96% CI: 5.7, NE)	1.9 (96% CI: 1.8, 3.6)	Stratified HR 0.22 (96% CI, 0.13, 0.36) p<0.0001 Sensitivity analyses support the primary analysis	Main study XL184-311
OS	Median overall survival	Events, n (%)	17 (14)	14 (23)	HR 0.54 (0.27, 1.11)	Main study XL184-311
Favourable Effects Data cut-off: **08 February 2021**			**Cabozantinib N=170**	**Placebo N=88**		
PFS	Progression Free Survival (Full ITT population, N=258)	Median in months	11.0 (96% CI: 7.4, 13.8)	1.9 (96% CI: 1.9, 3.7)	Stratified HR 0.22 (96% CI, 0.15, 0.32) p<0.0001	Main study XL184-311
OS		Events, n (%)	37(22)	21 (24)	HR 0.76 (0.45, 1.31)	
ORR[1]	Objective Response Rate		**Cabozantinib N=67**	**Placebo N=33**		
	Overall response	Events, n (%)	10 (15)		0 (0)	
	Complete response		0		0	

Effect	Short description	Unit	Treatment Cabozantinib N=125	Control Placebo N=62	Uncertainties / Strength of evidence	References
	Partial response		10 (15)		0	
	Stable disease		46 (69)		14 (42)	
	Progressive disease		4 (6)		18 (55)	
Unfavourable Effects						
Most frequent SAEs		Frequency (%)				Main study XL184-311
	Diarrhoea		3.2	0		
	Pleural effusion		3.2	4.8		
	Pulmonary embolism		3.2	0		
	Dyspnoea		2.4	6.5		
	Deep vein thrombosis		1.6	0		
	Disease progression		1.6	0		
	General physical health deterioration		1.6	0		
	Hypertension		1.6	0		
	Hypocalcaemia		1.6	0		
	Pneumonia		1.6	1.6		

[l] Based on the first 100 patients included in the study with a median follow-up of 8.9 months, n=67 in CABOMETYX group and n=33 in placebo group.

Abbreviations: PPE, palmar-plantar erythrodysaesthesia syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results of the pivotal study provide clear evidence of a clinically meaningful improvement in PFS for cabozantinib compared to placebo in adult subjects with RAI refractory metastatic DTC who have progressed after treatment with sorafenib or lenvatinib. The median PFS gain of ~ 9 months is of clinical relevance in this setting, although the estimate of median PFS of 11 months in the cabozantinib arm is uncertain taking into consideration the rather low number of patients left at risk at that time point. The PFS effect appears to be consistent in all the updated subgroup analyses performed.

The observed ORR was rather low (15%), however as in the pivotal study, more subjects reached stable disease in the cabozantinib arm vs. placebo, there is a possible indication that the effect of cabozantinib might primarily be caused by disease stabilisation, rather than a decrease in tumour burden.

Notwithstanding confounding of the OS analysis due to cross-over of placebo patients with progressive disease into the cabozantinib arm, there is positive initial signals in terms of OS improvement and no apparent detrimental effect on OS by cabozantinib.

Overall, adult patients with metastatic, progressive RAI refractory DTC have a relatively poor prognosis, with an estimated median survival time of 2.5-3.5 years. After progression on the TKIs lenvatinib or sorafenib, this patient population has few alternative treatment options. New therapies (selpercatinib, entrectinib, larotrectinib) are recently approved for treatment of tumours expressing specific gene fusions/rearrangements (RET and NTRK) and which is also relevant in thyroid cancers. However, for patients harbouring tumours without these specific molecular characteristics or for those who of other reasons are ineligible for treatment with these new agents, there is a need of new treatment alternatives which can improve the prognosis and increase the clinician's therapeutic options. In this context, the observed efficacy of cabozantinib appears promising.

The overall safety profile of cabozantinib in adult subjects with RAI-refractory DTC appears manageable with dose modifications and was consistent with the expected safety profile of the drug.

3.7.2. Balance of benefits and risks

A clinically relevant benefit in terms of PFS is observed in adult patients belonging to a patient group with currently limited treatment options. The beneficial PFS effect is also noted across the majority of subgroups. Furthermore, no indication of detrimental effect in OS was observed in the cabozantinib arm.

The overall safety profile of cabozantinib in adult subjects with RAI-refractory DTC appears manageable and was consistent with the expected safety profile of the drug.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Cabometyx (cabozantinib) 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 is positive

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 Cabometyx as monotherapy treatment of adults 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; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The MAH also took the opportunity to update the local representative for Spain. Version 6.1 of the RMP has also been submitted.

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 Nexavar within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

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 'Cabometyx-H-C- 004163/II/0023