21 July 2016
EMA/664123/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

CABOMETYX

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/004163/0000

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Administrative information

Name of the medicinal product:	CABOMETYX
Applicant:	Ipsen Pharma 65, quai Georges Gorse 92100 Boulogne-Billancourt FRANCE
Active substance:	CABOZANTINIB S-MALATE
International Non-proprietary Name/Common Name:	cabozantinib
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, protein kinase inhibitors (L01XE26)
Therapeutic indication(s):	Cabometyx is indicated in the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	20 mg, 40 mg and 60 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PCTFE) and bottle (HDPE)
Package size(s):	28 tablets and 30 tablets

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	adequate tumour assessment
ATC	Anatomical Therapeutic Chemical
BOR	best overall response
BSR	bone scan response
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
CAD	computer-aided detection
CAP	chest / abdomen / pelvis
CHMP	Committee for medicinal products for human use
CI	confidence interval
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DOR	duration of response
DRS	disease-related symptoms
(e)CRF	(electronic) case report form
CV%	percent coefficient of variation
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPO	erythropoietin
ER	emergency room
ESA	erythropoiesis-stimulating agent
ESC	Exelixis Safety Committee
FACT	Functional Assessment of Cancer Therapy
FBE	free base equivalent
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FKSI-19	FACT Kidney Symptom Index questionnaire
FT4	free thyroxine
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
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
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRC	independent radiology committee

IRT	interactive response technology
ITT	intent-to-treat
IVRS	interactive voice record system
IWRS	interactive web record system
JNC	Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure
KPS	Karnofsky performance scale
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
MedDRA	medical dictionary for regulatory activities
MET	hepatocyte growth factor receptor protein
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
ND	not determined
NE	not estimable
NPACT	nonprotocol anticancer therapy
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PD	progressive disease
PK	pharmacokinetics
PE	pulmonary embolism
PFS	progression-free survival
PITT	primary endpoint intent-to-treat population
PPD	Pharmaceutical Product Development, Incorporated
PPES	palmar-plantar erythrodysesthesia syndrome
PR	partial response
PS	performance status
qd	once daily
QT	time interval in ECG reading
QTcF	corrected QT interval by Fridericia
R	responder
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
SoD	sum of lesion diameters
SoD	sum of lesion diameters
SRE	skeletal-related event
TBS	technetium bone scans
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TORC1	target of rapamycin complex 1
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)
VHL	von Hippel-Lindau gene
WBC	white blood cell
XL184	code name for investigational product cabozantinib

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Exelixis International UK Ltd submitted on 8 January 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for CABOMETYX, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 February 2015. On 20 June 2016, the applicant changed to Ipsen Pharma.

The applicant applied for the following indication: treatment of advanced renal cell carcinoma (RCC) in patients who have received one prior therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cabozantinib was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

Additional Data exclusivity / Marketing protection

The applicant requested consideration of one additional year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004, as Cometriq and Cabometyx belong to the same global marketing authorisation.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 May 2014 and from Sweden on 21 January 2013, Germany on 24 January 2013, the Netherlands on 28 January 2013 and UK on 28 January 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Bjorg Bolstad

- The application was received by the EMA on 8 January 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 22 October 2015.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 April 2016. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 13 May 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 13 May 2016.
- During the meeting on 26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 May 2016.
- On 20 June 2016, the marketing authorisation application was transferred to Ipsen Pharma.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 June 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 July 2016.
- During the meeting on 18-21 July 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to CABOMETYX on 21 July 2016.

2. Scientific discussion

2.1. Problem statement

Cabozantinib is an oral multiple receptor tyrosine kinase inhibitor. Cabozantinib was approved as an orphan medicine in the EU as Cometriq capsules in the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma in March 2014.

The applicant applied for the following indication:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received one prior therapy.

The approved indication further to the CHMP review is:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

2.1.1. Disease or condition

Renal cell carcinomas are kidney tumours which represent approximately 90% of cases of kidney cancer in adults (Wahal and Mardi, 2014). These tumours arise from the cells of the proximal renal tubular epithelium.

According to the American Joint Committee on Cancer, both metastatic (M1 – distant metastasis present) and locally unresectable (T4 – tumor invades beyond Gerota's fascia; N - any; M0) RCC are classified as Stage IV (Edge, et al., 2010). The terms "unresectable advanced RCC" and "metastatic RCC" are used interchangeably, and since both represent Stage IV RCC, the treatment of adult patients with advanced RCC is stated in the approved indications for second-line agents.

2.1.2. Epidemiology, clinical presentation, diagnosis and stage / prognosis

Kidney cancer represents approximately 3% of all cancers worldwide (Cohen, et al., 2005, Garcia and Rini, 2007). The incidence of RCC has been rising steadily and the 5-year prevalence of RCC in the EU-28 (plus Iceland and Norway) in 2015 was estimated to be 229,465 cases (adapted from Globocan 2012). Despite substantial progress in the understanding and treatment of mRCC in recent years, its incidence is increasing, and the disease is still considered incurable. Smoking and obesity are established risk factors for RCC development. Several hereditary types also exist, with von Hippel–Lindau (VHL) disease being the most common (NCCN guidelines). RCC also appears to be more common in patients with end-stage renal failure, acquired renal cystic disease and tuberous sclerosis. Approximately 2%–3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau disease. In recent years, many new genes associated with RCC have been reported (such as PBRM1, SETD2, BAP1) (ESMO guidelines, 2014; NCCN guidelines 2016).

2.1.3. Biologic features and pathogenesis

Clear cell RCC is the most frequent pathological subtype of sporadic RCC in adults (70%–85%), with loss of 3p and the classical clear aspect of the cells due to glycogen and lipids in their cytoplasm. Other subtypes historically called non clear RCC include papillary RCC (7%–15%) shows distribution of malignant cells around capillary cores (papillae), chromophobe RCC (5%–10%) is made up of typical polygonal cells with a clear

delimitation of the cytoplasmic membrane and reticular cytoplasm, renal medullary carcinoma, etc (Escudier et al, 2014). Due to a better understanding of the correlation between chromosomal alterations, histological subtypes and molecular pathway abnormalities, new morphological variants of RCC are now recognised according to the Vancouver classification (Escudier et al, 2014). Each of the most frequent morphological genetic RCC subtypes correlates with a specific molecular pathway. Examples include the hypoxia-inducible pathway (clear-cell, papillary type II through the FH gene), the mTOR signalling pathway (clear-cell and papillary type II), the c Met-RAF-MEK-ERK pathway (papillary type I and translocation RCC).

Inactivation of the von Hippel–Lindau (VHL) tumour suppressor protein is a characteristic of clear cell tumours, resulting in the deregulation of the VEGF signalling pathway. VEGFRs are typical receptor tyrosine kinases with an extracellular domain for ligand binding, a transmembrane domain and a cytoplasmic domain, including a tyrosine kinase domain. Activation of VEGF signalling pathways promote the growth of tumour blood cells. The major pro-angiogenic signal is generated from the ligand-activated VEGFR-2.

MET and AXL are also deregulated in RCC VHL-deficient cells. MET is the receptor tyrosine kinase for hepatocyte growth factor (HGF). HGF binding induces recruitment of the adaptor protein GAB1 and activation of multiple signalling, leading to promotion of cell survival, proliferation, migration, invasion and angiogenesis. Deregulation of MET signalling has been associated with poor prognosis in a variety of human cancers. AXL is a member of the TAM family of receptor tyrosine kinases, which also includes MER and TYRO-3. Interaction with growth arrest-specific gene 6 (GAS6) activates pathways to promote proliferation, survival and tumour angiogenesis and metastasis.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

More than 50% of RCCs are currently detected incidentally. However, some patients with RCC still present with clinical symptoms, such as flank pain, gross haematuria and palpable abdominal mass (the classical triad); metastatic symptoms like bone pain or lung nodules; or paraneoplastic syndromes, such as hypercalcaemia, unexplained fever, erythrocytosis or wasting syndromes (Escudier et al, 2014). About 30% of patients with RCC have metastatic disease at the time of diagnosis, and a significant proportion of patients with localized disease treated with curative nephrectomy relapse subsequently with metastatic disease. Metastatic RCC is associated with a high quality-of-life burden, based on physical, psychological, and social criteria, and drastically reduced survival; only about 8% to 22.5% of mRCC patients survive for five years or more as compared to 90% of patients with localized renal cancer. The extent of tumour burden and site of metastasis contribute to local symptoms. The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain. Among solid cancer types, RCC has the second highest incidence of brain metastases. Risks assessment models have been developed to provide prognostic information for patients and to inform on eligibility and risk stratification factors for clinical trials. The Memorial Sloan-Kettering Cancer Centre (MSKCC) stratifies according to 6 risk factors; Karnofsky performance status (KPS), haemoglobin level, corrected serum calcium, time from diagnosis to treatment, platelets and neutrophil levels. Relapsed RCC is an aggressive tumor and the optimal sequencing of therapies, or combination of therapies,that would lead to durable responses and minimize relapse remains a challenge.

2.1.5. Management

Management of local disease includes partial or radical nephrectomy. The role of neo-adjuvant or adjuvant therapy is not yet established. In the advanced disease setting systemic therapy is used. Until the development of agents that target tumour angiogenesis and other signaling pathways, systemic therapy with the cytokines

interleukin 2 (IL-2) or interferon (IFN)-α was the main treatment for advanced RCC. However, the use of both agents has declined substantially since the introduction of molecular targeted therapies.

Current approved treatments for metastatic RCC in the first-line setting comprise targeted therapies, either tyrosine kinase inhibitors (TKI: sunitinib and pazopanib) or mammalian target of rapamycin (mTOR) inhibitors (temsirolimus) administered as single agents, bevacizumab + interferon (IFN), or high-dose interleukin-2 (IL-2) (NCCN, 2016; ESMO, 2014).

Approved second-line agents include TKIs: sorafenib, sunitinib, axitinib, and pazopanib; the mTOR inhibitor everolimus.

A novel immunotherapeutic agent, Opdivo (nivolumab), belonging to a class of immune checkpoint inhibitors (PD-1/PD-L1), has been recently granted approval by EC on 19/06/2015 for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy. The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Relapsed RCC is an aggressive tumor and the optimal sequencing of therapies, or combination of therapies, that would lead to durable responses and minimize relapse remains a challenge. Current strategies have focused on the development of new therapeutic agents, optimal sequencing, and combinations of these agents to maximize their impact on clinical outcomes. To date, however, results of combination-therapy studies (ie, temsirolimus plus bevacizumab, temsirolimus plus sunitinib, erlotinib plus bevacizumab, everolimus plus bevacizumab) have shown no advantage in PFS over monotherapy with approved single agents and, in some cases, an unacceptably high degree of toxicity (Bukowski et al., 2007; Dorff, et al., 2014; Feldman, et al., 2009; Graves, et al., 2013; Hainsworth, et al., 2010; Kanesvaran, et al., 2015; Negrier, et al., 2011; Powles, et al., 2014; Ravaud, et al., 2013). Therefore, there remains a significant unmet medical need for more effective treatment options, with a manageable safety profile in patients with advanced RCC.

Table 1 - Approved indications of Second line therapies in advanced RCC

INN	Date Authorized	Indication
Sorafenib	Jul 2006	Treatment of patients with advanced RCC who have failed prior interferon-alpha- or interleukin 2-based therapy or are considered unsuitable for such therapy
Everolimus	Aug 2009	Treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy
Pazopanib	Jun 2010	In adults for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease
Axitinib	Sep 2012	Treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine
Nivolumab	Apr 2016	Treatment of advanced RCC after prior therapy in adults

About the product

Cabozantinib (XL184) inhibits multiple receptor tyrosine kinases (RTKs) implicated in angiogenesis, invasion, or metastasis in renal cell carcinoma (RCC), including MET (hepatocyte growth factor [HGF] receptor protein),

vascular endothelial growth factor receptors (VEGFRs), and AXL (Zhou et al 2015; Yu et al 2015; Rankin et al 2014; Ciamporcero et al 2015; Gibney et al 2013; Harshman and Choueiri 2013; Sennino et al 2012; Yakes et al 2011).

Overall, the preclinical data generated to date demonstrate that cabozantinib exhibits potent antiangiogenic and antitumor activity in multiple cancer models.

Cabozantinib capsules were initially evaluated in a Phase 1 study and showed activity in subjects with progressive metastatic medullary thyroid cancer (MTC; Kurzrock et al 2011). Results of the subsequent randomized, double-blind, placebo-controlled Phase 3 study XL184-301 (Elisei et al 2013) established the efficacy and safety of cabozantinib capsules at the 140 mg dose in the MTC population. Cabozantinib capsules (Cometriq) were approved in the United States at an oral dose of 140 mg (freebase equivalent [FBE] weight) once daily (qd) for the treatment of patients with progressive, metastatic MTC. In Europe, Cometriq is approved at an oral dose of 140 mg FBE qd for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. Further efficacy and safety data have been collected since the time of approval and long-term follow-up of over 3 years has not indicated any changes in the overall safety profile of cabozantinib in MTC patients.

The 140 mg capsule dose was also evaluated in a Phase 1 drug interaction study XL184-008, which included a cohort of subjects with RCC. Among all the permitted dose levels, a dose of 60 mg was the most frequent last dose and the dose with the longest treatment duration. Subsequently, a 60 mg dose using a tablet formulation was used in the Phase 3 RCC study XL184-308 and is the same formulation proposed for commercial use in advanced RCC.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

- The benefit-risk balance is positive.
- The applicant has provided comprehensive data
- Unmet medical needs will be addressed since even if drugs targeting the VEGF and mTOR pathway have been approved for RCC and have demonstrated clinical benefit, patients do experience disease progression and there remains a need for additional active treatments in this setting. As such, there is a need for additional therapeutic options for patients who have received one prior therapy.
- Cabozantinib could have a major impact on medical practice and the evidence to support the claim of major public health benefit was considered to be adequate for the purpose of a benefit risk assessment.

2.2. Quality aspects

2.2.1. Introduction

CABOMETYX is presented as immediate release film-coated tablets containing 20 mg, 40 mg, 60 mg of cabozantinib (as (*S*)-malate) as active substance.

Other ingredients in the tablet cores are microcrystalline cellulose, anhydrous lactose, hydroxypropyl cellulose, croscarmellose sodium, anhydrous colloidal silicon dioxide and magnesium stearate.

Ingredients in the film coating include hypromellose, titanium dioxide (E171), triacetin and iron oxide yellow (E172), as described in section 6.1 of the SmPC.

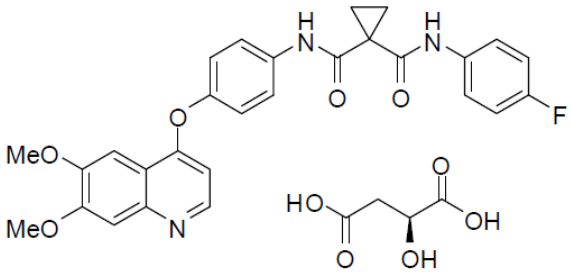
The finished product may be available in polyvinylchloride/polychlorotrifluoroethylene/aluminum (PVC/PCTFE/Alu) blisters or in high density polyethylene (HDPE) bottles with silica gel dessicant canisters and a polypropylene (PP) child-resistant closure, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of cabozantinib (*S*)-malate is *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N′*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (2*S*)-hydroxybutanedioate, corresponding to the molecular formula $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$. Its molecular weight is 635.6 (501.5 for freebase) and it has the structural formula shown in figure 1:

Figure 1 - Cabozantinib (S)-malate



There is no monograph of cabozantinib in the European Pharmacopoeia.

Cabozantinib (*S*)-malate is a white to off-white, non-hygroscopic, crystalline substance. Cabometyx contains the malate salt of cabozantinib because the freebase is insoluble in water. Cabozantinib has a non-chiral molecular structure.

Manufacture, characterisation and process controls

Cabozantinib is a known active substance (having been approved in 2014 for Cometriq 80 mg and 20 mg capsules). Adequate specifications and control methods have been presented for the starting materials, isolated intermediate products and reagents. The in-process controls applied during the synthesis are considered appropriate and sufficient. Process validation was conducted on three consecutive production-scale batches. Detailed information on the manufacturing process of the active substance and its development has been provided in the dossier and is considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities, including potentially genotoxic impurities (GTIs), were well discussed with regards to their origin and characterised. All potential impurities including GTIs are adequately controlled in steps performed under GMP.

The primary polyethylene bag material is in compliance with EU Directive 72/2002/EC.

Specification

The active substance specificationincludes tests for appearance, identification (HPLC, FTIR), assay (free base, HPLC), purity (HPLC), impurities (HPLC), genotoxic impurities (HPLC & LCMS), water content (KF), malic acid content (HPLC), organic volatile impurities (GC), residue on ignition, crystal form (XRPD), particle size distribution (laser diffraction) and heavy metals (Ph. Eur.).

The specifications were established in accordance with ICH Q6A and are supported by the release and stability data from representative batches which were manufactured at the intended commercial scale. The proposed GTI specification limits are below the threshold of toxicological concern (TTC, 1.5 µg/day) considering the highest dose of 60 mg, and are therefore considered to be acceptable.

The analytical methods used have been adequately described and the non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

Batch analysis data have been provided on 16 commercial scale batches produced by the proposed manufacturer and process. In addition, batch analysis results from historical batches were presented. The results are within the specifications and demonstrate that the active ingredient can be manufactured reproducibly.

Stability

Stability data on ten commercial scale batches of active substance manufactured by the commercial process for up to 36 months under long term conditions at 25 °C/60 % RH and on three commercial scale batches under accelerated storage conditions (40 °C / 75% RH) for six months were provided in accordance with ICH Q1A guidelines. The container closure system was representative of the intended commercial package.
The following parameters were tested: appearance, assay, impurities including GTIs, water content and crystal form. The analytical methods used in the stability testing were the same as those used at release and they have been demonstrated to be stability indicating.

The results did not show any significant changes. The GTIs were monitored throughout the stability studies and their levels remain within the specifications at all time points in both conditions.

The stability profile of AS manufactured by alternative processes demonstrated similar stability behaviour.A photostability study in accordance with ICH Q1B guideline was performed on one batch. It was concluded that direct exposure of the active substance to intense light should be avoided. Light protection by the proposed container closure system was confirmed.

A forced degradation study was also conducted on one batch under different stress conditions (acid, base, heat, oxidation, UV/visible light). No degradation was observed under heat- and photo-stressed conditions tested. Slight degradation was observed (relative retention time for products shown) under the basic hydrolysis and oxidative conditions, and significant degradation was observed under acidic hydrolysis.

Heat-stress studies were performed with testing of appearance, assay, impurities, GTIs and water content. No significant changes in appearance, assay, impurities (including GTIs) and water content were observed.

Based on presented stability data, the proposed retest period of 24 months and storage conditions (“Do not store above 25 ºC”) are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Cabometyx is an immediate release film-coated tablet. 20 mg tablets are yellow, round, debossed with “XL” on one side and “20” on the other side. 40 mg tablets are yellow, triangle-shaped, debossed with “XL” on one side and “40” on the other side. 60 mg tablets are yellow, oval-shaped, debossed with “XL” on one side and “60” on the other side.

Cabometyx contains the following list of excipients:

Tablet: Microcrystalline cellulose, Anhydrous lactose, Hydroxypropyl cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate.

Film-coating: Hypromellose 2910, Titanium dioxide (E171), Triacetin, Iron oxide yellow (E172)

The formulation history has been presented. A tablet formulation was considered as the most desirable and was developed for later Phase 3 studies. The formulation has been optimised with regard to the the drug loading and excipients ratio and dissolution performance; the choice of excipients has been justified. The selected film coating system was selected among other following an evaluation with regard to their effect on stability and dissolution.The manufacturing consists of high-shear wet granulation, fluid bed drying, milling, blending, compression, and film coating. All tablet strengths are dose proportional and are prepared from a common final blend. Each tablet strength is differentiated by shape. Throughout the course of development (and to support clinical manufacturing), minor process modifications were implemented to improve manufacturability and process robustness. A risk analysis was used to identify process parameters that are likely to have the greatest impact on product quality and manufacturability of the tablets. Based on prior knowledge and the analysis, appropriate experiments were designed and executed to evaluate the significance of process parameters and to optimise them for adequate quality and manufacturability.

The dissolution medium becauseMoreover, the discriminatory capability of the method was also evaluated. In bioequivalence study XL184-010, the commercialised capsule formulation of cabozantinib (Cometriq) and the proposed tablet formulation (for treatment of Renal Cell Carcinoma) were compared. The Cmax acceptance criterion exceeded the standard upper limit of 125% and bioequivalence of the two formulations has not been demonstrated but no new PK-related safety concerns were identified. The tablet formulation will be the only marketed cabozantinib drug product formulation for the treatment of patients with RCC. It is clearly stated in the proposed SmPC (section 4.2) that the tablet and capsule formulations are not bioequivalent and should not be used interchangeably.

Cabometyx film coated tablets may be packed in PVC/PCTFE/Alu blisters or in high density polyethylene (HDPE) bottles with silica gel desiccant canisters and a polypropylene child-resistant closure, as described in section 6.5 of the SmPC. The packaging material complies with the relevant EU regulations and Ph. Eur. requirements.

Manufacture of the product and process controls

The manufacturing process comprises the following main steps: dispensing and excipient de-lumping, pre-mixing, granulation, wet milling, fluid bed drying, dry milling, extra-granular blending, lubrication blending, tablet compression, film coating. The process is considered to be a standard process.

Critical steps have been identified and the process parameters for both critical and non-critical steps have been described. The parameters are supported by the manufacturing development. The in-process controls are appropriate for this type of manufacturing process and pharmaceutical form.

Batch size has been clearly defined. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process for cabozantinib 20 mg, 40 mg and 60 mg tablets will be validated prior to commercial launch in accordance with GMP. A process validation scheme has been presented.

Product specification

The finished product release and shelf life specification include tests and limits for: appearance, identification (HPLC, UV), assay (HPLC-UV), impurities (HPLC), content uniformity (Ph. Eur.), water content (KF), dissolution (Ph. Eur., HPLC), GTIs (LC/MS) and microbial limits (total aerobic count (Ph. Eur.), total combined yeasts and molds (Ph. Eur.)).

The impurity limits are in line with ICH guidance (for related impurities) or below the TTC for genotoxic impurities considering the highest dose of 60 mg, and are therefore considered to be acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

Batch analyses results from 32 batches covering all three strengths were provided. Five batches were manufactured at smaller scale but 27 batches were manufactured at the commercial scale. All batches were manufactured with a process representative of the proposed commercial manufacturing process and used representative batches of active substance. All batches were manufactured at the commercial manufacturing site.

Stability of the product

Stability data from a total of 24 batches of cabozantinib tablets, packaged in HDPE bottles and stored under long-term (25 ºC ± 2 ºC/60 % ± 5 % RH) and accelerated conditions (40 ºC ± 2 ºC/75 % ± 5 % RH) in accordance with ICH Q1A guidelines were provided. An additional 6 batches were also placed on stability under long term and accelerated conditions. Each of these batches was split into either HDPE bottles or PVC/ PCTFE/ Alu blisters.

Long term stability data up to 36 months and for 6 months under accelerated conditions was presented. The tests carried out on stability were appearance, assay, impurities, water content, dissolution and GTIs. Microbial quality testing is performed at 12, 24 and 36 months which is considered acceptable.

For tablets packaged in HDPE bottles (long-term data up to 36 months available and 6 months accelerated data available), no significant changes with respect to appearance, potency, individual impurities, total impurities, water content, and dissolution were demonstrated. An upward trend for a genotoxic impurity is detected under accelerated conditions; however the specification limit is met.

For tablets packaged in blisters (up to 24 months long term data and 6 months accelerated data available), no significant differences with respect to appearance, potency, individual impurities, total impurities, and dissolution were observed. An upward trend for a genotoxic impurity is detected under accelerated conditions;

however the specification limit is met. Higher water content was observed compared to the bottles. The results remain within the proposed commercial specifications for all time points for both strengths, confirming equivalency between bottle and blister packaging configurations.

Based on this study acceptable bulk holding time has been established.Photostability was performed in line with ICH Q1B guidelines and the tablets were demonstrated to be photostable.

Based on the overall stability data the proposed shelf life of 3 years for both packaging configurations is acceptable without any special storage condition as stated in the SmPC (sections 6.3 and 6.4).

Adventitious agents

It is confirmed that the lactose used in Cabometyx is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The development, manufacture and controls of the finished product have been sufficiently documented and justified. The results of tests of active substance and finished product carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAA for Cometriq (cabozantinib) capsules for the treatment of progressive, metastatic medullary thyroid carcinoma (MTC) was authorised on 21 March 2014. This present MAA is being submitted for the cabozantinib tablet formulations, which will be commercialized under a different trade name, Cabometyx.

The body of text of this non-clinical assessment is based on the data for Cometriq, but updated with new information as assessed in the variations for Cometriq to include information generated as part of the PAMs agreed for the MA approval.

A new Ecotoxicity/Environmental Risk Assessment has been provided.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics studies with cabozantinib (XL184) consisted of in vitro receptor binding assays and of several functional cell-based assays. In vivo studies focused first on target pharmacodynamic effects and tumour cellular responses to treatment. Furthermore multiple murine tumour models were used to explore the efficacy of XL184 with regard to tumour growth inhibition and regression in vivo.

Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.The most important metabolites in humans are XL184 desmethyl sulphate (M2a or EXEL1644) and XL184 monohydroxy sulphate (M4). It appears that the pharmacological activity of 1644 is limited (>50% residual control activity at a concentration of 1 µM). However, human Cmax is above the tested concentration and human exposure is relative extensive. Based on the higher protein binding of the metabolite than the parent compound (99.950 to 99.996% against 99.7 to >99%) it appears likely that this metabolite does not significantly contribute of the pharmacological activity of the current product. No data on in vitro substrate/inhibition of the various Cyps have been provided for this metabolite because in vitro and in vivo data suggested that cabozantinib has minimal to no clinically-relevant CYP induction potential.

Metabolite M4 (EXEL-1646) has more broader and potent inhibition of several kinases, when compared to 1644. However, the inhibition of 48 kinases were compared between M4 and the parent cabozantinib and cabozantinib parent showed a much greater potency over a broader range of kinases than did M4. Therefore, it shows that EXEL-1646 does not contribute substantial to the cabozantinib's pharmacodynamic activity. The Applicant provided the same rationale for the lack of data on potential substrate/inhibition of Cyps for this metabolite as for metabolite 1644. For M4 this justification is agreed. The activity of two other major metabolites of XL184, M1 and M8 were found to be less active against the primary targets of XL184 (MET, VEGFR2) and both can be considered not to have a significant contribution to the pharmacologically activity of XL184.

Also in cellular systems exposure to XL184 inhibited basal or growth factor-induced auto-phosphorylation of RTKs, proliferation of tumour cell lines (including only one cell line relevant for the current indication, i.e. TT medullary thyroid tumour cell line containing a RET mutation, Ret C634W), microvascular endothelial cell migration, and VEGF-driven tube formation. These data indicate that XL184 may have an anti-tumour effect in vivo on tumours that depend on signalling via one of several RTKs RET/MET/VEGFR/… for growth and/or migration/metastasis formation. In these studies only limited attention has been paid to the RET tyrosine kinase and its clinically relevant mutations. In vitro inhibition generally is seen in the nM range. Extrapolation of these concentrations to in vivo situation is not always possible due to the extremely high protein binding of XL184 (>99.9%). However it is noted that human plasma concentrations are in the low µM range suggesting that the free plasma concentrations may be within the pharmacological active range.

The relationship between dosing, plasma concentration and target RTK inhibition was studied in several studies in nude athymic mice tumour models. Prolonged inhibition of several RTKs was noted which corresponded to the plasma concentrations of XL184 in that inhibition was diminished when plasma levels fell below approximately 10 µM (5 µg/ml) for MET, 15 µM for RET (7,5 µg/ml), and 5 µM (2,5 µg/ml) for VEGFR2. This is within the range or slightly above the clinical plasma levels (2-4 µM). In the target tissue the concentrations of XL184 behaved in a similar manner to plasma concentrations. The concentration in lung was similar (study XL184-disc-010) or ~ 2 fold higher (study XL184-disc-015) to plasma, the concentration in tumour was the similar to (study

XL184-disc-011) or ~ 2-fold lower (study XL184-disc-009 and disc-014) than plasma concentration. In liver the concentration was ~2-3 fold higher than in plasma (study XL184-disc-013).

Data from several rat or murine tumour models indicate that once daily administration of XL184 can inhibit tumour growth, and even tumour regression at high doses when plasma levels are in low µM range. Histopathology of tumour tissue revealed reduced cellular proliferation and microvessel density and increased necrosis in XL184 treated animals. Also relatively large sized tumours were sensitive to XL184 treatment. No data is available on regrowth of tumour following multiple dosing, it is assumed that tumours regrow following end of treatment, however it is not clear if there may be a rebound effect (increased tumour growth) following end of treatment. In only one study a tumour cell line relevant for the indication was used (TT). In this xenograft model (study XL184-disc-025) clear tumour growth inhibition was shown, but regression was only seen at the highest dose.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed. A screen consisting of 75 pharmacological targets, including receptors, transporters, and enzymes specific inhibition was seen only of the adenosine A3 receptor (IC50 <0.9 µM) and the ML1 (melatonin) receptor (IC50> 1 µM). CHMP agreed that these potential interactions do not represent a toxicologically or clinically significant risk. As no unexpected risks have been identified, further non-clinical studies were not deemed necessary.

Safety pharmacology programme

In *in vivo* safety pharmacology studies, no adverse effects on neurobehavioral function at up to 300 mg/kg or respiratory-system function at up to 900 mg/kg occurred in rats administered XL184.

The *in vitro* safety pharmacology data were not performed according to GLP, and data provided in several study reports was limited. The data suggest that cabozantinib is not a potent hERG inhibitor, but has an effect on hERG trafficking, which might lead to delayed QT prolongation in patients. *In vivo* in dogs, no effect on ECG parameters were observed after a single dose, nor after 26 weeks of dosing (see repeated dose toxicity). In patients, detailed evaluation of the effect of cabozantinib on QT interval was performed in a clinical trial, which revealed a slight, but not clinically relevant prolongation of the QT interval. Considering the available clinical data and the lack of a relevant effect on ECG parameters, further non-clinical data or discussion is not required. *In vivo*, no effect other than a transient effect on diastolic blood pressure was seen. Hypertension is a known class effect of these types of products and this has also been observed in clinical trials. Further monitoring on a clinical level is warranted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed (see discussion on Non-clincal aspects).

2.3.3. Pharmacokinetics

Cabozantinib is a highly permeable compound with a generally rapid absorption after oral administration. Absolute bioavailability of the malate salt of cabozantinib administered via an oral capsule (clinical formulation) is moderate to high in dog and rat, respectively.

Kinetics of cabozantinib after repeated once-daily dosing were generally linear in rats over the dose range 0.1 – 15 mg/kg, but increased more than dose-proportional over the dose range 5 – 15 mg/kg. In dogs, cabozantinib

exposure increased less than linearly with dose over the dose range 0.2 – 5 mg/kg but more than linear with dose over the range 10 – 100 mg/kg.

Cabozantinib showed to be highly bound to plasma proteins in all pre-clinical species and in humans (>99.7%) and widely distributed into body tissues, including passage over the blood:brain barrier, the blood:testes barrier and the placenta, as expected based on the moderate to high volume of distribution. In addition, cabozantinib has potential to bind to melanin. Partitioning into red blood cells has not been studied pre-clinically but data provided in the clinical section showed that XL184 is mainly present in plasma and to a limited extent distributed into erythrocytes. Elimination from plasma is slower in rat than in the other pre-clinical species as indicated by lower plasma clearance values. In addition, excretion data in rat show that within 24 hours only about a third was excreted. Cabozantinib is mainly excreted via faeces in rats.

Entero-hepatic recirculation of cabozantinib may occur in humans as well as in rats and dogs. However, based on the chemical structures of the metabolites readily enabling back-transformation to parent cabozantinib is not expected. For the glucuronide conjugates however back transformation is possible by the intestinal flora. Drug-drug interactions with antibiotics could occur. Also disruption of the enterohepatic recirculation of cabozantinib by other drugs, such as cholestagel or cholestyramine, could occur. In bile duct cannulated rats and dogs administered 14C-XL184, mean recoveries of approximately 29% and 15%, respectively, of the administered dose were present in bile, suggesting that hepato-biliary excretion plays a predominant role in the elimination of absorbed 14C-XL184-related radioactivity in both species. It is unknown whether cabozantinib is excreted in milk of lactating animals.

Hepatic clearance does not play a large role in the elimination of cabozantinib in the pre-clinical species as cabozantinib has a low intrinsic clearance value and in vivo only approximately a tenth in rat and a third in mouse is metabolised by CYP3A4 and to a much lesser extent CYP2C9. However, not all CYPs are studied for involvement in the formation of these metabolites (except for M1). In addition, no data on enzyme involvement are available for the other metabolites. In humans however, metabolism is more prominent than in the pre-clinical species. The major component in plasma is unchanged parent and exposure to XL184-monohydroxysulfate (M4), the main human metabolite, was 25% relative to total plasma exposure. Unchanged 14C-XL184 was the major radioactive component detected in plasma and feces from rats and dogs; however, it was present at low levels in bile from both species (unchanged 14C-XL184 accounted for only 0.2% of the radioactive dose in dog bile).

Cabozantinib is an inhibitor, but not a substrate, of P-glycoprotein with an IC50 value of 7 µM. The Applicant will perform a study investigating whether cabozantinib is a substrate or inhibitor of MRD1, BCRP, BSEP, MRP2, OAT1, OAT3, ACT1, OCT1, OCT2, OATP1B1 and OATP1B3 in 2Q13. Potential inhibitory effects on MATE1 and MATE2k also will be addressed. Evaluation of CYP2B6 inhibition by cabozantinib showed a concentration dependent inhibition over the range 0.41 to 16 µM with an IC50 value of 10.1 µM. As this IC50 value is higher than the IC50 value for CYP2C8 and a clinical drug-drug interaction study did not show inhibitory effects of cabozantinib on CYP2C8 in vivo, it is not expected that cabozantinib will inhibit CYP2B6 in vivo. Cabozantinib is not expected to inhibit or induce CYPs in humans at clinically relevant concentrations.

2.3.4. Toxicology

Single dose toxicity

Acute effects in rats showed as possible hepatotoxicity and hematopoietic tissue toxicity with death at 300 mg/kg. Dogs showed less sensitive for acute doses with minimal evidence of toxicity at 2000 mg/kg.

Table 5 - Single dose toxicity studies with cabozantinib (XL184)

Study ID	Species / Sex / Number / Group	Dose / Route	Observed max non-lethal dose	Major findings
XL184-Disc-038 Dose range-finding Non-GLP	Rat F/2	500, 1000, 2000 mg/kg Oral gavage	500 mg/kg	≥1000: death, weight↓, ALT↑, AST↑, CK↑, GGT↑, LDH↑
XL184-NC-003 GLP	Rat M+F/5	100, 300, 900 mg/kg Oral gavage	100 mg/kg	≥100: ALT, AST, ALP, cholesterol, total bilirubin↑ ≥300: death, histopathologic changes in adrenal gland, lung 900: prostration, coldness to touch, abnormal respiration; clinical pathology changes indicative of liver and hematopoietic toxicity, dehydration; histopathologic changes in GI tract, lymphoid tissues, bone marrow, adrenal gland, lung, testes, kidney, pancreas
XL184-NC-001 Dose range-finding Non-GLP	Dog M/2	30, 60, 120, 240, 480 mg/kg Oral gavage	>480 mg/kg	≥120: hypoactivity (F) ≥240: Ca, PO4↓ 480: WBC, neutrophil, and monocyte counts, cholesterol, ALT, AST↑
XL184-NC-004 GLP	Dog M+F/2	400, 1000, 2000 mg/kg Oral gavage	>2000 mg/kg	2000: excessive salivation

Repeat dose toxicity

In rats the most important target tissues for cabozantinib-related toxicity after 2 weeks of oral gavage are GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, liver and kidney. The adverse effects were generally dose related and seen from 5 mg/kg/day and above and were generally reversible upon discontinuation of treatment. 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. Because one animal died possibly test article-related, the NOAEL was considered 0.3 mg/kg/day. Based on the AUC of plasma exposures this is 0.2- to 0.3-fold of the intended clinical exposure.

At high dose (≥100 mg/kg for 4-14 days), cabozantinib causes hematopoietic- and hepatotoxicity, and dehydration in dogs. Also targets for toxicity are GI-tract, lymphoid tissues, testes, bone, pancreas, gallbladder, eye and possibly CNS tissues. Lesions were reversible at 100 mg/kg. No treatment-related histopathologic changes were present at 10 mg/kg for 14 days. At the maximum dose of 5 mg/kg/day during the 6 month study, no signs of toxicity were evident, but some effects occurred in reproductive tissues. An extra chronic study with 20 mg/kg showed some reversible hematopoietic- and hepatotoxicity, and effects on skin. 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. The NOAEL was considered to be 5 mg/kg, which is about 0.2-fold of the intended clinical exposure.

Moderate to severe hypopigmentation was observed in a 6-month repeat-dose toxicity study in dogs (XL184-NC-018), at exposure levels below expected human exposure level, leading to discoloured skin and hair, resembling vitiligo in humans. Rat distribution studies have demonstrated that XL184-related radioactivity is retained and accumulated in pigmented ocular tissue. Due to the use of non-pigmented animals in the long-term repeat-dose rat study, similar findings in pigmented rats cannot be excluded. Although cabozantinib appears to accumulate and retain in ocular tissue, the skin and hair depigmentation observed with cabozantinib is most likely related to inhibition of c-KIT, and is not considered a concern for the pigmentation of the eye.

Table 6 - Repeat-dose toxicity studies with cabozantinib (XL184).

Study ID	Species/ Sex/Numb er/Group	Dose/Route	Duration	NOAEL (mg/kg/ day)	Major findings
XL184-Disc-036 Dose range-finding Non-GLP	Rat F/6	1, 3, 10, 30, 100 mg/kg Oral gavage	8 days	<1	≥1: follicular necrosis, submucosal edema and inflammation in stomach ≥3: ALT, AST, LDH, GGT, lipase, amylase↑ ≥10: CK↑ 100: death, histopathologic changes in adrenals, bone marrow, kidney, lungs, lymph nodes, ovaries, stomach
XL184-NC-005 GLP	Rat M+F/10	1, 5, 15 mg/kg Oral gavage	14 days	1	≥5: Bodywght, food cons↓, bonemarrow depletion, necrosis in thymus, spleen, ileum 15: death; hematopoietic, liver, GI, and/or renal toxicity; histopathologic changes in adrenals, lymphoid tissues, GI tract, bone marrow and pancreas
XL184-NC-013 GLP	Rat M+F/20	0.1, 0.3, 1 mg/kg Oral gavage	6 months	0.3	1: death (1M), bodywght (F)↓, ALT↑, chronic progressive nephropathy
XL184-NC-002 Dose range-finding Non-GLP	Dog M/2	500, 2000 mg/kg Oral gavage	500: 4 days 2000: single dose	<500	≥500: Vomitus and abnormal feces; bodywght, food cons↓, histopathologic changes in GI tract, lymphoid tissues, and/or testes
XL184-NC-006 GLP	Dog M+F/2-5	Phase 1: 100, 300, 1000 mg/kg Phase 2: 10, 100 mg/kg Oral gavage	Phase 1: 7, 6, 5 days Phase 2: 14, 5 days resp.	10	100: death (3/3 M and 3/3 F following Dosing D 7); reversible histopathologic changes in bone marrow, lymphoid tissues, GI tract; secondary changes in bone, pancreas, eye, gallbladder, and central nervous system 300: histopathologic changes not reverible; ALT, AST↑ urea nitrogen, creat, PO4↓
XL184-NC-012 GLP	Dog M+F/4	0.2, 1, 5 mg/kg Oral gavage	26 weeks	5	≥0.2: Microscopic findings in ovaries (corpus luteum absent) considered to reflect incomplete sexual maturation in young adult dogs
XL184-NC-018 GLP	Dog M+F/4	30 mg/kg × 10 days→11 non-dosing days→20 mg/kg × 111 days (M) or 161 days (F) Oral gavage	20 mg/kg: 16 weeks (M) 23 weeks (F)	nd	death (2 M, 1 F); body wght, food cons↓; testes and ovary wght↓; microscopic findings in testes (bilateral hypospermatogenesis), ovaries (corpus luteum absent), thymus (lymphoid depletion), mammary gland and uterus (decreased glandular tissue)

Nd: not determined

Genotoxicity

XL184 is considered non-genotoxic, based on negative findings in a standard test battery *in vitro* and *in vivo*.

Table 7 - Overview of genotoxicity studies in cabozantinib

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria 7359-193 Non-GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	10–5000 µg/plate +/- S9	negative
Gene mutations in bacteria XL184-NC-010 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	10–5000 µg/plate +/- S9	negative
Gene mutations in mammalian cells 7359-194 Non-GLP	L5178Y/TK+/- mouse lymphoma cells	50-500 µg/ml +/- S9	negative
Gene mutations in mammalian cells XL184-NC-011 GLP	Human peripheral blood lymphocytes	5-750 µg/ml +/- S9	negative
Chromosomal aberrations in vivo XL184-NC-019 GLP	Mouse, micronuclei in bone marrow	500, 1000, 2000 mg/kg	negative

Carcinogenicity

Although not required for the indication in advance RCC, a two-year carcinogenicity study in rats is currently ongoing, and will be submitted when finalised. XL184 was not carcinogenic in a 26-week oral carcinogenicity study in rasH2 mice at estimated plasma exposure levels close to expected clinical exposure levels.

Reproductive Toxicity

Cabozantinib-related effects on male and female reproductive organs were observed in rats, leading to reduced fertility at ≥1 mg/kg/day for females and ≥2.5 mg/kg/day for males. Paternal toxicity showed from 2.5 mg/kg/day (death, pale ears, thin appearance, missing teeth, extremely white, excessively long, malocclusion, cut or curved upward; hair coat yellow, red or rough in appearance, and faecal changes). Comparable toxicity showed in females also from 2.5 mg/kg, but less severe. Weights of testes, epididymis, prostate and seminal vesicles decreased and reductions occurred in sperm count and concentration from 2.5 mg/kg. No fertile males were present at 2.5 and above. A dose-related prolongation of diestrus showed at 2.5 mg/kg. Although the majority of females had confirmed matings, the male/female fertility index was 0% at 2.5 and 5 mg/kg; there were no pregnancies in either group. Female fertility and embryo/foetal viability were reduced at 1 mg/kg. Effects are below or around the intended human exposure.

In line with these findings, histopathological findings were observed in repeat-dose toxicity studies in dogs (reduced testes weight and hypospermatogenensis at > 1 mg/kg/day; reduced ovary weight at ≥0.2 mg/kg/day). At present, the reversibility of the effects on male and female fertility is not known. Consequently, the need for advice regarding fertility preservation measures is stated in the SmPC in section 4.6.

In rats, maternal toxicity showed at 5 mg/kg cabozantinib. Embryo/foetal viability and development were adversely affected at ≥ 0.6 mg/kg. Based on a treatment-related increase in post-implantation loss at ≥0.03 mg/kg/day, the NOEL for embryo/foetal viability was determined to be 0.01 mg/kg/day, which is <1% than the human exposure.

In rabbits, the NOAEL for maternal toxicity and embryo-foetal viability and growth was 3 mg/kg. The NOEL for teratology was 1.0 mg/kg, equating to a plasma exposure <0.1-fold of the intended human dose.

Malformations were not observed in the decisive embryo-foetal study in rats dosed up to 0.1 mg/kg/day. However, oedema, cleft palate/lip, dermal aplasia and kinked/rudimentary tail were observed in the dose-range study at 0.6 mg/kg/day, without maternal toxicity. In rabbits, cabozantinib-related foetal visceral variations / malformations occurred at 3 mg/kg/day in the decisive study, reflected by small or missing intermediate lobe of lungs, reduced spleens (7 foetuses in one litter), and a significant increase in the foetal incidence of total malformations, albeit at a maternally toxic dose.

Thus animal studies show reproductive toxicity at exposure levels far below human exposure levels at the intended clinical dose, therefore, cabozantinib should not be used during pregnancy.

In a definitive pre- and postnatal development study in rats (study results submitted as part of variation II/12 for Cometriq), pregnant dams were dosed from gestation day (GD) 10, and not from GD6, as indicated in ICH S5(R2). However, due to the substantial post-implantation loss in the embryo-foetal toxicity study when dosed from GD6, dosing from GD10 is considered acceptable. No significant XL184-related effects were observed in the definitive study at maternal doses up to 0.3 mg/kg/day. The level in milk was not determined, but measurable plasma concentrations were present in pups on PND4 and PND21, indicating exposure via milk. At NOAEL, maternal plasma levels (71.4 ng/ml) were substantially below expected human exposure (1220 ng/ml). The relevance of such a study is therefore questionable.

Table 8 - Overview of reproduction toxicity studies performed with cabozantinib

Study type / Study ID / GLP	Species; Number /group	Route & dose	Dosing period	Major findings	NOAEL / AUC ng.h / ml
Fertility XL184-NC-020 GLP	Rat M+F/22	Oral 1, 2.5, 5 mg/kg	M: 10 weeks (4 weeks prior to mating) F: 2 weeks prior to mating through GD 7	**≥1: (F)** % pre- and post-implantation losses and resorptions ↑ **≥2.5: (M)** body weights, food consumption, reproductive tissue weights, fertility, and sperm counts↓ **(F)** altered estrus cycling; 100% non-pregnant **5: (M)** moribund sacrifice (Day 39)	1 mg/kg (M) AUC: 20700 (M) 19300 (F)
Embryo-fœtal development XL184-NC-021 Non-GLP	Rat F/6	Oral 0.03, 0.1, 0.6, 1, 2.5, 5, 7.5 mg/kg	GD 6-17	**≥0.03:** uterine weights ↓ (primarily due to fetal weights↓) **≥0.6:** external variations (swollen hindpaw, curly tail) and malformations (edema, cleft palate, hare lip, kinked/ rudimentary tail, dermal aplasia); uterine weights ↓ (primarily due to post-implantation loss↑) **≥1:** complete early resorption of all fetuses **≥5:** body weights, food consumption↓ ; unscheduled deaths	ND
Embryo-fœtal development XL184-NC-022 GLP	Rat F/25	Oral 0.01, 0.03, 0.1 mg/kg	GD 6-17	**≥0.03:** post-implantation loss ↑	0.01 mg/kg AUC: 168
Embryo-fœtal development XL184-NC-023 Non-GLP	Rabbit F/6	Oral 0.5, 2.5, 7.5, 15, 30 mg/kg	GD 7-20	**≥2.5:** incidence fetal variations↑ (swollen hind paws) **≥7.5:** unscheduled deaths; body weights, food consumption, uterine weights, fetal viability ↓ (early and total resorptions and post-implantation losses↑); abortions↑	0.5 mg/kg AUC: ND
Embryo-fœtal development XL184-NC-024 GLP	Rabbit F/20	Oral 0.3, 1, 3 mg/kg	GD 7-20	**3:** fetal spleen size↓ (no maternal toxicity or fetal skeletal or external malformations)	1 mg/kg AUC: 984

Juvenile toxicity

Juvenile animals were dosed at PND 21-70. Major, reversible findings following treatment from PND21-35 (cohort 1) were limited to increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), and reduced bone mineral content and density. Major findings following treatment from PND21-70 (cohort 2) were increased WBC parameters, increased haematopoiesis, tooth abnormalities, reduced bone mineral density and content, liver pigmentation and bile

duct hyperplasia. The observed effects on uterus/ovaries and decreased haematopoiesis seen in cohort 1 were not seen in cohort 2, suggesting transient effects, while effects on bone parameters and liver pigmentation were sustained. Findings from the juvenile toxicity study have been included in the SPC section 5.3.

Toxicokinetic data

An overview of the toxicokinetics of XL184 in rat and dog is provided in table 9. For comparison, human data are also added and the ratio between animal exposure and human exposure is calculated.

Table 9 -Toxicokinetics and interspecies comparison of cabozantinib

Species/ Time/ Study ID	**Daily Dose (mg/kg)**	**Animal AUC (ng.h/ml)**		**Cmax (ng/ml)**		**T ½ (h)**		**A:H exp****
		♂	♀	♂	♀	♂	♀	
Rat 8 days XL184-Disc-036	1	-	24484	-	1408	-	13.1	**0.65**
	3	-	57700	-	3231	-	12.3	**1.5**
	10	-	286332	-	15010	-	21.7	**7.6**
	30	-	640268	-	29925	-	-	**17**
Rat 14 days XL184-NC-005	1 (NOAEL)	10978	-	853	-	9.62	-	**0.29**
	5	52152	-	4690	-	16.0	-	**1.4**
	15	512771	-	26733	-	21.5	-	**14**
Rat * 14 days XL184-NC-014	1 (NOAEL)	6780	-	464	-	10.1	-	**0.18**
	5	36200	-	2650	-	8.04	-	**0.96**
Rat 26 weeks XL184-NC-013	0.1	2632	4753	165	298	-	-	**0.07/0.13**
	0.3 (NOAEL)	7851	14416	523	881	26.1	-	**0.21/0.38**
	1	29736	44086	2590	2740	22.8	-	**0.79/1.2**
Dog 4/1 days XL184-NC-002	500	784626	-	23332	-	25.6	-	**21**
	2000	377233	-	16989	-	17.6	-	**10**
Dog * 5-14 days	100	199566	135198	12967	10163	5.06	4.65	**5.3/3.6**
	300	464851	310576	26500	19120	8.34	8.06	**12.3/8.2**

Species/ Time/ Study ID	Daily Dose (mg/kg)	Animal AUC (ng.h/ml)		Cmax (ng/ml)		T ½ (h)		A:H exp**
		♂	♀	♂	♀	♂	♀	
XL184-NC-006	1000	447389	431916	25134	25120	-	-	**11.8/11.4**
	10 (NOAEL)	8406	11408	824	1400	6.02	6.01	**0.22/0.30**
	100	237419	222059	15650	13500	7.62	9.96	**6.3/5.9**
Dog 26 weeks XL184-NC-012	0.2	285	323	33.8	73.4	4.89	5.09	**0.01/0.01**
	1	2027	2012	317	426	8.53	9.97	**0.05/0.05**
	5 (NOAEL)	7757	6327	706	1008	12.6	8.58	**0.20/0.17**
Dog 16/23 weeks XL184-NC-018	20	18800	24800	2600	2500	6.06	7.65	**0.50/0.66**
Rabbit	1 (NOEL)	-	984	-	86.2	-	8.3	**0.03**
Gestation days 7-20 XL184-NC-024	3	-	4240	-	295	-	7.6	**0.11**
Human	2.9	37850		-		91		**1**

*) Day 1 post-dose values.

**) A:H exp = Animal:Human Exposure Multiple

Interspecies comparison

There are some differences in oral bioavailability of the L-malate salt between the pre-clinical species investigated: ~90% in rats and ~55% in dogs. No absolute bioavailability was determined for humans.

Volume of distribution was comparable across mouse and rat (i.e. ~0.9 and ~0.6 L/kg, respectively) but was significantly lower than in dog and monkey (i.e. ~2.1 and ~2.7 L/kg). Further, plasma clearance was approximately one order of magnitude lower in rat (i.e. ~0.030 – 0.045 L/kg/hr) than in the other pre-clinical species (i.e. 0.23 – 0.64 L/kg/hr). In line with this, plasma half-lives were also comparable between mouse, dog and monkey (i.e. ~3 – 4 hours) and longer in rat (i.e. ~12 – 13 hours). In humans, elimination of XL184 was much slower than in the pre-clinical species. The volume of distribution (Vc/F) was much larger in humans than in the pre-clinical species, i.e. ~5.8 L/kg. The clearance (CL/F) was in the same order of magnitude as in rats (0.07 L/kg/hr), but plasma half-life was much longer with 120 hours.

Plasma protein binding of XL184 was high in all species, including humans.

Metabolism of XL184 is more prominent in humans than in the pre-clinical species. However, no unique human metabolites were found. Furthermore, XL184 is mainly excreted via faeces in both rats and humans but urine is a more important route of excretion in humans than in rats. Further comparison of metabolism and excretion across pre-clinical species and humans is hampered by several facts: 1) *in vivo* metabolism of XL184 in the different species is elucidated at different dosages and dosing regiments; 2) the excretion of XL184 has not been investigated in dog, which is considered as a key animal species for preclinical assessment; 3) the excretion of XL184 in bile has not been investigated while the presence of entero-hepatic recirculation is assumed in humans; 4) the metabolite profile of the excreta has not been determined.

Local Tolerance

No specific studies have been conducted to evaluate local tolerance to XL184 administration.

Other toxicity studies

Metabolites and impurities

Table 10 - Overview of genotoxicity studies in metabolites

Metabolite / Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
XL184 n-oxide (M1) Gene mutations in bacteria BMSAmes-927982 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate - S9	negative
parafluoroaniline (p-FA) Gene mutations in bacteria BMSAmesSQ-008953 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive

Table 11 - Repeat-dose toxicity study with cabozantinib and impurity

Study ID	Species / Sex / Number / Group	Dose / Route	Duration	NOAEL (mg / kg / day)	Major findings
XL184-NC-014 GLP	Rat M+F/10	1, 5 mg/kg Oral gavage	14 days	1	5: Bodywght, food cons↓ glomerular membrane thickening, tubular Degeneration in kidney, corpora lutea necrosis, pituitary and adrenal gland necrosis

Table 12 - Overview of genotoxicity studies in impurities

Metabolite / Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
XL184-1-1 Gene mutations in bacteria BMSAmes-655335 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive
XL184-1-4 Gene mutations in bacteria BMSAmes908145 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive
4-Fluoroaniline Gene mutations in bacteria BMSAmesSQ-008953 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive
4-aminophenol Yoshida et al, 1998 Non-GLP	E. coli WP2uvrA/pKM101	500 - 1500 µg/plate - S9	positive
XL184-1-2 Gene mutations in bacteria BMSAmes-908148 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	negative
XL184-2-2 Gene mutations in bacteria BMSAmes-908146 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	negative

Photoxicity

Cabozantinib showed no phototoxicity in the 3T3 NRU-PT test (data not shown).

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), an environmental risk assessment has been submitted for XL184.

The Applicant has conducted a study for determining Kow. The presented Kow (5.15 at pH 7.4) is above 4.5, and a PBT assessment is required. A Bio-concentration Factor study in accordance with OECD 305 is ongoing, and an interim study report (RPT750A-102) has been provided indicating that cabozantinib is not bio-accumulative. The final study report will be submitted when finalised (please see conclusion on Non-clinical aspects).

A refined $PEC_{SURFACEWATER}$ value based on prevalence data for advanced RCC has been calculated to be 0.008 µg/L,in accordance with the ERA guideline. This is below the action limit of 0.01 µg/L, and a Phase II environmental fate and effect analysis is not triggered.

Table 13 - Summary of main study results

Substance (INN/Invented Name): XL184 (Cabozantinib)			
CAS-number (if available): 1140909-48-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Log K_{ow} = 3.96 (a pH 5) Log K_{ow} = 5.15 (at pH 7.4)	Potential PBT: Y
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
Default $PEC_{surfacewater}$ Refined $PEC_{surfacewater}$ (e.g. prevalence, literature)	0.3 0.012	µg/L	> 0.01 threshold Y

2.3.6. Discussion on non-clinical aspects

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2. No pharmacodynamic drug interaction studies were performed. It is agreed that co-medication with products having the same pharmacological targets is unlikely. Therefore the absence of pharmacodynamic drug interaction studies is agreed.

The bioavailability of cabozantinib is moderate to high, and it is highly bound to plasma proteins. There are four major metabolites, of which the 6-desmethyl half-dimer sulphate (M2a) and the monohydroxysulphate (M4) are the most important. In rats Cabozantinib is mainly excreted via faeces. Cabozantinib is an inhibitor, but not a substrate, of P-glycoprotein with an IC50 value of 7 µM. No other transporters were investigated. Cabozantinib is not expected to inhibit or induce CYPs in humans at clinically relevant concentrations.

It is unknown whether cabozantinib is excreted in milk of lactating animals. It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breast-feeding during treatment with cabozantinib, and for at least 4 months after completing therapy (see SmPC section 4.6).

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: In rat and dog repeat-dose toxicity studies up to 6 months duration, target organs for toxicity were GI tract, bone marrow, lymphoid tissues, kidney, adrenal and reproductive tract tissues. The no observed adverse effect level (NOAEL) for these findings were below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3).

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays.

Regarding the results of the 26-week oral carcinogenicity study in rasH2 mice model the following text is included in the SmPC: “Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the human therapeutic exposure”, in line with the Cometriq SmPC.

Fertility studies in rats have shown reduced male and female fertility and shows reproductive toxicity at lower levels than the intended human exposure. Further, hypospermatogenesis was observed in male dogs at exposure levels below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3).

There are no data on human fertility. Both men and women should be advised to seek advice and consider fertility preservation before treatment (see SmPC sedction 4.6).

Embryo-foetal development studies were performed in rats and rabbits. In rats, cabozantinib caused postimplantation loss, foetal edema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations. NOAEL for embryo-foetal toxicity and teratogenic findings were below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3). There are no studies in pregnant women using cabozantinib. The potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib (see SmPC sections 4.6).

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as “effective methods of contraception,” they should be used together with another method, such as a barrier method (see SmPC sections 4.6 and 4.5 and Discussion on clinical pharmacology).

Juvenile rats (comparable to a >2 year old pediatric population) administered cabozantinib showed 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 bile duct hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Evaluations in juvenile rats (comparable to a <2 year old pediatric population) have not been performed (see SmPC section 5.3).

In accordance with ICH S9, evaluation of metabolites is generally not warranted in patients with advanced cancer. However, metabolites M1, M2a (EXEL 1644), M4 and M8 are in much higher concentrations in humans than in the used animal models, especially M2a and M4 (about 39% and 13% of the total amount respectively). M1 and M8 are of low abundance in humans and are not expected to be genotoxic (M1 is not mutagenic in Ames test and M8 has no structural alert). M4 shows little pharmacodynamic activity and is not mutagenic in the Ames test. According to ICH S9 it is not necessary to test metabolites M1, M4 and M8 further for toxicity.

The toxicity and pharmacology studies performed with metabolites EXEL-1644 and EXEL-1646 do not indicate a safety concern.

The applicant qualified the impurity ortho-fluoro cabozantinib in a 2 week rat study. It is not expected that ortho-fluoro cabozantinib will influence the safety of the product.

Potential genotoxic impurities in XL184 drug substance were identified and found positive in the Ames test. The specifications of the genotoxic impurities in the product are slightly higher than the threshold of toxicologic concern (TTC) value of 1.5 µg/day. However, it is agreed that specifications higher than the TTC may be acceptable under certain conditions, e.g. short-term exposure, for treatment of a life-threatening condition, or when life expectancy is less than 5 years (Guideline on the limits of genotox impurities), which is the case.

Cabozantinib is not phototoxic.

In order to complete the PBT assessment, the study report for the ongoing bioconcentration factor study has to be submitted when completed. Provided that the final report confirms the interim study report indicating a BCFk below 2,000, cabozantinib is not considered a PBT substance, and no further actions will be required. The final study report should be submitted as a post-approval commitment.

2.3.7. Conclusion on the non-clinical aspects

In general, the non-clinical data were of good quality and meet the requirements to support this application.

The CHMP recommended that the submission of the final report of the ongoing two-year carcinogenicity study in rats (Study XL184-NC-036) should be submitted post approval.

The CHMP also recommended that the ongoing bio -concentration factor study needs to be submitted when completed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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 14 – Overview of clinical studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Patient Population
XL184-004	Food effect on cabozantinib dosing	Open, randomized, two-period, two-sequence crossover	Cabozantinib 140 mg; once; oral	Healthy subjects
XL184-016	PK of 2 capsules containing different amounts of 2 cabozantinib	Open, randomized, two-period, two-sequence crossover	Cabozantinib 100 mg; once; oral	Healthy subjects

	crystal forms			
XL184-010	Bioequivalence of cabozantinib tablets and capsules	Open-label, randomized, single-dose, two treatment, two-way crossover	Cabozantinib 140 mg tablet dose once; oral and cabozantinib 140 mg capsule dose once; oral	Healthy subjects
XL184-012	Mass balance	Open-label, single dose	Cabozantinib 140 mg [14C-labeled; 100µCi] solution formulation; oral	Healthy subjects
XL184-020	Dose-linearity	Open-label, randomized, single-dose, three treatment, parallel PK study	Cabozantinib 20 mg; oral, once; or cabozantinib 40mg, oral, once; or cabozantinib 60 mg; oral, once	Healthy subjects
XL184-003	Hepatic impairment study	Open-label, parallel cohort, single-dose	Cabozantinib 60 mg; oral, once	Healthy and hepatic impairment subjects
XL184-017	Renal impairment study	Open-label, parallel cohort, single-dose	Cabozantinib 60 mg; oral; once	Healthy and renal impairment subjects
XL184-006	Drug-drug interaction with rifampin (CYP3A4 inducer)	Open-label, two treatment, single sequence	Cabozantinib 140 mg and rifampin 600 mg; oral	Healthy subjects
XL184-007	Drug-drug interaction with ketoconazole (CYP3A4 inducer)	Open-label, two treatment, single sequence	Cabozantinib 140 mg and ketoconazole 400 mg; oral	Healthy subjects
XL184-018	Drug-drug interaction with esomeprazole	Open-label, two treatment, single sequence, drug-drug interaction	Cabozantinib 100 mg and esomeprazole 40 mg; oral	Healthy subjects
XL184-308	Efficacy and safety of cabozantinib	Open-label, randomized, controlled	Cabozantinib 60 mg tablet; oral qd or everolimus 10 mg; oral qd	Advanced RCC (post VEGFR TKI)
XL184-306	Safety	Double-blind, randomized, controlled	Cabozantinib 60 mg tablet; oral qd or mitoxantrone infusion (3 week cycle) + prednisone 5 mg; oral bid	mCRPC (post docetaxel and abiraterone or enzalutamide)
XL184-307	Safety	Double-blind, randomized, controlled	Cabozantinib 60 mg tablet; oral qd or prednisone 5 mg; oral bid	Metastatic CRPC (post-docetaxel and abiraterone or enzalutamide)

XL184-008	Drug-drug interaction with rosiglitazone; safety and preliminary efficacy	Open-label, one sequence, cross-over	Cabozantinib 140 mg qd and rosiglitazone 4 mg on Day 1 and Day 22	Metastatic or unresectable solid tumours (DTC or RCC)

2.4.2. Pharmacokinetics

The body of text of this PK assessment is based on the data for Cometriq. However, for the RCC indication, three additional main clinical studies (XL184-010, XL184-020 and XL184-308) supporting the pharmacokinetics of the tablet formulation and the pharmacokinetics in the RCC population have been submitted. Also updated new information was submitted, as assessed in the variations for Cometriq to include information generated as part of the PAMs agreed for the MA approval.

Method validations established linearity, sensitivity. Inter- and intra-assay precision of all methods was within ±15% relative standard deviation, and accuracy within ±15%.

Pharmacokinetic parameters from plasma concentrations of cabozantinib were calculated using non-compartmental techniques for the biopharmaceutical studies and population-PK analysis for the clinical pharmacology studies.

Descriptive analysis was provided for the biopharmaceutical studies.

Absorption

Following a single oral dose, cabozantinib was absorbed with maximum plasma concentrations of cabozantinib achieved at median time of 2 to 5 hours post-dose across studies in healthy volunteers and cancer patients. Multiple peaks in the plasma concentration-time profile following a single oral dose suggest that cabozantinib is enterohepatically recirculated.

The absolute bioavailability of cabozantinib has not been determined. Based on the provided mass balance study, however, at least 27% of the administered cabozantinib is renally excreted, and thus at least this fraction of the administered dose was absorbed.

A high-fat meal moderately increased cabozantinib Cmax and AUC values by 41% and 57%, respectively, relative to fasted conditions in healthy volunteers. Based on this food-effect study, the Applicant decided to administer cabozantinib under fasted conditions, i.e., the patients are instructed not to eat for at least 2 hours before and 1 hour after taking cabozantinib. The fasting conditions was applied in all clinical studies.

- **Bioavailability and bioequivalence**

The cabozantinib tablet dosage form is an immediate-release formulation consisting of cabozantinib (S)-malate drug substance combined with standard excipients and film-coated. The same cabozantinib tablet formulation that was used in pivotal Phase 3 study XL184-308 in subjects with renal cell carcinoma (RCC) is the proposed commercial formulation. Prior to the tablet formulation, cabozantinib was provided as capsules using the same cabozantinib drug substance. Capsules were dosed in many of the clinical studies, including the first-in-human study XL184-001, clinical pharmacology studies, and Phase 3 study XL184-301 in medullary thyroid cancer (MTC).

The tablets yield higher exposure than the capsules, and the two formulations are not bioequivalent, as such the two formulations are not interchangeable: the tablet formulation will be the only marketed cabozantinib drug product formulation for the treatment of RCC, and will be marketed as a distinct product from the cabozantinib capsules.

Distribution

Cabozantinib was highly plasma protein bound at all concentration levels tested; the percentage not extensively bind to erythrocytes. The popPK estimated volume of the central compartment (Vc/F) was approximately 350 l in MTC. The popPK estimate of Vc/F in the combined HV and RCC patients analysis was 81.45 (68.5, 96.8)) L.

Metabolism

The following metabolites of cabozantinib were characterised in plasma: XL184-N-oxide, XL184-monohydroxysulphate, XL184 half dimer, half-dimer methyl ester, 6-demethyl half-dimer sulphate, 7-demethyl half-dimer sulphate, demethyl XL184 glucuronide A and B. The 6-demethyl half-dimer sulfate metabolite is the main circulating metabolite, and more abundant than cabozantinib in plasma. Based on LC-MS/MS analysis, mean exposure ratios for cabozantinib and metabolites XL184-half-dimer, XL184-N-oxide, XL184-sulfate and 6-demethyl half-dimer sulfate relative to total exposure (AUC0-t (each analyte)/AUC0-t (parent + 4 metabolites)) were 32.4%, 3.09%, 4.90%, 13.8% and 45.9%, respectively. The t1/2 of the major 6-demethyl half-dimer sulfate metabolite could not be determined, but is much longer than that of cabozantinib and the other characterised metabolites. In vitro data indicate that the formation of the XL184-N-oxide metabolite is dependent on CYP3A4, and to a lesser extent on CYP2C9. Formation of a number of other metabolites seems to be dependent on CYP3A4 as well, although only a limited number of CYPs were tested. It appears that non-conjugated metabolites are present only at low levels, and are less active than cabozantinib.

Elimination

The plasma terminal half-life of cabozantinib in single dose studies was approximately 120 hours. Cabozantinib is eliminated both via the hepatic (at least 54% of the administered dose) and renal route (at least 27%). Cabozantinib is not directly excreted in urine, but is present to some extent in faeces. Both in urine and faeces, multiple metabolites are detected, with dequinolinyl XL184 glucuronide, dequinolinyl XL184 sulfate, and XL184 half dimer being the main metabolites in urine, while cabozantinib, M11 (minor metabolite, not identified), demethyl XL184, and XL184 oxidation B were the main metabolites in faeces. The popPK estimate of CL/F in the combined HV and RCC patients analysis is 2.23 (2.13, 2.34) L/hr.

Dose proportionality and time dependencies

Dose proportional cabozantinib pharmacokinetics was demonstrated for the powder-in-bottle suspension formulation up to a dose of approximately 1000 mg. For the capsule formulation dose proportionality was assessed less extensively. In cancer patients, comparable - and thus not dose proportional- exposures were observed for a 175 and 250 mg cabozantinib malate capsule dose, both after a single dose and under steady-state conditions. This may point at limited absorption at this dose, potentially caused by limited solubility of cabozantinib. At lower doses in healthy volunteers, the dose-normalised exposure upon administration of 100 mg or 175 mg cabozantinib malate (78 mg and 138 mg cabozantinib freebase, respectively) appears comparable, indicating dose-proportional behaviour between these two doses.

The relationship between 3 different cabozantinib tablet strengths (20, 40, and 60 mg [FBE]) and their respective PK parameter values was assessed in study XL184-020 in healthy adult subjects. Single doses of cabozantinib tablets at 20, 40, and 60 mg FBE dose strengths showed dose-proportional increases in mean plasma cabozantinib Cmax and AUC0-t values. Therefore, dose proportionality was concluded for the single-dose PK parameters Cmax, AUC0-t, and AUC0-inf. CL/F was also similar across tablet strengths.

Dose-normalized exposures (AUC0-inf/dose) for the 20, 40, and 60 mg FBE cabozantinib tablet strengths in study XL184-020 (520, 528 and 535 ng.h/mL/mg, respectively) were similar to that of the 140 mg FBE cabozantinib tablet dose (1x100 mg + 2x20 mg) (470 ng.h/mL/mg) evaluated in the BE study, suggesting dose-proportionality over the 20-140 mg tablet dose range.

Accumulation of cabozantinib upon multiple dosing (AUC and Cmax increase 4.6 and 3.9-fold, respectively) is reasonably in line with expected, based on a t1/2 of approximately 120 hours. Steady state appears to be reached after 15 days of OD dosing. No major differences are apparent in cabozantinib PK between healthy volunteers and cancer patients, with Cmax, AUC and tmax, as well as interindividual variability being comparable.

Target population

Across the healthy subject studies, after a single dose of cabozantinib (XL184), absorption was slow with the median T_{max} that occurred at 4 to 5 hours (range: 1.1-24.1); some individual subjects had a prolonged absorption phase with a Cmax occurred as late as 24 hours after dosing. Following the peak, plasma concentrations declined slowly with the mean terminal t1/2 of 111 to 124 hours across the studies. Cmax, AUCs and t1/2 values from healthy subjects dosed at 140 mg FBE capsule dose are consistent across studies XL184-004, XL184-006, XL184-007 and XL184-010, and are also consistent with the data observed at a 140 mg FBE capsule dose in cancer subjects (Study Report XL184-001.PK.001); mean Cmax and AUC0-24 values were approximately 6% and 12% lower in healthy subjects compared with subjects with cancer.

Population PK model and Exposure-response model

A population pharmacokinetic analysis of cabozantinib was performed using data collected from 282 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 20 mg, 40 mg, and 60 mg.

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

Exposure-Response:

- No statistically significant relationship was identified between average cabozantinib concentration and early overall survival based upon a dataset from a pre-specified interim analysis cut-off (22 May 2015).
- A statistically significant relationship was identified between average cabozantinib concentration and progression free survival. Increases in cabozantinib concentrations are predicted to decrease the rate of disease progression. At expected steady-state average cabozantinib concentrations for the 20 mg, 40 mg, and 60 mg doses, limited separation in the survivor functions for progression free survival is predicted. Subjects with shorter times to disease progression for prior tyrosine kinase therapy (< 3 months) were predicted to have a decreased cabozantinib maximum effect relative to subjects that had progressive disease after 3 months on earlier therapy, resulting in an increased hazard ratio and a steeper progression free survival curve.
- A statistically significant relationship was identified between individual predicted cabozantinib clearance and the rate of dose modifications (i.e., reductions, holds, or interruptions). Decreases in cabozantinib clearance were predicted to increase the rate of dose modifications.
- A statistically significant relationship was identified between average cabozantinib concentration and fatigue/asthenia, PPE, hypertension, and diarrhea.
- No statistically significant relationship was identified between average cabozantinib concentration and nausea/vomiting or stomatitis.

Special populations

Impaired renal and hepatic function

The results of Study XL184-017 in subjects with mild or moderate impaired renal function showed that Cmax and AUCs (AUC0-t and AUC0-inf) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function when given a 60 mg dose. Both Cmax and AUC values (AUC0-t and AUC0-inf) of cabozantinib appeared to be similar between the moderate impairment and the control cohorts (differences: less than 3% and 7%, respectively).

The results of Study XL184-003 in patients with mild and moderate hepatic impairment showed an 81% and 63% increase in cabozantinib AUC after a 60 mg dose.

Gender, race, age and weight

In the population-PK analysis of cabozantinib in RCC patients, female gender and Asian race were significant covariates on CL/F, where female subjects had 21% lower CL/F compared with male subjects and Asian subjects had 27% lower CL/F compared with White subjects.

While the attributes of Asian race and female gender were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. In addition, the small number of Asian females (n=3) included in this PopPK analysis were insufficient to perform a meaningful analysis to understand the combined effect of a potential interaction between Asian race and female gender effects; however, these 3 Asian females did have individual clearance and drug exposure (AUC) values within the range of all other subjects in the study and were not considered outliers. In addition, the predicted effects of female gender and Asian race on CL/F are both lower than the calculated inter-individual variability in clearance (%CV of CL/F = 46%).

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

The PK of cabozantinib has not yet been characterized in the paediatric population.

Pharmacokinetic interaction studies

The Applicant has carried out four drug interaction studies of cabozantinib with rifampin (rifampicin) (Study XL184-006), ketoconazole (Study XL184-007), rosiglitazone (Study XL184-008), and esomeprazole, a proton pump inhibitor (Study XL184-018). The results from these studies are included in the SmPC for cometriq capsules and are carried through to the SmPC for Cabometyx.

Effect of other drugs on cabozantinib pharmacokinetics.

Cabozantinib is a substrate for CYP3A4 and to a lesser extent CYP2C9. Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC) by 38%. Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77% (see Discussion on clinical pharmacology). The solubility of cabozantinib is pH dependent, with very low solubility observed at a pH >3. The type II variation for cometriq (EMEA/H/C/2640/II/0006) included the results of study XL184-018 to assess interactions with drugs affecting gastric pH. The SmPC and the package leaflet were updated to delete the warning on concomitant use with proton pump inhibitors.

Effect of cabozantinib on PK of other drugs.

Based on the in vitro inhibition assays, cabozantinib is not expected to inhibit CYPs in vivo to a significant extent. Cabozantinib did not significantly inhibit CYP2C8 in vivo in a rosiglitazone drug-drug interaction study. With respect to induction by cabozantinib, no in vivo induction of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 is suggested by in vitro studies. Results of study reports XL184-NC-039, 043 and 048 provided post approval for Cometriq, provided sufficient data related to substrate and inhibition characteristics of cabozantinib towards different transporters (including interaction with P-glycoprotein). Based on these data, the removal of the safety warning regarding “drug interaction with individual drug transporters including P glycoprotein substances” was found acceptable.

2.4.3. Pharmacodynamics

Mechanism of action

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, and metastatic progression of cancer. Cabozantinib was evaluated in non-clinical studies for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors, In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

Primary pharmacology

Plasma markers of angiogenic pathways have been evaluated in previous clinical studies of anti-VEGFR2 tyrosine kinase inhibitors, e.g. for sunitinib. The common finding from trials of small molecule anti-VEGFR2 agents is an increase in the circulating levels of *VEGF* and *PlGF*, and a decrease in the level of soluble VEGFR2 (*sVEGFR2*) upon treatment. Therefore, in the Phase 1 dose finding Study XL184-001, these three plasma markers were investigated.

In addition to these three VEGFR2 pathway biomarkers, two additional plasma proteins were assessed on an exploratory basis in Study XL184-001. Soluble MET (*sMET*) was chosen due to the possible effects of MET or VEGFR2 inhibition on regulation of the MET receptor, and erythropoietin (*EPO*) was evaluated, as levels of EPO have been shown increase as a consequence of VEGF pathway inhibition in preclinical models ascribed to an upregulation of hepatic erythropoietin expression.

In thl phase 3 study of cabozantinib XL184-301, changes in soluble KIT receptor (sKIT) were evaluated as a biomarker of KIT pathway inhibition as well.

In Study XL184-001, the change in plasma levels for VEGF, sVEGFR2, PlGF, EPO, and sMET were monitored. Three of the markers (sVEGFR2, PlGF, EPO) demonstrated statistically significant changes upon treatment when Day 29 pre-dose levels (175 mg daily cohort only) when compared to pre-treatment levels (Table 11).

Table 15 - Summary of change in plasma biomarkers between day 1 and day 29 after O.D. treatment with 175 mg cabozantinib as capsule formulation (Study XL184-001)

Assay	Time Points	N	Relative Change (mean, SD)	P Value (2 sided t-test)	Significant ($p < 0.05$)
VEGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	3.660, 2.985	0.0900	no
PlGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	3.623, 2.578	< 0.0001	yes
EPO	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	2.059, 1.244	0.0007	yes
sVEGFR2	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	0.7115, 0.3180	< 0.0001	yes
sMET	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.126, 0.3235	0.0619	no
OPN	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.410, 1.838	0.1072	no
HGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.116, 0.5638	0.1799	no
ANG2	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	0.8611, 0.5004	0.1237	no

Relationship between plasma concentration and effect

In Study XL184-001, to understand whether there is a concentration dependency in the exposure/response relationship for XL184 plasma exposure and the biomarkers, the plasma levels for VEGF, sVEGFR2, PlGF, EPO, and sMET were plotted against the concurrent plasma concentration, the calculated plasma C_{max}, and the average plasma concentration (C_{ave}) of XL184. No statistically significant relationship exists between the C_{max} values of XL184 and the plasma biomarker concentrations (data not shown). Use of C_{ave} instead of XL184 concentrations led to a weaker relationship between exposure and response; only PlGF and sVEGFR2 maintained statistical significance. While there was clear evidence for a concentration dependence of the effect of XL184 on the four plasma biomarkers described above, the slopes of the effect curves were relatively flat, indicating that this pharmacodynamic effect is not highly dependent upon concurrent XL184 concentration and that the effect is measurable over a broad range of concentrations.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology package for cabozantinib (Cabometyx) in advanced RCC builds on the clinical pharmacology package for cabozantinib in MTC (Cometriq), with three additional studies to characterize the new tablet formulation and the pharmacokinetics in RCC patients. This was considered acceptable.

The tablets yield higher exposures than the capsules, and the two formulations are not bioequivalent. The two formulations are not interchangeable: the tablet formulation will be the only marketed cabozantinib drug product formulation for the treatment of RCC, and will be marketed as a distinct product from the cabozantinib capsules.

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 5 hours post dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in an approximately a 4 to 5 fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state is achieved by approximately Day 15. A high-fat meal moderately increased Cmax and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 140 mg oral cabozantinib dose. There is no information on the precise food effect when taken 1 hour after administration of cabozantinib (see SmPC section 5.2). Based on the population-pharmacokinetic (PK) model, the volume of distribution (V/F) is approximately 349 L (SE: ± 2.73%).

The sponsor has not submitted new phase I/II dose finding PK/PD studies for the current application. Sparse PK data has been collected in the pivotal study XL-184-308 to characterize the PK in RCC patients and confirm that the expected exposure levels is reached. No major differences was reported in cabozantinib PK between healthy volunteers and MTC cancer patients, with Cmax, AUC and tmax, as well as interindividual variability being comparable to a reasonable extent. The population model shows different PK estimates of CL and Vd in RCC patients compared to MTC patients. However, an exact cause has yet to be identified. Based on the integrated PopPK analysis, non-MTC cancer patient cohorts (including RCC patients) appear to have comparable cabozantinib clearance to that of healthy volunteers. Thus based on this analysis, no specific starting dosing adjustments are required when administering cabozantinib to RCC patients.

Cabozantinib is highly protein bound in vitro in human plasma (≥ 99.7%). Results from a study in subjects with hepatic impairment (Study Report XL184-003) indicated that exposure (AUC0-inf) was increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CIs for AUC0-inf: 121.44, 270.34% for mild impairment and 107.37, 246.67% for moderate impairment) compared with healthy subjects after a 60mg dose. Patients with severe hepatic impairment have not been studied. Based on the potential magnitude of increased cabozantinib exposure in subjects with mild or moderate hepatic impairment, a more conservative proposal of a reduced (40 mg once daily) starting dose of Cabometyx in patients with mild or moderate hepatic impairment can be justified in order to minimize risk of treatment-related AEs due to elevated cabozantinib plasma exposures in these patient populations. Cabometyx is not recommended for use in patients with severe hepatic impairment.

Cabozantinib was metabolized in vivo. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: XL184 N oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6 desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N oxide and XL184 amide cleavage product), which possess <1% of the on-target kinase inhibition potency of parent cabozantinib, each represent <10% of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism in vitro, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction).

The plasma terminal half-life of cabozantinib in single dose studies in healthy volunteers is approximately 120 hours. Mean clearance (CL/F) at steady-state in cancer patients was estimated to be 4.4 L/hr in a population PK analysis. Within a 48 day collection period after a single dose of 14C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Data obtained in study XL184-017 to assess the PK of cabozantinib in subjects with impaired renal function was assessed as part of variation II/11 for Cometriq. The results of Study XL184-017 in subjects with mild or

moderate impaired renal function showed that C_{max} and AUCs (AUC_{0-t} and AUC_{0-inf}) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function when given a 60 mg dose. Both C_{max} and AUC values (AUC_{0-t} and AUC_{0-inf}) of cabozantinib appeared to be similar between the moderate impairment and the control cohorts (differences: less than 3% and 7%, respectively). The CHMP considered that in light of the safety profile of cabozantinib at the recommended starting dose of 140 mg, a 30% increase in AUC in case of mild renal impairment warrants caution, in line with the caution advised in case of interaction between cabozantinib and CYP3A4 inhibitors. Therefore, a warning has been included in the SmPC regarding dosing in renal impairment.

There is little experience with cabozantinib in non-White patients (see SmPC sections 4.2 and 5.2).

No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended.

Cabozantinib has not yet been investigated in the paediatric population. The lack of data in the population <18 years is indicated in the SmPC (see section 4.2).

Cabozantinib is a substrate for CYP3A4 and to a lesser extent CYP2C9. Co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution. Chronic co-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [Hypericum perforatum]) with cabozantinib should be avoided. Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered (see SmPC sections 4.2, 4.4 and 4.5).

Non-conjugated metabolites are present only at relatively low (total as well as unbound) levels, and are less active than cabozantinib. Low activity of the relatively abundant XL184 monohydroxysulphate and 6 demethyl half-dimer sulfate metabolite was observed. Therefore, cabozantinib parent is indicated to be pivotal for its cabozantinib's PD activity.

Considering the limited importance of a number of metabolites (<10% of parent cabozantinib) further data regarding into identification of UGT pathways (leading to M3 and M8) and carboxyamidases (leading to M7) are not considered necessary. However, considering the importance of the 6-demethyl half-dimer sulfate (M2a) and XL184 monohydroxy sulfate (M9), the applicant was recommended (as part of Cometriq's MA) to perform further in vitro experiments on the identification of the sulphotransferases responsible for formation of 6-demethyl half-dimer sulfate (M2a) and XL184 monohydroxy sulfate (M9) metabolites. The results of this study were assessed as part of variation II/07 for Cometriq.The sulphotransferases involved in the metabolism of EXEL-5526 (XL184 monohydroxy) and EXEL-1744 (XL184 mono-desmethyl hydroxy amide cleavage product) have been identified. Multiple SULTs are involved for both metabolites, i.e., SULT1A1, SULT1A2, SULT2A1 and SULT1A3 for EXEL-5526, and SULT1A1, SULT1A2, SULT1A3 and SULT1E1 for EXEL-1744. It was further demonstrated that back-transformation of cabozantinib XL184 does not occur upon deconjugation of EXEL-1646 and EXEL-1644.

At the time of granting the marketing authorisation of Cometriq, the MAH was requested to conduct an additional study to assess interactions with drugs affecting gastric pH as part of the pharmacovigilance plan of the risk-management plan (RMP). In variation II/06, the MAH submitted the results of a Drug-Drug Interaction Study XL184-018 with medicinal products affecting gastric pH, esomeprazole and Famotidine. Results from the phase I drug-drug interaction study XL184-018 to investigate the effect of esomeprazole on the single-dose plasma pharmacokinetics of cabozantinib (XL184) demonstrated that co-administration of multiple doses esomeprazole 40 mg did not result in any statistically significant decrease in cabozantinib plasma PK

parameters. Therefore, no clinically significant drug-drug interaction in subjects taking both cabozantinib and a proton pump inhibitor was considered likely.

At the time of granting the marketing authorisation of Cometriq, the MAH was requested to conduct an additional nonclinical Study XL184-NC-039 evaluating Cabozantinib as a Substrate and Inhibitor of a Panel of Human Drug Transporters (MEA 006) as part of the pharmacovigilance plan of the risk-management plan (RMP). The MAH submitted the results of this study in variation II/05 for Cometriq. Cabozantinib may be a substrate of transporter MRP2, but not of the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BRCP, BSEP or P-gp. In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations (see SmPC section 4.4).

Cabozantinib demonstrated the potential to inhibit drug transporters MATE1 and MATE2-K (estimated IC_{50} values of 5.94 and 3.12 µM, respectively), but showed no marked inhibition of BRCP, BSEP, MRP2, P-gp, OAT1, OAT3, OCT1, OATP1B1 and OATP1B3 (i.e., IC_{50} values exceeded the assay incubation concentration evaluated of 15 µM, or the cabozantinib solubility limit). In principle therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered concomitant medications that are substrates of MATE1 or MATE2-K. However, although cabozantinib is an inhibitor of drug transporters MATE1 and MATE2-K in vitro, the risk of a clinically-relevant drug interaction by cabozantinib inhibition in vivo appears unlikely, since the IC_{50} (3-6 µM) is > 50 fold the unbound Cmax of 40 nM.

Cabozantinib is an inhibitor of P-gp in vitro. A warning against combination of cabozantinib and P-gp substrates has been included in the SmPC (see sections 4.4 and 4.5). At present, the outcome of different in vitro P-gp inhibition studies are not in agreement, precluding taking a decision on the need of an in vivo study. In the currently provided studies, cabozantinib (50 µM final concentration) showed minimal inhibition potential of P-gp mediated transport activities in a Caco-2 cell assay system. However, an IC_{50} of 7.0 µM for P-gp transport activities was determined previously for cabozantinib in a bi-directional assay system using MDCK-MDR1 cells (Study Report No. XL184-Disc-037). Therefore, cabozantinib may still have the potential to increase plasma concentrations of coadministered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended (see SmPC section 4.5).

Though cabozantinib is known to inhibit multiple RTKs involved in tumour growth and angiogenesis and metastatic progression of cancer, the precise mechanism of action of cabozantinib is not known. In line with the in vitro data regarding inhibition of multiple RTKs, certain pathways indeed appeared to be affected in vivo upon treatment with 175 mg cabozantinib (S)-malate (138 mg cabozantinib freebase), as shown by changes in biomarkers related to inhibition of VEGF, MET and KIT. Overall, the pattern of plasma marker modulation measured after cabozantinib exposure, with a significant increase in the circulating levels of VEGF and PlGF, and significant decreases in soluble forms of cabozantinib target receptors sVEGFR2 and sKIT after 29 days of treatment, is consistent with results reported for other inhibitors of the VEGFR2 signalling pathway, such as sunitinib and bevacizumab. Exposure to cabozantinib led to inhibition of the VEGFR2 and KIT receptors and downstream signalling pathways. The exposure-dependency of the VEGF, PlGF, VEGFR2 and KIT biomarkers to concurrent cabozantinib concentration was statistically significant, though modest. Therefore, a target concentration for optimal PD effects cannot be derived from this analysis.

According to current guidelines, additional ECG data are considered appropriate if a new indication or patient population are being pursued. The applicant investigated QT interval effects of the 60 mg daily dose in the XL-184-308 study. Two QTc F prolongation events > 500ms were observed by investigator assessments in the pivotal study. No events were observed by Independent Central Review. However, due to sustained uncertainty regarding an effect on QTc-prolongation even when administering this considerable lower dose, a warning in Section 4.4 in the SmPC is considered appropriate.

A substantial amount of patients (79% from 140 mg to 100 mg) in the pivotal XL-184-301 study for the MTC indication had to be adjusted to a lower dose. The same was true for patients in the two safety monitoring studies XL184-306 and 307 in advanced castrate-resistant prostate cancer, where a dose reduction rate up to 74 % was observed. Forty % of the patients enrolled in the pivotal phase 3 RCC study (XL-184-308) remained at 60 mg throughout the study period. Ten % discontinued study drug due to adverse events, and this was similar to the everolimus arm.

Due to the expressed concerns regarding the proper dose in the advanced MTC setting, a dose-finding study was required and a post-authorisation measure (SOB 001.2) was adopted during the approval process. The new study in MTC patients is intended to investigate effect and adverse events by cabozantinib treatment in relation to dosing with capsules at 140 and 60 mg. Finalisation of the study is not until 2019.

As a high proportion of patients needed dose reductions also with a starting dose of 60 mg in the RCC setting (to 40mg and 20 mg) there was an uncertainty on whether the benefit/risk balance could be improved with the use of a lower starting dose. The applicant provided additional information on the relation between cabozantinib plasma concentration and effect. Overall, the analyses support the view that the 60 mg dose provides the best anti-tumour response, although there is no significant separation of the three dose levels. As expected, higher predicted risk of individual AEs were simulated for the 60 mg dose vs the 40 mg and 20 mg dose levels, although the simulated 40 mg starting dose was not predicted to dramatically reduce the requirement for dose reductions. Overall, the analyses do not provide sufficient evidence to support a change to the current starting dose of 60 mg.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of cabozantinib in the RCC population and the new tablet formulation have been reasonably well characterized. The new data presented in this submission do not alter the understanding of cabozantinib PK.

2.5. Clinical efficacy

Activity of cabozantinib in RCC was first observed in the phase I drug interaction study XL184-008. Afterwards the sponsor initiated a phase III study with a tablet formulation at a dose of 60 mg in subjects with advanced RCC who had received at least one prior VEGFR-TKI.

Table 18 – Clinical studies for Cabozantinib submitted for the current application

Study Identifier	Study title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Patient Population
XL184-308 Efficacy and safety of cabozantinib	A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy. The primary endpoint duration of PFS (among the first 375 randomized subjects), as determined by a blinded central independent radiology committee (IRC) per RECIST 1.1. Secondary endpoints were duration of OS and ORR per IRC (among all randomized subjects).	Open-label, randomized, controlled Crossover between treatment arms was not allowed	Cabozantinib 60 mg tablet; oral qd or everolimus 10 mg; oral qd	Advanced RCC (post VEGFR TKI)
XL184-008 Drug-drug interaction with rosiglitazone; safety and preliminary efficacy	A Phase 1 Drug-Drug Interaction Study of the Effects of XL184 (Cabozantinib) on the Pharmacokinetics of a Single Oral Dose of Rosiglitazone in Subjects with Solid Tumours	Open-label, one sequence, cross-over	Cabozantinib 140 mg qd and rosiglitazone 4mg on Day 1 and Day 22	Metastatic or unresectable solid tumours (DTC or RCC)

2.5.1. Dose response study

No formal dose response studies have been carried out for the RCC indication. The single-agent maximum tolerated dose of cabozantinib was determined to be 140 mg on a daily dosing schedule. This dosing regimen was selected based on the results of the phase I dose escalation XL184-001 study, assessed during Cometriq's initial MA. This is the accepted posology for the cabozantinib locally advanced or metastatic medullary thyroid carcinoma indication.

In the phase I XL184-008 study, a dose of 60 mg was the most frequent last dose and the dose with the longest duration of treatment for RCC subjects. Clinical activity of a starting dose of 60 mg has also been observed in other indications (e.g. castrate resistance prostate cancer and non-small cell lung cancer), higher rates of dose

reductions have been associated with a 100 mg dose and there are apparent lower levels of activity observed at a 40 mg dose.

2.5.2. Main study

A phase 3, randomized, controlled study of cabozantinib (xl184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy

Methods

Study Participants

Inclusion criteria

1. Documented histological or cytological diagnosis of renal cell cancer with a clear-cell component.
2. Measurable disease per RECIST 1.1 as determined by the investigator.
3. Must have received at least one VEGFR-targeting TKI (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib).
4. For the most recently received VEGFR-targeting TKI the following criteria must apply:

    a. Must have radiographically progressed during treatment, or been treated for at least 4 weeks and radiographically progressed within 6 months after the last dose.

    Radiographic progression is defined as unequivocal progression of existing tumour lesions or developing new tumour lesions as assessed by the investigator on CT or MRI scans.

    b. The last dose must have been within 6 months before the date of randomization.
5. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy.
6. Age eighteen years or older on the day of consent.
7. Karnofsky Performance Status (KPS) score of ≥ 70%.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 10 days before randomization:

    a. Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L).

    b. Platelets ≥ 100,000/mm3 (≥ 100 GI/L).

    c. Haemoglobin ≥ 9 g/dL (≥ 90 g/L).

    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal.

    e. Total bilirubin ≤ 1.5 × the upper limit of normal. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L).

    f. Fasting serum triglycerides ≤ 2.5 × upper limit of normal AND total cholesterol ≤ 300 mg/dL

(≤ 7.75 mmol/L). Lipid-lowering medication is allowed.

g. HbA1c ≤ 8%. For subjects with a condition (eg, hemoglobin variant) that affects the interpretation of HbA1c results, a fasting glucose ≤ 160 mg/dL (≤ 8.9 mmol/L).

h. Serum creatinine ≤ 2.0 × upper limit of normal or calculated creatinine clearance

≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockroft-Gault equation (see Table 5-2 for Cockroft-Gault formula).

i. Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g.

9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document

10. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception during the course of the study and for 4 months after the last dose of study treatment.

11. Female subjects of childbearing potential must not be pregnant at screening.

Exclusion criteria

1. Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (eg, temsirolimus), or cabozantinib.

2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization.

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

4. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomization. Systemic treatment with radionuclides within 6 weeks before randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

5. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization.

6. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

7. Chronic treatment with corticosteroids or other immunosuppressive agents (with the exception of inhaled or topical corticosteroids or corticosteroids with a daily dosage equivalent ≤ 10 mg prednisone if given for disorders other than renal cell cancer). Subjects with brain metastases requiring systemic corticosteroid are not eligible.

8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders:

i. Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.

ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.

iii. Stroke (including TIA), myocardial infarction, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before randomization.

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

i. Tumours invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

ii. Abdominal fistula, gastrointestinal perforation, bowel obstruction, or intra-abdominal abscess within 6 months before randomization.

Note: Complete healing of an intra-abdominal abscess must be confirmed before randomization

c. Clinically significant haematuria, hematemesis, or haemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary haemorrhage) within

3 months before randomization.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) - related illness, or chronic hepatitis B or C infection.

ii. Serious non-healing wound/ulcer/bone fracture.

iii. Malabsorption syndrome.

iv. Uncompensated/symptomatic hypothyroidism.

v. Moderate to severe hepatic impairment (Child-Pugh B or C).

vi. Requirement for haemodialysis or peritoneal dialysis.

vii. History of solid organ transplantation.

9. Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 2 months before randomization.

10. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 msec within 10 days before randomization. Three ECGs must be performed. If the average of these three consecutive results for

QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

11. Pregnant or lactating females.

12. Inability to swallow tablets or capsules.

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

14. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low grade tumours deemed cured and not treated with systemic therapy.

Treatments

Subjects who met all the study eligibility criteria were randomly assigned to either cabozantinib or everolimus.

Table 19 – Treatment aspects

Treatments	Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd) - yellow film coated tablets	Everolimus arm: Oral everolimus (10 mg) once daily (qd)
Prior therapy/ concomitant therapy	Prior and subsequent cancer and radiation therapies were recorded by study site staff. No concurrent investigational agents were permitted. All medications used by the subject during the period from 28 days before randomization through 30 days after the date of the decision to permanently discontinue study treatment were recorded in the CRFs.	
First dose	The first dose of study treatment was to be taken in the clinic (defined as Week 1 Day 1; W1D1). The subject was instructed to fast (with the exception of water) for at least 2 hours before receiving study treatment. Subjects were given their assigned treatment, either 60 mg oral cabozantinib with a minimum of 240 mL of water or 10 mg of everolimus with a glass of water and then continued to fast for 1 hour while under observation to monitor for potential AEs.	
Treatment phase/ duration of treatment	Subjects received treatment as long as they continue to experience clinical benefit in the opinion of the investigator (including after progression) or until there was unacceptable toxicity or the need for subsequent systemic anticancer treatment.	
Dose reduction/ treatment delay	Dose reductions for cabozantinib were allowed for unacceptable toxicity, and doses may have been modified at any time. First dose level reduction to 40 mg, second dose reduction to 20 mg. Dose interruption and reduction criteria recommendations for cabozantinib in order to manage treatment-related AEs were according to toxicity criteria (CTCAE v4). Dose reductions for everolimus were allowed for management of severe or intolerable adverse reactions. If dose reduction was required, the suggested dose was approximately 50% lower than the daily dose previously administered; investigators were instructed to refer to the most recent product package insert/drug label for detailed instructions.	

Maintenance Phase	When sufficient data had been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects could continue study treatment and enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considered that the safety and efficacy profile of the drug had been sufficiently established for regulatory purposes.
Subject withdrawal	Subjects could discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice.
Crossover	Not permitted.

Objectives

The objective of the study was to evaluate the effect of cabozantinib compared with everolimus on progression-free survival (PFS) and overall survival (OS) in subjects with advanced renal cell cancer that had progressed after prior VEGFR tyrosine kinase inhibitor therapy.

Outcomes/endpoints

Table 20 – Outcomes and endpoints

Primary endpoint	
Progression-free survival	The primary efficacy variable was duration of PFS as assessed by the IRC per RECIST 1.1 and was defined as the time from randomization to the earlier of the following events: documented PD per RECIST 1.1 or death due to any cause.
Secondary endpoints	
Overall survival	Survival status was determined at scheduled visits and every 8 weeks (± 7 days) after the Post-Treatment Follow-up Visit. Subjects were followed until death, consent withdrawn or Sponsor decision to no longer collect these data.
Objective response rate (ORR)	The ORR was defined as the proportion of subjects for whom the best overall response at the time of data cut-off was complete response (CR) or partial response (PR) as assessed by the IRC per RECIST 1.1, which was confirmed by a subsequent visit ≥ 28 days later.
Additional endpoints	
Duration of radiographic response	Duration of response (DOR) was defined as the time from the first tumour assessment that documented PR or CR that was subsequently confirmed at least 28 days later until the date of documented progression by IRC, per RECIST 1.1
Changes in bone scans	A bone scan response was defined as ≥ 30% decrease from baseline in the bone scan lesion area compared to baseline, evaluated by the central IRC. Stable Disease, Not meeting the criteria for responder, progressive disease, or unable to evaluate, Greater than 30% increase from baseline in bone scan lesion area in areas attributable to metastatic disease; or two or more new areas of radiotracer uptake attributable to metastatic disease in regions of bone that had not previously shown radiotracer uptake. A central radiology vendor was used to quantitate bone scan tumour burden using computer-assisted detection (CAD) to measure bone scan lesion area and defined criteria for response.

Safety and tolerability	Safety analyses were performed using the Safety population (those that received at least one dose of study treatment) New or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment (related SAEs at any time) were documented. Adverse event information was collected at study visits and may also have been collected at any time over the phone or by spontaneous subject report. Adverse event seriousness, severity grade, and relationship to study treatment were assessed by the investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4. An event was assessed as related to study treatment when there was a reasonable possibility that the study treatment caused the event. Routine safety evaluations included physical examination, vital signs, performance status, 12-lead ECG, haematology, serum chemistries, lipid tests, coagulation tests, urine tests, serum pregnancy tests (in females of childbearing potential), and thyroid function tests.
Characterization of the pharmacokinetics (PK) of cabozantinib	Limited PK blood samples were obtained from all subjects in both the cabozantinib and everolimus arms.
Change in kidney-cancer related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19)	The FKSI-19 instrument is a 19-item self-reported questionnaire that assesses the most important disease-related symptoms (DRS), treatment side effects, and function/well-being associated with advanced kidney cancer. The FKSI instrument has been utilized in other pivotal TKI studies in RCC. Self-completed by the subject. Subjects were to complete the questionnaires prior to each clinic visit or if completed on the day of the visit, before seeing the study site personnel.
Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)	The standardized measure of health status EQ-5D-5L, developed by the EuroQol, was used in order to provide a generic measure of health for clinical and economic appraisal Self-completed by the subject. Subjects were to complete the questionnaires prior to each clinic visit or if completed on the day of the visit, before seeing the study site personnel.
Proportion of subjects with post-randomization skeletal-related events (SREs)	Skeletal-related events were defined as any one of the following: Radiation therapy to bone, including the use of bone-targeted radiopharmaceuticals, Pathological fracture, Spinal cord compression, Surgery to bone
Biomarkers	Relationship of baseline and changes in plasma biomarkers, serum bone markers, serum calcium, and circulating tumour cells (CTCs) with treatment and/or clinical outcome
Health care resource utilization	This data included hospital admissions, emergency room visits, intensive care unit admissions, length of stay and relevant procedures (e.g., surgeries, transfusions).

Tumour assessments

Screening occurred ≤ 28 days before randomization. Scheduling of assessments post randomisation is shown in the table below:

Table 21 – Scheduling of assessments post randomisation

Assessment	Post-Randomization
Tumour assessment: CT/MRI Chest, abdomen, pelvis	CT/MRI of the chest, abdomen, and pelvis were performed in all subjects at screening and every 8 weeks (±5 days) after randomization (at W9D1, W17D1 etc). Upon completion of 12 months on study, these assessments were performed every 12 weeks (± 7 days). CT/MRIs were performed per the protocol-defined schedule regardless of whether study treatment was reduced, held, or discontinued. For subjects who discontinued study treatment before radiographic PD or within 8 weeks* after radiographic PD, final radiographic tumour assessments were performed 8 weeks* after radiographic PD. For subjects who continued to receive study treatment for more than 8 weeks* after radiographic PD, tumour assessments were continued per the protocol-defined schedule until study treatment was permanently discontinued (*12 weeks for subjects remaining on study treatment for more than 1 year.)
Tumour assessment: MRI/CT Brain	MRI (or CT) of the brain was performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain were only required in subjects with known brain metastasis. Assessments were performed every 8 weeks (± 5 days) throughout the first 12 months on study. Upon completion of 12 months on study, these assessments were performed every 12 weeks (± 7 days). (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 3 months before randomization. Subjects without documented brain metastasis during the screening assessment were not required to undergo post-randomization brain imaging unless clinically indicated). MRI/CTs were performed per the protocol-defined schedule regardless of whether study treatment was reduced, held, or discontinued. For subjects who discontinued study treatment before radiographic PD or within 8 weeks* after radiographic PD, final radiographic tumour assessments were performed 8 weeks* after radiographic PD. For subjects who continued to receive study treatment for more than 8 weeks* after radiographic PD, tumour assessments were continued per the protocol-defined schedule until study treatment was permanently discontinued. (*12 weeks for subjects remaining on study treatment for more than 1 year.)
Tumour assessment: Bone scan Whole body	Technetium bone scans were performed in all subjects at screening. After randomization, bone scans were performed only in subjects with known bone metastasis every 16 weeks (± 7 days) throughout the first 12 months on study. Upon completion of 12 months on study, these assessments were performed every 24 weeks (± 14 days). (Note: subjects without documented bone metastasis during the screening assessment were not required to undergo post-randomization bone scan imaging unless clinically indicated). Bone scan evaluations ended on the date of the last CT/MRI scan. If the bone scan schedule did not coincide with the last CT/MRI scan, no additional bone scan was needed after the last CT/MRI was performed.

Independent radiology committee

For the purpose of determination of the study endpoints of PFS and ORR, a central IRC reviewed all available radiographic studies. The IRC was blinded to treatment identity and to clinical data that may lead to inadvertent unblinding.

Only adequate tumour assessments (ATAs) were considered in the determination of progression and censoring dates. An adequate tumour assessment was defined as an evaluation performed per RECIST 1.1 that resulted in an overall response assessment of complete response (CR), partial response (PR), stable disease (SD), PD, or not applicable (NA; no target lesion identified at baseline). Unless PD was otherwise evident, partially missing tumour data or indeterminate lesions for a particular tumour assessment resulted in an overall response of "not evaluable" and the tumour assessment was not considered adequate. The recorded progression date was defined as the date of the tumour assessment visit at which progression was declared.

Sample size

The study was designed to provide adequate power for event-driven analyses of both PFS and OS. The median PFS and OS estimates for the everolimus arm were based on values published from the RECORD-1 study which compared everolimus with placebo in subjects with RCC that had progressed on prior treatment with VEGFR inhibitors.

For the primary endpoint of PFS, assuming exponential PFS, proportional hazards, and a 1:1 treatment allocation ratio, 259 events were required to provide 90% power to detect an HR of 0.667 (5 months in the everolimus arm vs 7.5 months in the cabozantinib arm) using the log-rank test and a 2-sided significance level of 5%. Under this design, the minimum observed effect that would result in statistical significance for PFS was a 27.8% improvement (HR = 0.783) in PFS from 5 to 6.39 months when 259 events were observed in the first 375 subjects randomized into the study.

For the key secondary efficacy endpoint of OS, assuming a single interim analysis at the 33% information fraction (at the time of the primary analysis of PFS) and a subsequent primary analysis, 408 deaths were required to provide 80% power to detect a HR of 0.75 (15 months in the everolimus arm vs 20 months in the cabozantinib arm) using the log-rank test and a 2-sided significance level of 4%. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS was a 22.5% improvement (HR=0.816) in OS from 15 to 18.38 months.

Using an average accrual rate of 32 subjects per month and a 1:1 treatment allocation ratio, a total of 650 subjects (325 per treatment arm) were required to observe the required number of events within the planned study duration (21 months accrual; approximately 17 months to observe the required PFS events among 375 subjects and approximately 36 months to observe the required deaths for OS among 650 subjects).

Randomisation

Eligible subjects were randomized in a 1:1 ratio to either the cabozantinib or everolimus treatment arm. The study site used an interactive voice record system (IVRS) or interactive Web record system (IWRS) for randomization.

Randomization was stratified by the following factors:

- Number of prior VEGFR-targeting TKI therapies: 1 vs 2 or more

  Number of risk factors per Memorial Sloan-Kettering Cancer Center prognostic criteria for previously treated patients with RCC (Motzer 2004): 0 vs 1 vs 2 or 3

- Risk factors are the following:
- Karnofsky performance status score < 80%
- Haemoglobin < 13 g/dL (< 130 g/L) for males and < 11.5 g/dL (< 115 g/L) for females
- Corrected calcium > upper limit of normal

Blinding (masking)

The pivotal study had an open-label design.

Statistical methods

Analysis of primary endpoint: Progression-Free Survival (PFS)

The primary efficacy endpoint was duration of PFS in the first 375 subjects randomized (PITT population). Duration of PFS was defined as the time from randomization to the earlier of the following events: disease progression as determined by the IRC per RECIST 1.1 or death due to any cause.

PFS (months) = (earliest date of progression, death, or censoring -date of randomization+ 1)/30.4375

It was estimated that 375 subjects would be adequate to evaluate the primary endpoint of PFS alone. However, a much larger sample size would be needed to provide reasonable power for OS. As a result, the number of events necessary to trigger the primary analysis of PFS may occur before the study was fully accrued and the PFS events may be biased toward patients who progressed early. Thus, to allow longer, more robust PFS follow up among a fewer number of subjects, the primary analysis of PFS would be conducted after at least 259 PFS events had been observed among the first 375 randomized patients and the enrolment of 650 subjects had been completed. Only the first 375 subjects randomized would be included in the population for the primary PFS analysis (PITT population).

Hypothesis testing between the two treatment arms was performed using the stratified log-rank test with a 2-sided 0.05 level of significance. The stratification factors were those used to stratify the randomization.

The median duration of PFS and the associated 95% confidence interval for each treatment arm was estimated using the Kaplan-Meier method. The hazard ratio (HR) was estimated using a Cox regression model and included the same stratification factors described above.

Determination of a HR of < 1 and a statistically significant p-value for the stratified log-rank test would result in rejection of the null hypothesis of no difference in PFS and inference that PFS was superior in the group receiving cabozantinib compared with the group receiving everolimus.

Censoring

- Subjects who received subsequent anticancer therapy (including radiation other than to bone) before experiencing an event were right censored at the date of the last adequate tumour assessment on or prior to the date of initiation of subsequent treatment.
- Subjects who received tumour resection surgery post-randomization before experiencing an event were right censored at the date of the last adequate tumour assessment on or prior to the date of the surgery.
- Subjects who had not experienced an event (and were not otherwise censored) at the time of data cutoff were right censored on the date of their last adequate tumour assessment.

- Subjects who missed two or more consecutive scheduled tumour assessments immediately followed by an event were right censored on the date of their most recent ATA prior to the missing/inadequate assessments.
    - If the two or more consecutive missing adequate assessments were immediately followed by an adequate assessment with an overall response assignment of SD, PR, or CR, this was deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations were ignored.

Sensitivity analyses

To demonstrate robustness of the primary analysis, supportive (sensitivity) analyses of duration of PFS used the following alternative definitions of progression events and censoring schemes:

- To correct for potential ascertainment bias in follow-up schedules between the two treatment arms, an analysis designated PFS2 in the SAP defined the date of radiographic progression (as determined by IRC) as the scheduled tumour assessment date.
- To evaluate PFS based upon investigator claims, an analysis designated PFS3 included death and the following as progression events: investigator assessment of radiographic progression, clinical deterioration, initiation of subsequent anticancer therapy and surgery that impacted tumour lesions.
- To evaluate PFS based upon investigator assessment of radiographic progression, an analysis designated PFS4 included deaths and progression events based on the investigator (rather than IRC) assessment of radiographic progression. Clinical deterioration determined by the investigator was not considered to be a progression event.
- To explore the effect of potentially informative censoring, four sensitivity analyses, designated PFS11-14 in the SAP, were conducted by reclassifying subjects censored for potentially informative reasons as events differentially between the treatment arms in various patterns. In the most conservative of these analyses, PFS14, all subjects with potentially informative censoring were counted as events in the cabozantinib arm and remained censored in the everolimus arm.
- The primary analysis (PFS1) was repeated in the ITT population.

Testing of key secondary endpoints

Formal hypothesis testing was planned for key secondary efficacy endpoints (duration of OS and ORR).

Overall survival (OS)

Duration of OS = (Date of death or censoring – date of randomization) + 1

For subjects who were alive at the time of data cut-off or were permanently lost to follow-up, duration of OS was right censored at the earlier of the data cut-off date or the date the subject was last known to be alive.

Formal hypothesis testing of OS was performed using the stratified log-rank test with the same stratification factors as for PFS analyses using the entire ITT population and was repeated for the PITT population. The stratification factors were the same used to stratify the randomization.

The median duration of OS was estimated using the Kaplan-Meier method. The HR was estimated using a Cox regression model with treatment arm as the only main effect and stratifying by the same stratification factors as were used for the log-rank test.

A prespecified single interim analysis for the key secondary efficacy endpoint of OS was conducted at the time of the primary analysis of PFS. The information fraction was 49% for OS (202 deaths were observed out of 408 required for the final OS evaluation). Type I error for the interim analysis was controlled by a Lan-DeMets O'Brien-Fleming alpha spending function to account for the actual information fraction at the time of the interim analysis (critical value 0.0019).

Objective response rate (ORR)

The ORR was defined as the proportion of subjects who have measurable disease at baseline for whom the best overall response (BOR) at the time of data cut-off was complete response (CR) or partial response (PR) as assessed by the IRC per RECIST 1.1, which was confirmed by a subsequent visit ≥ 28 days later. Only time points prior to the date of censoring triggers defined in the corresponding PFS analysis were considered for BOR analyses. The primary analysis of ORR used the ITT population. The ORR was also calculated for the PITT population. Subjects who did not have any post-baseline tumour assessments were counted as non-responders.

Hypothesis testing was performed using the 2-sided chi-squared test at the 0.01 α level.

Point estimates of ORR, the difference in response rates between the two treatment arms, and associated confidence intervals were provided. Confidence intervals were calculated using exact methods.

Interim analyses

A prespecified single interim analysis for the key secondary efficacy endpoint of OS was conducted at the time of the primary analysis of PFS. The information fraction was 49% for OS (202 deaths were observed out of 408 required for the final OS evaluation). Type I error for the interim analysis was controlled by a Lan-DeMets O'Brien-Fleming alpha spending function to account for the actual information fraction at the time of the interim analysis (critical value 0.0019). The protocol does not include criteria for early stopping for futility. Testing between the two treatment arms was performed by the stratified log-rank test with the same stratification factors as for PFS analyses. The median duration of OS was estimated using the Kaplan-Meier method. The stratified HR was estimated using a Cox regression model with treatment arm as the main effect and the above stratification factors.

By 31 December 2015 a second, unplanned interim analysis was conducted. The information fraction was 78% (320 deaths) and minimum 13 months follow-up. Survival status was determined for the majority (97.6%) of the 658 randomized subjects. The study was designed to test OS at the 2-sided 4% alpha level. The Lan-DeMets O'Brien-Fleming alpha spending function specified in the SAP that was applied to control Type 1 error at the prior planned interim analysis was also applied at this current unplanned analysis. The critical value for rejecting the null hypothesis at the current analysis was $p<0.0163$.

Handling of multiplicity

The multiplicity issue resulting from analysis of one primary endpoint (PFS), two key secondary efficacy endpoints (ORR and OS), and performing one interim analysis (of OS) was addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha spending function.

The primary endpoint (PFS) was tested using a 2-sided 5% significance level. If this was positive the two secondary endpoints could be looked at. OS was to be tested at 2-sided 0.04 level and ORR at 2-sided 0.01. For

OS there was an interim analysis planned at the time of the primary PFS analysis which had a critical value of 2-sided 0.0019. A second interim analysis (unplanned) was conducted with cut-off date 31 December 2015 to give a minimum of 12 months follow-up from the last subject enrolled. The primary OS analysis will be conducted after 408 deaths are observed in the study. The primary ORR analysis was conducted at the same time at the PFS analysis.

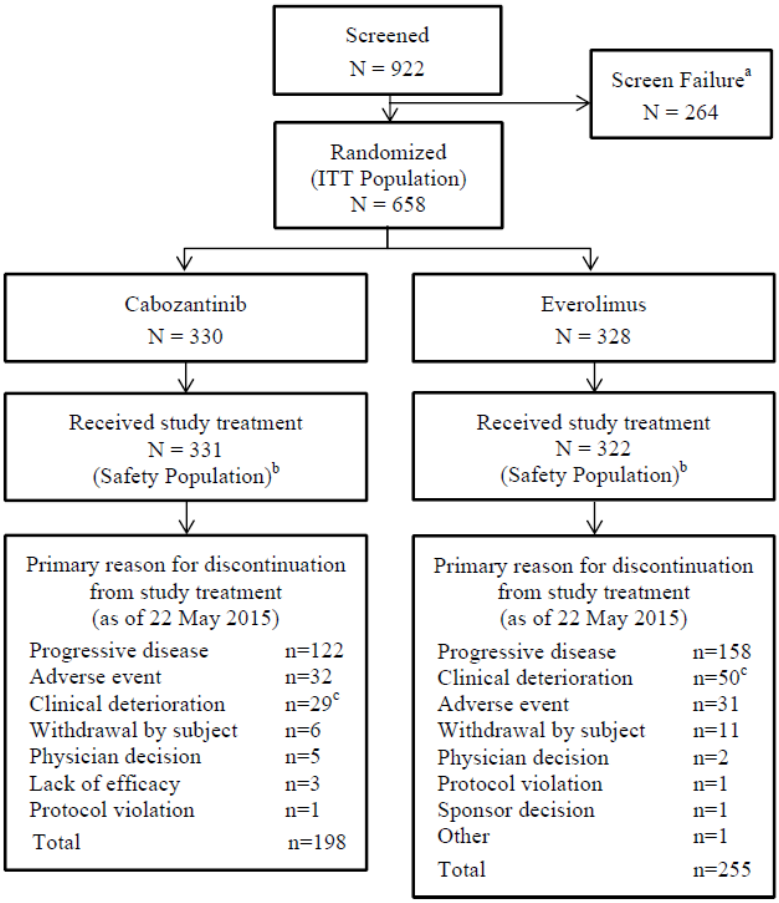
P-values for tests of all other endpoints and subgroup analyses are considered descriptive.

Results

Participant flow

A total of 658 subjects (ITT population) were randomized to receive cabozantinib (n = 330) or everolimus (n = 328). The participant flow is illustrated in the diagram below:

Figure 5 – Participant flow



Clinical deterioration comprises AEs or SAEs related to disease progression.

[a] Screen failure reasons are provided in Table 9.

[b] Five subjects randomized to the everolimus arm did not receive study treatment. In addition, one subject (Subject 1417-3624) randomized to receive everolimus received cabozantinib as study treatment; this subject was evaluated in the cabozantinib arm for the Safety population.

[c] Subject 1417-3624 was randomized to receive everolimus but received cabozantinib and discontinued study treatment due to clinical deterioration. Discontinuation reasons are shown in the flow chart for the Safety population, but the source table summarizes the ITT population.

Recruitment

A total of 658 subjects were randomized in 25 countries: 36% were enrolled in North America, 49% in Europe, 13% in Asia Pacific (includes Australia), and 1.8% in Latin America. There were a total of 181 investigators at 173 unique sites (including 3 sites that were satellites of other sites) in 25 countries. Countries that had 10 or more sites included the United States (70), Germany (18), Australia (14), Canada (14), Spain (13), United Kingdom (13), France (11) and Italy (10).

The first subject was enrolled 8 August 2013. The data cut-off date for the primary analysis was 22 May 2015, providing a minimum follow-up of approximately 5.9 months. The study was still ongoing at the time of the application with data in this report up to 31 Dec 2015.

Conduct of the study

There was one amendment to the original protocol in addition to several country-specific amendments.

Protocol Amendment 1.0 (17 April 2014) had the following key changes:

- A Maintenance Phase was added to the Treatment Period to be implemented when sufficient data had been collected to adequately evaluate all study endpoints
- The study population was limited to including approximately 10% of subjects (maximum of approximately 65 subjects) who had previously been treated with antibodies targeting the programmed cell death immune receptor, PD-1, or its ligands, PD-L1/L2
- Two additional study endpoints were added: changes in bone scans and changes in serum calcium from baseline
- Clarifications on the incidence and management of QTcF interval prolongation were added
- Clarifications on imaging including time points of assessments were added

The majority of subjects were enrolled on the original protocol (78% Cabozantinib arm and 76% everolimus arm)

Changes to the Planned Analyses

There were three versions of the SAP. SAP v2 was completed before analysis of the primary endpoint. SAP v3 was completed after analysis of the primary endpoint and contains minor changes in operational conventions that were adopted prior to analysis of the primary endpoint and minor editorial changes. In addition, a second unplanned interim analysis of OS is described in SAP v3 that is to be conducted with a data cut-off of 31 December 2015, providing a minimum of 12 months of follow-up.

The primary endpoint was planned to include at least 259 PFS events (radiographic progression per IRC or death) but actually included 247 events.

Protocol deviations

Eligibility criteria deviations were balanced between the cabozantinib and everolimus arms: a total of 37 subjects (11%) failed at least one eligibility criterion in each treatment arm. The most common deviations in inclusion criteria were not meeting required screening laboratory values within the required time periods and

receipt of the last dose of the most recently received VEGFR-TKI more than 6 months before the date of randomization.

The most common deviations in exclusion criteria were not meeting the required criteria for QTcF by either not performing ECGs in triplicate or by performing ECGs outside of the required time periods (no deviations of triplicate QTcF > 500 ms occurred) and receipt of any type of small molecule kinase inhibitor within two weeks before randomization.

Important protocol deviations that did not involve eligibility criteria were also balanced between treatment arms. The most frequently observed category was randomization irregularities that potentially impacted efficacy. Deviations observed in this category included stratification errors by incorrect determination of the MSKCC risk group or the number of prior VEGFR-TKIs. A high incidence of protocol deviations categorized as 'other' that could have potentially impacted safety or efficacy was also observed (51% in the cabozantinib arm and 44% in the everolimus arm for those potentially impacting safety and 29% in the cabozantinib arm and 28% in the everolimus arm for those potentially impacting efficacy). Deviations in this category that potentially impacted safety included ECGs and vital signs not obtained per protocol, and revised ICF not signed by subject either in a timely manner or not at all (all subjects signed an ICF). Deviations in this category that potentially impacted efficacy included tumour imaging not obtained per protocol and subject HRQOL questionnaires not completed per protocol. A review of these deviations suggested that they did not have a notable impact on the safety or efficacy of the study.

Baseline data

Table 22 - Demographic and Baseline Characteristics (ITT and PITT Populations) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Age (years)				
Median	62.5	62.0	62.0	61.0
(range)	(32, 86)	(31, 84)	(36, 83)	(31, 84)
< 65, n (%)	196 (59)	198 (60)	118 (63)	116 (62)
≥ 65, n (%)	134 (41)	130 (40)	69 (37)	72 (38)
65 to < 75, n (%)	107 (32)	94 (29)	56 (30)	54 (29)
75 to <85, n (%)	26 (7.9)	36 (11)	13 (7.0)	18 (9.6)
≥ 85, n (%)	1 (0.3)	0	0	0
Male, n (%)	253 (77)	241 (73)	142 (76)	130 (69)
Female, n (%)	77 (23)	86 (26)[a]	45 (24)	57 (30)[a]
White, n (%)	269 (82)	263 (80)	157 (84)	147 (78)
Asian, n (%)	21 (6.4)	26 (7.9)	12 (6.4)	20 (11)
Black/African American, n (%)	6 (1.8)	3 (0.9)	4 (2.1)	2 (1.1)
Other, n (%)	19 (5.8)	13 (4.0)	10 (5.3)	6 (3.2)
Not Reported, n (%)	15 (4.5)	22 (6.7)[a]	4 (2.1)	12 (6.4)[a]
North America, n (%)	118 (36)	122 (37)	76 (41)	64 (34)
Europe, n (%)	167 (51)	153 (47)	83 (44)	84 (45)
Asia Pacific, n (%)	39 (12)	47 (14)	25 (13)	36 (19)
Latin America, n (%)	6 (1.8)	6 (1.8)	3 (1.6)	4 (2.1)
Stratification factors (per CRF), n (%)				
Prior VEGFR-TKI = 1	235 (71)	229 (70)	137 (73)	136 (72)
Prior VEGFR-TKI ≥ 2	95 (29)	99 (30)	50 (27)	52 (28)
MSKCC risk factors = 0 (favorable) (Motzer et al 2004)[b]	150 (45)	150 (46)	80 (43)	83 (44)
MSKCC risk factors = 1 (intermediate)	139 (42)	135 (41)	80 (43)	75 (40)
MSKCC risk factors = 2 or 3 (poor)	41 (12)	43 (13)	27 (14)	30 (16)
Prior VEGFR-TKI = 1, MSKCC risk factors = 0	102 (31)	100 (30)	55 (29)	59 (31)
Prior VEGFR-TKI = 1, MSKCC risk factors = 1	107 (32)	103 (31)	64 (34)	58 (31)
Prior VEGFR-TKI = 1, MSKCC risk factors = 2 or 3	26 (7.9)	26 (7.9)	18 (9.6)	19 (10)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors =0	48 (15)	50 (15)	25 (13)	24 (13)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors = 1	32 (9.7)	32 (9.8)	16 (8.6)	17 (9.0)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors = 2 or 3	15 (4.5)	17 (5.2)	9 (4.8)	11 (5.9)
Heng Prognostic Criteria, n (%) (Heng et al 2009)[c]				
0 adverse factors (favorable risk)	66 (20)	62 (19)	38 (20)	33 (18)
1-2 adverse factors (intermediate risk)	210 (64)	214 (65)	114 (61)	120 (64)
3-6 adverse factors (poor risk)	54 (16)	52 (16)	35 (19)	35 (19)
Karnofsky Performance Status, n (%)[d]				
70	29 (8.8)	22 (6.7)	15 (8.0)	16 (8.5)
≥ 80	301 (91)	306 (93)	172 (92)	172 (91)

Hgb, haemoglobin, (P)ITT, (Primary) endpoint intent-to-treat; IVRS/IWRS, interactive voice recognition/web response system; KPS, Karnofsky Performance Status; LLN (ULN), lower (upper) limit of normal; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a] In addition, gender and race for one subject in the everolimus arm were missing.

[b] KPS < 80%, Hgb < 13 g/dL for males and < 11.5 g/dL for females, corrected serum calcium > ULN

[c] Hemoglobin < LLN, corrected calcium > ULN, KPS < 80%, time from initial diagnosis to initiation of therapy of < 1 year, absolute neutrophil count > ULN, and platelets > ULN

[d] KPS (protocol-permitted scores): 100 (normal activity), 90 (normal activity, minor signs and symptoms), 80 (normal activity with effort, some signs and symptoms), 70 (unable to carry on normal activity or to work, cares for self)

Table 13 - Baseline Disease History and Baseline Status (ITT and PITT) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Diagnosis of RCC with a clear cell component by histology or cytology, n (%)	330 (100)	327 (100)[a]	187 (100)	187 (99)[a]
Time from initial histological/cytological diagnosis to randomization, n (%)				
< 1 year	59 (18)	76 (23)	34 (18)	44 (23)
≥ 1 year	271 (82)	251 (77)	153 (82)	143 (76)
Median (years)	2.8	2.5	2.6	2.4
Current Disease Stage, n (%)				
Stage IV	272 (82)	287 (88)	153 (82)	166 (88)
Stage III	34 (10)	24 (7.3)	20 (11)	13 (6.9)
Unknown	24 (7.3)	16 (4.9)	14 (7.5)	8 (4.3)
Extent of Baseline Disease by IRC, n (%)				
Bone (CT or MRI)	77 (23)	65 (20)	39 (21)	32 (17)
Visceral	241 (73)	245 (75)	139 (74)	142 (76)
Lung	204 (62)	212 (65)	115 (61)	126 (67)
Liver	88 (27)	103 (31)	52 (28)	58 (31)
Brain	2 (0.6)	1 (0.3)	2 (1.1)	1 (0.5)
Lymph Node	206 (62)	199 (61)	124 (66)	110 (59)
Kidney	70 (21)	66 (20)	46 (25)	36 (19)
Other	23 (7)	21 (6.4)	16 (8.6)	10 (5.3)
Number of Involved Organs by IRC, n (%)				
1	59 (18)	56 (17)	31 (17)	31 (16)
2	101 (31)	77 (23)	57 (30)	48 (26)
≥ 3	168 (51)	190 (58)	98 (52)	105 (56)
Missing	2 (0.6)	5 (1.5)	1 (0.5)	4 (2.1)
SoD (mm), median (range)	65.2 (0, 291)	65.0 (0, 258)	70.0 (0, 291)	77.0 (0, 231)
MET Immunohistochemistry Status[b], n (%)				
High	48 (15)	48 (15)	30 (16)	26 (14)
Low	138 (42)	151 (46)	83 (44)	90 (48)
Unknown	144 (44)	129 (39)	74 (40)	72 (38)

IRC, independent radiology committee; (P)ITT, (Primary) Intent to Treat; RCC, renal cell carcinoma; SoD, sum of lesion diameters

a One subject (Subject 4933 3382) had a diagnosis of undifferentiated RCC and is excluded from the numerator. For the other subject (Subject 1522 3098), the pathologist could not verify a clear cell histology because of limited tissue, but a clear cell histology was favoured; this subject is included in the numerator.

b Status of high and low based on cutoff of ≥ 50% of tumour tissue stained with an intensity of 2+ or 3+.

Table 24 - Prior Nephrectomy, Cancer, and Radiation Therapy (ITT and PITT) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Prior nephrectomy, n (%)	283 (86)	279 (85)	157 (84)	153 (81)
Prior systemic non-radiation treatment agents Median (range) per subject	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 6)	1.0 (1, 7)
Number of prior VEGFR-TKI agents per subject, n (%)				
1	235 (71)	229 (70)	137 (73)	136 (72)
2	84 (25)	91 (28)	42 (22)	49 (26)
≥ 3	11 (3.3)	8 (2.4)	8 (4.3)	3 (1.6)
Median (range) per subject	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 4)
Type of prior VEGFR-TKIs, n (%)				
Sunitinib	210 (64)	205 (63)	114 (61)	113 (60)
Pazopanib	144 (44)	136 (41)	87 (47)	78 (41)
Axitinib	52 (16)	55 (17)	28 (15)	28 (15)
Sorafenib	21 (6.4)	31 (9.5)	11 (5.9)	19 (10)
Other VEGFR-TKI	8 (2.4)	10 (3.0)	4 (2.1)	6 (3.2)
Selected prior systemic anti-cancer therapies (non VEGFR-TKI), n (%)				
Bevacizumab	5 (1.5)	11 (3.4)	1 (0.5)	7 (3.7)
Interleukin 2[a]	19 (5.8)	29 (8.8)	10 (5.3)	13 (6.9)
Interferon-α	19 (5.8)	23 (7.0)	6 (3.2)	12 (6.4)
Anti-PD-1/PD-L1/PD-L2 targeting agents	18 (5.5)	14 (4.3)	9 (4.8)	11 (5.9)
Nivolumab[b]	17 (5.2)	14 (4.3)	9 (4.8)	11 (5.9)
Atezolizumab/MDPL3280A[b]	1 (0.3)	0	0	0
First VEGFR-TKI treatment duration, n (%)				
≤ 6 months	88 (27)	102 (31)	54 (29)	62 (33)
> 6 months	242 (73)	224 (68)	133 (71)	126 (67)
Radiographic progression during treatment or within 6 months after last dose of most recent VEGFR-TKI therapy, n (%)	325 (98)	323 (98)	186 (99)	185 (98)
Median time from radiographic progression after most-recent VEGFR-TKI to randomization (months)	1.02	1.25	0.94	1.23
Median (range) types of prior radiation therapies per subject	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 3)
Prior Radiation Therapies, n (%)	110 (33)	108 (33)	56 (30)	61 (32)
EBRT	106 (32)	105 (32)	53 (28)	58 (31)
Brachytherapy	6 (1.8)	4 (1.2)	4 (2.1)	3 (1.6)
Radioisotopes	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)

anti-PD-1, anti-programmed cell death immune receptor-1 or its ligands (PD-L1/PD-L2); EBRT, external beam radiation therapy; (P)ITT, (Primary) Intent to Treat; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

a Note in the post-text tables, interleukin-2 is cited as "interleukins"

b Enrollment of subjects previously treated with agents targeting PD-1 or its ligands (PD-L1/PD-L2) was limited to approximately 10% of the population (a maximum of approximately 65 subjects). Note in the post-text table, nivolumab is cited as "monoclonal antibodies" and atezolizumab is cited as an "investigational drug".

c Other types of EBRT were received by <10% of subjects in either treatment arm

Numbers analysed

Intent-to-Treat (ITT) population

The ITT population, defined as all randomized subjects, was used for efficacy analyses (other than for the primary analysis of PFS), with analyses according to the randomization assignment.

- A total of 658 subjects:
    - 330 cabozantinib
    - 328 everolimus

Safety population and Primary Endpoint Intent-to-Treat (PITT) population

Table 25 - Subject Disposition (Overall Safety and PITT Safety Populations)

	Safety Population		PITT Safety Population	
	Cabozantinib (N = 331) n (%)	Everolimus (N = 322) n (%)	Cabozantinib (N = 187) n (%)	Everolimus (N = 185) n (%)
Subjects who discontinued study treatment	198 (60)	255 (79)	131 (70)	152 (82)
Primary reason for discontinuation from study treatment				
Adverse event (excluding AEs of disease progression)	32 (9.7)	31 (9.6)	21 (11)	20 (11)
Clinical deterioration	29 (8.8)	50 (16)	18 (9.6)	29 (16)
Lack of efficacy	3 (0.9)	0	2 (1.1)	0
Lost to follow-up	0	0	0	0
Protocol violation	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)
Physician decision	5 (1.5)	2 (0.6)	4 (2.1)	2 (1.1)
Withdrawal by subject	6 (1.8)	11 (3.4)	3 (1.6)	7 (3.8)
Sponsor decision	0	1 (0.3)	0	0
Progressive disease	122 (37)	158 (49)	82 (44)	92 (50)

Non-PITT population

The non-PITT population consisted of all subjects randomized after the first 375 subjects

- 283 subjects:
    - 143 cabozantinib
    - 140 everolimus

Per-Protocol Population

A Per-Protocol (PP) population was planned but never fully defined, and analyses of the PP population were not performed.

Pharmacokinetic (PK) population

All subjects in the safety population that had at least one reported plasma PK

Outcomes and estimation

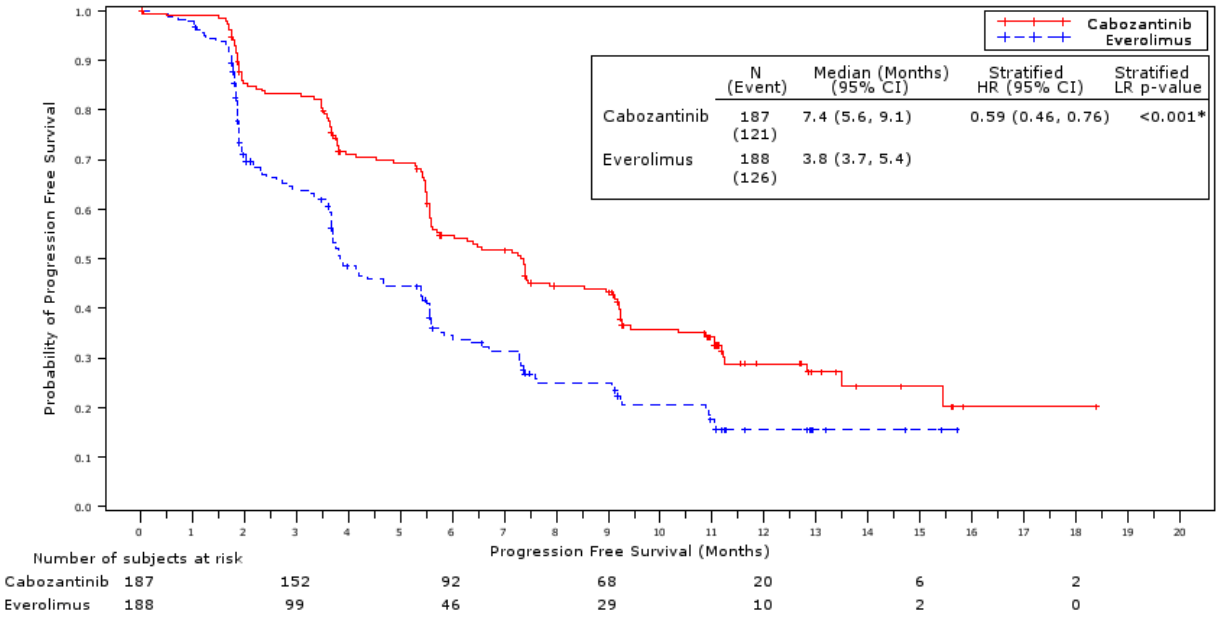
Primary endpoint - Progression-Free Survival (PFS)

Table 26 - Study XL184-308: Progression-Free Survival per IRC through the 22nd May 2015 Cut-Off Date (PITT Population)

	Cabozantinib (N=187)	Everolimus (N=188)
Number (%) of Subjects		
Censored	66 (35)	62 (33)
2 or more missed ATA prior to event	1 (0.5)	5 (2.7)
Anti-cancer therapy	24 (13)	31 (16)
No event by last ATA	39 (21)	23 (12)
No post-baseline ATA	0	3 (1.6)
Surgery	2 (1.1)	0
Event	121 (65)	126 (67)
Death	8 (4.3)	13 (6.9)
Documented progression	113 (60)	113 (60)
Duration of progression-free survival (months)		
Median (95% CI) [a]	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
25th percentile, 75th percentile[a]	3.7, 13.5	1.9, 9.1
Range	0.03+, 18.4+	0.03+, 15.7+
p-value (stratified log-rank test)[b]	<0.001	
Hazard ratio (95% CI; stratified)[c]	0.59 (0.46, 0.76)	
p-value (unstratified log-rank test)	<0.001	
Hazard ratio (95% CI; unstratified)	0.59 (0.46, 0.76)	
Landmark estimates (percent of subjects event-free)	Cabozantinib (N=187)	Everolimus (N=188)
6 months	55%	34%
12 Months	29%	15%
18 Months	20%	NE
24 months	NE	NE

+ indicates a censored observation; ATA, adequate tumor assessment; CI, confidence interval; IRC, independent radiology committee, NE, not estimable; PFS, progression-free survival; PITT, primary endpoint intent-to-treat. [a] Median and percentiles are based on Kaplan-Meier estimates. [b] Stratification factors were prior VEGFR-targeting TKI therapy (1 vs 2 or more) and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2 or 3; Motzer et al 2004). [c] Estimated using the Cox proportional hazard model adjusted for stratification factors. HR <1 indicates PFS in favor of cabozantinib.

Figure 6 - Study XL184-308: Kaplan-Meier Plot of Progression-Free Survival per IRC through the 22nd May 2015 Cut-Off Date (PITT Population)



HR, hazard ratio; IRC, independent radiology committee, LR, log-rank test; PITT, primary endpoint intent-to-treat * indicates p-value ≤ 0.05. Source: XL184-308

Secondary endpoints

Overall survival

First planned Interim Analysis - 22nd May 2015

The interim analysis demonstrated a trend in improvement in duration of OS for subjects in the cabozantinib arm compared to everolimus. The HR, adjusted for stratification factors was 0.68 (95% CI: 0.51, 0.90; stratified log-rank p-value = 0.006). The OS results nearly meet the criteria required to reject the null hypothesis at the interim analysis; the critical p-value was ≤ 0.0019 (HR ≤ 0.645). Results for the unstratified ITT analysis were similar to those of the stratified test.

Table 27 - Study XL184-308: Interim Analysis of Overall Survival through the 22nd May 2015 Cut-Off Data (ITT Population)

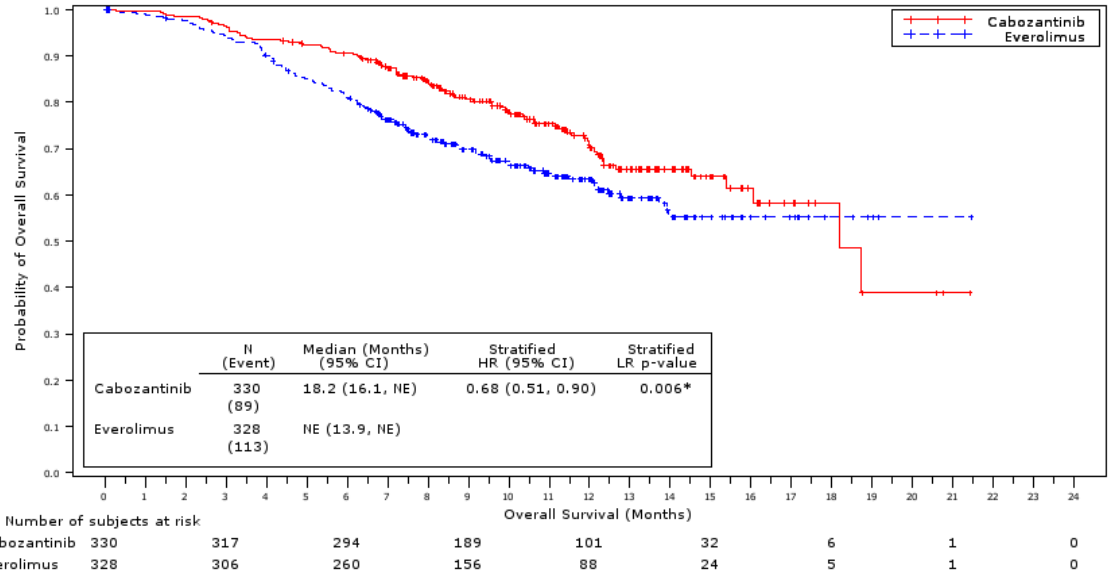
	Cabozantinib (N=330)	Everolimus (N=328)
Number (%) of Subjects		
Censored	241 (73)	215 (66)
Death	89 (27)	113 (34)
Duration of overall survival (months)		
Median (95% CI)	Not yet estimated	
25th percentile, 75th percentile		
Range		
p-value (stratified log-rank test)[a]	0.006	
Hazard ratio (95% CI; stratified)[b]	0.68 (0.51, 0.90)	
p-value (unstratified log-rank test)	0.010	
Hazard ratio (95% CI; unstratified)	0.69 (0.53, 0.92)	

CI, confidence interval; ITT, intent-to-treat; NE, not estimable

[a] Stratification factors were Prior VEGFR-targeting TKI therapy: 1 vs 2 or more, and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2 or 3; Motzer et al 2004).

[b] Estimated using the Cox proportional hazard model adjusted for stratification factors. A hazard ratio <1 indicates overall survival in favor of cabozantinib.

Figure 7 - Study XL184-308: Kaplan-Meier Plot of Interim Overall Survival Analysis through the 22nd May 2015 Cut-Off Date (ITT Population)



HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test; NE, not estimable

* indicates p-value ≤ 0.05 Source: XL184-308, Figure 14.2.2.2

Unplanned interim analysis - 31st December 2015

This analysis provides a minimum follow up of 12 months from the last subject enrolled and 7 additional months follow up from the first (planned) interim analysis. Survival status was determined for the majority (97.6%) of the 658 randomized subjects (16 subjects could not be established, 6 in the cabozantinib arm and 10 in the everolimus arm).

Table 28 - Study XL184-308: Interim Analysis of Overall Survival through the 31st December 2015 Cut-Off Date (ITT Population)

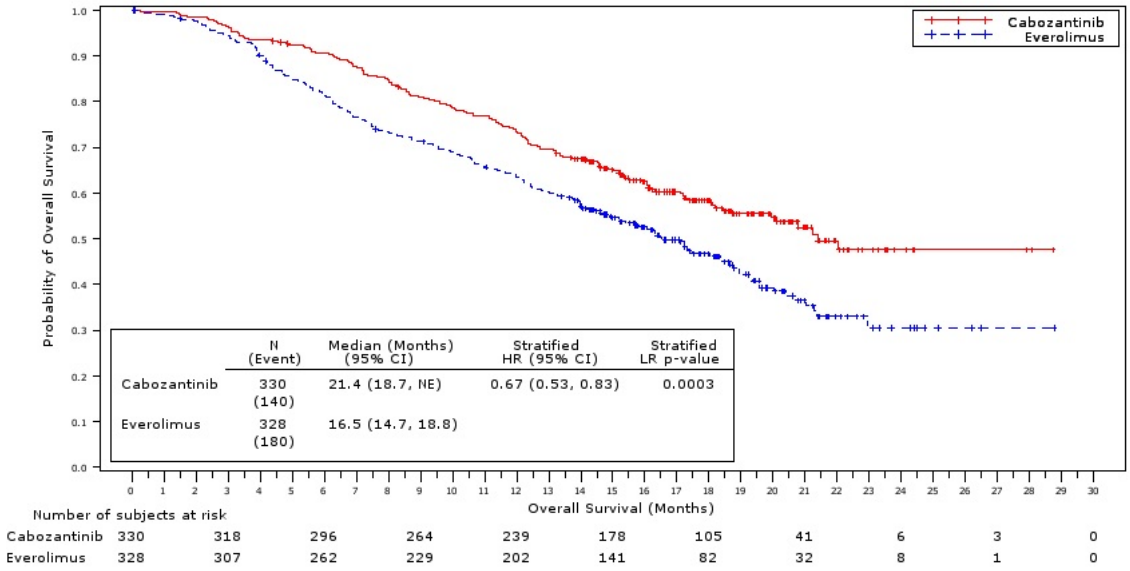
	Cabozantinib (N=330)	Everolimus (N=328)
Number (%) of Subjects		
Censored	190 (58)	148 (45)
Death	140 (42)	180 (55)
Duration of overall survival (months)		
Median (95% CI)	21.4 (18.7, NE)	16.5 (14.7, 18.8)
25th percentile, 75th percentile	11.5, NE	7.5, NE
Range	0.26, 28.7+	0.07+, 28.8+
p-value (stratified log-rank test)[a]	0.0003	
Hazard ratio (95% CI; stratified)[b]	0.67 (0.53, 0.83)	
p-value (unstratified log-rank test)	0.0004	
Hazard ratio (95% CI; unstratified)	0.67 (0.54, 0.84)	
Landmark estimates (% of subjects event-free)	Cabozantinib (N=330)	Everolimus (N=328)
6 months	91%	81%
12 months	73%	63%
18 months	58%	47%
24 months	48%	31%

+ indicates a censored observation; CI, confidence interval; ITT, intent-to-treat; NE, not estimable

[a] Stratification factors were prior VEGFR-targeting TKI therapy: 1 vs 2 or more, and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2 or 3; Motzer et al 2004).

[b] Estimated using the Cox proportional hazard model adjusted for stratification factors. A hazard ratio <1 indicates overall survival in favor of cabozantinib.

Figure 8 - Study XL184-308: Kaplan-Meier Plot of Interim Overall Survival Analysis through the 31st December 2015 Cut-Off Date (ITT Population)



Nonprotocol Anticancer Therapy (NPACT; ITT Population)

Any nonprotocol NPACT was not to be initiated until after study treatment had been discontinued. Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions was not permitted (unless Sponsor-approved if unavoidable) until radiographic tumor assessments had been discontinued per protocol defined criteria.

More subjects in the everolimus arm than the cabozantinib arm received NPACT (Table 29).

Table 29 - Overview of Nonprotocol Anticancer Therapy (NPACT; ITT Population)

	Cabozantinib N = 330 n (%)	Everolimus N = 328 n (%)
Any non-surgical NPACT	145 (44)	183 (56)
Systemic nonradiation therapy	125 (38)	155 (47)
Local therapy (EBRT)	41 (12)	69 (21)
Surgery that impacted tumor lesions	12 (3.6)	8 (2.4)

EBRT, external beam radiation therapy; NPACT, nonprotocol anticancer therapy; ITT, intent-to-treat
Note: Subjects may have received more than one type of anticancer therapy.
Source: Table 14.3.1.2.2 and Table 14.3.1.2.8

Objective Response Rate (ORR) - (IRC-Determined)

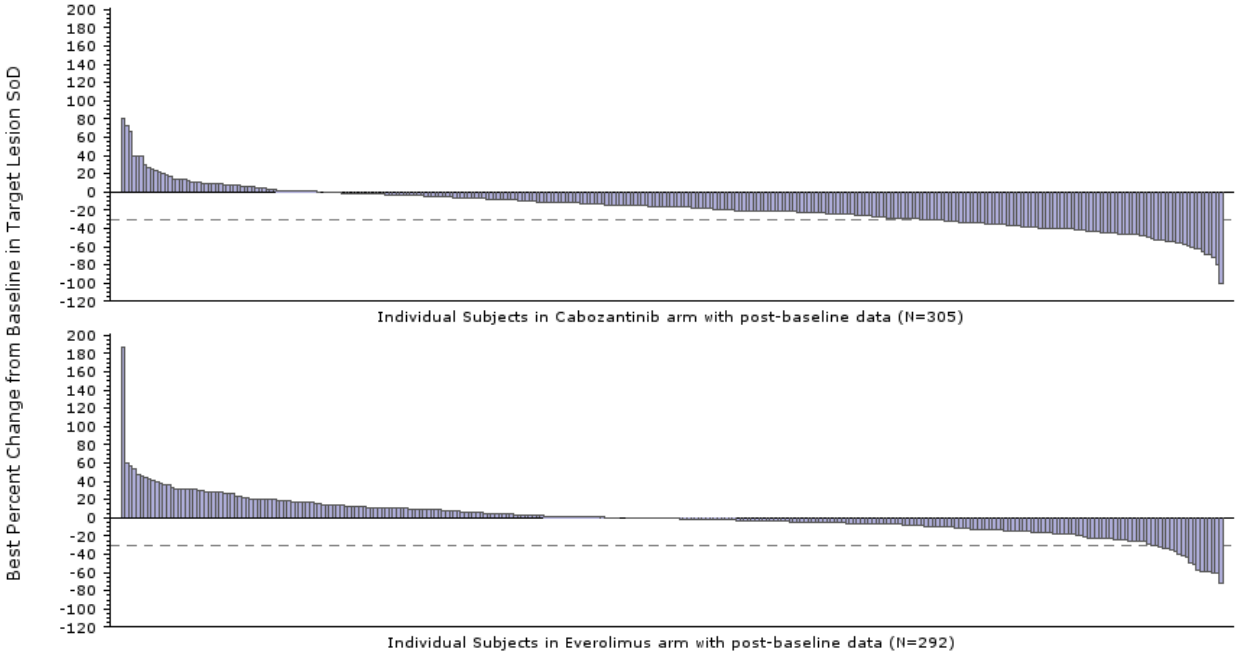
Table 30 - Study XL184-308: Tumour Response per RECIST 1.1 as of the 22 May 2015 Cut-off Date per IRC (ITT Population)

	Cabozantinib (N=330)	Everolimus (N=328)
Best Overall Response (n, %)[a]		
Confirmed complete response (CR)	0	0
Confirmed partial response (PR)	57 (17)	11 (3)
Stable disease (SD)[b]	216 (65)	203 (62)
Progressive disease	41 (12)	88 (27)
Unable to evaluate	2 (0.6)	2 (0.6)
Missing[c]	14 (4)	24 (7)
Objective Response Rate (ORR=CR+PR)[d]		
n (%)	57 (17)	11 (3)
95% confidence interval	(13, 22)	(2, 6)
Stratified CMH test p-value[e]	<0.001	
Unstratified chi-squared test p-value	<0.001	

CMH, Cochran-Mantel-Haenszel; IRC, Independent Radiology Committee; ITT, intent-to-treat; RECIST, Response Evaluation Criteria In Solid Tumors;
[a] Best overall response determined by the IRC for the overall ITT population.
[b] Includes subjects for whom the best overall response is stable disease or non-CR/non-PD
[c] No qualifying post-baseline assessment for overall response.
[d] ORR is defined as the proportion of subjects achieving an overall response of CR or PR confirmed by a subsequent scan at least 28 days later.
[e] p-value from CMH test with stratification factors of prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria (0 vs 1 vs 2 or 3; Motzer et al 2004).

A total of 75% cabozantinib subjects and 48% everolimus subjects had a post-baseline reduction in sum of lesion diameters (SoD); the waterfall plots of best percentage change in tumour size in each arm is shown below:

Figure 9 - Study XL184-308: Waterfall of Best percentage Change in Tumor Size from Baseline (IRC-Determined, ITT Population)



IRC, independent radiology committee; ITT, Intent-to-treat

Objective Response Rate per Investigator

The ORR per Investigator for the ITT population was 24% (95% CI: 19, 29) cabozantinib and 4% (95% CI: 2, 7) everolimus (unstratified p-value < 0.001).

Additional endpoints

Duration of response (DOR): IRC-determined.

The Kaplan-Meier estimate of median duration of objective response per IRC among responders was not estimable (NE) in the cabozantinib arm (95% CI: 7.2 months, NE) and was 7.4 months (95% CI: 1.9 months, NE) in the everolimus arm.

Time to Response

The median (range) time to objective response per IRC was 1.91 (1.6, 11.0) months in the cabozantinib arm and 2.14 (1.9, 9.2) months in the everolimus arm. This was approximately the time of the first scheduled tumour assessment.

Changes in bone scans: IRC-determined

Bone scan response, as determined by the IRC was assessed in subjects who had baseline bone scans showing bone lesions (105 subjects [32%] in the cabozantinib arm and 73 subjects [22%] in the everolimus arm). A trend for improved BSR with cabozantinib treatment was observed: Bone scan response was 18% (95% CI: 11, 27) in the cabozantinib arm and 10% (95% CI: 4, 19) in the everolimus arm.

Skeletal-Related Events (SREs)

Bone is a frequent site of metastatic spread in patients with advanced RCC, negatively impacting quality of life.

Table 31 - Post-Randomization Investigator-Assessed Skeletal Related Events (ITT)

	Cabozantinib (N = 330) n (%)	Everolimus (N = 328) n (%)
A. Subject-incidence of any SRE post randomization	38 (12)	46 (14)
Pathologic fractures	16 (4.8)	11 (3.4)
Spinal cord compression	4 (1.2)	8 (2.4)
Surgery to bone	11 (3.3)	10 (3.0)
External radiation therapy to bone	25 (7.6)	35 (11)
Subjects with a prior SRE	91 (28)	90 (27)
B. Subjects with an SRE among subjects who had a prior SRE	15 (16)	31 (34)
Pathologic fractures	9 (9.9)	8 (8.9)
Spinal cord compression	0	5 (5.6)
Surgery to bone	6 (6.6)	7 (7.8)
External radiation therapy to bone	8 (8.8)	23 (26)

SRE, skeletal-related event.
Treatment-emergent SREs recorded from the adverse event case report form page; categories are not mutually exclusive.
For the determination of subject incidence, only the first event per subject is counted.
Percentages are based on (A) the total number of subjects or number of subjects or (B) the number of subjects who had an SRE prior to randomization.

The use of concomitant bisphosphonates (cabozantinib 38 [11%], everolimus 36 [11%]) or denosumab (18 [5.4%], 21 [6.5%]) was similarly low in each treatment arm.

Health-Related Quality of Life

Two HRQoL instruments were used the FKSI-19 and the EQ-5D-5L. For both, assessments were performed pre-dose on Day 1, every 4 weeks through W25D1, and every 8 weeks thereafter.

FKSI-19

The FKSI-19 instrument is a 19-item self-report questionnaire that assesses the most important disease-related symptoms (DRS), treatment side-effects (TSE) and function/well-being (F/WB) associated with advanced kidney cancer. It queries symptom severity and interference in activity, and general health perceptions.

The median FKSI-19 total score at baseline was 77/95 for the cabozantinib arm and 77/95 for the everolimus arm. The number of FKSI questionnaires completed dropped to approximately 50% of the original number of subjects by Week 20 in the everolimus arm and Week 32 in the cabozantinib arm.

Overall, there were no major differences between treatment arms in the FKSI-total and subscale scores over time, although the FKSI-Treatment Side Effects subscale was higher (better) for the everolimus arm. The only specific side effects evaluated for this subscale were nausea and diarrhoea, both of which had a higher incidence in the cabozantinib arm. No notable treatment difference over time was observed in the FKSI-Function/Well-Being subscale score - measures subjects' self-assessment of their ability to work, enjoy life, and their overall contentment.

Health-related quality of life showed no clinically significant treatment differences in the FKSI-Total score, although some individual measures favoured cabozantinib and some favoured everolimus, probably reflecting the safety profiles. The biggest treatment difference was a worse score for cabozantinib for diarrhoea.

Figure 10 - Estimated Mean of Change from Baseline in FKSI-19 Total Score by Visit (Cabozantinib vs Everolimus; ITT Population)

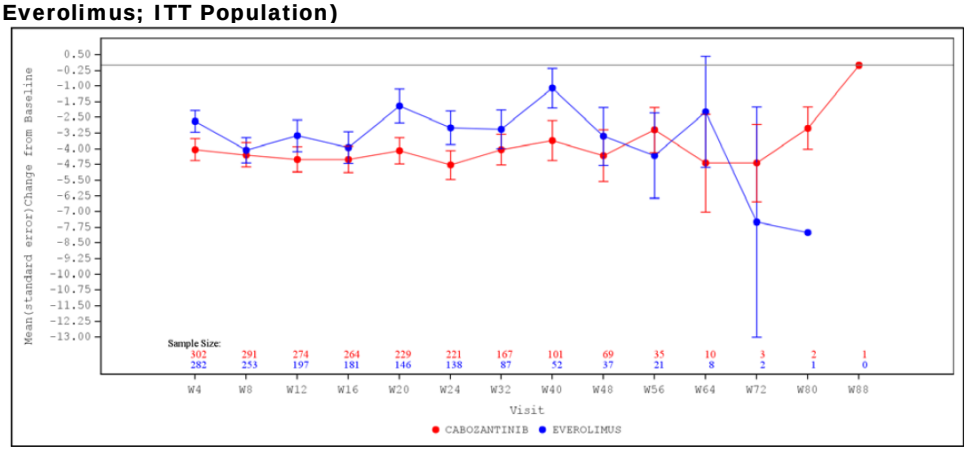


Table 32 - Changes from Baseline in FKSI-19, Repeated Measures Analysis (ITT Population)

	Cabozantinib N = 330			Everolimus N = 328			Difference in Mean Change[a]	Pooled SD	p-value[a]	Effect Size[b]
	n	LSMean	SD	n	LSMean	SD				
DRS-Physical	319	-1.093	6.288	303	-1.386	6.354	0.294	6.323	0.129	0.046
Lack of energy	319	-0.244	1.139	303	-0.207	1.121	-0.037	1.132	0.260	-0.033
Pain	314	0.125	1.152	302	0.067	1.079	0.058	1.124	0.077	0.052
Losing weight	314	-0.533	1.147	297	-0.301	1.054	-0.232	1.112	<0.0001	-0.209
Fatigued	317	-0.325	1.158	302	-0.305	1.113	-0.020	1.139	0.560	-0.017
Short of breath	318	0.029	0.991	301	-0.271	1.011	0.299	1.016	<0.0001	0.295
Fevers	314	0.056	0.566	298	-0.021	0.660	0.077	0.609	<0.0001	0.126
Bone pain	317	0.049	1.073	301	0.057	0.958	-0.008	1.026	0.792	-0.008
Coughing	318	0.237	0.998	303	-0.059	1.110	0.296	1.059	<0.0001	0.279
Weak all over	318	-0.281	1.079	302	-0.265	1.065	-0.016	1.073	0.624	-0.015
Blood in my urine	318	0.005	0.251	300	-0.001	0.299	0.006	0.272	0.383	0.023
Good appetite	318	-0.166	1.567	300	0.181	1.438	-0.347	1.521	<0.0001	-0.228
Sleeping well	315	0.018	1.432	299	-0.152	1.428	0.169	1.432	<0.0001	0.118
DRS-Emotional	317	0.398	1.252	301	0.393	1.104	0.005	1.192	0.891	0.004
Worry condition worsen	317	0.398	1.252	301	0.393	1.104	0.005	1.192	0.891	0.004

	Cabozantinib N = 330			Everolimus N = 328			Difference in Mean Change[a]	Pooled SD	p-value[a]	Effect Size[b]
	n	LSMean	SD	n	LSMean	SD				
Treatment Side Effects (TSE)	319	-2.416	2.749	302-	-0.814	2.023	-1.602	2.577	<0.0001	-0.621
Nausea	318	-0.236	1.012	301	0.069	0.691	-0.305	0.899	<0.0001	-0.340
Diarrhea	318	-1.280	1.328	302	-0.326	0.838	-0.954	1.244	<0.0001	-0.767
Side effects of treatment	296	-0.850	1.397	278-	-0.523	1.325	-0.327	1.372	<0.0001	-0.238
Function/Well-Being (FWB)	317	-0.230	3.232	303	-0.169	3.400	-0.061	3.304	0.517	-0.019
Able to work	314	-0.151	1.311	299	-0.101	1.412	-0.050	1.355	0.199	-0.037
Enjoy life	316	-0.017	1.211	302-	-0.014	1.297	-0.003	1.249	0.931	-0.002
Content with quality life	315	-0.035	1.266	303	-0.017	1.251	-0.018	1.260	0.620	-0.014
Total Score	**319**	**-3.483**	**9.798**	**303**	**-2.214**	**9.712**	**-1.269**	**9.768**	**<0.0001**	**-0.130**

EQ-5D-5L

EQ-5D-5L scores are summarized by five functional and symptom dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) .

At baseline, the median index value was 0.8200 in the cabozantinib arm and 0.8270 in the everolimus arm. The index questionnaire completion rate dropped to approximately 50% of the original number of subjects by Week 16 in the everolimus arm and Week 32 in the cabozantinib arm. Index scores over time generally showed no treatment difference.

Figure 11 - Mean Change from Baseline in EQ Index Score (ITT Population; Countries in which Index is Validated)

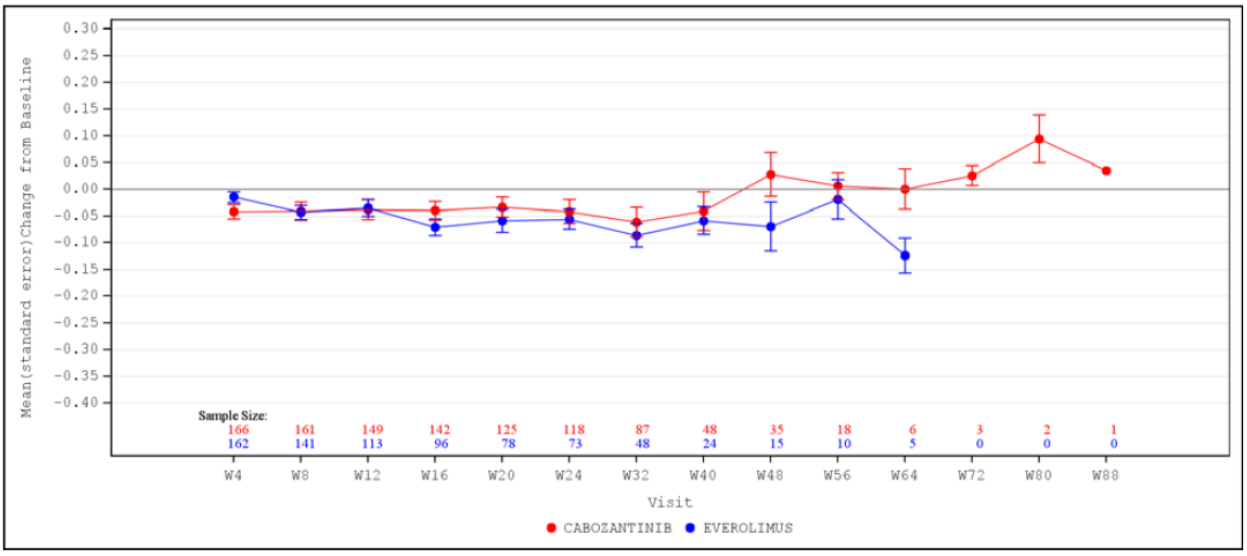
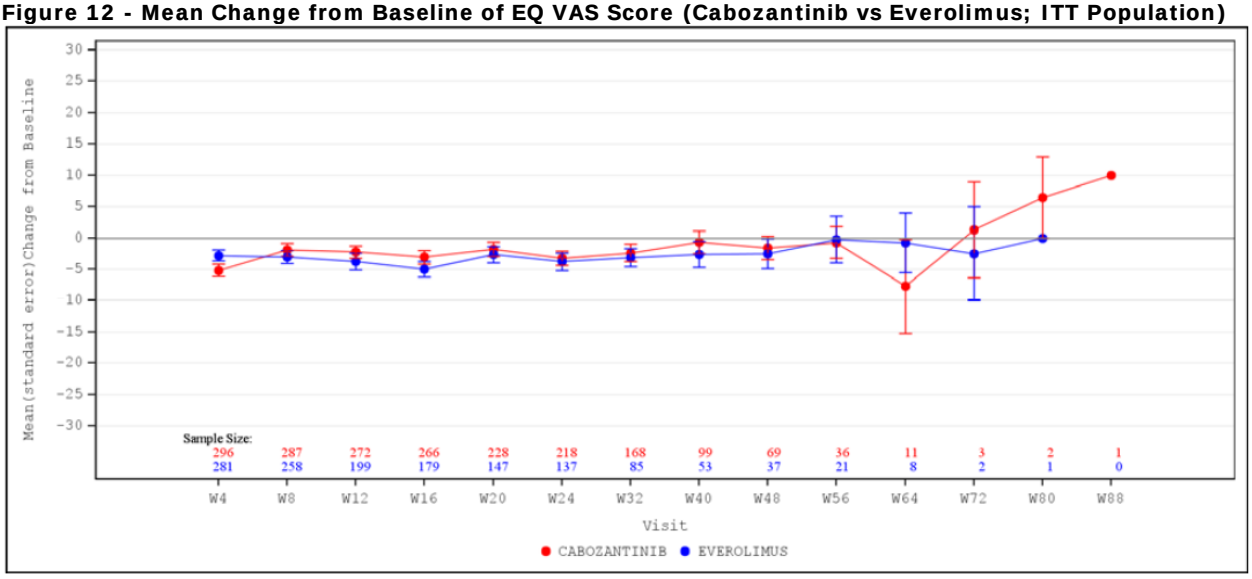


Figure 12 - Mean Change from Baseline of EQ VAS Score (Cabozantinib vs Everolimus; ITT Population)



Healthcare Resource Utilization

There was a slight trend in the cabozantinib arm for lower rates of hospitalization (37% vs 40% of subjects; 6.41 vs 10.24 days per person-year) and for lower rates of ICU visits (1.2% vs 2.1% of subjects; 0.07 vs 0.32 days per person-year). The proportion of subjects with surgery was similar in each arm (32% cabozantinib, 31% everolimus), but the rate of surgery was lower in the cabozantinib arm (0.90 vs 1.35 surgeries per person-year)

Red Blood Cell (RBC) Transfusions

RBC transfusions in the 28 days prior to randomization were required in 4.2% of subjects in the cabozantinib arm and 7.1% of subjects in the everolimus arm. Only 11% of subjects in the cabozantinib arm required an RBC transfusion after randomization compared with 26% of subjects in the everolimus arm; a favourable effect was seen regardless of whether subjects had or had not received a prior RBC transfusion in the 28 days prior to randomization.

Ancillary analyses

Sensitivity analyses using alternative definitions of progression events & alternative censoring schemes

Pre specified sensitivity analyses were carried out using alternative definitions for the PITT population.

- PFS2 analysis: used the scheduled tumour assessment date (or the next scheduled tumour assessment date if between assessments) rather than the date progression was recorded by the IRC as the date of radiographic progression:
  - HR 0.59 (95% CI 0.45, 0.76)
- PFS3 analysis events: earliest of death, radiographic progression as assessed by the investigator, clinical deterioration, initiation of subsequent anticancer therapy, and surgery that impacted tumour lesions:
  - HR 0.59 (95% CI 0.47, 0.74)
- PFS4 analysis events: earlier of death or radiographic progression as determined by the investigator. Clinical deterioration was not considered a progression event:

- HR 0.61 (95% CI 0.48, 0.77)

To explore the effect of potentially informative censoring resulting from (a) discontinuation of radiographic assessments prior to progression/receipt of subsequent treatments or (b) progression by investigator prior to receipt of subsequent treatments or (c) receipt of subsequent treatments prior to progression, four sensitivity analyses, designated PFS11-14, were conducted. Subsequent treatments included non-protocol systemic anticancer therapy, radiation other than to bone and surgical resection of the tumour lesions. These analyses reclassified subjects censored for the above reasons as events differentially between the treatment arms as follows:

- In PFS11 subjects with criteria (a) and (b) were classified as events in the cabozantinib arm only:
  - HR 0.73 (95% CI 0.57, 0.92)
- In PFS12, subjects in the cabozantinib arm meeting criteria (a), (b), and (c) and those in the everolimus arm satisfying criteria (c) were classified as events:
  - HR 0.70 (95% CI 0.56, 0.89)
- In PFS13, subjects in the cabozantinib arm meeting criteria (a) and (b) and those in the everolimus arm satisfying criteria (b) were classified as events:
  - HR 0.58 (95% CI 0.46, 0.73)
- In PFS14, all subjects meeting criteria (a), (b), and (c) were counted as events in the cabozantinib arm and remained censored in the everolimus arm. This was the most conservative analysis:
  - HR 0.75 (95% CI 0.59, 0.95)

Comparison of IRC and Investigator Assessment of Radiographic Progressive Disease

The table below provides a summary of concordance and discordance between the IRC- and the investigator-determined assessments of PD status (yes vs no).

Concordance between IRC and Investigator Read in Progressive Disease Status for Tumour Assessment (PITT Population)

Table 33 - Concordance between IRC and Investigator Read in Progressive Disease Status for Tumour Assessment (PITT Population)

	Cabozantinib N = 187			Everolimus N = 188			Total N = 375 n (%)
	IRC Read, n (%)						
Investigator Read	Yes	No	Total	Yes	No	Total	
Yes	111 (60)	20 (11)	131 (71)	110 (62)	24 (13)	134 (75)	265 (73)
No	12 (6.5)	42 (23)	54 (29)	17 (9.6)	27 (15)	44 (25)	98 (27)
Total	123 (66)	62 (34)	185 (100)	127 (71)	51 (29)	178 (100)	363 (100)
IRC No, Investigator Yes		20 (11)			24 (13)		44 (12)
IRC Yes, Investigator No		12 (6.5)			17 (9.6)		29 (8.0)
Concordance		153 (83)			137 (77)		290 (80)
Discordance		32 (17)			41 (23)		73 (20)

IRC, independent radiology committee; PITT, primary endpoint intent-to-treat
Percentages are calculated using the number of subjects with nonmissing status as the denominator.
Source: Table 14.2.4.38

The table below provides a summary of concordance and discordance between the IRC- and investigator-determined assessments of PD dates.

Table 34 -Concordance between IRC and Investigator Read in Date of Progressive Disease for Tumour Assessments among Subjects Who Progressed (PITT Population)

	Cabozantinib N = 111 n (%)	Everolimus N = 110 n (%)	Total N = 221 n (%)
Concordant	47 (42)	57 (52)	104 (47)
Discordant	64 (58)	53 (48)	117 (53)

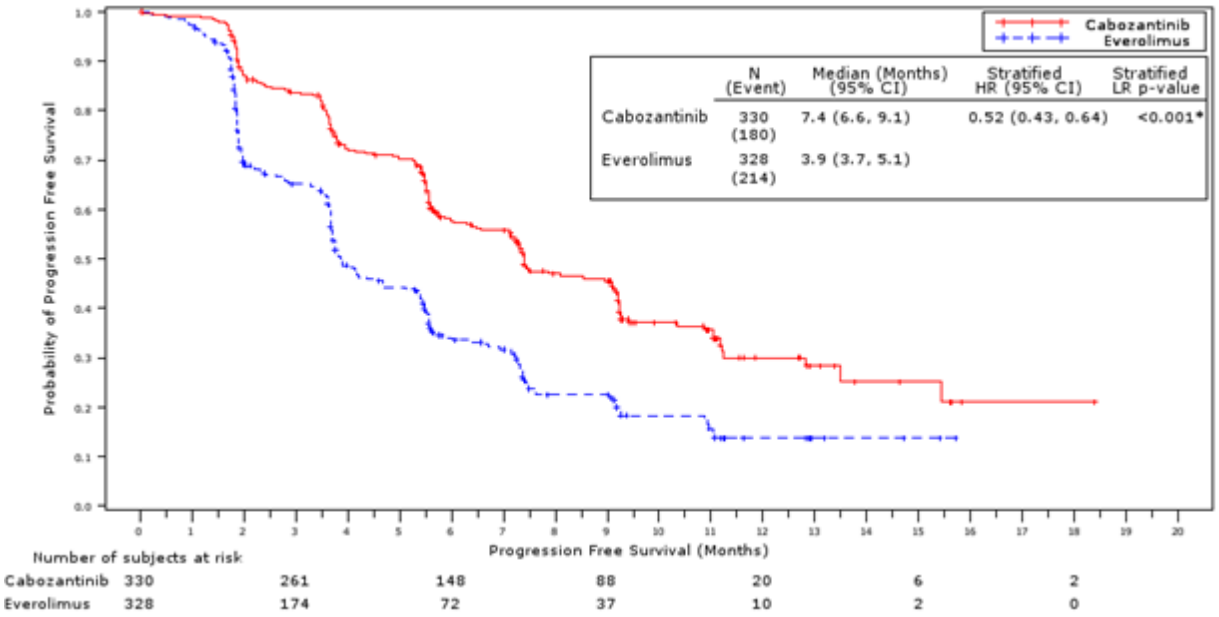
IRC, independent radiology committee; PITT, primary endpoint intent-to-treat.
[a] Subjects who progressed according to both the IRC and investigator.
Source: Table 14.2.4.39

Overall, the IRC and investigator agreed on subjects' radiographic PD status 83% of the time for the cabozantinib arm and 77% of the time for the everolimus arm, and when both the IRC and investigator agreed PD had occurred, the IRC and investigator agreed on the dates of PD 42% of the time for the cabozantinib arm and 52% of the time for the everolimus arm.

Progression-Free Survival (IRC-Determined, ITT Population)

The HR adjusted for stratification factors was 0.52 (95% CI: 0.43, 0.64). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs 3.9 months in the everolimus arm, an estimated 3.5 month difference in the medians.

Figure 13 - Kaplan-Meier Plot of PFS (IRC-Determined, ITT Population)



Subgroup Analyses of Progression-Free Survival

Analyses of PFS by subgroups of demographic and baseline charateristics were conducted in the PITT and ITT populations to assess the potential for differing efficacy results among these subgroups.

Table 35 - Subgroup Analyses for PFS (IRC-Determined) (PITT and ITT Populations)

Subgroup Level	PITT Population							ITT Population						
	Cabozantinib (N = 187)			Everolimus (N = 188)			Unstratified HR (95% CI)[a]	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)[a]
	n	Events	Median	n	Events	Median		n	Events	Median	n	Events	Median	
Overall	187	121	7.36	188	126	3.84	0.59 (0.46, 0.76)	330	180	7.39	328	214	3.88	0.52 (0.42, 0.63)
Age (years)														
< 65	118	75	7.33	116	82	3.75	0.55 (0.40, 0.75)	196	109	7.36	198	133	3.75	0.53 (0.41, 0.68)
>= 65	69	46	7.39	72	44	4.70	0.64 (0.42, 0.98)	134	71	9.17	130	81	3.91	0.50 (0.36, 0.69)
Gender														
F	45	35	5.59	57	37	5.55	1.03 (0.65, 1.63)	77	48	5.75	86	55	4.70	0.72 (0.49, 1.07)
M	142	86	7.89	130	88	3.71	0.48 (0.36, 0.65)	253	132	7.89	241	158	3.81	0.46 (0.36, 0.58)
Region														
Asia Pacific	25	19	7.43	36	25	3.61	0.60 (0.33, 1.10)	39	21	9.20	47	33	3.61	0.43 (0.25, 0.75)
Europe	83	51	7.33	84	62	3.84	0.54 (0.37, 0.79)	167	92	7.33	153	105	3.91	0.54 (0.41, 0.72)
Latin America	3	3	11.04	4	2	NE	1.29 (0.21, 7.92)	6	4	11.04	6	2	NE	1.38 (0.25, 7.66)
North America	76	48	7.16	64	37	4.17	0.60 (0.39, 0.93)	118	63	7.36	122	74	4.11	0.50 (0.35, 0.70)
Race														
Non-White	26	18	6.57	28	20	2.83	0.49 (0.26, 0.94)	46	27	7.39	42	28	3.55	0.49 (0.28, 0.83)
White	157	100	7.36	147	96	4.14	0.60 (0.45, 0.79)	269	142	7.89	263	169	3.91	0.50 (0.40, 0.63)
MSKCC Risk Factors by CRF														
0	80	51	7.39	83	56	4.67	0.54 (0.37, 0.79)	150	79	7.49	150	92	5.13	0.51 (0.38, 0.69)
1	80	49	7.39	75	47	3.71	0.56 (0.37, 0.84)	139	74	7.46	135	89	3.75	0.47 (0.35, 0.65)
2 OR 3	27	21	4.14	30	23	2.30	0.84 (0.46, 1.53)	41	27	5.42	43	33	3.48	0.70 (0.42, 1.16)
Baseline ECOG from Karnofsky Score														
0	129	79	7.39	116	76	4.37	0.54 (0.39, 0.74)	226	114	9.13	216	137	4.21	0.46 (0.36, 0.59)
1	58	42	5.52	72	50	3.65	0.71 (0.47, 1.08)	104	66	5.55	112	77	3.68	0.64 (0.46, 0.90)
Heng Criteria Group														
Favorable	38	22	11.17	33	22	5.55	0.50 (0.27, 0.91)	66	34	9.20	62	37	5.52	0.47 (0.30, 0.76)
Intermediate	114	69	7.89	120	77	3.88	0.54 (0.39, 0.75)	210	107	8.08	214	137	3.81	0.48 (0.37, 0.62)
Poor	35	30	5.39	35	27	2.63	0.83 (0.49, 1.41)	54	39	5.39	52	40	2.63	0.67 (0.43, 1.04)
Prior nephrectomy														
No	30	18	6.41	35	22	5.39	0.64 (0.34, 1.21)	47	25	6.57	49	32	4.37	0.51 (0.30, 0.86)
Yes	157	103	7.36	153	104	3.81	0.57 (0.43, 0.75)	283	155	7.39	279	182	3.88	0.51 (0.41, 0.64)
Time from diagnosis to randomization														
< 1 year	34	22	5.52	44	31	2.83	0.60 (0.35, 1.04)	59	37	5.49	76	57	2.73	0.55 (0.36, 0.84)
≥ 1 year	153	99	7.39	143	94	4.37	0.59 (0.44, 0.78)	271	143	7.89	251	156	4.37	0.51 (0.41, 0.65)
Number of prior VEGFR-TKIs														
1	137	87	7.36	136	95	3.75	0.56 (0.42, 0.75)	235	131	7.39	229	155	3.84	0.52 (0.41, 0.66)
≥ 2	50	34	6.05	52	31	5.55	0.67 (0.41, 1.10)	95	49	7.39	99	59	4.04	0.51 (0.35, 0.74)
Treatment Duration on first VEGFR-TKI														
≤ 6 months	54	37	5.59	62	44	3.65	0.56 (0.36, 0.88)	88	56	5.59	102	70	3.71	0.62 (0.44, 0.89)
> 6 months	133	84	7.43	126	82	4.37	0.59 (0.44, 0.81)	242	124	8.97	224	142	3.91	0.48 (0.38, 0.62)
Radiographic progression after most recent VEGFR-TKI														
< 3 months	159	102	6.57	146	97	3.81	0.61 (0.46, 0.81)	275	154	7.33	262	170	3.81	0.55 (0.44, 0.69)
≥ 3 months	27	18	7.43	42	29	4.17	0.48 (0.27, 0.88)	52	23	9.43	65	43	4.14	0.35 (0.21, 0.58)

Subgroup Level	PITT Population							ITT Population						
	Cabozantinib (N = 187)			Everolimus (N = 188)			Unstratified HR (95% CI)[a]	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)[a]
	n	Events	Median	n	Events	Median		n	Events	Median	n	Events	Median	
Prior treatment with agents targeting PD-1, PD-L1/PD-L2														
No	178	116	7.33	177	118	3.88	0.61 (0.47, 0.78)	312	174	7.39	314	203	3.88	0.54 (0.44, 0.66)
Yes	9	5	7.36	11	8	3.91	0.36 (0.10, 1.22)	18	6	NE	14	11	4.14	0.22 (0.07, 0.65)
SoD by IRC at baseline														
< Median	87	56	6.05	79	48	5.52	0.85 (0.58, 1.25)	165	87	8.08	163	98	5.13	0.63 (0.47, 0.84)
≥ Median	100	65	7.36	108	77	3.71	0.42 (0.30, 0.58)	165	93	7.39	164	115	3.75	0.41 (0.31, 0.54)
Number of organs with metastases														
1	31	19	7.46	31	18	6.60	0.99 (0.52, 1.90)	59	33	7.39	56	32	6.34	0.84 (0.52, 1.37)
2	57	38	7.36	48	33	5.55	0.68 (0.42, 1.09)	101	52	7.89	77	48	5.36	0.60 (0.40, 0.89)
≥ 3	98	64	7.16	105	73	3.48	0.40 (0.29, 0.57)	168	95	7.33	190	132	3.68	0.38 (0.29, 0.50)
Lung metastases														
No	72	46	7.39	62	35	5.39	0.86 (0.55, 1.33)	126	69	7.46	116	67	4.67	0.67 (0.48, 0.94)
Yes	115	75	6.57	126	91	3.71	0.47 (0.34, 0.64)	204	111	7.36	212	147	3.71	0.44 (0.34, 0.56)
Liver metastases														
No	135	83	7.39	130	84	5.39	0.62 (0.45, 0.83)	242	126	7.49	225	146	4.14	0.51 (0.40, 0.64)
Yes	52	38	7.16	58	42	3.68	0.53 (0.34, 0.83)	88	54	7.23	103	68	3.68	0.56 (0.39, 0.80)
Brain metastases														
No	185	120	7.36	187	126	3.84	0.58 (0.45, 0.75)	328	179	7.39	327	214	3.88	0.51 (0.42, 0.63)
Yes	2	1	NE	1	0	NE	NE (NE, NE)	2	1	NE	1	0	NE	NE (NE, NE)
Bone metastases on CT or MRI														
No	148	95	7.36	156	106	3.88	0.60 (0.45, 0.79)	253	140	7.39	263	169	4.21	0.57 (0.45, 0.71)
Yes	39	26	5.59	32	20	3.84	0.50 (0.27, 0.92)	77	40	7.39	65	45	2.73	0.33 (0.21, 0.51)
Visceral metastases														
No	48	28	7.46	46	24	5.59	0.92 (0.53, 1.59)	89	44	8.54	83	47	5.36	0.64 (0.42, 0.97)
Yes	139	93	7.26	142	102	3.71	0.50 (0.38, 0.67)	241	136	7.36	245	167	3.71	0.48 (0.38, 0.60)
Visceral metastases and bone metastases														
No	153	98	7.39	163	108	4.17	0.62 (0.47, 0.82)	270	145	7.46	276	175	4.53	0.56 (0.45, 0.70)
Yes	34	23	5.55	25	18	2.92	0.33 (0.17, 0.65)	60	35	5.59	52	39	1.87	0.26 (0.16, 0.43)
Tumor MET IHC status														
High	30	19	7.36	26	18	3.65	0.48 (0.25, 0.92)	48	26	7.36	48	36	3.71	0.41 (0.24, 0.68)
Low	83	54	6.41	90	59	4.70	0.69 (0.47, 1.00)	138	79	7.16	151	97	4.14	0.58 (0.43, 0.79)
Unknown	74	48	8.97	72	49	3.71	0.53 (0.35, 0.79)	144	75	9.10	129	81	3.71	0.50 (0.36, 0.68)
Only prior VEGFR-TKI sunitinib														
Yes	76	45	9.13	77	58	3.71	0.41 (0.28, 0.61)	135	74	9.10	132	97	3.71	0.43 (0.32, 0.59)
Only prior VEGFR-TKI pazopanib														
Yes	55	38	6.41	49	30	5.39	0.81 (0.50, 1.31)	88	51	7.36	83	49	5.13	0.67 (0.45, 0.99)

Progression-Free Survival (IRC-Determined, Non-PITT Population)

PFS analysis per IRC was repeated for the non-PITT population subjects, (283 subjects; includes all subjects randomized after the 375th subject) (cabozantinib 143, everolimus 140). The stratified HR was 0.44 (95% CI: 0.31, 0. 61).

Subgroup analyses for Overall Survival as of 31st December 2015 - ITT Population

Subgroup analyses were performed in the ITT population to further examine the robustness of the findings in this study.

Table 36 - Subgroup Analyses for Overall Survival as of 31st December 2015 (ITT Population)

Subgroup Level	ITT Population						
	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)[a]
	n	Events	Median	n	Events	Median	
Overall	330	140	21.39	328	180	16.53	0.67 (0.54, 0.84)
Age (years)							
< 65	196	86	21.39	198	107	17.12	0.72 (0.54, 0.95)
>= 65	134	54	21.26	130	73	16.26	0.62 (0.44, 0.88)
Gender							
F	77	37	18.10	86	53	16.26	0.74 (0.48, 1.12)
M	253	103	22.01	241	126	17.22	0.66 (0.51, 0.85)
Region							
Asia Pacific	39	16	NE	47	32	12.78	0.49 (0.27, 0.90)
Europe	167	71	22.01	153	88	16.36	0.67 (0.49, 0.91)
Latin America	6	2	NE	6	3	NE	0.49 (0.08, 2.97)
North America	118	51	21.26	122	57	19.58	0.79 (0.54, 1.16)
Race							
Non-White	46	22	20.11	42	25	15.18	0.65 (0.37, 1.15)
White	269	110	NE	263	143	16.36	0.65 (0.51, 0.83)
MSKCC Risk Factors by CRF							
0	150	48	NE	150	66	19.25	0.66 (0.46, 0.96)
1	139	64	19.94	135	79	14.85	0.67 (0.48, 0.94)
2 OR 3	41	28	10.45	43	35	6.47	0.65 (0.39, 1.07)
Baseline ECOG from Karnofsky Score							
0	226	81	NE	216	105	18.79	0.65 (0.49, 0.87)
1	104	59	14.62	112	75	10.68	0.72 (0.51, 1.02)
Heng Criteria Group							
Favorable	66	14	NE	62	17	NE	0.70 (0.34, 1.41)
Intermediate	210	89	21.39	214	121	16.46	0.65 (0.49, 0.85)
Poor	54	37	9.94	52	42	8.11	0.74 (0.48, 1.15)
Prior nephrectomy							
No	47	24	16.30	49	32	12.45	0.75 (0.44, 1.27)
Yes	283	116	22.01	279	148	17.22	0.66 (0.52, 0.84)
Time from diagnosis to randomization							
< 1 year	59	35	12.35	76	52	12.19	0.89 (0.58, 1.37)
≥ 1 year	271	105	NE	251	127	18.00	0.66 (0.51, 0.85)
Number of prior VEGFR-TKIs							
1	235	98	21.39	229	130	16.53	0.65 (0.50, 0.85)
≥ 2	95	42	20.80	99	50	17.22	0.73 (0.48, 1.10)
Treatment Duration on first VEGFR-TKI							
≤ 6 months	88	42	21.26	102	65	13.77	0.69 (0.47, 1.01)
> 6 months	242	98	22.01	224	114	18.40	0.69 (0.52, 0.90)
Time from radiographic progression after most recent prior VEGFR-TKI to randomization							
< 3 months	275	122	21.26	262	141	17.12	0.74 (0.58, 0.94)
≥ 3 months	52	16	NE	65	38	16.46	0.42 (0.23, 0.76)

Subgroup Level	ITT Population						
	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)*
	n	Events	Median	n	Events	Median	
Prior treatment with agents targeting PD-1, PD-L1/PD-L2							
No	312	133	21.39	314	171	16.53	0.68 (0.54, 0.85)
Yes	18	7	NE	14	9	16.31	0.56 (0.21, 1.52)
SoD by IRC at baseline							
< Median	165	57	22.01	163	72	19.25	0.76 (0.54, 1.08)
≥ Median	165	83	18.07	164	107	12.22	0.60 (0.45, 0.80)
Number of organs with metastases							
1	59	18	NE	56	24	20.76	0.72 (0.39, 1.34)
2	101	38	NE	77	37	19.58	0.73 (0.47, 1.16)
≥ 3	168	84	18.10	190	117	13.01	0.65 (0.49, 0.86)
Lung metastases							
No	126	49	NE	116	57	18.79	0.74 (0.51, 1.08)
Yes	204	91	20.80	212	123	16.07	0.64 (0.49, 0.84)
Liver metastases							
No	242	91	NE	225	123	16.53	0.60 (0.46, 0.78)
Yes	88	49	16.10	103	57	15.70	0.89 (0.61, 1.31)
Brain metastases							
No	328	139	21.39	327	179	16.53	0.67 (0.54, 0.84)
Yes	2	1	NE	1	1	21.29	NE (NE, NE)
Bone metastases on CT or MRI							
No	253	105	NE	263	137	17.48	0.71 (0.55, 0.91)
Yes	77	35	20.11	65	43	12.09	0.54 (0.34, 0.84)
Visceral metastases							
No	89	32	NE	83	40	19.35	0.70 (0.44, 1.12)
Yes	241	108	21.26	245	140	16.07	0.66 (0.52, 0.85)
Visceral metastases and bone metastases							
No	270	111	22.01	276	140	18.37	0.73 (0.57, 0.93)
Yes	60	29	20.11	52	40	10.68	0.45 (0.28, 0.72)
Tumor MET IHC status							
High	51	20	22.01	50	27	15.18	0.55 (0.31, 0.99)
Low	150	63	20.80	162	87	18.37	0.72 (0.52, 1.00)
Unknown	129	57	21.26	116	66	14.98	0.67 (0.47, 0.95)
Only prior VEGFR-TKI sunitinib							
Yes	135	59	21.39	132	80	16.46	0.66 (0.47, 0.93)
Only prior VEGFR-TKI pazopanib							
Yes	88	34	22.01	83	42	17.48	0.66 (0.42, 1.04)
Time from start of most recent prior VEGFR-TKI to subsequent PD							
< 3 months	44	25	15.24	68	45	11.04	0.76 (0.47, 1.24)
≥ 3 months	283	113	NE	259	134	18.40	0.68 (0.53, 0.88)

CRF, case report form; CI, confidence interval; CT, computed tomography; HR, hazard Ratio; IHC, immunohistochemistry; IRC, independent radiology committee; ITT, intent-to-treat; MRI, magnetic resonance imaging; NE, not estimable; PD, progressive disease; PD-1/L1/L2, programmed cell death receptor-1 and its ligands (PD-L1 and PD-L2); SoD, sum of lesion diameters; VEGFR, vascular endothelial growth factor.

MSKCC risk factors = 0 (favorable), 1 (intermediate), 2 or 3 (poor) (Motzer et al 2004); Heng risk factors = 0 (favorable), 1-2 (intermediate), 3-6 (poor) (Heng et al 2009).

Rows for Missing data are not tabulated

* Estimated from the Cox proportional hazards model. HR < 1 indicates survival in favor of cabozantinib.

Source: Table 14.2.1.15

PFS and OS Endpoints (Comparison of Stratification Data from CRF and IVRS/IWRS)

Stratified statistical analyses of PFS in the first 375 randomized subjects (primary endpoint ITT analysis) and OS in the overall population (ITT analysis) based on stratification values from the IVRS/IWRS entered at the time of randomization rather than stratification values entered onto the CRF are presented in the table below:

Table 37 - Study XL184-308: PFS and OS Endpoints (Comparison of Stratification Data from CRF and IVRS/IWRS)

	Cabozantinib	Everolimus
Endpoint, population	PFS from CRF, Primary Endpoint ITT (N=375)	
n	187	188
Median (months)	7.4	3.8
logrank p-value, stratified	<0.001[a]	
HR (95% CI), stratified	0.59 (0.46, 0.76)	
Endpoint, population	PFS from IVRS/IWRS, Primary Endpoint ITT (N=375)	
N	187	188
Median (months)	7.4	3.8
logrank p-value, stratified	<0.0001	
HR (95% CI), stratified	0.58 (0.45, 0.74)	
Endpoint, population	OS from CRF, Secondary Endpoint ITT (N=658)	
N	330	328
Median (months)	21.4	16.5
logrank p-value, stratified	0.0003	
HR (95% CI), stratified	0.67 (0.53, 0.83)	
Endpoint, population	OS from IVRS/IWRS, Secondary Endpoint ITT (N=658)	
N	330	328
Median (months)	21.4	16.5
logrank p-value, stratified	0.0003	
HR (95% CI), stratified	0.66 (0.53, 0.83)	

CI, confidence interval; CRF, case report form; HR, hazard ratio; ITT, intent-to-treat; IVRS/IWRS, interactive voice/web response system; OS, overall survival; PFS, progression-free survival; PFS data cutoff date 22May2015, OS data cutoff date 31 December 2015

[a] Calculated to three decimal places

Summary of main study

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

Table 38 - Summary of Efficacy for trial XL184-308

Title: Phase 3, randomized, controlled study of cabozantinib (xl184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy				
Study identifier	XL184-308			
Design	Phase IIII, multicentre, international, 1:1 randomized, open-label, study of cabozantinib versus everolimus. 4 periods: Pre-Treatment Period, Treatment Period, Maintenance phase & Post-Treatment Period The defined patient population is advanced RCC who experienced disease progression on or after prior VEGFR targeted therapy			
	Duration of main phase:		First subject was enrolled on the 8th of August 2013 and the data cut-off point was the 22nd May 2015. A second interim OS (unplanned) analysis to 31st December 2015	
Hypothesis	Superiority			
Treatments groups	Cabozantinib (test)		Oral cabozantinib (60 mg) once daily Supplied by Exelixis, Inc Total randomised to cabozantinib: 330 subjects	
	Everolimus (reference)		Oral everolimus (10 mg) once daily Purchased from Novartis Total randomised to everolimus: 328 subjects	
Endpoints and definitions	Primary endpoint	PFS	Duration of PFS as assessed by the IRC per RECIST 1.1	
	Secondary endpoint	OS	Survival status	
	Secondary endpoint	ORR	ORR per IRC	
Database lock	22nd May 2015			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	The Primary Endpoint Intent-to-Treat (PITT) population consisted of the first 375 randomized subjects - cutoff 22nd May 2015			
Descriptive statistics and estimate variability	Treatment group (PITT) 22nd May 2015 cutoff		Cabozantinib	Everolimus
	Number of subjects		N=187	N=188
	Median PFS (months)		7.4	3.8

	95% confidence interval	5.6, 9.1	3.7, 5.4
	Treatment group (ITT) Number of subjects	N=330	N=328
	Objective Response Rate (ORR=CR+PR)	17%	3%
	95% confidence interval	13, 22	2, 6
	Treatment group (ITT) 31st December 2015 cutoff (second interim analysis)	Cabozantinib	Everolimus
	Number of subjects	N=330	N=328
	Median OS (months)	21.4	16.5
	95% confidence interval	18.7, NE	14.7, 18.8

Effect estimate per comparison	**PFS** (PITT) 22nd May 2015	Comparison groups	Cabozantinib vs everolimus
		Stratified Hazard Ratio (95% CI)	0.59 (0.46, 0.76)
		P-value	<0.001
	OS (ITT) 31st December 2015	Stratified Hazard Ratio (95% CI)	0.67 (0.53, 0.83)
		P-value	0.0003

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

None

Clinical studies in special populations

Results from two independent population pharmacokinetic (PopPK) analyses of cabozantinib in subjects with RCC or MTC (Study XL184-308.PopPK.001 and XL184-301.Pop.PK.001, respectively) concluded that age was not a statistically significant covariate for CL/F. Scatter plots from the RCC PopPK analysis do not indicate that variability around mean clearance values changes perceptibly for subject population ages of < 64 years relative to ≥ 65 years.

A total of 124 elderly subjects (≥ 65 years age range: 65-74 [n=96]; 75-84 [n=27]; ≥ 85 [n=1]) were included in the 381 pooled subjects included in the RCC PopPK analysis. The mean (SD) age was 57.6 (13.2) years (range 19-86). Thus, the elderly population constituted a high percentage of total subjects evaluated for possible effects of age on cabozantinib clearance in this PopPK analysis. Moreover, for the two covariates that were shown to have a statistically significant effect on CL/F in this PopPK analysis (female gender and Asian race), the magnitude of their effect on CL/F (21% and 27% lower clearance compared to males and White subjects, respectively) was less than the inter-subject variability (%CV) for CL/F in this analysis (46%). Thus, even the two statistically significant covariates identified in this analysis were not considered to be clinically meaningful covariates requiring dose adjustments.

As only sparse steady-state PK sampling was performed in pivotal RCC study XL184-308, the effect of age on cabozantinib exposure (clearance) was further examined in subjects enrolled in the pivotal MTC study XL184-301 where detailed PK sampling was conducted.

Of the 289 pooled subjects included in the MTC PopPK analysis a total of 75 were elderly subjects (≥ 65 years age range: 65-74 [n=62]; 75-84 [n=12]; ≥ 85 [n=1]). The mean (SD) age was 54 (13) years; range 20-86. As observed in the RCC PopPK analysis, the elderly population also constituted a high percentage of total subjects in the MTC PopPK analysis and age was also not determined to be a statistically significant covariate affecting cabozantinib clearance.

Exposure values (AUC_{0-6}) were determined in 39 subjects ≥ 65 years of age in the Phase 3 study of cabozantinib in subjects with MTC (Study XL184-301.PK.001). Based on the limited dataset, there were no apparent differences in mean AUC_{0-6} values measured on Day 1 of dosing in elderly subjects (cohorts: ≥ 65 years; 66-74 years, 75-84 years, ≥ 85 years) administered a single 140 mg FBE cabozantinib dose relative to that in the entire PK Safety population (n=200; age range: 20-86) (Table).

Table 39 - Study XL184-301: Exposure (AUC_{0-6}) by Age Group

	XL184-301				
	Overall PK Safety Population	PK Safety Population ≥ 65 Years	PK Safety Population 66-74 Years	PK Safety Population 75-84 Years	PK Safety Population ≥ 85 Years
Sample size (n)	200	39	29	9	1
Age range:	20-86	66-86	66-74	75-84	86
AUC_{0-6} (ng.h/mL) Dosing Day 1					
Mean	2110	1930.13	1987.04	1718.25	2186.65
SD	918	754.79	752.07	763.92	-

AUC_{0-6}, area under the plasma concentration-time curve from 0-6 h; SD, standard deviation

For the clinical pharmacology and PK studies of cabozantinib conducted in healthy subjects, PK data are generally unavailable for elderly subjects based on age-related protocol enrollment criteria (ie, no subjects ≥ 65 years). One exception is the matched normal organ function cohort (n=12) in the hepatic impairment study

(Study XL184-003), where 5 subjects ≥ 65 years of age were enrolled (individual ages: 66, 66, 67, 68 and 72 years). However, due to the exposure variability and small sample size, no difference in mean (SD) exposure (AUC_{0-inf}) was apparent in this elderly cohort administered a single 60 mg cabozantinib FBE dose when compared to the 7 normal organ function subjects <65 years of age: 39,720 (7,180) ng.h/mL vs 28,257 (8087) ng.h/mL.

No dose adjustment is recommended for Cabometyx in mild or moderate renal impaired subjects based on the smaller magnitude increase in exposure observed in these subject populations relative to the inter-subject variability in exposure for cabozantinib in cancer patients. In patients with mild or moderate hepatic impairment, a reduced (40 mg once daily) starting dose of Cabometyx will be recommended in order to minimize the risk of treatment-related AEs due to elevated cabozantinib plasma exposures in this patient population.

Supportive studies

The only supportive study for the indication in RCC is study XL184-008, a phase I drug interaction study. The study is described above.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A single pivotal study (XL184-308) was submitted in support of this new indication in Renal Cell Carcinoma for cabozantinib. This was a phase III, randomized, controlled study of cabozantinib vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.

No CHMP advice was sought regarding the design of the RCC pivotal study. However, 4 national agencies (MPA, DKMA, MEB and MHRA) broadly agreed with the approach and design of the pivotal study, including that everolimus was an acceptable comparator and that PFS was an acceptable primary endpoint, whilst OS should be considered an important secondary endpoint. The primary PFS endpoint was assessed by an IRC blinded to study treatment.

Key inclusion and exclusion criteria were considered acceptable in the context of the objectives of the clinical study.

It was decided by CHMP to restrict the approved indication to patients who had a prior vascular endothelial growth factor (VEGF)-targeted therapy instead of the broader indication applied by the applicant, since it did not reflect the population included in the pivotal study. According to the inclusion criteria, patients should have received treatment with at least one prior VEGFR TKI.

Everolimus is an established 2nd line treatment option for RCC which has demonstrated to confer a PFS benefit compared to placebo in a single pivotal study (RECORD-1). The choice of everolimus as the comparator in this study was considered acceptable, and in is in line with previous recommendation given in all the national scientific advices.

PFS was selected as primary endpoint for this study which is consistent with other approved products for RCC. In line with the CHMP anti-cancer guideline in man (EMA/CHMP/205/95/Rev.4), overall survival was considered to be an important secondary endpoint. Although OS would have been the preferred primary endpoint, the chosen primary endpoint PFS, in combination with the secondary endpoint OS and ORR, is considered adequate in the context of the disease and treatment setting. This is also in line with the national scientific advices provided.

A 1:1 randomisation was considered appropriate. Stratification by important factors was carried out for prior TKI therapies and a number of factors as per MSKCC criteria which is endorsed by CHMP.

Although a double-blind study would have been preferred, the practical difficulties were acknowledged regarding over-encapsulating everolimus. In addition, the open-label design enabled appropriate dose modifications for adverse events in both study arms. As the primary endpoint was PFS per IRC and OS was a key secondary endpoint, potential bias conferred by the open-label design is partly overcome.

Eligibility criteria and protocol deviations were generally balanced between the cabozantinib and everolimus arms. No major issues were identified.

The patients included in the study are typical of a population of subjects with advanced RCC.

There are some small differences in baseline characteristics which could indicate that the everolimus arm included more patients with slightly worse prognosis than the cabozantinib arm. These differences include more patients in the everolimus arm with Stage IV disease, more subjects with ≥ 3 involved organs, more patients with less than 1 year from diagnosis to randomization, median time from progression on most recent VEGFR-TKI to randomisation was slightly longer, and more patients had progressed earlier than 3 months from start of most recent VEGFR-TKI. The applicant was requested to elaborate on the implications of the seemingly worse prognosis of the everolimus patients on the study outcome. It was concluded that minor baseline imbalances between arms in individual risk factors, even in aggregate, are highly unlikely to have influenced study outcomes. CHMP agreed that an OS benefit for cabozantinib treatment was observed in all analysed subgroups (HR < 1).

Biomarker investigation was an exploratory endpoint in the study, including the relationship of changes in plasma biomarkers and CTCs with treatment outcomes. These analyses have not yet been initiated. Pilot studies were recently initiated to determine feasibility of the exploratory CTC analysis. These should be provided post approval when available.

The statistical methods are standard for the analysis of time-to-event trials and were agreed. The approaches for handling multiplicity are acceptable to control the type I error at 5%. Hypothesis testing between the two treatment arms was performed using the stratified logrank test with a 2-sided 0.05 level of significance. The stratification factors were those used to stratify randomization.

In a study with a stratified randomisation the expected analysis is one that is stratified for the factors used for stratifying the randomisation; this was indeed done for the primary analysis and is agreed. As a supportive analysis an unstratified analysis was also supplied – as would be expected the results were consistent between the two and it is clear that the positive findings are robust to the precise method of analysis used.

The primary analysis of PFS was event-based and was to be conducted after at least 259 events were observed in the PITT population, and the enrolment of all 650 subjects (ITT population) was completed. Type I error for the interim analysis was controlled by a Lan-DeMets O'Brien-Fleming alpha spending function to account for the actual information fraction at the time of the interim analysis (critical value 0.0019).

Sensitivity and subgroup analyses were performed to further examine the robustness of the findings in this study.

An Applicant's review of protocol deviations concluded that they would not have a notable impact on the safety or efficacy of the study. The applicant was requested to provide more details of this specific assessment. Important eligibility criteria deviations were balanced between the cabozantinib and everolimus arms: a total of 37 subjects (11%) failed at least one important eligibility criterion in each treatment arm. Given the small

number of subjects that had an important eligibility deviation and the nature of these deviations, the Applicant judged that these deviations could not possibly have had a notable impact on the safety outcomes of the study. There were only two categories with appreciable number of deviations: treatment deviation (potentially affecting safety) and randomization irregularity (potentially affecting efficacy). Both of these categories had a similar incidence in each treatment arm. Other categories had too few subjects to reasonably have been expected to impact safety or efficacy. Treatment deviations included dosing errors (isolated cases of missed doses or incorrect doses received) which did not impact safety. Randomization irregularities were stratification errors in IVRS/IWRS by incorrect determination of the MSKCC risk group or the number of prior VEGFR-TKIs. A summary of PFS and OS showed similar results using randomization stratification data entered on the CRF compared with using the original randomization stratification data entered in IVRS/IWRS.

No formal dosing studies have been carried out. Based on the totality of evidence from different oncology indications, the exposure-response (E-R) analysis and from experience in using cabozantinib in RCC patients in study XL184-008 (phase I), a starting dose of 60 mg was proposed to be optimal in terms of balancing overall tolerability whilst maintaining clinically meaningful activity. The availability of 40 mg and 20 mg strength tablets allows for two levels of dose reduction for the management of adverse events as appropriate. Overall the scientific rationale and evidence to support the dosing strategy can be accepted.

No major GCP issues have been highlighted with respect to the review of the clinical data. Overall the conduct of the study appears acceptable and in line with international standards.

Overall, the design of the study is in line with relevant EU scientific guidelines. CHMP considered that the trial was well-designed, well-conducted and considered sufficient in this setting to assess the benefit risk balance for this marketing authorization application.

Efficacy data and additional analyses

The PFS results demonstrate a statistically significant and clinically meaningful improvement for subjects in the cabozantinib arm compared to everolimus (HR= 0.58 [0.45, 0.74], p<0.0001). The HR adjusted for stratification factors was 0.59 (95% CI: 0.46, 0.76; stratified log-rank p-value < 0.001). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm, 3.6 month difference (median PFS in the everolimus registration study (RECORD) was 4.9 months and in the axitinib (AXIS) study was 6.8 months).

The PFS HR among all enrolled subjects (ITT population) was 0.52 (95% CI: 0.43, 0.64). Sensitivity analyses using alternative definitions of progression were similar, demonstrating the robustness of the data. A PFS treatment benefit was observed across the majority of the baseline and demographic subgroups evaluated for the PITT and the ITT population. Of interest, MET is a cabozantinib therapeutic target and high levels of MET expression are seen in RCC. There is a trend for differences between high and low MET expression in terms of benefit for PSF and OS.

PFS and OS results based on stratification values from the IVRS/IWRS entered at the time of randomization rather than stratification values entered onto the CRF, source data verified, and used in the CSR were similar for each method. These PFS and OS analyses based on IVRS/IWRS stratification values were incorporated in Section 5.1 of the Cabometyx SmPC.

Secondary endpoints were supportive. The ORR per IRC was conducted in the ITT population at the time of the primary PFS analysis and showed a statistically significant benefit with cabozantinib treatment. The ORR was 17% for subjects who received cabozantinib and 3% for subjects who received everolimus. All the responses were confirmed PRs. Confirmed objective tumour responses were seen in 2% of subjects in the everolimus

(RECORD) study and the objective response rate was 19.4% in the axitinib (AXIS) study. The majority of subjects in the cabozantinib arm had a post-baseline reduction in tumour size (75% cabozantinib, 48% everolimus). At the time of the analysis, the median duration of response had not been reached for the cabozantinib arm.

At the cut-off May 2015, a trend for longer survival for cabozantinib treated subjects was observed, 0.68 (95% CI: 0.51, 0.90; stratified logrank p-value = 0.006), despite a higher number of subjects in the everolimus arm (47%) receiving subsequent systemic anti-cancer treatment compared to those in the cabozantinib arm (38%). At the data cut-off of 31st December 2015 (unplanned analysis), the HR adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified logrank p-value = 0.0003). The Kaplan-Meier estimates of median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm, 4.9 month difference.

Although positive overall survival results of cabozantinib treatment has been observed in both interim analyses performed, the final analysis is lacking to confirm the observed improvement in OS. The final OS analysis should be provided post authorisation and this is reflected as an annex II post-authorisation efficacy study.

2.5.4. Conclusions on the clinical efficacy

The efficacy data in previously treated advanced RCC patients show improvements in both PFS and OS. The magnitude of the effects is considered to be clinically meaningful and cabozantinib offers a new therapeutic option for these patients.

The CHMP considers the following measures necessary to address issues related to efficacy:

In order to address the uncertainty regarding the survival advantage of cabozantinib compared with everolimus in patients with advanced renal cancer that has progressed after VEGF TKI therapy, the MAH should submit the final analysis of OS for XL184-308, a phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy by September 2017.

Biomarker investigation was an exploratory endpoint in the study, including relationship of changes in plasma biomarkers and CTCs with treatment outcomes. This analysis is currently not available and CHMP recommended that it should be provided post approval.

2.6. Clinical safety

Patient exposure

The study population for Study XL184-308 had diagnoses of RCC with a clear-cell component and had to have progressed on prior treatment with at least one VEGFR-targeting TKI. Key demographic, baseline, and disease characteristics and prior cancer therapy have been described in the efficacy section.

Cut-off date for study XL184-308 was 22nd of May 2015.

In Study XL184-308, the median duration of exposure was longer in the cabozantinib arm compared with everolimus (32 weeks [range 1, 89] vs 19 weeks [range 1, 82]). A total of 40% of subjects in the cabozantinib arm remained on treatment as of the data cut-off compared with 21% of subjects in the everolimus arm.

Table 40 - Study Treatment Exposure (Safety Population)

	Cabozantinib N = 331	Everolimus N = 322
Duration of exposure (weeks)a		
Mean (SD)	33.11 (16.838)	23.94 (17.085)
Median (range)	32.14 (1.1, 89.3)	18.93 (0.9, 82.1)
Average daily dose (mg/day)b		
Mean (SD)	45.15 (13.072)	8.43 (1.987)
Median (range)	45.31 (14.2, 82.7)	9.22 (2.8, 14.2)
Dose intensity (%)c		
Mean (SD)	75.25 (21.787)	83.90 (19.834)
Median (range)	75.51 (23.7, 137.8)	91.53 (28.3, 142.3)
SD, standard deviation a Duration of exposure = (date of decision to discontinue study treatment – date of first dose + 1)/7. b Sum of doses received (mg)/duration of exposure (days). c Cabozantinib arm: dose intensity = 100*(average daily dose [mg/day]/assigned dose level [mg/day]) Everolimus arm: dose intensity = 100*(average daily dose [mg/day]/assigned dose level per investigator [mg/day])		

Dose reductions and interruptions

A total of 59.8% of subjects in the cabozantinib arm had a dose reduction due to an AE. The median time to first dose reduction was 55.0 days. A second dose-level reduction due to an AE occurred in 19.3% of subjects. The median time to second dose reduction was 93.0 days. Adverse events that led to dose reduction in ≥5% of subjects in the cabozantinib treatment arm (Safety Population) included Diarrhoea 54 (16), palmar-plantar erythrodysaesthesia syndrome 38 (11), fatigue 33 (10) and hypertension 25 (7.6).

A total of 24.2% of subjects in the everolimus arm had a dose reduction due to an AE. A second dose-level reduction to 2.5 mg occurred in 1.6% of subjects; the median time to first dose reduction was 60.0 days and the median time to second dose reduction was 93.0 days.

Cabozantinib Dose Reductions (Safety Population)

- Subjects with any dose reduction resulting from AE, n (%) 198 (59.8)
- Received dose level, n(%)
    - Assigned dose level (60 mg) 331 (100.0)
    - First dose-level reduction (40 mg) resulting from AE 192 (58.0)
    - Second dose-level reduction (20 mg) resulting from AE 64 (19.3)
- Lowest dose level received (excluding dose interruptions), n (%)
    - Assigned dose level (60 mg) 133 (40.2)
    - First-level dose reduction (40 mg) resulting from AE 132 (39.9)

- Second-level dose reduction (20 mg) resulting from AE 65 (19.6)

- Last dose level received (excluding dose interruptions), n (%)
  - 60 mg 142 (42.9)
  - 40 mg 132 (39.9)
  - 20 mg 56 (16.9)
  - Other dose level > 0c 1 (0.3)

- Last dose level received (including dose interruptions), n (%)
  - 60 mg 98 (29.6)
  - 40 mg 97 (29.3)
  - 20 mg 45 (13.6)
  - 0 mg 91 (27.5)

- Median (range) time to first dose reduction resulting from AE (days) 55.0 (10, 355)
- Median (range) time to second dose reduction resulting from AE (days) 93.0 (29, 317)

Dose interruptions due to Adverse Event

Study drug was interrupted due to an AE for 70% of subjects in the cabozantinib arm and 59% of subjects in the everolimus arm.

Adverse events

A summary of AEs is presented in the tables below:

Table 41 - Summary of Adverse Events (Safety Population)

	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
AE	331 (100)	321 (100)
Related AE	322 (97)	293 (91)
Serious AE	131 (40)	139 (43)
Serious and related AE at any time	50 (15)	41 (13)
Worst AE, Grade 3 or 4	226 (68)	186 (58)

Worst related AE, Grade 3 or 4	195 (59)	131 (41)
Worst AE, Grade 4	26 (7.9)	26 (8.1)
Worst related AE, Grade 4	11 (3.3)	10 (3.1)
Grade 5 AE at any time a,b	23 (6.9)	28 (8.7)
Grade 5 AE ≤ 30 days after last dose of study treatment	15 (4.5)	23 (7.1)
Grade 5 AE > 30 days after last dose of study treatment	8 (2.4)	5 (1.6)
Related Grade 5 AE at any time	1 (0.3)	2 (0.6)
Deaths	90 (27)	110 (34)
Death ≤ 30 days after last dose of study treatment	15 (4.5)	23 (7.1)
Death > 30 days after last dose of study treatment	75 (23)	87 (27)

AE, adverse event. A small fraction of the total AEs reported could not be coded in MedDRA at the time of the database snapshot. These uncoded AEs included some high-grade events and clinically important events (Section 12.3.4.5); a review revealed that the uncoded events do not meaningfully impact the frequencies of AEs described herein. Subjects are counted only once in each category but may be counted in multiple categories. Includes only events within the AE observation period defined as the time from first dose date until the earlier of 30 days after the date of decision to discontinue study treatment, date of death, date of consent withdrawal, or the data cutoff date except where indicated 'at any time.' a The Grade 5 AE and death summary information reflects data as of the May 22, 2015 cutoff date. b Grade 5 AEs were not necessarily reported for subject deaths due to progressive disease.

Table 42 - Study XL184-308: Frequent Adverse Events Regardless of Causality (PTs with ≥ 10% Incidence in Either Treatment Arm) (Safety Population)				
	Cabozantinib N = 331 n (%)		Everolimus N = 322 n (%)	
	Grade		Grade	
Preferred Term	All	3/4	All	3/4
Number of subjects with at least one AE	331 (100)	226 (68)	321 (100)	186 (58)
Diarrhoea	245 (74)	38 (11)	89 (28)	7 (2.2)
Fatigue	186 (56)	30 (9.1)	150 (47)	22 (6.8)
Nausea	166 (50)	13 (3.9)	90 (28)	1 (0.3)
Decreased appetite	152 (46)	9 (2.7)	109 (34)	3 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	139 (42)	27 (8.2)	19 (5.9)	3 (0.9)
Hypertension	122 (37)	49 (15)	23 (7.1)	10 (3.1)
Vomiting	106 (32)	7 (2.1)	45 (14)	3 (0.9)
Weight decreased	104 (31)	6 (1.8)	40 (12)	0
Constipation	83 (25)	1 (0.3)	62 (19)	1 (0.3)
Dysgeusia	78 (24)	0	30 (9.3)	0
Stomatitis	74 (22)	8 (2.4)	77 (24)	7 (2.2)
Hypothyroidism	68 (21)	0	2 (0.6)	1 (0.3)
Dysphonia	66 (20)	2 (0.6)	12 (3.7)	0
Mucosal inflammation	64 (19)	3 (0.9)	73 (23)	11 (3.4)
Dyspnoea	63 (19)	10 (3.0)	92 (29)	14 (4.3)
Asthenia	62 (19)	14 (4.2)	50 (16)	7 (2.2)
Cough	60 (18)	1 (0.3)	107 (33)	3 (0.9)
Aspartate aminotransferase increased	58 (18)	6 (1.8)	18 (5.6)	1 (0.3)
Anaemia	56 (17)	18 (5.4)	123 (38)	50 (16)
Back pain	56 (17)	7 (2.1)	47 (15)	7 (2.2)
Abdominal pain	53 (16)	12 (3.6)	32 (9.9)	4 (1.2)
Alanine aminotransferase increased	53 (16)	8 (2.4)	19 (5.9)	1 (0.3)
Hypomagnesaemia	52 (16)	16 (4.8)	5 (1.6)	0
Rash	50 (15)	2 (0.6)	92 (29)	2 (0.6)
Pain in extremity	47 (14)	4 (1.2)	25 (7.8)	1 (0.3)
Muscle spasms	42 (13)	0	16 (5.0)	0
Proteinuria	41 (12)	8 (2.4)	30 (9.3)	1 (0.3)
Dyspepsia	40 (12)	1 (0.3)	15 (4.7)	0
Arthralgia	38 (11)	1 (0.3)	46 (14)	4 (1.2)
Hypokalaemia	38 (11)	15 (4.5)	22 (6.8)	6 (1.9)
Dry skin	37 (11)	0	32 (9.9)	0
Headache	37 (11)	1 (0.3)	39 (12)	1 (0.3)
Dizziness	36 (11)	0	21 (6.5)	0
Hypophosphataemia	33 (10)	12 (3.6)	19 (5.9)	8 (2.5)
Oedema peripheral	31 (9.4)	0	74 (23)	6 (1.9)
Pyrexia	28 (8.5)	2 (0.6)	51 (16)	1 (0.3)
Pruritus	25 (7.6)	0	48 (15)	1 (0.3)
Hypertriglyceridaemia	20 (6.0)	4 (1.2)	40 (12)	9 (2.8)

Hyperglycaemia	15 (4.5)	2 (0.6)	62 (19)	16 (5.0)
Blood creatinine increased	15 (4.5)	1 (0.3)	35 (11)	0
Epistaxis	12 (3.6)	0	46 (14)	0
Pneumonitis	0	0	33 (10)	6 (1.9)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, preferred term
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. Includes only events within the AE observation period defined as the time from first dose date until the earlier of 30 days after date of decision to discontinue study treatment, date of death, date of consent withdrawal, or the data cut-off date. AEs were graded per CTCAE v4; reported AEs were coded using MedDRA v17.0.

Treatment-Related Adverse Events

A summary of treatment related AEs is presented in the table below:

Table 43 - Treatment Related Adverse Events Reported in ≥ 10% of Subjects in the Either Treatment Arm Ordered by Decreasing Frequency and Presented by Grade (Safety Population)

Preferred Term	Cabozantinib| N = 331 n (%)		Everolimus N = 322 n (%)	
	Grade		Grade	
	All	3/4	All	3/4
Number of subjects with at least one related AE	322 (97)	195 (59)	293 (91)	131 (41)
Diarrhoea	227 (69)	35 (11)	65 (20)	6 (1.9)
Fatigue	164 (50)	26 (7.9)	114 (35)	14 (4.3)
Nausea	145 (44)	9 (2.7)	56 (17)	1 (0.3)
Palmar-plantar erythrodysaesthesia Syndrome	136 (41)	27 (8.2)	14 (4.3)	2 (0.6)
Decreased appetite	129 (39)	8 (2.4)	77 (24)	1 (0.3)
Hypertension	109 (33)	47 (14)	10 (3.1)	6 (1.9)
Weight decreased	79 (24)	5 (1.5)	26 (8.1)	0
Vomiting	75 (23)	3 (0.9)	18 (5.6)	0
Dysgeusia	72 (22)	0	27 (8.4)	0
Stomatitis	67 (20)	7 (2.1)	75 (23)	7 (2.2)
Mucosal inflammation	62 (19)	3 (0.9)	70 (22)	11 (3.4)
Hypothyroidism	61 (18)	0	1 (0.3)	1 (0.3)
Dysphonia	55 (17)	2 (0.6)	2 (0.6)	0
Aspartate aminotransferase increased	52 (16)	4 (1.2)	16 (5.0)	1 (0.3)
Asthenia	52 (16)	8 (2.4)	34 (11)	2 (0.6)
Alanine aminotransferase increased	49 (15)	6 (1.8)	15 (4.7)	1 (0.3)
Rash	40 (12)	0	73 (23)	2 (0.6)
Hypomagnesaemia	38 (11)	11 (3.3)	0	0
Anaemia	37 (11)	7 (2.1)	84 (26)	30 (9.3)
Dyspepsia	36 (11)	1 (0.3)	8 (2.5)	0
Proteinuria	36 (11)	7 (2.1)	25 (7.8)	1 (0.3)
Pruritus	22 (6.6)	0	41 (13)	1 (0.3)
Dyspnoea	20 (6.0)	1 (0.3)	46 (14)	4 (1.2)
Cough	15 (4.5)	0	58 (18)	1 (0.3)
Oedema peripheral	12 (3.6)	0	43 (13)	5 (1.6)
Hyperglycaemia	9 (2.7)	1 (0.3)	52 (16)	11 (3.4)
Hypertriglyceridaemia	9 (2.7)	1 (0.3)	36 (11)	9 (2.8)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Denominators for percentages are N, the total number of subjects in each treatment arm.
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. Includes only events within the AE observation period defined as the time from first dose date until the earlier of 30 days after date of decision to discontinue study treatment, date of death, date of consent withdrawal, or the data cutoff date. From the Exelixis dictionary based on MedDRA version 17.0.

Events to Monitor

A set of Events to Monitor (ETMs) has been defined in order to track events known to be associated with TKIs, VEGF pathway inhibition, and other events with potentially serious consequences. Each ETM comprises a set of AEs that are related pathophysiologically.

The ETMs of diarrhoea, PPES, and hypertension include AEs that were reported in high frequency in previous cabozantinib studies and have been commonly observed with VEGFR-TKIs. Less frequent but potentially life-threatening AEs that have been reported for subjects receiving cabozantinib, and other VEGF pathway inhibitors, are represented by the ETMs of GI perforations, fistulas, abscesses-all, intra-abdominal and pelvic abscesses, hemorrhages (≥ Grade 3), arterial thrombotic events, venous and mixed/unspecified thrombotic events, wound complications, osteonecrosis, proteinuria, and RPLS (reversible posterior leukoencephalopathy syndrome). In the interest of routine surveillance, AEs associated with corrected QT interval (QTc) prolongation are tracked in the form of the QTc Prolongation ETM.

Incidences of ETMs for both arms of Study XL184-308 are summarized in Table 44.

Table44 - Study XL184-308 Incidence of Events to Monitor (Safety Analysis Set)

ETM	RCC (XL184-308)					
	Cabozantinib (60 mg) N=331			Everolimus (10 mg) N=322		
	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI perforation	3 (0.9)	2 (0.6)	0	3 (0.9)	1 (0.3)	1 (0.3)
Fistula[a]	4 (1.2)	1 (0.3)	0	0	0	0
Abscess—all	7 (2.1)	4 (1.2)	0	6 (1.9)[b]	1 (0.3)[b]	0
Intra-abdominal and pelvic abscess	4 (1.2)	4 (1.2)	0	1 (0.3)	0	0
Haemorrhage (≥ Grade 3)	7 (2.1)[c]	5 (1.5)	2 (0.6)[d]	5 (1.6)[c,e]	5 (1.6)[e]	0
Arterial thrombotic events	3 (0.9)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Venous and mixed/unspecified thrombotic events	24 (7.3)	12 (3.6)	0	8 (2.5)[f,g]	3 (0.9)[f]	0
Wound complications	8 (2.4)	1 (0.3)	0	4 (1.2)	1 (0.3)	0
Hypertension	128 (39)	52 (16)	0	24 (7.5)	10 (3.1)	0
Osteonecrosis	2 (0.6)	1 (0.3)	0	2 (0.6)[h]	2 (0.6)	0
PPES	139 (42)	27 (8.2)	NA	19 (5.9)	3 (0.9)	NA
Proteinuria	41 (12)	8 (2.4)	NA	30 (9.3)	1 (0.3)	NA
RPLS	0	0	0	0	0	0
Diarrhoea	245 (74)	38 (11)	0	89 (28)	7 (2.2)	0
QTc prolongation	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0

ETM, event to monitor; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; NA, not applicable; PPES, palmar-plantar erythrodysaesthesia syndrome; RCC, renal cell carcinoma; RPLS, reversible posterior leukoencephalopathy syndrome.
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.
[a] In addition to the subjects summarized in the table, one subject experienced a Grade 2 AE of 'fistula anus' which was uncoded.
[b] In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'periodontal abcess' [sic].
[c] For the Haemorrhage ETM, this cell summarizes subject-incidence of events of ≥ Grade 3 only.
[d] Subject 4444-3161 had a post procedural haemorrhage on Day 52, 12 days after last dose; Subject 4501-3191 had an extradural hematoma on Study Day 362, 31 days after the last dose.
[e] In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'stroke hemorrhagic'.
[f] In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'blood clot'.
[g] In addition to the events summarized in the table, one subject in the everolimus arm experienced an event of embolism that was not included as an venous and mixed/unspecified thrombotic event.
[h] In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 2 AE of 'medication related osteonecrosis of the jaw'.

Median times to ETMs for the cabozantinib arm of Study XL184-308 are summarized in Table 45.

Table 45 - Time to First Occurrence of Event to Monitor (Safety Analysis Set)

ETM	RCC (XL184-308) Cabozantinib (60 mg) N=331 Time to First Occurrence (weeks) Median (25th, 75th Percentiles)
GI perforation	10.0 (7.9, 40.0)
Fistulas	30.3 (26.2, 35.4)
Abscess–all	22.3 (12.3, 27.6)
Intra-abdominal and pelvic abscess	23.3 (16.2, 31.0)
Haemorrhage (≥ Grade 3)	20.9 (4.6, 35.3)
Arterial thrombotic events	11.4 (9.1, 32. 1)
Venous and mixed/unspecified thrombotic events	16.1 (8.1, 25.8)
Wound complications	11.0 (5.6, 25.1)
Hypertension	3.0 (2.0, 6.1)
Osteonecrosis	10.0 (7.0, 13.0)
PPES	3.4 (2.3, 6.1)
Proteinuria	4.1 (2.4, 8.1)
RPLS	NA
Diarrhoea	4.9 (2.7, 8.1)
QT prolongation	8.4 (8.4, 8.4)

ETM, event to monitor; GI, gastrointestinal; NA, not applicable; PPES, palmar-plantar erythrodysaesthesia syndrome; RCC, renal cell carcinoma; RPLS, reversible posterior leukoencephalopathy syndrome.
Time to first occurrence was the defined as (date of first occurrence of ETM – first dose date +1).

GI Perforation

The incidence of GI perforations were reported for 3 subjects [0.9%] each) in Study XL184-308. Grade 3 events were reported for 2 subjects (0.6%) in the cabozantinib arm (GI perforation and small intestine perforation). Two Grade 4 AEs (peritonitis and intestinal perforation were reported for one subject in the everolimus arm, and a Grade 5 AE of GI perforation was reported in the everolimus arm.

One subject in the cabozantinib arm experienced a Grade 2 AE of appendicitis perforated. The subject had a concurrent event of abdominal abscess (Grade 3). Both events were considered SAEs.

Fistulas

The fistula ETMs in the cabozantinib arm of Study XL184-308 were reported for four subjects (1.2%), and no events were reported in the everolimus arm. A Grade 3 event of anal fistula was reported for one subject in the cabozantinib arm; all other events were ≤ Grade 2. In addition, one subject in the cabozantinib arm experienced an uncoded Grade 2 AE of 'fistula anus'.

Abscess—All

The ETMs of abscess–all Study XL184-308 were reported for7 cabozantinib-treated subjects (2.1%) and 6 everolimus-treated subjects (1.9%). Four of these subjects in the cabozantinib arm had Grade 3 events of abscess (all intra-abdominal AEs, see below). The majority of the reported PTs for cabozantinib-treated subjects were also included in the intra-abdominal and pelvic abscess ETM, and relative to the intra-abdominal and pelvic abscess ETM, no further events of ≥ Grade 3 were reported for the cabozantinib arm. However, a Grade 3 event of abscess neck was reported for a subject in the everolimus arm, and in addition to the events summarized in the table below, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'periodontal abcess' [sic].

Intra-abdominal and Pelvic Abscess

The intra-abdominal and pelvic abscess ETMs in Study XL184-308 were reported for four subjects (1.2%) in the cabozantinib arm and one subject (0.3%) in the everolimus arm. Grade 3 events were reported for all four subjects with events in the cabozantinib arm (2 subjects each [0.6%] with PTs of abdominal abscess and anal abscess); the perineal abscess reported in the everolimus arm was Grade 2.

Abscess was associated with an anal fistula in the two subjects who experienced an anal abscess, and with an appendicitis perforated in a subject who experienced an abdominal abscess. In general, intra-abdominal and pelvic abscesses are linked pathophysiologically to fistulas and GI perforations.

Hemorrhage (≥ Grade 3)

The hemorrhage (≥ Grade 3) ETMs in Study XL184-308 were reported for 7 cabozantinib-treated subjects (2.1%) and 5 everolimus-treated subjects [1.6%]). In addition, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'stroke hemorrhagic'.

One subject in the cabozantinib arm experienced two Grade 4 events (hemarthrosis and hemorrhagic anemia), and two Grade 4 events were reported for two subjects in the everolimus arm (renal hemorrhage and hemoptysis). Grade 5 events were reported for two subjects in the cabozantinib arm; both were assessed by the investigator as not related to study treatment.

- One subject died on Study Day 52, 12 days after the last dose of cabozantinib. The subject died from post-procedural hemorrhage following treatment of an AE of Grade 3 peripheral ischemia with thrombectomy of the groin and fasciotomy of the legs; heparin had been administered for blood clot prophylaxis.

- One subject died on Study Day 364, 31 days after the last dose of cabozantinib. The subject died due to extradural hematoma derived from bone metastases to the skull; the event initiated as a Grade 4 AE on Study Day 362. The subject had been discontinued from study treatment due to disease progression. Prior to the AE of extradural hematoma, the subject had been hospitalized for treatment of Grade 3 pneumonia.

Arterial Thrombotic Events

The incidence of arterial thromboses reported in Study XL184-308 included 3 cabozantinib-treated subjects (0.9%) and 1 everolimus subject (0.3%). All events in both treatment arms were ≤ Grade 3. Both Grade 3 events for subjects in the cabozantinib arm were reported as SAEs (carotid artery occlusion; and carotid artery thrombosis).

Venous and mixed/unspecified thrombotic events

Table 46 summarizes the reported ETMs of venous and mixed/unspecified thrombosis by PT in Study XL184-308.

The incidence of venous and mixed/unspecified thrombotic ETMs in Study XL184-308 was 7.3% (24 subjects) in the cabozantinib arm and 2.5% (8 subjects) in the everolimus arm. The most frequently reported events of any grade in the cabozantinib arm were pulmonary embolism (12 cabozantinib-treated subjects [3.6%], 1 everolimus subject [0.3%]), deep vein thrombosis (DVT; 5 [1.5%], 2 [0.6%]), and portal vein thrombosis (2 [0.6%], 1 [0.3%]); all other events were reported in no more than one subject per treatment arm.

Grade 3 or 4 venous or mixed/unspecified thrombotic events were reported for 12 subjects (3.6%) in the cabozantinib arm and 3 subjects (0.9%) in the everolimus arm. The majority of the cabozantinib-treated

subjects had pulmonary embolism (8 subjects [2.4%]); one of which had a Grade 4 pulmonary embolism. In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'blood clot'.

Table 46 - Incidence of Venous and Mixed/Unspecified Thrombotic Events to Monitor in Study XL184-308 by Preferred Term (Safety Analysis Set)

	RCC (XL184-308)					
	Cabozantinib (60 mg) N=331			Everolimus (10 mg) N=322		
MedDRA Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Subjects with a venous and mixed/unspecified thrombotic events ETM[a]	24 (7.3)	12 (3.6)	0	8 (2.5)[b]	3 (0.9)[b]	0
Deep vein thrombosis	5 (1.5)	1 (0.3)	0	2 (0.6)	0	0
Haemorrhoids thrombosed	1 (0.3)	0	0	0	0	0
Hepatic vein thrombosis	0	0	0	1 (0.3)	0	0
Intracranial venous sinus thrombosis	1 (0.3)	1 (0.3)	0	0	0	0
Pelvic venous thrombosis	1 (0.3)	0	0	0	0	0
Portal vein thrombosis	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Pulmonary embolism	12 (3.6)	8 (2.4)	0	1 (0.3)	1 (0.3)	0
Pulmonary thrombosis	1 (0.3)	1 (0.3)	0	0	0	0
Splenic vein thrombosis	1 (0.3)	1 (0.3)	0	0	0	0
Subclavian vein thrombosis	1 (0.3)	0	0	0	0	0
Thrombophlebitis superficial	1 (0.3)	0	0	1 (0.3)	0	0
Thrombosis	1 (0.3)	0	0	1 (0.3)	0	0
Tumour thrombosis	0	0	0	1 (0.3)	1 (0.3)	0
Venous thrombosis	1 (0.3)	0	0	0	0	0
Venous thrombosis limb	1 (0.3)	0	0	0	0	0

AE, adverse event; ETM, event to monitor; MedDRA, Medical Dictionary for Regulatory Activities; RCC, renal cell carcinoma; 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.

[a] In addition to the events summarized in the table, there were two AEs of Grade 2 embolism reported in Study XL184-308. Subject 1563-3097 (cabozantinib arm) experienced the embolism AE on Study Day 170, and the subject also had AEs of portal vein thrombosis and splenic vein thrombosis. Subject 2002-3762 (everolimus arm) experienced the embolism AE on Study Day 56 and had no other venous thrombotic ETMs. Neither embolism event was reported as an SAE.

[b] In addition to the events summarized in the table, one subject in the everolimus arm experienced an uncoded Grade 3 AE of 'blood clot'.

Among the cabozantinib-treated subjects who experienced pulmonary embolism AEs, three reported a second AE defined as a venous and mixed/unspecified thrombotic ETM; one subject experienced an AE of subclavian vein thrombosis, and two subjects experienced deep vein thromboses (DVTs).

Wound Complications

The incidence of wound complications in Study XL184-308 were reported for8 cabozantinib-treated subjects (2.4%) and 4 everolimus-treated subjects (1.2%). The most frequent event of any grade reported in the cabozantinib arm was impaired healing (3 cabozantinib-treated subjects [0.9%], 0 everolimus-treated subjects). The most frequent event of any grade reported in the everolimus arm was wound infection (1 cabozantinib subject [0.3%], 2 everolimus-treated subjects [0.6%]). All other events were each reported for one subject in either treatment arm.

There was one Grade 3 event reported for each treatment arm: impaired healing for cabozantinib,

wound infection for everolimus.

Wound complications for cabozantinib-treated subjects in Study XL184-308 were primarily post-surgical events, and all but one AE were low grade (≤ Grade 2). The Grade 3 AE (impaired healing) occurred in the context of PPES; the event was non-serious and resolved within 2 weeks of onset.

Hypertension

The incidence of hypertension ETMs was higher in the cabozantinib arm (128 subjects [39%]) compared with the everolimus arm (24 subjects [7.5%]). The most frequently reported ETM PT was hypertension in both treatment arms (37% cabozantinib, 7.1% everolimus).

The incidence of Grade 3 hypertension ETMs was also higher in the cabozantinib arm (52 subjects [16%]) compared with the everolimus arm (10 subjects [3.1%]).

Two cabozantinib-treated subjects had AEs reported by the investigator as hypertensive crisis (note: the data presented do not meet the definition for hypertensive crisis for either subject). No cabozantinib-treated subjects had documented evidence of malignant hypertension, hypertensive urgency, or hypertensive emergency.

Osteonecrosis

The incidence of osteonecrosis ETMs in Study XL184-308 were reported for2 cabozantinib-treated subjects (0.6%) and 2 everolimus-treated subjects (0.6%). Events were reported for only one PT, osteonecrosis of the jaw (ONJ). Grade 3 events were reported for one cabozantinib subject (0.3%) and two everolimus-treated subjects (0.6%). At baseline, the cabozantinib subject with the Grade 3 AE of ONJ had an ongoing AE of Grade 2 ONJ assessed as related to prior therapy. This subject also received concomitant denosumab on study. The cabozantinib subject who experienced the Grade 2 AE also had a prior history of ONJ which resolved before enrolling in Study XL184-308.

In addition, one subject in the everolimus arm experienced an uncoded Grade 2 AE of 'medication related osteonecrosis of the jaw'.

The use of concomitant bisphosphonates (11% cabozantinib, 11% everolimus) and denosumab (5.4%, 6.5%) was similarly low in either treatment arm. Tooth abscess occurred in one cabozantinib subject and two everolimus-treated subjects.

Palmar-plantar erythrodysaesthesia syndrome (PPES)

The incidence of events of PPES was high in the cabozantinib arm (139 subjects [42%]); 19 subjects (5.9%) had PPES in the everolimus arm. No events of PPES > Grade 3 were reported for either treatment arm.

Proteinuria

Proteinuria is an expected event in this subject population due the high rate of prior nephrectomy and the requirement for prior VEGFR-TKI therapy. The incidence of proteinuria events in the cabozantinib arm was 12% (41 subjects) and was 9.3% (30 subjects) in the everolimus arm. There were no proteinuria events reported in either arm with severity > Grade 3. Kidney toxicity has been reproted some animal models (see pre-clinical AR). Caution should be taken in patients with severe renal impairment as described in the SmPC.

RPLS

Events of RPLS have been reported for subjects treated with cabozantinib in non-RCC studies, but no

such events were reported for either arm of Study XL184-308.

Diarrhoea

The incidence of diarrhea events was 74% (245 subjects) in the cabozantinib arm and 28% (89 subjects) in the everolimus arm; diarrhea was the most frequently reported AE for subjects in the cabozantinib arm. No diarrhea events of severity > Grade 3 were reported on either treatment arm of Study XL184-308. Diarrhea was reported as an SAE in 2.1% of cabozantinib-treated subjects.

While dose modifications (ie, reductions and interruptions) due to AEs of diarrhea were frequent (26%) for cabozantinib-treated subjects in Study XL184-308, there was a low rate (0.9%) of cabozantinib-treated subjects who discontinued study treatment due to diarrhea.

QTc Prolongation

The incidence of events of QTc prolongation was low for both treatment arms (one subject each).

- Subject (4929-3536) in the cabozantinib arm had a Grade 2 nonserious AE of ECG QT prolonged on Study Day 59. The subject was receiving cabozantinib at a dose of 60 mg qd at the time of the onset of the AE, and no modifications in study treatment were implemented as a result of the event. No QTc correction by the Fridericia's formula (QTcF) >500 ms was reported for this subject, and the absolute increase in QTcF from baseline for this subject was unknown.
- Subject (7006-3190) in the everolimus arm had a Grade 3 non-serious AE of ECG QT prolonged on Study Day 57. The subject was receiving everolimus at a dose of 10 mg qd at the time of the onset of the AE, and no modifications in study treatment were implemented as a result of the event. The subject had one single ECG read with a QTcF > 500 ms assessed by the investigator, but the findings were not confirmed by independent ECG review.

Serious adverse event / deaths / other significant events

A summary of SAEs is presented in the table below:

Table 47 - Study XL184-308: Serious Adverse Events Reported in ≥ 1.5% of Subjects in Either Treatment Arm Regardless of Causality (Safety Population)

Preferred Term	Cabozantinib N = 331 n (%)		Everolimus N = 322 n (%)	
	All SAEs	Related SAEs	All SAEs	Related SAEs
Number of subjects with at least one SAE	131 (40)	50 (15%)	139 (43)	41 (13%)
Renal cell carcinoma	11 (3.3)	0	11 (3.4)	0
Abdominal pain	10 (3.0)	3 (0.9)	2 (0.6)	0
Pleural effusion	10 (3.0)	1 (0.3)	6 (1.9)	0
Diarrhoea	7 (2.1)	6 (1.8)	2 (0.6)	1 (0.3)
Nausea	7 (2.1)	2 (0.6)	2 (0.6)	0
Anaemia	6 (1.8)	2 (0.6)	12 (3.7)	7 (2.2)
Back pain	6 (1.8)	0	4 (1.2)	0
Dyspnoea	6 (1.8)	0	13 (4.0)	4 (1.2)
Fatigue	6 (1.8)	4 (1.2)	5 (1.6)	0
Pneumonia	6 (1.8)	0	13 (4.0)	2 (0.6)
Pulmonary embolism	6 (1.8)	5 (1.5)	1 (0.3)	1 (0.3)
Vomiting	6 (1.8)	1 (0.3)	4 (1.2)	0
Pain	5 (1.5)	0	4 (1.2)	0
General physical health deterioration	4 (1.2)	0	6 (1.9)	0
Dehydration	3 (0.9)	3 (0.9)	7 (2.2)	4 (1.2)
Metastases to central nervous system	1 (0.3)	0	5 (1.6)	0
Pneumonitis	0	0	8 (2.5)	8 (2.5)
Renal failure acute	0	0	5 (1.6)	1 (0.3)

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. Includes only events within the AE observation period defined as the time from first dose date until the earlier of 30 days after date of decision to discontinue study treatment, date of death, date of consent withdrawal, or the data cut-off date.

Treatment-Related Serious Adverse Events

A summary of treatment related SAEs is presented in the table below:

Table 48 - Treatment-Related Serious Adverse Events Reported in ≥ 1% of Subjects in Either Treatment Arm (Safety Population)

Preferred Term	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Number of subjects with at least one treatment related SAE	50 (15)	41 (13)
Diarrhoea	6 (1.8)	1 (0.3)
Pulmonary embolism	5 (1.5)	1 (0.3)
Fatigue	4 (1.2)	0
Hypomagnesaemia	4 (1.2)	0
Dehydration	3 (0.9)	4 (1.2)
Anaemia	2 (0.6)	7 (2.2)
Pneumonitis	0	8 (2.5)
Dyspnoea	0	4 (1.2)

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.
Includes only events within the AE observation period defined as the time from first dose date until the earlier of
30 days after date of decision to discontinue study treatment, date of death, date of consent withdrawal, or the data cut-off date.

Deaths - up to 22nd May 2015

A total of 200 deaths were reported in the safety population as of the cutoff date of 22nd May 2015, which included 90 subjects (27%) in the cabozantinib arm and 110 subjects (34%) in the everolimus arm. 38 deaths occurred through 30 days of the last dose: 15 (4.5%) in the cabozantinib arm and 23 (7.1%) in the everolimus arm; deaths were attributed to progressive disease (8 subjects [2.4%] cabozantinib, 11 [3.4%] everolimus).

A total of 162 deaths occurred more than 30 days after last dose of study drug: 75 (23%) in the cabozantinib arm and 87 (27%) in the everolimus arm. Most of these deaths were due to progressive disease (145 out of 162), with more PD deaths occurring in the everolimus arm (65/331 subjects [20%] cabozantinib, 80/322 [25%] everolimus).

Table 49 - Deaths and Primary Reason for Death (Safety Population)

	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Alive	241 (73)	212 (66)
Expired	90 (27)	110 (34)
Deaths ≤ 30 days after the date of last dose of study treatment	15 (4.5)	23 (7.1)
Progression of disease under study	8 (2.4)	11 (3.4)
Other	7 (2.1)	12 (3.7)
Death causally associated with renal cell carcinoma?		
Yes	2 (0.6)	8 (2.5)
No	3 (0.9)	3 (0.9)
Unknown	2 (0.6)	1 (0.3)
Deaths > 30 days after the date of last dose of study treatment	75 (23)	87 (27)
Progression of disease under study	65 (20)	80 (25)
Other	10 (3.0)	7 (2.2)
Death causally associated with renal cell carcinoma?		
Yes	3 (0.9)	2 (0.6)
No	1 (0.3)	1 (0.3)
Unknown	6 (1.8)	4 (1.2)

Deaths - up to 31st December 2015

With a cutoff date of 31st December 2015, there were 320 total deaths, representing 78% (320/408) of the total deaths required for the planned final analysis of OS, 137 in the cabozantinib arm and 170 in the everolimus arm.

Laboratory findings

Serum chemistry parameters that most frequently (≥5%) showed a shift in the cabozantinib arm from < Grade 3 at baseline to ≥ Grade 3 post-baseline were sodium decreased (28/331 [8.5%]), phosphate decreased (27/331 [8.2%]), and LDH increased (21/331 [6.3%]). Serum chemistry parameters that most frequently (≥ 5%) showed a shift in the everolimus arm from < Grade 3 at baseline to ≥ Grade 3 post-baseline were triglycerides increased (39/322 [12%]), gammaglutamyl transpeptidase (GGT) increased (28/322[8.7%]), and

glucose increased (26/322 [8.1%]), sodium decreased (18/322 [5.6%]), and phosphate decreased (16/322 [5.0%]).

The most frequent (≥40%) treatment-emergent serum chemistry laboratory abnormalities of any grade reported in the cabozantinib arm by decreasing frequency were AST increased, ALT increased, creatinine increased, triglycerides increased, and phosphate decreased. Most of the treatment-emergent chemistry abnormalities were of Grade 1 or 2 severity in both treatment arms.

Increases in liver transaminases (ALT, AST) were frequent in both arms but there was a low incidence of severe abnormalities. There were no cases that met Hy's Law criteria (concurrent ALT or AST >3 x ULN, total bilirubin >2 x ULN, and ALP <2 x ULN).

The only hematology abnormality (Grade 3 or 4) that had a ≥ 5% incidence in the Study XL184-308 cabozantinib arm was decreased lymphocytes. In the everolimus arm, Grade 3 or 4 abnormalities that had a ≥ 5% incidence were decreases in hemoglobin and lymphocytes.

Table 50 - Subject Incidence of Selected Laboratory Abnormalities by CTCAE Grade (≥ 10% in Either Treatment Arm) (Safety Population)

	Cabozantinib (N = 331) n (%)			Everolimus (N = 322) n (%)		
Laboratory Parameter	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Serum Chemistry						
AST increased	245 (74)	11 (3.3)	0	129 (40)	2 (0.6)	0
ALT increased	224 (68)	10 (3.0)	1 (0.3)	103 (32)	1 (0.3)	0
Creatinine increased	192 (58)	0	1 (0.3)	229 (71)	0	0
Triglycerides increased	176 (53)	12 (3.6)	0	235 (73)	35 (11)	6 (1.9)
Phosphate decreased	160 (48)	27 (8.2)	0	116 (36)	16 (5.0)	0
Glucose increased[a]	123 (37)	7 (2.1)	0	190 (59)	27 (8.4)	0
Albumin decreased	118 (36)	7 (2.1)	0	89 (28)	2 (0.6)	0
ALP increased	116 (35)	6 (1.8)	0	94 (29)	4 (1.2)	0
Magnesium decreased	102 (31)	14 (4.2)	10 (3.0)	14 (4.3)	1 (0.3)	0
Sodium decreased	100 (30)	26 (7.9)	2 (0.6)	84 (26)	17 (5.3)	2 (0.6)
GGT increased	88 (27)	14 (4.2)	2 (0.6)	140 (43)	28 (8.7)	1 (0.3)
Amylase increased	55 (17)	6 (1.8)	0	24 (7.5)	1 (0.3)	1 (0.3)
Potassium decreased	55 (17)	16 (4.8)	2 (0.6)	32 (9.9)	6 (1.9)	2 (0.6)
Cholesterol increased	54 (16)	0	3 (0.9)	103 (32)	4 (1.2)	5 (1.6)
Lipase increased	47 (14)	10 (3.0)	3 (0.9)	30 (9.3)	8 (2.5)	1 (0.3)
Calcium corrected, decreased	41 (12)	9 (2.7)	1 (0.3)	14 (4.3)	1 (0.3)	1 (0.3)
Glucose decreased[a]	40 (12)	0	0	24 (7.5)	0	0
Potassium increased	36 (11)	5 (1.5)	0	37 (11)	5 (1.6)	4 (1.2)
Total bilirubin increased	35 (11)	4 (1.2)	1 (0.3)	5 (1.6)	0	1 (0.3)
Haematology						
WBC decreased	117 (35)	2 (0.6)	0	100 (31)	2 (0.6)	0
Hemoglobin decreased	102 (31)	14 (4.2)	0	230 (71)	54 (17)	0
ANC decreased	101 (31)	8 (2.4)	0	56 (17)	2 (0.6)	0
Platelets decreased	84 (25)	2 (0.6)	0	86 (27)	2 (0.6)	1 (0.3)
Lymphocytes decreased	83 (25)	23 (6.9)	0	124 (39)	37 (11)	1 (0.3)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma glutamyl transferase. Considers worst value after first dose for each abnormality per subject. Laboratory results from both central and local laboratories were included. Grade 0 assigned to nonmissing values that did not meet the criteria for Grade 1 or higher in the direction of interest (ie, may include abnormal values in the opposite direction). [a] Fasted glucose was the protocol-specified analyte; however, glucose was analyzed regardless of fasting status.

Safety in special populations

Table 51 – Safety in special populations

MedDRA Terms	Cabozantinib (60 mg) (N=331) n (%)			
	< 65 (N=197)	65-74 (N=107)	75-84 (N=26)	≥ 85 (N=1)
Number of events				
Total Related AEs[a]	2808	1551	404	50
Total Related SAEs	33	45	7	0
Fatal	1	0	0	0
Hospitalization/prolong existing hospitalization	29	42	6	0
Life-threatening	3	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	0	0	0	0
Subject Incidence[b]				
Drug Withdrawal (SMQ)	0	0	0	0
Psychiatric Disorders (SOC)	45 (22.8)	23 (21.5)	6 (23.1)	0
Nervous System Disorders (SOC)	101 (51.3)	58 (54.2)	14 (53.8)	1 (100.0)
Accidents and Injuries (SMQ)	23 (11.7)	20 (18.7)	4 (15.4)	0
Cardiac Disorders (SOC)	14 (7.1)	9 (8.4)	3 (11.5)	0
Vascular Disorders (SOC)	88 (44.7)	47 (43.9)	11 (42.3)	1 (100.0)
Cerebrovascular Disorders (SMQ)	0	4 (3.7)	1 (3.8)	0
Infections and Infestations (SOC)	78 (39.6)	47 (43.9)	12 (46.2)	1 (100.0)
Quality of Life Decreased (PT)	0	0	0	0
Anticholinergic syndrome	23 (11.7)	16 (15.0)	4 (15.4)	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures (PTs)	26 (13.2)	16 (15.0)	8 (30.8)	0
Anaemia (PT)	23 (11.7)	24 (22.4)	9 (34.6)	0
AEs Leading to Dropout	14 (7.1)	12 (11.2)	8 (30.8)	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SMQ, standard MedDRA query; SOC, System Organ Class.

[a] These data represent an over-estimate of related AE episodes because a unique record is documented for every change in severity grade, up or down, even within a single AE episode.

[b] Each subject is counted only once at each level of summarization.

From the Exelixis dictionary based on MedDRA v17.0.

Safety related to drug-drug interactions and other interactions

Drug-drug interaction studies have been carried out in vitro and in the clinic. Knowledge to date is adequately reflected in the SmPC.

Discontinuation due to adverse events

The incidence of AEs that led to discontinuation of study drug was similar between treatment arms (10% cabozantinib, 9.6% everolimus). The most frequent AEs leading to discontinuation of cabozantinib (≥ 1% incidence) were decreased appetite (1.8%) and fatigue (1.2%).

Post marketing experience

Cabozantinib capsules (Cometriq) were first approved by the FDA on 29 November 2012 for the treatment of patients with progressive, metastatic MTC at a dose of 140 mg qd. Cometriq was made commercially available in the United States on 24 January 2013. On 21 March 2014, cabozantinib capsules (Cometriq) at the 140-mg

dose received approval through the centralized procedure by the European Commission for the treatment of adults with progressive, unresectable locally advanced or metastatic MTC.

The post-marketing patient population through 22 May 2015 comprised 1149 total patients exposed including approximately 1083 in the US, 42 in the EU (marketed and named patient use [NPU]), and 24 from other countries (NPU).

Through 22 May 2015, patients in the US marketed setting have received cabozantinib for treatment of thyroid cancer (n=453) as well as malignancies other than the approved indication, including prostate cancer (n=184), renal cancer (n=183), hepatocellular cancer (n=19), and lung cancer (n=61). In the EU, patients have thus far received marketed drug for MTC (n=11), pheochromocytoma (n=1), and HCC (n=1). Cumulatively, 587 serious adverse reactions (SARs) have been reported in the post-marketing setting through 22 May 2015.

Through 22 May 2015, 75 post-marketing SARs for 49 cases were received in subjects who received Cometriq off-label for the indication of renal cancer (including RCC and malignant neoplasm of the renal pelvis). With the exception of unknown cause of death (death [n=11]), pneumonia (n=4), dehydration (n=3), rectal haemorrhage (n=3), hypertension (n=2), hypotension (n=2), vomiting (n=2), and pain in extremity (n=2), the occurrence of any individual SAR was limited to one event.

After the 22 May 2015 cut-off, one unconfirmed case of posterior reversible encephalopathy syndrome (PRES; also called RPLS) was reported by a non-study physician via the post-marketing process for a subject who was enrolled in Study XL184-308. The report was not contemporaneous with the event (made >1 year afterwards) and there was inconsistent information in the report regarding the date of the event relative to study treatment. The patient also had confounding factors including receipt of a prior VEGFR-TKI and radiation for brain metastases. There is no evidence of imaging supporting the diagnosis of RPLS, and the event was not confirmed by the investigator. Additional follow-up is ongoing.

2.6.1. Discussion on clinical safety

The safety population included subjects that received at least one dose of study treatment. The size of the safety data package was considered sufficient for the assessment of risks in a marketing authorisation application in this disease setting.

A total of 59.8% of subjects in the cabozantinib arm and 24.2% of subjects in the everolimus arm had a dose reduction due to an AE. Dose interruptions due to an AE occurred in 70% subjects in the cabozantinib and 59% of everolimus arms subjects.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Cabometyx therapy. Dose reductions are adequately described in the SmPC (see section 4.2). Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made (see SmPC section 4.2)

All subjects in the cabozantinib arm had an AE. The types of adverse events reported are generally in line with the known profile of cometriq (cabozantinib) and/ or TKIs.

The overall incidence of AEs in trial XL184-308 (regardless of causality) was similar in both arms, but the safety profile was different as expected based on the different mechanisms of action.

ETMs consist of groupings of AE preferred terms known to be associated with VEGFR-TKIs as well as AEs with potentially serious consequences. These ETMs comprise GI perforation, fistula, abscess-all, intra-abdominal and pelvic abscess, hemorrhage (≥ Grade 3), arterial thrombotic event, venous and mixed/unspecified thrombotic event, wound complication, hypertension, osteonecrosis, PPES, proteinuria, RPLS, diarrhea, and QTc prolongation.

The most frequent ETMs occurring on cabozantinib treatment were diarrhea (74%), PPES (42%) and hypertension (39%), proteinuria (12%) and median time to the first occurrence of these ETMs were also the shortest ones: hypertension (3.0 weeks), PPES (3.4 weeks), proteinuria (4.1 weeks), and diarrhea (4.9 weeks).

The median time to first occurrence of ETMs of GI perforations, arterial/venous/mixed/unspecified thrombotic events and wound complications was at least 10 weeks, for abcesses, fistulas and ≥ Grade 3 hemorrhages, median time to first occurrence was at least 20 weeks.

The ETMs of thromboembolic events, haemorrhage, wound complications, hypertension, PPES, proteinuria, RPLS, fistulas, GI perforations and QT prolongation are adequately described in warning/precaution texts in the section 4.4. of the SmPC.

2.6.2. Conclusions on the clinical safety

No new safety signals were observed for cabozantinib. The safety profile of cabozantinib appears similar to other VEGFR-TKIs used to treat RCC. Overall, the safety profile of cabozantinib in RCC appears manageable and no major safety concerns were raised.

2.7. Risk Management Plan

Safety concerns

Table 52 – Summary of safety concerns

Summary of safety concerns	
Important identified risks	GI Perforation GI and non-GI Fistula Thromboembolic events Haemorrhage (Grade ≥ 3) Wound complications Hypertension Reversible posterior leukoencephalopathy syndrome (RPLS) Diarrhoea Palmar-plantar erythrodysaesthesia syndrome (PPES) Hypothyroidism

Summary of safety concerns	
	Osteonecrosis Proteinuria
Important potential risks	QT prolongation Renal failure Hepatotoxicity Fertility impairment Embryotoxicity Medication error
Missing information	Use in paediatric population Use in pregnant or lactating women Use in patients with cardiac impairment Use in patients with severe hepatic impairment Use in patients with severe renal impairment Carcinogenicity

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that the routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 53 – Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
GI Perforation	SPC sections 4.4 and 4.8	None
GI and non-GI Fistula	SPC sections 4.4 and 4.8	None
Thromboembolic events	SPC sections 4.4 and 4.8	None
Haemorrhage (Grade ≥ 3)	SPC sections 4.4 and 4.8	None
Wound complications	SPC section 4.4	None
Hypertension	SPC sections 4.4 and 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Reversible posterior leukoencephalopathy syndrome (RPLS)	SPC sections 4.4 and 4.8	None
Diarrhoea	SPC sections 4.4 and 4.8	None
Palmar-plantar erythrodysaesthesia syndrome (PPES)	SPC sections 4.4 and 4.8	None
Hypothyroidism	SPC section 4.8	None
Osteonecrosis	SPC section 4.8	None
Proteinuria	SPC sections 4.4 and 4.8	None
QT prolongation	SPC sections 4.4 and 5.1	None
Renal failure	SPC section 4.2	None
Hepatotoxicity	SPC sections 4.2 and 4.8	None
Fertility impairment	SPC sections 4.6 and 5.3	None
Embryotoxicity	SPC sections 4.6 and 5.3	None
Medication error	SPC section 4.2	None
Use in paediatric population	SPC section 4.2	None
Use in pregnant or lactating women	SPC section 4.6	None
Use in patients with cardiac impairment	SPC section 4.2	None
Use in patients with severe hepatic impairment	SPC sections 4.2 and 5.2	None
Use in patients with severe renal impairment	SPC sections 4.2 and 5.2	None
Carcinogenicity	SPC section 5.3	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Cometriq. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, CABOMETYX (cabozantinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant initially claimed the following indication:

CABOMETYX (cabozantinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received one prior therapy.

The current agreed indication is:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Renal cell carcinoma is the third leading urologic cancer. About 30% of patients with RCC have metastatic disease at the time of diagnosis, and a significant proportion of patients with localized disease treated with curative nephrectomy relapse subsequently with metastatic disease. Metastatic RCC is associated with a high quality-of-life burden. About 8% to 22.5% of mRCC patients survive for five years or more as compared to 90% of patients with localized renal cancer, but survival rates increase with the use of new therapies and depend on several prognostic factors. Patient population is heterogeneous in terms of clinical (prognostic factors) and molecular determinants.

The incidence of mRCC is increasing, and the disease is still considered incurable. The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain.

In patients with advanced RCC, the aim of therapy is to prolong PFS, to achieve high response rate, to prolong survival and to improve quality of life. In second line setting only few agents could demonstrate benefit in terms of OS (e.g. nivolumab) and most of therapies approved in second line could show PFS benefit in randomised phase 3 trials, although with different magnitude of effect (median PFS ranging from 4 to 7 months).

The aim of therapy with cabozantinib is to delay progression and to prolong survival. The pivotal study supporting the application for cabozantinib was designed to provide adequate power for evaluation of both the primary endpoint PFS, and the key secondary endpoint, OS.

3.1.2. Available therapies and unmet medical need

The current standard of care for advanced RCC patients whose disease has progressed on or who are resistant to VEGFR-TKI therapy is treatment with everolimus or axitinib. Sorafenib is also recommended in this setting based on a study in patients who had progressed on a prior systemic (mainly cytokine-based) therapy. However, none of these agents has demonstrated a survival benefit in the second-line setting. Everolimus is the most frequently used second-line therapy following a VEGFR-TKI in patients with RCC. CHMP has recently adopted a positive opinion for nivolumab in the second-line treatment of RCC, based on data showing statistically significant improvement in overall survival compared to everolimus. Despite the encouraging results for nivolumab, 75% of the patients do not show response to the treatment.

The vast majority of patients with advanced RCC will experience disease progression due to acquired or a priori resistance to VEGFR- or mTOR-targeted therapy. The extent and location of tumour metastases in patients with advanced RCC contribute to significant morbidity. Metastatic symptoms include airway obstruction, venous thromboembolism, bone pain, skeletal related events (SREs), and hypercalcemia. In addition, paraneoplastic syndromes (hypertension and disorders of the endocrine, hepatic, and neuromuscular system impact quality of life of patients with advanced RCC (Cella. The Oncologist 2011;16(suppl 2):23–31). The median overall survival for patients with advanced RCC ranges from about 8 months (poor risk score) to 4 years (favourable risk score). Therefore, an unmet need remains for treatments that will prolong time to progression and improve survival.

3.1.3. Main clinical studies

The main study is of acceptable design. The pivotal study is XL184-308, a phase III, randomized, controlled study of cabozantinib vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy. No major GCP issues have been highlighted with respect to the review of the clinical data. Overall the conduct of the study appears satisfactory and in line with international standards. 658 subjects were randomised in study XL184-308, 330 in the cabozantinib arm and 328 in the everolimus arm.

3.2. Favourable effects

The primary endpoint was PFS. The results demonstrate a statistically significant and clinically meaningful improvement in PFS for subjects in the cabozantinib arm compared to everolimus, an acceptable comparator in this setting. The HR adjusted for stratification factors was 0.59 (95% CI: 0.46, 0.76; stratified log-rank p-value < 0.001). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm.

The PFS HR among all enrolled subjects (ITT population) was 0.52 (95% CI: 0.43, 0.64) and sensitivity analyses using alternative definitions of progression demonstrate robustness and consistency of the effect. A PFS treatment benefit was observed across the majority of the pre-specified baseline and demographic subgroups evaluated for the PITT (primary analysis) and the ITT population.

PFS and OS results based on stratification values from the IVRS/IWRS entered at the time of randomization rather than stratification values entered onto the CRF, source data verified, and used in the CSR were similar for each method. These PFS and OS analyses based on IVRS/IWRS stratification values were incorporated in Section 5.1 of the Cabometyx SmPC.

The ORR per IRC showed a statistically significant benefit with cabozantinib treatment. The ORR was 17% for subjects who received cabozantinib and 3% for subjects who received everolimus. All the responses were confirmed PRs. The majority of subjects in the cabozantinib arm had a post-baseline reduction in tumour size (75% cabozantinib, 48% everolimus).

At the cut-off May 2015, a trend for longer survival for cabozantinib treated subjects was observed, 0.68 (95% CI: 0.51, 0.90; stratified logrank p-value = 0.006), despite a higher number of subjects in the everolimus arm (47%) receiving subsequent systemic anti-cancer treatment compared to those in the cabozantinib arm (38%).

At the data cut-off of 31st December 2015 (unplanned analysis), the HR adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified logrank p-value = 0.0003). The Kaplan-Meier estimates of median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm, 4.9 month difference. The extreme nature of the result and the consistency of the estimate of the HR with the previous (planned) analysis of OS give confidence that there is an OS benefit for cabozantinib compared to everolimus.

3.3. Uncertainties and limitations about favourable effects

There are some indications that the everolimus arm included more patients with slightly worse prognosis than the cabozantinib arm; i.e. more patients in the everolimus arm with Stage IV disease, more subjects with ≥ 3 involved organs, more patients with less than 1 year from diagnosis to randomization, median time from progression on most recent VEGFR-TKI to randomisation was slightly longer, more patients had progressed earlier than 3 months from start of most recent VEGFR-TKI. Thus the improvement in PFS with cabozantinib compared to everolimus could be somewhat overestimated.

Although positive trends for OS of cabozantinib treatment has been observed in both interim analyses performed, the final analysis is lacking to confirm the observed improvement in OS. The Applicant will submit the final OS results by September 2017.

3.4. Unfavourable effects

All subjects in the cabozantinib arm had an AE. The types of adverse events reported are generally in keeping with the known profile of cometriq (cabozantinib) and/ or TKIs.

The incidence of treatment-related AEs was 97% in the cabozantinib arm and 91% in the everolimus arm.

The incidence of SAEs was 40% in the cabozantinib arm and 43% in the everolimus arm.

Serious AEs reported for ≥1.5% of subjects in the cabozantinib arm by decreasing frequency were renal cell carcinoma, abdominal pain, pleural effusion, diarrhoea, nausea, anaemia, back pain, dyspnoea, fatigue, pneumonia, pulmonary embolism, vomiting, and pain. The overall incidence of treatment-related SAEs was 15% in the cabozantinib arm and 13% in the everolimus arm. Treatment-related SAEs reported for ≥1% of subjects

in the cabozantinib arm by decreasing frequency were diarrhoea, pulmonary embolism, fatigue and hypomagnesaemia.

The incidence of venous and mixed/unspecified thrombotic ETMs was clearly higher in the cabozantinib arm 7.3% (24 subjects) compared to 2.5% (8 subjects) in the everolimus arm, of which 12/24 and 3/8 subjects, respectively, had event of grade 3 or 4. This difference between treatment arms were mainly driven by a higher incidence of pulmonary embolism in the cabozantinib arm (12 cabozantinib-treated subjects [3.6%] vs 1 everolimus subject [0.3%]). However, also other single events of serious venous thrombosis occurred more often in the cabozantinib arm. As these ETMs occurred relatively late in the treatment period, the higher incidence could be related to the longer exposure in the cabozantinib arm. The acknowledged risk is considered adequately reflected in the SmPC.

Most of the treatment-emergent serum chemistry abnormalities were of Grade 1 or 2 in severity in both treatment. There were no cases that met the screening criteria for Hy's Law.

A total of 59.8% of subjects in the cabozantinib arm and 24.2% of subjects in the everolimus arm had a dose reduction due to an AE. Dose interruptions due to an AE occurred in 63% subjects in the cabozantinib and 42% of everolimus arms subjects

3.5. Uncertainties and limitations about unfavourable effects

There is missing information for the following safety concerns: use in paediatric population, use in pregnant or lactating women, use in patients with cardiac impairment, use in patients with severe hepatic impairment, use in patients with severe renal impairment and carcinogenicity. However, those have been appropriately addressed in the RMP.

3.6. Effects Table

Table 54 - Effects Table for cabozantinib in study XL184-308 (data cut-off: ORR and PFS - 22nd May 2015, OS - 31st December 2015)

Effect	Short Description	Unit	Cabozantinib	Everolimus	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS **(Primary endpoint)**	The Kaplan-Meier estimates for median duration of PFS	Month	7.4 months	3.8 months	Blinded independent review and support from sensitivity analysis give reassurance regarding the robustness of the data Prolongation of PFS was observed in nearly all subgroups	XL184-308 (22nd May 2015)

Effect	Short Description	Unit	Cabozantinib	Everolimus	Uncertainties/ Strength of evidence	References
					investigated HR adjusted for stratification factors from the IVRS/IWRS was 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value <0.0001)	
ORR	ORR per IRC	%	17%	3%	All responses were confirmed PR, supported by post-baseline reduction in tumour size (75% cabozantinib vs. 48% everolimus)	XL184-308 (22nd May 2015)
OS	Overall survival Unplanned interim analysis	Month	21.4 months	16.5 months	Unplanned interim analysis Not formally part of the pre-specified statistical testing programme Extreme nature of the result and the consistency of the estimate of the HR with the previous (planned) analysis of OS give confidence that there is an OS benefit	XL184-308 (31st December 2015)
Unfavourable Effects						
TEAE	G3 or 4	%	59%	41%		
Diarrhoea		%	74%	28%		XL184-308
Fatigue		%	56%	47%		XL184-308

Effect	Short Description	Unit	Cabozantinib	Everolimus	Uncertainties/ Strength of evidence	References
Nausea		%	50%	28%		XL184-308
Decreased appetite		%	46%	34%		XL184-308
Palmar-plantar erythrodysaesthesia syndrome (PPES)		%	42%	5.9%		XL184-308
Hypertension		%	37%	7.1%		XL184-308
Vomiting		%	32%	14%		XL184-308
Weight decreased		%	31%	12%		XL184-308
Constipation		%	25%	19%		XL184-308

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Therapeutic breakthroughs in recent years have transformed the treatment paradigm of patients in the advanced RCC setting. However, despite these advances, previously treated advanced RCC patients are difficult to treat and have a high unmet medical need. New therapeutic options are required to improve outcomes, particularly in terms of overall survival. In study XL184-308 the observed improvement in PFS with cabozantinib compared to everolimus in the pivotal study is considered of clinical importance. The median PFS for cabozantinib was estimated to be 3.6 months longer (HR=0.59; 95% CI: 0.46, 0.76; stratified log-rank p-value <0.001). This increase in PFS was followed by a trend for improved survival of 4.9 months (HR 0.67; 95% CI: 0.53, 0.83; stratified logrank p-value = 0.0003), which is considered important for patients with RCC as they have a relatively poor prognosis.

There are uncertainties regarding the observed differences in PFS and OS between treatment arms of the pivotal study as they may be somewhat overestimated due to differences in baseline characteristics and differences in next-line therapies. Still, differences in PFS and OS are of such a magnitude that there is reason to believe that although the effect size could be smaller, it would still be of clinical relevance.

The safety population in RCC included subjects that received at least one dose of study treatment. The size of the safety data package is sufficient for the assessment of risks in a marketing authorisation application in this disease setting

The safety profile appears similar to other VEGFR-TKIs used to treat RCC. Adverse events leading to discontinuation of cabozantinib were seen in 10% of the study population.

The overall frequency of grade 3 or 4 AEs for cabozantinib in RCC subjects was higher than observed with everolimus, a difference mainly due to higher incidence of hypertension, diarrhoea, and PPES. Overall, however, there was a similar incidence in each arm of AEs of Grade 4 and Grade 5.

The risks of cabozantinib treatment were in most cases manageable with dose modifications, and only about 10% in each arm permanently discontinued therapy due to AEs, which is an acceptable level.

The appropriateness of the starting dose proposed for registration (i.e. 60 mg daily), was questioned as it seems rather poorly tolerated. Exposure-response (E-R) analysis of cabozantinib in patients with RCC support the view that the 60 mg dose provides the best anti-tumour response. As expected, higher predicted risk of individual AEs were simulated for the 60 mg dose vs the 40 mg and 20 mg dose levels, although the simulated 40 mg starting dose was not predicted to dramatically reduce the requirement for dose reductions.

3.7.2. Balance of benefits and risks

The efficacy data have been derived from a well conducted and designed phase III study in previously treated advanced RCC subjects. These subjects show improvements in PFS, ORR and OS. The magnitude of the effects is considered to be clinically meaningful and supports cabozantinib as a new therapeutic option in this condition with a high unmet need.

There are no major safety concerns. Overall, the safety profile of cabozantinib in RCC appears manageable, with dose reductions where required. Given the efficacy and safety data submitted, the benefit-risk is considered positive.

3.8. Conclusions

The overall B/R of Cabozantinib is positive provided the final OS analysis is submitted by September 2017.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cabozantinib is not similar to Nexavar and Torisel within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cabometyx is favourable in the following indication:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to address the uncertainty regarding the survival advantage of cabozantinib compared with everolimus in patients with advanced renal cancer that has progressed after VEGF TKI therapy, the MAH should submit the final analysis of OS for XL184-308, a phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.	September 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Additional Data/Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.