Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Cabozantinib

Proprietary Product Name: Cabometyx

Sponsor: Ipsen Pty Ltd

Date of first round report: 21 April 2017

Date of second round report: 26 September 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24-hours
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
Bid	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
^{14}C	Carbon-14 isotope
C_{max}	Observed maximum plasma concentration
µCi	Micro Curies
CI	Confidence Interval
CL/F	Apparent total body clearance
CP	Childs-Pugh
CRF	Case report form
CT	Computed tomography
CV	coefficient of variation
CTCAE	Common toxicity criteria for adverse events
dL	Decilitre
ECOG	Eastern Cooperative Oncology Group
g	Grams

Abbreviation	Meaning
GLS	Geometric least square
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FBE	Free Base Equivalent
FDA	Food and Drug Administration (US)
FT4	Free T4
h	Hours
HGF	hepatocyte growth factor
ICF	Informed consent form
IC_{50}	Concentration require for 50% inhibition
IRC	Independent Radiology Committee
ITT	Intent to treat
KPS	Karnofsky Performance Status
kg	Kilograms
L	Litres
LLOQ	Lower limit of quantitation
LSM	Least square mean
m	metres
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
NCI	National Cancer Institute

Abbreviation	Meaning
ng	Nanograms
ONJ	Osteonecrosis of the Jaw
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PIB	Powder in bottle
PITT	Primary endpoint intent to treat
qd	Once daily
QTcF	Fridericia's correction of QT interval
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SoD	Sum of lesion diameter
T_{max}	Time to reach maximum plasma concentration
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
UPCR	Urine protein creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)
V/F	Apparent total volume of distribution
WCC	White cell count

Abbreviation	Meaning
XL184	Sponsor identifier for cabozantinib

1. Submission details

1.1. Identifying information

Submission number	PM-2016-04459-1-4
Sponsor	Ipsen Pty Ltd
Trade name	Cabometyx
Active substance	Cabozantinib

1.2. Submission type

This is an application to register the new active substance cabozantinib.

1.3. Drug class and therapeutic indication

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) and vascular endothelial growth factor receptors (VEGFRs).

The proposed indication is: *Cabometyx (cabozantinib tablets) is indicated for the treatment of advanced RCC in patients who have received one prior therapy.*

Cabozantinib thus inhibits a broad range of tyrosine kinases associated with angiogenesis in malignancy.

1.4. Dosage forms and strengths

The proposed dosage forms and strengths are:

- Cabometyx cabozantinib 20 mg film coated tablet
- Cabometyx cabozantinib 40 mg film coated tablet
- Cabometyx cabozantinib 60 mg film coated tablet.

1.5. Dosage and administration

The proposed administration is:

> *Therapy with Cabometyx should be initiated by a physician experienced in the administration of anticancer medicinal products.*
>
> *The recommended dose of Cabometyx is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.*
>
> *Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Cabometyx therapy (see Table 5). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. 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.

Table 1: Recommended cabometyx dose modifications for adverse reactions

Adverse reaction and severity	Treatment Modification
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Consider adding supportive case as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue CABOMETYX.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4)

2. Background

2.1. Information on the condition being treated

Renal cell carcinoma (RCC) originates in the renal cortex and constitutes 80% to 85% of primary renal neoplasms.

RCC can be classified as:

- Localised disease when it is confined to the renal cortex.
- Advanced disease when the tumour invades beyond the renal fascia or extends into the associated adrenal gland.

Many patients present with advanced or unresectable disease at initial diagnosis and up to one third of patients relapse after surgical treatment with curative intent of initially localised disease.

Diagnosis is usually established by radiographic detection of a renal mass. 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 systems) impact quality of life of patients with advanced RCC. Patients with advanced RCC may also develop brain metastases during the disease; these cause debilitating neurological symptoms and

shorten survival. The median overall survival (OS) for patients with advanced RCC ranges from about 8-months (poor risk score) to 4 years (favourable risk score). 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.

As there is currently no curative treatment regime for advanced RCC the aims of treatment are to reduce symptoms burden, reduce the rate of progression and prolong survival.

2.2. Current treatment options

Table 2 summarises the products currently registered (on the ARTG) for the treatment of advanced RCC.

Table 2: Products on the ARTG for the Treatment of RCC

INN	Indication
Axitinib	Treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy
Bevacizumab	in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer
Everolimus	Treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib
Nivolumab	Treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults
Pazopanib	Treatment of advanced and/or metastatic renal cell carcinoma
Sorafenib	Treatment of patients with advanced renal cell carcinoma
Sunitinib	Treatment of advanced renal cell carcinoma.

2.3. Clinical rationale

The clinical rationale for development is not summarised in the sponsor's Clinical overview. The sponsor states in their covering letter that there remains an unmet medical need for new treatments for advanced RCC that show benefit in terms of progression free survival (PFS) and/or overall survival (OS) beyond that of existing therapies.

2.4. Formulation

2.4.1. Formulation development

The proposed commercial formulation for cabozantinib drug product is an immediate release tablet for oral administration. The three commercial strengths of cabozantinib tablets proposed for commercialization will be 20 mg, 40 mg and 60 mg (expressed as freebase equivalent weight).

Cabozantinib drug product was initially provided as a powder-in-bottle oral suspension formulation for initiation of the Phase I XL184-001 study. A capsule formulation was later

developed and used in Phase 2 studies, a Phase III study in medullary thyroid cancer, and various clinical pharmacology studies. Subsequently, cabozantinib capsules (20 mg and 80 mg) (Cometriq) were approved and commercialized for treatment of advanced medullary thyroid cancer. A more desirable formulation (tablet) was later developed and has been used in the other Phase III efficacy and/or safety studies, including Study XL184-308. Furthermore, the tablet formulation allows each dose to be administered as single tablet strength.

2.5. Guidance

No guidance was sought from the TGA.

2.6. Evaluator's commentary on the background information

The background information is acceptable and there are no concerns. Importantly, the formulation of the product used in later development is the same as that intended to be marketed.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier includes a full clinical development program of pharmacology, efficacy and safety studies.

Ten clinical pharmacology studies providing pharmacokinetic and safety pharmacology data were submitted. A single population safety analysis and one pivotal efficacy safety study. Also included are two studies that are evaluable for safety only.

3.2. Paediatric data

No paediatric data has been submitted this is acceptable given the proposed indication.

3.3. Good clinical practice

The sponsor has provided a statement that the studies complied with ICH guidelines for GCP.

3.4. Evaluator's commentary on the clinical dossier

The submission is adequately presented. There are limited data about pharmacodynamics in clinical studies, but given the proposed mechanism of action and what is known about TKIs this is acceptable.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 3: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	XL-184-020	
	Mass Balance	XL184-012	
	Bioequivalence †- Single dose	XL184-016 XL184-010	
	- Multi-dose	No studies	
	Food effect	XL184-004	
PK in special populations	Target population §- Single dose	No studies	
	- Multi-dose	XL-184-001 XL-184-308	
	Hepatic impairment	XL-184-003	
	Renal impairment	XL184-017	
	Neonates/infants/children/adolescents	Not applicable	
	Elderly	XL184-308 PopPK 001	
	Other special population (MTC)	XL184-001	
Genetic/gender related PK	Males versus females	XL184-308 PopPK 001	
	Other genetic variable	XL184-308 PopPK 001	
PK interactions	Rifampicin	XL184-006	
	Ketoconazole	XL184-007	
	Esomeprazole	XL184-018	
Population PK analyses	Healthy subjects	XL184-308 PopPK 001	
	Target population	XL184-308 PopPK 001	

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Cabozantinib (S)-malate is a white to off-white crystalline substance. Two crystalline solid forms (N-1 and N-2) exist, together with an amorphous form.

N-1 was identified as the thermo-dynamically stable form and the polymorphic system was classified as monotropic. The N-2 form is readily formed in the final salt formation step and has been shown not to interconvert to the N-1 form under the process conditions. Therefore, form N-2 was selected for commercial development based on process advantages and controls.

Cabozantinib demonstrates a pH-dependent solubility profile; solubility decreases with increasing pH and is practically insoluble above pH 4.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanism of absorption

Cabozantinib is a highly permeable compound with a generally rapid absorption after oral administration.

Multiple peaks in the plasma-concentration time curve were seen following the administration of a single oral dose suggesting enterohepatic circulation, delayed or multiple sites of absorption that have not been identified.

As cabozantinib is insoluble at pH 4 the sponsor undertook a study in which cabozantinib was administered with a proton-pump inhibitor to investigate the effect of increased pH on absorption.

4.2.2.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of cabozantinib has not been determined. The sponsor has submitted a mass balance study approximately 54% was faecally excreted and 27% recovered in the urine.

Bioavailability relative to an oral solution or micronized suspension

In a Phase I dose escalation study in subjects with solid tumours (XL184-001A), the capsule formulation yielded approximately 2-fold higher dose-normalized $AUC_{0\text{-}24\ h}$ after a single dose compared to an oral liquid formulation (PIB suspension).

Study XL184-012 used a true solution, and was different from the liquid suspension formulation studied in XL184-001.

A single 140 mg FBE oral XL184 dose formulated as a solution yielded an earlier T_{max}, higher C_{max} and $AUC_{0\text{-}inf}$, and less inter-subject variability compared to the capsule or tablet formulation used in healthy subjects at the same cabozantinib (XL184) dose level.

Bioequivalence of clinical trial and market formulations

The pivotal clinical efficacy studies utilised the same formulation of cabozantinib that is intended for marketing.

Bioequivalence of different dosage forms and strengths

Although the dose form used in the clinical studies was the tablet form, and is the formulation intended to be marketed, a capsule formulation and a tablet formulation were used in the clinical development program. The PK parameters and use of the two formulations are summarised below:

Table 4: Single dose mean (%CV) PK parameters of cabozantinib across studies after an 80 or 140 mg FBE capsule

Study	Study XL184-004[b] Food Effect	Study XL184-006[b] DDI with Rifampin	Study XL184-007[b] DDI with Ketoconazole	Study XL184-010[b] BE	Study XL184-016[b] BE
Population Formulation Dose (mg) Food intake	HS Capsule 140 Fast 10 h before and 4 h after dose	HS Capsule 140 Fast 10 h before and 4 h after dose	HS Capsule 140 Fast 10 h before and 4 h after dose	HS Capsule 140 Fast 10 h before and 4 h after dose	HS Capsule[c] 80 Fast 10 h before and 4 h after dose
N	47	28	28	72	43
C_{max}, ng/mL	536 (38)	582 (45)	488 (41)	554 (43)	294 (61)
T_{max}, h[a]	4 (2, 24.03)	4 (1.98, 24.08)	4 (1.13, 24.05)	4 (2, 5.04)	5 (2, 24.02)
AUC_{0-t}, h·ng/mL	59200 (27)	55500 (27)	47600 (29)	54900 (37)	29600 (38)
AUC_{0-24}, h·ng/mL	7420 (33)	7860 (38)	6220 (36)	6830 (35)	3980 (55)
AUC_{0-inf}, h·ng/mL	63200 (28)	58800 (28)	50400 (32)	58300 (39)	31300 (39)
$t_{½}$, h	124 (24)	111 (27)	122 (33)	112 (26)	111 (30)

Table 5: Single dose mean (%CV) PK parameters of cabozantinib after a tablet dose of 20, 40, 60, 80 or 140 mg FBE

Study	Study XL184-010 BE	Study XL184-018[b] Gastric pH Effect	Study XL184-003[b] Hepatic Impaired	Study XL184-017[b] Renal Impaired	Study XL184-020 Dose-Linearity		
Population	HS	HS	HS	HS	HS	HS	HS
Formulation	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Dose (mg)	140	80	60	60	60	40	20
Food intake	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose	Fast 10 h before and 4 h after dose		
N	72	21	10	10	21	21	21
C_{max}, ng/mL	702 (54)	647 (30)	353 (21)	341 (28)	343 (41)	239 (56)	117 (72)
T_{max}, h[a]	3 (2, 24)	3 (2, 5)	4 (2, 5)	4 (3.00, 4.03)	4 (2, 8)	3 (2, 48)	3 (1, 120)
AUC_{0-t}, h·ng/mL	61900 (44)	55800 (25)	31100 (27)	29720 (26)	29800 (38)	19800 (42)	9290 (50)
AUC_{0-24}, h·ng/mL	8140 (47)	7580 (31)	NR	3915 (20)	3880 (33)	2620 (53)	1280 (59)
AUC_{0-inf}, h·ng/mL	65800 (46)	58900 (25)	32700 (29)	32030 (27)	32100 (39)	21100 (42)	10400 (48)
$t_{½}$, h	115 (31)	117 (25)	108 (26)	126 (22)	111 (18)	122 (22)	131 (25)

The geometric least squared mean (LSM) values for AUC_{0-t} and AUC_{0-inf} values were slightly (8%) higher for the tablet formulation treatment relative to the capsule formulation treatment. The 90% CIs around the ratios of geometric LSM values were within the pre-specified bioequivalence limits of 80.00% - 125.00% for both AUC_{0-t} and AUC_{0-inf}. The C_{max} value was 19% higher for the tablet formulation cohort compared to the capsule formulation cohort, and the upper limit of the 90% CI around the ratio of geometric LSM value (131.65%) was outside the specified BE limit acceptance range of 80.00% - 125.00%. Therefore, the BE of the two formulations could not be demonstrated.

Comment: The tablet formulation is intended to be the final dose form for marketing and was used in the pivotal clinical studies.

Influence of food

Food effects were investigated in Study XL184-004. A high fat meal was shown to significantly increase cabozantinib systemic exposure (C_{max} and AUC values by 39% and 56%, respectively)

in normal healthy subjects. Therefore, administration of cabozantinib capsule formulation is recommended in the fasted state.

Comment: The prescribing information has the instructions not to eat for at least 2 hours before and 1 hour after taking cabozantinib.

Dose proportionality

Dose proportionality was investigated in study XL184-020. Cabozantinib tablets were demonstrated to be dose proportional across the range 20 mg to 140 mg.

Bioavailability during multiple-dosing

After multiple daily doses, the AUC and Cmax values of XL184 increased; the mean AUC ratio on Day 19 (steady-state) to Day 1 was 5.4-fold at the 175 mg (S)-malate salt weight (140 mg FBE) capsule dose.

4.2.2.3. Distribution

Volume of Distribution

Based on population PK modelling the estimated volume of distribution is 319L.

Plasma protein binding

Cabozantinib was highly plasma protein bound at all concentration levels tested; the percentage bound was >99.9% for both the 0.2 and 1.0 μM levels, and 99.7% at 10 μM level. The slightly lower percentage at 10 μM suggests that protein binding sites may start to become saturated at high cabozantinib concentrations. For comparison, once-daily dosing with 60 mg cabozantinib (XL184) freebase equivalent (FBE) /day yields steady-state plasma concentrations values of approximately 2.5 μM in subjects with RCC.

Plasma protein binding of cabozantinib was evaluated in vitro (pre-dose samples) and in vivo (after 4 hours' post-dose samples) in subjects with renal impairment (Study Report XL184-017). In the in vitro assay, the mean protein binding of cabozantinib in the mild and moderate renal impairment groups (99.86% and 99.76%, respectively) was similar to that of the matched healthy subjects (99.70%). In the 4-hour post-dose in vivo samples, the mean protein binding of cabozantinib in the healthy control group (99.72%) was also approximately equivalent to that in the mild renal impairment group (99.76%) and the moderate renal impairment group (99.64%).

Erythrocyte distribution

In the mass balance study (XL184-012) the mean percent total radioactivity associated with erythrocytes in blood was less than 13%. The mean values of systemic exposures (AUC_{0-24} and AUC_{0-72}) in plasma were around 1.6 times higher than those in whole blood. The mean percent total radioactivity concentration present in erythrocytes relative to whole blood were determined and ranged from 0.174 +/- 4.51% to 12.3 +/- 3.71% within 72 hours after single dosing, indicating that radioactivity was present primarily in plasma and not markedly associated with red blood cells.

4.2.2.4. Metabolism

Sites of metabolism and mechanisms / enzyme systems involved

In-vitro data suggest that cabozantinib metabolism is dependent in part on hepatic cytochrome P450 systems, a limited number were tested but appear to be CYP3A4 and to a lesser extend CYP2C9 dependent.

Metabolites identified in humans: active and other

Figure 1: Cabozantinib metabolites identified in human plasma, urine and faeces

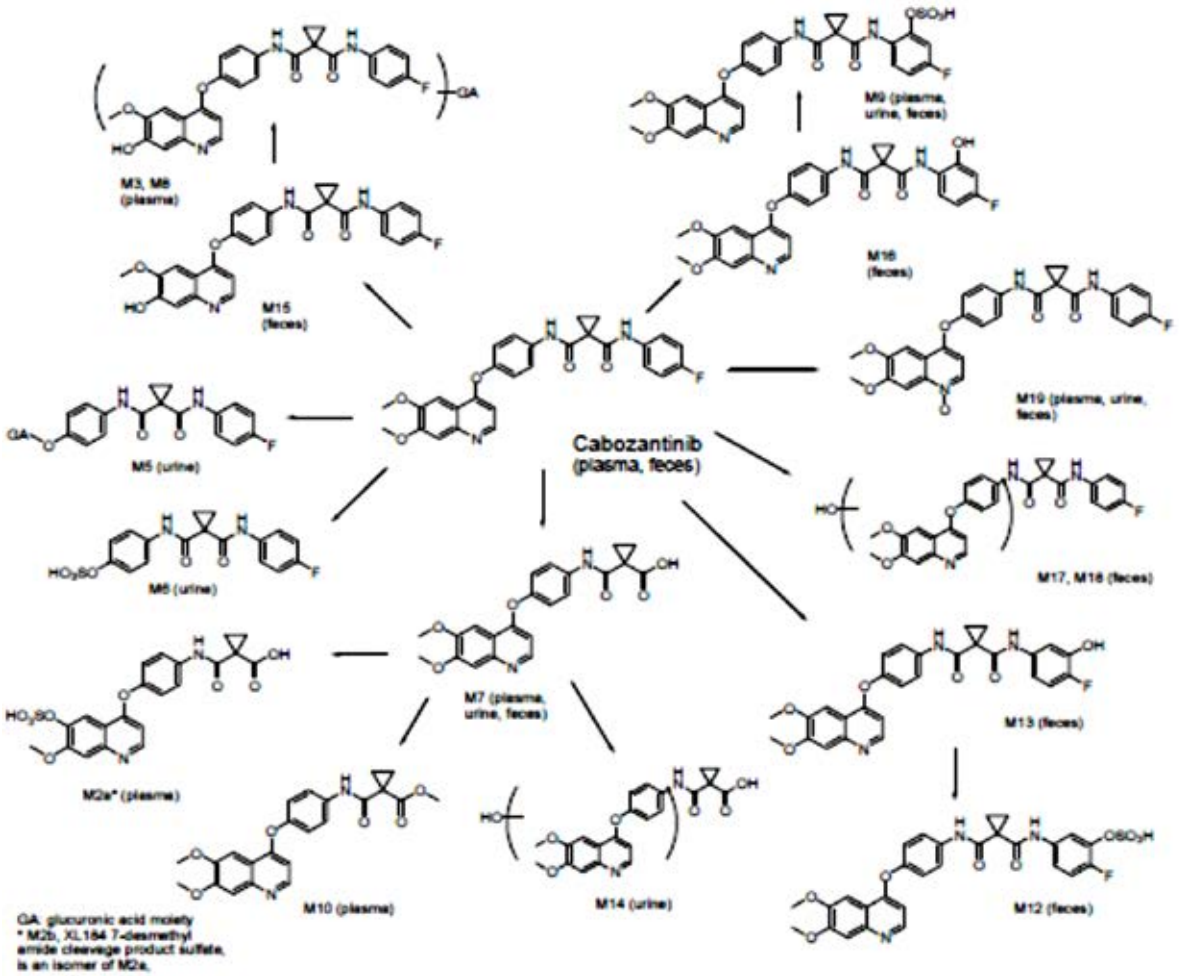


Table 6: Estimated IC50 values (nM) for Selected Kinases for Cabozantinib and Metabolites

Kinase	Cabozantinib	EXEL-1646	EXEL-5162	EXEL-5366	EXEL-1644
Aurora-A	381	152	ND	ND	1000
Aurora-B	23	52	>3600	>3600	>1000
AXL	8	87	ND	ND	>1000
KIT	752	>1,000	>3600	>3600	>1000
EGFR	>1,000	>1,000	>3600	>3600	>1000
FLT1	13	>1,000	>3600	>3600	>1000
FLT3	21	155	530	>3600	>1000
FLT4	3	175	ND	ND	>1000
VEGFR2/KDR	14	308	140	>10000	>1000
MET	2	199	190	5000	>1000
PDGFRβ	575	>1,000	>3600	>3600	>1000
RET	8	234	>1000	>1000	>1000
RON	46	>1,000	ND	ND	<1000[a]
TIE2	13	60	ND	ND	>1000

Non-conjugated metabolites are present only at low levels, and are less active than cabozantinib

Pharmacokinetics of metabolites

The $t_{1/2}$ of the major 6-demethyl half-dimer sulphate metabolite could not be determined, but is much longer than that of cabozantinib and the other characterised metabolites.

Consequences of genetic polymorphism

It is not anticipated that the metabolism will be affected by genetic polymorphism.

4.2.2.5. Excretion

Routes and mechanisms of excretion

Both the urinary and faecal excretion pathways are the main routes of elimination of cabozantinib.

Mass balance studies

27.29±4.65 % and 53.79±4.52 % of the administered radioactive dose (140 mg cabozantinib FBE containing 100 ì Ci [14C]-XL184) was recovered in the urine and faeces, respectively. A mean (±SD) percent recovery of 81.09±}1.56 % (range: 78.14% to 83.38%) of the total radioactivity dose was recovered in the urine and faeces through 48-days post dose.

Approximately 1% total mean radioactivity was recovered in faeces and urine after Day-28post-dose.

4.2.2.6. Intra and inter individual variability of pharmacokinetics

In healthy subject subjects following a single capsule or tablet dose, the inter-subject variability (%CV) ranged from 20 to 59% for AUC values and from 28 to 72% for C_{max} across the studies. The within-subject variability (%CV) was 39% for C_{max} and 28% for AUC values (XL184-010).

The inter-subject variability in cancer subjects was 43% for C_{max} and 34% for AUC after a single dose (XL184-001), and 39% for C_{max} and 38% for AUC at steady state (XL184-008). Exposure variability in cancer subjects and healthy subjects was similar.

4.2.3. Pharmacokinetics in the target population

Study XL184-001 and 008 investigated the pharmacokinetics of cabozantinib in subjects with advanced solid malignancies; these subjects either had DTC or RCC.

Table 7: Pharmacokinetic results from Studies XL184-001 and 008

Study	Study XL184-001 Phase 1 Dose Escalating	Study XL184-001 Phase 1 Dose Escalating	Study XL184-001 Phase 1 Dose Escalating	Study XL184-001 Phase 1 Dose Escalating	Study XL184-008[c] Phase 1 DDI
Subject Population	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors
Formulation	Capsule	PIB	Capsule	PIB	Capsule
Sampling	Dense	Dense	Dense	Dense	Dense
Food intake	Fast 2 h before and 1 h after dose	Fast 2 h before and 1 h after dose	Fast 2 h before and 1 h after dose	Fast 2 h before and 1 h after dose	Fast 2 h before and 2 h after dose
	Single-Dose		Repeated Dose at Steady-State		
Day	1	1	19	19	22
N	34-35	3	25-29	2-3	30-32
C_{max}, ng/mL	570 (43)	306 (60)	2220 (37)	1410 (50)	1970 (39)
T_{max}, h[a]	2 (2, 24)	2 (1, 8)	2 (0, 25)	2 (2, 8)	2 (0, 25)
$AUC_{0\text{-}24}$, h·ng/mL	8228 (34)	4300 (49)	37850 (43)	21350 (34)	29700 (38)
Predose conc, ng/mL	NC	NC	1710 (44)	815 (40)	1484 (48)
Accumulation ratio	NA	NA	5.4 (64)[b]	6.9 (29)[b]	NC

Comment: The mean C_{max} and AUC_{0-24} are slightly higher in subjects with cancer (by about 6% and 12% respectively) and is not expected to be clinically significant.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Study XL184-003 investigated the PK in subjects with mild or moderate hepatic impairment. After a single oral administration of a 60 mg cabozantinib capsule dose, exposure (AUC0-inf) cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment respectively. A doubling of exposure could not be excluded,

Comment: More careful monitoring for intolerability/adverse events is warranted in patients with mild or moderate hepatic impairment. The PK of cabozantinib in subjects with severe hepatic impairment is unknown.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

Study XL184-017 investigated the PK in subjects with mild or moderate renal impairment. Based on the ratios of geometric LS mean for plasma cabozantinib, 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. 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 upper bound of the 90% CI for plasma cabozantinib AUC_{0-inf} ratios between subjects with mild or moderate renal impairment and healthy subjects was < 200%.

Evaluator's Comment: Plasma concentration of cabozantinib seem to be minimally impacted by mild or moderate renal impairment. This could be anticipated as the major route of metabolism (and elimination) is hepatic.

4.2.4.3. Pharmacokinetics according to age

See Population PK.

4.2.4.4. Pharmacokinetics in other special population / with other population characteristic

See Population PK.

4.2.5. Population pharmacokinetics

4.2.5.1. XL184-308 poppk-001

A population pharmacokinetic (PopPK) analysis of cabozantinib was performed using data collected from subjects with RCC (XL184-308) and normal healthy subjects (XL184-020).

A two-compartment model with two parallel (fast and slow) lagged first-order absorption processes adequately described the population pharmacokinetics of cabozantinib. The absorption rate constant for the faster absorption process was dose dependent.

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 haemoglobin, baseline total bilirubin, baseline alanine aminotransferase, baseline serum albumin, baseline calculated creatinine clearance and population (healthy subjects or subjects with RCC).

4.2.6. Pharmacokinetic interactions

4.2.6.1. Rosiglitazone

Study XL184-008 was designed to determine if exposure to ≥ 21 daily doses of ≥ 100 mg cabozantinib (XL184) FBE /day in capsule form affected the PK of a single dose of rosiglitazone (4 mg), a CYP2C8 substrate drug.

No significant difference in rosiglitazone plasma C_{max}, AUC_{0-24}, or AUC_{0-inf} values was observed on planned visit Day 22 (test: that is, rosiglitazone after ≥ 21 daily doses of ≥ 100 mg FBE/day cabozantinib) compared with Day-1. The test/reference ratios (90% CI) for C_{max}, AUC_{0-24}, and AUC_{0-inf} were 1.0396 (0.9261–1.1671), 1.0464 (0.9906-1.1053), and 1.0656 (1.0080–1.1265), respectively, and fell within standard bioequivalence limits (that is, between 0.8 and 1.25).

Comment: No clinically relevant effect of cabozantinib on CYP450 substrates is anticipated.

4.2.6.2. Ketoconazole (CYP3A4 inhibitor)

The effect of ketoconazole, a potent CYP3A4 inhibitor, on XL184 plasma PK was investigated in Study XL-184-007.

The geometric mean values for C_{max}, AUC_{0-t} and AUC_{0-inf} for XL184 following co-administration of ketoconazole decreased by 3%, and increased by 34 % and 38 %, respectively, compared with the values when XL184 was administered alone. The ratios of geometric means were: 97.37% (90% CI: 83.07%-114.11%) for C_{max}, 134.30% (90% CI; 122.45 %- 147.30%) for AUC_{0-t}, and 138.05% (90% CI: 124.51 % - 153.07%) for AUC_{0-inf}. The findings from this study indicate that cabozantinib, a substrate of CYP3A4, is susceptible to interaction with ketoconazole, a potent 3A4 inhibitor. Therefore, concomitant use of strong inhibitors of CYP3A4 should be used with caution as they would be anticipated to potentially increase systemic exposure (AUC values) of cabozantinib XL184 markedly.

4.2.6.3. Esomeprazole

Cabozantinib was determined to have reduced solubility at pH >3 and practically insoluble at pH4 or greater; for this reason, Study XL184-018 was undertaken in healthy subjects designed to determine if daily administration of 40 mg esomeprazole, a proton pump inhibitor, affected the PK of a single dose of cabozantinib by raising gastric pH.

The geometric LSM values for C_{max}, AUC_{0-t}, and AUC_{0-inf} were similar (between approximately 108 and 111%) for a single 100 mg FBE cabozantinib dose administered alone or following 6 daily doses of 40 mg esomeprazole. The 90% CIs around the ratio of LS means were within the limits of 80.00% - 125.00% for AUC_{0-t} and AUC_{0-inf} parameters; the upper 90% CI for C_{max} was determined to be 125.1%. Co-administration of multiple doses of esomeprazole with a single dose of cabozantinib did not statistically significantly alter cabozantinib plasma exposure.

Comment: The use of proton pump inhibitors or other substances that raise gastric pH by decreasing hydrogen ion concentration is not anticipated to have a clinically significant effect on the absorption of cabozantinib.

4.2.7. Clinical implications of in vitro findings

Nonclinical data has demonstrated that cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (for example, warfarin, diazepam, furosemide, dicloxacillin, and propranolol) have the potential to cause a displacement interaction that could increase free concentrations of cabozantinib and/or the co-administered highly protein-bound drug (and a corresponding increase in pharmacologic

effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic profile of cabozantinib has been adequately characterised. The proposed formulation for marketing (tablet dose form) leads to higher exposure, currently no other dose form exists in Australia.

Cabozantinib is highly protein bound and the primary route of metabolism is hepatic. It is anticipated that impaired hepatic function will increase plasma levels of cabozantinib and this was confirmed in a clinical study. The PI recommends a lower starting does (40 mg versus 60 mg) in these patients with instruction to adjust the dose as needed. Further the PI states that the safety and efficacy in severe hepatic impairment has not been established and this is acceptable.

Although mild or moderate renal impairment has negligible impact on the PK the PI contains instruction to use cabozantinib with caution in such patients and does not recommend its use in patients with severe renal impairment and this would seem prudent.

The PK data are adequately reflected in the PI.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

No pharmacodynamic studies in health subjects or subjects with RCC have been submitted.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Pharmacodynamic information comes primarily from in vitro studies, in which inhibition of several systems is demonstrated,

Cabozantinib is an inhibitor of several RTKs: key targets are MET and VEGFR2, with cell-based IC_{50} values of 8 and < 3 nM, respectively. In addition, cabozantinib inhibited phosphorylation of AXL, RET, KIT, FLT3, ROS1, and RON. Mechanism of inhibition studies revealed that the binding of cabozantinib is competitive with adenosine triphosphate (ATP) and fully reversible. In X-ray crystallography studies, cabozantinib was found to occupy the ATP-binding site of its target MET.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Not applicable.

5.2.2.2. Secondary pharmacodynamic effects

Not applicable.

5.2.2.3. Time course of pharmacodynamic effects

Not applicable.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

Not applicable.

5.2.4. Genetic, gender and age related differences in pharmacodynamic response

Not applicable.

5.2.5. Pharmacodynamic interactions

Not applicable.

5.3. Evaluator's overall conclusions on pharmacodynamics

No pharmacodynamic data derived from healthy volunteers or subjects with RCC have been submitted. The PD of cabozantinib was derived form in vitro and murine models and is described in the nonclinical evaluation. Given the mechanism of action and what is already know about TKIs this is acceptable.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

None submitted.

6.2. Phase II dose finding studies

No formal dose finding studies have submitted. Study XL184-001 investigated the maximum tolerated dose of cabozantinib and was determined to be 140 mg once per day.

6.3. Phase III pivotal studies investigating more than one dose regimen

Study SL184-308 was the pivotal study for this application. The initial starting dose was 60 mg once per day. Dose adjustments were allowed for tolerability and are summarised in **7**.

Table 8: Cabozantinib dose reductions in Study XL184-308

	Cabozantinib N = 331
Subjects treated, n (%)	331 (100.0)
Subjects with any dose reduction resulting from AE[a], n (%)	198 (59.8)
Received dose level, n(%)[b]	
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)[b], 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 > 0[c]	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)
Other dose level > 0	0
Median (range) time (days) on treatment at:[d]	
More than 0 mg	
Assigned dose level (60 mg)	73.0 (3, 560)
First dose-level reduction (40 mg), resulting from AE	83.5 (1, 472)
Second dose-level reduction (20 mg), resulting from AE	117.0 (2, 426)
0 mg	6.0 (1, 148)
Median (range) time to first dose reduction resulting from AE (days)[d,e]	55.0 (10, 355)
Median (range) time to second dose reduction resulting from AE (days)[d,e]	93.0 (29, 317)

AE, adverse event

[a] Each subject is only counted once even though multiple dose reductions may have occurred.

[b] Includes dosing records for which the prior interval ended due to 'AE' or 'Treatment resumed/re-escalated.' Excludes dosing records for which the prior interval ended due to 'Subject noncompliance other than AE' or 'Site error' or 'Other.'

[c] Subject 1253-3505 was to take cabozantinib at a dose of 20 mg every other day (shown as 10 mg qd in the CRFs).

[d] Time on treatment = sum of total days subject actually received the specified dose level; all subjects who received treatment at that dose level are included. Dose interruptions are excluded from calculations for nonzero doses.

[e] Dosing records were excluded where the dose was zero or was higher than the most recent prior nonzero dose. Time to dose reduction is the arithmetic median among subjects with a dose reduction (or with a second dose reduction) from first dose until first (or second) dose reduction.

Dose reductions occurred for 70% of subjects and equal proportions of patients were taking the 60 mg dose and 40 mg dose at the data cut-off.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

No formal dose finding has been undertaken. The 60 mg dose was carried forward into the pivotal study. At the data cut-off point an equal proportion of patients were receiving the 40 mg and 60 mg doses. This would indicate that the lowest effective dose may not have been established. The prescribing information contains sufficient information about dose adjustment based on tolerability.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

Studies to support the indication Treatment of RCC:

- XL184-308 A Phase III, Randomised, Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy.

7.2. Pivotal or main efficacy studies

7.2.1. XL184-308

A Phase III, Randomised, Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy.

7.2.1.1. Study design, objectives, locations and dates

This was a randomised, open-label, active controlled study undertaken in subjects with advanced RCC who had to have progressed after at least one year of VEGF TKI therapy.

The objective of this study was to evaluate the effect of cabozantinib on progression-free survival (PFS) and overall survival (OS) in subjects with advanced RCC that had progressed after prior VEGFR tyrosine kinase activity versus everolimus.

The primary endpoint was PFS, the secondary OS.

The study was conducted in 25 countries and involved 173 unique sites. The main countries in terms of the number of sites were: United States (70), Australia (14), Canada (14), Spain (13), United Kingdom (13), France (11) and Italy (10).

The first subject was enrolled on 8 August 2013 and the data cut-off date for the primary analysis of progression free survival was 22 May 2015.

A prespecified interim analysis for the secondary endpoint, overall survival, was undertaken on 22 May 2015, an addendum to the final study report is included that has an unplanned second interim analysis for overall survival with a prospectively defined data cut-off date of 31 December 2015.

The projected completion date of the study for the secondary endpoint, overall survival is February 2017 allowing for up to 36-months of data for this endpoint.

Comment: The unplanned second interim analysis for overall survival was based on an observed trend that favoured cabozantinib at the time of the pre-specified interim analysis. At the time of the pre-specified analysis 49% of the total deaths for the final event had occurred and the additional interim analysis was conducted to provide a minimum of 12-months overall survival data, the statistical analysis plan was amended to reflect this additional analysis. The additional analysis was undertaken in consultation with the European Medicines Agency.

As a single pivotal study has been submitted to support this indication the evaluation will consider the design, conduct and results in line with the European Medicines Agency Points to Consider on Application with 1. Meta-analyses; 2 One Pivotal Study CPMP/EWP/2330/99 as adopted by the TGA.

7.2.1.2. Inclusion and exclusion criteria

Inclusion

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 (for example, sorafenib, sunitinib, axitinib, pazopanib or tivozanib). Prior treatment with other anticancer therapies including cytokines (for example, interleukin-2, interferon-alfa), monoclonal antibodies, (for example, bevacizumab), and cytotoxic chemotherapy is allowed (except Exclusion Criterion #1).
4. For the most recently received VEGFR-targeting TKI the following criteria applied:
    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 was 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 randomisation.
5. Recovery to baseline or ≤ Grade 1 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4) from toxicities related to any prior treatments, unless AE(s) were clinically nonsignificant 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 all of the following laboratory criteria within 10 days before randomisation:
    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 x the upper limit of normal. For subjects with Gilbert's disease ≤ 3mg/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 was allowed
    g. HbA1c ≤ 8%. For subjects with a condition (for example, haemoglobin variant) that affected 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
    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 have agreed to use medically accepted methods of contraception (for example, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) 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 have been pregnant at screening. Females of childbearing potential were defined as premenopausal females capable of becoming pregnant (that is, females who had any evidence of menses in the past 12-months, with the exception of those who had prior hysterectomy). However, women who had been amenorrhoeic for 12 or more-months were still considered to be of childbearing potential if the amenorrhea was possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression, or other reasons.

Exclusion

1. Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (for example temsirolimus) or cabozantinib.
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomisation.
3. Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before randomisation.
4. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomisation. Systemic treatment with radionuclides within 6 weeks before randomisation. Subjects with clinically relevant ongoing complications from prior radiation therapy were 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 randomisation. Eligible subjects must have been neurologically asymptomatic and without corticosteroid treatment at the time of randomisation.
6. Concomitant anticoagulation at therapeutic doses, with oral anticoagulants (for example, warfarin, direct thrombin, and Factor Xa inhibitors) or platelet inhibitors (for example, clopidogrel).
7. Note: Low-dose aspirin for cardio-protection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) were permitted. Anticoagulation with therapeutic doses of LMWH were allowed in subjects without radiographic evidence of brain metastasis, who were on a stable dose of LMWH for at least 12 weeks before randomisation, and who had experienced no complications from a thromboembolic event or the anticoagulation regimen.
8. 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 were not eligible.
9. The subject had 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 blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.

iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, or other ischemic event, or thromboembolic event (for example, deep venous thrombosis, pulmonary embolism) within 6-months before randomisation.

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 randomisation Note: Complete healing of an intra-abdominal abscess must have been confirmed before randomisation.

c. Clinically significant haematuria, hematemesis, or haemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (for example, pulmonary haemorrhage) within 3-months before randomisation.

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

10. Major surgery (for example, GI surgery, removal or biopsy of brain metastasis) within 2-months before randomisation. Complete wound healing from major surgery must have occurred 1-month before randomisation and from minor surgery (for example, simple excision, tooth extraction) at least 10-days before randomisation. Subjects with clinically relevant ongoing complications from prior surgery were not eligible.
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 10-days before randomisation. Three ECGs were performed. If the average of these three consecutive results for QTcF was ≤ 500 ms, the subject met this eligibility criterion.
12. Pregnant or lactating females.
13. Inability to swallow tablets or capsules.
14. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
15. Diagnosis of another malignancy within 2-years before randomisation, except for superficial skin cancers, or localized, low grade tumours deemed cured and not treated with systemic therapy.

7.2.1.3. Evaluator's comments

The inclusion criteria are reflective of a population of participants who have advanced RCC that have experienced disease progression after VEGFR targeted therapy. The proposed indication is a broader indication in that it proposes that cabozantinib is used in adults with RCC following prior therapy. As this is not supported by the inclusion criteria it cannot be justified.

The proposed indication should be amended to reflect the pivotal study population.

The exclusion criteria are acceptable. Importantly patients with cerebral metastases or endobronchial manifestation of RCC, Class 3 or 4 Heart failure, history of stroke, a number of gastrointestinal conditions were excluded and as such this should be represented in the prescribing information and suitable risk mitigation activities proposed as part of the RMP.

7.2.1.4. Study treatments

There were two treatment arms:

- Cabozantinib: Oral cabozantinib (60 mg) once daily (qd) - yellow film coated tablets Supplied by Exelixis, Inc, 60 mg (oval shape) and 20 mg (round shape) tablets using the following lot numbers: 20 mg: HZWX, KKDK, MMZN, NFYB, MSMM, NTBX, PFKD. 60 mg: MDCX, MMZS, MSMY, NFYH, NTBZ, PFKH, MSMX.
- Everolimus: Oral everolimus (10 mg) once daily (qd). Purchased from Novartis and supplied by Exelixis as 10 mg, 5mg, and 2.5mg tablets using the following lot numbers: 2.5 mg: F0007, S0013, S0019 5 mg: S0038, S0013A, S0039, S0026, S0027, S0031A. 10 mg: S0033A, S0013A, S0029, S0030, S0035.

Following randomisation, the first dose of study drug was administered at the study site. (Week 1 Day 1). The study medication was administered under fasting conditions. Subjects received either 60 mg of oral cabozantinib or 10 mg of everolimus taken with at least 240 mL of water.

During the treatment phase subjects assigned to the cabozantinib arm continued to take their medication under fasting conditions, subjects in the everolimus arm could take their medication without regard to food.

Subjects in both arms were instructed to take their medication at the same time each day.

Dose reductions were allowed for both subjects receiving cabozantinib and everolimus as outlined below:

*Cabozantinib dose reduction***:** allowed for unacceptable toxicity, and doses may have been modified at any time.

Two reductions were allowed. 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).

*Everolimus dose reduction***:** was allowed for management of severe or intolerable adverse reactions. If dose reduction was required, the proposed 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.

Prior/Concomitant therapy: No concomitant investigational agents were allowed during the study. Prior treatments (including radiation) for cancer were recorded.

All medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies and nutritional supplements) during the period from 28 days before randomisation through 30 days after the date of the decision to permanently discontinue study treatment were recorded in the case report forms.

Antiemetics and antidiarrheal medications were allowed prophylactically according to standard clinical practice if clinically indicated.

Granulocyte colony-stimulating factors (G-CSF or GM-CSF) were allowed if used per clinical guidelines.

Drugs used to control bone loss (for example, bisphosphonates and denosumab) were allowed if started before randomisation and the benefit outweighed the risk per the investigator's discretion. Frequent monitoring for potentially overlapping toxicities with study treatment was recommended. After randomisation, the use of these drugs required sponsor approval with the exception of management of disease-related hypercalcaemia in emergency situations. However, this was to be subsequently reported to the sponsor for acknowledgement and post-initiation approval.

Transfusions, hormone replacement, and short term higher doses of corticosteroids (above the physiologic replacement dose) were utilized as indicated by standard clinical practice.

Individualised anticoagulation therapy with heparin was allowed if the benefit outweighed the risk per the investigator's discretion under the following circumstances. Low dose heparins for prophylactic use were allowed if clinically indicated. Therapeutic doses of low molecular weight heparins (LMWH) at the time of randomisation were allowed if the subject had no evidence of brain metastasis, had been on a stable dose of LMWH for at least 12 weeks, and had had no complications from a thromboembolic event or the anticoagulation regimen. Therapeutic doses of low molecular weight heparins (LMWH) after randomisation were allowed if clinically indicated. Therapeutic doses of oral anticoagulants (for example, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardio protection per local applicable guidelines) were not allowed after randomisation until study treatment was permanently discontinued.

Comment: Everolimus is listed on the ARTG with the following relevant indication: Treatment of Advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib, the dose for this indication recommended dose for this indication is 10 mg and a 50% dose reduction is allowed for adverse events. Therefore, everolimus is an acceptable comparator and its use considered to be appropriate.

7.2.1.5. Efficacy variables and outcomes

Primary

The primary efficacy endpoint was duration of progression-free survival per response evaluation criteria in solid tumours (RECIST-1) as determined by the IRC. This was defined as the time form randomisation to either documented PD or death by any cause.

This endpoint was a radiological endpoint assessed by:

A CT (or MRI) scan of the chest abdomen and pelvis at screening then at every 8 weeks throughout the first 12-months of the study after which assessments occurred every 12 weeks.

A CT (or MRI) scan of the brain performed at screening. After randomisation, MRI (or CT) scans of the brain were only required in subjects with known brain metastasis. Assessments were performed every 8 weeks throughout the first 12-months on study. Upon completion of 12-months on study, these assessments were performed every 12 weeks. If a CT scan of the brain was performed instead of an MRI scan, ambiguous results were confirmed by MRI. Subjects without documented brain metastasis during the screening assessment were not required to undergo post-randomisation brain imaging unless clinically indicated.

Technetium bone scans (TBS) were performed in all subjects at screening. After randomisation, bone scans were performed only in subjects with known bone metastasis every 16 weeks throughout the first 12-months on study. Upon completion of 12-months on study, these

assessments were performed every 24 weeks. Subjects without documented bone metastasis during the screening assessment were not required to undergo a post-randomisation bone-scan imaging unless clinically indicated.

Tumour assessments were continued on the protocol-defined schedule regardless of whether study treatment was given, reduced, held, or discontinued. The same imaging modalities used at screening were used for subsequent tumour assessments after randomisation.

For the purpose of determination of the study endpoints of PFS and response rates, a blinded, central review of radiographic images was conducted by an IRC. All radiographic tumour assessments were sent in digital format from the investigative sites to the IRC, which also reviewed prior radiation history data for the purpose of selection of target lesions.

Comment: Progression free survival is a clinically relevant endpoint for advanced renal cell carcinoma.

Progression free survival has been used as the basis for approval of a number of medicines approved for the treatment of renal cell carcinoma; sunitinib, bevacizumab, sorafenib, pazopanib these medicines are on the ARTG and have the indication for the treatment of renal cell carcinoma.

Progression free survival is accepted as an endpoint according to the EMA, CHMP Guideline on evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev 4). Importantly overall survival is evaluated as a secondary endpoint (see below).

Secondary endpoints

- Overall survival. Study subjects were followed until death, withdrawal of their consent or at time that the study sponsor determined that these data should no longer be collected.
- Objective response rate (ORR), per RECIST 1.1, per IRC. 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. Tumour assessment was the same as for the primary endpoint.

Additional endpoints

- 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.
- Safety and tolerability.
- Characterization of the pharmacokinetics of cabozantinib.
- Change in kidney cancer-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney 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. It queries symptom severity and interference in activity and general health perceptions. This instrument has been used in a number of studies investigating the treatment of RCC.
- 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).
- Proportion of subjects with post-randomisation skeletal-related events (SREs).

- Relationship of baseline and changes in plasma biomarkers, serum bone markers, serum calcium, and circulating tumour cells (CTCs) with treatment and/or clinical outcome. Serum calcium was analysed as part of the routine clinical laboratory assessments. At selected sites, serial blood samples were collected for the enumeration of CTCs. Molecular markers related to RCC and/or study treatment mechanism(s) of action were also to be potentially assessed in CTC samples. In addition, tumour tissue (archival or recently biopsied) was obtained at enrolment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with RCC or the mechanism(s) of action of study treatment, as predictive biomarkers.
- Health care resource utilization parameters were collected on or after the first dose through the Post-Treatment Follow-up Visit. These included hospital admissions, emergency room visits, intensive care unit admissions, length of stay and relevant procedures (for example, surgeries, transfusions).

Comment: There do not appear to be protocol defined criteria for undertaking brain imaging or bone scans at any other point other than at screening. The protocol states that these should be undertaken as clinically indicated and leave it to the discretion of the investigator. As this was an open-label study there is a potential for bias with regard to the need to perform or the timing of these investigations.

It appears that an attempt was made to identify and measure biomarkers in the study however the results for this have not been provided.

The sponsor should provide an analysis of the number of subjects in each arm that developed cerebral or bony metastasis that were not present at screening and the timing of these events, and comment on the steps taken (if any) to eliminate bias with regard to the need for imaging/bone scans (as appropriate) for these subjects.

The sponsor should provide the data for the analysis of biomarkers or provide information on the availability (or otherwise) of these data.

7.2.1.6. Randomisation and blinding methods

This was an open-label study to allow for dose modification for AEs. Subjects were randomly assigned to treatment in a 1:1 ratio either using an interactive voice record system or interactive web record system.

The IRC were blind to study treatment.

Pre-specified stratification took place for the following:

- Number of prior VEGFR-targeting TKI therapies: 1 versus 2 or more.
- Memorial Sloan-Kettering Cancer Centre prognostic criteria for previously treated patients with RCC risk score criteria (Motzer 2004): 0 versus 1 versus 2 or 3 risk factors. 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) in females
  - Corrected calcium > upper limit of normal.

7.2.1.7. Analysis populations

The analysis populations are summarised in the table below:

Table 9: Study XL184-308 Analysis Population

	Cabozantinib n (%)	Everolimus n (%)
Intent-to-Treat (ITT) population[a]	330 (100)	328 (100)
Primary Endpoint Intent-to-Treat (PITT) population[b]	187 (100)	188 (100)
Safety population[c]	331 (100)	322 (98.2)

[a] Includes all randomised subjects. With the exception of the PITT population and non-PITT population, percentages are based on the ITT population. [b]Includes the first 375 randomised subjects. [c] Includes all subjects in the ITT population who received any amount of study treatment. Note: One subject (1417-3624) was randomised to receive everolimus but received cabozantinib as study treatment and therefore was evaluated in the cabozantinib arm for the Safety population.

The ITT population included a total of 658 subjects, 330 subjects in the cabozantinib arm and 328 subjects in the everolimus arm.

The Safety population included all randomised subjects who received at least one dose of study treatment (653 subjects); 331 subjects in the cabozantinib arm and 322 subjects in the everolimus arm.

Five subjects randomised to receive everolimus did not receive any study treatment; another subject was randomised to the everolimus arm but received cabozantinib as study treatment and therefore was evaluated in the cabozantinib arm for the Safety population.

The PK population consisted of all subjects in the Safety population who had at least one reported plasma PK concentration; PK analysis was restricted to the cabozantinib arm.

The PITT population (the first 375 subjects randomised) included 187 subjects in the cabozantinib arm and 188 subjects in the everolimus arm.

Comment: The ITT was used for the efficacy analyses other than for the primary analyses for PFS, for which the PITT was used. This was pre-specified in the statistical analysis plan. This was event-based and at least 259 events were required to be observed. The analysis was repeated in the ITT population. This is acceptable.

7.2.1.8. Sample size

The study was designed to have adequate statistical power both the primary endpoint and OS.

For the primary endpoint of PFS, assuming exponential PFS, proportional hazards, and a 1:1 treatment allocation ratio, at least 259 events are required to provide 90% power to detect a HR of 0.667 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 is a 27.8% improvement (HR = 0.783) in PFS from 5 to 6.39-months conducted when 259 events are observed in the first 375 subjects randomised into the study.

With regard to OS; with an average accrual rate of 32 subjects per month and using 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 observed the required PFS events among 375 subjects and approximately 36-months to observe the required deaths for OS among 650 subjects).

7.2.1.9. Statistical methods

Hypothesis testing between the two treatment arms will be performed using the stratified logrank test with a 2-sided 0.05 level of significance.

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

The analysis was stratified according to the factors for randomisation. An analysis of unstratified results was also provided.

The primary analysis of OS was event-based and will be conducted after study enrolment is complete and at least 408 deaths have been observed in the study. For subjects who are alive at the time of data cut-off or are permanently lost to follow-up, duration of OS will be right censored at the earlier of the data cut-off date or the date the subject was last known to be alive.

Statistical methods for the primary, supportive, and exploratory analyses of OS will be applied as described for the primary endpoint of PFS.

An interim analysis of OS was performed at the time of the primary analysis of PFS using the entire ITT population available at that time. It was anticipated that it would occur at approximately the 33% information fraction for OS (that is, after approximately 135 deaths have been observed).

Type I error for the interim analysis will be controlled by a Lan-DeMets O'Brien-Fleming alpha spending function; the critical value being 0.0019.

An amendment to the SAP is included for the additional unplanned interim analysis of OS data.

Comment: The statistical methods are accepted methods for a study evaluating PFS and OS. The alpha setting function (for OS) was determined for a single interim analysis; it is not known what effect, if any, the unplanned interim analysis would have on the predetermined significance level. The sponsor should clarify the effect of the unplanned interim analysis on the predetermined level of significance required for the final analysis of OS.

7.2.1.10. Participant flow

Figure 2: Subject Disposition ITT Population

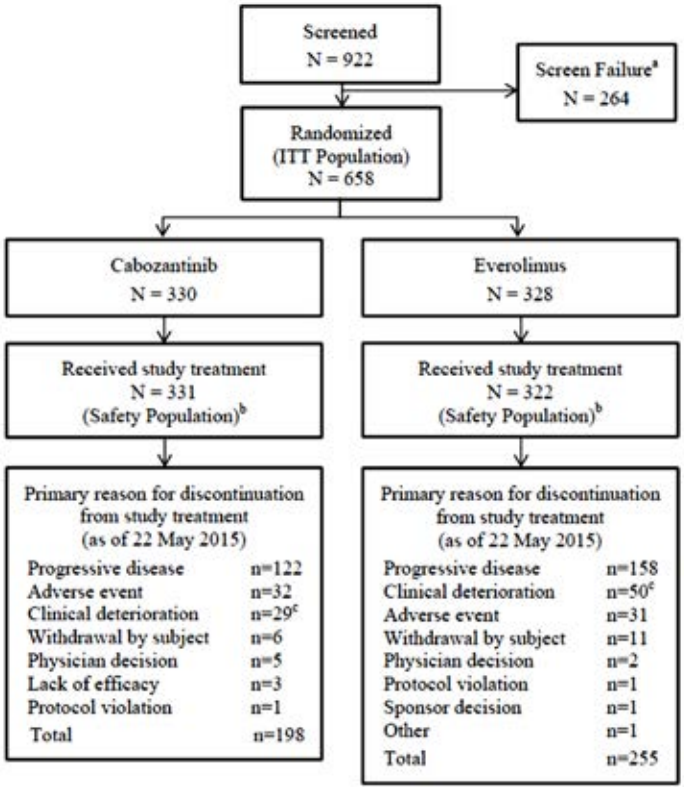


Figure 3: Subject Disposition PITT Population

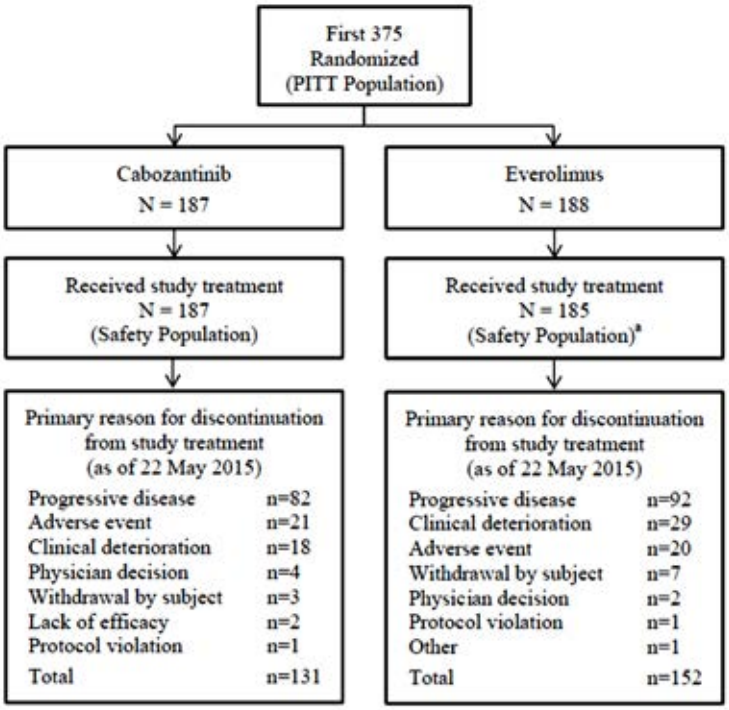


Table 10: Subject Disposition Safety and PITT Safety Populations

	Safety Population[a]		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)
Other	0	1 (0.3)	0	1 (0.5)
Discontinued study follow-up	94 (28)	117 (36)	68 (36)	82 (44)
Primary reason for discontinuation from study follow-up				
Death	88 (27)	105 (33)	63 (34)	72 (39)
Withdrawal by subject	5 (1.5)	11 (3.4)	4 (2.1)	9 (4.9)
Lost to follow-up	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)
Sponsor decision	0	0	0	0
Other	0	0	0	0

Comment: As of the data cut-off date (22 May 2015). There was a lower rate of discontinuation in subjects randomised to the cabozantinib arm compared to those randomised to everolimus treatment. The main reasons for discontinuation were disease progression (158 everolimus versus 122 cabozantinib) adverse events (31 everolimus versus 32 cabozantinib). There was a higher rate of death in the everolimus arm compared to the cabozantinib arm (39% versus 34%).

7.2.1.11. Major protocol violations/deviations

Important protocol deviations are summarised below:

Table 11: Important Protocol Deviations

	Cabozantinib (N = 330) n (%)				Everolimus (N = 328) n (%)			
	Potential Impact				Potential Impact			
Deviation	Safety	Efficacy	Both	Other	Safety	Efficacy	Both	Other
Prohibited medication	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)	3 (0.9)	2 (0.6)	0
Treatment deviation	9 (2.7)	0	4 (1.2)	0	9 (2.7)	0	0	0
Withdrawal deviation	0	0	0	0	0	1 (0.3)	0	0
Randomization irregularity[a]	1 (0.3)	23 (7.0)	0	0	0	24 (7.3)	0	0

Comment: Protocol deviations were balanced across the treatment arms and were unlikely to influence the overall results of the study.

7.2.1.12. Baseline data

Table 12: Baseline data

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N=330)	Everolimus (N=328)	Cabozantinib (N=187)	Everolimus (N=188)
Median (range) age (years)	62.5 (32, 86)	62.0 (31, 84)	62.0 (36, 83)	61.0 (31, 84)
≥ 65 years, n (%)	134 (41)	130 (40)	69 (37)	72 (38)
65 to < 75	107 (32)	94 (29)	56 (30)	54 (29)
75 to < 85	26 (7.9)	36 (11)	13 (7.0)	18 (9.6)
≥ 85 years	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, 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)
Karnofsky Performance Status, n (%)[b]				
70	29 (8.8)	22 (6.7)	15 (8.0)	16 (8.5)
≥ 80	301 (91)	306 (93)	172 (92)	172 (91)
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 (favourable)	150 (45)	150 (46)	80 (43)	83 (44)
MSKCC risk factors =1 (intermed')	139 (42)	135 (41)	80 (43)	75 (40)
MSKCC risk factors =2 or 3 (poor)	41 (12)	43 (13)	27 (14)	30 (16)
Heng Prognostic Criteria, n (%)[d]				
0 adverse factors (favorable risk)	66 (20)	62 (19)	38 (20)	33 (18)
1-2 adverse factors (intermediate)	210 (64)	214 (65)	114 (61)	120 (64)
3-6 adverse factors (poor risk)	54 (16)	52 (16)	35 (19)	35 (19)
Median time since initial histological/cytological diagnosis to randomization (years)	2.8	2.5	2.6	2.4
Median time from radiographic progression after most-recent VEGFR-TKI to randomization (months)	1.02	1.25	0.94	1.23
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 baseline disease by IRC, n(%)				
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)
Bone	77 (23)	65 (20)	39 (21)	32 (17)
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)

Table 12 continued: Baseline data

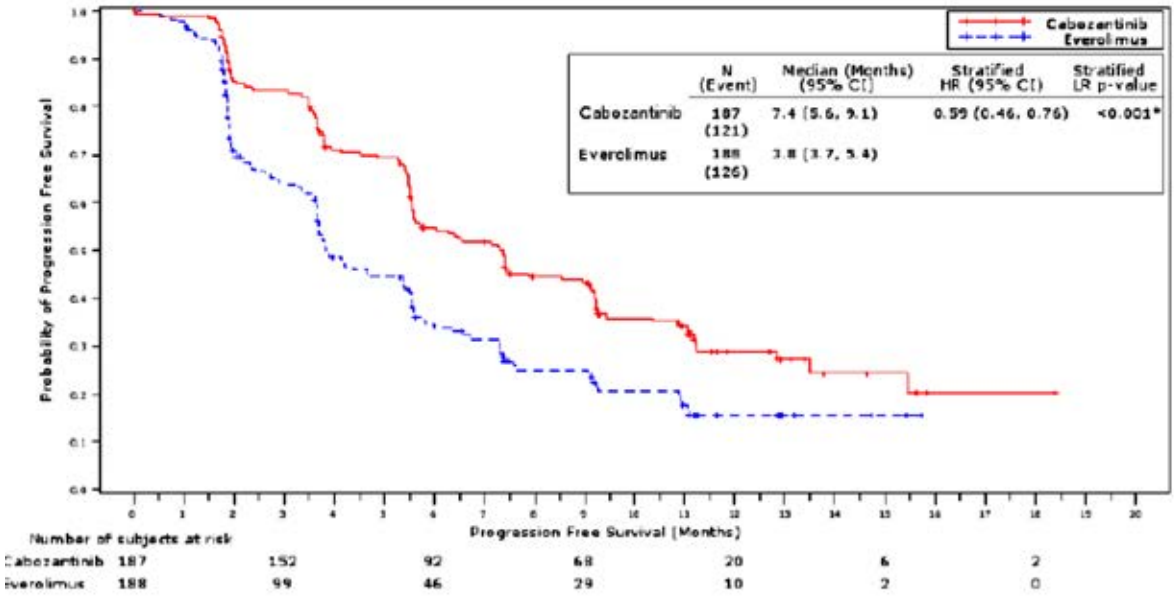
Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N=330)	Everolimus (N=328)	Cabozantinib (N=187)	Everolimus (N=188)
≥ 3	11 (3.3)	8 (2.4)	8 (4.3)	3 (1.6)
Median (range)	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 4)
Type of prior VEGFR-TKIs, n (%)				
Sunitinib	210 (64)	205 (63)	114 (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	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[e]	18 (5.5)	14 (4.3)	9 (4.8)	11 (5.9)
Nivolumab	17 (5.2)	14 (4.3)	9 (4.8)	11 (5.9)
Atezolizumab/MPDL3280A	1 (0.3)	0	0	0
MET immunohistochemistry status				
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)
Sum of lesion diameters (mm) Median (range)	65.2 (0,291)	65.0 (0,258)	70.0 (0,291)	77.0 (0,231)
Nephrectomy, n (%)	283 (86)	279 (85)	157 (84)	153 (81)
Radiotherapy, n (%)	110 (33)	108 (33)	56 (30)	61 (32)

anti-PD-1, anti-programmed cell death immune receptor-1 or its ligands (PD-L1/PD-L2); KPS, Karnofsky Performance Status; LLN (ULN), lower (upper) limit of normal; MSKCC, Memorial Sloan Kettering Cancer Center; (P)ITT, (Primary) Intent to Treat; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor: [a] In addition, gender and race for one subject in the everolimus arm were missing. [b] 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). [c] KPS < 80%, hemoglobin <13 g/dL for males and <11.5 g/dL for females, corrected serum calcium >ULN. [d] Haemoglobin <LLN, corrected calcium >ULN, KPS < 80%, time from initial diagnosis to initiation of therapy of < 1 year, absolute neutrophil count >ULN, and platelets > ULN. [e] Enrolment 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). Source: SCE, Section 2.7.3.2.1.2

Comment: The baseline characteristics were generally well balanced between treatment arms. A greater proportion of patients in the everolimus arm had stage IV disease compared to the cabozantinib arm (88% versus 82%). Most patients had received sunitinib as a prior VEGFR-TKI therapy (approx. 60%).

7.2.1.13. Results for the primary efficacy outcome: Progression Free Survival

Figure 4: Kaplan-Meier Plot of Progression-Free Survival as determined by IRC through the 22nd May 2015 Cut-Off Date (PITT Population)



The results of the analysis demonstrated a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the everolimus arm. 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 versus 3.8-months in the everolimus arm, an estimated 3.6-month difference in the medians.

Table 13: Progression-Free Survival through the 22 May 2015 Cut-off Date as determined by the IRC (PITT Population) Stratified versus Unstratified analysis

	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. Source: XL184-308, Table 14.2.1.1

The results for the primary endpoint were also evaluated for the ITT population:

Figure 5: Kaplan-Meier Plot of Progression-Free Survival as determined by IRC through the 22nd May 2015 Cut-Off Date (ITT Population)

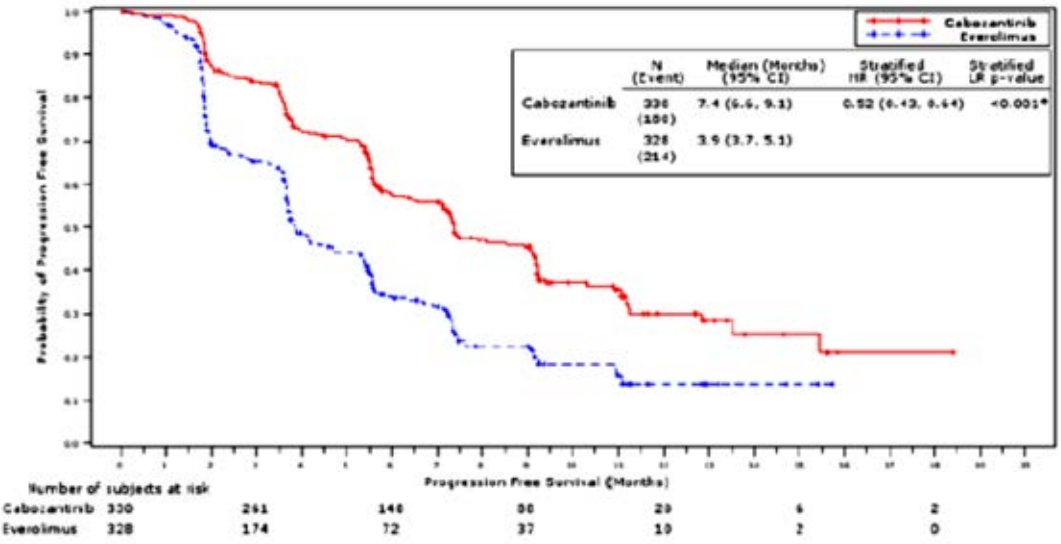


Table 14: Progression-Free Survival through the 22 May 2015 Cut-off Date as determined by the IRC (ITT Population) Stratified versus Unstratified analysis

	Cabozantinib N = 330	Everolimus N = 328
Number (%) of subjects		
Censored	150 (45)	114 (35)
2 or more missed ATA prior to event	1 (0.3)	6 (1.8)
Anticancer therapy	35 (11)	49 (15)
No event by last ATA	104 (32)	50 (15)
No post-baseline ATA	2 (0.6)	7 (12.1)
Surgery	8 (2.4)	2 (0.6)
Event	180 (55)	214 (65)
Death	16 (4.8)	18 (5.5)
Documented progression	164 (50)	196 (60)
Duration of progression free survival (months)		
Median (95% CI)	7.4 (6.6, 9.1)	3.9 (3.7, 5.1)
25[th] percentile, 75[th] percentile[a]	3.7, 15.4	1.9, 7.4
Range	0.03+, 18.4+	0.03+, 15.7+
Log-rank p-value (stratified[b] /unstratified)	<0.001/<0.001	
Hazard ratio (95% CI; stratified[c] /unstratified)	0.52 (0.43, 0.64)/ 0.52 (0.42, 0.63)	

+ indicates a censored observation; ATA, adequate tumor assessment; CI, confidence interval; IRC, Independent Radiology Committee; PITT, primary endpoint intent-to-treat

Several pre-specified sensitivity analyses were undertaken that utilised differing definitions for PFS. The results are shown below:

Table 15: Sensitivity Analyses of the PFS for the PITT Population

	PFS1[a]		PFS2[b]		PFS3[c]		PFS4[d]	
	Primary Analysis		Uniform dates		Investigator claims		Investigator-documented Radiographic PD	
	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus
Total censored, n (%)	66 (35)	62 (33)	70 (37)	66 (35)	44 (24)	30 (16)	54 (29)	47 (25)
Total events, n (%)	121 (65)	126 (67)	117 (63)	122 (65)	143 (76)	158 (84)	133 (71)	141 (75)
Median (months)	7.4	3.8	7.4	3.9	7.3	4.0	7.4	5.3
Stratified HR	0.59		0.59		0.59		0.61	
95% CI	0.46, 0.76		0.45, 0.76		0.47, 0.74		0.48, 0.77	
p-value, stratified / unstratified logrank	< 0.001/< 0.001		< 0.001/< 0.001		< 0.001/< 0.001		< 0.001/< 0.001	

CI, confidence interval; HR, hazard ratio; IRC, independent review committee; PD, progressive disease; PFS, progression-free survival; PITT, primary endpoint intent-to-treat.
[a] PFS1 analysis events: earlier of death or radiographic progression as determined by the IRC.
[b] PFS2 analysis: used the scheduled tumor assessment date (or the next scheduled tumor assessment date if between assessments) rather than the date progression was recorded by the IRC as the date of radiographic progression.
[c] PFS3 analysis events: earliest of death, radiographic progression as assessed by the investigator, clinical deterioration, initiation of subsequent anticancer therapy, and surgery that impacted tumor lesions.
[d] PFS4 analysis events: earlier of death or radiographic progression as determined by the investigator. Clinical deterioration was not considered a progression event.

Further pre-specified analyses were undertaken for differing sensitivity schemes and are summarised below:

Table 16: Sensitivity Analyses of PFS to Evaluate Potentially Informative Censoring (PITT Population)

	PFS11		PFS12		PFS13		PFS14	
	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus
Total censored	38 (20%)	62 (33%)	33 (18%)	53 (28%)	38 (20%)	32 (17%)	33 (18%)	62 (33%)
Total events	149 (80%)	126 (67%)	154 (82%)	135 (72%)	149 (80%)	156 (83%)	154 (82%)	126 (67%)
Median (months)	5.7	3.8	5.6	3.7	5.7	3.7	5.6	3.8
Stratified HR	0.73		0.70		0.58		0.75	
95% CI	0.57, 0.92		0.56, 0.89		0.46, 0.73		0.59, 0.95	
p-value, stratified logrank	0.009		0.003		< 0.001		0.018	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PITT, primary endpoint intent-to-treat.
For PFS11-14 analyses, subjects censored for potentially informative reasons in the primary analysis PFS1 had the events reclassified 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.

Comment: A statistically significant difference between the treatment arms favouring cabozantinib was seen for the primary endpoint. The HR adjusted for stratification factors was 0.59.

The Kaplan-Meier estimates for median duration of PFS were 7.4-months in the cabozantinib arm versus 3.8-months in the everolimus arm, a difference of 3.6-months favouring cabozantinib.

As of the prespecified data cut-off date only 247 out of the required 259 events had occurred in order to satisfy the statistical power calculation for the PITT population in order for the study to have 90% power to detect a to detect a HR of 0.667 using the log-rank test and a 2-sided significance level of 5%. As the p value was <0.001 the lower event rate is unlikely to have an impact on the results, however it has not been commented on by the sponsor.

The degree of statistical significance is in line with that which would expected for an application that includes a single pivotal study (that is, stronger than p<0.05).

Numerous sensitivity analyses have been undertaken, regardless of the assumptions statistical significance favouring cabozantinib was demonstrated.

Subgroup analyses for the primary endpoint PFS was undertaken in both the PITT and ITT populations as summarised below:

Table 17: 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)*	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)*
	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	35	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)
Heinz 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)*	Cabozantinib (N = 330)			Everolimus (N = 328)			Unstratified HR (95% CI)*
	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	82	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	0.43 (0.28, 0.68)	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)

CRF, case report form; CT, computed tomography; HR, hazard Ratio; IHC, immunohistochemistry; IRC, independent radiology committee; MRI, magnetic resonance imaging; NE, not estimable; PD, programmed cell death; PFS, progression-free survival; PITT, primary endpoint intent-to-treat; 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).

Comment: Although a number of prespecified subgroup analyses have been undertaken no adjustment for multiplicity was made. In general, regardless of the subgroup results favoured treatment with cabozantinib with the exception of female subjects and

subjects with only one organ metastasis, the number of subjects in each of these subgroups was small and makes the relevance of these findings uncertain.

7.2.1.14. Results for other efficacy outcomes

Secondary Endpoint: Overall Survival

First interim analysis: Planned, 22 May 2015.

A prespecified interim analysis of OS was conducted for the ITT population (as of the 22 May 2015 database cut-off) at the time of the primary analysis of PFS. There were 202 total deaths by the cut-off date, representing 49% (202/408) of the total deaths required for the prespecified primary analysis of OS. The minimum time of follow-up (from randomisation of the 658th subject through 22 May 2015) was 5.9-months.

The analysis demonstrated a trend for longer OS for subjects in the cabozantinib arm compared with the everolimus arm (Figure 6 and Table 18): the HR adjusted for stratification factors was 0.68 (95% CI: 0.51, 0.90; stratified logrank p-value = 0.006). The p-value of ≤ 0.0019 (49% information fraction) required to achieve statistical significance at the time of the interim analysis was not reached.

Figure 6: Kaplan-Meier Plot of Interim Overall Survival through the 22 May 2015

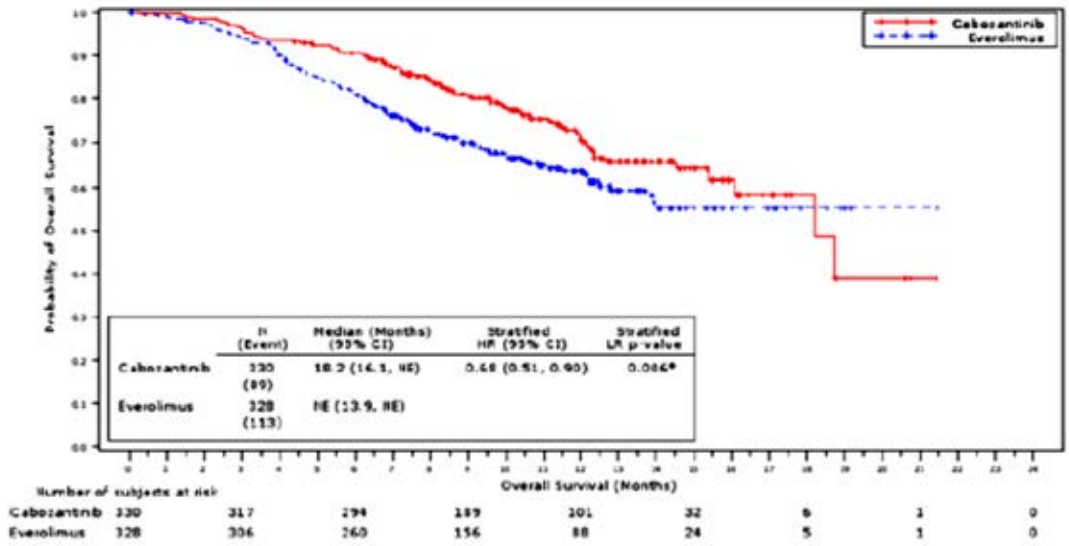


Table 18: Interim Analysis of Overall Survival through the 22 May 2015 Cut-off Date

	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.

Given these interim analysis results, the conditional power for rejecting the null hypothesis of no difference in OS at the final analysis is 99.5% under current trend and 97% under the original study hypothesis. A second, unplanned interim analysis will be conducted with data through 31 December 2015 to provide a minimum of 12-months of follow-up from the last subject enrolled.

The use of non-protocol anticancer therapy was higher for subjects who had received everolimus (47% of subjects) versus those who had received cabozantinib (38% of subjects).

Second Interim Analysis: Unplanned 31 December 2015 cut-off

The analysis included 320 total deaths, representing 78% (320/408) of the total deaths required for the planned final analysis of OS. The minimum time of follow-up (from randomisation of the 658th subject through 31 December 2015) was 13-months. Survival status as of 31 December 2015 was determined for the majority (97.6%) of the 658 randomised subjects. For the 16 subjects for which it could not be established (6 in the cabozantinib arm and 10 in the everolimus arm), 13 of these withdrew consent and 3 were lost to follow-up. These subjects were censored at the date of most-recent contact prior to the data cut-off. All other subjects who were not deceased through 31 December 2015 were documented to be alive (and censored on) this date.

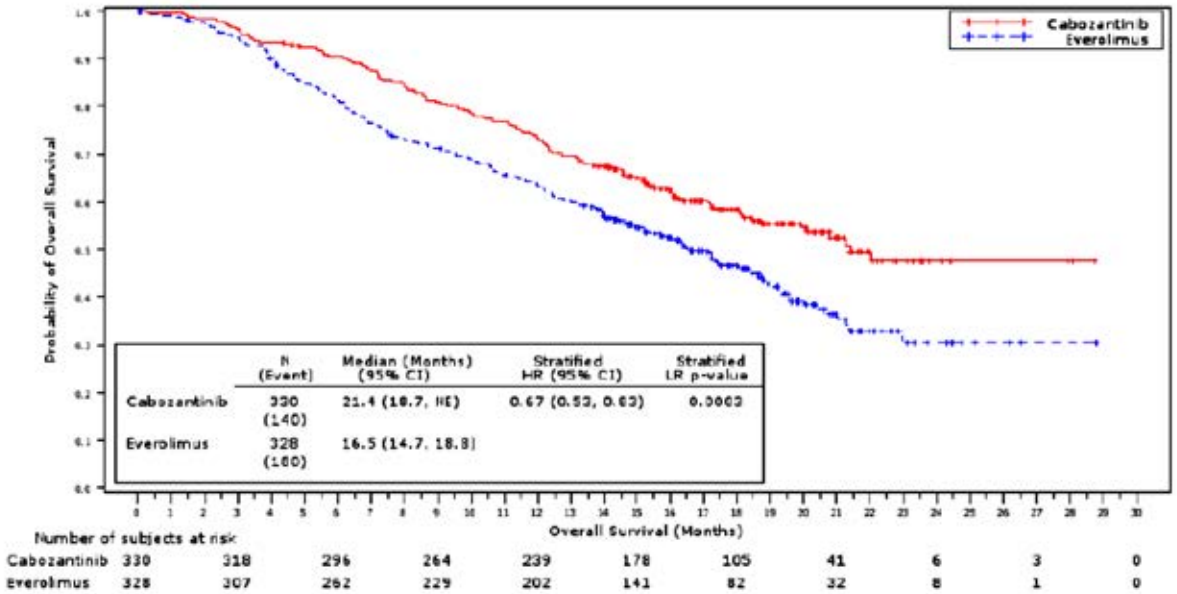
Table 19: Interim Analysis of Overall Survival through the 31 December 2015 Cut-off Date (ITT Population)

	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[a]	11.5, NE	7.5, NE
Range	0.26, 28.7+	0.07+, 28.8+
p-value (stratified log-rank test[b])	0.0003	
Hazard ratio (95% CI; stratified[c])	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)	

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 analysis. The critical value for rejecting the null hypothesis at the current analysis was $p < 0.0163$.

The analysis demonstrated a statistically significant difference in duration of OS for subjects in the cabozantinib arm compared with the everolimus arm: the HR adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified logrank p-value = 0.0003). Kaplan-Meier estimates of median duration of OS were 21.4-months in the cabozantinib arm and 16.5-months in the everolimus arm, an estimated 4.9-month difference in the medians.

Figure 7: Kaplan-Meier Plot of Interim Overall Survival through the 31 December 2015 Cut-off Date (ITT Population)



The use of non-protocol anticancer therapy was higher for subjects who had received everolimus (63% of subjects) versus those who had received cabozantinib (57% of subjects).

Comment: The planned interim analysis showed a trend of improvement in overall survival for subjects receiving cabozantinib versus those receiving everolimus. Although p=0.005 this cannot be considered to be statistically significant due to the pre-specified criterion for significance derived from the alpha spending function.

With regard to the second unplanned interim analysis the trend observed for the planned analysis was maintained in that OS for subjects treated with cabozantinib was improved (increased by 4.9-months) versus those treated with everolimus. This benefit was statistically significant when the same criterion for significance was applied as for the planned interim analysis. This analysis was not pre-specified and therefore no inference should be made with regard to testing of the null hypothesis, however it represents the most mature data that are currently available for OS and the estimate of HR is concordant with that for the planned analysis. It is likely that there is an OS survival benefit for subjects who received cabozantinib versus those that received everolimus. These results should be confirmed in the final analysis of the OS survival data.

The sponsor should provide an analysis of the final OS data for this study as soon as practical after it is available. The sponsor should indicate when this is likely to be and comment on the impact of additional spending of alpha, due to the unplanned analysis, on the results.

Secondary endpoint: objective response rate

The primary analysis of ORR was conducted in the ITT Population at the time of the primary analysis of PFS. The same data cut-off date was used as for the PFS analysis. Tumour assessments that occurred after the individual subject PFS-censoring dates were excluded from this analysis.

Tumour response is summarised in the table below for the ITT population. The ORR was 17% (95% CI: 13, 22) and 3% (95% CI: 2, 6) for subjects in the cabozantinib and everolimus arms, respectively (unstratified p-value < 0.001). All objective responses were PRs. The median time to objective response was 1.91-months (range 1.6, 11.0) in the cabozantinib arm and 2.14-months (range 1.9, 9.2-months) in the everolimus arm. The incidence of PD as best response as low in the cabozantinib arm (12% cabozantinib, 27% everolimus), indicating a low incidence of primary refractory disease to cabozantinib treatment in this study population.

Table 20: Tumour Response per RECIST 1.1 as of the 22 May 2015 Cut-off Date (ITT population)

Subjects in ITT Population	Cabozantinib N = 330	Everolimus N = 328
Subjects with any tumor reduction compared with baseline, n (%)	249 (75)	158 (48)
Best overall response, n (%)		
Confirmed complete response (CR)	0	0
Confirmed partial response (PR)	57 (17)	11 (3)
Stable disease (SD)[a]	216 (65)	203 (62)
Progressive disease	41 (12)	88 (27)
Unable to evaluate	2 (0.6)	2 (0.6)
Missing[b]	14 (4)	24 (7)
Objective response rate (ORR)[c]		
n (%)	57 (17)	11 (3)
95% confidence interval, %	(13, 22)	(2, 6)
Stratified CMH test p-value[d]	< 0.001	
Unstratified chi-squared test p-value	< 0.001	

CMH, Cochran-Mantel-Haenszel ; IRC, independent radiology committee; ITT, intent-to-treat; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a] Includes subjects for whom the overall response result is stable disease or non-CR/non-PD.

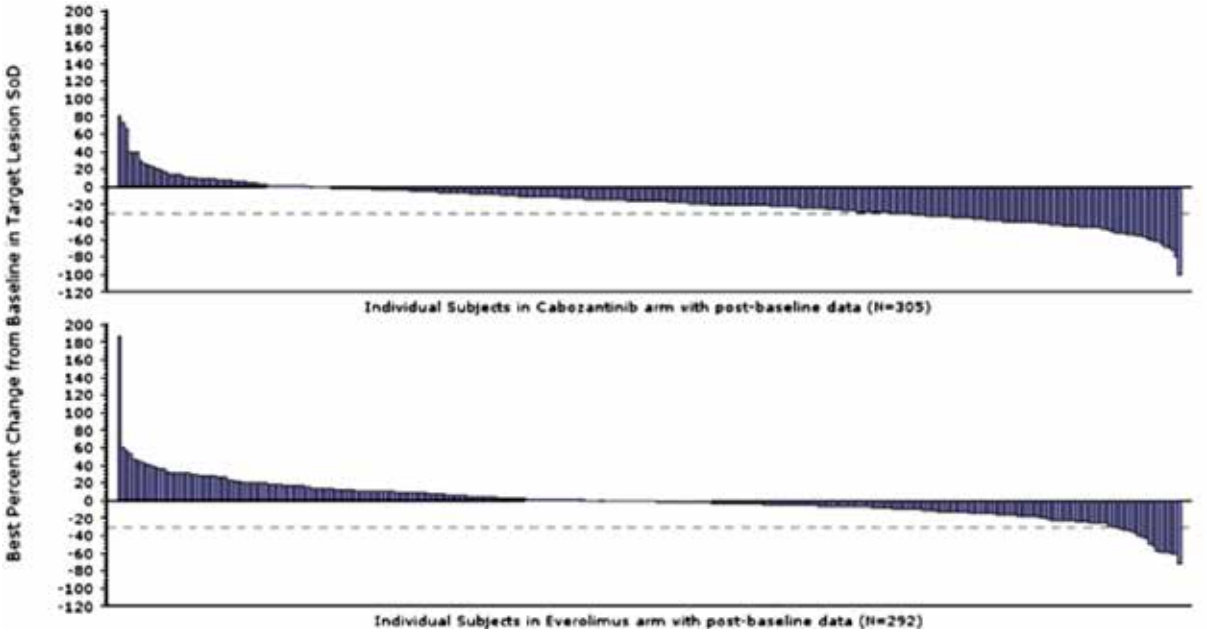
[b] No qualifying post-baseline assessment for overall response.

[c] 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.

[d] p-value from CMH test with stratification factors of prior VEGFR-targeting TKI therapy (1 vs 2 or more), and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) (Motzer et al 2004).

A total of 75% and 48% of subjects in the cabozantinib and everolimus arms (ITT population), respectively, had a post-baseline reduction in sum of lesion diameters (SoD); the waterfall plot of best percentage change in tumour size is shown in Figure 8.

Figure 8: Waterfall Plot of Best Percentage Change in Tumour Size from Baseline (IRC Determined, ITT Population)



Comment: The ORR was 17% for subjects receiving cabozantinib versus 3% for those receiving everolimus.

Additional endpoints

Duration of response (DOR)

The Kaplan-Meier estimate of median DOR was not estimable (NE; 95% CI: 7.2, NE) for the cabozantinib arm and 7.4-months (95% CI 1.9, NE) for the everolimus arm.

Changes in bone scans

Bone scan response, as determined by the IRC, was an exploratory endpoint that was analysed for 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: BSR was 18% (95% CI: 11, 27) in the cabozantinib arm and 10% (95% CI: 4, 19) in the everolimus arm. The median duration of BSR was not estimable for subjects who had a response in either treatment arm.

Characterization of the pharmacokinetics of cabozantinib

The PK analysis was restricted to subjects in the cabozantinib arm and was performed two ways. The first method was based on all concentration records that met analysis eligibility requirements (Table 21).

The second method of analysis was based on a dataset that was further filtered to select analysis eligible concentration records where approximate steady-state concentrations at the initial cohort-assigned dose were expected (for example, where 14 of 15 of the 60 mg/day cabozantinib doses were received over the 15-days immediately prior to the PK visit. Based on the long plasma half-life determined previously for cabozantinib, steady-state cabozantinib concentrations were achieved by Week-5 Day-1, the first scheduled PK collection time point (Table 22).

Table 21: Summary table of Cabozantinib Plasma PK Concentrations by Visit for RCC Subjects in the Cabozantinib Arm (Subjects with Analysis Eligible Records)

		Concentration (ng/mL) at Scheduled Visit					
		Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female
60	N	244	66	310	224	66	290
	Mean	1180	1390	1230	937	987	949
	SD	587	675	611	477	611	510
	CV%	49.6	48.6	49.9	50.9	61.9	53.7
	Geo Mean[b]	ND	1160	ND	800	ND	ND
	SD (Logs)[b]	ND	0.726	ND	0.652	ND	ND
	Min	0	51.9	0	18.0	0	0
	Median	1170	1370	1200	896	925	899
	Max	3040	3360	3360	3480	2630	3480

CV%, coefficient of variation; Geo, Geometric; Max, maximum; Min, minimum; ND, not determined; SD, standard deviation; SD (Logs), standard deviation of the logs.

[a] A concentration record had to meet specific requirements to be considered analysis eligible, which included the following: 1) The sample met stability requirements, 2) The PK concentration was measured at least 14 days after the first dose of cabozantinib, (ie, ≥ Study Day 15 relative to first cabozantinib dose), 3) The PK concentration was not missing, 4) The actual visit was within 21 days of the planned visit, and 5) The PK plasma sample was associated with a planned visit (ie, was not unscheduled or taken during screening).

[b] The geometric mean and SD (Logs) could not be determined in those cases were zero values were present.

Table 22: Summary table of Cabozantinib Plasma PK Concentrations by Visit for RCC Subjects in the Cabozantinib Arm (subjects with Analysis Eligible Records at Approximately 60 mg/day Steady State[a])

		Concentration (ng/mL) at Scheduled Visit					
		Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female
60	N	172	39	211	121	27	148
	Mean	1230	1400	1260	1030	1160	1050
	SD	551	583	559	474	619	504
	CV%	44.8	41.6	44.4	46.1	53.5	47.9
	Geo Mean[b]	ND	1250	ND	936	992	946
	SD (Logs)[b]	ND	0.534	ND	0.439	0.605	0.472
	Min	0	191	0	265	194	194
	Median	1180	1410	1220	961	1020	975
	Max	2870	2780	2870	3480	2630	3480

CV%, coefficient of variation; Geo, Geometric; Max, maximum; Min, minimum; SD, standard deviation; SD (Logs), standard deviation of the logs.

[a] Filtered steady state dataset: subject must have received at least 14 of 15 60 mg/day doses of cabozantinib over the 15 days immediately prior to the visit for inclusion of the concentration at that visit, and the record must meet analysis eligibility requirements.

[b] The geometric mean and SD (Logs) could not be determined in those cases were zero values were present.

One hundred thirty-four (134) subjects contributed data to summary statistics calculations after filtering to select pre-dose concentration records at approximate steady state (these subjects took at least 14 of 15 of the 60 mg/day cabozantinib doses over the 15-days immediately prior to the PK visits and had PK samples collected and analysed at both Week-5 Day-1 and Week-9 Day-1). In this subset, the mean steady-state pre-dose plasma concentration of cabozantinib at Week-5 Day-1 was 1220 ng/mL (n = 134) with a CV% of 46.0%. The mean steady-state pre-dose plasma concentration of cabozantinib at Week-9 Day-1 was lower at 1040 ng/mL (n = 134) with a CV% of 48.2%.

In the Steady-State population, mean plasma concentrations were somewhat lower at Week-9 than Week-5 and somewhat higher in females than males across all comparisons. However, concentrations between these two time points and between genders were not meaningfully different when considering the variability in cabozantinib plasma exposure parameter values (CV% of 42%-62% across all analysis eligible subjects).

Change in kidney cancer-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19)

The median FKSI-19 total score at baseline was 77 for the cabozantinib arm and 77 for the everolimus arm out of a total possible score of 95. 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. In general, there were no notable differences between treatment arms in the FKSI-total and subscale scores over time.

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 EQ-5D-5L was converted into a single index value normalized across the nine different countries where the index has been validated. Index values range from 0 to 1, and a higher index score indicates better health. At baseline, the median index value was 0.8200 in the

cabozantinib arm and 0.8270 in the everolimus arm. Index scores over time generally showed no treatment difference.

Proportion of subjects with post-randomisation skeletal-related events (SREs)

Pathological fractures, spinal cord compression, surgery to bone, and radiation therapy to bone were defined as SREs. A total of 12% of subjects in the cabozantinib arm and 14% of subjects in the everolimus arm had an SRE post-randomisation. For subjects who had an SRE prior to randomisation, the incidence of post-randomisation SREs was lower in the cabozantinib arm than the everolimus arm (15/91 [16%] cabozantinib, 31/90 [34%] everolimus).

Table 23: Subjects with Post-Randomisation Investigator-Assessed Skeletal-Related Events (ITT Population)

	Cabozantinib N = 330 n (%)	Everolimus N = 328 n (%)
Subject-incidence of any SRE post randomization, n (%)	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)
Subject with SRE prior to randomization	91 (28)	90 (27)
Subjects with an SRE who had an SRE prior to randomization[a], n (%)	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)

ITT, intent-to-treat; 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.
[a] The denominator for percentages is the number of subjects with a prior SRE.

Relationship of baseline and changes in plasma biomarkers, serum bone markers, serum calcium, and circulating tumour cells (CTCs) with treatment and/or clinical outcome

No analysis provided.

Health care resource utilization

Among all subjects hospitalization rates (37% versus 40% of subjects; 6.4 versus 10.2 days per person year), ICU visit rates (1.2% versus 2.1% of subjects; 0.07 versus 0.32 days per person-year) and surgeries per person-year (0.90 versus 1.35) were lower in the cabozantinib arm than the everolimus arm. The median number of hospitalizations, ICU visits, or surgeries per subject, among those who experienced these events, was similar in each treatment group.

7.2.1.15. Evaluator commentary

The pivotal study was a Phase III randomised open label study using an active comparator-everolimus that is a recognised treatment for advanced RCC and is on the ARTG with this indication. Dosing was appropriate.

In general, the study was well designed and the information well presented.

There is potential for bias as radiographic evaluation of bony and cerebral metastasis was only undertaken at screening and followed per protocol in patients with known metastasis. The decision to undertake further radiographic studies to investigate for bony or cerebral metastasis was according to clinical indications as determined by the investigator. As the investigators were aware of treatments received there is a potential to influence their decision with regard to the necessity or timing of these investigations.

The endpoint PFS is accepted as a relevant endpoint in patients with advanced RCC, this was the primary endpoint. OS was the secondary endpoint this is in compliance with TGA adopted guidelines.

The alpha setting function (for OS) was determined for a single interim analysis, it is not known what effect, if any, the unplanned interim analysis would have on the predetermined significance level and a second unplanned interim analysis was undertaken.

Investigation of biomarkers was an endpoint of this study but the results were not included in the clinical study report.

The inclusion and exclusion criteria were acceptable.

A statistically significant difference between the treatment arms favouring cabozantinib was seen for the primary endpoint. The HR adjusted for stratification factors was 0.59 ($p<0.001$). The Kaplan-Meier estimates for median duration of PFS were 7.4-months in the cabozantinib arm versus 3.8-months in the everolimus arm, a difference of 3.6-months favouring cabozantinib this is considered clinically significant. However only 247 out of the 259 events required were the power calculation had occurred at the data cut-off and the sponsor should have commented on this in the clinical study report. Numerous sensitivity analyses have been undertaken, regardless of the assumptions statistical significance favouring cabozantinib was demonstrated.

At the data cut-off for the first interim analysis of OS, May 2015, a trend for improved overall survival for cabozantinib treated subjects was observed, 0.68 (95% CI: 0.51, 0.90; stratified log rank p-value = 0.006). The magnitude of this response was approximately an additional five months of survival which can be considered clinically meaningful. A second, unplanned, interim analysis was undertaken to provide OS data for at least 12 months that demonstrated a similar HR and magnitude of response, statistical significance was met, however as it was not prespecified the relevance needs to be considered uncertain. Mature OS data is pending.

Only a single pivotal study is submitted in this application, the degree of statistical significance for the results of the primary endpoint, PFS ($p<0.001$) is in line with that which would expected for an application that includes a single pivotal study (that is, stronger than $p<0.05$).

The number of subjects who received non-protocol anticancer therapy was higher in those who had received everolimus as part of the study compared to those who had received cabozantinib.

The secondary endpoint ORR was supportive of the results seen for PFS and OS.

In conclusion, although there are points for clarification, the study is of an acceptable design and complies with the TGA adopted EMA, CHMP, Guideline on evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev 4). The study is of an acceptable design and the results are sufficient to comply with the TGA adopted guideline European Medicines Agency Points to Consider on Application with 1 Meta-analyses; 2 One Pivotal Study CPMP/EWP/2330/99.

7.3. Other efficacy studies

7.3.1. Study ID XL184-008 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

This is a Phase I interaction study and included patients with RCC. The efficacy parameter was exploratory, the number of patients with RCC was 25 and the assessment of endpoints investigator determined. Finally, a different formulation (capsule) and different dose was investigated. This study is therefore not considered further with regard to efficacy.

7.3.2. Evaluator commentary on other efficacy studies

Not applicable.

7.4. Analyses performed across trials: pooled and meta analyses

None.

7.5. Evaluator's conclusions on clinical efficacy

The efficacy presented demonstrates improvement in both OS and PFS in subjects with advanced RCC that had previously received VEGFR-TKI therapy who are treated with cabozantinib. The results for PFS and OS are supported by an improvement in ORR in terms of tumour burden.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.1.2. Pivotal and/or main efficacy studies

The main study providing safety data was Study XL184-308.

Safety was assessed on a schedule based on the date of the first dose and at minimum every 2 weeks until week-9 day-1, and every 4 weeks thereafter. A safety follow-up visit was performed at least 30 (+14) days after the date of the decision to permanently discontinue study treatment. 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. Subjects also reported, and were asked to describe any AEs experienced through 30 days after the date of the decision to permanently discontinue study treatment.

At each scheduled or unscheduled study visit, evaluations of AEs were performed after informed consent and through 30 days after the last dose of study treatment. An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject who was enrolled in the study and who may have been administered an investigational product, regardless of whether or not the event was assessed as related to the study treatment.

Overall safety was monitored by an independent monitoring committee that was independent of the study sponsor and the investigators.

The *Safety Population* was defined as all subjects who had received any amount of study treatment.

8.1.3. Other studies

8.1.3.1. Studies with evaluable safety data: Dose finding and pharmacology

Study XL184-008 was a Phase I 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.

8.1.3.2. Studies evaluable for safety only

Study XL184-306

This study was a Phase III, randomised, double-blind, controlled study of cabozantinib versus prednisone plus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer.

The study was conducted in men with previously treated metastatic CRPC with bone-dominant disease who had experienced disease progression while on docetaxel-containing chemotherapy and either abiraterone or enzalutamide.

Subjects had to have documented pain from bone metastases requiring opioid narcotics. During a 7 day Run-In Stage, subjects had to meet stringent pain (average daily worst pain score ≥ 4 and ≤ 8 on the BPI scale of increasing pain from 0 to 10) and narcotic use criteria to be eligible for the study.

Subjects received study treatment as long as they continued to experience clinical benefit, as determined by the investigator. Reasons for discontinuation of treatment included, among others, an unacceptable toxicity or the need for non-protocol systemic anticancer therapy (including the use of bone-targeted radiopharmaceuticals). Crossover between protocol treatment arms was not allowed.

Clinic visits occurred at minimum every 3 weeks through treatment discontinuation with extended follow-up to assess survival status and to document receipt of subsequent anticancer therapy. Routine safety evaluations included assessments of AEs, vital signs, laboratory tests, and concomitant medications. New or worsening AEs were collected at study visits, over the phone, or by spontaneous subject report from informed consent through 30 days after the date of the decision to discontinue study treatment.

The study was terminated early due the lack of survival benefit seen in a second study.

Study XL184-307

This study was a Phase III randomised double-blind, controlled study of cabozantinib (XL184) versus prednisone in metastatic castration-resistant prostate cancer patients who have received prior docetaxel and prior abiraterone or enzalutamide.

Subjects in this study were male and ≥ 18 years of age with a documented histological or cytological diagnosis of prostate cancer and evidence of its metastasis to bone (as determined by a bone scan). Subjects were to have received prior docetaxel (with a minimum cumulative dose of 225 mg2) and either abiraterone or enzalutamide with evidence of investigator-assessed prostate cancer progression on each agent independently. If a subject had an AE related to a prior treatment, the AE was to have resolved to baseline or CTCAE v4 ≤ Grade 1. Subjects without prior orchiectomy must have been taking luteinizing hormone-releasing hormone (LHRH) analogue therapy at baseline and concomitantly throughout the study. In addition, subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, a serum testosterone level of <50 ng/dL (<1.75 nmol/L), and adequate organ and marrow function as determined by clinical laboratory tests.

Eligible subjects were randomised 2:1 to the cabozantinib and prednisone treatment arms, respectively. Randomization was stratified by the following factors: prior treatment with cabazitaxel (yes/no), baseline pain severity (self-assessed worst pain score recalled over the prior 24 hours [Brief Pain Inventory {BPI}- Item 3 scale of 0 to 10] of < 4 versus ≥ 4), and ECOG performance status (0–1 versus 2).

Based on treatment assignment, subjects received either, oral cabozantinib (60 mg, qd) plus prednisone-matched placebo (twice daily [bid]) or oral prednisone (5 mg, bid) plus cabozantinib-matched placebo (qd).

Clinic visits occurred at minimum every 3 weeks after treatment was initiated through Week 12 and then every 6 weeks thereafter. Routine safety evaluations included assessments of AEs, vital signs, laboratory tests, and concomitant medications. New or worsening AEs were collected at study visits, over the phone, or by spontaneous subject report from informed consent through 30 days after the date of the decision to discontinue study treatment.

The study did not meet its primary endpoint of OS. Active subjects were required to discontinue study treatment and revert to standard of care thereby limiting the overall exposure to treatment on the study.

8.1.4. Studies that assessed safety as the sole primary outcome

Not applicable.

8.2. Patient exposure

Table 24: Clinical Study Providing Safety Data

Study (Phase)	Study Report	Proposed Role of Study in Application		Number of Subjects	
		Efficacy	Safety	Experimental Arm	Comparator Arm
XL184-308[a] (METEOR) (Phase 3)	Full CSR, Primary analysis[a]	√	√	Cabozantinib 60 mg: 331 RCC (safety)	Everolimus: 322 RCC (safety)
XL184-008 (Phase 1)	Full CSR, Primary analysis	√	√	Cabozantinib 140 mg: 25 RCC (safety)	-
XL184-306 (COMET-2) (Phase 3)	Full CSR, Primary analysis	-	√	Cabozantinib 60 mg: 60 CRPC (safety)	Mitoxantrone + Prednisone[b]: 57 CRPC (safety)
XL184-307 (COMET-1) (Phase 3)	Full CSR, Primary analysis	-	√	Cabozantinib 60 mg: 681 CRPC (safety)	Prednisone[b]: 342 CRPC (safety)

CRPC, castration-resistant prostate cancer; CSR, clinical study report; RCC, renal cell carcinoma
Cabozantinib dose expressed as the freebase equivalent weight.
[a] A total of 658 subjects with advanced metastatic RCC were randomly assigned 1:1 to one treatment arm. The prespecified Primary Endpoint Intent-to-Treat (PITT) population consisted of the first 375 randomized subjects (187 cabozantinib, 188 everolimus) for the primary endpoint analysis of progression-free survival

Cabozantinib has been evaluated in two randomised, double-blind, controlled, Phase III studies in subjects with metastatic CRPC (Study XL184-307 and Study XL184-306). In both studies, subjects were administered the same dose and formulation as received by RCC subjects in StudyXL184-308 (that is, 60 mg tablets qd).

As the studied indication was CRPC the patient population differed in that it was an older population with metastatic disease and had received docetaxel, abiraterone or enzalutamide prior to entry.

Study XL184-004 was a Phase I study to evaluate the PK of cabozantinib when administered with rosiglitazone.

Table 25: Study Drug Exposure to Cabozantinib (Study XL184-308) as of Data-cut-off

Tumor Type:	RCC	
Study:	XL184-308[a] Cabozantinib (N = 331)	XL184-308[a] Everolimus (N = 322)
Duration of exposure (weeks)[b]		
N	331	322
Mean (SD)	33.11 (16.838)	23.94 (17.085)
Median	32.14	18.93
Min, max	1.1, 89.3	0.9, 82.1

RCC, renal cell carcinoma; Max, maximum; Min, minimum; SD, standard deviation.

[a] The study drug exposure presented for Study XL184-308 is limited to that available at the time of the primary analysis of PFS; subjects continued to receive study treatment in both treatment arms after that point.

[b] Duration of exposure = (Date of decision to discontinue treatment – Date of first dose + 1)/7.0

The mean duration of exposure (as of data cut-off 22 May 2015) was 33 weeks for cabozantinib and 22 weeks for everolimus.

Table 26: Duration of Overall Exposure in Pivotal Study XL184-308

	Indication: RCC Study XL184-308 (N=331)	
Overall Exposure	Persons n (%)	Person time (Person Weeks)
≥ 4 weeks	329 (99.4)	10954
≥ 8 weeks	312 (94.3)	10857
≥ 12 weeks	291 (87.9)	10655
≥ 16 weeks	279 (84.3)	10491
≥ 20 weeks	245 (74.0)	9922
≥ 24 weeks	239 (72.2)	9793
≥ 28 weeks	215 (65.0)	9195
≥ 32 weeks	179 (54.1)	8122
≥ 36 weeks	128 (38.7)	6430
≥ 40 weeks	105 (31.7)	5560
≥ 44 weeks	90 (27.2)	4942
≥ 48 weeks	71 (21.5)	4072
≥ 52 weeks	53 (16.0)	3180
≥ 56 weeks	37 (11.2)	2318
≥ 60 weeks	21 (6.3)	1396
≥ 64 weeks	10 (3.0)	714
≥ 68 weeks	6 (1.8)	452
≥ 72 weeks	3 (0.9)	243
≥ 76 weeks	2 (0.6)	169
≥ 80 weeks	2 (0.6)	169
≥ 84 weeks	1 (0.3)	89
≥ 88 weeks	1 (0.3)	89
Total person time		10959

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Integrated safety analyses

Not applicable.

8.3.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.1.3. Pivotal and/or main efficacy studies

A summary of the frequency adverse events in the Safety Population as of the date of data cut-off (22-May 2015) is shown in Table 27 below:

Table 27: Summary of Adverse Events Study XL184-308

	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[a]	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)

All subjects experienced at least one AE regardless of the study treatment that they had received.

Adverse events that were reported for at least 10% of subjects are summarised in Table 28 below.

Table 28: Summary of Frequently Observed Adverse Events Study XL184-308

	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)

Table 28 continued: Summary of Frequently Observed Adverse Events Study XL184-308

	Cabozantinib N = 331 n (%)		Everolimus N = 322 n (%)	
	Grade		Grade	
Preferred Term	All	3/4	All	3/4
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)

Adverse events reported for ≥ 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhoea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPES), hypertension, vomiting, weight decreased, constipation, dysgeusia, stomatitis, hypothyroidism, and dysphonia.

Adverse events reported for ≥ 20% of subjects in the everolimus arm by decreasing frequency were fatigue, anaemia, decreased appetite, cough, dyspnoea, rash, diarrhoea, nausea, stomatitis, mucosal inflammation, and peripheral oedema.

Comment: Only a single study subject (who had received everolimus) did not report an adverse event. The frequency of adverse event was similar in both arms however the safety profile of cabozantinib compared to everolimus was different.

The nature of AEs experienced by subjects was different for subjects who had received cabozantinib versus those who had received everolimus. Fatigue, PPES, dysgeusia, hypertension, stomatitis, hypothyroidism and dysphonia have been reported for, and are in the product information for, other TKIs (sorafenib, sunitinib and pazopanib).

AEs of increased liver transaminases occurred among XL184-308 cabozantinib-treated subjects (18% AST increased, 16% ALT increased). However, there were no cases that met Hy's Law criteria (concurrent ALT or AST >3 x ULN, total bilirubin >2 x ULN, and alkaline phosphatase [ALP] <2 x ULN). This is discussed in greater detail elsewhere in this report.

Grade 3 and 4 adverse events were reported more frequently by subjects that had received cabozantinib versus those that had received everolimus, whereas the obverse was seen for Grade 5 adverse events.

8.3.1.4. Other studies

Other efficacy studies

Not applicable.

Studies with evaluable safety data: dose finding and pharmacology

Table 29: Frequent Adverse Events (≥ 20%) for Subjects with RCC in Study XL184-008 (Safety Population N-25)

Preferred Term	Any Grade n (%)	≥ Grade 3 n (%)
Fatigue	20 (80)	5 (20)
Diarrhoea	16 (64)	3 (12)
Hypophosphataemia	15 (60)	10 (40)
Hypothyroidism	12 (48)	0
Nausea	11 (44)	0
Hypomagnesaemia	10 (40)	0
Lipase increased	10 (40)	3 (12)
Decreased appetite	9 (36)	1 (4)
Palmar-plantar erythrodysaesthesia syndrome	9 (36)	1 (4)
Proteinuria	9 (36)	2 (8)
Vomiting	9 (36)	1 (4)
Dyspnoea	8 (32)	0
Hypertension	8 (32)	1 (4)
Hyponatraemia	8 (32)	5 (20)
Aspartate aminotransferase increased	7 (28)	1 (4)
Alanine aminotransferase increased	7 (28)	0
Constipation	7 (28)	0
Amylase increased	6 (24)	1 (4)
Blood creatinine phosphokinase increased	6 (24)	1 (4)
Dysgeusia	6 (24)	0
Dysphonia	6 (24)	2 (8)
Mucosal inflammation	6 (24)	0
Rash	6 (24)	0
Cough	5 (20)	0
Gastrointestinal reflux disease	5 (20)	0
Weight decreased	5 (20)	0

RCC, renal cell carcinoma

The most frequent ≥ Grade 3 AEs (≥ 10% incidence) were hypophosphatemia (40%), fatigue (20%), hyponatremia (20%), diarrhoea (12%), lipase increased (12%), and pulmonary embolism (12%). Grade 4 AEs were reported for 24% of subjects and comprised pulmonary embolism (3 subjects), blood uric acid increased, hyponatremia, mental status changes, and peritoneal haemorrhage (1 subject each). No Grade 5 AEs were reported.

Studies evaluable for safety only

Table 30: Frequent Adverse Events (≥ 20% Incidence) for Cabozantinib-Treated Subjects with CRPC for Pooled studies XL184-306 and 307 (Safety Population N=741)

Preferred Term	Any Grade n (%)	≥ Grade 3 n (%)
Any AE	**740 (> 99)**	**641 (87)**
Decreased appetite	439 (59)	56 (7.6)
Nausea	433 (58)	51 (6.9)
Diarrhoea	381 (51)	55 (7.4)
Fatigue	381 (51)	130 (18)
Vomiting	302 (41)	39 (5.3)
Constipation	257 (35)	9 (1.2)
Weight decreased	262 (35)	26 (3.5)
Asthenia	254 (34)	87 (12)
Anaemia	232 (31)	121 (16)
Hypertension	213 (29)	148 (20)
Palmar-plantar erythrodysaesthesia syndrome	209 (28)	42 (5.7)
Dysgeusia	188 (25)	1 (0.1)
Dysphonia	192 (26)	0
Dyspnoea	155 (21)	24 (3.2)

CRPC, castration-resistant prostate cancer.
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Integrated safety analyses

Not applicable.

8.3.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.2.3. Pivotal and/or main efficacy studies

Frequently reported treatment-related AEs (those reported for at least 10% of subjects in either treatment arm is summarised in Table 31.

Table 31: Treatment Related Adverse Events Reported for At Least 10% of Subjects

	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 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)

The overall incidence of treatment-related AEs was similar in both arms (97% cabozantinib, 91% everolimus). Treatment-related AEs reported for ≥ 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhea, fatigue, nausea, PPES, decreased appetite, hypertension, weight decreased, vomiting, dysgeusia, and stomatitis. Treatment-related AEs reported for ≥ 20% of subjects in the everolimus arm by decreasing frequency were fatigue, anaemia, decreased appetite, rash, stomatitis, mucosal inflammation, and diarrhea.

Treatment-related AEs were Grade 3 or 4 for 59% and 41% of subjects in the cabozantinib and everolimus arms, respectively, and Grade 5 for 0.3% and 0.6% in the respective treatment arms.

Comment: The frequency and nature of TAES are similar to those for all AEs. The TAEs observed in subjects who had received cabozantinib are AEs that had been observed for other TKIs.

8.3.2.4. Other studies

Other efficacy studies

Not applicable.

Studies with evaluable safety data: dose finding and pharmacology

Not applicable.

Studies evaluable for safety only

Not applicable.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Integrated safety analyses

Not applicable.

8.3.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.3.3. Pivotal and/or main efficacy studies

A total of 200 deaths were reported in the Safety population as of the cut-off date of 22 May 2015 which included 90 subjects (27%) in the cabozantinib arm and 110 subjects (34%) in the everolimus arm. Thirty-eight 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 PD (8 subjects [2.4%] cabozantinib, 11 [3.4%] everolimus) and other reasons (7 subjects [2.1%] cabozantinib, 12 [3.7%] 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 PD (145 out of 162), with more PD deaths occurring in the everolimus arm (65/331 subjects [20%] cabozantinib, 80/322 [25%] everolimus).

Table 32: Deaths and Reason for Death Up to Data Cut-off 22 May 2015 Study XL184-308

	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)

Up to the date of the unplanned interim analysis (Data cut-off 31 December 2015) there were 137 of subjects that had received cabozantinib and 170 of subjects that had received everolimus had died. In terms of the overall survival analysis this represents 320/408 (78%) of the events required for the final analysis.

Comment: The primary reason for death for both arms was progressive disease.

8.3.4. Serious Adverse Events

8.3.4.1. Grade 5 AEs

Table 33: Summary of Grade 5 Adverse Events through 30 Days after Last Dose of Study Drug by Preferred Term Sorted by Incidence in the XL184-308 Cabozantinib Arm

	RCC (XL184-308)	
	Cabozantinib (60 mg) N=331	Everolimus (10 mg) N=322
MedDRA Preferred Term	n (%)	n (%)
Subjects with a Grade 5 AE	15 (4.5)	23 (7.1)
Renal cell carcinoma[a]	8 (2.4)	11 (3.4)
Death	2 (0.6)[b]	0
Cardiac failure	1 (0.3)	0
General physical health deterioration	1 (0.3)	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Post procedural haemorrhage	1 (0.3)[c]	0
Urosepsis	1 (0.3)	0
Aspergillus infection	0	1 (0.3)
Circulatory collapse	0	1 (0.3)
Gastrointestinal perforation	0	1 (0.3)
Hydrothorax	0	2 (0.6)
Multi-organ failure	0	1 (0.3)
Pneumonia aspiration	0	3 (0.9)
Respiratory failure	0	1 (0.3)

Excluding AEs of disease progression, the most frequently reported (≥ 2 subjects) Grade 5 AE through 30 days after last dose of study treatment for subjects in the cabozantinib arm was death (0.6% cabozantinib arm, 0% everolimus arm). The most frequent events in the everolimus arm (≥ 2 subjects) were pneumonia aspiration (0% cabozantinib arm, 0.9% everolimus arm) and hydrothorax (0%, 0.6%).

8.3.4.2. Other serious adverse events

A summary of serious adverse events reported for at least 1.5% of subjects is shown in Table 34.

Table 34: Serious Adverse Events Reported in ≥ 1.5% of Subjects in Either Treatment Arm Study XL184-308

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

The overall incidence of SAEs was similar in both treatment arms (40% cabozantinib, 43% everolimus). Serious AEs reported for ≥ 1.5% of subjects in the cabozantinib arm by decreasing frequency were renal cell carcinoma, abdominal pain, pleural effusion, diarrhea, nausea, anaemia, back pain, dyspnoea, fatigue, pneumonia, pulmonary embolism, vomiting, and pain. Serious AEs reported for ≥ 1.5% of subjects in the everolimus arm by decreasing frequency were dyspnoea, pneumonia, anaemia, renal cell carcinoma, pneumonitis, dehydration, general physical health deterioration, pleural effusion, fatigue, metastases to the central nervous system, and renal failure acute.

SAEs that were judged by the investigator as related to treatment are summarised in Table 35.

Table 35: Treatment-Related Serious Adverse Events Reported in ≥ 1% of Subjects in Either Treatment Arm Study XL184-308

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)

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 hypomagnesemia. Treatment-related SAEs reported for ≥ 1% of subjects in the everolimus arm by decreasing frequency were pneumonitis, anaemia, dehydration, and dyspnoea.

8.3.4.3. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Study XL184-008

Two deaths were recorded both occurred within 30-days of the last dose of study treatment; one in a 60-year old male in the DTC cohort who died from massive haemoptysis following an aortotracheal fistula. This was considered related to study treatment. The second in a 62-year old female in the RCC cohort who died of progression of disease.

Comment: The development of fistula has been associated with VEGF TKIs and was an event to monitor in the pivotal study.

Studies evaluable for safety only

There were 120 deaths (16%) reported through 30 days after last dose of study treatment in the cabozantinib arms of Studies XL184-307 and XL184-306. Seventy (70) of these had causes of death of prostate cancer or were assessed as related to disease under study. The remaining fifty subjects had a cause of death assessed as 'other'.

For both studies, Grade 5 AEs were to be reported for all deaths not related to disease progression that occurred through 30 day after last dose of study treatment. The most frequently reported AEs (≥ 2 subjects) not related to disease progression were general physical health deterioration (1.9%), death (death of unknown cause; 0.5%), euthanasia (0.4%), pneumonia (0.4%), pulmonary embolism (0.4%), sepsis (0.4%), multi-organ failure (0.3%), renal failure (0.3%), respiratory failure (0.3%), and septic shock (0.3%).

Table 36: Frequent Serious Adverse Events (≥ 2% Incidence) for Pooled Subjects in Study XL184-307 and Study XL184-306 (Sorted by Descending Order of Frequency; Safety Population, N=741)

Preferred Term	SAE n (%)
Any SAE	**463 (62)**
Prostate cancer	61 (8.2)
General physical health deterioration	52 (7.0)
Pulmonary embolism	45 (6.1)
Anaemia	35 (4.7)
Vomiting	30 (4.0)
Nausea	25 (3.4)
Dehydration	23 (3.1)
Pneumonia	21 (2.8)
Asthenia	20 (2.7)
Fatigue	20 (2.7)
Metastatic pain	19 (2.6)
Bone pain	18 (2.4)
Pyrexia	18 (2.4)
Back pain	16 (2.2)
Decreased appetite	15 (2.0)
Urinary tract infection	15 (2.0)

A total of 463 subjects (62%) in the pooled CRPC studies had SAEs.

8.3.5. Discontinuations due to adverse events

8.3.5.1. Integrated safety analyses

Not applicable.

8.3.5.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.5.3. Pivotal and/or main efficacy studies

The pivotal efficacy study was designed such that dose reduction/modification was allowed for tolerability therefore adverse events that lead to dose reduction/modification or interruption are considered separately.

Table 37: Adverse Events That Led to Dose Reduction Study XL184-308

Preferred Term	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Number of subjects with at least one AE that led to dose reduction[a]	200 (60)	78 (24)
Diarrhoea	54 (16)	3 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	38 (11)	2 (0.6)
Fatigue	33 (10)	11 (3.4)
Hypertension	25 (7.6)	0

Table 38: Adverse Events That Led to Dose Interruption Study XL184-308

Preferred Term	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Number of subjects with at least one AE that led to dose interruption[a]	233 (70)	189 (59)
Diarrhoea	72 (22)	8 (2.5)
Palmar-plantar erythrodysaesthesia syndrome	46 (14)	5 (1.6)
Fatigue	41 (12)	19 (5.9)

AE, adverse event; CRF, case report form.

Table 39: Adverse Events that Led to Discontinuation of Study Treatment Study XL184-308

Preferred Term	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Number of subjects with at least one AE that led to treatment discontinuation (excluding AEs of disease progression)	34 (10)	31 (9.6)
Decreased appetite	6 (1.8)	3 (0.9)
Fatigue	4 (1.2)	3 (0.9)
Pneumonitis	0	7 (2.2)

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 day**s.**

Dose interruptions due to an AE occurred in 63% and 42% of subjects on the cabozantinib and everolimus arms, respectively. The median time to first dose interruption was 37.0 and 41.5 days, respectively.

The subject incidence of AEs that led to discontinuation of study drug was similar between treatment arms (10% cabozantinib, 9.6% everolimus).

8.3.5.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Table 40: Dose Reduction Levels for Adverse Events in Study SL184-008

Starting Dose	First Dose Level Reduction	Second Dose Level Reduction	Third Dose Level Reduction	Fourth Dose Level Reduction
140 mg	100 mg	60 mg	40 mg	20 mg

FBE, freebase equivalent.
Dose strengths in this table are expressed in FBE weight. In the XL184-008 protocol, dose strengths were expressed as the corresponding malate salt weight.

80% of subjects underwent at least one dose reduction due to AEs and 56% underwent at least a second reduction. The median average daily dose was 75.5 mg.

A total of six (24%) RCC subjects experienced AEs that led to study treatment discontinuation in Study XL184-008. The AEs that lead to study treatment discontinuation were diarrhoea, large intestine perforation, fatigue, blood creatine phosphokinase increased, proteinuria, and haemoptysis (each reported for one subject).

Table 41: Adverse Events Leading to Discontinuation of Study Treatment Study XL184-008

System Organ Class Preferred term	DTC (N=15) n (%)	RCC (N=25) n (%)	Total (N=40) n (%)
Any AE leading to discontinuation	3 (20.0)	6 (24.0)	9 (22.5)
Gastrointestinal disorders			
Any event	0	2 (8.0)	2 (5.0)
Diarrhoea	0	1 (4.0)	1 (2.5)
Large intestine perforation	0	1 (4.0)	1 (2.5)
General disorders and administration site conditions			
Any event	0	1 (4.0)	1 (2.5)
Fatigue	0	1 (4.0)	1 (2.5)
Injury, poisoning and procedural complications			
Any event	1 (6.7)	0	1 (2.5)
Wound	1 (6.7)	0	1 (2.5)
Investigations			
Any event	0	1 (4.0)	1 (2.5)
Blood CPK increased	0	1 (4.0)	1 (2.5)
Renal and urinary disorders			
Any event	0	1 (4.0)	1 (2.5)
Proteinuria	0	1 (4.0)	1 (2.5)
Respiratory, thoracic and mediastinal disorders			
Any event	2 (13.3)	1 (4.0)	3 (7.5)
Acquired trachea-oesophageal fistula	1 (6.7)	0	1 (2.5)
Haemoptysis	0	1 (4.0)	1 (2.5)
Pneumonia aspiration	2 (13.3)	0	2 (5.0)

AE, adverse event; CPK, creatine phosphokinase; DTC, differentiated thyroid cancer; RCC, renal cell carcinoma; SOC, system organ class.

Overall, nine subjects (22.5%) had an AE that led to the discontinuation of study treatment.

Studies evaluable for safety only

In studies XL184-306 & 307 the most frequent AEs that lead to study treatment discontinuation (≥ 1.5% incidence) were fatigue (3.5%), decreased appetite (2.3%), nausea (2.3%), general physical health deterioration (1.9%), vomiting (1.8%), asthenia (1.6%), and diarrhoea (1.5%).

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity

8.4.1.1. Integrated safety analyses

Not applicable

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable

8.4.1.3. Pivotal and/or main efficacy studies

AEs in the SOC Hepatobiliary Disorder are summarised in Table 42.

Table 42: Incidence of AEs in the Hepatobiliary Disorders SOC

	Cabozantinib N = 331 n (%)				Everolimus N = 322 n (%)			
System Organ Class Preferred Term	Any AE	Gr 3/4 AE	Gr 5 AE	SAE Any Grade	Any AE	Gr 3/4 AE	Gr 5 AE	SAE Any Grade
Hepatobiliary disorders	14 (4.2)	7 (2.1)	0	5 (1.5)	10 (3.1)	4 (1.2)	0	3 (0.9)
Bile duct obstruction	2 (0.6)	2 (0.6)	0	2 (0.6)	0	0	0	0
Cholangitis	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)
Cholangitis acute	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Cholecystitis	0	0	0	0	1 (0.3)	1 (0.3)	0	1 (0.3)
Cholecystitis acute	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)
Cholecystitis chronic	0	0	0	0	1 (0.3)	0	0	0
Cholelithiasis	1 (0.3)	0	0	0	0	0	0	0
Gallbladder pain	0	0	0	0	1 (0.3)	0	0	0
Hepatic steatosis	0	0	0	0	1 (0.3)	0	0	0
Hepatic vein thrombosis	0	0	0	0	1 (0.3)	0	0	0
Hepatitis cholestatic	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0	0
Hepatocellular injury	1 (0.3)	0	0	0	0	0	0	0
Hepatosplenomegaly	1 (0.3)	0	0	0	0	0	0	0
Hepatotoxicity	0	0	0	0	1 (0.3)	0	0	0
Hyperbilirubinaemia	4 (1.2)	0	0	0	0	0	0	0
Jaundice	1 (0.3)	0	0	0	1 (0.3)	0	0	0
Liver tenderness	0	0	0	0	1 (0.3)	0	0	0
Portal vein thrombosis	2 (0.6)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0	0

Table 43: Subject Incidence of Treatment-Emergent Liver Test Abnormalities

Laboratory Parameter	Cabozantinib N = 331	Everolimus N = 322
Number of subjects with post-baseline assessments of each parameter	329	319
ALT, n (%)		
> 3 × ULN, ≤ 5 × ULN	24 (7.3)	11 (3.4)
> 5 × ULN, ≤ 10 × ULN	9 (2.7)	1 (0.3)
> 10 × ULN, ≤ 20 × ULN	1 (0.3)	0
> 20 × ULN	1 (0.3)	0
AST, n (%)		
> 3 × ULN, ≤ 5 × ULN	20 (6.1)	5 (1.6)
> 5 × ULN, ≤10 × ULN	10 (3.0)	2 (0.6)
> 10 × ULN	1 (0.3)	0
> 20 × ULN	0	0
Alkaline phosphatase, n (%)		
> 1.5 × ULN, ≤ 2 × ULN	35 (11)	30 (9.4)
> 2 × ULN	30 (9.1)	35 (11)
Total bilirubin, n (%)		
> 1.5 × ULN, ≤ 2 × ULN	9 (2.7)	0
> 2 × ULN	8 (2.4)	1 (0.3)

Table 44: Incidence of Liver Test Abnormalities by Laboratory Screening Criteria for Drug Induced Liver Injury

> 3 × ULN ALT or AST, > 2 × ULN Total Bilirubin, AND	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
< 2 × ULN ALP (total subjects; potential Hy's Law cases)	0	0
≥ 2 × ULN ALP (total subjects)	2 (0.6)	1 (0.3)
≥ 2 × ULN ALP (subjects without confounding factors)	0	0

Comment: No subjects met the Hy's Law criteria. The most frequent hepatobiliary AEs were laboratory abnormalities with elevation of ALT, AST or ALP.

8.4.1.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

One subject had a Grade 3 increase in ALT and Grade 2 increase in AST that led to dose reduction and dose interruption of study treatment.

Studies evaluable for safety only

Table 45: Incidence of AEs (Hepatobiliary Disorders SOC) Study XL184-306

	Cabozantinib (N = 60) n (%)			Mitoxantrone + Prednisone (N = 57) n (%)		
	Grade			Grade		
Preferred Term[a]	All	3/4	5	All	3/4	5
Hepatobiliary disorders (system organ class)[a]	3 (5.0)	1 (1.7)	0	2 (3.5)	1 (1.8)	0
Cholecystitis acute	0	0	0	1 (1.8)	0	0
Hepatic failure	0	0	0	1 (1.8)	1 (1.8)	0
Hepatic steatosis	2 (3.3)	0	0	0	0	0
Hyperbilirubinaemia	1 (1.7)	1 (1.7)	0	0	0	0

Table 46: Incidence of Increased Liver Enzyme by Laboratory Screening Criteria

Increases in Liver Enzymes >3 × ULN ALT or AST, >2 × ULN Total Bilirubin, and the Following:	Cabozantinib (N = 60) n (%)	Mitoxantrone + Prednisone (N = 57) n (%)
<2 × ULN ALP (total subjects)	0	0
Without predisposing conditions	0	0
≥ 2 × ULN ALP (total subjects)	3 (5.0)	0
Without predisposing conditions	0	0

Using Hy's Law criteria to screen for potential DILI, three subjects in the cabozantinib arm were identified [information redacted].

Subject [information redacted]:

Subject [information redacted], a [information redacted] year-old black or African-American male, initiated study treatment (60 mg once daily cabozantinib and 12 mg/m^2 once every 3 weeks, mitoxantrone-matching placebo infusion, and 5 mg twice daily prednisone-matched placebo) on 18 Dec 2012 for castration resistant prostate cancer (CRPC). The subject had a baseline ECOG performance status of 1 with a pain score of 6.9. Previous anti-cancer treatment included docetaxel and abiraterone.

The subject was found to have deranged LFTs as shown in the table below.

Table 47: Liver enzyme values for subject

Date	Study Day	ALT Normal Range 5-37 (U/L)	AST Normal Range 10-37 (U/L)	Bilirubin Normal Range 0-1 (mg/dL)	ALP Normal Range 45-129 (U/L)	GGT Normal Range 0-73 (U/L)
11 Dec 2012[a]	-7	35	38	0.4	1287	105
08 Jan 2013	22	44	63	0.4	1438	162
29 Jan 2013	43	74	96	0.6	1200	301
19 Feb 2013	64	142	208	0.9	1496	690
26 Feb 2013	71	124	175	2.4	1481	752

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase

[a] No baseline values available

The cabozantinib was interrupted on 19 Feb due to elevations in the AST and ALT. The subject was subsequently hospitalised due to hypotension. Nine-days following discontinuation of cabozantinib the ALT had decreased to Grade 1 severity. (Not shown in table). The sponsor has assessed this case as not related to study treatment.

Comment: This subject had a number of confounding co-morbidities, including hepatic metastasis and hypotension; however, the hypotension was not profound and there is a temporal relationship between discontinuation of cabozantinib and improvement in ALT therefore the deterioration in LFT should be considered as at least possibly related to study medication.

Subject [information redacted]

[information redacted] White male, initiated study treatment (60 mg once daily cabozantinib, 12 mg/m^2 once every 3 weeks mitoxantrone-matched placebo infusion, and 5 mg twice daily prednisone-matched placebo) on 27 Nov 2012 for castration-resistant prostate cancer (CRPC). The subject had a screening ECOG performance status of 1 (baseline ECOG performance status was not performed) with a pain score of 6.7. Previous anti-cancer treatment included docetaxel, abiraterone, MDV3100, and cabazitaxel.

The subject was found to have deranged LFTs as shown in the table below:

Table 48: Liver enzyme values for subject

Date	Study Day	ALT Normal Range 17-63 (U/L)	AST Normal Range 15-41 (U/L)	Bilirubin Normal Range .3-1.5 (mg/dL)	GGT Normal Range <41 (U/L)	ALP Normal Range 38-126 (U/L)
27 Nov 2012	1	8	16	0.9	21	211
02 Dec 2012	6	20	59	1.0	ND	399
03 Dec 2012	7	21	64	0.9	29	443
05 Dec 2012	9	19	39	0.6	ND	511
18 Dec 2012	22	45	58	0.7	274	636
05 Jan 2013	40	56	102	1.1	ND	633
06 Jan 2013	41	54	100	1.2	ND	638
08 Jan 2013	43	52	147	0.8	843	1068
16 Jan 2013	51	64	142	1.1	ND	798
29 Jan 2013	64	92	231	2.2	1062	810
03 Feb 2013	69	79	367	3.6	ND	1053
04 Feb 2013	70	69	267	3.3	ND	898
ND, not done; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; ALP, alkaline phosphatase						

The subject had a concurrent urinary tract infection and was hospitalised for dehydration on 3 Feb 2013. Cabozantinib was discontinued on 29 January. A CT-scan showed marked progression of hepatic metastasis on 3 February.

The sponsor has assessed the elevation in hepatic transaminases (29 January) as related to treatment but the elevation in ALP as unrelated. The sponsor states that the aetiology of the deterioration in liver function is unclear yet dismisses cabozantinib as a contributing agent. The sponsor states that this event is not DILI but more likely related to progression of metastasis.

Comment: Progression of hepatic metastasis confounds this case, however, as with the previous narrative; there is a temporal association between the interruption of study treatment and improvement in ALT, AST and ALP.

Subject [information redacted]

[information redacted] old White male, initiated study treatment of 60 mg once daily cabozantinib on 24 Apr 2013, 12 mg/m^2 once every 3 weeks mitoxantrone-matched placebo infusion on 24 Apr 2013, and 5 mg twice daily prednisone-matched placebo on 15 May 2013 for castration-resistant prostate cancer (CRPC). The subject had a baseline ECOG performance status of 1 with a pain score of 6.9. Previous anti-cancer treatment included docetaxel, abiraterone, MDV3100, and cabazitaxel.

The subject was found to have deranged LFTs as shown in the table below:

Table 49: Liver enzyme values for subject

Date	Study Day	ALT Normal Range 6-43 (U/L)	AST Normal Range 11-36 (U/L)	Bilirubin Normal Range 0.2-1.2 (mg/dL)	ALP Normal Range 35-125 (U/L)
22 Apr 2013[a]	-2	8	15	0.4	70
26 Aug 2013	125	21	46	0.3	111
16 Sep 2013	146	361	335	6.7	1411
21 Sep 2013	NA	247[b]	236[d]	4.7[c]	ND

NA, not available; ND, not done; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase

[a] No baseline values available

[b] Normal Range 20-70 U/L

[c] Normal Range 0.2-1.3 mg/dL

[d] Normal Range 10-45 U/L

On 16 Sep 2013 (Study Day 146), the subject was hospitalized for hyperbilirubinemia (Grade 3), elevated ALT (Grade 3), and elevated AST (Grade 3). On the same day, laboratory values met the criteria for potential Hy's Law.

A computed tomography demonstrated predominantly stable bulky adenopathy, sclerotic bone lesions and diffuse biliary dilatation. A biliary drain was placed and cabozantinib interrupted on 16_September.

The sponsor has assessed the reason for deranged LFTs as due to hepatic metastasis.

Comment: The presence of hepatic metastasis confounds this case, any temporal relationship in the improvement of LFTs occurred following the placement of a biliary drain. It is more likely that the derangement in LFT was due to biliary obstruction as opposed to DILI.

Table 50: Incidence of AEs (Hepatobiliary Disorders SOC) Study XL184-307

SOC / Preferred Term	Cabozantinib (N = 681) n (%)			Prednisone (N = 342) n (%)		
	Grade			Grade		
	All	3/4	5	All	3/4	5
Hepatobiliary disorders	33 (4.8)	10 (1.5)	1 (0.1)	8 (2.3)	2 (0.6)	0
Bile duct obstruction	(0.1)	1 (0.1)	0	0	0	0
Bile duct stenosis	0	0	0	1 (0.3)	1 (0.3)	0
Biliary colic	1 (0.1)	0	0	0	0	0
Cholecystitis	2 (0.3)	2 (0.3)	0	1 (0.3)	0	0
Cholelithiasis	5 (0.7)	0	0	1 (0.3)	0	0
Cholestasis	1 (0.1)	0	0	0	0	0
Hepatic failure	4 (0.6)	3 (0.4)	1 (0.1)	0	0	0
Hepatic function abnormal	3 (0.4)	1 (0.1)	0	0	0	0
Hepatic pain	1 (0.1)	0	0	0	0	0
Hepatic steatosis	4 (0.6)	0	0	1 (0.3)	0	0
Hepatitis	1 (0.1)	1 (0.1)	0	0	0	0
Hepatocellular injury	6 (0.9)	0	0	0	0	0
Hepatomegaly	0	0	0	1 (0.3)	0	0
Hydrocholecystis	1 (0.1)	0	0	0	0	0
Hyperbilirubinaemia	3 (0.4)	2 (0.3)	0	1 (0.3)	1 (0.3)	0
Hypertransaminasaemia	1 (0.1)	0	0	0	0	0
Jaundice	2 (0.3)	1 (0.1)	0	2 (0.6)	0	0
Portal vein thrombosis	2 (0.3)	1 (0.1)	0	0	0	0

Table 51: Incidence of Increased Liver Enzyme by Laboratory Screening Criteria Study XL184-307

Increases in Liver Enzymes	Cabozantinib (N = 681) n (%)	Prednisone (N = 342) n (%)
Subjects meeting Hy's Law screening criteria [>3× ULN (ALT or AST), <2× ULN ALP, and >2× ULN Total Bilirubin]	1 (0.1)	1 (0.3)
Subjects meeting Hy's Law screening criteria [>3× ULN (ALT or AST), ≥ 2× ULN ALP, and >2× ULN Total Bilirubin]	9 (1)	5 (1)

One subject in each treatment arm met Hy's Law screening criteria 1 (concurrent ALT or AST > 3x ULN, total bilirubin > 2x ULN, and ALP < 2x ULN). Nine subjects (1%) in the cabozantinib arm and 5(1%) in the prednisone arm met Hy's Law screening criteria 2 (concurrent ALT or AST > 3x ULN, total bilirubin > 2x ULN, and ALP < or > 2x ULN). These cases were confounded by liver metastases or hepatobiliary disease. There was one case in the cabozantinib arm where drug-induced liver injury could not be ruled out (Subject [information redacted]); this subject had a Grade 2 AE of ALT increased.

8.4.2. Renal function and renal toxicity

8.4.2.1. Integrated safety analyses

Not applicable.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.2.3. Pivotal and/or main efficacy studies

Table 52: Shift in Sponsor-Defined Grade from Baseline to Worst Grade for Urine Protein Creatinine Ration (UPCR) Study XL184-308

	Post-Baseline			
	Cabozantinib N = 331 n (%)		Everolimus N = 322 n (%)	
Baseline	Grade 2	Grade 3	Grade 2	Grade 3
Grade 0	6 (1.8)	3 (0.9)	14 (4.3)	0
Grade 1	29 (8.8)	6 (1.8)	14 (4.3)	4 (1.2)
Grade 2	2 (0.6)	0	1 (0.3)	0

CTCAE, Common Terminology Criteria for Adverse Events; UPCR, urine protein-creatinine ratio
Laboratory results from both central and local laboratories are included.
Sponsor-defined Grade for UPCR: Grade 1: ≥ 0.15 to ≤ 1.0 mg/mg; Grade 2: >1.0 to ≤ 3.5 mg/mg; Grade 3: > 3.5 mg/mg; 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).

Renal function was monitored by evaluation of the urine protein creatinine ratio (UPCR). Grade 3 (sponsor defined) abnormities occurred in 2.7% of subjects in the cabozantinib treatment arm and 2.2 % in the everolimus treatment arm.

8.4.2.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Most UPCR values were Grade 0 or Grade 1 at Baseline, and remained at Grade 0 or normal at any postbaseline visit. There were no shifts to Grade 3 or Grade 4 in the DTC cohort, and one shift from Grade 2 to Grade 3 in the RCC cohort. Proteinuria, a VEGF-associated AE, was reported in 16 subjects (40.0%) overall: seven subjects (46.7%) with DTC and nine subjects (36.0%) with RCC. In three subjects (7.5%) these episodes of proteinuria were of ≥Grade 3 intensity: one subject (6.7%) with DTC and two (8.0%) with RCC.

No episodes of proteinuria were considered to be serious. One episode of non-serious proteinuria in a subject with RCC (1141-1408) led to the permanent discontinuation of study treatment. Four subjects experienced dose modifications due to episodes of non-serious proteinuria.

Studies evaluable for safety only

Table 53: Worst Shift from Baseline in Sponsor-Defined Grade for Urine Protein-Creatinine Ration Study XL184-306

Parameter	Baseline Grade	Post-Baseline					
		Cabozantinib (N = 60) n (%)			Mitoxantrone + Prednisone (N = 57) n (%)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
UPCR decreased	Grade 0	11 (18)	1 (1.7)	0	16 (28)	1 (1.8)	0
	Grade 1	7 (12)	2 (3.3)	0	7 (12)	0	0
	Grade 2	0	0	0	0	0	0

UPCR, urine protein/creatinine ratio

In Study XLL184-306, post-baseline UPCR abnormalities of any grade were reported for 40% of subjects in the cabozantinib arm and 42% of subjects in the mitoxantrone plus prednisone arm'

Table 54: Worsening from Baseline of Sponsor-Defined Grades for Urine Protein-Creatinine Ratio Study XL184-307

Baseline	Post-Baseline			
	Cabozantinib (N = 681) n (%)		Prednisone (N = 342) n (%)	
	Grade 2	Grade 3	Grade 2	Grade 3
Grade 0	16 (4)	3 (0.7)	2 (1)	0
Grade 1	35 (17)	5 (2)	14 (12)	2 (2)
Grade 2	9 (60)	1 (7)	4 (50)	2 (25)

UPCR, urine protein-creatinine ratio.

In Study XL184-307, post-baseline Grade 3 UPCR abnormalities were recorded for 9/681 (1.3%) subjects in the cabozantinib arm and 4/342 (1.2%) subjects in the prednisone arm.

8.4.3. Other clinical chemistry

8.4.3.1. Integrated safety analyses

Not applicable.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.3.3. Pivotal and/or main efficacy studies

Thyroid Function Tests

At baseline, 225 subjects (68%) in the cabozantinib arm and 216 (67%) in the everolimus arm had normal TSH and FT4 levels. Of these subjects, 64% (143/225) of subjects in the cabozantinib arm and 8% (17/216) in the everolimus arm had post-baseline increased TSH with normal FT4. A further 8% (17/225) of subjects in the cabozantinib arm and 0.5% (1/216) in the everolimus had post-baseline increased TSH with FT4 decreased. As the effect of concomitant thyroid hormone replacement therapy has not been evaluated, AE reporting may be more reflective of the incidence of hypothyroidism.

Table 55: Thyroid hormone levels

Worst Post-Baseline Status (Possible Clinical Condition)	Cabozantinib N = 225 n (%)	Everolimus N = 216 n (%)
TSH increased and FT4 decreased (potential clinical hypothyroidism)	17 (8)	1 (0.5)
TSH increased and FT4 normal (potential subclinical hypothyroidism)	143 (64)	17 (8)
TSH decreased FT4 increased (clinical hyperthyroidism or replacement therapy with thyroid hormone)	2 (0.9)	17 (8)
TSH decreased, FT4 normal (replacement therapy with thyroid hormone)	0	12 (6)

TSH, thyroid-stimulating hormone; FT4, free thyroxine.
Subject status for TSH and FT4 post-baseline assessment are presented in descending hierarchical order as deemed important by the sponsor. Subjects appear only in the highest row for which a post-baseline assessment of TSH and FT4 at any time point met the criteria for that row even if other assessments at other time points met the criteria for other rows. Subjects with abnormal or missing baseline TSH or FT4 status were not included in this summary.
Subjects who had normal post-baseline TSH and FT4 status or missing post-baseline FT4 status at all time points are not presented in the table above but were summarized in the source table.
The denominator for proportions presented in each cell is the number of subjects with normal values for TSH and FT4 at baseline for that treatment arm.

8.4.3.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

No abnormalities reported.

Studies evaluable for safety only

In Study XL184-306 maximum post-baseline TSH levels were reported as high for 30 of 60 (50%) subjects in the cabozantinib arm and 4 of 57 (7.0%) subjects in the mitoxantrone plus prednisone arm.

In Study XL184-307 a total of 300/681 (44%) subjects in the cabozantinib arm had a high TSH after first dose compared with 11/342 (3%) in the prednisone arm

8.4.4. Haematology and haematological toxicity

8.4.4.1. Integrated safety analyses

Not applicable.

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.4.3. Pivotal and/or main efficacy studies

There were no haematology abnormalities with ≥.40% incidence in the cabozantinib arm.

In the everolimus arm, the most frequent haematology abnormality (≥.40% incidence) was haemoglobin decreased (71%).

Most haematology abnormalities were Grade 1 or 2 severity in both treatment arms. Haematology abnormalities with ≥.Grade 3 severity reported for ≥.5% of subjects were lymphocytes decreased in the cabozantinib arm and haemoglobin decreased and lymphocytes decreased in the everolimus arm Table 56.

Table 56: Subject Incidence of Selected Haematology Abnormalities by CTCAE Grade

Hematologic Abnormality	Cabozantinib N = 331 n (%)			Everolimus N = 322 n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
ANC decreased	101 (31)	8 (2.4)	0	56 (17)	2 (0.6)	0
Hemoglobin decreased	102 (31)	14 (4.2)	0	230 (71)	54 (17)	0
Hemoglobin increased	22 (6.6)	0	0	2 (0.6)	0	0
Lymphocytes decreased	83 (25)	23 (6.9)	0	124 (39)	37 (11)	1 (0.3)
Lymphocytes increased	8 (2.4)	0	0	2 (0.6)	0	0
Platelets decreased	84 (25)	2 (0.6)	0	86 (27)	2 (0.6)	1 (0.3)
WBC decreased	117 (35)	2 (0.6)	0	100 (31)	2 (0.6)	0
WBC increased	0	0	0	0	0	0

ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; WBC, white blood cell.

Haematology parameters that most frequently (≥.5%) showed a shift from < Grade 3 at baseline to ≥.Grade 3 post-baseline were haemoglobin decreased (14/331 [4.2%] cabozantinib, 54/322 [17%] everolimus) and lymphocytes decreased (23/331 [6.9%] cabozantinib, 38/322 [12%] everolimus) Table 57.

Table 57: Shift in CTCAE Grade from Baseline to Worst Grade for Selected Haematological parameters

Baseline CTCAE Grade for Laboratory Parameter		Post-Baseline					
		Cabozantinib N = 331 n (%)			Everolimus N = 322 n (%)		
		Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
ANC decreased	Grade 0	32 (9.7)	8 (2.4)	0	11 (3.4)	1 (0.3)	0
	Grade 1	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
	Grade 2	1 (0.3)	0	0	0	0	0
Hemoglobin decreased	Grade 0	8 (2.4)	1 (0.3)	0	26 (8.1)	10 (3.1)	0
	Grade 1	21 (6.3)	6 (1.8)	0	60 (19)	32 (9.9)	0
	Grade 2	13 (3.9)	7 (2.1)	0	13 (4)	12 (3.7)	0
Hemoglobin increased	Grade 0	1 (0.3)	0	0	1 (0.3)	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
Lymphocytes decreased	Grade 0	41 (12)	14 (4.2)	0	68 (21)	23 (7.1)	1 (0.3)
	Grade 1	3 (0.9)	1 (0.3)	0	3 (0.9)	1 (0.3)	0
	Grade 2	26 (7.9)	8 (2.4)	0	19 (5.9)	13 (4)	0
Lymphocytes increased	Grade 0	8 (2.4)	0	0	2 (0.6)	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	2 (0.6)	0	0	2 (0.6)	0	0
Platelets decreased	Grade 0	1 (0.3)	1 (0.3)	0	4 (1.2)	2 (0.6)	1 (0.3)
	Grade 1	1 (0.3)	1 (0.3)	0	0	0	0
	Grade 2	0	0	0	0	0	0
WBC decreased	Grade 0	41 (12)	1 (0.3)	0	20 (6.2)	1 (0.3)	0
	Grade 1	6 (1.8)	1 (0.3)	0	4 (1.2)	1 (0.3)	0
	Grade 2	1 (0.3)	0	0	1 (0.3)	0	0
WBC increased	Grade 0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0

ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; WBC, white blood cell.

ANC decreased	101 (31)	8 (2.4)	0	56 (17)	2 (0.6)	0
Hemoglobin decreased	102 (31)	14 (4.2)	0	230 (71)	54 (17)	0
Hemoglobin increased	22 (6.6)	0	0	2 (0.6)	0	0
Lymphocytes decreased	83 (25)	23 (6.9)	0	124 (39)	37 (11)	1 (0.3)
Lymphocytes increased	8 (2.4)	0	0	2 (0.6)	0	0
Platelets decreased	84 (25)	2 (0.6)	0	86 (27)	2 (0.6)	1 (0.3)
WBC decreased	117 (35)	2 (0.6)	0	100 (31)	2 (0.6)	0
WBC increased	0	0	0	0	0	0

Red Blood cell transfusions

Fourteen subjects (4.2%) in the cabozantinib arm and 23 subjects (7.1%) in the everolimus arm had at least one RBC transfusion within 28 days prior to randomisation. Only 36 (11%) subjects in the cabozantinib arm required RBC transfusion after randomisation compared with 85 (26%) in the everolimus arm Table 58.

Table 58: Red Blood Cell Transfusions after Randomisation

	Cabozantinib N = 331	Everolimus N = 322
Subject with prior RBC Transfusion ≤ 28 days before randomization	14 (4.2%)	23 (7.1%)
Subject with any RBC transfusion after randomization	36 (11%)	85 (26%)
Number of RBC Transfusions after randomization[a]		
Total number of transfusions	69	235
Mean (range) number of transfusions		
for all subjects	0.2 (0, 10)	0.7 (0, 9)
for subjects with any transfusion	1.9 (1, 10)	2.8 (1, 9)

8.4.4.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

No relevant adverse events reported.

Studies evaluable for safety only

Table 59: Subject Incidence of Selected Haematology Abnormalities by CTCAE Grade Study XL184-306

Laboratory Category Abnormality	Cabozantinib (N = 60) n (%)			Mitoxantrone + Prednisone (N = 57) n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
ANC decreased	23 (38)	2 (3.3)	0	23 (40)	6 (11)	8 (14)
Hemoglobin decreased	53 (88)	13 (22)	0	55 (96)	11 (19)	0
Lymphocytes decreased	49 (82)	22 (37)	3 (5.0)	47 (82)	30 (53)	5 (8.8)
Lymphocytes increased	1 (1.7)	0	0	1 (1.8)	0	0
Platelets decreased	27 (45)	0	3 (5.0)	27 (47)	5 (8.8)	1 (1.8)
White blood cells decreased	39 (65)	3 (5.0)	0	34 (60)	8 (14)	9 (16)

Table 60: Worst Shift from Baseline in CTCAE Grade for Selected Haematology Parameters Study XL184-306

Hematology Parameter	Baseline Grade	Post-Baseline					
		Cabozantinib (N = 60) n (%)			Mitoxantrone + Prednisone (N = 57) n (%)		
		Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
ANC decreased	Grade 0	14 (23)	1 (1.7)	0	5 (8.8)	6 (11)	8 (14)
	Grade 1	0	1 (1.7)	0	0	0	0
	Grade 2	0	0	0	0	0	0
Hemoglobin decreased	Grade 0	0	1 (1.7)	0	4 (7.0)	0	0
	Grade 1	12 (20)	3 (5.0)	0	13 (23)	4 (7.0)	0
	Grade 2	10 (17)	9 (15)	0	11 (19)	7 (12)	0
Lymphocytes decreased	Grade 0	8 (13)	4 (6.7)	1 (1.7)	8 (14)	13 (23)	3 (5.3)
	Grade 1	3 (5.0)	2 (3.3)	0	2 (3.5)	1 (1.8)	1 (1.8)
	Grade 2	8 (13)	10 (17)	1 (1.7)	1 (1.8)	13 (23)	0
Lymphocytes increased	Grade 0	1 (1.7)	0	0	1 (1.8)	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
Platelets decreased	Grade 0	6 (10)	0	1 (1.7)	10 (18)	3 (5.3)	1 (1.8)
	Grade 1	1 (1.7)	0	2 (3.3)	1 (1.8)	2 (3.5)	0
	Grade 2	0	0	0	0	0	0
WBC decreased	Grade 0	16 (27)	1 (1.7)	0	7 (12)	8 (14)	7 (12)
	Grade 1	2 (3.3)	2 (3.3)	0	0	0	1 (1.8)
	Grade 2	0	0	0	0	0	1 (1.8)

ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; WBC, white blood cells.

A decrease in total white cell count was observed for 65% of subjects in the cabozantinib arm at any grade. The majority of the observed reductions were mild and not clinically relevant.

In Study XL184-307 haematology abnormalities (all grades) with a ≥ 5% higher incidence in the cabozantinib arm were: white blood cells decreased (cabozantinib 47%, prednisone 14%), absolute neutrophil count decreased (36%, 6%), and platelets decreased (34%, 24%).

Haematology parameters that most frequently showed a shift from a Grade < 3 value at baseline to a Grade ≥ 3 value post-baseline in the cabozantinib arm were haemoglobin decreased (120/681 [18%] cabozantinib versus 60/342 [18%] prednisone) and lymphocytes decreased (109/681 [16%] versus 63/342 [18%]).

8.4.5. Other laboratory tests

8.4.5.1. Integrated safety analyses

Not applicable.

8.4.5.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.5.3. Pivotal and/or main efficacy studies

Hypercalcemia is a condition that can be associated with RCC and was monitored as an event of special interest. Subject incidence of Grade 3 and Grade 4 AEs of hypercalcemia was low and is summarised in Table 61.

Table 61: Subject Incidence of CTCAE Grade 3 and Grade 4 Hypercalcemia Study XL184-308

CTCAE Grade	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
Grade 3 or 4	2 (0.6)	6 (1.9)
Grade 4	1 (0.3)	3 (0.9)

8.4.5.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Nil significant reported.

Studies evaluable for safety only

This was not treated as an event of interest in either of study XL184-306 or 307.

8.4.6. Electrocardiograph findings and cardiovascular safety

8.4.6.1. Integrated safety analyses

Not applicable.

8.4.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.6.3. Pivotal and/or main efficacy studies

Two subjects (0.6%) in the cabozantinib arm and no subjects in the everolimus arm had postbaseline ECG assessments that appeared to show prolonged QTcF interval (QTcF > 500 ms) per investigator evaluation. In accordance with the protocol, these were independently evaluated by a core ECG laboratory. Such submissions were supposed to include triplicate ECGs to allow for confirmation by central ECG review, but may have been limited to single or double readings only. Based on independent review, no subjects in either treatment arm experienced a QTcF triplicate average > 500 ms post-baseline.

Table 62: Subject Incidence of Clinically Meaningful Changes in QTcF

	Cabozantinib N = 331 n (%)	Everolimus N = 322 n (%)
QTcF triplicate average after first dose > 500 ms per investigator	2 (0.6%)[a]	0[b]
QTcF triplicate average after first dose > 500 ms per independent review	0	0

QTcF, Fridericia's correction of QT interval.
[a] One subject (Subject) in the cabozantinib arm had a single ECG reading with QTcF > 500 ms. The reading was not sent for independent review, but two days later the subject had a QTcF triplicate average < 500 ms per investigator.
[b] Two subjects (Subjects) in the everolimus arm had single ECG readings with QTcF > 500 ms which were not confirmed by independent review.

8.4.6.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

No clinically significant changes in QT interval were listed for Study XL184-008.

Study XL184-301 was a randomised, double-blinded, multi-centre, placebo-controlled Phase III study of unresectable, locally advanced, or metastatic MTC. A total of 330 subjects were randomised in a 2:1 ratio to receive either XL184 or cabozantinib or placebo, respectively. The report for this study was submitted as a PD report, the report largely pertains to ECG data subjects that had received 175mg of cabozantinib per day.

Twelve-lead ECGs were recorded in triplicate (recording repeated three times consecutively within 30 minutes with an interval of at least 2 minutes between ECG). All ECG assessments (except for screening) were time matched with pharmacokinetic samples such that the ECG assessments were performed just prior to the blood sample collection. The concentration of XL184 was measured in plasma samples taken at selected intervals throughout the study.

All ECGs were digitally analysed by a validated ECG laboratory, ERT. The central vendor placed ECG machines at sites under contract with the study sponsor. ECGs were transmitted to ERT for analysis.

ECGs were taken in triplicate at screening, C1D1 pre-dose and 2, 4, and 6 hours' post-dose andC2D1 pre-dose and 2, 4, and 6 hours' post-dose.

The ECG data showed a small signal of a -4 to -6 bpm change in heart rate. There was no clinical signal for a change in AV conduction as measured by the PR interval duration, cardiac depolarization as measured by the QRS interval duration or on cardiac wave form morphology or new rhythms.

The data from the central tendency by time averaging across the study and by comparing the baseline to each time point demonstrated no clear signal of any effect on cardiac repolarisation on, after the first dose but by steady state for subjects with uninterrupted 175 mg/day dosing there was a clear positive effect on QTcF of about 10 ms (upper 1-sided 95% CI bound: 11.4 ms) by time averaging the data with a range of 10-15 ms as viewed in the time point analysis.

Studies evaluable for safety only

Table 63: Incidence of Prolonged QT Adverse Events Study XL184-306

	Cabozantinib (N = 60) n (%)			Mitoxantrone + Prednisone (N = 57) n (%)		
	Grade			Grade		
Preferred Term[a]	All	3/4	5	All	3/4	5
Electrocardiogram QT prolonged	3 (5.0)	1 (1.7)	0	2 (3.5)	0	0

Table 64: Incidence of Prolonged QT Adverse Events Study XL184-307

	Cabozantinib (N = 681) n (%)			Prednisone (N = 342) n (%)		
	Grade			Grade		
Preferred Term	All	3/4	5	All	3/4	5
Electrocardiogram QT prolonged	8 (1.2)	2 (0.3)	0	1 (0.3)	1 (0.3)	0

Comment: QT prolongation was consistently observed there is a precaution in the prescribing information with regard to the use of cabozantinib and QT prolongation.

8.4.7. Vital signs and clinical examination findings

8.4.7.1. Integrated safety analyses

Not applicable.

8.4.7.2. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.7.3. Pivotal and/or main efficacy studies

Blood pressure

Hypertension was reported as an AE in 37% of subjects in the cabozantinib arm and 7.1% of subjects in the everolimus arm. The incidence of Grade 3 or 4 hypertension was 15% and 3.1% in the respective treatment arms and SAEs of hypertension had an incidence of 0.3% in cabozantinib-treated subjects and 0% in everolimus-treated subjects.

Adverse events of hypertension resulted in dose modification in 9.1% and 0% of subjects in the cabozantinib and everolimus arms, respectively. In addition to hypertension, blood pressure increased was reported as an AE in 1.5% of subjects on the cabozantinib arm and 0% of subjects on the everolimus arm, with an incidence of Grade 3 or 4 AEs of 0.6% in cabozantinib-treated subjects none of which was an SAE or resulted in dose modification.

Weight

Clinically-meaningful losses in body weight occurred in 46% of subjects in the cabozantinib arm and 19% of subjects in the everolimus arm.

ECOG Performance Status

At baseline the majority of subjects in both treatment arms had an ECOG PS of 1. Over the course of the study, 43% and 35% of subjects in the cabozantinib and everolimus arms, respectively, had an increase in ECOG PS of ≥ 1; and 9.1% and 6.8% of subjects in the two respective treatment arms had an increase of ≥ 2.

8.4.7.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Not applicable.

Studies evaluable for safety only

Not applicable.

8.4.8. Immunogenicity and immunological events

8.4.8.1. Integrated safety analyses

Not applicable.

8.4.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.8.3. Pivotal and/or main efficacy studies

Not applicable.

8.4.8.4. Other studies

Other efficacy studies

Not applicable.

Studies with evaluable safety data: dose finding and pharmacology

Studies evaluable for safety only

Not applicable.

8.4.9. Serious skin reactions

8.4.9.1. Integrated safety analyses

Not applicable.

8.4.9.2. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.9.3. Pivotal and/or main efficacy studies

Palmar-plantar erythrodysaesthesia syndrome

PPES is a side effect frequently associated with the use of other VEGF-TKIS, leading to erythema and swelling of the palms of the hands and/or soles of the feet. This can lead to blistering

The incidence of PPES in subjects that received cabozantinib was high. 139 subjects [42%]); 19 subjects (5.9%) had PPES in the everolimus arm. PPES was one of the most frequent reasons for interruption or discontinuation of study treatment.

8.4.9.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

In Study XL184-008 40% of subjects in the DTC arm and 36% of subjects in the RCC arm experienced PPES of any severity.

Studies evaluable for safety only

In the pooled analysis of studies 306 and 307 PPES was reported for 28% of subjects and lead to dose interruption /modification or discontinuation in 8.9% of subjects.

8.4.10. Other safety parameters

8.4.10.1. Integrated safety analyses

Not applicable.

8.4.10.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.10.3. Pivotal and/or main efficacy studies

Events to Monitor

A number of AEs to monitor were prespecified and termed events to monitor (ETM). The ETM were selected based on the known safety profile of TKIs, VEGF inhibition and potential severity. The frequency of ETMs is summarised in the table below that is taken from the Summary of Clinical Safety.

Table 65: Incidence of Events to Monitor

	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
ETM	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.

[information redacted]

[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'.

Gastrointestinal perforation

Gastrointestinal perforations were reported for three subjects (0.9%) in the cabozantinib arm and two subjects (0.6%) in the everolimus arm.

Two subjects in the cabozantinib arm had Grade 3 events (gastrointestinal perforation and intestinal perforation).

For the everolimus arm, one subject had a Grade 4 intestinal perforation and the other had a Grade 5 gastrointestinal perforation.

There were no Grade 5 events of GI perforation in the cabozantinib arm. In addition, no AEs of peritonitis were reported in the cabozantinib arm. In the everolimus arm, one subject had an AE of serious Grade 4 peritonitis and one subject had an AE of serious Grade 2 bacterial peritonitis.

Fistula

Fistula was reported for 1.5% of subjects who received cabozantinib and none who had received everolimus.

Abscess—All

The incidence of abscess was low in both treatment arms. Grade 3 AEs of abdominal abscess and anal abscess (0.6% each) were reported for the cabozantinib arm. Grade 3 AEs of neck abscess and uncoded: periodontal abscess (0.3% each) was reported for the everolimus arm.

Intra-abdominal and pelvic abscess

As may be expected form the incidence of all abscesses the incidence of intrabdominal and/or pelvic abscess was low; events reported for four subjects (1.2%) in the cabozantinib arm and one subject (0.3%) in the everolimus arm.

Haemorrhage

Haemorrhagic events ≥ Grade 3 were reported for 6 subjects (1.8%) and 4 subjects (1.2%) in the cabozantinib and everolimus arms, respectively. Each ≥ Grade 3 AE PT was reported in no more than one subject per treatment arm. Grade 3 or 4 AEs reported for the cabozantinib arm were cerebral hematoma, gastric haemorrhage, and ulcer haemorrhage (each Grade 3) and haemarthrosis and haemorrhagic anaemia (reported in the same subject; both Grade 4). Grade 3 or 4aAEs reported for the everolimus arm were gastric haemorrhage and upper gastrointestinal haemorrhage (both Grade 3) and renal haemorrhage and uncoded: stroke haemorrhagic (Grade 3).

There were two Grade 5 haemorrhagic events reported in the cabozantinib arm: an extradural haematoma derived from exophytic growth of bone metastases to the skull which occurred 31 days after the last dose of cabozantinib and a post procedural haemorrhage following surgical treatment of peripheral ischemia and concomitant heparin administration for blood clot prophylaxis. There were no Grade 5 events of haemorrhage in the everolimus arm.

Arterial thrombotic events

The incidence of arterial thromboses was low in both treatment arms (3 subjects [0.9%] cabozantinib arm, 1 subject [0.3%] everolimus arm)

Venous and mixed/unspecified thrombotic events

The most frequent (≥ 1%) venous and mixed thrombotic events in the cabozantinib arm were pulmonary embolism (3.6% cabozantinib, 0.3% everolimus) and deep vein thrombosis (1.5% cabozantinib, 0.6% everolimus). Grade 3 or 4 pulmonary embolism was reported for 2.4% of subjects in the cabozantinib arm (one subject had a Grade 4 AE) and 0.3% of subjects in the everolimus arm (a Grade 3 AE was reported). Grade 3 deep vein thrombosis occurred in 0.3% of subjects in the cabozantinib arm and no subjects in the everolimus arm.

Wound complications

The incidence of wound complications was low for both arms of Study XL184-308 (8 cabozantinib-treated subjects [2.4%], 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.

Osteonecrosis

Osteonecrosis of the jaw (ONJ) was reported for two subjects (0.6%) in the cabozantinib arm; one subject experienced a Grade 3 SAE. Both subjects had a history of ONJ prior to randomisation. In comparison, ONJ was reported for two subjects (0.6%) on the everolimus arm, and both of these subjects experienced Grade 3 SAEs. No AEs of ONJ were reported as Grade 4 or higher in either treatment arm.

RPLS

RPLS was not reported for any subjects in this study.

Diarrhoea

The incidence of diarrhea events was 74% (245 subjects) in the cabozantinib arm and 28% (89 subjects) in the everolimus arm; diarrhoea was the most frequently reported AE for subjects in the cabozantinib arm.

8.4.10.4. Other studies

Studies with evaluable safety data: dose finding and pharmacology

Studies evaluable for safety only

Table 66 compares show incidence of the adverse event to monitor across the studies with relevant data.

Table 66: Rate of Events to Monitor Across Studies

	Tumor Type					
	RCC (XL184-308) 60 mg		CRPC (XL184-307 & XL184-306) 60 mg		MTC (XL184-301) 140 mg	
	N = 331		N = 741		N = 219	
Category[a]	Any AE n (%)	≥ Grade 3 n (%)	Any AE n (%)	≥ Grade 3 n (%)	Any AE n (%)	≥ Grade 3 n (%)
GI perforation	3 (0.9)	2 (0.6)	9 (1.2)	8 (1.1) 1 Grade 5 AE	7 (3.3)	7 (3.3)
Fistulas	4 (1.2)	1 (0.3)	9 (1.2)	3 (0.4)	10 (4.6)[b]	5 (2.3) 3 Grade 5 AEs
Intra-abdominal and pelvic abscesses	4 (1.2)	4 (1.2)	11 (1.5)	8 (1.1)	5 (2.3)	1 (0.5)
Haemorrhage (≥ Grade 3)	NA	7 (2.1) 2 Grade 5 AEs	NA	35 (4.7) 6 Grade 5 AEs	NA	7 (3.3) 2 Grade 5 AEs
ATE	3 (0.9)	2 (0.6)	23 (3.1)	12 (1.6)	5 (2.3)	2 (0.9)
VTE	24 (7.3)	12 (3.6)	95 (13.0)	66 (8.9) 3 Grade 5 AEs	12 (5.6)	10 (4.7)
Wound complications	8 (2.4)	1 (0.3)	15 (2.0)	5 (0.7)	4 (1.9)	2 (0.9)
Hypertension	128 (39)	52 (16)	213 (29)	149 (20)	70 (33)	18 (8.4)
ONJ	2 (0.6)	1 (0.3)	22 (3.0)	9 (1.2)	3 (1.4)	1 (0.5)
PPES	139 (42)	27 (8.2)	209 (28)	42 (5.7)	107 (50)	27 (13)
Proteinuria	41 (12)	8 (2.4)	18 (2.4)	2 (0.3)	4 (1.9)	2 (0.9)
RPLS	0	0	0	0	1 (0.5)	1 (0.5)
QTc prolongation	1 (0.3)	0	11 (1.5)	3 (0.4)	5 (2.3)[c]	1 (0.5)
Diarrhoea	245 (74)	38 (11)	381 (51)	55 (7.4)	135 (65)	34 (16)

AEOI, adverse event of interest; ATE, arterial thrombotic events; CRPC, castration-resistant prostate cancer; ETM, event to monitor; GI, gastrointestinal; MTC, medullary thyroid cancer; NA, not applicable; ONJ, osteonecrosis of jaw; PPES, palmar-plantar erythrodysaesthesia syndrome; RCC, renal cell carcinoma; RPLS, reversible posterior leukoencephalopathy syndrome; US PI, United States prescribing information; VTE, venous (and mixed/unspecified) thrombotic events.

[a] The data presented are taken from the ETMs for Studies XL184-308, XL184-307, and XL184-306 and the AEOIs for Study XL184-301.

[b] In Study XL184-301, GI fistulas and non-GI fistulas were considered separately, and the majority of fistulas were non-GI (incidences: non-GI 3.7%, GI 0.9%).

[c] In Study XL184-301, a mean increase in QTc correction by the Fridericia's formula (QTcF) of 10-15 ms relative

Comment: Adverse events associated with VEGF TKI use were seen consistently across studies. There is adequate information with regard to these adverse events in the prescribing information.

8.5. Other safety issues

8.5.1. Safety in special populations

The following factors were considered by the sponsor:

- Gender
- Age at screening (< 65 years, ≥ 65 years, ≥ 75 years) and (< 65 years, 65-74 years, 75-84 years, and ≥ 85 years).
- Race (White, Black/African-American, Asian, other)
- Weight at baseline (< 60 kg, ≥ 60 to ≤ 80 kg, > 80 kg)
- ECOG performance status at baseline (0, ≥ 1)

For the groups: gender, race, weight and ECOG performance status there were no significant differences between the groups for AEs or ETMs.

When grouped by age the incidence of anaemia in cabozantinib-treated subjects from 75 to 84 years old (35%) was higher than that reported in the younger age groups (< 65 years, 12%; 65 to 74 years, 22%). There was also a somewhat higher incidence of anaemia in the everolimus arm for the 65 to 74-year-old (45%) and 75 to 84-year-old (44%) age groups compared with the < 65-year-old group (35%). Conversely, the incidence of PPES among cabozantinib-treated subjects from 75 to 84 years old (23%) was lower than that reported for younger subjects (< 65 years, 45%; 65 to 74 years, 42%). Both observations may be confounded by the relatively low total number of subjects in the 75 to 84-year-old age group. No other significant differences were observed.

8.5.1.1. Hepatic impairment

Study XL184-003 was a comparative PK study in subjects with mild or moderate hepatic impairment and healthy subjects. The number of subjects in the safety population was 16, while no differences was observed between subjects that had normal hepatic function versus those with impaired function, the duration of exposure and number of subjects is too small to draw any conclusions. Plasma exposure to cabozantinib was greater in subjects with mild to moderate hepatic impairment and dose modification has been recommended in such patients.

8.5.1.2. Renal impairment

Study XL184-017 was a comparative PK study in subjects with mild or moderate renal impairment and healthy subjects. The total number of subjects in the safety population was 32 while no differences was observed between subjects that had normal renal function versus those with impaired function, the duration of exposure and number of subjects is too small to draw any conclusions. There was no difference in terms of plasma exposure to cabozantinib.

8.5.1.3. Extrinsic factors

The sponsor analysed AEs reported in study XL184-308 by, number of prior anti-cancer therapies received and by Global region, no differences were seen in the rate or nature of adverse events.

8.5.2. Safety related to drug-drug interactions and other interactions

Non-clinical data has demonstrated that cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (for example, warfarin, diazepam, furosemide, dicloxacillin, and propranolol) have the potential to cause a displacement interaction that could increase free concentrations of cabozantinib and/or the co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib.

8.5.2.1. Clinical pharmacology

Drug-drug interaction studies are discussed earlier in this report and are summarised in Table 67**.**

Table 67: Summary of Dug-Drug Interaction Studies

Study Identifier	Population	Conclusions
XL184-006	Healthy subjects (N=56)	Strong CYP3A4 inducer rifampicin decreased single dose plasma exposures 76-77%, a finding consistent with cabozantinib metabolism via the CYP3A4 pathway.

Study Identifier	Population	Conclusions
XL184-007	Healthy subjects (N=28)	Strong CYP3A4 inhibitor ketoconazole increased cabozantinib plasma exposures 34-38%, a finding consistent with cabozantinib metabolism via the CYP3A4 pathway
XL184-008	Subjects with RCC or DTC (N=40)	Daily cabozantinib administration did not affect plasma exposure of rosiglitazone, a CYP2C8 substrate. CYP2C8 is the isozymes most potently inhibited by cabozantinib *in vitro*
XL184-018	Healthy subjects (N=22)	The 90% CIs for the ln-transformed ratio of the test to reference treatment for both AUC0-t and AUC0-∞ were within the limits of 80% - 125%, although the upper 90% CI for Cmax was determined to be 125.1%. Esomeprazole administration did not result in any statistically significant decrease in cabozantinib plasma PK parameters.

8.6. Post marketing experience

The sponsor has submitted the following post-marketing experience data taken form the Summary of Clinical Safety:

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 centralised 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, and 24 from other countries.

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 have been reported in the post-marketing setting though 22 May 2015. No new safety findings bearing on the known overall safety profile of cabozantinib were identified.

Through 22 May 2015, 75 post-marketing serious adverse reactions 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 serious adverse reaction 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 study investigator. Additional follow-up is ongoing.

Comment: Very limited post-marketing data have been provided and should be supplemented by the most recent available data.

8.7. Evaluator's overall conclusions on clinical safety

Overall the safety profile for cabozantinib was consistent across the clinical studies submitted by the sponsor.

All subjects who received cabozantinib experienced at least one AE. The most frequent AEs of any severity were diarrhoea, PPES, nausea, fatigue, decreased appetite.

Dose reductions and interruptions were frequent and are necessary to ameliorate AEs. Most AEs requiring dose modification or interruption occurred early on commencing cabozantinib treatment (median time to first reduction 55-days and first dose interruption 38-days) and patients will require close supervision during the first 8 weeks of treatment this is covered in the PI under precautions but for clarity is probably best placed under dosage and administration.

The incidence of TAEs in the cabozantinib was 97% in patients who received cabozantinib in the pivotal study versus 91% for those who had received everolimus.

The safety analysis did not include an analysis of subjects with renal or hepatic impairment; however PK studies in subjects with these conditions were included. The prescribing information adequately covers these patient groups.

Data from the pivotal study (in mRCC) and the two supporting studies (in previously treated metastatic CRPC with bone-dominant disease who had experienced disease progression while on docetaxel-containing chemotherapy and either abiraterone or enzalutamide) indicate that cabozantinib is associated with an increase in hepatic transaminases. In the mCRPC studies, there were four cases which met Hy's Law criteria, but have been attributed to disease progression due to confounding factors (hepatic metastasis). In three of these cases there was a clear temporal association between discontinuation of cabozantinib and improvement in hepatic function. Other TKIs are associated with hepatic dysfunction. Monitoring of hepatic function should be included in the prescribing information particularly in patients with known intra-hepatic metastasis.

The majority of deaths were due to disease progression and this could be anticipated given the nature of the clinical study populations, there was no clear indication that deaths were related to a single AE (such as cardiac arrhythmia).

The overall safety profile of cabozantinib is consistent with that of VEGFR-TKIs.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 68: Discussion of first round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
A statistically significant difference between the treatment arms favouring cabozantinib was seen for the primary endpoint PFS. The HR adjusted for stratification factors was 0.59 (p<0.001). The Kaplan-Meier estimates for median duration of PFS were 7.4-months in the cabozantinib arm versus 3.8-months in the everolimus arm, a difference of 3.6-months favouring cabozantinib this is considered clinically significant. At the data cut-off for the first interim analysis of OS, May 2015, a trend for improved overall survival for cabozantinib treated subjects was observed, 0.68 (95% CI: 0.51, 0.90; stratified log rank p-value = 0.006). The magnitude of this response was approximately an additional five months of survival which can be considered clinically meaningful. A second, unplanned, interim analysis was undertaken to provide OS data for at least 12-months that demonstrated a similar 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 result is consistent with that seen for the first planned analysis of OS. A single pivotal study is submitted in this application, the degree of statistical significance for the results of the primary endpoint, PFS (p<0.001) is in line with that which would expected for an application that includes a single pivotal study (that is, stronger than p<0.05). The number of subjects who received non-protocol anticancer therapy was higher in those who had received everolimus as part of the study compared to those who had received cabozantinib. The secondary endpoint ORR was supportive of	The proposed starting dose of 60 mg is poorly tolerated and by the end of the pivotal study approximately equal proportion of subjects were receiving 60 mg and 40 mg. There is uncertainty with regard the lowest effective dose. Screening for cerebral or bony metastasis that were not present only occurred at study entry. Subsequent imaging for metastasis only occurred based on the investigator's assessment of clinical symptoms. As this was an open label study there is a potential for bias comment on the steps taken (if any) to eliminate bias with regard to the need for imaging/bone scans (as appropriate) for these subjects should be provided. The second analysis undertaken to provide OS data for at least 12-months was unplanned the relevance needs to be considered uncertain. Mature OS data is pending and the final analysis should be provided as soon as practical.

Indication	
Benefits	**Strengths and Uncertainties**
the results seen for PFS and OS. A statistically significant benefit was seen. The ORR was 17% for subjects who received cabozantinib and 3% for subjects who received everolimus. A reduction in tumour size from baseline was greater for subjects that had received cabozantinib compared to those who had received everolimus, 75% v 48% respectively.	

9.2. First round assessment of risks

Table 69: Discussion of first round assessment of risks

Risks	Strengths and Uncertainties
All subjects that received cabozantinib experienced at least one AE. AEs were experienced by 97% of subjects that received cabozantinib versus 91% of those that received everolimus. Serious AEs reported for ≥1.5% of subjects in the cabozantinib arm by decreasing frequency were, abdominal pain, pleural effusion, diarrhoea, nausea, anaemia, back pain, dyspnoea, fatigue, pneumonia, pulmonary embolism, vomiting, and pain. 68 % of subjects experience Grade 3 or 4 AEs. Serious (Grade ≥3) AEs associated with cabozantinib included: · Haemorrhage (2.1% versus 1.6 % with everolimus) · Gastrointestinal perforation and/or fistula (1.2% versus 0% everolimus · Hypertension (15% versus 7.1%everolimus · Diarrhoea (11% versus 2% everolimus) · Palmer-plantar erythrodysesthesia syndrome (42% versus 6% everolimus) A low rate of significant increase in liver transaminases was seen for subjects that received cabozantinib that improved when cabozantinib was stopped particularly in subjects with hepatic metastasis. QT prolongation was consistently observed across studies for subjects that received	The safety profile of subjects with hepatic or renal impairment or those with pre-existing cardiovascular disease has not been analysed. Reversible posterior leukoencephalopathy syndrome has also been reported with cabozantinib but the significance of this is unestablished.

Risks	Strengths and Uncertainties
cabozantinib. The risk of VTE was higher in subjects that received cabozantinib compared to those that received everolimus.	

9.3. First round assessment of benefit-risk balance

Advanced RCC is an incurable and all patients will experience disease progression median overall survival is around 12 months for patients with Stage 4 disease.

The primary goal of treatment is to prevent disease progression and extend overall survival.

The results of the pivotal study (XL184-308) demonstrate a statistically and clinically significant improvement in terms of PFS versus everolimus in subjects that had previously been treated with VEGF targeted therapy and not for the proposed indication, treatment of advanced RCC.

A trend to an improvement in OS was also seen for in a planned interim analysis for subjects treated with cabozantinib versus everolimus however mature data are pending.

In terms of AEs these were frequently observed but were generally managed with dose modification or interruption.

The safety profile appears to be consistent with that seen for other VEGFR-TKIs.

Cabozantinib has demonstrated benefit over an established treatment that is on the ARTG for the treatment of advanced RCC.

Overall the benefit-risk balance of cabozantinib for the treatment of advanced RCC is for the proposed indication is unfavourable but would become favourable if the changes recommend in below are adopted.

10. First round recommendation regarding authorisation

Approval of cabometyx is recommended subject to a modification of the indication as per below:

> *The treatment of advanced renal cell carcinoma in adults following prior treatment with vascular endothelial growth factor targeted therapy.*

The sponsor should also commit to supply mature overall survival data to the TGA as soon as is practical and indicate a time frame for doing so. The sponsor should comment on the impact of additional spending of alpha, due to the unplanned analysis of OS, on the final results.

Other changes to the PI should be undertaken as recommended.

11. Clinical questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

Please provide the data for the analysis of biomarkers from Study XL184-308 or provide information on the availability (or otherwise) of these data.

11.3. Efficacy

Please clarify the exposure response relationship to justify the proposed starting dose of 60 mg. These data are missing from the submitted dossier.

With Regard to Study XL184-308:

An evaluation for the presence of cerebral or bony metastasis was only undertaken at the screening visit; there do not appear to be protocol defined criteria for undertaking brain imaging or bone scans at any other point other than at screening and it was left to the investigator's discretion to conduct further imaging to determine if such metastasis had developed in a study in which treatment was unblinded leading to the possibility of bias.

Please provide an analysis of the number of subjects in each treatment that developed cerebral or bony metastasis that were not present at the time of screening and comment on the steps taken, if any, to eliminate bias with regard to the investigator's judgement ion the timing of the event.

Please commit to supply mature overall survival data to the TGA as soon as is practical and indicate a time frame for doing so. Please also comment on the impact of additional spending of alpha, due to the unplanned analysis of OS, on the final results.

11.4. Safety

Please provide up to date post-marketing data for cabozantinib form the EU or US particularly indicating any changes to the prescribing information for Cabometyx since approval in either/both jurisdictions.

11.4.1. PI and CMI

The indication should be amended to: *the treatment of advanced renal cell carcinoma in adults following prior treatment with vascular endothelial growth factor targeted therapy.*

12. Second round evaluation

The second round clinical evaluation will consist of review of the following relevant documents provided by the sponsor in their response:

- Response to Questions
- Brief review for updated results and safety findings of 'Addendum 2'/updated clinical study report (CSR) for Study XL184-308 with reference to appendices if relevant.
- Brief review for new safety issues of global periodic safety update report (PSUR) for the period to 28 November 2016.

12.1. Response to questions

12.1.1. Question 1 pharmacodynamics

Please provide the data for the analysis of biomarkers from Study XL184-308 or provide information on the availability (or otherwise) of these data.

12.1.1.1. Sponsor's response

High MET expression in patients with advanced RCC has been associated with a poor prognosis. Therefore, MET expression by immunohistochemistry (IHC) was first investigated as a potentially predictive biomarker for cabozantinib in Study XL184-308: subjects were evaluated for baseline tumour MET status (high, low, or unknown) based on IHC analysis (Spigel et al. 2013; Santoro et al. 2013). Across both the cabozantinib and everolimus treatment arms, high and low MET IHC status was observed in approximately 15% and 45% of subjects, respectively. The MET status was unknown in approximately 40% of subjects. Subgroup analyses of the primary endpoint of PFS (data cut-off 22 May 2015) in the PITT population and the secondary endpoint of OS (unplanned interim analysis data cut-off 31 December 2015) in the ITT population demonstrated benefits for treatment with cabozantinib over everolimus for subjects irrespective of baseline MET status. Other biomarkers in the tumour samples leftover after the MET IHC analysis will be investigated, such as AXL. The data will likely be available by 2018. However, a limitation of this analysis is that archival tumour tissue was used in most cases rather than a fresh biopsy obtained before study treatment initiation, which may result in marker expression values that are not contemporaneous with the disease state during study treatment. In addition, due to missing or insufficient tumour tissue, approximately one-third of the randomised subjects will have an unknown biomarker status primarily. The limitations of the analysis as described above may lead to inconclusive results.

References

Spigel DR, Ervin TJ, Ramlau RA, Daniel DB, Goldschmidt JH Jr, Blumenschein GR Jr, et al. Randomised Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer. J Clin Oncol 2013; 31

Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013;14:55-63

12.1.1.2. Evaluator comment:

The sponsor's response is accepted.

12.1.2. Clinical question 2 efficacy

Please clarify the exposure response relationship to justify the proposed starting dose of 60 mg. These data are missing from the submitted dossier.

12.1.2.1. Sponsor's response

Results from the exposure-response (E-R) analysis of cabozantinib in patients with RCC (Study Report XL184-308.ER.001) showed the following relationships for individual efficacy endpoints:

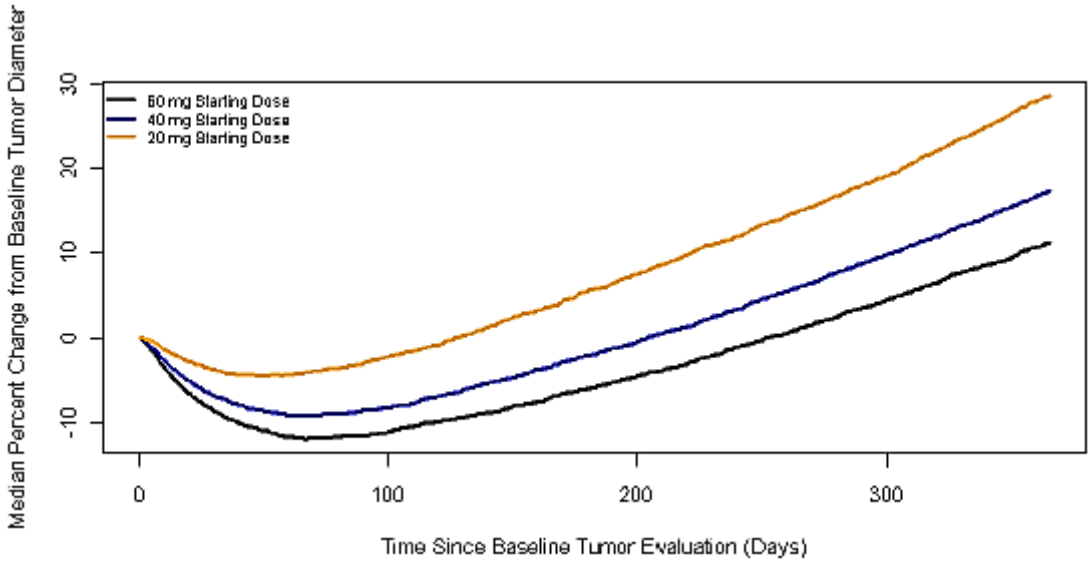
- Modelled Kaplan-Meier efficacy curves showed reduced predicted rates of progressive disease or death at simulated steady-state cabozantinib plasma concentrations for 20 mg (375 ng/mL), 40 mg (750 ng/mL) and 60 mg (1125 ng/mL); the 60-mg dose providing the best response, although the 95% confidence intervals (CIs) overlapped for all three dose levels. The efficacy (increased PFS) evident at simulated 20, 40 and 60 mg cabozantinib dose levels best fit (most statistically significant) a non-linear model that yielded an EC_{50} value (100 ng/mL) that was lower than the simulated steady-state concentration at the 20 mg dose.
- Modelled Kaplan-Meier safety endpoint curves showed higher predicted rates of dose-modification correlating with decreasing simulated cabozantinib clearance. Higher predicted risk of individual AEs (fatigue/asthenia, PPE, diarrhea, hypertension) correlated with increasing steady-state cabozantinib plasma concentrations for the simulated 20 mg (375 ng/mL), 40 mg (750 ng/mL) and 60 mg (1125 ng/mL) dose levels.

This E-R analysis suggests that the benefit-risk ratio of cabozantinib might be improved if a lower dose would be equally efficacious as the proposed starting dose, while being better tolerated.

To further evaluate the E-R relationship for cabozantinib, additional E-R analyses were conducted to characterise whether a 60 mg starting dose may provide greater efficacy than starting doses of 40 mg or 20 mg. Copies of the follow-up E-R reports are provided with this submission (Study Report XL184-308.ER.003). These additional E-R analyses are summarised below:

A population E-R model was developed to characterise the relationship between cabozantinib exposure and longitudinal measurements of the sum of tumour diameter in subjects with RCC in Study XL184-308. Simulations were performed to compare dose reduction levels and longitudinal tumour size changes in subjects with RCC receiving an initial dose of 20 mg, 40 mg or 60 mg daily. The tumour size model was used to simulate the time course of tumour diameter for each of the 1000 subjects in the 20 mg, 40 mg, and 60 mg starting dose treatment groups. Figure 9 shows the median percent change from baseline tumour diameter for the 20 mg, 40 mg, and 60 mg starting dose treatment groups.

Figure 9: Comparison of predicted median percent change from baseline tumour diameter for 20 mg, 40 mg and 60 mg cabozantinib starting doses



This figure illustrates the E-R relationship noted for cabozantinib. Subjects in the 20 mg once daily starting dose treatment group are predicted to have a smaller maximum reduction in tumour (median percent change from baseline = -4.45% for the 20 mg starting dose treatment group) size relative to the 40 mg and 60 mg starting dose treatment groups. In addition, the figure shows that subjects in the 40 mg starting dose group have a modestly lower median percent reduction from baseline (-9.1% for 40 mg compared with -11.9% for 60 mg) in tumour diameter relative to those in the 60 mg starting dose group.

In addition, the estimated EC_{50}, EC_{80} and EC_{90} values for the tumour regression listed in the table below suggest the 60 mg once daily cabozantinib dose will yield estimated plasma concentrations (1125 ng/mL) near the plateau of the dose-response curve.

Table 70: Estimated EC_{50}, EC_{80} and EC_{90} values for the tumour regression (sum of lesion diameters) at a cabozantinib dose of 60 mg

EC_{50} (90% CI ng/mL	EC_{80} (90% CI) ng/mL	EC_{90} (90% CI) ng/mL
251 (169, 375)	1004 (676, 1500)	2259 (1521, 3375)

To further assess the clinical relevance of the differences noted in Figure 9, the Best Overall Response (BOR) metric was computed based on the simulated tumour size data for the 20 mg, 40 mg, and 60 mg starting dose groups the response to treatment. Complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) were computed at baseline and every 8 weeks for 1 year using the longitudinal sum of tumour diameter predictions. The response value was computed in accordance with the response criteria specified for Study XL184-308. From the longitudinal response data, the BOR was computed for each subject. The predicted percentage of subjects with CR, PR, SD, or PD for a 20 mg, 40 mg, and 60 mg starting dose treatment regimen are provided in Table 71. A higher percentage of subjects achieve an Overall Response (CR plus PR) and a lower percentage of subjects have PD in the 60 mg starting dose treatment group relative to the 20 mg and 40 mg starting dose treatment groups.

Table 71: Percentage of simulated subjects (N=1000) achieving each best overall response category

Best Overall Response (BOR)	20 mg Starting Dose (%)	40 mg Starting Dose (%)	60 mg Starting Dose (%)
Complete Response (CR)	0.10	0.00	0.00
Partial Response (PR)	8.60	15.6	19.10
Stable Disease (SD)	81.1	76.3	73.40
Progressive Disease (PD)	10.2	8.10	7.50

Population E-R models were developed to characterise the relationship between cabozantinib exposure and all dose modifications in subjects with RCC. Table 72 shows the percentage of subjects that were on 20 mg, 40 mg, and 60 mg (excluding dose interruptions) at 6 months and 12 months for the observed dataset, the simulated 20 mg starting dose dataset, the simulated 40 mg starting dose dataset, the simulated 40 mg starting dose dataset permitting escalation to 60 mg based on observed probabilities, and the simulated 60 mg starting dose dataset. Based on this analysis, the simulated 40 mg starting dose was not predicted to dramatically reduce the requirement for dose reductions. At 6 months, 24% of subjects in the simulated 40 mg starting dose group required a dose reduction versus 52% (45%) in the 60 mg observed (simulated) starting dose groups. Moreover, at 6-months a greater proportion of subjects in the simulated 40 mg starting dose group were being treated at the reduced 20 mg dose level (24%) than in the 60 mg starting dose group (16% actual, 10% simulated). Notably, at this time-point approximately 50% of subjects in the 60 mg starting dose group (observed or simulated) were still on the 60 mg dose.

Table 72: Percentage of simulated subjects on 20 mg, 40 mg or 60 mg once daily treatment regimens at Month 6 and Month 12

Time Point	Dose (mg)	Observed (%)	Simulated 20 mg Starting Dose (%)	Simulated 40 mg Starting Dose (%)	Simulated 60 mg Starting Dose (%)
6 Months	20	15.81	100	24.10	9.80
6 Months	40	35.87	NA	75.90	35.10
6 Months	60	48.02	NA	NA	55.10
12 Months	20	17.02	100	36.70	20.8
12 Months	40	39.82	NA	63.3	43.3
12 Months	60	42.86	NA	NA	35.90

In summary, in subjects with RCC in Study XL184-308, the 60 mg cabozantinib dose demonstrated clinical efficacy (PFS, OS, ORR), and showed greater antitumour effects than a 40 mg or 20 mg dose based on an exposure-response analysis. As expected, higher predicted risk of individual AEs was simulated for the 60 mg dose versus 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 support the current starting dose of 60 mg.

The above evaluation by the sponsor is consistent with the PopPK evaluation report conducted by the TGA which considers the exposure -response analyses for longitudinal sum of tumour diameter and repeated time to event dose modifications of cabozantinib in patients with RCC. The TGA evaluation states that the important inferences from the exposure-response analyses would be:

1. A starting dose of 60 mg daily of cabozantinib is expected to result in a greater reduction in baseline tumour size than 40 mg daily (-11.9% versus -9.1%, respectively).
2. The inhibitory effect of cabozantinib therapy on tumour growth was predicted to attenuate over time, with a half-life of about 25 days. This suggests that cabozantinib therapy has its primary benefit in terms of reducing tumour size within the first 4-5-months of therapy, after which disease progression will become the primary determinate of tumour size.
3. Subjects starting on 60 mg daily are predicted to require more dose reductions than those starting on a 40 mg daily dose, presumably because of an increased likelihood of adverse effects with the 60 mg daily. Note however, that a 40 mg daily starting dose would come at the cost of reduced efficiency in terms of tumour growth inhibition.

12.1.2.2. Evaluator comment:

It is presumed the abbreviation PPE (not defined in the document) is used to represent palmar-plantar erythrodysesthesia. The sponsor's response is accepted.

12.1.3. Clinical question 3 efficacy

With Regard to Study XL184-308:

An evaluation for the presence of cerebral or bony metastasis was only undertaken at the screening visit; there do not appear to be protocol defined criteria for undertaking brain imaging or bone scans at any other point other than at screening and it was left to the investigator's discretion to conduct further imaging to determine if such metastasis had developed in a study in which treatment was unblinded leading to the possibility of bias: Please provide an analysis of the number of subjects in each treatment that developed cerebral or bony metastasis that were not present at the time of screening and comment on the steps taken, if any, to eliminate bias with regard to the investigator's judgement in the timing of the event.

12.1.3.1. Sponsor's response

Cerebral metastases

In the METEOR study (Study XL184-308), subjects with known brain metastases or cranial epidural disease were not allowed to participate unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3-months before randomization. Given these restrictions, at baseline only 3 patients had brain metastases (2 in the cabozantinib group and one in the everolimus arm).

In oncology trials, the occurrence of brain metastases during follow-up, in patients without brain metastases at baseline is usually detected following the onset of neurologic symptoms; brain scans are not normally included in routine follow-up testing in patients without neurologic symptoms. It is not justified to perform a systematic imaging procedure every 8 weeks in all patients included in the METEOR study while this is justified in patients with known cerebral metastases to measure the size of the metastasis under treatment.

Over the >36-months of the trial duration, among patients with no cerebral metastases at baseline there were 7 (1.1%) subjects who developed symptomatic cerebral metastases. These events were recorded as treatment emergent adverse events. A total of 5 (1.6%) patients in the everolimus arm and 2 (0.6%) patients in the cabozantinib arm reported neurology symptoms leading to a brain CT or MRI and a diagnosis of cerebral metastasis at the last cut-off date 2 Oct 2016. All patients reported the AEs the same day or after they had been classified as 'documented progression' by the independent IRC or were censored because of anticancer therapy. It is unlikely that an investigator would have delayed an imaging procedure if necessary when a patient develops neurological symptoms.

Given that there are more subjects who developed brain metastases in the everolimus arm in comparison with the cabozantinib arm, even if these events had been detected earlier by an imaging procedure in the absence of clinical symptoms, it would not have favoured cabozantinib.

A listing of patients with AEs of brain metastases in the population of patients without brain metastases at baseline is shown below.

Table 73: Patients with AEs of brain metastases in the population of patients without brain metastases at baseline

Sex	Age	Bone metastasis at baseline	Actual Treatment	TEAE	Lowest Level Term
M	70	N	Everolimus	Y	Bone metastases
M	74	N	Cabozantinib	Y	Bone metastases
M	66	N	Everolimus	Y	Bone metastases
M	62	N	Cabozantinib	Y	Bone metastases
F	62	N	Everolimus	Y	Spinal metastases
F	70	N	Cabozantinib	Y	Bone metastases
M	53	N	Cabozantinib	Y	Metastases to spine

Bone metastases

Technetium bone scans (TBS) were performed in all subjects at screening. Bone metastases were present in 23% of patients in the cabozantinib arm and in 20% of patients in the everolimus arm. After randomisation, bone scans were performed only in subjects with known bone metastases 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). Lesions identified on bone scans were not recorded as target, non-target or new lesions. Bone scans were used to direct corroborative imaging with CT/MRI if necessary (these CT/MRI findings were used for RECIST 1.1 evaluation). Bone scan findings alone were not used for the determination of progression per RECIST 1.1.

In oncology trials, the occurrence of bone metastases during follow-up, in patients without bone metastases at baseline, is usually detected following the onset of clinical symptoms (e.g. bone pain or fracture). TBS are not normally included in routine follow-up testing in patients without new symptoms. It is not justified to perform a systematic imaging procedure every 16 weeks in all patients included in the METEOR study while this is justified in patients with known bone metastases to measure the size of the metastasis under treatment.

Over the >36-months of study duration, 15 (2.3%) patients developed bone metastases which were reported as treatment emergent adverse events: 8(2.4%) in the cabozantinib arm and 7 (2.2%) in the everolimus arm. Among these patients, only 4 in the cabozantinib arm and 3 in the everolimus arm had no bone metastasis at study entry and therefore had no repeated bone scan per protocol after randomization. It is unlikely that any investigator would have delayed the imaging procedure in any patient with symptoms suggestive of bone metastasis.

Given that there is similar number of patients in both arms who developed bone metastases, even if these events had been reported earlier, this would not have influenced the primary endpoint.

In conclusion, a small number of patients have reported new bone or cerebral metastases after the onset of clinical symptoms that have triggered imaging procedures. Given that these events are well balanced between treatment groups, it is unlikely that an earlier detection of these events would have influenced the primary endpoint. A listing of patients with bone metastases in the population of patients without bone metastases at baseline is shown below.

Table 74: Patients with AEs of bone metastases in the population of patients without bone metastases at baseline

Sex	Age	Bone metastasis at baseline	Actual Treatment	TEAE	Lowest Level Term
M	70	N	Everolimus	Y	Bone metastases
M	74	N	Cabozantinib	Y	Bone metastases
M	66	N	Everolimus	Y	Bone metastases
M	62	N	Cabozantinib	Y	Bone metastases
F	62	N	Everolimus	Y	Spinal metastases
F	70	N	Cabozantinib	Y	Bone metastases
M	53	N	Cabozantinib	Y	Metastases to spine

12.1.3.2. Evaluator comment

The sponsor's response is accepted.

12.1.4. Clinical question 4 efficacy

Please commit to supply mature overall survival data to the TGA as soon as is practical and indicate a time frame for doing so. Please also comment on the impact of additional spending of alpha, due to the unplanned analysis of OS, on the final results.

12.1.4.1. Sponsor's response

The results of the unplanned second interim analysis of overall survival (OS) in the intent-to-treat population with a data cut-off date of 31 December 2015 was provided in the initial submission to the TGA (XL184-308 CSR Addendum). As with the first interim analysis, the Lan-DeMets O'Brien-Fleming alpha spending function specified in the statistical analysis plan was applied to control Type 1 error in this analysis. The critical value for rejecting the null hypothesis was $p < 0.0163$. The analysis demonstrated a statistically significant difference in duration of OS for subjects in the cabozantinib arm compared with the everolimus arm: the HR adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified logrank p-value = 0.0003). Therefore, the null hypothesis was rejected and this analysis was done under rigorous type 1 error control with well-established methods that are specifically designed to accommodate unplanned analyses. As such, this is the final statistically-valid analysis of this endpoint.

The third and final OS analysis has been performed, with a cut-off date of 02 October 2016. Given that the null hypothesis was rejected in the previous unplanned second interim analysis and no type 1 error control method was applied to this analysis, the analysis is considered supplemental, with results purely descriptive.

A copy of the final CSR, which includes updated descriptive OS results, OS by subgroups of demographics and baseline characteristics and updates on subject disposition, NPACT and safety is provided in this response package. This OS analysis confirmed the statistically significant improvement in OS for patients randomised to the cabozantinib arm compared with the everolimus arm, which was observed during the second interim analysis.

12.1.4.2. Evaluator comment

The sponsor's response is accepted.

12.1.5. Clinical question 5 safety

Please provide up to date post-marketing data for cabozantinib form the EU or US particularly indicating any changes to the prescribing information for Cabometyx since approval in either/both jurisdictions.

12.1.5.1. Sponsor's response

The most recent EU PSUR with a DLP of 28th Nov 2016 is provided in Module 5.3.6 as requested for cabometyx. Please note that this PSUR also includes the Cometriq capsules marketed in Europe but not proposed for registration in Australia.

12.1.5.2. Evaluator comment

The sponsor's response is accepted.

12.1.6. Clinical question 6 PI/CMI

The indication should be amended to: the treatment of advanced renal cell carcinoma in adults following prior treatment with vascular endothelial growth factor targeted therapy.

12.1.6.1. Sponsor's response

Indication has been amended as recommended.

12.1.6.2. Evaluator comment

The sponsor's response is accepted.

12.2. Clinical study report (CSR) Addendum 2 for Study XL184-308

Per the sponsor's response to Clinical question 4, the follow-up analysis of OS has been provided in the form of the second addendum clinical study report (CSR) for study XL184-308.

PFS was the primary endpoint in Study XL184-308. Results for PFS and ORR and two interim OS analyses (the first pre-planned, the second unplanned) have been reported in previous CSR and addendum. The unplanned second interim analysis for OS resulted in rejection of the null hypothesis and was considered the final analysis. However, a follow-up analysis of OS has been performed after 100% of the predetermined events per protocol were reached. The results of that OS analysis, as well as safety data through to the data cut-off date of 2 October 2016, are reported in 'Addendum 2'.

Efficacy: the follow-up OS result confirms the previous OS results but as described by the sponsor is considered purely descriptive as the final statistically valid finding was that of the second (unplanned) analysis.

The results are reported by the sponsor as follows in their table:

Table 75: Follow-up analysis of overall survival through the 2 October 2016 cut-off date (ITT population)

	Cabozantinib (N=330)	Everolimus (N=328)
Number (%) of Subjects		
Censored	132 (40)	96 (29)
Death	198 (60)	232 (71)
Duration of overall survival (months)		
Median (95% CI)	21.4 (18.6, 23.5)	17.1 (14.9, 18.9)
25th percentile, 75th percentile	11.5, NE	7.5, 29.5
Range	0.26, 37.8+	0.07+, 35.5+
p-value (stratified log-rank test)[a]	0.0002	
Hazard ratio (95% CI; stratified)[b]	0.70 (0.58, 0.85)	
p-value (unstratified log-rank test)	0.0006	
Hazard ratio (95% CI; unstratified)	0.72 (0.59, 0.87)	

+ indicates a censored observation; CI, confidence interval; ITT, intent-to-treat; IxRS, interactive record system; NE, not estimable; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a] Stratification factors (based on IxRS) 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.

The different results for OS at each of the three analyses is summarised in sponsor's table below:

Table 76: Overall survival at each information fraction

Study Report	Total Deaths/Required Deaths	Stratified Hazard Ratio[a]	Duration of Overall Survival, Median (Months)	
			Cabozantinib	Everolimus
CSR	202/408 (49%[b])	0.68	18.2	NE
CSR Addendum	320/408 (78%[c]), Final	0.67	21.4	16.5
CSR Addendum 2	430/408, Follow-up	0.70	21.4	17.1

CRF, case report form; IxRS, interactive record system; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
[a] Stratification factors (based on IxRS, unless otherwise noted) 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] Reported in the XL184-308 CSR. Stratification factors were based on CRF.
[c] Reported in the first XL184-308 CSR Addendum. Stratification factors were based on CRF.

Post-progression non-protocol therapies are summarised in sponsor's table:

Table 77: Systemic non-protocol anticancer therapies (ITT population)

	Cabozantinib N = 330 n (%)	Everolimus N = 328 n (%)
Number of subjects with at least one therapy	187 (57)	205 (63)
VEGFR-TKI Therapies	90 (27)	165 (50)
Axitinib	67 (20)	97 (30)
Cabozantinib[a]	2 (0.6)	14 (4.3)
Lenvatinib	1 (0.3)	0
Pazopanib	5 (1.5)	23 (7)
Sorafenib	13 (3.9)	33 (10)
Sunitinib	18 (5.5)	36 (11)
Other Selected Systemic Therapies		
Everolimus[b]	109 (33)	16 (4.9)
Temsirolimus	5 (1.5)	4 (1.2)
Bevacizumab	9 (2.7)	11 (3.4)
Interleukins (Interleukin 2)	0	4 (1.2)
Interferon-α/Peginterferon	7 (2.1)	8 (2.4)
PD-1/PD-L1 targeting agents[c]	45 (14)	51 (16)
Chemotherapy	11 (3.3)	14 (4.3)

ITT, Intent-to-treat; PD-1, programmed cell death immune receptor 1; PD-L1, programmed cell death immune receptor ligand 1; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor.
Note: subjects may have received more than one type of anticancer therapy.
[a] Cabozantinib (CABOMETYX® or COMETRIQ®) obtained commercially by the subject rather than as part of study treatment.
[b] Everolimus (AFINITOR®) obtained commercially by the subject rather than as part of study treatment.
[c] Antibodies targeting the PD-1 immune checkpoint inhibitor or its ligands (eg, PD-L1): in the cabozantinib arm 43 subjects received nivolumab, one received MK-3475/pembrolizumab, and two received atezolizumab; in the everolimus arm 48 subjects received nivolumab, two subjects received AMP-514, and one subject received atezolizumab. In the post-text table, nivolumab was listed as monoclonal antibodies and the other therapies were listed as investigational drugs.

Updated safety results are summarised by the sponsor as follows:

As of the data cut-off for the CSR (22 May 2015), 133 subjects (40%) remained on cabozantinib treatment compared to 67 subjects (21%) in the everolimus arm. As of the data cut-off for this

addendum (02 October 2016), 36 subjects (11%) remained on cabozantinib treatment compared to 8 subjects (2.5%) in the everolimus arm. Data for both arms is presented for reference, but in general, direct comparisons are not made due to the differences in exposure between arms.

Based on subject disposition, low rates of study treatment discontinuations due to AEs (excluding AEs of disease progression) were observed in both treatment arms (13% cabozantinib, 11% everolimus).

The median duration of exposure was 36 weeks for the cabozantinib arm and 19 weeks for the everolimus arm. The mean duration of exposure was 49 weeks in the cabozantinib arm compared with 30 weeks in the everolimus arm. The median daily dose (intensity) of cabozantinib was 43 mg (71%) and that of everolimus was 9.1 mg (90%).

The overall incidence of AEs was similar in both treatment arms. The incidence of Grade 3 or 4 AEs regardless of causality was higher in the cabozantinib arm (71% versus 61%) mainly due to a higher incidence of hypertension, diarrhea, and palmar-plantar erythrodysesthesia syndrome. However, the incidence of Grade 4 AEs (8.2%, 8.7%) and Grade 5 AEs (9.4%, 8.1%) was similar in each arm.

The incidence of SAEs was also similar for both treatment arms (49% cabozantinib, 48% everolimus).

The overall death rate was lower in the cabozantinib arm (199 subjects [60%]) than the everolimus arm (227 subjects [70%]). There were 21 deaths (6.3%) in the cabozantinib arm and 23 (7.1%) in the everolimus arm through 30 days after the last dose of study drug, and there were 178 deaths (54%) in the cabozantinib arm and 204 (63%) in the everolimus arm greater than 30 days after last dose of study drug. The majority of deaths were due to PD in both study arms. Causes of death other than PD were reported for 9 subjects (2.7%) in the cabozantinib arm and 12 subjects (3.7%) in the everolimus arm through 30 days after the last dose; the causes of death varied between treatment arms and multiple causes may have contributed to individual deaths including preexisting comorbidities and cancer-related complications.

A total of 21 subjects (6.3%) in the cabozantinib arm and 23 subjects (7.1%) in the everolimus arm experienced Grade 5 AEs through 30 days after the last dose of study treatment. Of these subjects, 6 subjects in the cabozantinib arm and 0 subjects in the everolimus arm experienced Grade 5 AEs after the CSR data cut-off date (22 May 2016).

Overall the observed AEs in both treatment arms were consistent with the known safety profiles for each agent in patients with advanced RCC and reflected class-specific mechanisms of action.

12.2.1.1. Evaluator comment

The updated report does not present significant changes to efficacy or safety findings.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The OS benefit seen in the unplanned second interim analysis of Study XL184-308 has been confirmed by the final follow-up (descriptive) OS analysis and is of a similar magnitude.

The benefit is otherwise unchanged by the second round evaluation.

13.2. Second round assessment of risks

No new safety risks have become apparent in the second round evaluation.

Modifications to the PI recommended by the first round evaluator have been made or acceptable justification given for changes that have not been made.

13.3. Second round assessment of benefit-risk balance

- Advanced RCC is incurable, all patients experience disease progression and median overall survival is around 12-months for patients with Stage 4 disease. The primary goal of treatment is to prevent disease progression and extend overall survival.
- The results of the pivotal study (XL184-308) demonstrate a statistically and clinically significant improvement in PFS and OS in subjects that had previously been treated with anti-VEGF therapy, by comparison to everolimus, a medicine registered in Australia for the treatment of patients with advanced RCC.
- The safety profile of cabozantinib appears similar to other anti-VEGF TKIs and manageable.

Overall the benefit-risk balance of cabozantinib for the treatment of advanced RCC in the proposed indication is favourable.

14. Second round recommendation regarding authorisation

Approval of cabometyx is recommended subject to negotiation of PI content with the Delegate, based on recommendations made by the second round evaluator.

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