20 September 2018
EMA/704052/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: CABOMETYX

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/004163/II/0005

Marketing authorisation holder (MAH): Ipsen Pharma

Note

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

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Table of contents

List of abbreviations

AE	adverse event
AFP	alpha fetoprotein
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
ATA	adequate tumour assessment
AUC(0-∞)	area under the plasma concentration-vs-time curve (from t=0 to t=∞)
BCLC	Barcelona Clinic Liver Cancer
BMI	body mass index
BOR	best overall response
BSAP	bone-specific alkaline phosphatase
BSC	best supportive care
CAP	chest, abdomen, pelvis
CI	confidence interval
CLIP	Cancer of the Liver Italian Program
CMH	Cochran Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
CTx	C-terminal cross-linked telopeptides of type I collagen
CV%	coefficient of variation
CYP	cytochrome P450
DILI	drug-induced liver injury
DVT	deep vein thrombosis
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eGFR	estimated glomerular filtration rate
ESC	Exelixis Safety Committee
FFPE	formalin-fixed paraffin embedded
FT4	free thyroxine
FXa	coagulation factor X
GERD	gastroesophageal reflux disease
GGT	γ -glutamyltransferase
HbA1c	Haemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HKLC	Hong Kong Liver Cancer
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
INR	international normalized ratio
IRC	Independent Radiology Committee
ITT	intent-to-treat
IxRS	interactive voice/web response system
LDH	lactate dehydrogenase
LT	liver test
LLN	lower limit of normal

LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important differences
mRECIST	modified Response Evaluation Criteria in Solid Tumours
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NPACT	non-protocol anticancer therapy
NTx	N-terminal cross-linked telopeptides of type I collagen
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PPES	palmar-plantar erythrodysaesthesia syndrome
PR	partial response
PT	preferred term
qd	once daily
QTc	corrected QT interval
QTcF	corrected QT interval calculated by the Fridericia formula
RDT	randomized discontinuation trial
RECIST	Response Evaluation Criteria in Solid Tumours
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SIRT	selective internal radiation therapy
SMT	Safety Management Team
SOC	system organ class
SoD	sum of target lesion diameters
TACE	transarterial chemoembolization
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TNM	tumour, node, and metastasis
TSH	thyroid-stimulating hormone
UE	unable to evaluate
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VAS	visual analogue scale
VEGFR	vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Ipsen Pharma submitted to the European Medicines Agency on 14 March 2018 an application for a variation.

The following variation was requested:

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

Extension of indication to include the treatment of advanced hepatocellular carcinoma in adults following prior systemic therapy for Cabometyx; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the risk management plan (version 4.0) are also updated accordingly.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date	14 March 2018
Start of procedure:	31 March 2018
CHMP Rapporteur Assessment Report	24 May 2018
CHMP Co-Rapporteur Assessment Report	25 May 2018
PRAC Rapporteur Assessment Report	31 May 2018
PRAC members comments	6 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	18 June 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2018
Request for supplementary information (RSI)	28 June 2018
CHMP Rapporteur Assessment Report	23 August 2018
PRAC Rapporteur Assessment Report	23 August 2018
PRAC members comments	28 August 2018
Updated PRAC Rapporteur Assessment Report	5 September 2018
PRAC Outcome	6 September 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteur Assessment Report	13 September 2018
Opinion	20 September 2018

2. Scientific discussion

2.1. Introduction

Problem statement

Disease or condition

The company applied for the following indication:

"CABOMETYX is indicated for the treatment of advanced hepatocellular carcinoma (HCC) in adults following prior systemic therapy".

Epidemiology

Liver cancer is the second most frequent cause of cancer deaths worldwide. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer (accounting for approximately 90% of cases).

The highest incidence is reported in regions where infection with hepatitis B virus (HBV) is endemic i.e. Southeast Asia and sub-Saharan Africa. However, liver cancer also represents a significant burden in developed countries. The estimated incidence and mortality in the European Union (EU) were 52,000 and 48,000 cases, respectively (Ferlay et al 2013). The incidence of HCC generally increases with advancing age: the average age at diagnosis is in the mid-60s, with a shift over the last decade to diagnosis at an earlier age (Cancer Research UK 2017). There is a strong male preponderance, with HCC occurring more than twice as often in men than in women. In contrast to the trends for most other cancers, liver cancer incidence and death rates have increased in recent years in Europe (Cancer Research UK 2017).

Risk factors for HCC include conditions that lead to cirrhosis or other liver dysfunction: HBV or hepatitis C virus (HCV) infection, alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) especially non-alcoholic steatohepatitis. As the incidence of obesity, diabetes and metabolic syndrome increase, NAFLD/NASH is becoming a major cause of HCC in developed countries. Some degree of cirrhosis is present in 80-90% of patients with HCC.

In HBV-infected patients, nucleotide therapy may mitigate the cirrhotic process and consequent development or recurrence of HCC. In HCV-infected patients, direct-acting antivirals can eradicate HCV infection, but do not tend to reduce the occurrence and recurrence of HCC in most patients.

Patients with HCC may experience no symptoms until their disease is advanced. Disease-related symptoms include anorexia and unexplained weight loss, nausea and vomiting, hepato- or splenomegaly, abdominal or shoulder pain, abnormal bruising or bleeding, jaundice and fever. If the patient is cirrhotic, ascites, hepatic encephalopathy and GI bleeding may occur. Laboratory abnormalities, other than elevated liver function tests (LFTs), include hypercalcemia, hypoglycaemia, elevated serum cholesterol, erythrocytosis and thrombocytopenia.

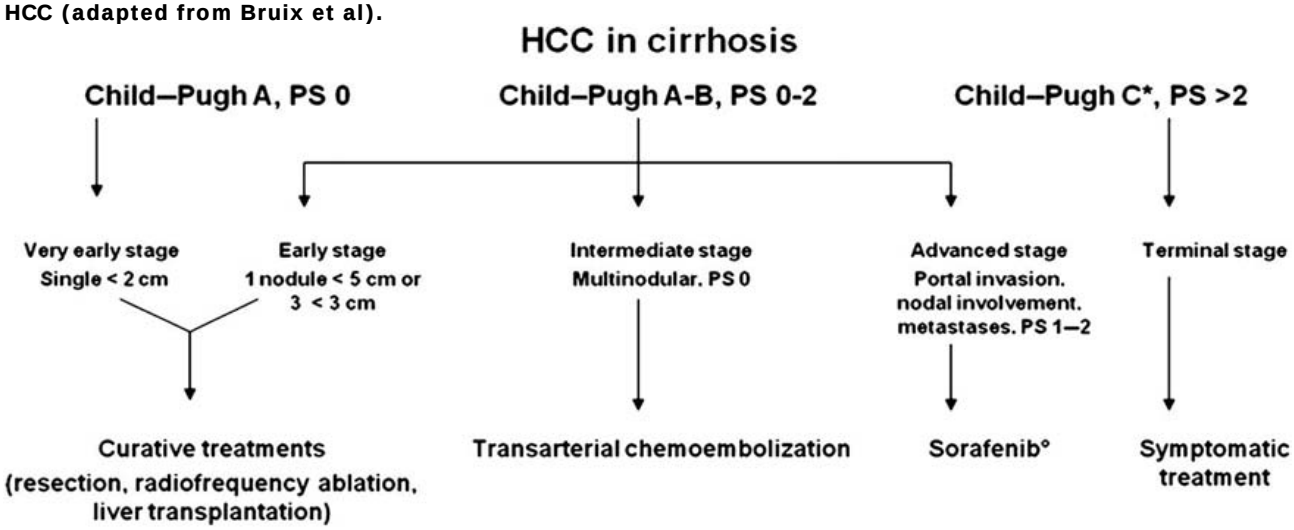
Management

Treatment options and prognosis are determined by extent of HCC disease as well as the severity of the underlying cirrhosis. The Child-Pugh classification has been used to assess hepatic reserve in cirrhotic patients by scoring five variables (serum albumin, total bilirubin, ascites, encephalopathy and prothrombin time). Patients with a score of 5 or 6 are classified as Child-Pugh class A and are considered to have well-compensated liver disease. Child-Pugh B or C patients have higher scores and a worse prognosis.

Various classification systems have been constructed to prescribe treatment and predict outcome in HCC. The Barcelona Clinic Liver Cancer (BCLC) is widely used and comprises four elements: tumour extension, liver functional reserve [Child-Pugh grade], physical status [ECOG PS] and cancer related symptoms.

Surgical resection, liver transplantation or percutaneous ablation are potentially curative in patients with early stage disease; however, these interventions are not an option for most patients because of tumour size or location. Patients who present with advanced disease or those with recurrence after locoregional therapy have a very poor prognosis. HCC is usually resistant to systemic cytotoxic chemotherapy and this is not recommended outside of a clinical trial. Palliative transarterial chemoembolization (TACE) is a widely-used option for patients with unresectable disease without extrahepatic involvement.

Table 1: ESMO Guidelines: Strategy for staging and treatment assignment in patients diagnosed with HCC (adapted from Bruix et al).



*Poor liver synthetic function due to tumour involvement of the liver. °Only Child–Pugh A.

Table 2: Impact of therapy on prognosis, according to BCLC stages

	Natural history (median survival)	Prognosis with therapy
Very early stage (stage 0)	>36 months	70%–90% 5-year survival (OLT, ablation, resection)
Early stage (stage A)	36 months	50%–70% 5-year survival (OLT, ablation, resection)
Intermediate stage (stage B)	16 months	20-month median survival (transarterial chemoembolization)
Advanced stage (stage C)	4–8 months	6–11-month median survival (sorafenib)
Terminal stage D (stage D)	<4 months	

OLT, orthoptic liver transplantation

Sorafenib, a small-molecule inhibitor of VEGFR and other protein kinases, was shown in a Phase 3 randomized placebo-controlled study (SHARP) to improve OS compared with best supportive care (BSC) in subjects with advanced HCC and relatively well-preserved liver function (Child-Pugh A) who had not received previous systemic treatment. Median OS was 10.7 months in the sorafenib and 7.9 months in the placebo arm (HR 0.69; 95% CI 0.55, 0.87; p-value < 0.001). The SHARP trial was conducted primarily in Europe and Australasia with HCV and alcohol being the most frequent HCC aetiologies (Sorafenib EPAR).

In a corresponding placebo-controlled Phase 3 trial conducted in an Asian-Pacific population HBV was the main cause of HCC: median OS was 6.5 months vs 4.2 months (HR 0.68; 95% CI 0.50, 0.93; p-value = 0.014).

Recently, lenvatinib was shown to be non-inferior to sorafenib in subjects who had not received prior systemic therapy (Lenvima EPAR).

Disease progression usually occurs following sorafenib or lenvatinib and more therapeutic options are needed. Several randomized placebo-controlled Phase 3 trials in subjects with advanced HCC who had received prior sorafenib treatment failed to demonstrate an overall survival advantage with other systemic therapies, including brivanib [Llovet et al 2013], everolimus [Zhu et al 2014], ramucirumab [Zhu et al 2015] and tivantinib [Arqule 2017].

Regorafenib demonstrated positive OS results in the Phase 3 placebo-controlled RESORCE trial in subjects who had progressed on prior sorafenib (Bruix et al [Lancet] 2017). Median OS for regorafenib compared to placebo was 10.6 vs 7.8 months; HR = 0.63 (95% CI 0.50, 0.79; p < 0.0001). The RESORCE trial excluded patients who did not tolerate sorafenib, defined as < 400 mg qd for ≥ 20 of the last 28 days before discontinuation (Regorafenib EPAR).

About the product

Cabozantinib (XL 184) inhibits multiple receptor tyrosine kinases known to influence tumour growth, metastasis and angiogenesis, including vascular endothelial growth factor receptors (VEGFRs), MET (hepatocyte growth factor [HGF] receptor protein) and AXL.

Cabozantinib (Cabometyx), a film-coated tablet formulation, has been authorised in the EU at a dose of 60mg QD for the treatment of advanced renal cell cancer (RCC) following prior VEGF targeted therapy since September 2016. In March 2018 the CHMP adopted an extension to the existing indication to include previously untreated patients with advanced RCC (EMEA/H/C/004163/II/0003).

The tablet and the capsule are not bioequivalent and should not be used interchangeably.

The MAH applied for the following indication:

CABOMETYX is indicated for the treatment of advanced hepatocellular carcinoma (HCC) in adults following prior systemic therapy

Further to the CHMP assessment the following indication is agreed:

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

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

This application is to expand the use of Cabometyx for advanced Hepatocellular Carcinoma (HCC). An ERA addendum has been prepared to refine the Fpen and PEC.

An assessment for PBT indicated that cabozantinib does not meet the criteria for bioaccumulation designation.

Using the refined Fpen, based on the incidence or prevalence of advanced renal cell carcinoma and advanced HCC, the $PEC_{SURFACEWATER}$ value is below the action limit of 0.01µg/L.

Table 3: **Environmental risk assessment**

Substance (INN / Invented Name): Cabozantinib (S)-malate			
CAS-number (if available): 1140909-48-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	Log Dow = 3.88 at pH 5.0 Log Dow = 5.15 at pH 7.4	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log Dow = 5.15 at 7.4	Potentially B
	BCF	BCF KgL= 118, 418,280 in edible, non-edible, whole fish tissue respectively	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ refined (prevalence)	0.0069	µg/L	> 0.01 threshold (N)

Other concerns (e.g. chemical class)					(N)
Phase II b Studies					
Study type	***Test protocol***	***Endpoint***	***value***	***Unit***	***Remarks***
Bioaccumulation	OECD 305	BCF SSL = 246/ BCF KgL=	246/ 312 719/ 745 (conc.: 0.83 and 9.1 µg/L)	L/kg	%lipids: 5% SSL: steady state, lipid corr. KgL: kinetic, growth and lipid corrected

2.2.2. Discussion and conclusion on non-clinical aspects

A Phase I ERA conducted calculating the Fpen and PECSURFACEWATER using up to date (January 2018) data for RCC and HCC resulted in a PEC value of 0.015µg/L, which is above the trigger value of 0.01µg/L. A Phase II environmental effect analysis was therefore needed, in accordance with EMEA/CHMP/SWP/4447/00 corr 2.

The Applicant was requested to provide a refinement of the Fpen and the PECSURFACEWATER, based on the incidence or prevalence of only advanced RCC and advanced HCC. Using the refined Fpen the $PEC_{SURFACEWATER}$ value is below the action limit of 0.01µg/L.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of cabozantinib.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 4: Clinical Study Reports included in the Marketing Application

Study (Phase)	**Study Report**	**Number of Subjects**	
XL184-309 (CELESTIAL) (Phase 3; ongoing) [a]	Full CSR, Primary analysis	Cabozantinib 60 mg: 470 HCC (efficacy); 467 HCC (safety)	Placebo: 237 HCC (efficacy); 237 HCC (safety)
XL184-203 RDT[b] (Phase 2)	Full CSR, Primary analysis	Cabozantinib 100 mg: 41 HCC (efficacy); 41 HCC (safety)	Not applicable

CSR, clinical study report; HCC, hepatocellular carcinoma; RDT, randomized discontinuation trial
a Total of 707 subjects had enrolled as of the XL184-309 database cut-off date (01 June 2017). Study has subsequently fully enrolled (773 subjects as of 18 September 2017, planned total 760) and closed to enrolment. Subjects continued to receive blinded study treatment as of the database cut-off date.

b This was a nine-cohort study in subjects with advanced solid tumours; results for non-HCC cohorts are provided in the CSR

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) data analysis and the bioanalytical assay results are provided in the following reports:

• Clinical Pharmacokinetics Report for XL184-309 (XL184-309.PK.001)

• Bioanalytical Report for XL184-309 (EXE-R4078)

Bioanalysis

Concentrations of cabozantinib in plasma (**XL184-309**) were analysed using a validated LC-MS/MS method at Frontage Laboratories (Exton, PA). The lower limit of quantification (LLOQ) was 0.5 ng/mL. PK samples were not assayed for break-down products of cabozantinib. Plasma cabozantinib concentrations (**XL184-203.RTD**) were measured using a validated LC-MS/MS method (BA-SR-165.00 and AD13-339).

Pharmacokinetics in Study XL184-309

Bioanalytical Method

Method BTM-1662-R0 is a validated LC-MS/MS method for the determination of cabozantinib (XL184) in K_2EDTA human plasma using XL184-d4 as the isotope-labelled internal standard (IS). Cabozantinib (XL184) in K2EDTA human plasma was stable for 350 days at -70 °C and cabozantinib (XL184) stock and spike solutions were stable at -20 °C for 349 days. At least 836 days at -70 °C of sample storage stability is required to sufficiently cover the longest span of time from collection date until date of analysis for the study samples evaluated in Watson Runs 1-36. An evaluation for extended sample storage stability at -70 °C will be conducted prior to the issuance of the final cumulative bioanalytical assay report for Study XL184-309.

Calibration Standards and QC Samples

The QC samples, at concentrations of 1.50 ng/mL, 80.0 ng/mL, 800 ng/mL and 2500 ng/mL (Dilution QC) for cabozantinib (XL184), were prepared in four batches. The QC samples were stored at -70 ºC.

RESULTS

Concentrations of QC Samples

The concentrations for the QC samples should be within ±15.0% of the nominal concentration. No more than 1/3 of the QC samples may be out of specification. At each concentration, at least 50% of the QC samples should be within the above specification. All the injected batch runs met the defined acceptance criterion.

Back-calculated Concentrations of Calibration Standards

For a batch run to be acceptable, at least 75% of the total number of calibration standards or at least twelve calibration standards in the calibration range, including the LLOQ and ULOQ, must not deviate by greater than ±15.0% (±20.0% at the method LLOQ concentration) from their nominal values.

Plasma Cabozantinib Concentrations in Placebo Arm Subjects

A total of 233 placebo subjects had PK concentration data (PK population); a total of 230 placebo subjects had 563 eligible records in the analysis dataset. Most of the samples were below the limit of quantification of 0.5 ng/mL, except for 5 records with measurable concentrations (ranged from 0.834 to 33. 3 ng/mL). The levels are considered low and negligible and are likely due to contamination.

Plasma Cabozantinib Concentrations in All Cabozantinib Arm Subjects

A total of 453 cabozantinib subjects had PK concentration data (PK population); a total of 449 cabozantinib subjects had 1111 eligible records in the analysis dataset. Summary statistics for the concentrations are presented in Table 5.

The mean plasma concentration values were higher for females than for males, but the spread of the standard deviations between males and females overlapped.

The Analysis Eligible Population included all subjects: subjects remained on the same dose, subjects experienced dose reductions or dose hold prior to PK assessments and subjects may not have achieved steady-state concentrations at the cohort-assigned dose (i.e., did not receive at least 14 of 15 days of the 60 mg FBE/day cabozantinib doses over the 15 days immediately prior to the PK visit) due to a prior dose interruption, reduction, or discontinuation.

Table 5: Summary table of cabozantinib plasma PK concentrations by visit for HCC subjects in the cabozantinib arm ([a]Filtered to select analysis eligible records)

		Concentration (ng/mL) at Scheduled Visit								
		Week 3 Day 1			Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female	Males	Females	Male & Female
60	N	269	68	337	335	80	415	292	66	358
	Arithmetic Mean	1140	1570	1230	927	1220	983	658	988	719
	SD	622	741	669	637	754	670	465	631	515
	CV%	54.6	47.3	54.6	68.7	62.1	68.2	70.7	63.8	71.7
	Geo Mean	-	1390	-	663	954	711	-	706	-
	SD(Logs)	-	0.509	-	1.01	0.772	0.974	-	1.07	-
	Min	0	304	0	5.33	113	5.33	0	9.88	0
	Median	987	1400	1110	837	1120	884	595	869	629
	Max	3500	3360	3500	3510	3450	3510	2130	2610	2610

CV%, coefficient of variation; Geo, Geometric; Max, maximum; Min, minimum; SD, standard deviation; SD (Logs), standard deviation of the logs.
- = not determined based on the presence of individual values of '0' in the dataset.
[a] PK samples were to be taken approximately 8 hours or more after the previous dose of placebo or cabozantinib. Accurate timing of the sample collection was not deemed critical to the steady-state PK evaluation given the long half-life and low fluctuation of steady-state cabozantinib concentrations.

Plasma Cabozantinib Concentrations in Subject Receiving 60 mg for at least 14 of 15 Days Prior to Individual PK Assessments (Steady-State Population on Week 3, Week 5 and/or Week 9)

The ADPC exposure dataset was filtered to select only subjects who received at least 14 of 15 days of the 60 mg FBE /day cabozantinib doses over the 15 days immediately prior to the PK visit on W3D1, W5D1 and/or W9D1 (i.e., the Steady-State Population). Summary statistics for the concentrations are presented in Table 2.

Table 6: Summary table of cabozantinib plasma PK concentrations by visit for HCC subjects in the cabozantinib arm ([a]Filtered to select analysis eligible records at approximate 60 mg/day steady state)

		Concentration (ng/mL) at Scheduled Visit								
		Week 3 Day 1			Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female	Males	Females	Male & Female
60	N	43	11	54	144	37	181	71	10	81
	Arithmetic Mean	1150	1520	1220	1150	1310	1180	789	852	796
	SD	646	566	643	521	663	554	400	448	404
	CV%	56.3	37.3	52.6	45.2	50.8	46.8	50.8	52.6	50.7
	Geo Mean	978	1430	1060	1040	1140	1060	-	742	-
	SD(Logs)	0.629	0.367	0.602	0.487	0.565	0.503	-	0.578	-
	Min	69.4	896	69.4	177	316	177	0	247	0
	Median	980	1280	1090	1130	1300	1140	726	723	726
	Max	3390	2500	3390	3150	3450	3450	1840	1560	1840

CV%, coefficient of variation; Geo, Geometric; Max, maximum; Min, minimum; SD, standard deviation; SD (Logs), standard deviation of the logs.
- = not determined based on the presence of individual values of '0' in the dataset.
[a] Filtered steady state dataset: Subject must receive 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. 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, (i.e., ≥ 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 (i.e., was not unscheduled or taken during screening).
Note: For the Week 3 Day 1, Week 5 Day 1 and Week 9 Day 1 visits, on-treatment PK samples were to be taken approximately 8 hours or more after the previous dose of cabozantinib. Accurate timing of the sample collection was not deemed critical to the steady-state PK evaluation given the long half-life and low fluctuation of steady-state cabozantinib concentrations.

Plasma Cabozantinib Concentrations in Subject Receiving 60 mg for All PK Visits (Steady-State Population on Week 3, Week 5 and Week 9)

The ADPC exposure dataset was filtered to select only subjects who received at least 14 of 15 of the 60 mg FBE/day cabozantinib doses over the 15 days immediately prior to the PK visit (i.e., the Steady-State Population) and had PK samples collected and analyzed at all visits, (i.e., W3D1, W5D1 and W9D1). There were 12 subjects (1 female and 11 males) in the cabozantinib treatment arm who met eligibility based on the number of doses received and PK sample collection below. Summary statistics for the concentrations are presented in Table 7.

Table 7: Summary table of cabozantinib plasma PK concentrations by visit for HCC subjects in the cabozantinib arm ([a]Filtered to select analysis eligible records at approximate 60 mg/day steady state AND each subject must have a qualifying concentration measurement for all visits displayed)

		Concentration (ng/mL) at Scheduled Visit								
		Week 3 Day 1			Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female	Males	Females	Male & Female
60	N	11	1	12	11	1	12	11	1	12
	Arithmetic Mean	1080	896	1070	1020	884	1010	742	510	723
	SD	561	-	538	444	-	426	415	-	401
	CV%	51.8	-	50.4	43.4	-	42.1	55.9	-	55.5
	Geo Mean	984	896	976	915	884	912	536	510	534
	SD(Logs)	0.441	-	0.421	0.536	-	0.511	1.14	-	1.08
	Min	493	896	493	295	884	295	24.8	510	24.8
	Median	1060	896	978	946	884	942	726	510	681
	Max	2580	896	2580	1770	884	1770	1320	510	1320

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 receive 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.
Note: PK samples were to be taken approximately 8 hours or more after the previous dose of cabozantinib. Accurate timing of the sample collection was not deemed critical to the steady-state PK evaluation given the long half-life and low fluctuation of steady-state cabozantinib concentrations.

Population Pharmacokinetics analysis

OBJECTIVES

The primary objectives of this analysis were to:

• Develop a population PK model to characterize the cabozantinib concentration-time profile in healthy volunteers and subjects with various cancer types including HCC

• Investigate selected covariate effects especially those leading to potential differences in PK for subjects with HCC compared to healthy volunteers and subjects with other cancer types.

Study Design

The population PK analysis included integrated plasma cabozantinib concentration-time data from healthy subjects and cancer patients with different types of malignancies. Pertinent details regarding the design and pharmacokinetic sampling scheme for each study are provided in Table 8.

Table 8: Summary of study design and pharmacokinetic sampling scheme

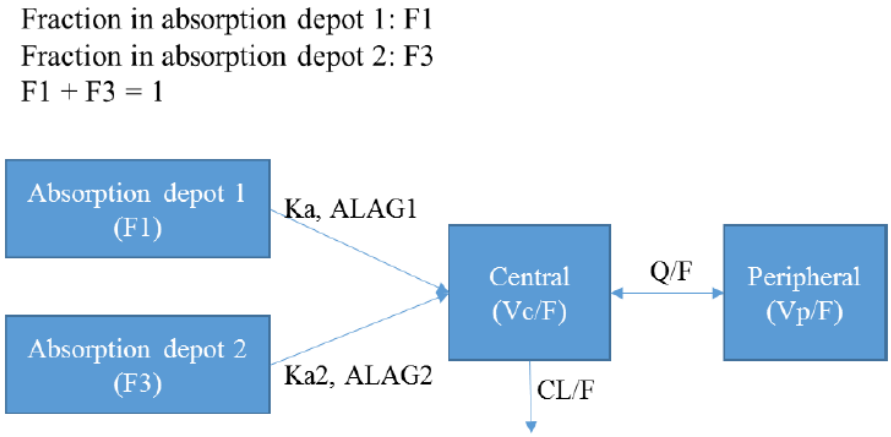
Study No.	Design	Subject Type	Nominal Doses	Planned PK Sampling
XL184-001	Phase 1, non-randomized, open-label, dose-finding, FIH study of cabozantinib (XL184) in subjects with advanced malignancies	Cancer patients with advanced solid tumors	175 or 250 mg (salt form) capsules (140 or 200 mg FBE)	Day1 and 19: pre-dose, 30 minutes and 1, 2, 4, 8, and 24 hours post-dose; Day5: predose and 4 hours post dose; Day15 and 29: predose
XL184-010	Phase 1 two-way cross-over pharmacokinetic studies to compare BE of tablet and capsule formulations in healthy subjects	Healthy volunteers	140 mg FBE tablet or capsule, single dose	Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24 48, 72, 120, 168, 240, 288, 336, 408, and 504 hour each period
XL184-020	Phase 1 pharmacokinetic study of cabozantinib (XL184) tablet formulation in healthy adult subjects	Healthy volunteers	20, 40, 60 mg FBE tablet, single dose	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120, 168, 240, 288, 336, 408, and 504 hours post-dose
XL184-201	Phase 2 multi-center, open-label, single-agent cabozantinib (XL184), non-comparator study in subjects with recurrent or progressive glioblastoma multiforme (GB)	Cancer patients with GB	Cohort A: 175 mg salt form (140 mg FBE) capsule qd	Every 28 days as a cycle Cycle 1: pre-dose and 4 hrs post-dose on C1D1 (Day 1) and C1D15 (Day 15) Cycle 2: pre-dose and 4 hrs post-dose on C2D1 (Day 29) and C2D15 (Day 43) Cycle 3 and beyond: pre-dose on Day 1 (± 4 Days)
XL184-203	Phase 2, randomized discontinuation and non-randomized extension study of cabozantinib (XL184) in subjects with advanced solid tumors	Cancer patients with advanced solid tumors (CRPC or HCC)	RDT cohort: 100 mg FBE capsule qd; NRE cohort: 40 mg or 100 mg FBE capsule qd	RDT: predose at the end of "even" weeks after week 12 lead-in period (e.g., 18, 24 et al.), or early termination or adverse event; NRE: pre-dose on W1D1, pre-dose on End of Week 3, End of Week 6, End of Week 12, End of Week 18, and End of Week 24, unscheduled, early termination or adverse event.
XL184-301	Phase 3, randomized, double-blinded, parallel-group, placebo-controlled study of cabozantinib (XL184) in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC)	Cancer patients with MTC	175 mg salt form (140 mg FBE) capsule qd	C1D1 (Day 1): pre-dose and 2, 4, and 6 hours post-dose C2D1 (Day 29): pre-dose and 2, 4, and 6 hours post-dose
XL184-306	Phase 3, randomized, double-blind, controlled trial of cabozantinib (XL184) vs. mitoxantrone plus prednisone in men with previously treated symptomatic CRPC	Cancer patients with CRPC	60 mg FBE tablet qd	Week 1 Day 1, Week 4 Day 1, Week 7 Day 1, and Week 13 Day 1
XL184-307	Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs. prednisone in metastatic castration-resistant prostate cancer patients who have received prior docetaxel and prior abiraterone or MDV3100	Cancer patients with CRPC	60 mg FBE tablet qd	End of Week 3 and end of Week 12
XL184-308	Phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (RCC) that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Cancer patients with RCC	60 mg FBE tablet qd	~8 or more hours after the prior evening dose on the W5D1 (Day 29) and W9D1 (Day 57) visits
XL184-309	Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with HCC Who Have Received Prior Sorafenib	Cancer patients with HCC	60 mg FBE tablet qd	~8 or more hours after the previous dose of study treatment on the WK3D1, WK5D1, and WK9D1 visits

PK = pharmacokinetic; BE = bioequivalence; FBE = free base equivalent; RDT = randomized discontinuation trial; NRE = non-randomized extension; VEGFR = vascular endothelial growth factor receptor; po = oral; qd = once daily; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma; W = week; C = cycle; D = day

METHODS

An integrated population PK model was previously developed to characterize the cabozantinib concentration-time profile in healthy volunteers (140 and subjects with various cancer types). All studies listed in Table 8 were used to develop this model except Study XL184-309 and HCC subjects from Study XL184-203. The integrated PK model was a two-compartment model with first-order elimination and combined zero-order and first-order absorption (Figure 1). The first-order absorption process included a lag time and a dose dependent effect on the absorption rate (ka) which was characterized using a power model. In addition, a formulation effect was included on ka and relative bioavailability to quantify differences in the rate and extent of absorption between the capsule and tablet formulations. Ka and relative oral bioavailability for the capsule formulation were 58% and 14% lower than that for the reference tablet formulation, respectively. Several demographic covariate effects were included in the integrated PK model; however, the magnitude of these covariate effects

was generally small. The exception was for the MTC population which was predicted to have an approximately 93% increase in apparent clearance resulting in over 40% lower Cmax,ss and 50% lower Cmin,ss relative to healthy subjects.



F1 = fraction of dose in the first depot; F3 = fraction of dose in the second depot; Ka = depot 1 absorption rate constant; Ka2 = depot 2 absorption rate constant; ALAG1 = depot 1 absorption lag time; ALAG2 = depot 2 absorption lag time; Vc/F = apparent volume of distribution (central compartment); Vp/F = apparent volume of distribution (peripheral compartment); Q/F = apparent flow between plasma (central) and peripheral compartments; CL/F = apparent plasma clearance

Figure 1: Diagram of cabozantinib PK model

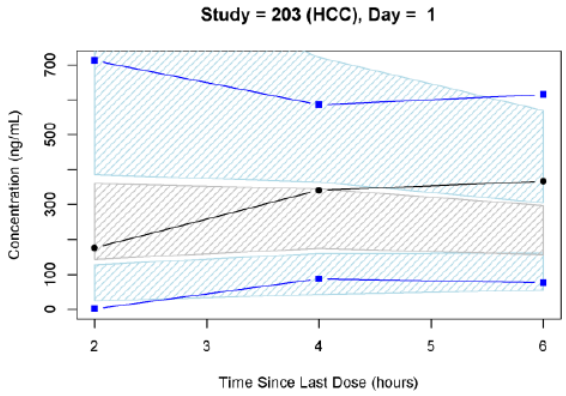
Modelling: Software and Strategy

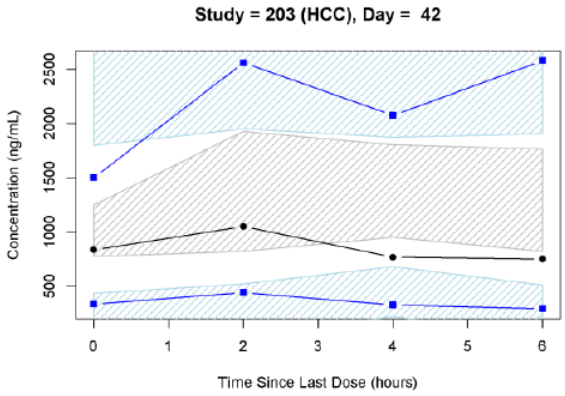
The analysis was performed using nonlinear mixed effects modelling methodology as implemented in the NONMEM software system, version 7.3 (ICON Development Solutions, Ellicott City, MD).

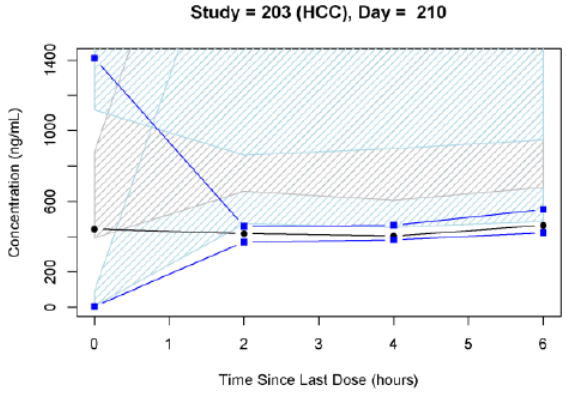
RESULTS

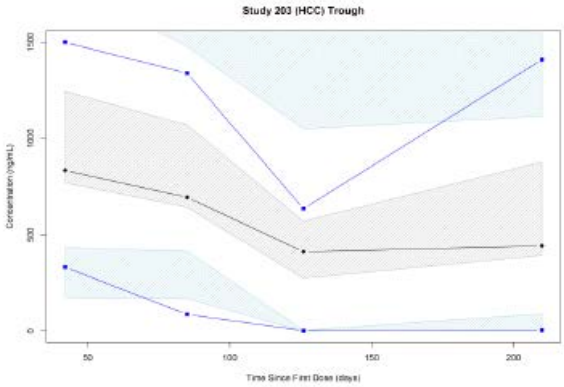
External Visual Predictive Check

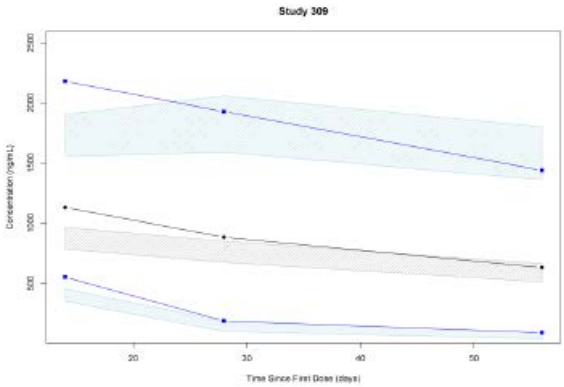
Cabozantinib concentrations in patients with HCC were predicted using the previously described integrated PK model. This model included tumour type as a covariate; however, HCC was not among the tumour types evaluated. Therefore, the predictive performance of the model was evaluated assuming the reference condition for HCC relative to RCC patients. VPC results in Figure 2 showed that, overall, the observed concentrations were generally contained within the prediction intervals, suggesting that cabozantinib PK is similar between HCC and RCC patients.











Lower, middle and upper shaded areas correspond to 90% prediction intervals for 10th (blue solid squares), 50th (black solid circles) and 90th percentiles (blue solid squares), respectively. Blue solid squares and black solid circles represent observed data.

HCC = hepatocellular carcinoma

Figure 2: External visual predictive check plots for HCC patients in study XL184-203 and study XL184-309

Updated Population PK Model

The analysis dataset was updated with the addition of PK data in patients with HCC from Study XL184-203 and Study XL184-309 including a total of 1883 patients. Initially, the HCC population effect on CL/F and Vc/F was evaluated in addition to previously defined covariates. Subsequently, the effect of hepatic impairment on CL/F and Vc/F was assessed using the categorical covariates of mild and combined moderate/severe liver dysfunction.

Goodness-of-fit plots (data not shown) for the updated integrated PK model for cabozantinib suggested good agreement between geometric mean observed data and model predictions [i.e. typical individual predictions (PREDs) and individual predictions (IPREDs)].

Parameter estimates and corresponding 90% confidence intervals are shown in Table 6 for the updated integrated model including HCC patients and for the same model including the assessment of liver dysfunction effects on cabozantinib PK. With the addition of HCC patients, PK parameter estimates and covariate effects were similar to the previous integrated PK model. For a White male subject, CL/F at steady state was estimated as 2.48 L/hr and Vc/F as 212 L. Inter-individual variability (expressed as percent coefficient of variation [%CV]) was approximately 46% for CL/F and 67% for Vc/F.

Table 9: Parameter estimates (90% CI) for updated cabozantinib integrated PK models

Parameter	Including HCC Population (Final Updated Integrated Model)			Including HCC Population + Liver Dysfunction Covariates		
	Estimate	SE	Transformed Estimate (90% CI)	Estimate	SE	Transformed Estimate (90% CI)
PK parameters						
Ka (hr-1)	0.213	0.229	1.24 (0.849, 1.8)	0.207	0.237	1.23 (0.833, 1.82)
Infusion duration D (hr)	0.908	0.0737	2.48 (2.2, 2.8)	0.928	0.0713	2.53 (2.25, 2.84)
CL/F (L/hr)	0.908	0.0539	2.48 (2.27, 2.71)	0.906	0.0536	2.47 (2.26, 2.7)
Vc/F (L)	5.36	0.1	212 (180, 250)	5.36	0.0993	214 (181, 251)
Q/F (L/hr)	3.4	0.0569	30.0 (27.3, 33)	3.41	0.0554	30.2 (27.6, 33.1)
Vp/F (L)	5.18	0.0413	177 (165, 189)	5.19	0.04	179 (167, 191)
ALAG1 (hr-1)	-0.197	0.0196	0.821 (0.795, 0.848)	-0.198	0.0191	0.82 (0.795, 0.846)
Fraction of dose in first absorption depot F1[a]	1.62	0.146	1.62 (1.38, 1.86)	1.61	0.149	1.61 (1.37, 1.86)
Dose dependent Ka	0.734	0.245	0.734 (0.331, 1.14)	0.564	0.259	0.564 (0.138, 0.989)
Covariates						
Capsule on Ka[b]	-0.911	0.358	0.402 (0.223, 0.725)	-0.639	0.385	0.528 (0.28, 0.994)
Capsule on overall relative oral availability[b]	-0.166	0.0127	0.847 (0.83, 0.865)	-0.173	0.0125	0.841 (0.824, 0.859)
Age on CL/F	-0.157	0.0647	-0.157 (-0.264, -0.0509)	-0.16	0.0646	-0.16 (-0.266, -0.0539)
Female on CL/F[b]	-0.274	0.0382	0.76 (0.714, 0.81)	-0.272	0.0381	0.762 (0.715, 0.811)
Black on CL/F[b]	0.162	0.0743	1.18 (1.04, 1.33)	0.164	0.074	1.18 (1.04,1.33)
Asian on CL/F[b]	-0.0668	0.0446	0.935 (0.869, 1.01)	-0.0686	0.0445	0.934 (0.868, 1)
Other Race on CL/F[b]	0.0279	0.0788	1.03 (0.903, 1.17)	0.0236	0.0784	1.02 (0.9, 1.16)
Weight on CL/F	-0.0393	0.0652	-0.0393 (-0.147, 0.0679)	-0.0209	0.0652	-0.0209 (-0.128, 0.0863)
RCC on CL/F[b]	-0.139	0.0625	0.87 (0.785, 0.965)	-0.148	0.0624	0.862 (0.778, 0.956)
CRPC on CL/F[b]	-0.0115	0.0616	0.989 (0.893, 1.09)	-0.0328	0.0616	0.968 (0.874, 1.07)
MTC on CL/F[b]	0.643	0.0626	1.9 (1.72, 2.11)	0.63	0.0625	1.88 (1.69, 2.08)
GB on CL/F[b]	0.178	0.11	1.2 (0.997, 1.43)	0.182	0.11	1.2 (1, 1.44)
Other malignancies on CL/F[b]	0.171	0.0995	1.19 (1.01, 1.4)	0.135	0.0997	1.14 (0.971, 1.35)

Age on Vc/F	0.0644	0.129	0.0644 (-0.148, 0.277)	0.077	0.13	0.077 (-0.136, 0.29)
Female on Vc/F[b]	0.0939	0.0737	1.1 (0.973, 1.24)	0.073	0.074	1.08 (0.952, 1.22)
Black on Vc/F[b]	0.0441	0.183	1.05 (0.773, 1.41)	0.0653	0.184	1.07 (0.789, 1.44)
Asian on Vc/F[b]	-0.363	0.134	0.696 (0.558, 0.867)	-0.303	0.132	0.739 (0.595, 0.918)
Other Race on Vc/F[b]	-0.126	0.219	0.882 (0.615, 1.26)	-0.0355	0.212	0.965 (0.681, 1.37)
Weight on Vc/F	1.19	0.158	1.19 (0.934, 1.46)	1.2	0.16	1.2 (0.934, 1.46)
RCC on Vc/F[b]	-0.422	0.286	0.656 (0.41, 1.05)	-0.341	0.273	0.711 (0.454, 1.11)
CRPC on Vc/F[b]	-0.297	0.128	0.743 (0.602, 0.917)	-0.327	0.129	0.721 (0.583, 0.891)
MTC on Vc/F[b]	-0.0657	0.103	0.936 (0.79, 1.11)	-0.0919	0.104	0.912 (0.769, 1.08)
GB on Vc/F[b]	-0.735	0.221	0.479 (0.333, 0.689)	-0.803	0.235	0.448 (0.304, 0.659)
Other malignancies on Vc/F[b]	-0.272	0.152	0.762 (0.593, 0.979)	-0.289	0.152	0.749 (0.583, 0.962)
HCC Covariates						
HCC on CL/F	-0.13	0.0609	0.878 (0.794, 0.971)	-0.198	0.0644	0.82(0.738,0.912)
HCC on Vc/F	-0.166	0.121	0.847 (0.694, 1.03)	-0.211	0.132	0.81(0.652,1.01)
Liver Dysfunction (NCI-ODWG) Covariates						
LD=2[c] on CL/F				0.111	0.0316	1.12 (1.06, 1.18)
LD=2[c] on Vc/F				0.0411	0.0861	1.04 (0.904, 1.2)
LD=3/4[c] on CL/F				-0.0227	0.137	0.978 (0.781, 1.22)
LD=3/4[c] on Vc/F				0.0595	0.291	1.06 (0.658, 1.71)
Variance						
σ2	0.127	0.00235	0.127 (0.123, 0.131)	0.127	0.00232	0.127 (0.123, 0.131)
ω2_Ka	2.02	0.262	2.02 (1.59, 2.45)	2.21	0.328	2.21 (1.67, 2.75)
ω2_CL	0.213	0.00903	0.213 (0.198, 0.227)	0.210	0.00888	0.210 (0.195, 0.224)
ω2_CL:Vc	0.211	0.0205	0.211 (0.178, 0.245)	0.199	0.0201	0.199 (0.166, 0.232)
ω2_Vc	0.443	0.0444	0.443 (0.370, 0.516)	0.430	0.0423	0.430 (0.361, 0.5)
ω2_F1	2.55	0.335	2.55 (1.99, 3.1)	2.73	0.382	2.73 (2.11, 3.36)

Estimate = log of PK parameter; Transformed Estimate = PK parameter obtained by exponentiating the original estimate; Ka = absorption rate constant from the 1st absorption depot; CL/F = apparent clearance; Vc/F = apparent distribution volume of the central compartment; Q/F = apparent flow parameter between compartments; Vp/F = apparent distribution volume of the peripheral compartment; ALAG1 = absorption lag time for the 1st absorption depot; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer ; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma; LD = liver dysfunction; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; σ2 = variance of population predicted concentration; ω2 = variance of population parameter

[a] Anti-logit transformation was used to obtain F1.
[b] For categorical covariates (e.g., capsule), transformed estimates correspond to fractional change from the reference level.
[c] LD=2 represents mild liver dysfunction; LD=3/4 represents combined moderate and severe liver dysfunction

Note: Liver dysfunction was classified according to NCI-ODWG criteria based on total bilirubin (TB) and aspartate aminotransferase (AST) as follows:

Normal hepatic function:	TB ≤ upper limit of normal (ULN) and AST ≤ ULN
Mild hepatic dysfunction:	TB ≤ ULN and AST > ULN or TB > 1.0 to 1.5 x ULN and any AST value
Moderate hepatic dysfunction:	TB > 1.5 to 3.0 x ULN and any AST value
Severe hepatic dysfunction:	TB > 3 x ULN and any AST value

Cabozantinib exposure parameters for a 60 mg daily dose at steady state are provided in Table 10.

Table 10: Summary of predicted mean (SD) exposure measures at steady state following 60 mg cabozantinib once daily

Parameter	HCC Patients Study XL184-309	RCC Patients Study XL184-308	All Cancer Patients[a] except MTC	MTC Cancer Patients Study XL184-301	Healthy Subjects Studies XL184-010 and XL184-020
N	452	282	1673	210	140
$C_{min,ss}$ (ng/mL)	1271 (594)	1198 (440)	1078 (512)	432 (160)	1038 (438)
$C_{max,ss}$ (ng/mL)	1607 (696)	1519 (538)	1358 (616)	586 (188)	1269 (563)
$AUC_{(0-24),ss}$ (ng·hr/mL)	33073 (14728)	31296 (11034)	28161 (12824)	11936 (4034)	26898 (11229)

SD = standard deviation; $C_{min,ss}$ = steady state minimum plasma drug concentration; $C_{max,ss}$ = steady state maximum plasma drug concentration; $AUC_{(0-24,ss)}$ = steady state area under the plasma drug concentration-time curve over the 24 hour dosing interval
[a] Includes subjects in Studies XL184-001, XL184-201, XL184-203, XL184-306, XL184-307, XL184-308 and XL184-309

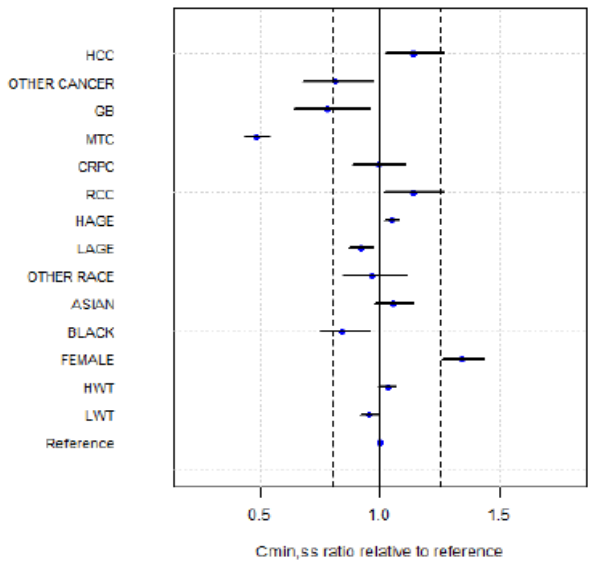
Graphical Summaries of Covariate Effects

Forest Plots

The impact of covariates was assessed on steady state minimum plasma drug concentration (Cmin,ss), steady state maximum plasma drug concentration (Cmax,ss), steady state area under the plasma drug concentration-time curve over the 24 hour dosing interval (AUC(0-24,ss)), CL/F and Vc/F for specified covariate values (i.e. test conditions) relative to a reference set of covariate values. Specifically, the reference condition was defined as a White male, healthy subject with a body weight of 80 kg, 60 years of age, receiving a 60-mg free base equivalent cabozantinib tablet once daily with steady state PK profile simulated on Day 57. The test condition differs from the reference by changing a specific covariate value. All other covariate values were identical to the reference. For continuous covariates

such as age and weight, 5th and 95th percentiles in the updated integrated analysis dataset (age: 37 and 79 years; weight: 54 and 109 kg) were used to represent extreme covariate values.

Similar to the previous analysis, age, body weight and race did not have impact on cabozantinib CL/F. The MTC cancer type had the largest effect on cabozantinib PK parameters and exposure metrics among the covariates examined. The CL/F estimate was 24% lower in females, resulting in 27% higher Cmax,ss and 35% higher Cmin,ss and AUC(0-24,ss). Covariate effects on Vc/F included glioblastoma multiforme (~50% decrease in Vc/F), high body weight (~50% increase in Vc/F) and low body weight (~30% decrease in Vc/F).

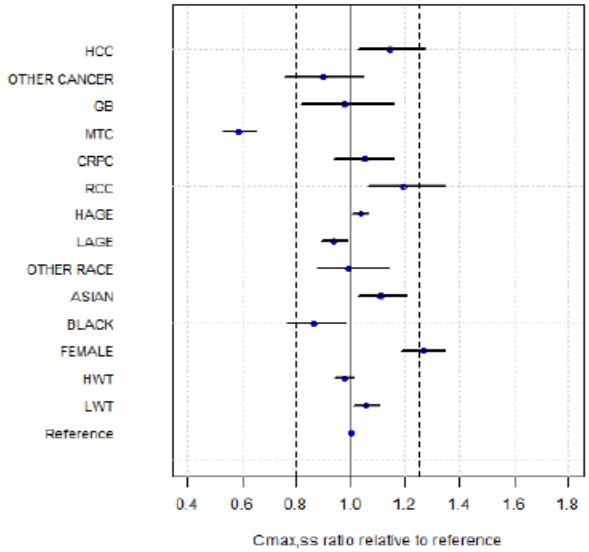


Note: A reference subject (Reference) is defined as a White, male, healthy subject, with body weight of 80 kg and 60 years of age. Other test conditions are defined as follows: LWT: a subject with body weight of 54 kg; HWT: a subject with body weight of 109 kg; LAGE: a 37-year old subject; HAGE: a 79-year old subject; RCC: a cancer patient with RCC; CRPC: a cancer patient with CRPC; MTC: a cancer patient with MTC; GB: a cancer patient with GB; OTHER CANCER: a patient with a cancer type included in Study XL184-001; HCC: a cancer patient with HCC.

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

$C_{min,ss}$ = steady state minimum plasma drug concentration; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

Figure 3: Impact of covariates on Cmin,ss

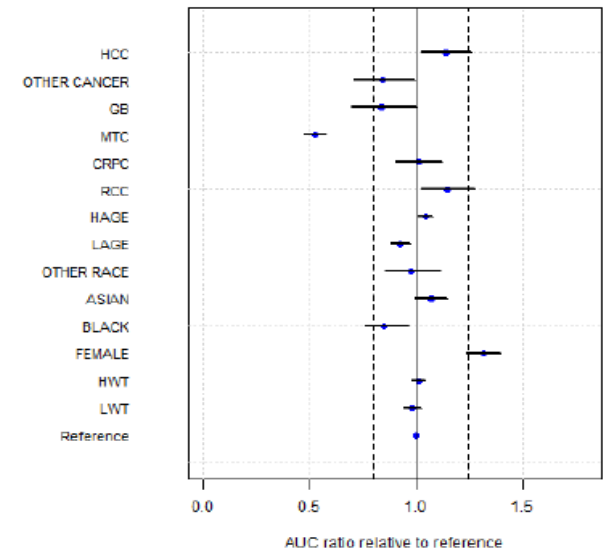


Note: A reference subject (Reference) is defined as a White, male, healthy subject, with body weight of 80 kg and 60 years of age. Other test conditions are defined as follows: LWT: a subject with body weight of 54 kg; HWT: a subject with body weight of 109 kg; LAGE: a 37-year old subject; HAGE: a 79-year old subject; RCC: a cancer patient with RCC; CRPC: a cancer patient with CRPC; MTC: a cancer patient with MTC; GB: a cancer patient with GB; OTHER CANCER: a patient with a cancer type included in Study XL184-001; HCC: a cancer patient with HCC.

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

$C_{max,ss}$ = steady state maximum plasma drug concentration; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

Figure 4: Impact of covariates on Cmax,ss

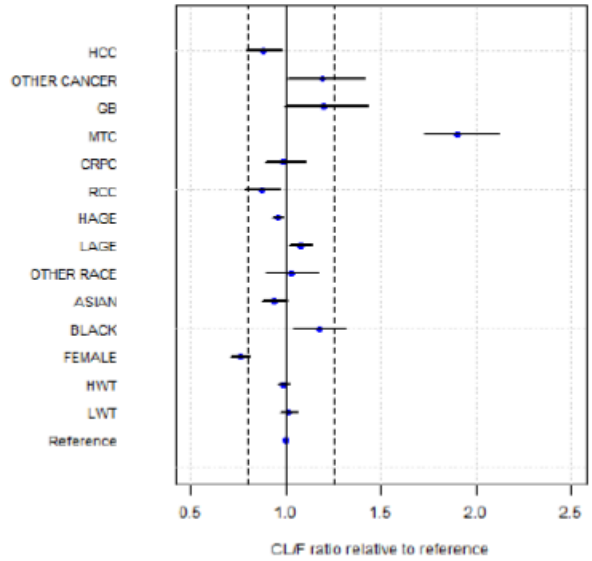


Note: A reference subject (Reference) is defined as a White, male, healthy subject, with body weight of 80 kg and 60 years of age. Other test conditions are defined as follows: LWT: a subject with body weight of 54 kg; HWT: a subject with body weight of 109 kg; LAGE: a 37-year old subject; HAGE: a 79-year old subject; RCC: a cancer patient with RCC; CRPC: a cancer patient with CRPC; MTC: a cancer patient with MTC; GB: a cancer patient with GB; OTHER CANCER: a patient with a cancer type included in Study XL184-001; HCC: a cancer patient with HCC.

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

$AUC_{(0\text{-}24,ss)}$ = steady state area under the plasma drug concentration-time curve over the 24 hour dosing interval; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

Figure 5: Impact of covariates on AUC(0-24,ss)

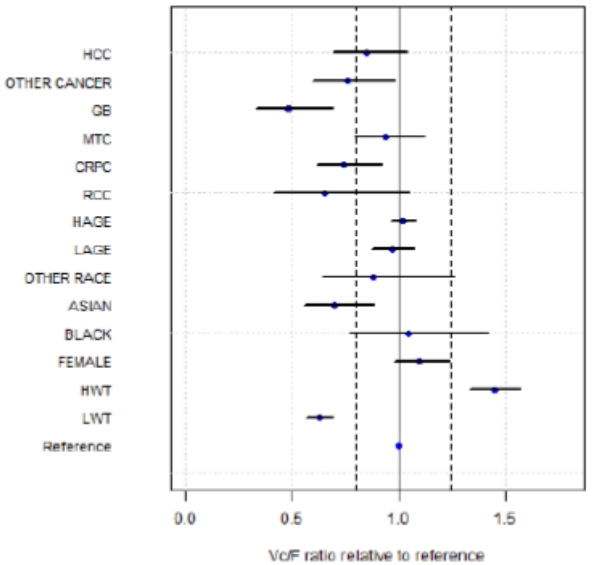


Note: A reference subject (Reference) is defined as a White, male, healthy subject, with body weight of 80 kg and 60 years of age. Other test conditions are defined as follows: LWT: a subject with body weight of 54 kg; HWT: a subject with body weight of 109 kg; LAGE: a 37-year old subject; HAGE: a 79-year old subject; RCC: a cancer patient with RCC; CRPC: a cancer patient with CRPC; MTC: a cancer patient with MTC; GB: a cancer patient with GB; OTHER CANCER: a patient with a cancer type included in Study XL184-001; HCC: a cancer patient with HCC.

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

CL/F = apparent clearance; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

Figure 6: Impact of covariates on steady state CL/F



Note: A reference subject (Reference) is defined as a White, male, healthy subject, with body weight of 80 kg and 60 years of age. Other test conditions are defined as follows: LWT: a subject with body weight of 54 kg; HWT: a subject with body weight of 109 kg; LAGE: a 37-year old subject; HAGE: a 79-year old subject; RCC: a cancer patient with RCC; CRPC: a cancer patient with CRPC; MTC: a cancer patient with MTC; GB: a cancer patient with GB; OTHER CANCER: a patient with a cancer type included in Study XL184-001; HCC: a cancer patient with HCC.

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

Vc/F = apparent central distribution volume; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

Figure 7: Impact of covariates on steady state Vc/F

Updated Integrated Model Predictive Performance

The predictive performance of the updated integrated PK model was evaluated using a VPC. The VPC statistics (data not shown) were largely contained within the 90% prediction intervals indicating that the updated integrated PK model could simulate concentration-time data that were consistent with the observed data.

Absorption

No new data have been submitted on the absorption profile of cabozantinib.

Distribution

No new data on the protein binding or distribution profile of cabozantinib, other than the popPK estimate of V/F, have been submitted. In the original popPK analysis, the apparent volume of distribution was 319 L (SE ±2.7%). The volume of distribution of the central compartment (Vc/F) is now estimated to be 212 L.

Elimination

No new data on the metabolism of cabozantinib have been submitted. No new data on the elimination of cabozantinib, other than the popPK estimate of CL/F, have been presented with the current application. lasma half-life and estimated mean steady state CL/F have been changed from 99 hours to 110 hours and from 2.2 L/hr to 2.48 L/hr, respectively.

Dose proportionality and time dependencies

No new data on dose proportionality and time dependencies of cabozantinib have been submitted.

Intra- and inter-individual variability

The inter-subject variability (%CV) of CL/F and Vc/F in the popPK model analysis were estimated to be 46% and 67%, respectively. Intra-individual variability has not been reported.

Special populations

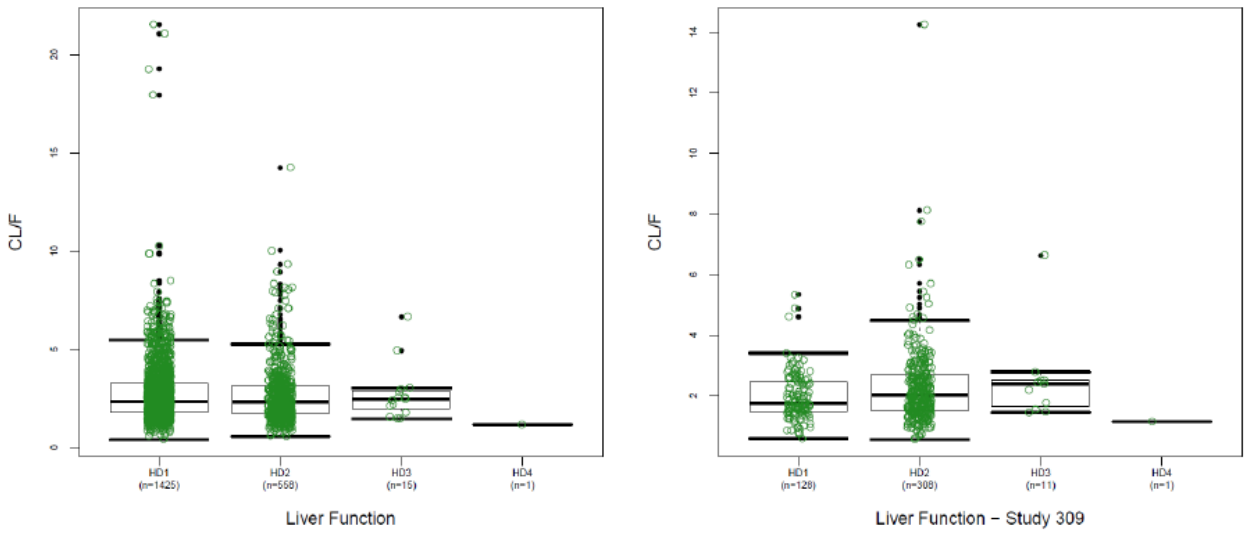
With the addition of HCC patients, the model-estimated PK parameters and covariate effects were similar to the previous integrated PK model (**XL184-308.PopPK.002**).

Hepatic impairment

The mean 60 mg steady state plasma concentration at W5D1 in RCC subjects (**XL184-308**, subjects with normal liver function) was 1260 ± 559 ng/mL (n=211), whereas the mean 60 mg ss value at W5D1 in HCC subjects (**XL184-309**, mostly subjects with Child-Pugh A) was 1180 ± 554 ng/mL (n=181). This is in contrast to the hepatic impairment study (**XL184-003**), where non-cancer subjects with mild hepatic impairment (Child-Pugh class A) had an 81% increase in single-dose cabozantinib exposure ($AUC_{0\text{-}inf}$) and a 75% increase in terminal half-life compared with subjects with normal hepatic function. The increase in cabozantinib exposure in subjects with moderate hepatic impairment (Child-Pugh B) relative to normal hepatic function (63% increase in AUC and 70% increase in terminal half-life) was slightly lower than observed for Child-Pugh A subjects.

The PopPK analysis updated to evaluate PK of cabozantinib in patients with HCC showed that HCC and RCC subjects receiving a 60 mg daily cabozantinib dose appeared to have similar CL/F and s-s exposure (AUC). Furthermore, popPK results indicated that liver dysfunction, as defined by NCI-ODWG criteria, had no discernible effect on cabozantinib clearance: subjects with mild hepatic impairment appeared to have similar cabozantinib PK as subjects with normal hepatic function (Figure 8). There was no observed difference for subjects with moderate hepatic impairment (n=15) relative to subjects with normal hepatic function; however, the sample size was small.

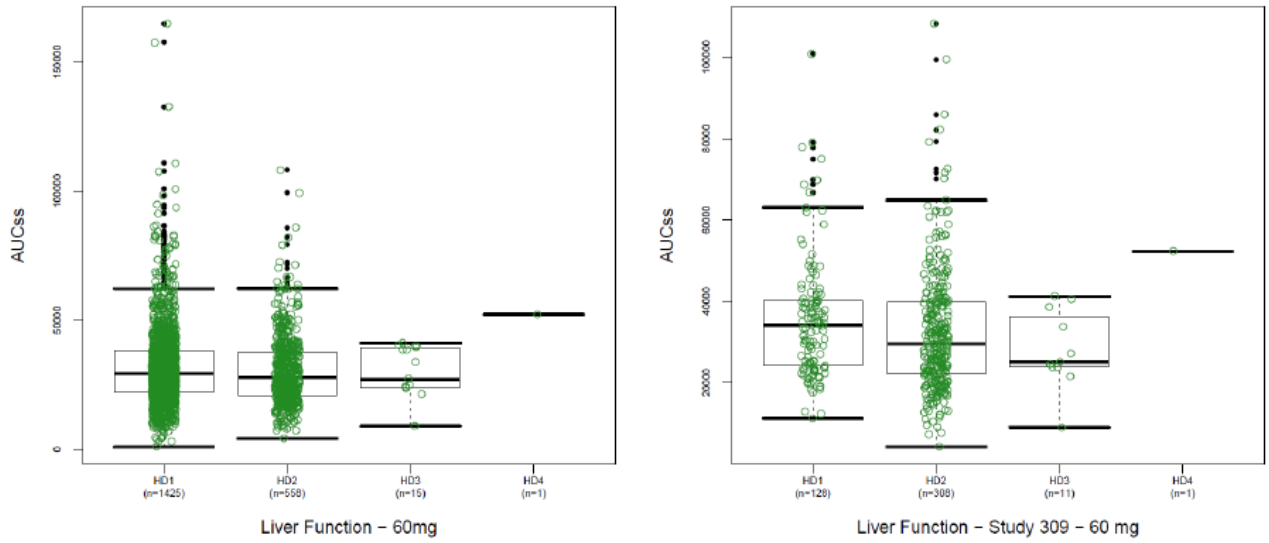
Normal-to-mild hepatic dysfunction (NCI-ODWG) was shown to correlate with Child-Pugh A status in a Phase I study in cancer subjects administered imatinib mesylate (Patel et al 2004).



CL/F = apparent clearance

Liver dysfunction scores are defined as: HD1 = normal, HD2 = mild, HD3 = moderate and HD4 = severe, according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria based on total bilirubin (TB) and aspartate aminotransferase (AST) as follows:

Normal hepatic function:	TB ≤ upper limit of normal (ULN) and AST ≤ ULN
Mild hepatic dysfunction:	TB ≤ ULN and AST > ULN or TB > 1.0 to 1.5 x ULN and any AST value
Moderate hepatic dysfunction:	TB > 1.5 to 3.0 x ULN and any AST value
Severe hepatic dysfunction:	TB > 3 x ULN and any AST value



$AUC_{(0\text{-}24,ss)}$ = steady state area under the plasma drug concentration-time curve over the 24 hour dosing interval

Figure 8: Cabozantinib apparent clearance and AUCss with liver function for all studies (left panels) and study XL184-309 only (right panels) (XL184-309.PopPK.001)

2.3.3. Pharmacodynamics

Mechanism of action

Cabozantinib inhibits VEGFR2, MET and AXL with cell-based IC50 values of 8, 2 and 77 nM, respectively. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumour xenografts grown in athymic nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, at least 50% inhibition lasted for over 8 hours post-dose at a single dose level of 100 mg/kg. Cabozantinib abrogated tumour growth by dual blockade of VEGFR2 and MET in an HCC xenograft mouse model. Cabozantinib prolonged survival in a MET -driven transgenic mouse model of HCC.

2.3.4. PK/PD modelling

Exposure-Response Analyses: Efficacy

Time-to-event ER models were developed using Cox proportional hazards (CPH) methodology. Efficacy endpoints evaluated were: overall survival-early (OSE; survival among subjects with ≤8 weeks of study treatment), overall survival-late (OSL; survival among subjects with ≥12 weeks of study treatment) and PFS. The covariates evaluated included baseline ECOG score, disease aetiology and presence/ absence of extrahepatic spread.

The exposure metric for OSE analysis was the cabozantinib average concentration (Cavg) over the first four weeks of treatment (CAVGOSE) while the exposure metric for OSL analysis was the cabozantinib Cavg calculated over the 28 days prior to the Week 12 landmark (CAVGOSL). Nonlinear models were evaluated over a grid of fixed EC50 values for average cabozantinib plasma concentrations ranging from 100 to 3000 ng/mL.

The relationship of tumour size (sum of target tumour diameters) with cabozantinib average exposure was described using a longitudinal model that incorporated first-order tumour growth, linear decay due to drug treatment and attenuation of the drug effect.

Table 11: Number of Events and Number of Subjects at Risk in Efficacy Analysis Datasets

Efficacy Endpoint	Event	Number of Events and Subjects at Risk			
		Cabozantinib		Placebo	
		Number of Events	Subjects with at least one measurable cabozantinib concentration	Number of Events	Subjects receiving at least one dose of placebo
OSE ≤ 8 weeks of study treatment	Death	16	452	12	237
OSL ≥ 12 weeks of study treatment	Death	112	272	35	89
PFS	Disease progression or death	299	419	185	223

OSE = overall survival-early (survival among subjects with ≤ 8 weeks of study treatment); OSL = overall survival-late (survival among subjects with ≥ 12 weeks of study treatment); PFS = progression-free survival

Overall survival early (OSE):

The linear, nonlinear and step function models did not result in statistically significant reductions in the negative 2 log likelihood value (-2LL) compared to the model without cabozantinib exposure. Therefore, no relationship was identified for OSE and cabozantinib plasma exposure.

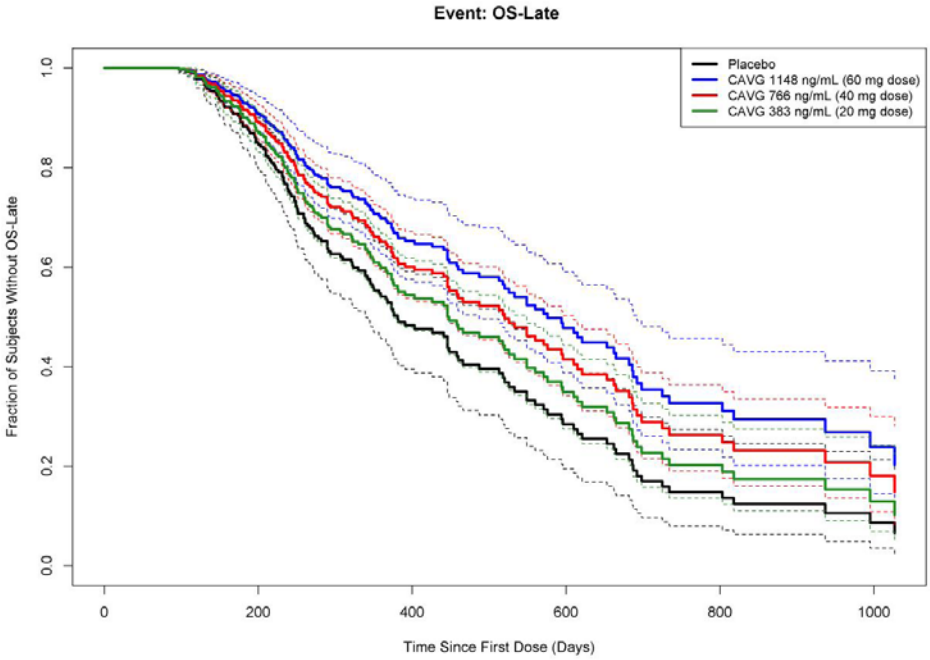
Overall survival late (OSL):

A statistically significant relationship between individually predicted cabozantinib Cavg and survival was observed in subjects receiving cabozantinib for at least 12 weeks (OSL). For all comparisons the confidence interval does not include one. Relative to a 60 mg dose, higher HRs were estimated for OSL for a 40 mg and 20 mg dose (1.19 and 1.43 respectively) based on predicted average s-s cabozantinib concentrations (Cavg) values, suggesting that OSL was improved with increasing cabozantinib plasma exposure. No significant covariates were observed based on the full model results.

Table 12: Overall Survival-Late Hazard Ratios for Selected Exposure Levels

Hazard Ratio Relative to CAVGOSL = 0 ng/mL (Placebo)		
CAVGOSL[a]	HR	95% CI
Placebo	1.00	(1.00, 1.00)
383 ng/mL (20 mg dose)	0.84	(0.73, 0.96)
766 ng/mL (40 mg dose)	0.70	(0.53, 0.92)
1148 ng/mL (60 mg dose)	0.59	(0.39, 0.88)
Hazard Ratio Relative to CAVGOSL = 383 ng/mL		
CAVGOSL[a]	HR	95% CI
383 ng/mL (20 mg dose)	1.00	(1.00, 1.00)
766 ng/mL (40 mg dose)	0.84	(0.73, 0.96)
1148 ng/mL (60 mg dose)	0.70	(0.54, 0.92)
Placebo	1.20	(1.04, 1.37)
Hazard Ratio Relative to CAVGOSL = 1148 ng/mL		
CAVGOSL[a]	HR	95% CI
1148 ng/mL (60 mg dose)	1.00	(1.00, 1.00)
766 ng/mL (40 mg dose)	1.19	(1.04, 1.37)
383 ng/mL (20 mg dose)	1.43	(1.09, 1.87)
Placebo	1.71	(1.14, 2.55)

a Cabozantinib concentrations correspond to model predicted typical individual steady-state average concentrations for the 20 mg, 40 mg, and 60 mg once daily dosing regimens.



Note: The solid line represents the fraction of subjects at each dose level without progression of disease or death over time. The dashed lines represent 95% confidence intervals.

Figure 9: Predicted Fraction of Subjects with Overall Survival-Late

Progression-free survival (PFS):

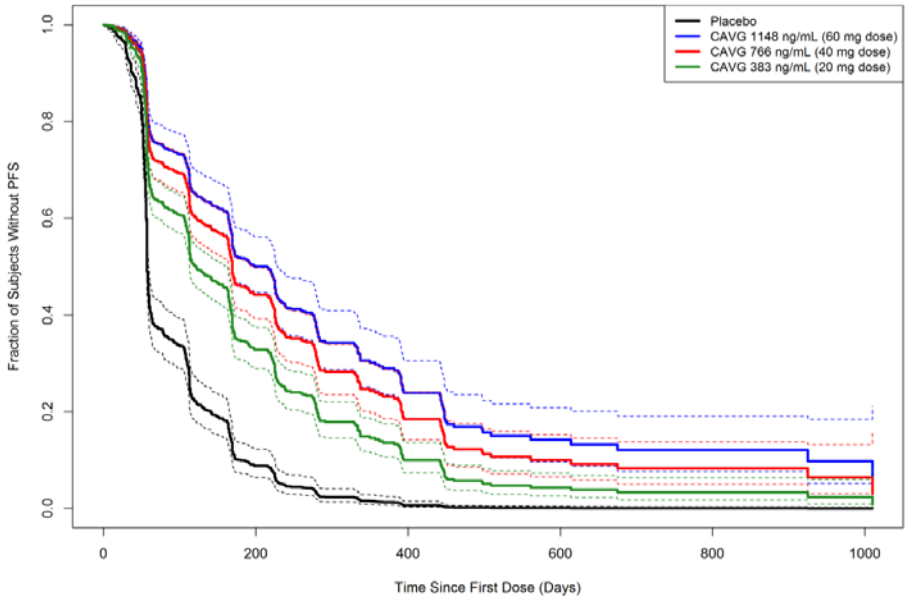
A statistically significant relationship was also identified between cabozantinib plasma Cavg and the risk of disease progression or death (PFS). Increases in cabozantinib plasma concentration are predicted to decrease the risk of disease progression or death in a nonlinear manner. The EC50 value for PFS for the Emax model was 500 ng/mL. The typical individual predicted s-s cabozantinib plasma

Cavg for the 60 mg dose (1148 ng/mL) is approximately 2-fold greater than the estimated EC50 value, suggesting that the anticipated s-s exposures from the 60 mg dose would fall in the range of efficacious concentrations on the Emax ER curve. Relative to a 60 mg dose, higher HR values were estimated for PFS for a 40 mg and 20 mg dose (1.18 and 1.60 respectively) based on predicted s-s cabozantinib Cavg values.

Table 13: Progression Free Survival Emax Model Hazard Ratios for Selected Exposure Levels

Hazard Ratio Relative to CAVG3W = 0 ng/mL (Placebo)		
CAVG3W[a]	HR	95% CI
Placebo	1.00	(1.00, 1.00)
383 ng/mL (20 mg dose)	0.46	(0.40, 0.52)
766 ng/mL (40 mg dose)	0.34	(0.28, 0.40)
1148 ng/mL (60 mg dose)	0.29	(0.23, 0.35)
Hazard Ratio Relative to CAVGOSL = 383 ng/mL		
CAVG3W[a]	HR	95% CI
383 ng/mL (20 mg dose)	1.00	(1.00, 1.00)
766 ng/mL (40 mg dose)	0.73	(0.70, 0.77)
1148 ng/mL (60 mg dose)	0.62	(0.58, 0.67)
Placebo	2.18	(1.92, 2.48)
Hazard Ratio Relative to CAVGOSL = 1148 ng/mL		
CAVG3W[a]	HR	95% CI
1148 ng/mL (60 mg dose)	1.00	(1.00, 1.00)
766 ng/mL (40 mg dose)	1.18	(1.15, 1.21)
383 ng/mL (20 mg dose)	1.60	(1.48, 1.74)
Placebo	3.50	(2.84, 4.31)

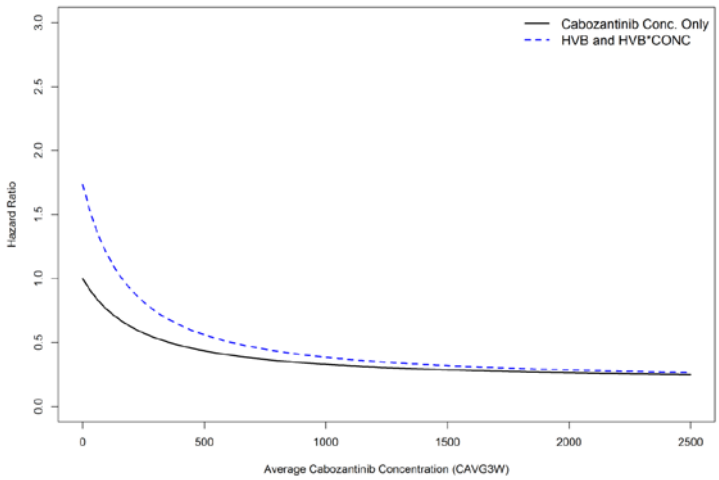
a Cabozantinib concentrations correspond to model predicted typical individual steady-state average concentrations for the 20 mg, 40 mg, and 60 mg once daily dosing regimens.



Note: The solid line represents the fraction of subjects at each dose level without progression of disease or death over time. The dashed lines represent 95% confidence intervals.

Figure 10: Predicted Survival Curves for Progression Free Survival

Covariate analysis was performed based on fixing EC50 = 500 ng/mL. The final model for PFS included the following three covariates: average cabozantinib exposure over the previous 3 weeks (EXNL), HBV and interaction between EXNL and HBV aetiology. Subjects with increasing cabozantinib concentrations are predicted to have a decreased risk of progressive disease or death; subjects with HBV are predicted to have a higher baseline risk of progressive disease or death. However, at higher cabozantinib concentrations the HR is similar with or without the HBV covariate effect.



CAVG3W = average cabozantinib concentration calculated over the three weeks prior to t; HBV = hepatitis B virus aetiology covariate; HBV*CONC = hepatitis B virus aetiology and cabozantinib concentration interaction covariate. The reference hazard represents hepatitis C virus or other aetiology and no extrahepatic spread of disease

Figure 11: Comparison of Predicted Hazard Ratio for Covariate Effects for the Final Progression Free Survival Model

Tumour size:

These plots are not representative of the actual magnitude of effect since the model does not consider patient dropout. Although the actual percent change in tumour size cannot be estimated, the model predicts inhibition of tumour growth at all cabozantinib doses (20, 40 and 60 mg/day); there was greater inhibition of tumour growth with increasing dose. Reduction in tumour size was observed only at a daily dose of cabozantinib 60 mg.

The attenuation half-life for the typical subject was 161.9 days indicating that the tumour decay rate due to drug was essentially zero by 648 days.

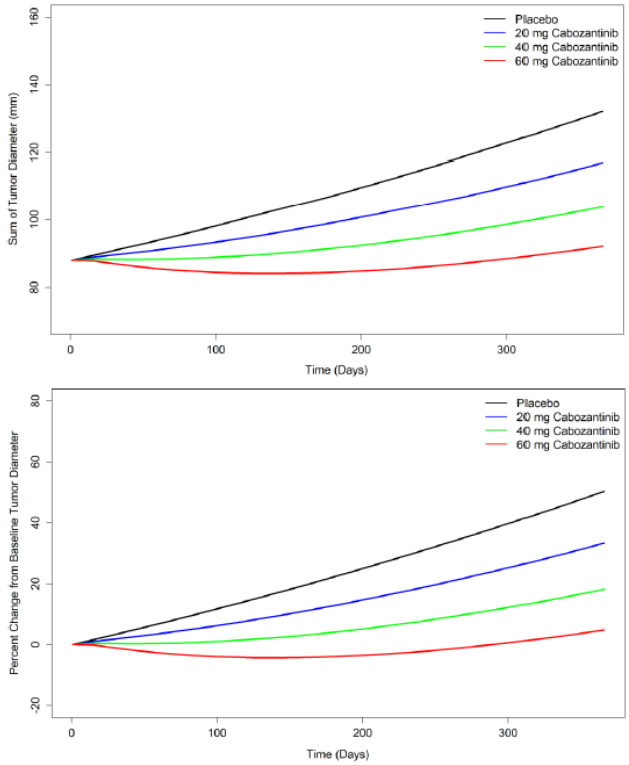


Figure 12: Model-Predicted Sum of Tumour Diameters (Left Panel) and Change from Baseline (Right Panel) with Cabozantinib Assuming no Patient Dropout

Exposure-Response Analysis: Safety

Time-to-event analyses using CPH methodology were performed to determine if ER relationships could be identified between cabozantinib plasma exposure and key safety endpoints: dose modification, fatigue, nausea/vomiting, PPES, diarrhoea, hypertension, ALT/AST elevation and total bilirubin elevation.

Table 14: Summary of Number of Events and Number of Subjects at Risk in Safety Analysis Datasets

Safety Endpoint	Number of Events and Subjects at Risk			
	Cabozantinib		Placebo	Total number of events[d]
	Subjects receiving at least one dose of cabozantinib	Subjects with at least one measurable cabozantinib concentration	Subjects receiving at least one dose of placebo	
Fatigue[a]	80	77	14	91
Nausea/Vomiting[a]	10	10	6	16
Palmar-Plantar Erythrodysesthesia[b]	217	217	12	229
Diarrhea[a]	46	46	4	50
Hypertension[c]	124	124	13	137
ALT/AST Elevated[a]	64	64	16	80
Total Bilirubin Elevated[a]	13	13	4	17
Dose Modification	377	369	74	443
Total Number of Subjects at Risk	**467**	**452**	**237**	**689**

[a] Adverse event of Grade 3 or higher.
[b] Adverse event of Grade 1 or higher.
[c] Systolic blood pressure > 160 mmHg or Diastolic blood pressure > 100 mm Hg.
[d] Total number of events including subjects with at least one measurable cabozantinib concentration and subjects receiving at least one dose of placebo.

Dose Modification

The relationship between individual predicted cabozantinib apparent clearance (CL/F) and the rate of dose modifications (reductions or interruptions) was assessed using the linear model described and the nonlinear models, evaluated over a grid of fixed EC50 values for CL/F ranging from 0.1 to 6 L/hr. A statistically significant relationship was identified between individual predicted cabozantinib CL/F and the rate of dose modifications. Increased cabozantinib clearance and the corresponding decreased cabozantinib exposure are predicted to decrease the rate of dose modifications e.g. a subject with a cabozantinib clearance of 0.95 L/hr is predicted to have 1.8-fold greater risk of dose modification relative to a subject with a CL/F of 1.95 L/hr.

Table 15: Hazard Ratios for Relative Rate of Dose Modification

Hazard Ratio Relative to CL/F = 0.95 L/hr		
CL/F	**HR**	**95% HR Confidence Limit**
CL/F = 0.95 L/hr	1.00	(1.00, 1.00)
CL/F = 1.95 L/hr	0.55	(0.46, 0.66)
CL/F = 2.95 L/hr	0.39	(0.29, 0.52)
Hazard Ratio Relative to CL/F = 1.95 L/hr		
CL/F	**HR**	**95% HR Confidence Limit**
CL/F = 0.95 L/hr	1.82	(1.52, 2.19)
CL/F = 1.95 L/hr	1.00	(1.00, 1.00)
CL/F = 2.95 L/hr	0.71	(0.64, 0.79)
Hazard Ratio Relative to CL/F = 2.95 L/hr		
CL/F	**HR**	**95% HR Confidence Limit**
CL/F = 0.95 L/hr	2.58	(1.93, 3.45)
CL/F = 1.95 L/hr	1.41	(1.27, 1.57)
CL/F = 2.95 L/hr	1.00	(1.00, 1.00)

Adverse Events

Statistically significant relationships between average cabozantinib concentration and the rate of some adverse events were noted. Increases in average cabozantinib plasma concentrations were associated with increases in the risk of PPES (≥ Grade 1), diarrhoea (≥ Grade 3) and hypertension (SBP > 160 mmHg or DBP > 100 mmHg). The predicted HRs were 3.24 (2.61, 4.02), 1.64 (1.28, 2.10) and 2.16 (1.75, 2.67) for PPES, diarrhoea and hypertension, respectively, based on the predicted steady-state average cabozantinib concentration for a 60 mg dose (1148 ng/mL) relative to a 20 mg dose (383 ng/mL).

Statistically significant treatment effects but not cabozantinib concentration effects were found for fatigue (≥ Grade 3) and ALT/AST elevation (≥ Grade 3). A higher rate of event (2.6 × for fatigue and 1.8 × for ALT/AST elevation) was predicted for cabozantinib compared with placebo treatment.

No significant relationships were found between cabozantinib exposure or treatment and nausea/vomiting (≥ Grade 3) or total bilirubin elevation (≥ Grade 3). However, the frequencies of events for these endpoints were low, 16 for N/V and 17 for total bilirubin elevation from a total of 689 subjects receiving either cabozantinib or placebo.

Repeated Time-to-Event (RTTE) Model for Dose Modifications of Any Kind (DMAK)

A RTTE model was developed to describe DMAK with cabozantinib treatment in HCC subjects. The DMAK model was used to simulate repeated dose modification event times over 12 months. All subjects started at 60 mg in Study XL184-309 so observed data are only reported for the 60 mg starting dose. The model included a baseline hazard and a nonlinear drug effect which was described by an Emax model using daily C_{avg} cabozantinib as the exposure parameter. The EC50 was predicted as 260 ng/mL (90%CI: 170-400 ng/mL), suggesting a high rate of dose modifications for the 60 mg dose with a predicted average exposure of 1148 ng/mL for a typical patient. Adaptive dose simulations predicted the percentage of patients on hold or on 20, 40 or 60 mg after 1, 3, 6 or 12 months of cabozantinib treatment.

The percentages of subjects on each dose were somewhat under-predicted at later times particularly when 'on hold' doses were included. Differences between the observed and simulated datasets may reflect the lack of a drop out model based on PD or death or may indicate that more complexity regarding the dose change model is necessary.

Table 16: Observed and Simulated Percent of Subjects at Doses of 0, 20, 40 or 60 mg/day by Time Using a Starting Dose of Cabozantinib 60 mg or 40 mg

Time (Month)	Dose (mg)	Percent of Subjects					
		60 mg Starting Dose		60 mg Starting Dose		40 mg Starting Dose	
		Observed[a] (%)	Observed[a] (%) Including On Hold Doses	Simulated (%)	Simulated (%) Including On Hold Doses	Simulated (%)	Simulated (%) Including On Hold Doses
1	0		28.1		44.3		43.7
1	20	2.8	2.0	4.0	2.2	9.4	5.3
1	40	23.1	16.6	14.4	8.0	89.2	50.2
1	60	74.2	53.3	81.7	45.5	1.4	0.8
3	0		61.4		70.5		67.7
3	20	13.1	5.1	21.1	6.2	42.2	13.6
3	40	47.6	18.4	39.8	11.7	55.0	17.7
3	60	39.3	15.2	39.1	11.5	2.8	0.9
6	0		56.5		76.8		75.3
6	20	51.5	22.4	44.8	10.4	69.2	17.1
6	40	28.7	12.5	38.8	9.0	29.6	7.3
6	60	19.8	8.6	16.4	3.8	1.2	0.3
12	0		35.6		72.3		71.0
12	20	50.6	32.6	61.2	16.9	75.4	21.8
12	40	27.1	17.4	26.1	7.2	22.5	6.5
12	60	22.4	14.4	12.7	3.5	2.1	0.7

[a] Observed data using last observation carried forward.

2.3.5. Discussion on clinical pharmacology

The applicant updated the previously developed population PK model of cabozantinib in healthy subjects and cancer subjects with data from subjects with HCC from studies XL184-309 and the HCC cohort of XL184-203 RDT. The model predicted exposure parameters (Cmax, Cmin and AUC) appeared comparable across the HCC, RCC and all cancer patients (excluding MTC) groups. The covariates, age, body weight and race did not have significant effect on cabozantinib apparent oral clearance (CL/F), whereas the MTC population had ~ 90% increase in CL/F. Section 4.2 of the SmPC was therefore revised to state that no dose adjustment is necessary based on ethnicity.

Based on an integrated population pharmacokinetic analysis of cabozantinib in healthy subjects and cancer patients (including HCC), no clinically significant difference in the mean cabozantinib plasma exposure was observed amongst subjects with normal liver function (n=1425) and mild hepatic impairment (n=558). Therefore, no dose adjustment is required in patients with mild hepatic impairment.

There is limited data in patients with moderate hepatic impairment (n=15) as per NCI-ODWG (National Cancer Institute – Organ Dysfunction working Group) criteria. No dosing recommendation can be provided. Close monitoring of overall safety is recommended in these patients.

The pharmacokinetics of cabozantinib was not evaluated in patients with severe hepatic impairment (Child Pugh C) so cabozantinib is not recommended for use in these patients (see sections 4.2, 4.4 and 5.2 of the SmPC).

In the exposure response analysis of overall survival, no relationship was identified for OSE and cabozantinib plasma exposure in patients exposed for up to 8 weeks. A statistically significant relationship between individually predicted average cabozantinib concentration and survival in subjects receiving cabozantinib for at least 12 weeks was observed: OSL was improved with increasing cabozantinib plasma exposure. A 60 mg dose showed improvement in OSL and PFS over a modelled 40 mg starting dose. Relative to 60mg dose exposure, the HR at modelled 40mg dose exposure was 1.19. The EC50 and EC80 value for PFS was 500 ng/mL and 2000 ng/mL, respectively. The typical individual predicted steady-state average cabozantinib concentrations for the 60 mg tablet dose is 1148 ng/mL. Most of the cabozantinib exposures are thus expected to be in the steep phase of the dose-effect-hazard curve.

Reduction in average cabozantinib plasma concentrations were associated with reduction in the risk of PPES (≥ Grade 1), diarrhoea (≥ Grade 3) and hypertension (SBP > 160 mmHg or DBP > 100 mmHg). The predicted HRs were 0.66, 0.86, and 0.76 for PPES, diarrhoea and hypertension, respectively, based on the predicted steady-state average cabozantinib concentration for a 40 mg dose relative to a 60 mg dose.

Therefore, from the ER modelling, efficacy increases with the 60mg relative to a hypothetical 40mg starting dose, whilst some AEs are more likely with the increased dose. These AEs can be monitored and managed symptomatically and with dose reductions if required but may cause distress to patients. Diarrhoea can be difficult to manage. PPE and diarrhoea were a cause of treatment discontinuation.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology package is considered acceptable to support the extension of indication to HCC.

2.4. Clinical efficacy

2.4.1. Dose response studies

Dose experience from prior studies conducted in subjects with HCC and other tumour types

The single-agent maximum tolerated dose (MTD) of cabozantinib in the first-in-man study (**XL184-001**) in 85 subjects with advanced malignancies based on the first 28 days of continuous dosing was determined to be 140 mg qd (as capsules) (Kurzrock et al 2011). This dose was used in the pivotal Phase 3 randomized, placebo-controlled Study XL184-301 in subjects with medullary thyroid cancer. However, dose reductions were frequent (79%) and 41% of subjects required a second dose reduction to 60 mg.

The PopPK report for cabozantinib (XL184-308.PopPK.002) showed that subjects with MTC have 93% higher steady state (ss) CL/F than healthy subjects or subjects with other tumour types, including RCC, and thus ~45% lower ss plasma concentrations. A subject with MTC administered a 140 mg dose

would achieve an estimated ss plasma concentrations comparable to that of a ~77 mg dose in a subject with a non-MTC tumour type.

Cabozantinib at an assigned oral dose of 100 mg qd using an earlier development capsule formulation was studied in the nine-cohort Phase 2 randomised discontinuation study of XL184 in subjects with advanced solid tumours: XL184-203 RDT. Over half of the 41 HCC subjects (59%) required at least one dose reduction to 60 mg; however, only 24% required a second dose reduction to 40 mg. The median daily dose for the HCC cohort was 66 mg (the median daily dose for other cohorts containing $\geq$ 40 subjects ranged from 65 to 83 mg) and the median time to first dose reduction was 39.5 days. ss trough level PK exposures obtained in study XL184-203 RDT were consistent across different tumour types including the HCC cohort: geometric mean $C_{through}$ at the end of Week 6 were 781 ng/mL (HCC) and 864-1180 ng/mL (non-HCC).

When the Phase 3 study XL184-309 was initiated, preliminary results from a single-dose Phase 1 Study XL184-003 in non-cancer subjects had shown higher exposure in those with impaired hepatic function compared with normal hepatic function [AUC_{0-inf} increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for AUC_{0-inf}: 121.44% to 270.34% for mild and 107.37% to 246.67% for moderate)]. Based on these results, the estimated median daily exposure to cabozantinib in HCC subjects with mild hepatic impairment (Child-Pugh A) dosed at 60 mg was comparable to a 95 mg dose (60 mg × 159%) in non-hepatically impaired subjects. This was equal to or slightly lower than exposures associated with the assigned dose in Study XL184-203 RDT (100 mg) or the adjusted median daily in the HCC subjects (105 mg = 66 mg × 159%).

Clinical activity at a cabozantinib starting dose of 60 mg or lower had been observed in other indications with acceptable tolerability: at 20 and 40 mg in subjects with castration-recurrent prostate cancer (Lee et al 2013), although the lower dose of 20 mg was less active, and at 40 mg and 60 mg in subjects with non-small cell lung cancer (Nokihara et al 2015).

Based on these data, 60-mg/day dose was selected as the dose in Study XL184-309 because it was expected to provide increased tolerability, relative to the previously studied 100-mg dose, while maintaining efficacy in subjects with advanced HCC and providing an adequate safety margin for the expected increase in exposure in subjects with mild hepatic impairment compared with subjects with normal hepatic function.

Dose experience in subjects with HCC in Phase 3 Study XL184-309 (60mg tablet QD)

- 62% of cabozantinib-treated subjects had a dose reduction and 84% had a dose interruption due to an AE.
- Median average daily cabozantinib dose was 36 mg.
- Median time to first dose reduction (to 40 mg) and second dose reduction (to 20 mg) was 38 and 83 days, respectively.
- Most frequent last non-zero dose level (excluding dose interruptions) was equally split between the 60 mg, 40 mg, and 20 mg dose levels (39%, 28%, and 33% of subjects, respectively).
- Median time on the cabozantinib arm at the 60 mg, 40 mg, and 20 mg dose was 28 days, 33 days and 73 days, respectively.

In study XL184-308 (advanced RCC) using the same dose and formulation:

- 60% of cabozantinib-treated subjects had a dose reduction and 63% had a dose interruption due to an AE.
- Median average daily cabozantinib dose was 45 mg.
- Median time to first dose reduction (to 40 mg) and second dose reduction (to 20 mg) was 55 and 93 days, respectively.

- Most frequent last non-zero dose level (excluding dose interruptions) was 60 mg (43% of subjects) with the 40 mg and 20 mg dose levels received by 40% and 17% of subjects, respectively.
- Median time on the cabozantinib arm at the 60 mg, 40 mg, and 20 mg dose was 73 days, 83.5 days, and 117 days, respectively.

Observed cabozantinib ss exposures in Child-Pugh A hepatically impaired HCC subjects (XL184-309) were unexpectedly not higher than in non-hepatically impaired RCC subjects (XL184-308). The PopPK analysis updated to evaluate PK of cabozantinib in patients with HCC showed that HCC and RCC subjects receiving a 60 mg daily cabozantinib dose appeared to have similar CL/F and s-s exposure (AUC). Furthermore, covariates related to liver function were shown not to have a significant impact on cabozantinib PK (XL184-309.PopPK.001).

2.4.2. Main study

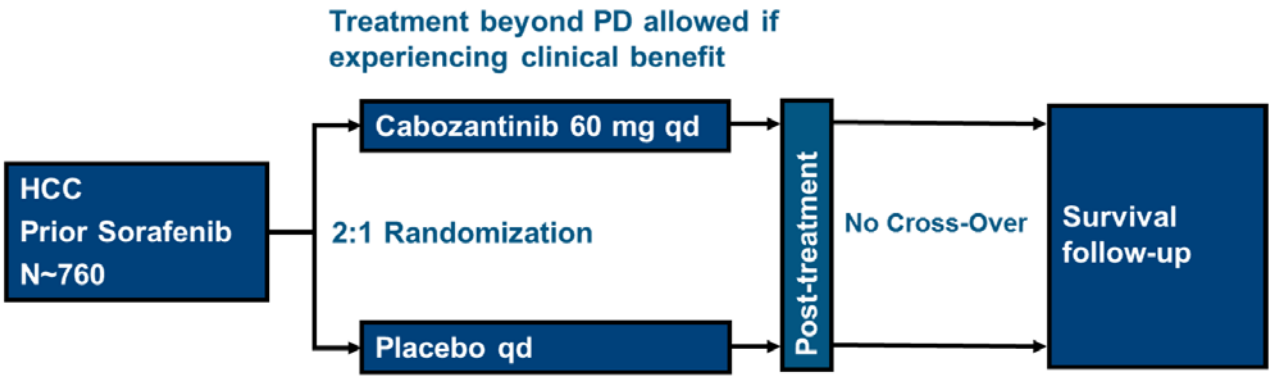
XL184-309: CELESTIAL. A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

Methods

This was a Phase 3 multi-centre, randomized, double-blind, placebo-controlled study of cabozantinib in subjects with HCC who had received prior sorafenib. At the time of study inception, there were no approved systemic therapies for the treatment of advanced HCC following sorafenib treatment.

PPD (Wilmington, NC) was the contract research organization for this study and was responsible for clinical conduct, monitoring, data management, biostatistical analysis, PK data analysis and medical writing in conjunction with Exelixis.

Study design



Study participants

The inclusion and exclusion criteria are from Protocol Amendment 2.0. The Sponsor did not grant waivers to study eligibility criteria.

Inclusion Criteria

1. Histological or cytological diagnosis of HCC (previous biopsy results were accepted)

2. Disease not amenable to a curative treatment approach (e.g. transplant, surgery, radiofrequency ablation)

3. Received prior sorafenib

4. Progression following at least 1 prior systemic treatment for HCC

5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the AEs were clinically nonsignificant and/or stable on supportive therapy

6. Age ≥ 18 years old on the day of consent

7. ECOG performance status of 0 or 1

8. Adequate haematologic function within 7 days before randomization:

- Absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 × 10^9/L)

- Platelets ≥ 60,000/mm^3 (≥ 60 × 10^9/L)

- Haemoglobin ≥ 8 g/dL (≥ 80 g/L)

9. Adequate renal function within 7 days before randomization:

- Serum creatinine ≤ 1.5 X upper limit of normal (ULN) or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation AND

- Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g

10. Child-Pugh Score of A

11. Within 7 days before randomization:

- Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L)

- Serum albumin ≥ 2.8 g/dL (≥ 28 g/L)

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 × ULN

14. Haemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results unavailable [e.g. haemoglobin variant] fasting serum glucose ≤ 160 mg/dL)

15. Antiviral therapy per local standard of care if active HBV infection

16. Sexually active fertile subjects and their partners must have agreed to use medically accepted methods of contraception (e.g. barrier methods) during the study and for 4 months after the last dose of study treatment

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

Exclusion criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma

2. Receipt of > 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy were allowed.

3. Any anticancer agent (including investigational) within 2 weeks before randomization.

4. Radiation therapy within 4 weeks (2 weeks for radiation to bone metastases) or radionuclide treatment (e.g. I-131 or Y-90) within 6 weeks of randomization

5. Prior cabozantinib treatment

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

7. Concomitant anticoagulation, at therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (e.g. clopidogrel). Low dose aspirin for cardioprotection, low-dose warfarin (≤ 1 mg/day), and low-dose LMWH were permitted.

8. Uncontrolled, significant intercurrent or recent illness including, but not limited to:

a. Cardiovascular disorders including:

- Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias

- Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment

- Stroke (including transient ischemic attack), myocardial infarction or other ischemic event within 6 months before randomization

- Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumour were eligible

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

- Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g. Crohn's), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

- Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization (complete healing of an intra-abdominal abscess must have been confirmed)

c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (e.g. simple excision, tooth extraction) must have occurred at least 7 days before randomisation

d. Cavitating pulmonary lesion(s) or endobronchial disease

e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery or aorta. Subjects with lesions invading the portal vasculature were eligible.

f. Clinically significant bleeding risk within 3 months of randomization including: haematuria, haematemesis, haemoptysis of > 2.5 mL of red blood or other signs indicative of pulmonary haemorrhage or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

- Active infection requiring systemic treatment, known HIV infection or AIDS-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy were eligible.

- Serious non-healing wound/ulcer/bone fracture

- Malabsorption syndrome

- Uncompensated/symptomatic hypothyroidism

- Requirement for haemodialysis or peritoneal dialysis

- History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry were eligible.

10. Moderate or severe ascites

11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

12. Inability to swallow tablets

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

14. Pregnant or lactating females

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

Treatments

Eligible subjects received oral cabozantinib 60mg qd or matched placebo. Subjects were instructed to take blinded study drug once daily, orally at bedtime, after a 2 hour fast (except for water) and to have no food for at least 1 hour after dosing. Study sites were supplied with cabozantinib as 60-mg and 20-mg yellow film-coated tablets. Placebo tablets were supplied to match the 20mg and 60mg cabozantinib tablets.

Subjects continued blinded study treatment whilst they experienced clinical benefit in the opinion of the Investigator (even after disease progression per RECIST 1.1), or until unacceptable toxicity, the need for subsequent systemic anticancer therapy or liver-directed local anticancer therapy, or other reasons for treatment discontinuation. Crossover between treatment arms was not allowed during the blinded treatment phase.

If one of the planned analyses showed statistically significant and clinically meaningful evidence of improved OS, the study could transition to an Open-Label Phase as decided by the Sponsor in discussion with regulatory authorities. Upon transitioning to the Open-Label Phase, the study was to be unblinded and subjects who were randomized to the placebo arm would have the option to crossover to receive treatment with cabozantinib provided they met the eligibility criteria. Data from the Open-Label Phase were not included in the CSR.

Two dose reductions, in decrements of 20 mg cabozantinib or matched placebo, were permitted to manage or prevent worsening of an AE or toxicity.

Dose Modification Criteria[a]

Toxicity Criteria	Recommended Guidelines for Management
Grade 1 AEs	Study treatment continued if AE tolerated
Grade 2 AEs which were intolerable and could not be adequately managed	At the discretion of the Investigator, study treatment dose reduced or interrupted. Note: dose interruptions should be as brief as possible.
Grade 3 (except clinically non-relevant laboratory abnormalities)	Study treatment interrupted unless toxicity easily managed with dose reduction and optimal medical care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Study treatment interrupted immediately and discontinued unless the following criteria were met: Subject deriving clear clinical benefit as determined by the Investigator and agreed by the Sponsor Toxicity managed with a dose reduction (40mg then 20mg) following recovery to Grade 1 (or baseline) and optimal medical care

[a] Study treatment dose adjustment was only needed if the toxicity was deemed related to study treatment or had an unclear relationship to study treatment.

Subjects could be re-escalated to the previous dose (but not higher than 60 mg/day) at the discretion of the Investigator, with agreement of the Sponsor, for AEs resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. All study treatment had to be discontinued if a once-daily dose of 20 mg cabozantinib/matched placebo was not tolerated. Guidelines for management and prevention of GI, hepatobiliary, blood system,

constitutional, skin, hypertension, thromboembolic events, proteinuria, QT prolongation, haemorrhagic events, GI perforation/fistula, non-GI fistula formation and osteonecrosis of the jaw were provided in the protocol.

Prophylactic antiemetics and anti-diarrhoeal medications were allowed in accordance with standard clinical practice if required. GCSF was acceptable but not to be administered prophylactically before initial treatment with study drug. Erythropoietic-stimulating agents (e.g. epoetin alfa and darbepoetin alfa) were not to be used. Hormone replacement and short-term systemic steroids could be utilized as indicated by standard clinical practice.

Co-administration of strong CYP3A4 inducers or inhibitors was to be avoided, per the current SmPC.

Therapeutic doses of heparins were allowed after randomization if clinically indicated and the benefit outweighed the risk per the Investigator's discretion. Therapeutic doses of oral anticoagulants (e.g. warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel) were not allowed.

Any herbal product used for the treatment of HCC was prohibited. If a subject required additional liver-directed local anticancer therapy, study treatment must have been discontinued. Palliative external beam radiotherapy to bone or skin/subcutaneous metastases was allowed but discouraged unless medically unavoidable.

Objectives

The study objective was to evaluate the effect of cabozantinib compared with placebo— both in the setting of BSC—on overall survival in subjects with previously treated advanced HCC.

Outcomes / endpoints

Primary efficacy endpoint:

- Overall survival (OS)

Secondary efficacy endpoints:

- Objective response rate (ORR)
- Progression-free survival (PFS)

Additional endpoints:

- Safety and tolerability of cabozantinib
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome
- Health-related quality of life (HRQoL)
- Pharmacokinetics (PK)

Duration of OS was defined as the time from randomization to death due to any cause.

ORR was defined as the proportion of subjects experiencing a complete response (CR) or partial response (PR) as determined by the Investigator using RECIST 1.1.

Duration of PFS was defined as the time from randomization to the earlier of the following events: radiographic progressive disease (PD) as determined by the Investigator per RECIST 1.1 or death due to any cause. Clinical deterioration was not an event for the primary analysis.

CT/MRI assessments were performed at screening, 8 weeks after randomization (W9D1) and every 8 weeks thereafter. Disease status was determined at the local site (i.e. investigator and/or radiologist) using RECIST version 1.1. The same imaging modalities used at screening were used for subsequent tumour assessments. Scan assessments continued per this schedule irrespective of whether study treatment was reduced, interrupted or discontinued, until the latter of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the Investigator or the date of the decision to permanently discontinue study treatment.

For the liver evaluation a non-contrast followed by a triphasic (arterial, portal and delayed venous) post-contrast CT study or a liver MRI with gadolinium imaging was obtained. MRI of the brain was acquired at screening if clinically indicated and post-baseline only if documented brain metastases or suspicion of brain metastasis on study. All subjects were to have a bone scan at screening. Follow-up bone scans were to be performed at 8 and 16 weeks after randomization, and every 16 weeks thereafter only for subjects with documented bone lesions on the screening bone scan or suspicion of bone metastases on study. Time point progression could be based solely on bone scans if there was unequivocal evidence of new bone scan lesions; increases in bone scan lesions present at baseline could not be used for the determination of progression per RECIST 1.1.

For the EuroQol questionnaire (EQ-5D-5L), subjects were to assess the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The options for each were: no problems, slight problems, moderate problems, severe problems or unable to/extreme problems. Then on a visual analogue scale (VAS), subjects were to quantitate their health between 100 (“best health you can imagine”) and 0 (“worst health you can imagine”). Subjects were given the questionnaire at baseline (W1D1), every 4 weeks until Week 25 and then every 8 weeks until the latter of 8 weeks after Investigator- determined radiographic progression per RECIST 1.1 or the date of the decision to permanently discontinue study treatment.

A blood sample for determination of serum AFP was obtained at the time of each radiographic (CT/MRI) disease assessment visit. Samples were analysed by a central laboratory; the results were not provided to the Investigator until the decision had been made to discontinue study treatment.

Assessment of plasma biomarkers by multiplexed array included target receptors and ligands (e.g. VEGF-A, HGF, soluble VEGFR2 and MET). These exploratory analyses were not reported. Circulating tumour cell (CTC) samples were collected at selected sites and exploratory analyses may be performed if adequate sample is available. Tumour tissue (archival or recently biopsied) was obtained at enrolment when available. An exploratory analysis for MET tumour expression was performed.

Sample size

A sample size of 760 subjects with a total of 621 events (and 2 interim analyses) provides the study with 90% power for a two-sided log-rank test at the 5% level of significance to detect a 31.6% increase in OS (HR = 0.76).

Assuming a median OS of 8.2 months in the placebo arm (based upon the BRISK trial; Llovet et al 2013) and exponential distribution, this corresponds to median OS of 10.8 months in the cabozantinib arm. For the primary OS endpoint, the minimum observed effect that would result in statistical significance at the two interim analyses and the final analysis are 42.1% improvement (HR = 0.70, from 8.2 to 11.7 months), 25.7% improvement (HR = 0.80, from 8.2 to 10.3 months) and 18.4% improvement (HR = 0.84, from 8.2 to 9.7 months), respectively.

Randomisation

Eligible subjects were randomised by an IxRS in a 2:1 fashion to receive cabozantinib or matched placebo. Randomisation was stratified by the following:

- Disease aetiology (HBV [with or without HCV], HCV [without HBV], Other)
- Geographic region (Asia, Other)
- Extrahepatic disease spread and/ or microvascular invasion (Yes, No)

Blinding (masking)

This was a double-blind study. Placebo was indistinguishable from cabozantinib. Study treatment assignment was unknown to the subjects, investigators, study centres, Sponsor (other than those authorized access to treatment assignment for IxRS or drug supply management) and any affiliated contract research organization. No individual subjects were unblinded prior to the data cut-off date.

An Independent Data Monitoring Committee (IDMC) monitored unblinded safety data to protect subject welfare and to provide recommendations regarding study conduct.

Statistical methods

Analysis populations

The Intent-to-Treat (ITT) population consisted of all randomized subjects regardless of whether any study treatment or the correct study treatment was received. The ITT population was used for efficacy analyses.

The Safety population consisted of all randomized subjects who received any amount of study treatment (either cabozantinib or cabozantinib-matched placebo). Analyses based on the Safety population were performed according to the actual treatment received. Subjects randomized to placebo who received any amount of cabozantinib in error were summarized in the cabozantinib group.

Analysis of the primary endpoint

The primary efficacy endpoint was OS. The primary analysis population was the ITT population. Duration of OS was defined as the time from randomization to death due to any cause. For subjects who were permanently lost to follow-up and not known to have died at the time of data cut-off, duration of OS was right censored at the date the subject was last known to be alive. Those who withdrew consent from follow-up and were alive were right censored at the date the subject withdrew consent from follow-up. Subjects alive on or after the data cut-off or those who died after the data cut-off were right censored at the date of data cut-off.

Hypothesis testing between the two treatment arms was performed using the stratified log-rank test. The stratification factors were the same as those used to stratify the randomisation.

The median duration of OS and the associated 95% CI for each treatment arm was estimated using the Kaplan-Meier method. The stratified HR and its 95% CI were estimated using a Cox proportional-hazard model with treatment arm as the independent variable and stratified by the same randomization stratification factors as were used for the log-rank test.

Interim analyses

Up to 3 OS analyses were planned: 2 interim analyses and a final analysis occurring when approximately 311, 466, and 621 deaths (i.e. ~ 50%, 75% and 100% of the required number of deaths) had been observed. To preserve the overall type I error of the study at 2-sided 0.05, a Lan-DeMets O'Brien- Fleming alpha-spending function was used. If exactly the planned number of events were seen at each analysis the critical p-values for rejecting the null hypothesis at each analysis were 0.0031, 0.0183 and 0.044, respectively. The actual critical values depended upon the true number of events observed at each analysis.

Results of interim analyses were evaluated by the IDMC to allow the trial to be stopped early if the null hypothesis for OS was rejected in favour of cabozantinib. Formal futility analyses were not planned.

Analysis of secondary endpoints

Progression-Free survival per investigator

Duration of PFS was defined as the time from randomization to the earlier of the following events: progressive disease (PD) or death due to any cause.

The hypothesis testing of PFS between the two treatment arms occurred only if the result of either an interim or the final OS analysis achieved statistical significance. Hypothesis testing was performed using the stratified log-rank test at the two-sided α =0.04 level of significance. The stratification factors were the same as those used for the primary analysis.

The median duration of PFS and the associated 95% CI for each treatment arm were estimated using the Kaplan-Meier method. The HR was estimated using a Cox regression model and included the same stratification factors noted for the log-rank test.

General censoring rules for the primary analysis of PFS were as follows:

- Subjects who received systemic or liver directed local NPACT, non-protocol radiation therapy (other than to bone), or surgery to resect tumour lesions before experiencing an event were right censored at the date of the last ATA on or prior to the date of initiation of subsequent therapy/surgery.
- Subjects who had not experienced an event (and were not otherwise censored) at the time of data cut-off were right censored on the date of their last tumour assessment after randomization that was on or prior to the data cut-off.
- Subjects missing two or more ATAs (defined as 126 days without an ATA) followed by an event (progression or death) were right censored on the date of their most recent ATA prior to the missing assessments.

If there were no such tumour assessment after randomization, the subjects were right censored on the date of randomization.

Two sensitivity analyses of PFS (PFS 2 and PFS 3) were defined in the SAP.

For PFS2 analysis, the following were considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Treatment discontinuation due to clinical deterioration
- Receipt of systemic NPACT/ local liver-directed NPACT/ radiation (other than to bone)/ surgery to resect tumour lesions

For PFS3 analysis, the following were considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Treatment discontinuation due to clinical deterioration

Objective Response Rate per Investigator

The ORR was defined as the proportion of subjects experiencing a CR or PR, confirmed ≥28 days after the response was first observed, as determined by the Investigator using RECIST 1.1.

The hypothesis testing of ORR between the two treatment arms occurred only if the result of either an interim or final OS analysis achieved statistical significance. Hypothesis testing per IxRS was performed using Fisher's exact test at the two-sided α =0.01 level of significance.

Adjustment for multiplicity

Up to three event-driven analyses of OS were planned as follows: two interim analyses and a final analysis. Inflation of Type 1 error associated with interim analyses was controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

Testing of the secondary endpoints of PFS and ORR occurred only if the result of either an interim analysis or the final analysis of OS achieved statistical significance. The hypotheses for PFS and ORR were tested in parallel. PFS was tested at the two-sided α=0.04 level of significance and ORR was tested at the two-sided α=0.01 level of significance.

All other statistical evaluations of efficacy were descriptive.

Subgroup analyses

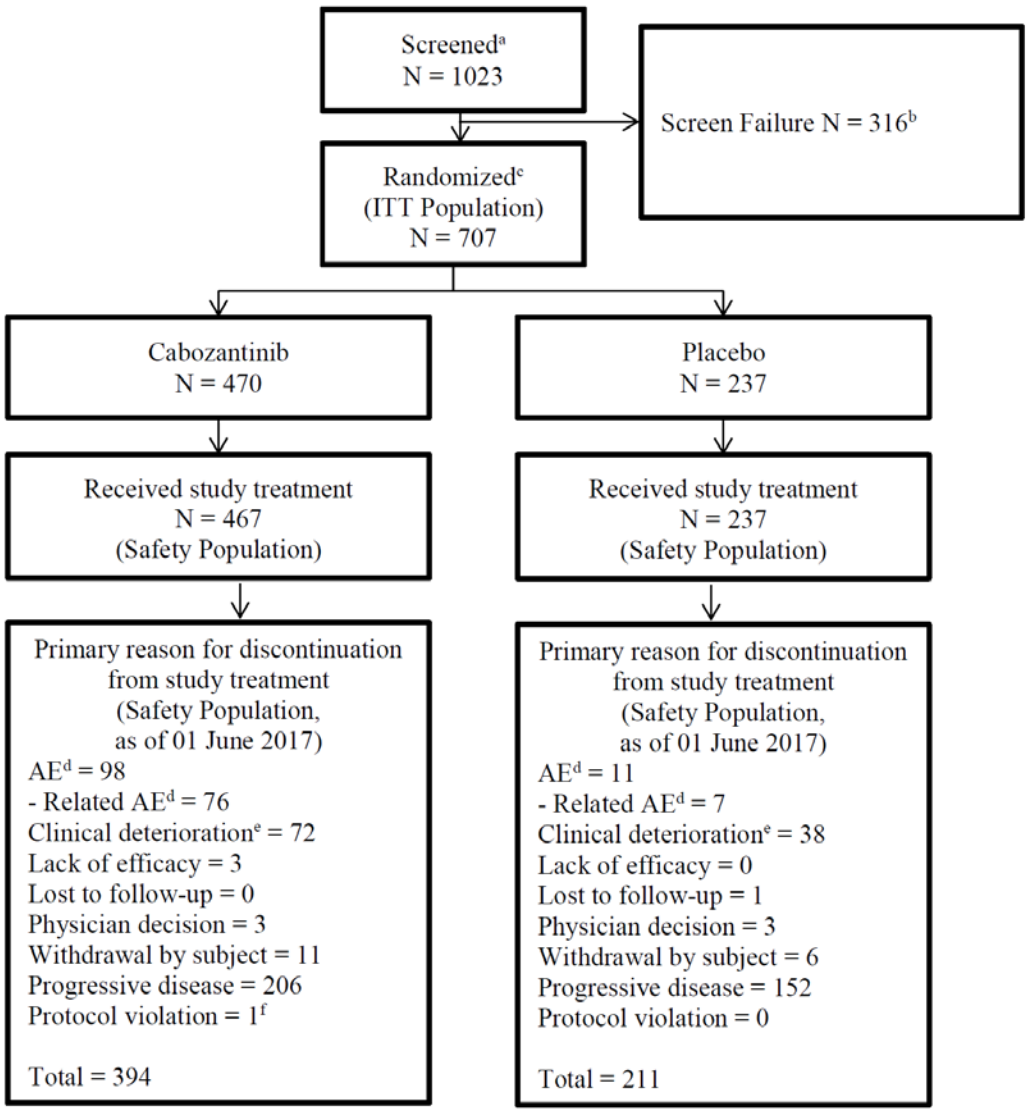
Exploratory analyses of OS, PFS, and ORR were conducted to explore the effect in subgroups defined by baseline characteristics. These comprised:

- Age (<65 years, 65 to <75 years, 75 to <85 years, ≥85 years)
- Sex (Male, Female)
- Race (Asian, Black or African American, White, Rest of the races reported/not reported)
- Geographic Regions 1 (Asia [excluding Japan], Europe/Australia/New Zealand, North America, Other)
- Geographic Regions 2 (Asia, Other)
- ECOG Performance status at baseline (0, 1, Missing)
- Aetiology of disease per stratification factors per IxRS (HBV [with or without HCV], HCV [without HBV], Other)
- Current aetiology of disease per cancer history CRF (HBV [without HCV], HCV [without HBV], HBV and HCV, Alcoholism, Non-alcoholic Steatohepatitis [NASH], Other [each = Yes/No/Unk])
- Presence of extrahepatic spread of disease and/or macrovascular invasion per IxRS (Yes, No)
- Presence of extrahepatic spread of disease and/or macrovascular invasion per cancer history CRF (Yes, No)

- Visceral sites other than liver, bone, bone + visceral sites other than liver per tumour assessment CRFs per Investigator. Visceral sites other than liver were based upon a manual review of the reported sites after all data has been entered in the database.
- Prior systemic non-radiation anti-cancer therapy regimens for advanced HCC per subject per history of non-radiation anti-cancer therapy CRF (1 vs ≥ 2)
- Prior receipt of PD-1/PD-L1 (Yes, No)
- Prior receipt of Regorafenib (Yes, No)
- Prior receipt of Lenvatinib (Yes, No)
- Prior receipt of Tivantinib (Yes, No)
- Prior receipt of Ramucirumab (Yes, No)
- VEGF-A amplification in circulating tumour cells (Yes, No, Unknown)
- AFP at baseline (<400 ng/mL, ≥ 400 ng/L)
- Tumour MET status (High Low or Negative Unknown)

Results

Participant flow



Disposition was similar in the ITT and Safety Populations. Three patients in the ITT population were randomised to cabozantinib but no study treatment was given. An explanation to why these patients did not receive treatment has not been provided.

Table 17: **Subject Disposition (ITT Population)**

	Cabozantinib (N=470) n (%)	**Placebo (N=237) n (%)**
Received study treatment	467 (99)	237 (100)
Discontinued study treatment No study treatment given	397 (84) 3 (0.6)	211 (89) 0
Discontinued study follow-up Death Withdrawal by subject	322 (69) 314 (67) 8 (2)	171 (72) 166 (70) 5 (2)

A total of 704 subjects received study treatment (Safety population): 467 subjects in the cabozantinib arm and 237 subjects in the placebo arm.

A total of 605 subjects in the Safety population discontinued study treatment as of the data cut-off date of 01 June 2017: 394 subjects (84%) in the cabozantinib arm and 211 subjects (89%) in the placebo arm. There was a higher rate of treatment discontinuation due to AEs in the cabozantinib arm (cabozantinib 21% vs placebo 5%), including AEs related to study treatment (16% vs 3%). Conversely, there was a higher rate of disease progression in the placebo arm (cabozantinib 44% vs placebo 64%). Other reasons had a similar incidence in each arm.

A total of 316 subjects failed screening as of the 01 June 2017 cut-off date. The main reasons were albumin too low or liver test too high or lymphopenia (n=50), Child-Pugh score B7 (or higher) (n = 46) and "other" (n= 170).

An additional 21 subjects were in screening with eligibility still pending at the cut-off date.

Table 18: **Reasons for Screen Failure (total to 1 June 2017 n=316)**

Reason	n
Albumin too low or liver tests too high or lymphopenia	50
Child-Pugh score B 7 (or higher)	46
Poor Performance Status	19
No biopsy/tissue diagnosis of HCC and unwilling to undergo biopsy	13
On anti-coagulants or clotting/bleeding risk	8
GI disorders including risk of perforation, fistula, or abscess formation	4
Varices fail to meet requirements [a]	3
Prior organ transplant	2
Receipt of > 2 systemic therapies for advanced HCC and/or no prior sorafenib	1
Other [b]	170

[a] Subjects treated with adequate endoscopic therapy without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry were eligible.
[b] Included one subject whose reason for screen failure was left blank. The IxRS database did not collect further details for screen fail reasons categorized as 'Other'.

Recruitment

At the 01 June 2017 cut-off date for the second planned interim OS analysis, a total of 707 subjects were randomized to receive study treatment (ITT population), 470 subjects in the cabozantinib arm and 237 subjects in the placebo arm. The study has subsequently been fully enrolled (773 subjects by 18 September 2017, planned total 760) and closed to enrolment.

Of the 707 subjects enrolled in the study by the cut- off date, 25% in each arm were enrolled in Asia and 75% in Other Regions (North America, Europe and Australia/New Zealand). Enrolment by region and by country was well balanced between treatment arms.

Conduct of the study

- **Protocol amendments**

The original protocol, dated 12 March 2013, was amended twice.

Amendment 1.0, dated 23 April 2014, introduced the following substantive changes:

Clarified three inclusion criteria:

- 1 - subjects without prior histological or cytological diagnosis of HCC required a biopsy
- 12- lower limit of serum albumin was 2.8 g/dL
- 14 - HbA1c testing window was extended to 28 days prior to randomization

Clarified four exclusion criteria:

- 8b(i) - subjects with Crohn's disease excluded
- 8e- subjects with disease invading the inferior vena cava excluded
- 8g(i) - subjects with active hepatitis infection controlled with antiviral therapy eligible
- 9 - subjects with history of variceal bleeding treated with adequate endoscopic therapy eligible

Added additional post-screening Child-Pugh testing time points

Added QT prolongation to the list of potential cabozantinib AEs requiring management and added information regarding use of drugs known to prolong QT

Specified that all subjects were to have hepatitis virus testing via central laboratory prior to enrolment but the results were not required for randomization

Introduced the Maintenance Phase, which subjects were to enter when sufficient data had been collected to evaluate all study endpoints

Amendment 2.0, dated 12 July 2016, had the following substantive changes:

Introduced the Open-Label Phase so that, following demonstration of statistically significant and clinically meaningful improvement in OS by cabozantinib, subjects in the placebo arm who met specific eligibility criteria could crossover to receive cabozantinib. Subjects randomized to the cabozantinib arm who were still receiving study treatment, and subjects randomized to the placebo arm who were still receiving study treatment and did not crossover to cabozantinib, could continue unblinded study treatment. The Sponsor would only implement the Open-Label Phase following review of the data and discussion with regulatory agencies.

Collection of healthcare resource utilization data (hospitalizations, intensive care unit and emergency department visits) for all reported SAEs. Thus, data would be assessed retrospectively in most cases.

Table 19: **Subject Enrolment by Protocol Amendment (ITT Population)**

	Cabozantinib (N=470) n (%)	**Placebo (N=237) n (%)**
Original Protocol Amendment 1 Amendment 2	126 (27) 311 (66) 33 (7)	71 (30) 150 (63) 16 (7)

- **Protocol deviations**

Protocol deviations recorded at the site that could have potentially impacted safety or efficacy were categorized based on ICH E3 guidelines.

Summary of Protocol Deviations

	Cabozantinib N=470 n (%)	**Placebo N=237 n (%)**
Failed ≥1 eligibility criteria ≥ 1 inclusion criterion ≥ 1 exclusion criterion	24 (5.1) 12 (2.6) 12 (2.6)	11 (4.6) 3 (1.3) 9 (3.8)
Prohibited medication [a] Randomisation irregularity Treatment deviation Other	1 (0.2) 45 (9.6) 13 (2.8) 61 (13)	0 21 (8.9) 2 (0.8) 22 (9.3)

[a] In addition, ticlopidine for ongoing treatment of vasculopathy and of thrombectomy (right internal carotid artery) was initially approved placebo arm). Upon review this medication was considered not to be permitted.

Eligibility criteria deviations were balanced between the cabozantinib and placebo arms: 24 (5.1%) and 11 subjects (4.6%), respectively, failed to meet at least one eligibility criterion. The most frequent inclusion criteria deviation was not meeting the requirement for a Child-Pugh score of A (6 [1.3%] and 1 [0.4%] subjects, respectively). One subject each arm did not have a histological/cytological diagnosis of HCC; both had baseline liver lesions, extrahepatic spread and macrovascular invasion. The most frequent exclusion criteria deviation was failure to meet the restrictions against use of concomitant anticoagulants (5 [1.1%] and 5 [2.1%] subjects respectively).

Review of on-study deviations suggested that they did not have a notable impact on study safety or efficacy. Important on-study protocol deviations were balanced between the cabozantinib and placebo treatment arms. Randomization irregularity was most frequent, including stratification errors by incorrect assignment of the disease aetiology and/or the presence of extrahepatic spread of disease and/or macrovascular invasion as reported in IxRS compared with CRF.

Important protocol deviations categorized as 'Other' that could have potentially impacted safety included revised ICF not signed by subject and ECGs not obtained per protocol or not reported to the independent central review vendor (ERT) in a timely manner or at all. Deviations categorized as 'Other' that potentially impacted efficacy included tumour imaging not obtained per protocol.

- **Changes to the planned analysis**

The original SAP (version 1.0) was dated 2 November 2015. Revisions to create the final SAP (version 2.0) were stated to occur before database lock and unblinding. Key changes included:

- Statistical tests of efficacy to be performed using IxRS stratification factors instead of stratification factors based on CRF
- Per protocol population deleted, as analyses by ITT population were deemed more robust
- Progression updated to accept new lesions identified on bone scan as evidence of progression consistent with the protocol. Adequate tumour assessments to include unscheduled assessments.
- PFS sensitivity analyses (PFS2 and PFS3) refined to exclude treatment discontinuation due to AEs

Table 20: **Summary of Differences in Stratification Factors per IxRS vs per CRF (ITT Population)**

	Cabozantinib (N = 470)		Placebo (N = 237)	
	n (%)		n (%)	
Stratification Factor	IxRS not CRF	CRF not IxRS	IxRS not CRF	CRF not IxRS
Etiology				
HBV [with or without HCV]	6 (1.3)	0	3 (1.3)	2 (0.8)
HCV [without HBV]	0	NA	0	NA
Presence of EHS and/or MVI	3 (0.6)	31 (6.6)	1 (0.2)	15 (6.3)

Treatment compliance

A similar proportion of subjects in the cabozantinib arm (99 subjects [21%]) and placebo arm (38 subjects [16%]) had their dose interrupted for reasons other than an AE. The primary reason was subject non-compliance (cabozantinib 16%, placebo 8.9%). Only one subject (cabozantinib arm) had an overdose (took 120mg on Days 2 and 6). No subjects received the wrong study treatment.

Baseline data

Table 21: **Baseline Demographic Characteristics (ITT Population)**

Subject Characteristic	**Cabozantinib (N = 470)**	**Placebo (N = 237)**
Age (years)		
Median (range)	64.0 (22, 86)	64.0 (24, 86)
< 65, n (%)	240 (51)	124 (52)
≥ 65, n (%)	230 (49)	113 (48)
65 to < 75	158 (34)	75 (32)
75 to < 85	67 (14)	35 (15)
≥ 85	5 (1)	3 (1)
Sex, n (%)		
Male	379 (81)	202 (85)
Female	91 (19)	35 (15)
Race, n (%)		
Asian	159 (34)	82 (35)
Black/African-American	8 (2)	11 (5)
White	264 (56)	130 (55)
Other	8 (1.6)	2 (0.8)
Not Reported	31 (7)	12 (5)
Geographic region, n (%)		
Australia/New Zealand	15 (3)	11 (5)
Asia	116 (25)	59 (25)
Europe	231 (49)	108 (46)
North America (USA/Canada)	108 (23)	59 (25)
Region (stratification factor per IxRS), n (%)		
Asia	116 (25)	59 (25)
Other Regions	354 (75)	178 (75)
Extrahepatic spread of disease and/or macrovascular invasion (stratification factor per IxRS), n (%)		
Yes	368 (78)	186 (78)
No	102 (22)	51 (22)
Disease aetiology (stratification factor per IxRS), n (%)		
HBV (with or without known HCV)	182 (39)	90 (38)
HCV (without known HBV)	100 (21)	51 (22)
Other (neither HBV nor HCV)	188 (40)	96 (41)
ECOG PS, n (%)		
0	245 (52)	131 (55)
1	224 (48)	106 (45)
2[a]	1 (0.2)	0
Smoking history, n (%)		
Current	78 (17)	42 (18)
Former	229 (49)	122 (51)
Never	160 (34)	71 (30)
Missing	3 (0.6)	2 (0.8)
Alcohol use, n (%)		
Current	65 (14)	30 (13)
Former	223 (47)	124 (52)
Never	176 (37)	81 (34)
Missing	6 (1)	2 (0.8)
Weight, median (range) (kg)	69.0 (35, 130)	71.5 (41, 125)

[a] One subject in the cabozantinib arm enrolled with a baseline ECOG PS of 2. Subject had an ECOG PS of 1 at screening.

Table 22: Baseline Disease History per Investigator/ per CRF (ITT Population)

Subject Characteristic	**Cabozantinib (N = 470)**	**Placebo (N = 237)**
Diagnosis of HCC by histology or cytology (Yes), n (%)	469 (>99) [a]	236 (>99) [a]
Current Aetiology (per CRF), n (%)[b]		
Hepatitis B (without Hepatitis C)	168 (36)	85 (36)
Hepatitis C (without Hepatitis B)	105 (22)	51 (22)
Hepatitis B and C	8 (2)	4 (2)
Hepatitis B (regardless of Hepatitis C)	178 (38)[c]	89 (38)
Hepatitis C (regardless of Hepatitis B)	113 (24)	55 (23)
Alcoholism	112 (24)	39 (16)

Non-alcoholic steatohepatitis (NASH)	43 (9)	23 (10)
Other [d]	99 (21)	63 (27)
Child-Pugh Grade (per CRF), n (%)		
A (score 5-6)	462 (98)	235 (99)
B (score 7-9)	7 (1)	2 (0.8)
Missing	1 (0.2)	0
Hepatic encephalopathy, n (%)		
None	467 (99)	236 (100)
Grade 1 or 2	3 (0.6)	1 (0.4)
Grade 3 or 4	0	0
Ascites, n (%)		
Absent	441 (94)	222 (94)
Slight	29 (6)	15 (6)
Time from histological/cytological diagnosis to randomization, (years)		
Median (range)	1.451 (0.02, 21.92)	1.331 (0.03, 17.40)
Current locally advanced disease [e] (per CRF), n (%)	298 (63)	176 (74)
Current metastatic disease (per CRF), n (%)	369 (79)	182 (77)
Current measurable disease per CT/MRI per Investigator, n (%)	465 (99)	237 (100)
Baseline HCC disease per CRF, n (%)[b]		
Portal vein invasion	100 (21)	66 (28)
Bile duct invasion	10 (2)	14 (6)
Macrovascular invasion	129 (27)	81 (34)
Extrahepatic spread	369 (79)	182 (77)
Other	5 (1)	2 (0.8)
Baseline disease per tumour assessment (≥ 2% in either arm), n (%)[b]		
Liver	395 (84)	216 (91)
Bone	60 (13)	34 (14)
Visceral (excluding liver)	215 (46)	105 (44)
Lung	184 (39)	91 (38)
Adrenal gland	51 (11)	24 (10)
Lymph node	155 (33)	71 (30)
Number of anatomic sites (including liver) per Investigator, n (%)[f]		
1	144 (31)	72 (30)
2	172 (37)	91 (38)
≥3	154 (33)	74 (31)
Tumour MET immunohistochemistry status, n (%)[g]		
High	33 (7)	15 (6)
Low/Negative	144 (31)	68 (29)
Unknown	11 (2)	4 (2)
Missing	282 (60)	150 (63)
AFP (ng/mL), n (%)		
< 400	278 (59)	136 (57)
≥400	192 (41)	101 (43)

[a] One subject in each arm had no histological/cytological diagnosis of HCC. Both had baseline liver lesions and metastatic disease including extrahepatic spread and macrovascular invasion.
[b] Subjects may be counted in more than one category
[c] Two subjects in the cabozantinib arm were HBV positive but had unknown HCV status.
[d] Most subjects summarized under 'Other' had unknown aetiology for HCC.
[e] Subjects met at least one of the following criteria: ≥ 2 liver lesions (target or target + non-target) with at least one target liver lesion > 5 cm; vascular invasion in the liver; multifocal liver lesions with ≥ 3 lesions (either target or target + non-target) with at least one target liver lesion >3 cm; multifocal liver lesions with ≥ 4 liver lesions with any size
[f] Each anatomic location was counted only once.
[g] Tumour tissue (archival or recently biopsied) was obtained at enrolment (where available) for exploratory analysis of MET. High or low/negative status was based on cut- off ≥50% of tumour tissue stained with an intensity of 2+ or 3+. Cut-off based on historical HCC and non-small cell lung cancer data.

Central laboratory assessment of hepatitis viral status was instituted following Protocol Amendment 1; a total of 510 subjects (344 cabozantinib arm, 166 placebo arm) enrolled in the study following implementation of this requirement.

Selected baseline laboratory values were well balanced between treatment arms. Approximately 42% of subjects had baseline AFP ≥400 ng/mL.

Child-Pugh scores were collected at screening and (following Protocol Amendment 1.0) every 8 weeks after randomization (W9D1, W17D1, etc). Nearly all subjects were Child-Pugh A at baseline as required in the protocol. At Week 9 Day 1, there was a similar rate of Child-Pugh A to B conversion in each arm: 39/249 (16%) in the cabozantinib and 20/136 (15%) in the placebo arm. The same distribution was

seen at later weeks but due to the high rates of treatment discontinuation, analysis of changes in Child-Pugh score at later time points was not robust and therefore not presented.

Table 23: Change in Child-Pugh Categories over Time (ITT Population)

Time Point Baseline Grade	Post Baseline Grade					
	Cabozantinib (N=470) n (%)			Placebo (N = 237) n (%)		
	Child-Pugh A	Child-Pugh B	Child-Pugh C	Child-Pugh A	Child-Pugh B	Child-Pugh C
At Week 9, Day 1	n=249			n=136		
Child-Pugh A	198 (80)	39 (16)	2 (0.8)	113 (83)	20 (15)	0
Child-Pugh B	4 (1.6)	6 (2.4)	0	1 (0.7)	2 (1.5)	0

Subjects with unknown Child-Pugh category are not summarized. Only subjects with a Child-Pugh grade at both baseline and the respective visit are counted.

Table 24: Prior Non - radiation Anticancer Therapy for HCC (ITT Population)

Subject Characteristic	Cabozantinib (N = 470)	Placebo (N = 237)
Therapy type for HCC, n (%)[a]		
Systemic therapy	470 (100)	237 (100)
Local liver-directed therapy	209 (44)	113 (48)
Local other locations	2 (0.4)	0
Number of prior systemic anticancer regimens for advanced HCC per subject, n (%)		
0	3 (0.6)[b]	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3[c]	2 (0.4)	1 (0.4)
Progression on most recent prior systemic agent for HCC, n (%)	459 (98)	231 (97)
Median (range) time from progression on most recent prior systemic agent for HCC to randomization, months	1.61 (0.0, 100.8)	1.68 (0.2, 69.4)
Progression while receiving sorafenib for HCC, n (%)	452 (96)	232 (98)
Progression while receiving sorafenib as most recent prior systemic agent for HCC, n (%)	322 (69)	166 (70)
Sorafenib for HCC at any time, n (%)[a]	470 (100)	237 (100)
Sorafenib for advanced HCC, n (%)	467 (99)	236 (100)
First-line per CRF	454 (97)	228 (96)
Second-line per CRF	25 (5)	18 (8)
Adjuvant sorafenib for HCC	5 (1)	2 (0.8)
Other route of sorafenib administration for HCC	3 (0.6)	1 (0.4)
Median (range) duration of prior sorafenib for HCC, months	5.32 (0.3, 70.0)	4.80 (0.2, 76.8)
Total duration of prior sorafenib (months) for HCC, n (%)		
< 1 month	11 (2)	8 (3)
≥ 1 to < 3 months	117 (25)	54 (23)
≥ 3 to < 6 months	130 (28)	67 (28)
≥ 6 months	211 (45)	108 (46)
Other prior non-radiation systemic anticancer agents, n (%)[a]		
PD-1/PD-L1 therapies	14 (3.0)	3 (1.3)
Anti-CTLA-4 therapies	3 (0.6)	0
Ramucirumab	8 (1.7)	1 (0.4)
TKI therapies (other than sorafenib)	19 (4.0)	12 (5.1)
Regorafenib	6 (1.3)	2 (0.8)
Axitinib	4 (0.9)	1 (0.4)
Investigational drug	5 (1.1)	3 (1.3)
Lenvatinib	0	1 (0.4)

Cytotoxic chemotherapy[d]	41 (8.7)	30 (13)
Received prior TACE for HCC, n (%) Median number of prior chemoembolizations per subject [e] 0, n (%) 1, n (%) 2, n (%) ≥ 3, n (%)	203 (43) 0 (0, 18) 267 (57) 70 (15) 48 (10) 85 (18)	111 (47) 0 (0, 17) 126 (53) 32 (14) 20 (8) 59 (25)
Other liver-directed therapy (from surgery CRF), n (%)	54 (11)	30 (13)

[a] Prior systemic agents could be taken together but are summarized separately. Subjects may be counted in more than one category.
[b] Three subjects on the cabozantinib arm received prior systemic anticancer therapy that was administered for adjuvant HCC treatment but not for advanced HCC treatment per the CRFs.
[c] In the cabozantinib arm, Subject 3366-3517 received sorafenib (multiple instances) and doxorubicin, and Subject 9102-3262 received sorafenib and concomitant bevacizumab plus rapamycin (recorded as separate regimens). In the placebo arm, Subject 1513-3278 received sunitinib and multiple instances of sorafenib. These three subjects were not included in the table of eligibility deviations regarding line of therapy.
[d] Specific systemic cytotoxic chemotherapeutic agents received by ≥ 1% of subjects in either arm were: doxorubicin, oxaliplatin, cisplatin, gemcitabine, capecitabine, fluorouracil
[e] Multiple episodes of TACE on the same day were counted as a single administration.
Prior therapies were defined as having a start date prior to first dose of study treatment.

Prior radiation therapy for HCC was well balanced between treatment arms and received by 176 subjects (37%) in the cabozantinib and 93 subjects (39%) in the placebo arm. The most frequent sites of radiation for HCC were soft tissue (cabozantinib 30%, placebo 28%) and bone (10%, 13%). The most frequent types of radiation therapy for HCC were external beam radiation therapy (EBRT; cabozantinib 15%, placebo 18%), radiofrequency ablation (15% of subjects in each arm), and radioembolization (cabozantinib 6%, placebo 5%).

Numbers analysed

Table 25: **Analysis Populations**

	Cabozantinib n (%)	**Placebo n (%)**
Total no. of randomized subjects (ITT population) [a] Safety population [b] Pharmacokinetic population [c]	470 (100) 467 (99) 453 (96)	237 (100) 237 (100) 233 (98)

ITT, intent-to-treat; PK, pharmacokinetic.
[a] Percentages for the populations were based on all randomized subjects.
[b] Safety population included all subjects who received any amount of study treatment.
[c] The PK population consisted of all subjects with available PK data.

Outcomes and estimation

Primary Efficacy Endpoint Analysis:

Overall Survival (OS)

Analysis of OS was based on a second planned interim analysis prespecified to be performed at approximately the 75% information fraction (i.e. ~ 466 deaths). By the data cut-off date for this event-driven analysis (01 June 2017), a total of 484 deaths (78% actual information fraction) were reported. Survival status was determined for 99% of the 707 randomized subjects as of the database cut-off date. A total of 13 subjects withdrew consent including for survival follow-up. In the OS analysis, 9 of these 13 subjects (5 cabozantinib, 4 placebo) were censored at their date of withdrawal of consent, the remaining 4 subjects (3 cabozantinib, 1 placebo) had death dates available from public record. All other subjects who were not deceased through 01 June 2017 were documented to be alive (and were censored) on this date.

Median follow-up time to 01 June 2017 was 22.9 months. No values were imputed.

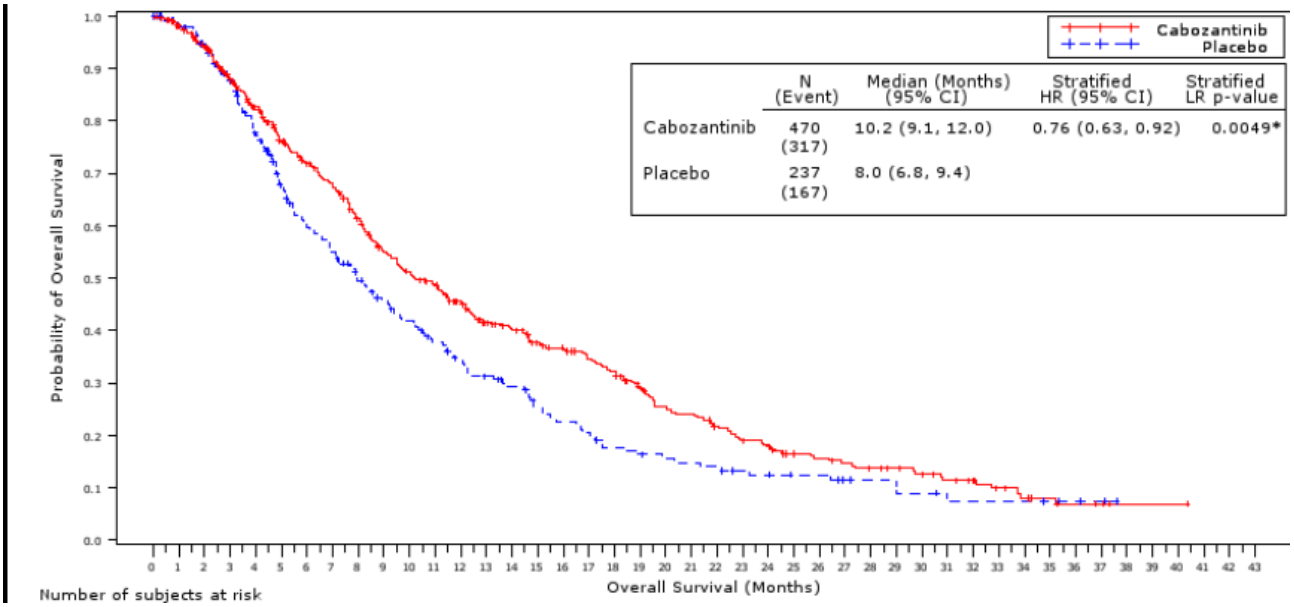


Figure 13: **Kaplan-Meier Plot of Overall Survival through the 01 June 2017 Data Cut-off Date (ITT Population)**

The primary analysis demonstrated a statistically significant improvement in duration of OS for subjects in the cabozantinib arm compared with the placebo arm.

Table 26: Overall Survival through the 01 June 2017 Data Cut-off Date (ITT Population)

	Cabozantinib (N = 470)	**Placebo (N = 237)**
Number (%) of subjects		
Censored	153 (33)	70 (30)
Death	317 (67)	167 (70)
Duration of overall survival (months) [a]		
Median (95% CI)	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)
25th percentile, 75th percentile	5.3, 20.0	4.3, 15.2
Range	0.1, 40.3+	0.03+, 37.6+
Critical p-value to reject null hypothesis of equal OS[b]	0.021	
Observed p-value (stratified log-rank test)[c]	0.0049	
Hazard ratio (95% CI; stratified)[c,d]	0.76 (0.63, 0.92)	
Observed p-value (unstratified log-rank test)	0.0072	
Hazard ratio (95% CI; unstratified)	0.77 (0.64, 0.93)	
Landmark Estimates (% of subjects event-free)		
3 months	88.4	87.6
6 months	71.8	60.6
12 months	45.6	34.3
18 months	32.3	17.7
24 months	17.8	12.5

+ indicates a censored observation (see OS censoring rules).
[a] Percentiles were based on Kaplan-Meier estimates.
[b] Per Lan-De Mets O' Brien-Fleming alpha spending function
[c] Stratification factors based on IxRS were disease aetiology (HBV [with or without HCV], HCV [without HBV] or Other), geographic region (Asia, Other), extrahepatic spread of disease and/or macrovascular invasion (Yes, No)
[d] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable).

Results for the stratified analysis per CRF were similar to those for the stratified analysis per IxRS. As the null hypothesis of no treatment difference in OS was rejected at the second prespecified interim analysis, no further analyses of OS are planned.

First Planned Interim Analysis

A prespecified first interim OS analysis was performed at approximately the 50% information fraction (321 events; 52% actual information fraction) and was reviewed by the IDMC, who recommended the trial continue in a blinded fashion. Exelixis learned of the results of the first interim analysis only after the primary endpoint was met at the second planned interim analysis. The treatment effect observed at the two planned interim analyses was similar. The critical p-value per the Lan-DeMets O' Brien

Fleming alpha spending function to reject the null hypothesis of no difference in OS at this analysis (0.0037) was not met.

Table 27: First Planned Interim Analysis of Overall Survival through the 15 June 2016 Cut-off Date (ITT Population)

	Cabozantinib (N=361)	Placebo (N=179)
Duration of overall survival (months)		
Median (95% CI) [a]	10.9 (9.1, 12.4)	7.7 (6.3, 9.7)
25th percentile, 75th percentile[a]	5.2, 21.1	4.3, 14.9
Range	0.03+, 30.2+	0.023+, 29.0
Critical p-value to reject null hypothesis of equal OS[b]	0.0037	
Observed p-value (stratified log-rank test)[c]	0.0041	
Hazard ratio (95% CI; stratified) [c,d]	0.71 (0.56, 0.90)	
Observed p-value (unstratified log-rank test)	0.0023	
Hazard ratio (95% CI; unstratified)	0.70 (0.56, 0.88)	

+ indicates a censored observation (subjects alive on or after the data cut-off or those who died after the data cut-off were right censored at the date of data cut-off)
[a] Median and percentiles are based on Kaplan-Meier estimates
[b] Per Lan-DeMets O' Brien-Fleming alpha spending function
[c] Stratification factors based on IxRS as previously
[d] Estimated using the Cox proportional hazard model adjusted for stratification factors.

The most frequent concomitant medications by ATC and WHO preferred name for each treatment arm generally had a similar incidence in each arm. However, there was a higher proportion of subjects receiving loperamide in the cabozantinib arm relative to the placebo arm (34% vs 12%).

Secondary Efficacy Endpoint Analysis:

Progression-Free Survival per Investigator per RECIST 1.1

The prespecified primary analysis of PFS (PFS1) included radiographic progression events as determined by the Investigator per RECIST 1.1 or death due to any cause.

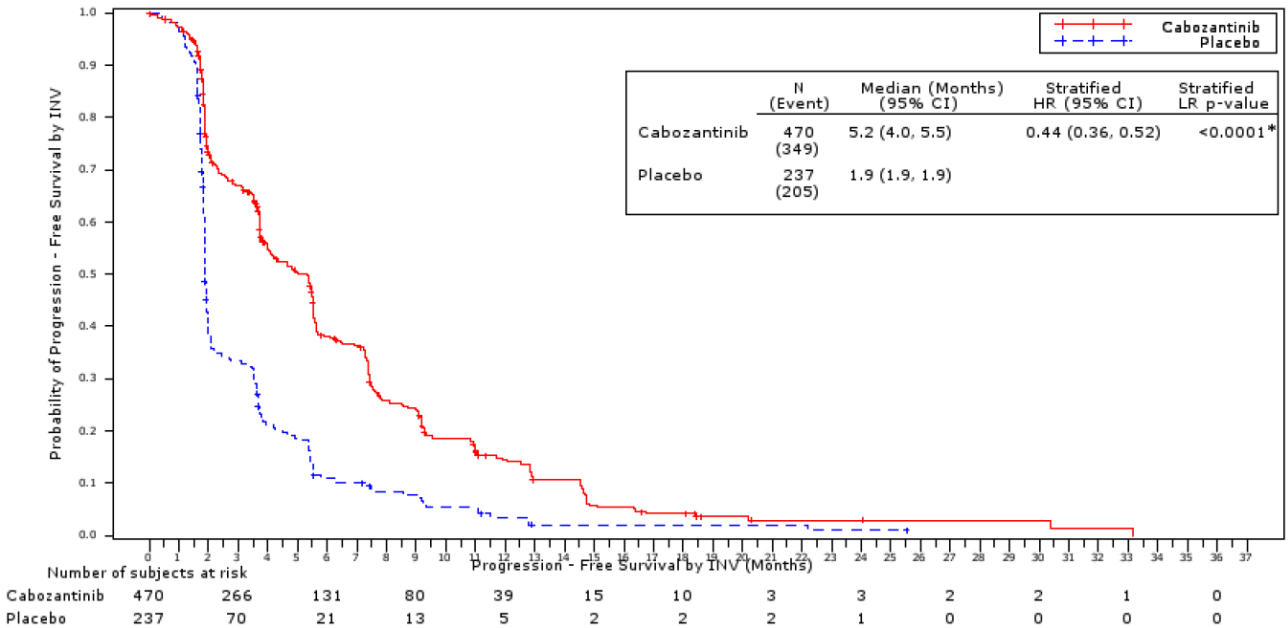


Figure 14: Kaplan-Meier Plot of Progression-Free Survival per Investigator through 01 June 2017 (ITT Population)

Table 28: **Progression-Free Survival per Investigator through 01 June 2017 (ITT Population)**

	Cabozantinib (N = 470)	Placebo (N = 237)
Number (%) of subjects		
Censored	121 (26)	32 (14)
2 or more missed ATAs (> 126 days) prior to event	18 (3.8)	2 (0.8)
Systemic or local liver-directed NPACT	15 (3.2)	1 (0.4)
No event by last ATA	57 (12)	14 (5.9)
No post-baseline ATA	22 (4.7)	10 (4.2)
Radiation (other than to bone)	5 (1.1)	2 (0.8)
Surgery	4 (0.9)	3 (1.3)
Event	349 (74)	205 (86)
Death	65 (14)	19 (8.0)
Progressive disease	284 (60)	186 (78)
Duration of progression-free survival (months)		
Median (95% CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)
25th percentile, 75th percentile[a]	1.9, 8.5	1.7, 3.7
Range	0.03+, 33.2	0.03+, 25.5+
Critical p-value to reject null hypothesis of equal PFS	0.04	
Observed p-value (stratified log-rank test)[b]	< 0.0001	
Hazard ratio (95% CI; stratified)[b,c]	0.44 (0.36, 0.52)	
Observed p-value (unstratified log-rank test)	< 0.0001	
Hazard ratio (95% CI; unstratified)[c]	0.46 (0.38, 0.55)	

Landmark estimates (% of subjects event-free)	**Cabozantinib (N = 470)**	**Placebo (N = 237)**
3 months	67.0	33.3
6 months	38.1	11.1
12 months	14.5	3.4
18 months	4.2	2.1
24 months	2.9	1.0

ATA, adequate tumour assessments; NPACT, non -protocol anticancer therapy
+ indicates a censored observation (see PFS censoring rules in Section 9.7.1.3.1).
Of note, 19 cabozantinib and 9 placebo subjects were randomized < 51 days before the data cut-off date i.e. too recently to have had a routine postbaseline tumour assessment.
[a] Percentiles were based on Kaplan-Meier estimates.
[b] Stratification factors (per IxRS) as described previously
[c] Estimated using the Cox proportional-hazard model (adjusted for stratification factors if applicable)

Results for the stratified analysis per CRF were similar to those for the stratified analysis per IxRS.

Pre-specified sensitivity analyses (PFS2 and PFS3) were performed with additional clinical outcomes as events.

Table 29: **Sensitivity Analyses of PFS (ITT Population)**

PFS Analysis	Cabozantinib No. of Events/ Subjects (%) Median Duration (mo)	Placebo No. of Events/ Subjects (%) Median Duration (mo)	Stratified Hazard Ratio	95% CI	Stratified Logrank p-value
Primary analysis, PFS1[a]	349/470 (74) 5.2	205/237 (86) 1.9	0.44	0.36, 0.52	<0.0001
PFS2[b]	374/470 (80) 4.4	211/237 (89) 1.9	0.46	0.38, 0.55	<0.0001
PFS3[c]	356/470 (76) 4.7	207/237 (87) 1.9	0.44	0.37, 0.53	<0.0001

[a] PFS1 analysis: earlier of radiographic progression per RECIST 1.1 or death due to any reason.
[b] PFS2 analysis: the following were PFS events – radiographic progression per RECIST 1.1, death due to any reason, systemic or local liver-directed NPACT, radiation (other than to bone), tumour resection, treatment discontinuation due to clinical deterioration.
[c] PFS3 analysis: the following were PFS events – radiographic progression per RECIST 1.1, death due to any reason, treatment discontinuation due to clinical deterioration

Objective Response Rate per Investigator per RECIST 1.1

ORR was tested at the 2-sided α =0.01 level of significance by applying a modified Bonferroni procedure. Tumour assessments that occurred after the individual subject PFS-censoring dates were excluded from the analysis. In the cabozantinib arm, 18 subjects (4%) had a BOR of PR compared with 1 subject (0.4%) in the placebo arm; no subjects had a CR.

Table 30: Objective Response Rate per Investigator (ITT Population)

	Cabozantinib (N = 470)	**Placebo (N = 237)**
Best overall response, n (%)[a]		
Confirmed complete response (CR)	0	0
Confirmed partial response (PR)	18 (4)	1 (0.4)
Stable disease (SD)	282 (60)	78 (33)
Unconfirmed PR (uPR)	13 (3)	2 (0.8)
Progressive disease (PD)	98 (21)	131 (55)
Missing	72 (15)	27 (11)
No post-baseline assessments	65 (14)	22 (9)
No qualifying post-baseline assessment on/ before the primary PFS analysis censoring or event date	7 (1)	5 (2)
Objective response rate (CR+PR), n (%)	18 (4)	1 (0.4)
95% CI	(2.3, 6.0)	(0.0, 2.3)
Treatment difference (cabozantinib – placebo) (95% CI)[b]	3.4 (1.49, 5.33)	
Critical p-value to reject null hypothesis of equal ORR	0.01	
Observed stratified CMH test p-value per IxRS[c]	0.0086	
Observed unstratified Fisher exact test p-value	0.0059	
Unstratified odds ratio per IxRS (95% CI)	9.4 (1.2, 70.8)	
Stratified odds ratio per IxRS (95% CI)[c]	9.4 (1.2, 71.0)	

a Best overall response was assessed based on RECIST 1.1 criteria and was calculated based on subjects in the ITT population. A CR or PR was not considered as an objective response if a subject progressed or received subsequent anti-cancer therapy prior to the first CR or PR. To be classified as a CR or PR, confirmation of response must have occurred > 28 days after the response was first observed.
b Using asymptotic confidence limits based on large number theorem
c Stratification factors (per IxRS) as described previously

Exploratory Endpoint Analyses

Serum Alpha – Fetoprotein

Serum AFP was assessed at baseline and every 8 weeks (W9D1, W17D1, etc), on the same schedule as tumour CT/MRI assessments. Among subjects with post-baseline data, 109/373 (29%) in the

cabozantinib arm and 13/192 (7%) in the placebo arm had ≥50% post-baseline decreases in serum AFP.

Change in Serum Alpha-Fetoprotein Compared with Baseline (ITT Population)

	Cabozantinib (N = 470)					Placebo (N = 237)				
	Baseline (n = 462)	Week 9 (n = 346)	Week 17 (n = 234)	Best Change[a] (n = 369)	Worst Change[a] (n = 369)	Baseline (n = 234)	Week 9 (n = 173)	Week 17 (n = 64)	Best Change[a] (n = 187)	Worst Change[a] (n = 186)
Median value (ng/mL)	154.70	115.20	135.20	94.70	309.60	208.75	144.40	68.15	144.40	335.55
Median % change from baseline	-	-19.00	0.00	-26.13	56.82	-	35.62	45.80	32.32	73.57

[a] Best change is the largest decrease (or smallest increase if no decrease) from baseline; worst change from baseline is the largest increase (or smallest decrease if no increase) from baseline

Serum Bone Biomarkers

Serum bone biomarkers (BSAP, CTx and NTx) were collected. Among subjects with post-baseline data:

- 6/410 (1%) in the cabozantinib arm and 0/219 (0%) in the placebo arm had a ≥ 50% postbaseline decrease in serum BSAP
- 123/412 (30%) in the cabozantinib arm and 3/218 (1%) in the placebo arm had a ≥ 50% postbaseline decrease in serum NTx
- 259/407 (64%) in the cabozantinib arm and 13/218 (6%) in the placebo arm had a ≥ 50% post-baseline decrease in serum CTx

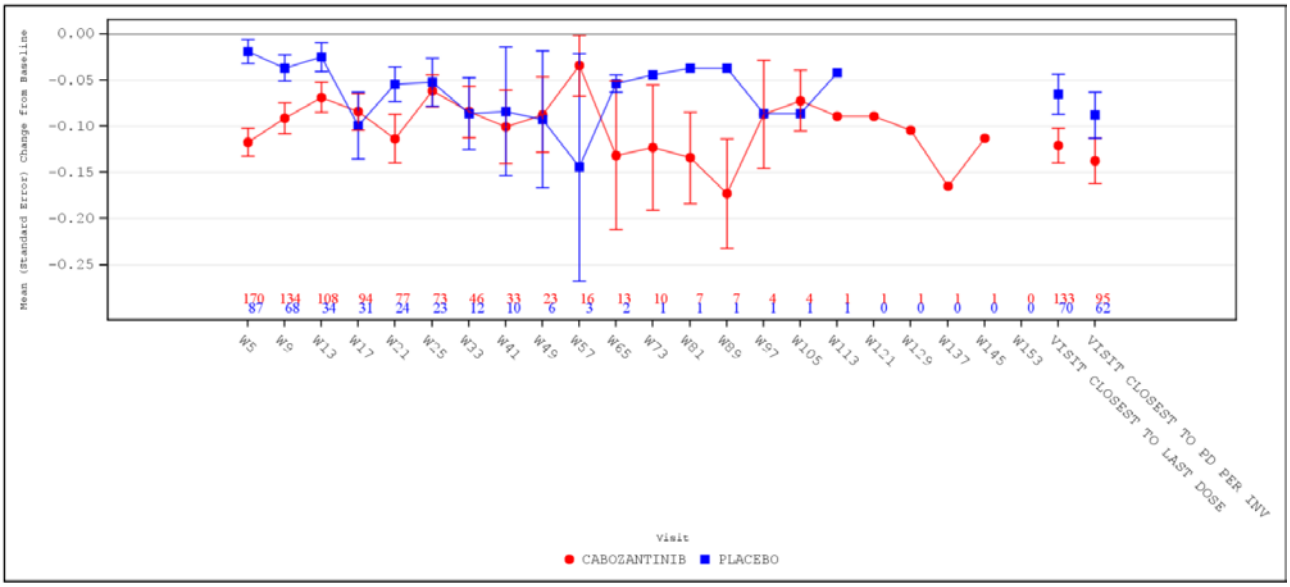
Health Related Quality of Life: EQ-5D-5L

EQ-5D-5L scores were summarized by five functional dimensions (mobility, selfcare, usual activities, pain/discomfort, anxiety/depression), each split into five increasing severity levels from 1 (no problem) to 5 (extreme problem). An effect size for change from baseline ≥ 0.3 was considered potentially clinically meaningful. The EQ-5D-5L was converted into a single index value normalized across 10 countries in which the index has been validated. EQ-Index values range from 0 (dead) to 1 (full health). The minimal important differences (MID) for these questionnaires in cancer patients were previously established as 0.06 to 0.08 for EQ-Index, and 7 for EQ-VAS (Pickard et al, 2007).

The EQ-5D-5L questionnaire completion rate (number of subjects who completed all questions/subjects still on study) remained above 85% in each treatment arm until Week 33. After W33D1, there were fewer than 20 subjects in the placebo arm.

For post-baseline changes, the largest treatment difference occurred at the W5D1 time point for mobility and usual activities (effect size difference in favour of placebo of 0.51 and 0.55, respectively). The proportion of subjects in the cabozantinib and placebo arm with any problem (Levels 2-5) at W5D1 was 61% vs 32% for mobility and 68% vs 43% for usual activities.

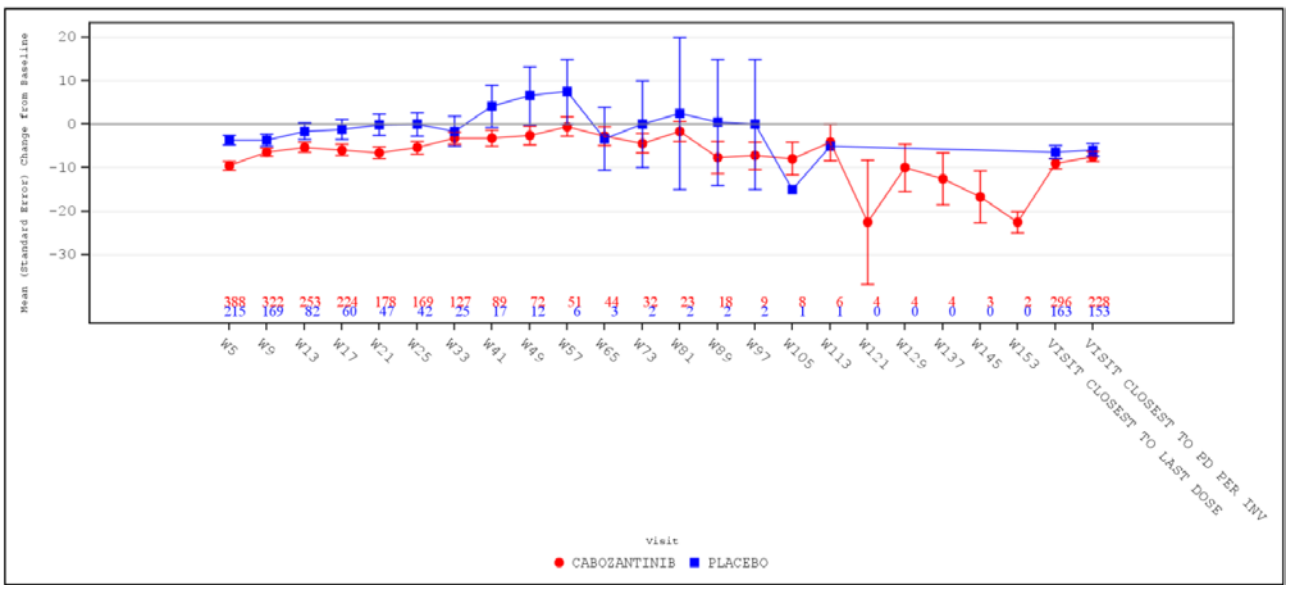
At baseline, mean EQ-Index scores were 0.792 in the cabozantinib and 0.855 in the placebo arm. At W5D1, EQ-Index change from baseline in the cabozantinib arm was more negative compared with placebo (mean change from baseline: -0.117 vs -0.019) and thus favoured placebo. Subsequent treatment differences in mean change from baseline EQ-Index values were < 0.06 through W25D1. Beyond this time point there were fewer than 20 subjects in the placebo arm.



EQ-Index is scored from 0 to 1. A higher score indicates better health-related quality of life status. Number of subjects at baseline with EQ-Index scores - 206 in the cabozantinib and 96 in the placebo arm

Figure 15: **Mean (±SE) Change from Baseline of EQ-Index Score (ITT Population; Countries in which EQ-Index Is Validated)**

At baseline, mean EQ-VAS scores were 73.5 in the cabozantinib arm and 76.1 in the placebo arm. All treatment differences in mean change from baseline EQ-VAS values were < 7 through W33D1. Beyond this time point there were fewer than 20 subjects in the placebo arm.



EQ-VAS is scored from 0 (worst health you can imagine) to 100 (best health you can imagine).
Original number of subjects at baseline was 452 (cabozantinib) and 234 (placebo)

Figure 16: **Mean (±SE) Change from Baseline of EQ-VAS Score (ITT Population)**

Ancillary analyses

Subgroup Analyses for OS and PFS

Many subgroups were analysed and the size and number of events in each subgroup varied widely. Subgroup analyses were not powered to detect a treatment difference.

Table 31: Subgroup Analyses for OS and PFS (ITT Population)

Subgroup Level	OS							PFS						
	Cabozantinib (N=470)			Placebo (N=237)			Unstratified HR (95% CI)[a]	Cabozantinib (N=470)			Placebo (N=237)			Unstratified HR (95% CI)[a]
	n	Events	Median	n	Events	Median		n	Events	Median	n	Events	Median	
Overall	470	317	10.18	237	167	7.98	0.77 (0.64, 0.93)	470	349	5.16	237	205	1.87	0.46 (0.38, 0.55)
Age (years)														
< 65	240	159	9.56	124	86	7.69	0.81 (0.62, 1.05)	240	179	4.99	124	107	1.87	0.45 (0.35, 0.57)
65 to < 75	158	108	10.87	75	56	7.92	0.70 (0.51, 0.97)	158	119	4.90	75	66	1.91	0.41 (0.30, 0.56)
75 to < 85	67	48	11.14	35	22	11.79	0.85 (0.51, 1.43)	67	49	5.52	35	30	2.23	0.53 (0.33, 0.85)
≥ 85	5	2	NE	3	3	8.74	1.03 (0.14, 7.42)	5	2	NE	3	2	3.68	2.35 (0.20, 27.18)
Sex														
M	379	254	10.05	202	143	7.92	0.79 (0.64, 0.97)	379	285	4.90	202	175	1.91	0.49 (0.40, 0.59)
F	91	63	11.14	35	24	8.90	0.68 (0.42, 1.09)	91	64	5.49	35	30	1.87	0.31 (0.20, 0.49)
Race														
Asian	159	112	9.66	82	56	8.48	0.86 (0.63, 1.19)	159	117	5.39	82	71	1.84	0.43 (0.32, 0.58)
Black/African American	8	4	20.40	11	9	6.08	0.29 (0.08, 1.11)	8	6	4.27	11	10	1.86	0.28 (0.09, 0.91)
White	264	175	11.14	130	91	8.34	0.81 (0.63, 1.04)	264	195	5.16	130	112	1.94	0.50 (0.40, 0.63)
Other/not reported	39	26	9.53	14	11	5.29	0.44 (0.21, 0.91)	39	31	4.21	14	12	3.65	0.39 (0.19, 0.78)
Geographic Region 1														
Asia	116	79	10.87	59	38	10.18	1.01 (0.68, 1.48)	116	86	5.39	59	50	1.84	0.46 (0.32, 0.67)
Europe/Australia/New Zealand	246	157	11.37	119	79	7.92	0.71 (0.54, 0.93)	246	181	5.32	119	99	1.91	0.41 (0.32, 0.53)
North America (USA/Canada)	108	81	9.13	59	50	6.80	0.71 (0.50, 1.01)	108	82	4.90	59	56	1.87	0.55 (0.39, 0.78)
Geographic Region 2														
Asia	116	79	10.87	59	38	10.18	1.01 (0.68, 1.48)	116	86	5.39	59	50	1.84	0.46 (0.32, 0.67)
Other	354	238	10.18	178	129	7.82	0.71 (0.57, 0.88)	354	263	5.16	178	155	1.91	0.45 (0.37, 0.56)
ECOG PS[b]														
0	245	154	12.42	131	93	9.30	0.69 (0.53, 0.89)	245	184	5.55	131	118	1.91	0.39 (0.31, 0.50)
1	224	162	8.57	106	74	6.41	0.87 (0.66, 1.14)	224	164	3.71	106	87	1.87	0.54 (0.41, 0.70)
Etiology of disease per stratification factors per CRF														
HBV (with or without HCV)	178	123	9.66	89	63	6.11	0.69 (0.51, 0.94)	178	132	4.37	89	77	1.81	0.31 (0.23, 0.42)
HCV (without HBV)	105	67	11.14	51	30	11.43	1.11 (0.72, 1.71)	105	76	4.11	51	44	1.91	0.61 (0.42, 0.88)
Other (without HBV and HCV)	187	127	11.14	97	74	8.74	0.72 (0.54, 0.96)	187	141	5.45	97	84	2.00	0.48 (0.36, 0.63)
Current etiology of disease per CRF														
HBV (without HCV) (YES)	168	113	9.66	85	60	5.82	0.69 (0.50, 0.94)	168	124	5.42	85	73	1.81	0.32 (0.23, 0.44)
HCV (without HBV) (YES)	105	67	11.14	51	30	11.43	1.11 (0.72, 1.71)	105	76	4.11	51	44	1.91	0.61 (0.42, 0.88)
HBV and HCV (YES)	8	8	7.38	4	3	8.57	0.76 (0.18, 3.20)	8	7	3.76	4	4	1.82	0.15 (0.03, 0.82)
Alcoholism (YES)	112	83	8.97	39	26	7.23	0.83 (0.53, 1.29)	112	83	4.83	39	32	1.92	0.52 (0.34, 0.78)
NASH (YES)	43	31	8.94	23	18	7.89	0.77 (0.43, 1.39)	43	36	3.81	23	18	2.69	0.78 (0.44, 1.39)
Other (YES)	99	61	12.02	63	51	8.34	0.62 (0.43, 0.90)	99	71	5.55	63	59	1.91	0.33 (0.23, 0.48)
Presence of extrahepatic spread of disease and/or MVI per stratification factors per CRF														
Yes	398	272	9.53	200	145	7.26	0.73 (0.60, 0.90)	398	298	4.99	200	174	1.87	0.45 (0.37, 0.54)
No	72	45	13.96	37	22	14.65	0.99 (0.59, 1.65)	72	51	5.55	37	31	2.00	0.46 (0.29, 0.74)
Metastases at baseline														
Visceral (excluding liver)[c]	215	153	8.71	105	79	6.87	0.79 (0.60, 1.04)	215	168	4.01	105	89	1.87	0.49 (0.38, 0.64)
Bone	60	45	7.69	34	29	6.57	0.86 (0.54, 1.37)	60	45	3.71	34	32	1.84	0.40 (0.25, 0.65)
Bone + visceral (excluding liver)[c]	36	30	7.59	21	19	6.11	0.92 (0.51, 1.64)	36	29	2.10	21	20	1.86	0.50 (0.28, 0.91)
Prior systemic nonradiation anticancer regimens for advanced HCC per subject[d]														
1	335	223	11.37	174	121	7.69	0.74 (0.59, 0.92)	335	252	5.49	174	152	1.87	0.43 (0.35, 0.52)
2	130	90	8.57	62	45	8.57	0.90 (0.63, 1.29)	130	94	3.71	62	52	1.87	0.58 (0.41, 0.83)
Prior PD-1/ PD-L1														
Yes	14	5	7.89	3	1	NE	0.39 (0.04, 4.33)	14	8	3.19	3	3	1.84	0.07 (0.01, 0.65)
No	456	312	10.61	234	166	7.98	0.77 (0.64, 0.93)	456	341	5.39	234	202	1.87	0.46 (0.38, 0.55)
Prior regorafenib														
Yes	6	6	9.97	2	2	7.59	0.45 (0.07, 2.78)	6	5	1.87	2	2	3.40	0.70 (0.11, 4.45)
No	464	311	10.61	235	165	7.98	0.77 (0.64, 0.94)	464	344	5.32	235	203	1.87	0.46 (0.38, 0.54)
Prior lenvatinib														
Yes	0	0	NE	1	1	2.43	NE (NE, NE)	0	0	NE	1	1	1.64	NE (NE, NE)
No	470	317	10.18	236	166	7.98	0.78 (0.64, 0.94)	470	349	5.16	236	204	1.87	0.46 (0.38, 0.55)
Prior tivantinib														
Yes	1	1	14.55	2	1	NE	0.00 (0.00, NE)	1	1	7.59	2	1	NE	0.00 (0.00, NE)
No	469	316	10.18	235	166	7.98	0.77 (0.64, 0.93)	469	348	5.16	235	204	1.87	0.45 (0.38, 0.54)
Prior ramucirumab														
Yes	8	3	NE	1	0	NE	NE (NE, NE)	8	7	1.97	1	0	NE	NE (NE, NE)
No	462	314	10.18	236	167	7.98	0.77 (0.64, 0.94)	462	342	5.32	236	205	1.87	0.45 (0.38, 0.54)
AFP														
< 400 ng/mL	278	175	13.86	136	89	10.25	0.81 (0.62, 1.04)	278	199	5.52	136	115	1.94	0.47 (0.37, 0.60)
≥ 400 ng/mL	192	142	8.51	101	78	5.19	0.71 (0.54, 0.94)	192	150	3.91	101	90	1.87	0.42 (0.32, 0.55)
Tumor MET IHC status[e]														
High	33	26	9.69	15	11	7.92	0.97 (0.47, 1.98)	33	28	3.75	15	13	2.81	1.10 (0.56, 2.16)
Low/negative	144	102	13.24	68	57	7.98	0.67 (0.48, 0.92)	144	104	5.45	68	61	1.87	0.41 (0.30, 0.57)
Unknown	11	9	8.51	4	2	3.45	1.03 (0.22, 4.90)	11	10	7.36	4	3	1.84	0.00 (0.00, NE)

[a] HR and 95% CI were estimates from the Cox proportional-hazard unstratified model.
[b] One subject in the cabozantinib arm enrolled in the study with a baseline ECOG PS of 2. This subject was not included in the corresponding subgroup analysis table.
[c] Visceral sites defined based upon review of the reported sites once data had been entered in the database.
[d] Three subjects enrolled having received ≥ 3 prior systemic anticancer regimens (SCE, Section 2.1.2.2). These subjects are not included in the corresponding subgroup analysis table.
[e] For the exploratory analysis of MET, status of high or low/negative was based on cut-off of ≥ 50% of tumour tissue stained with an intensity of 2+ or 3+. Cut-off based on historical HCC and non-small cell lung cancer data.

For each of these subgroups there was a consistently higher use of systemic NPACT in the placebo arm.

For subjects who received 1 prior regimen the OS HR was 0.74 (95% CI 0.59, 0.92) and PFS HR was 0.43 (95% CI 0.35, 0.52). For subjects who received 2 prior regimens the unstratified OS HR was 0.90 (95% CI 0.63, 1.29) and unstratified PFS HR was 0.58 (95% CI 0.41, 0.83).

Concomitant medications

Non-protocol anticancer therapy (NPACT) and OS

At the date of first receipt of NPACT; per protocol, subjects had to discontinue study treatment. The incidence of systemic non-radiation and local liver-directed systemic NPACT was 26% in the cabozantinib arm and 33% in the placebo arm.

Table 32: **Non-protocol Anticancer Therapy Categories that Led to censoring (ITT Population)**

	Cabozantinib (N = 470) n (%)	**Placebo (N = 237) n (%)**
Systemic OR local liver-directed NPACT	123 (26)	78 (33)
Radiation therapies (other than radiation to bone)	26 (5.5)	19 (8.0)
Surgery/procedure that affected the tumour lesion	6 (1.3)	10 (4.2)

The incidence of systemic non-radiation NPACT was 25% (117 subjects) in the cabozantinib arm and 30% (70 subjects) in the placebo arm. The incidence of local liver-directed non-radiation NPACT was 3.2% (15 subjects) in the cabozantinib arm and 5.5% (13 subjects) in the placebo arm.

There is a minor difference in censoring due to the use of NPACTs in the two treatment arms.

Table 33: Systemic NPACT used by ≥1% of subjects in either treatment arm (ITT Population)

	Cabozantinib (N = 470) n (%)	Placebo (N = 237) n (%)
Systemic nonradiation anticancer therapy	117 (25)	70 (30)
Selected therapies of interest:[a]		
PD-1/PD-L1 therapies	23 (4.9)	15 (6.3)
Nivolumab	17 (3.6)	14 (5.9)
Pembrolizumab	4 (0.9)	1 (0.4)
Durvalumab	1 (0.2)	1 (0.4)
Atezolizumab	1 (0.2)	0
Investigational drug	1 (0.2)	0
Anti-CTLA-4 therapies	6 (1.3)	2 (0.8)
Ipilimumab	4 (0.9)	2 (0.8)
Tremelimumab	2 (0.4)	0
TKI therapies	34 (7.2)	8 (3.4)
Sorafenib	19 (4.0)	4 (1.7)
Regorafenib	11 (2.3)	3 (1.3)
Investigational drug	3 (0.6)	1 (0.4)
Cabozantinib (non-study drug)	1 (0.2)	0
Erlotinib	1 (0.2)	0
Lenvatinib	1 (0.2)	0
Sunitinib	1 (0.2)	0
Cytotoxic chemotherapy[b]	57 (12)	40 (17)
Oxaliplatin	29 (6.2)	17 (7.2)
Capecitabine	18 (3.8)	9 (3.8)
Fluorouracil	18 (3.8)	15 (6.3)
Gemcitabine	16 (3.4)	7 (3.0)
Doxorubicin	14 (3.0)	7 (3.0)
Cisplatin	10 (2.1)	7 (3.0)
Cyclophosphamide	1 (0.2)	3 (1.3)
Etoposide	1 (0.2)	3 (1.3)

At each level of summarization, a subject was counted only once if the subject reported one or more therapies.
[a] Subjects may be counted in more than one category.
[b] Specific systemic cytotoxic chemotherapeutic agents shown are those received by ≥1% of subjects in either arm.

The median (range) time from randomization to first systemic non-radiation NPACT was 202 (26, 765) days in the cabozantinib arm and 99.5 (42, 590) days in the placebo arm.

As an exploratory analysis, the OS analysis was repeated censoring survival times for subjects who received a systemic or a local liver-directed NPACT after randomization prior to their date of death, consent withdrawal or last known to be alive at the date of first receipt of such therapy; per protocol, subjects receiving these therapies had to discontinue study treatment. Results were consistent with those of the primary OS analysis.

Table 34: Overall survival through the 01 June 2017 data Cut-off Date: effect of systemic non-radiation NPACT or Local Liver-Directed Non-radiation NPACT (ITT Population)

	Cabozantinib (N = 470)	Placebo (N = 237)
Number (%) of subjects		
Censored	237 (50)	127 (54)
Alive	100 (21)	46 (19)
Death after data cutoff date	14 (3)	3 (1.3)
Anticancer therapy	123 (26)	78 (33)
Death	233 (50)	110 (46)
Duration of overall survival (months) [a]		
Median (95% CI)	11.1 (9.1, 12.8)	6.9 (5.7, 8.9)
25th percentile, 75th percentile	5.3, 21.7	4.2, 14.5
Range	0.1, 37.3+	0.03+, 37.6+
P-value (stratified log-rank test)[b]	0.0005	
Hazard ratio (95% CI; stratified)[b,c]	0.66 (0.52, 0.84)	
P-value (unstratified log-rank test)	0.0010	
Hazard ratio (95% CI; unstratified)[c]	0.68 (0.54, 0.86)	

+ indicates a censored observation (for subjects who received systemic NPACT prior to their death date, withdrawal consent date, or date the subject was last known to be alive).

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

[b] Stratification factors (per IxRS) as detailed previously

[c] Estimated using the Cox proportional hazard model (adjusted for stratification factors if applicable)

Previous treatment with sorafenib only

In an ad hoc subgroup analysis of subjects who received sorafenib as the only prior agent for HCC (70% of subjects), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (unstratified HR 0.73, 95% CI: 0.58, 0.92; stratified HR per IxRS 0.70, 95% CI: 0.55, 0.88). Median PFS in this subgroup was 5.5 months with cabozantinib versus 1.9 months with placebo (unstratified HR 0.42: 95% CI: 0.34, 0.52; stratified HR per IxRS 0.40, 95% CI 0.32, 0.50).

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35: Summary of Efficacy for Study XL 184 – 309

Title: A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib		
Study identifier	XL 184 – 309	
Design	Multi-centre, randomised, double-blind, placebo -controlled	
	Duration of main phase:	Event driven. First subject enrolled 26 September 2013. Fully enrolled as of 18 September 2017 and closed enrolment.
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Cabozantinib		60mg qd, N= 470
	Matched placebo		60mg qd, N= 237
Endpoints and definitions	Primary endpoint	Overall Survival (OS)	Time from randomisation to death due to any cause; critical p value 0.021
	Secondary endpoint	Progression free survival (PFS)	Time from randomization to the earlier of: radiographic progression determined by Investigator per RECIST 1.1 or death due to any cause; 2- sided α 0.04
	Secondary endpoint	Objective response rate (ORR)	Proportion of subjects with a CR or PR, confirmed ⩾ 28 days after the response was first observed determined by Investigator per RECIST 1.1; 2 – sided α 0.01
Database lock	1 June 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (466 deaths; median FU 22.9 months)		
Descriptive statistics and estimate variability	Treatment group	Cabozantinib 60mg qd	Placebo
	Number of subjects	470	237
	Median OS months (Kaplan Meier)	10.2	8.0
	95% CI	9.1, 12.0	6.8, 9.4
	Median PFS months	5.2	1.9
	95% CI	4.0, 5.5	1.9, 1.9
	ORR % 95% CI	4 2.3, 6.0	0.4 0.0, 2.3
Effect estimates per comparison	Primary OS endpoint	Comparison groups	Cabozantinib vs. placebo
		Stratified HR	0.76
		95% CI	0.63, 0.92
		P-value (stratified log rank)	0.0049*
	Secondary PFS endpoint	Comparison groups	Cabozantinib vs. placebo
		Stratified HR	0.44
		95% CI	0.36, 0.52
		P-value (stratified log rank)	<0.0001*
	Secondary ORR endpoint	Comparison groups	Cabozantinib vs. placebo
		Stratified odds ratio	9.4
		95% CI	1.2, 71.0
		P-value (stratified CMH)	0.0086*

*Critical p value to reject null hypothesis of equal OS = 0.021; PFS = 0.04; ORR = 0.01

Supportive study

- **Phase 2 Study XL184-203 RDT**

Study XL184-203 RDT was a randomized phase 2 discontinuation study of cabozantinib in subjects with advanced solid tumours. Subjects were enrolled into one of nine cohorts based on tumour type. One of these cohorts comprised advanced HCC subjects.

The RDT design consisted of two stages.

Lead in stage: Eligible subjects with advanced solid tumours received open-label cabozantinib at a starting daily dose of 100 mg once daily for 12 weeks; all subjects underwent tumour assessment at 6 and 12 weeks.

Randomised stage or open-label extension: At the end of the 12-week open-label, single arm Lead-In Stage, subjects with demonstrated stable disease could enter the Randomized Stage and were randomised 1:1 to receive cabozantinib or matching placebo in a blinded manner. Subjects received blinded treatment until development of PD or an unacceptable toxicity. Subjects with an objective response (confirmed or unconfirmed CR or PR) at Week 12 could continue open-label cabozantinib and subjects with disease progression discontinued study treatment.

Primary Endpoints:

Lead-In Stage: Objective Response Rate (ORR) per mRECIST version 1.0, per investigator

Randomized Stage: Progression Free Survival (PFS) per mRECIST version 1.0, per investigator. The comparison of PFS between the cabozantinib and placebo arms was performed using the log-rank test in the randomized population.

Study population

A total of 526 subjects were enrolled at 42 sites in the US, Belgium, Israel and Taiwan, including a cohort of 41 subjects with advanced, recurrent or metastatic HCC and Child-Pugh A. Diagnosis was by core biopsy or by CT/MRI including angiography and serum alpha-fetoprotein (AFP) ≥ 400 ng/mL in subjects with liver cirrhosis and/or chronic HBV or HCV. Subjects could have received no more than one prior standard regimen.

The first subject was enrolled on 02 September 2009. The last subject last assessment across all cohorts was 30 May 2013 (the last assessment for the HCC cohort was 03 August 2012). A retrospective analysis of OS was conducted based on subjects' available survival status on 26 June 2013.

Subjects were mainly White (54%) or Asian (37%); 76% of subjects were male. Their median age was 60 years, and median weight was 71.5 kg. All subjects had ECOG PS of 0-1. The median time since diagnosis was 1.0 year. Subjects could have HCC based on multiple-recorded aetiologies: the most frequent reasons were cirrhosis (44%), unknown (29%), HBV (24%), HCV (24%) and alcohol-related (20%). A total of 20% of subjects had not received a prior treatment regimen. Prior sorafenib was received by 54% of subjects.

Study results

Two of 41 subjects with HCC (4.9%, 95% CI 0.9, 16.1) had a confirmed partial response (PR) on cabozantinib treatment during the 12-week Lead-in Stage and a further 31 subjects (76%) had stable disease. At Week 12, 27 subjects (66%, 95% CI 50.0, 79.5%) had disease stabilization (response or stable disease). Five subjects could not be evaluated or had missing assessments. Only three subjects (7.3%) showed evidence of primary refractory disease (PD as best response).

A total of 22 HCC subjects were randomized to receive either cabozantinib or placebo. The median PFS per Investigator during the Randomized Stage was 2.5 months in the cabozantinib arm and 1.4 months in the placebo arm (HR =0.815, 95% CI 0.313, 2.121; p=0.659).

Median PFS for all HCC subjects from the initial cabozantinib dose was 5.2 months by Kaplan-Meier estimate (5.2 months for sorafenib pre-treated subjects [n=22] and 4.2 months for sorafenib-naïve subjects [n=19]). Survival was assessed retrospectively; median OS for all treated patients (n=41)

from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study was a Phase 3, randomised, double- blind, placebo-controlled trial and the design is considered adequate. There were no second line therapies authorised for treatment of advanced HCC post sorafenib at the time that the study was initiated, although regorafenib has since received a MA (CHMP opinion June 2017). Therefore, the placebo-control is appropriate. The 2:1 randomization allowed more subjects the chance to receive active treatment.

The trial was worldwide, but recruitment was limited to 25% from Asian Geographic regions. This is appropriate given the differences in HCC aetiology between Asian and 'Western' populations, as well as variations in epidemiology, treatment approaches and treatment outcomes. Patients from Asian countries more typically have HBV associated HCC, which has been reported as having a worse outcome with TKIs compared with the more typical HCV -associated HCC in the West. Still, all patients with HBV were required to be treated with anti-viral therapy prior to enrolment.

The patient population was adequately selected with appropriate inclusion/ exclusion criteria to define a target population whilst avoiding those potentially at increased risk of adverse events. Most subjects were Child Pugh A with relatively preserved liver function; only 1.3% in the cabozantinib arm had a Child-Pugh score of B. This means that efficacy/ safety in patients with more severe liver disease is unknown therefore cabozantinib is not recommended for use in these patients (SmPC section 5.2).

Subjects who discontinued sorafenib due to intolerance could participate in the study, but it is not clear if any such subjects were recruited.

Patients with HBV and HCV disease were included in the study. The applicant confirmed that all patients with active disease also had to be treated to be eligible for the study. No information was collected related to the time from resolution of the infection, or time from reaching a sustained off-treatment virological response (SVR).

Overall survival was the primary efficacy endpoint. This is an accepted regulatory endpoint and is the most appropriate for this patient population, given the relatively short expected median OS. To avoid confounding, cross -over from placebo to cabozantinib was not permitted during the blinded treatment phase, although was in a subsequent 'open-label' phase. It is not clear if an open-label phase was instigated. Details of non-protocol anti-cancer therapies (NPACT) were collected and their influence on OS investigated in an exploratory analysis.

The secondary endpoints (PFS and ORR) were assessed only by Investigator with no independent radiology review. Although independent oversight is preferred, this is less important in a double-blind study and, also, they are secondary endpoints. However, bias in the readout might be introduced due to the toxicity profile being different between the two study arms.

RECIST 1.1 was used for soft tissue tumour response assessment and is a widely accepted method. Modified RECIST (mRECIST) criteria have emerged as more sensitive than RECIST 1.1 to assess response of hepatic lesions in HCC. With mRECIST, non-enhanced tumour is not measurable, so response reflects tumour vascularisation more accurately and has been found to predict OS in multivariate analyses (Meyer, et al., 2017). Other recent applications have utilised mRECIST as the primary radiographic assessment (Stivarga SmPC), whilst the historical sorafenib studies used RECIST

1.1. mRECIST may be technically challenging and difficult to implement with rigor in a multisite global clinical trial, without independent blinded centralised radiological review. Therefore, use of RECIST 1.1 is accepted. Use of mRECIST tends to result in higher reported ORR than RECIST 1.1 but uniform PFS times.

The analysis was changed from adjusting using the stratification factors per CRF to the IxRS, which is appropriate. The percentage discrepancies in reported aetiology (HBV/HCV) and presence of EHS/ MVI were similar in both arms between the CRF and the IxRS. The biggest discrepancy was in the determination of presence of EHS and/ or MVI with an extra ~6.5% of patients having EHS/MVI in the CRF vs. the IxRS. The CRF data is verified and corrected by study monitors. The IxRS data is based on (possibly limited) information available to investigators at the time of randomisation.

CT/MRI scans were performed every 8 weeks regardless of whether study treatment was given, so treatment interruptions did not influence the timing/ detection of radiological progression events.

There was no defined time scale from the end of previous therapy and recruitment to the cabozantinib trial. Median time from progression on the most recent systemic agent to randomisation was 1.61 months in the cabozantinib arm (range 0-100.8). Therefore, most patients continued quickly to cabozantinib therapy on progression. Presumably, those with a longer interval underwent local liver-directed therapy and could be surmised to have less active wide spread disease.

Efficacy data and additional analyses

Important baseline demographics and disease characteristics were well balanced between the treatment arms. Most subjects had extensive metastatic disease at enrolment. The most frequent sites of HCC disease at baseline per CRF were extrahepatic spread, with a similar distribution across both arms (79% in the cabozantinib arm vs 77% in the placebo arm). Approximately 41% of subjects had baseline AFP ≥ 400 ng/mL. Barcelona Clinic Liver Cancer (BCLC) status was not collected. It was assigned retrospectively using macrovascular invasion (MVI) as a surrogate for portal vein invasion. Whilst it is not clear that MVI is an appropriate surrogate, the treatment groups were well balanced in the BCLC stage B group (9% in cabozantinib arm versus 10% in placebo arm) and BCLC Stage C (91% in the cabozantinib arm versus 90% in placebo arm).

Prior treatment with sorafenib was a prerequisite for the Phase 3 study population. This was to ensure a consistent study population and because sorafenib was the only therapy authorised for first line advanced HCC at the time that the study was conducted. All patients had received prior sorafenib (3 in the Cabometyx arm in the adjuvant setting only) and the proportion (~25%) who had received two prior systemic therapies was well balanced between the two treatment arms. The number of subjects who had received prior TKI therapies other than sorafenib were similar in the two groups (19 [4%] subjects in the cabozantinib group vs 12 [5.1%] in the placebo group). Specifically, in the cabozantinib arm, the additional TKIs received were regorafenib (n=6), axitinib (n=4) and investigational drug (n=5). No patients had received prior lenvatinib. Only 1 patient (placebo arm) had received prior lenvatinib; this is explained by the fact that lenvatinib has primarily been investigated first line against sorafenib and all trial subjects had to have received sorafenib.

In view of the patient population treated in the pivotal trial, the indication was therefore restricted to treatment after prior sorafenib therapy. Cabozantinib is to be administered as monotherapy, which has also been reflected in the wording of the indication.

Patients were Child Pugh A and ECOG PS 0 or 1 so efficacy in patients with poor performance status or more advanced liver disease has not been investigated.

Results were analysed per the ITT population, which is acceptable; only 3 patients in the cabozantinib arm were randomised but not treated.

At the second pre-planned interim analysis, the prespecified event-driven primary analysis of the primary efficacy endpoint demonstrated a statistically significant improvement in OS for subjects in the cabozantinib 60 mg qd arm compared with placebo: the HR, adjusted for stratification factors (per IxRS), was 0.76 (95% CI: 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value to reject the null hypothesis of equal OS = 0.021). The Kaplan-Meier estimates for median duration of OS were 10.2 vs 8.0 months in the cabozantinib and placebo arms respectively, an estimated 2.2-month difference in the medians. The landmark estimate of the proportions of subjects that were event-free at 12 months was 46% compared with 34%.

For the primary OS analysis, the stratified HRs (95% CIs) were the same using stratification factors per IxRS and CRF.

The median duration of OS for the placebo arm was consistent with that seen in previous trials in a similar post-sorafenib setting in line with the target population with advanced disease [brivanib, 8.2 months, Llovet et al 2013; everolimus, 7.3 months, Zhu et al 2014 and ramucucirumab, 7.6 months, Zhu et al 2015].

The use of concomitant medications was similar between the two arms and is considered not to affect the OS outcome.

Crossover from placebo to cabozantinib was not permitted up to the database cut-off date. Post progression, more subjects in the placebo than the cabozantinib arm received non-radiation systemic therapies (25% cabozantinib arm, 30% placebo arm). Only 3.2% and 5.5% respectively received subsequent local liver – directed therapy. The relatively infrequent use of NPACT reflects the lack of approved alternative therapies in this setting and possibly the poor performance status of patients. The median time from randomization to first systemic NPACT was longer in the cabozantinib arm (202 days vs 100 days).

The incidence of systemic non-radiation and local liver-directed systemic non-protocol anticancer therapy (NPACT) was 26% in the cabozantinib arm and 33% in the placebo arm. Subjects receiving these therapies had to discontinue study treatment. An exploratory OS analysis censoring for the use of NPACT supported the primary analysis: the HR, adjusted for stratification factors (per IxRS), was 0.66 (95% CI: 0.52, 0.84; stratified logrank p-value = 0.0005). The Kaplan- Meier estimates for median duration of OS were 11.1 months in the cabozantinib arm versus 6.9 months in the placebo arm, an estimated 4.2-month difference in the medians (see section 5.1 of the SmPC).

The treatment effect at the prespecified first interim OS analysis performed by the IDMC, although not statistically significant [stratified log-rank p-value = 0.0041; critical p-value to reject the null hypothesis = 0.0037] was consistent (stratified HR 0.71, 95% CI 0.56, 0.90).

The primary analysis of PFS (PFS1) as determined by the Investigator yielded a median duration of PFS of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors (per IxRS), was 0.44 (95% CI: 0.36, 0.52, stratified log-rank p-value < 0.0001). Both PFS curves, but particularly that for placebo showed a marked drop at 2 months, the time of the first follow-up assessment, and this accounts for more than 50% of patients in the placebo group, so actual PFS in the placebo arm was shorter than 1.9 months. Results of additional sensitivity analyses of PFS (PFS2 and PFS3) were consistent with the primary PFS1 analysis.

There was a disparity between the median duration of cabozantinib exposure [3.8 months] (which includes time with dose interruptions) and PFS [5.2 months]. The explanation for the difference is likely to be that, while study treatment may end due to AEs or clinical progression, radiographic

progression may not occur or be documented until later due to the half-life of cabozantinib, tumour growth dynamics and the 8-week scanning interval.

The ORR rate was rather low; in the cabozantinib arm, 18 (4%) subjects had a BOR of PR compared with 1 (0.6%) subject in the placebo arm (unstratified Fisher exact test p-value per IxRS = 0.0059); there were no CRs in either arm. This was lower than seen with regorafenib (11% vs. 4%) but cabozantinib was assessed by RECIST v1.1 rather than mRECIST (regorafenib). The rate of stable disease in the cabozantinib arm relative to placebo was higher (60% vs 33%) and in line with regorafenib (65% vs. 36%). Conversely, more subjects in the placebo arm had PD as BOR (21% cabozantinib vs 55% placebo).

A higher number of subjects experienced a decrease in AFP in the cabozantinib arm as compared to the placebo arm, overall supporting the primary efficacy data.

Subgroup analyses showed a generally consistent effect on OS with HRs < 1 across most subgroups with ≥ 20 subjects in each treatment arm. No OS benefit was observed in subgroups with subjects from the Asian region (HR = 1.01, 95% CI: 0.68, 1.48), subjects with HCV (without HBV) per CRF (HR = 1.11, 95% CI: 0.72, 1.71) and subjects without extrahepatic spread and/or macrovascular invasion per CRF (HR = 0.99, 95% CI: 0.59, 1.65). However, median PFS with CABOMETYX treatment was shown in these subgroups.

Benefit for cabozantinib was shown in the MET low/negative subgroup (cabozantinib n = 144, placebo n = 68) with an OS HR of 0.67 (95% CI: 0.48, 0.92) and a PFS HR of 0.41 (95% CI: 0.30, 0.57). There were too few 'MET high' subjects in the placebo arm (cabozantinib n = 33, placebo n = 15) to determine relative benefit.

Many subgroups were analysed and the size and number of events in each subgroup varied. Some findings may have arisen by chance alone or been driven by unbalanced known or unknown confounding factors. Subgroup analyses were not powered to detect a treatment difference.

In an ad hoc subgroup analysis of subjects whose only prior therapy for HCC was sorafenib (70% of subjects), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (stratified HR [per IxRS] 0.70, 95% CI: 0.55, 0.88; unstratified HR 0.73, 95% CI: 0.58, 0.92).

For subjects who received 1 prior regimen the OS HR was 0.74 (95% CI 0.59, 0.92), whilst for subjects who received 2 prior regimens the unstratified OS HR was 0.90 (95% CI 0.63, 1.29).

Subjects could continue blinded study treatment after radiological disease progression, if, in the opinion of the investigator, they continued to receive benefit. A relatively high proportion of patients in both arms continued blinded treatment after radiological disease progression (32% in the cabozantinib and 49% in the placebo group), possibly until symptomatic progression as they were achieving clinical benefit or covering the time until new therapy was administered. The median number of days that treatment continued was short, but the full range was not presented: the median (Q1 to 3) was 13.50 (5.00 to 64.50) days in the cabozantinib arm and 7.00 (4.00 to 29.00) days in the placebo group.

Non-disease specific quality of life (QoL) was assessed using the EuroQoL EQ-5D-5L. A negative effect of Cabometyx versus placebo on the EQ-5D utility index score was observed during the first weeks of treatment. Only limited QoL data are available after this period (see section 5.1 of the SmPC).

The phase 2 RDT is supportive of the outcome in the pivotal study. There are limited results from patients who have not received sorafenib at all (n= 17 HCC patients in Phase 2 XL 184-203). In this small cohort (a mixture of treatment naïve and patients who received other agents, mostly chemotherapy) the estimated median PFS was 4.2 months. This is 1 month shorter than the median

PFS in the sorafenib pre-treated subgroup, although it is difficult to draw conclusions given the low patient numbers.

2.4.4. Conclusions on the clinical efficacy

A statistically significant benefit in overall survival for advanced HCC patients treated with cabozantinib as compared to placebo has been reported in the pivotal phase 3 study (CELESTIAL). This is further supported by a beneficial PFS outcome. Uncertainties remain with respect to extrapolation of the beneficial effect of cabozantinib over placebo to the population to be treated in the clinic, which is expected to be more heterogeneous and include more frail patients.

2.5. Clinical safety

Introduction

The safety summary mainly details the data from the HCC patients in the Phase 3 Study XL184-309, but a pooled safety analysis of safety data from 876 subjects is also provided, and differences highlighted if relevant.

Table 36: **Clinical Study Reports Provided for Pooled Safety Analyses**

Study (Phase)	**Study Report**	**Number of Subjects in the Cabozantinib Arm (Safety Population)**	**Data cut-off date**
XL184-309 (CELESTIAL) (Phase 3)	Full CSR, Primary analysis	Cabozantinib 60 mg: 467 HCC	1 June 2017
XL184-308 (METEOR) (Phase 3)	Full CSR, Primary analysis	Cabozantinib 60 mg: 331 RCC	22 May 2015
A031203 (CABOSUN) (Phase 2)	Full CSR, Primary analysis	Cabozantinib 60 mg: 78 RCC	15 September 2016

Data were pooled from Studies XL184-309, XL184-308 and A031203 for exposure, demographics, and adverse events (all Grade, Grade 3/4, Grade 5, SAEs, related SAEs and events to monitor [ETMs]). Laboratory results, vital signs and AEs leading to reductions, interruptions or modifications were not collected for Study A031203; for these pooled data from Studies XL184-309 and XL184-308 were presented.

A summary of safety results for 41 subjects in the HCC cohort of Study XL184-203 RDT (completion date 30 May 2013) who were assigned a higher dose of 100-mg cabozantinib (as development-stage capsules) was provided separately.

Patient exposure

In Study XL184-309, the median duration of cabozantinib exposure was 3.8 months [range 0.1, 37.3] compared with 2.0 months [range 0.0, 27.2] for placebo. At the data cut-off, 16% of subjects in the cabozantinib arm and 11% of subjects in the placebo arm remained on treatment. There was a higher rate in the cabozantinib arm of treatment discontinuation due to AEs (cabozantinib 21% vs placebo 5%), including AEs related to study treatment (16% vs 3%).

The assigned dose of study treatment was 60 mg with two dose reductions permitted (to 40 mg, then 20 mg) to manage AEs. The median relative dose intensity was 60% for the cabozantinib arm compared with 98% for the matched placebo arm. The median average daily cabozantinib dose was 36

mg. At the assigned dose, 62% of cabozantinib-treated subjects had a dose reduction due to an AE (13% in the placebo arm); 33% of cabozantinib-treated subjects had a second dose reduction (3.0% in the placebo arm). As allowed in the protocol, 9 subjects re-escalated study treatment from 40 mg to 60 mg.

The median time to first cabozantinib dose reduction was 38 days and the median time to second cabozantinib dose reduction was 83 days. The final dose of cabozantinib (excluding dose interruptions) was distributed between the 3 dose levels (60 mg: 39% of subjects, 40 mg: 28%, 20 mg: 33%). The last cabozantinib dose level received (including dose interruptions was): 60mg- 15% of subjects; 40mg – 12%; 20mg – 13%; 0mg – 59%.

The median time on treatment (excluding dose interruptions) for the three respective dose levels was 28, 33 and 73 days. The median time to the first dose interruption was 28.0 days in the cabozantinib arm, and to the second dose interruption was 70.0 days. The median duration of each dose interruption was 9.0 days in the cabozantinib arm, and the median total duration of dose interruptions was 25.0 days.

Table 37: Dose Interruptions Due to an Adverse Event (Safety Population)

Subjects with	**Cabozantinib (N = 467)**	**Placebo (N = 237)**
Any dose interruption, n (%)	390 (84)	88 (37)
Dose interruption: ≥ 7 days, n (%) ≥ 14 days ≥ 21 days	334 (72) 246 (53) 166 (36)	64 (27) 37 (16) 28 (12)
Number of dose interruptions per subject Mean (SD) Median (range)	 2.40 (2.723) 2.00 (1.0, 36.0)	 1.44 (0.842) 1.00 (1.0, 6.0)
Duration of total dose interruptions per subject (days)[a] Mean (SD) Median (range)	 32.69 (33.322) 25.00 (1.0, 366.0)	 19.24 (18.460) 13.00 (1.0, 110.0)

[a] Duration of each dose interruption = interruption stop date - interruption start date + 1; n = all subjects in Safety population.

The median cabozantinib exposure in the pooled population (XL184-309, XL184-308 and A031203) was longer - 5.6 months - and the median daily dose was higher - 41mg.

In the HCC cohort of the Phase 2 Study XL184-203 RDT, subjects received cabozantinib at a starting dose of 100 mg qd (freebase equivalent, development stage capsule formulation). The median treatment exposure for HCC subjects in the Continuous Cabozantinib Data Set was 89.0 days (range: 23 to 463 days). Over half (58.5%) underwent at least one dose reduction to 60mg due to AEs and 24.4% underwent at least a second level dose reduction to 40mg. Only 7.3% of subjects underwent further dose reductions to 20 mg qd. The median average daily cabozantinib dose was 65.7 mg, corresponding to a median dose intensity of 65.7%.

Adverse events

The overall incidence of any grade AEs was 99% in the cabozantinib arm and 92% in the placebo arm; reflecting the burden of advanced HCC and underlying liver disease in this patient population.

Table 38: **Study XL184-309: Overview of Treatment-Emergent Adverse Events (Safety Population)**

	Cabozantinib (N = 467) n (%)	**Placebo (N = 237) n (%)**
Any AE	460 (99)	219 (92)
Treatment-related AE	439 (94)	148 (62)
Serious AE	232 (50)	87 (37)

Treatment-related serious AE	82 (18)	14 (5.9)
Worst Grade 3 or 4 AE	316 (68)	86 (36)
Worst Grade 4 AE	46 (9.9)	6 (2.5)
Worst Grade 4 treatment-related AE	25 (5.4)	3 (1.3)
Grade 5 AE[a]	75 (16)	34 (14)
Grade 5 AE through 30 days after last dose	55 (12)	28 (12)
Grade 5 AE > 30 days after last dose[b]	20 (4.3)	6 (2.5)
Treatment-related Grade 5 AE	6 (1.3)	1 (0.4)
Death at any time (includes due to PD)	314 (67)	167 (70)
Death through 30 days after last dose	55 (12)	28 (12)
Death > 30 days after last dose	20 (4.3)	6 (2.5)
AE leading to treatment discontinuation (not related to PD) [c,d]	96 (21)	10 (4.2)
Related to study treatment	74 (16)	6 (2.5)
Unrelated to study treatment	27 (5.8)	4 (1.7)
AE leading to dose modification (reduction or interruption)	416 (89)	94 (40)
AE leading to dose reduction	300 (64)	30 (13)
AE leading to dose interruption	391 (84)	89 (38)

Two AEs reported for subjects in the cabozantinib arm could not be coded in MedDRA: Grade 2 AE (verbatim term "hypofosfatomy") and Grade 4 SAE (verbatim term "respiratory crisis"). Subjects are counted only once in each category but may be counted in multiple categories.

[a] 12 additional subjects (8 cabozantinib, 4 placebo) had Grade 5 AEs that were reported outside of the safety observation period. The preferred terms for these events in the cabozantinib arm were pneumonia general physical health deterioration hepatocellular carcinoma pneumothorax, and oesophageal varices haemorrhage. The preferred terms for these events in the placebo arm were lymphangiosis carcinomatosa and hepatic failure.

[b] Grade 5 AEs were not necessarily reported for subject deaths due to PD.

[c] Subjects could be assessed as having more than one AE that led to treatment discontinuation with differing causalities. The total proportion of subjects with an AE leading to treatment discontinuation may not equal the sum of the related and not related AEs leading to treatment discontinuation for a given treatment arm.

[d] In Table 4, 3 subjects (2 cabozantinib, 1 placebo) were summarized as discontinuing study treatment due to AE who were not summarized as having AEs leading to treatment discontinuation (not related to PD) in this table: Cabozantinib arm: Subject (blood bilirubin increased, Grade 2) and Subject (fatigue, Grade 3). Placebo arm: Subject (pulmonary haemorrhage, Grade 2).

The most *frequent AEs* (≥20% incidence) reported for subjects in the cabozantinib arm were diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension, vomiting, increased AST and asthenia. For subjects in the placebo arm, the most frequent AEs were fatigue and abdominal pain.

Adverse events that occurred at a ≥ 10% higher incidence in the cabozantinib arm compared with the placebo arm were palmar-plantar erythrodysaesthesia syndrome [PPES] (cabozantinib arm 46%, placebo arm 5.1%), diarrhoea (54%, 19%), decreased appetite (48%, 18%), hypertension (29%, 5.9%), dysphonia (19%, 2.1%), fatigue (45%, 30%), asthenia (22%, 7.6%), vomiting (26%, 12%), nausea (31%, 18%), mucosal inflammation (14%, 2.1%), ALT increased (17%, 5.5%), weight decreased (17%, 5.9%), AST increased (22%, 11%), stomatitis (13%, 2.1%), and thrombocytopenia (11%, 0.4%).

Table 39: Study XL184-309: Frequent Adverse Events Regardless of Causality (PTs with ≥ 10% Incidence in the Cabozantinib Arm) (Safety Population)

	Cabozantinib (N = 467) n (%) Grade		Placebo (N = 237) n (%) Grade	
Preferred Term	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
Number of subjects with at least one AE	460 (99)	316 (68)	219 (92)	86 (36)
Diarrhoea	251 (54)	46 (9.9)	44 (19)	4 (1.7)
Decreased appetite	225 (48)	27 (5.8)	43 (18)	1 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	217 (46)	79 (17)	12 (5.1)	0
Fatigue	212 (45)	49 (10)	70 (30)	10 (4.2)
Nausea	147 (31)	10 (2.1)	42 (18)	4 (1.7)
Hypertension	137 (29)	74 (16)	14 (5.9)	4 (1.7)
Vomiting	121 (26)	2 (0.4)	28 (12)	6 (2.5)
Aspartate aminotransferase increased	105 (22)	55 (12)	27 (11)	16 (6.8)
Asthenia	102 (22)	32 (6.9)	18 (7.6)	4 (1.7)
Dysphonia	90 (19)	3 (0.6)	5 (2.1)	0
Constipation	87 (19)	2 (0.4)	45 (19)	0
Abdominal pain	83 (18)	8 (1.7)	60 (25)	10 (4.2)
Weight decreased	81 (17)	5 (1.1)	14 (5.9)	0
Alanine aminotransferase increased	80 (17)	23 (4.9)	13 (5.5)	5 (2.1)
Mucosal inflammation	65 (14)	8 (1.7)	5 (2.1)	1 (0.4)
Pyrexia	64 (14)	0	24 (10)	1 (0.4)
Abdominal pain upper	63 (13)	3 (0.6)	31 (13)	0
Cough	63 (13)	1 (0.2)	26 (11)	0
Oedema peripheral	63 (13)	4 (0.9)	32 (14)	2 (0.8)
Stomatitis	63 (13)	8 (1.7)	5 (2.1)	0
Dyspnoea	58 (12)	15 (3.2)	24 (10)	1 (0.4)
Rash	58 (12)	2 (0.4)	14 (5.9)	1 (0.4)
Ascites	57 (12)	18 (3.9)	30 (13)	11 (4.6)
Dysgeusia	56 (12)	0	5 (2.1)	0
Hypoalbuminaemia	55 (12)	2 (0.4)	12 (5.1)	0
Headache	52 (11)	1 (0.2)	16 (6.8)	1 (0.4)
Thrombocytopenia	52 (11)	16 (3.4)	1 (0.4)	0
Insomnia	49 (10)	1 (0.2)	17 (7.2)	0
Dizziness	48 (10)	2 (0.4)	15 (6.3)	0
Dyspepsia	47 (10)	0	7 (3.0)	0

The incidence of frequent AEs of any grade in the cabozantinib arm of Study XL184-309 was generally consistent with that observed in the pooled population. Diarrhoea, fatigue, decreased appetite, and PPES were the most frequent any grade AEs in the pooled population and the cabozantinib arm of XL184-309.

Table 40: Study XL184-309: Related Adverse Event Preferred Terms Reported in ≥ 5 % of Subjects in the Either Treatment Arm Ordered by Decreasing Frequency and Presented by Grade (Safety Population)

Preferred Term	**Cabozantinib (N = 467) n (%)**			**Placebo (N = 237) n (%)**		
	Grade			**Grade**		
	All	**3 / 4**	**5**	**All**	**3 / 4**	**5**
Number of subjects with at least one related AE	439 (94)	304 (65)	6 (1.3)	148 (62)	44 (19)	1 (0.4)

Diarrhoea	216 (46)	42 (9.0)	0	29 (12)	2 (0.8)	0
Palmar-plantar erythrodysaesthesia syndrome	216 (46)	78 (17)	0	11 (4.6)	0	0
Fatigue	178 (38)	39 (8.4)	0	45 (19)	6 (2.5)	0
Decreased appetite	174 (37)	22 (4.7)	0	23 (9.7)	0	0
Hypertension	128 (27)	69 (15)	0	7 (3.0)	2 (0.8)	0
Nausea	115 (25)	7 (1.5)	0	18 (7.6)	0	0
Vomiting	80 (17)	1 (0.2)	0	7 (3.0)	2 (0.8)	0
Dysphonia	74 (16)	2 (0.4)	0	3 (1.3)	0	0
Asthenia	68 (15)	19 (4.1)	0	12 (5.1)	4 (1.7)	0
Aspartate aminotransferase increased	65 (14)	36 (7.7)	0	16 (6.8)	11 (4.6)	0
Mucosal inflammation	61 (13)	8 (1.7)	0	4 (1.7)	0	0
Stomatitis	60 (13)	8 (1.7)	0	4 (1.7)	0	0
Weight decreased	55 (12)	5 (1.1)	0	7 (3.0)	0	0
Alanine aminotransferase increased	54 (12)	16 (3.4)	0	9 (3.8)	3 (1.3)	0
Dysgeusia	53 (11)	0	0	4 (1.7)	0	0
Rash	48 (10)	2 (0.4)	0	9 (3.8)	0	0
Thrombocytopenia	38 (8.1)	12 (2.6)	0	0	0	0
Platelet count decreased	35 (7.1)	13 (2.8)	0	4 (1.7)	1 (0.4)	0
Abdominal pain	33 (7.1)	2 (0.4)	0	4 (1.7)	0	0
Alopecia	32 (6.9)	0	0	8 (3.4)	0	0
Dyspepsia	31 (6.6)	0	0	2 (0.8)	0	0
Dry skin	30 (6.4)	0	0	5 (2.1)	0	0
Hypothyroidism	30 (6.4)	1 (0.2)	0	1 (0.4)	0	0
Constipation	29 (6.2)	1 (0.2)	0	10 (4.2)	0	0
Blood bilirubin increased	27 (5.8)	4 (0.9)	0	6 (2.5)	1 (0.4)	0
Hypoalbuminaemia	26 (5.6)	0	0	1 (0.4)	0	0
Dizziness	25 (5.4)	0	0	6 (2.5)	0	0
Headache	24 (5.1)	0	0	5 (2.1)	0	0

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events. Denominators for percentages are N, the total number of subjects in each treatment arm.

Treatment related AEs (all grades) that had a ≥ 10% higher per-subject incidence in the cabozantinib arm compared with placebo were PPES (cabozantinib 46%, placebo 4.6%), diarrhoea (46%, 12%), decreased appetite (37%, 9.7%), hypertension (27%, 3.0%), fatigue (38%, 19%), nausea (25%, 7.6%), dysphonia (16%, 1.3%), vomiting (17%, 3.0%), mucosal inflammation (13%, 1.7%), and stomatitis (13%, 1.7%).

Severity of AEs

More Grade 3 or 4 AEs occurred in the cabozantinib arm (68% cabozantinib vs 36% placebo), chiefly due to the higher incidence of PPES (17% vs 0%) and hypertension (16% vs 1.7%). The most frequent Grade 3/4 AEs (≥ 5% incidence) reported for subjects in the cabozantinib arm in descending order of incidence were PPES, hypertension, increased AST, fatigue, diarrhoea, asthenia and decreased appetite. In the placebo arm, the most frequent Grade 3/4 AEs (≥ 5% incidence) in descending order were increased AST and anaemia.

The overall incidence of Grade 4 AEs was 9.9% in the cabozantinib arm and 2.5% in the placebo arm. Grade 4 AEs reported for ≥ 1% of subjects in the cabozantinib arm were increased γ-glutamyltransferase (GGT) (cabozantinib 1.3%, placebo 0.4%) and hypomagnesemia (1.1%, 0%).

Table 41: **Study XL184-309: Summary of Frequent Grade 3/4 Adverse Events (≥ 2% Incidence in the Cabozantinib Arm; Safety Population)**

Preferred Term	Cabozantinib[a] N = 467 n (%)	Placebo[b] N = 237 n (%)
Subjects with a Grade 3/4 AE	316 (68)	86 (36)
Palmar-plantar erythrodysaesthesia syndrome	79 (17)	0
Hypertension	74 (16)	4 (1.7)
Aspartate aminotransferase increased	55 (12)	16 (6.8)
Fatigue	49 (10)	10 (4.2)
Diarrhoea	46 (9.9)	4 (1.7)
Asthenia	32 (6.9)	4 (1.7)
Decreased appetite	27 (5.8)	1 (0.4)
Alanine aminotransferase increased	23 (4.9)	5 (2.1)
General physical health deterioration	21 (4.5)	6 (2.5)
Anaemia	19 (4.1)	12 (5.1)
Gamma-glutamyltransferase increased	19 (4.1)	9 (3.8)
Ascites	18 (3.9)	11 (4.6)
Hyponatraemia	18 (3.9)	5 (2.1)
Platelet count decreased	17 (3.6)	2 (0.8)
Blood alkaline phosphatase increased	16 (3.4)	1 (0.4)
Thrombocytopenia	16 (3.4)	0
Dyspnoea	15 (3.2)	1 (0.4)
Blood bilirubin increased	14 (3.0)	4 (1.7)
Pneumonia	14 (3.0)	3 (1.3)
Hepatic encephalopathy	13 (2.8)	2 (0.8)
Hypokalaemia	12 (2.6)	2 (0.8)
Nausea	10 (2.1)	4 (1.7)

[a] One reported Grade 4 AE for a subject in the cabozantinib arm could not be coded in MedDRA at the time of the database snapshot (verbatim term "respiratory crisis").

The incidence of frequent Grade 3/4 AEs in the cabozantinib arm of XL184-309 was generally consistent with that observed in the pooled population. However, certain Grade 3/4 AEs reported in ⩾ 2% of subjects in the pooled population are associated with advanced HCC and occurred primarily in subjects from Study XL184-309: increased AST, general physical health deterioration, increased GGT, ascites, increased blood bilirubin and decreased platelet count. Of these events, only AST increased (4.9%, 2.1%), general physical health deterioration (4.5%, 2.5%) and platelet count decreased (3.6%, 0.8%) had a ⩾ 2% higher incidence in the cabozantinib arm vs placebo arm in Study XL184-309. Thrombocytopaenia (3.4% vs. 0%) was reported separately from decreased platelet count.

ADRs for inclusion in the SmPC

The ADRs for inclusion in the SmPC were determined from review of the safety data for each pivotal study (2L RCC, 1L RCC and 2L HCC) and pooled data (across the RCC and HCC studies) as follows:

An initial screen involved AE frequency ≥10% in the cabozantinib arm (regardless of severity), AE frequency ≥5% difference between study treatment arms (regardless of severity), AE frequency ≥2% difference between study treatment arms for AEs with CTC Grade ≥3, laboratory parameter shifts representing a shift ≥2 CTCAE Grades between study treatment arms and EMA-defined designated medical events, irrespective of observed AE frequency.

This subset of identified adverse events was further evaluated using Bradford-Hill criteria, medical judgment and other information from pre-clinical, other clinical trials, post -marketing and literature sources. Then, the ADR frequency was defined by the observed number and percentage of subjects who experienced the treatment-emergent adverse event irrespective of reported causality.

Table 42: I**ndividual frequencies for each ADR**

MedDRA System Organ Class	**Very Common**	**Common**	**Uncommon**	**Not Known**
Infections and infestations		abscess (2.8%)		
Blood and lymphatic disorders	anaemia (15%)	thrombocytopenia (7.1%), neutropenia (3.9%)	lymphopenia (0.8%)	
Endocrine disorders	hypothyroidism (14%)			
Metabolism and nutrition disorders	decreased appetite (47%), hypomagnesaemia (11%), hypokalaemia (11%)	dehydration (4.1%), hypoalbuminaemia (9.8%), hypophosphataemia (8.2%), hyponatraemia (6.5%), hypocalcaemia (5.7%), hyperkalaemia (3.4%), hyperbilirubinemia (1.7%), hyperglycaemia (4.9%), hypoglycaemia (1.4%)		
Nervous system disorders	dysgeusia (19%), headache (11%), dizziness (12%)	peripheral sensory neuropathy (2.4%)	convulsion (0.5%)	cerebrovascular accident
Ear and labyrinth disorders		tinnitus (1.8%)		
Cardiac disorders				myocardial infarction
Vascular disorders	hypertension (36%), haemorrhage (19%)	venous thrombosis (3.7%), arterial thrombosis (1.5%)		
Respiratory, thoracic, and mediastinal disorders	dysphonia (20%), dyspnoea (15%), cough (15%)	pulmonary embolism (2.2%)		
Gastrointestinal disorders	diarrhoea (63%), nausea (39%), vomiting (28%), stomatitis (19%), constipation (21%), abdominal pain (17%), dyspepsia (12%), upper abdominal pain (11%)	gastrointestinal perforation (1.0%), fistula (1.3%), gastroesophageal reflux disease (5%), haemorrhoids (2.9%), oral pain (3.0%), dry mouth (7.8%)	pancreatitis (0.8%), glossodynia (0.6%)	
Hepatobiliary disorders		hepatic encephalopathy (3.2%)	hepatitis cholestatic (0.1%)	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome (44%), rash (12%)	pruritus (6.7%), alopecia (7.6%), dry skin (9.8%), dermatitis acneiform (4.1%), hair colour changes (3.4%)		
Musculoskeletal and connective tissue disorders	pain in extremity (11%)	muscle spasms (9.2%), arthralgia (8.3%)	osteonecrosis of the jaw (0.2%)	

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Renal and urinary disorders		proteinuria (7.2%)		
General disorders and administration site conditions	fatigue (51%), mucosal inflammation (15%), asthenia (19%), peripheral oedema (11%)			
Investigations	weight decreased (24%), serum ALT increased (20%), AST increased (24%)	blood ALP increased (6.8%), GGT increased (6.2%), blood creatinine increased (5.0%), amylase increased (2.6%), lipase increased (2.4%), blood cholesterol increased (1.4%), white blood cell count decreased (3.4%)	blood triglycerides increased (0.9%)	
Injury, poisoning and procedural complications			wound complications (0.1%)	

Serious adverse event / deaths / other significant events

Deaths

The incidence of all deaths in Study XL184-309 up to the 01 June 2017 cut-off date was 314 (67%) in the cabozantinib arm and 167 (70%) in the placebo arm.

The incidence of **deaths up to 30 days after the last dose of study drug** was similar in each arm: 57 (12%) subjects in the cabozantinib vs 28 (12%) in the placebo arm. Deaths were attributed to PD for 30 subjects (6.4%) and 21 subjects (8.9%) and to other reasons for 27 subjects (5.8%) and 7 subjects (3.0%), respectively, in the cabozantinib and placebo arms.

Table 43: Study XL184-309: Summary of Deaths through 30 Days after Last Dose of Study Treatment (Safety population)

	Cabozantinib N = 467 n (%)	Placebo N = 237 n (%)
Deaths through 30 days after last dose	57 (12)[a]	28 (12)
Disease progression	30 (6.4)	21 (8.9)
Other cause	27 (5.8)	7 (3.0)
Death Causally Associated with hepatocellular carcinoma		
No	9 (1.9)	2 (0.8)
Yes	16 (3.4)	4 (1.7)
Unknown	2 (0.4)	1 (0.4)

[a] Two of the deaths in the cabozantinib arm occurred outside of the AE observation period

Associated all-causality non-PD-related Grade 5 AEs that occurred in more than one subject in the cabozantinib arm were hepatic failure (5 subjects), multi-organ failure (2 subjects), and oesophageal varices haemorrhage (2 subjects) [and, in 1 subject each, acute lymphocytic leukaemia, acute respiratory distress syndrome, completed suicide, death, oesophagobronchial fistula, hepatorenal syndrome, intracranial tumour haemorrhage, ischaemic hepatitis, ischemic stroke, liver disorder, metastases to lung, portal vein thrombosis, prerenal failure, pulmonary embolism, respiratory failure, sepsis, tumour haemorrhage, and upper GI haemorrhage].

The Grade 5 AE in the placebo arm was hepatic failure (2 subjects) [and, in 1 subject each, death, biliary sepsis, intestinal perforation, pneumonia and aspiration pneumonia].

A summary of pooled Grade 5 AEs up until 30 days after the last dose of study treatment for the cabozantinib arm of Studies XL184-309, XL184-308 and A031203 is presented below. These were generally associated with the disease under study and comprised HCC, RCC, hepatic failure (all events in HCC subjects), death, general physical health deterioration, metastases to lung, metastatic RCC and oesophageal varices haemorrhage (both events in HCC subjects). The remaining Grade 5 AE PTs up to 30 days after the last dose occurred in 1 subject each.

Table 44: Pooled Studies XL184-309, XL184-308, and A031203: Summary of Grade 5 Adverse Events through 30 Days after Last Dose of Study Treatment (Safety Population, affecting ≥ 2 subjects)

Preferred Term	**Pooled Cabozantinib N = 876 n (%)**
Subjects with a Grade 5 adverse event	73 (8.3)
Hepatocellular carcinoma	24 (2.7)
Renal cell carcinoma	6 (0.7)
Hepatic failure	5 (0.6)
Death	4 (0.5)
General physical health deterioration	4 (0.5)
Metastases to lung	2 (0.2)
Metastatic renal cell carcinoma	2 (0.2)
Multi-organ failure	2 (0.2)
Oesophageal varices haemorrhage	2 (0.2)
Sepsis	2 (0.2)

There was an additional subject who died of jejunal perforation in Study A031202 (Grade 5 AE related to study treatment). He had a history of pancreatic metastases and a jejunal mass eroding adjacent bowel.

A total of 396 deaths occurred **more than 30 days after the last dose of study treatment**: 257 (55%) in the cabozantinib arm and 139 (59%) in the placebo arm. Most of these deaths were due to PD; 228 (49%) subjects in the cabozantinib arm and 119 (50%) subjects in the placebo arm.

In the cabozantinib arm, 20 subjects (4.3%) had Grade 5 AEs that occurred more than 30 days after the last dose. Ten events were attributed to HCC and 10 Grade 5 non-PD AEs were reported per Investigator: general physical health deterioration (n=3), cerebrovascular accident, hepatic cirrhosis, hepatic encephalopathy, hepatic failure, lung infection, pneumonia and staphylococcal sepsis (1 each).

In the placebo arm, 6 subjects (2.5%) had Grade 5 AEs that occurred more than 30 days after the last dose. Four events were attributed to HCC and 2 Grade 5 non-PD AEs were reported: chronic hepatic failure and hepatorenal syndrome.

None of the Grade 5 AEs in either treatment arm was assessed as related to study treatment.

Grade 5 events more than 30 days after the last dose that occurred in more than 1 subject in the pooled population were associated with the disease under study and comprised HCC, RCC and general physical health deterioration. The remaining Grade 5 AE PTs more than 30 days after the last dose occurred in 1 subject each. None of these events were assessed as related to study treatment.

Serious Adverse Events

The overall incidence of SAEs was 50% in the cabozantinib arm and 37% in the placebo arm.

The most frequent SAEs (≥ 2% incidence) reported for subjects in the cabozantinib arm were: HCC, general physical health deterioration, pneumonia, hepatic encephalopathy, ascites and dyspnoea.

The most frequent SAEs (≥ 2% incidence) reported for subjects in the placebo arm were: HCC, abdominal pain, general physical health deterioration, hepatic failure, pneumonia and oesophageal varices haemorrhage. The nature of the most frequent SAEs was generally similar for both treatment arms.

Hepatic encephalopathy was observed at higher incidence in the cabozantinib (3.2%) than in the placebo arm (0.4%).

GI perforations were reported in 0.9% of cabozantinib-treated patients (4/467). All events were Grade 3 or 4. Median time to onset was 5.9 weeks.

Table 45: Study XL184-309: Summary of Frequent Serious Adverse Events (≥ 1% Incidence in the Either Treatment Arm; Safety Population)

Preferred Term	Cabozantinib[a] N=467 n (%)	Placebo N=237 n (%)
Subjects with an serious adverse event	232 (50)	87 (37)
Hepatocellular carcinoma	39 (8.4)	22 (9.3)
General physical health deterioration	17 (3.6)	8 (3.4)
Pneumonia	16 (3.4)	6 (2.5)
Hepatic encephalopathy	15 (3.2)	1 (0.4)
Ascites	12 (2.6)	3 (1.3)
Dyspnoea	10 (2.1)	2 (0.8)
Asthenia	9 (1.9)	1 (0.4)
Hepatic failure	8 (1.7)	8 (3.4)
Oesophageal varices haemorrhage	7 (1.5)	5 (2.1)
Abdominal pain	6 (1.3)	9 (3.8)
Fatigue	6 (1.3)	1 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	6 (1.3)	0
Diarrhoea	5 (1.1)	1 (0.4)
Hyponatraemia	5 (1.1)	0
Thrombocytopenia	5 (1.1)	0
Vomiting	4 (0.9)	4 (1.7)
Haemoptysis	2 (0.4)	3 (1.3)
Metastases to central nervous system	2 (0.4)	3 (1.3)

[a] There was 1 un-coded serious adverse event reported in 1 subject in the cabozantinib arm: 'respiratory crisis'.

The overall incidence of related SAEs was 18% (n=82) in the cabozantinib arm and 5.9% (n=14) in the placebo arm. No related SAEs were reported for ≥2% of subjects in either arm.

Related SAEs that had a ≥ 1% higher per-subject incidence in the cabozantinib arm compared with placebo (all 0%) were hepatic encephalopathy (cabozantinib n=7, 1.5%), PPES (n=6, 1.3%), asthenia (n=5, 1.1%) and diarrhoea (n=5, 1.1%).

In the placebo arm, treatment-related SAEs of haemoptysis and vomiting were reported in 2 subjects (0.8%) each; all other reported SAEs occurred in 1 subject each.

Table 46: Study XL184-309: Summary of Frequent Treatment-Related Serious Adverse Events (≥ 2 Event Incidence in the Cabozantinib Arm; Safety Population)

Preferred Term	Cabozantinib N=467 n (%)	Placebo N=237 n (%)
Subjects with a related serious adverse event	82 (18)	14 (5.9)
Hepatic encephalopathy	7 (1.5)	0
Palmar-plantar erythrodysaesthesia syndrome	6 (1.3)	0
Asthenia	5 (1.1)	0
Diarrhoea	5 (1.1)	0
Fatigue	4 (0.9)	0
Thrombocytopenia	4 (0.9)	0
Epistaxis	3 (0.6)	0
Portal vein thrombosis	3 (0.6)	0
Pulmonary embolism	3 (0.6)	1 (0.4)
Anaemia	2 (0.4)	0
Decreased appetite	2 (0.4)	0
Dehydration	2 (0.4)	0
Dyspnoea	2 (0.4)	0
Gastric perforation	2 (0.4)	0
General physical health deterioration	2 (0.4)	0
Hypertension	2 (0.4)	1 (0.4)
Hypocalcaemia	2 (0.4)	0
Hypomagnesaemia	2 (0.4)	0
Nausea	2 (0.4)	0
Upper gastrointestinal haemorrhage	2 (0.4)	1 (0.4)

The most frequent SAEs in the pooled population included events associated with the disease under study (HCC [4.5%] and general physical health deterioration [2.4%]). Pneumonia was a frequent SAE in the pooled population [2.5%], with most events occurring in Study XL184-309; although the incidence was similar in the cabozantinib and placebo arms of that study (3.4 vs 2.5%).

Additionally, certain SAEs that are associated with advanced HCC were observed at ≥1% incidence in the pooled population and occurred primarily in subjects of Study XL184-309: hepatic encephalopathy and ascites. Diarrhoea (n=15, 1.7%), hypertension (10, 1.1%) and PPES (10, 1.1%) were the most frequent treatment-related SAEs in the pooled population.

Table 47: Pooled Studies XL184-309, XL184-308, and A031203: Summary of Frequent Serious Adverse Events (≥ 1% Incidence; Safety Population)

Preferred Term	Pooled Cabozantinib N = 876 n (%)
Subjects with an serious adverse event	401 (46)
Hepatocellular carcinoma	39 (4.5)
Pneumonia	22 (2.5)
General physical health deterioration	21 (2.4)
Abdominal pain	16 (1.8)
Diarrhoea	16 (1.8)
Dyspnoea	16 (1.8)
Hepatic encephalopathy	15 (1.7)
Ascites	13 (1.5)
Asthenia	13 (1.5)
Anaemia	12 (1.4)
Fatigue	12 (1.4)
Pleural effusion	12 (1.4)
Nausea	11 (1.3)
Renal cell carcinoma	11 (1.3)
Vomiting	11 (1.3)
Dehydration	10 (1.1)
Hypertension	10 (1.1)
Hyponatraemia	10 (1.1)
Palmar-plantar erythrodysaesthesia syndrome	10 (1.1)
Back pain	9 (1.0)
Pulmonary embolism	9 (1.0)

Adverse Events Leading to Dose Reduction

In HCC Study XL184-309, there was a higher incidence of all-grade AEs leading to dose reduction in the cabozantinib arm relative to placebo (64% vs 13%). The most frequent AEs leading to dose reduction occurring in ≥5% of cabozantinib-treated subjects by decreasing frequency were PPES, diarrhoea, fatigue, hypertension and increased AST.

Table 48: Study XL184-309: Frequent Adverse Events Leading to Dose Reduction (≥ 5% Incidence in the Cabozantinib Arm; Safety Population)

Preferred Term	Cabozantinib N=467 n (%)		Placebo N=237 n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Subjects with an AE	300 (64)	179 (38)	30 (13)	17 (7.2)
Palmar-plantar erythrodysaesthesia syndrome	101 (22)	34 (7.3)	0	0
Diarrhoea	47 (10)	20 (4.3)	1 (0.4)	1 (0.4)
Fatigue	35 (7.5)	17 (3.6)	5 (2.1)	3 (1.3)
Hypertension	35 (7.5)	26 (5.6)	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	26 (5.6)	21 (4.5)	5 (2.1)	4 (1.7)

Denominators for percentages are N, the total number of subjects in each treatment arm.
Data from the AE CRF with respect to action taken with study drug differ slightly from the dose reduction summaries based upon the Study Treatment CRF, and these minor differences were not reconciled.

In RCC Study XL184-308, the incidence of all-grade AEs leading to cabozantinib dose reduction was 60%, most frequently diarrhoea, PPES and fatigue.

Adverse Events Leading to Dose Interruption

The incidence of AEs leading to dose interruption was 84% in the cabozantinib arm versus 38% in the placebo arm. Adverse events that led to interruptions, including those for which treatment never resumed, are included in this summary; these events are included in the summary of AEs that led to study treatment discontinuation if relevant.

Table 49: Study XL184-309: Frequent Adverse Events Leading to Dose Interruption (≥ 5% Incidence in the Cabozantinib Arm; Safety Population)

Preferred Term	Cabozantinib N=467 n (%)		Placebo N=237 n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Subjects with an AE	391 (84)	307 (66)	89 (38)	62 (26)
Palmar-plantar erythrodysaesthesia syndrome	119 (25)	70 (15)	0	0
Diarrhoea	69 (15)	29 (6.2)	4 (1.7)	1 (0.4)
Fatigue	63 (13)	36 (7.7)	5 (2.1)	3 (1.3)
Aspartate aminotransferase increased	44 (9.4)	38 (8.1)	7 (3.0)	5 (2.1)
Asthenia	32 (6.9)	17 (3.6)	5 (2.1)	3 (1.3)
Decreased appetite	31 (6.6)	10 (2.1)	1 (0.4)	0
Hypertension	31 (6.6)	24 (5.1)	2 (0.8)	2 (0.8)
Alanine aminotransferase increased	25 (5.4)	15 (3.2)	4 (1.7)	2 (0.8)
Nausea	25 (5.4)	3 (0.6)	3 (1.3)	1 (0.4)

Data from the AE CRF with respect to action taken with study drug differ slightly from the dose interruption summaries based upon the Study Treatment CRF, and these minor differences were not reconciled.

The incidence of AEs leading to dose interruption per AE CRF was higher in the cabozantinib arm of Study XL184-309 (84%) than Study XL184-308 (70%). This included AEs of PPES (25% vs. 14%) and

increased AST (9.4% vs. 1.8%). Diarrhoea, PPES and fatigue were among the most frequent AEs leading to dose interruption in both studies.

In HCC Study XL184-309, there was a higher incidence of all-grade AEs leading to dose modification (reduction or interruption) in the cabozantinib arm relative to placebo (89% vs 40%). In RCC Study XL184-308, the incidence of all-grade AEs leading to dose modification was 77% in the cabozantinib arm. The somewhat higher incidence of AEs leading to cabozantinib dose modification in Study XL184-309 relative to Study XL184-308 may be explained by the higher incidence of events of PPES and AST increased.

Other Clinically Significant Adverse Events and Events to Monitor (ETM)

Hepatobiliary Disorders SOC

Adverse events in the hepatobiliary disorders SOC were reported at a similar incidence in the 2 treatment arms: 12% in the cabozantinib and 14% in the placebo arm. The most frequent AEs (≥ 1% incidence, any grade, either arm) were: hyperbilirubinemia (cabozantinib 2.4%, placebo 3.4%), hepatic failure (1.9%, 3.4%), jaundice (1.9%, 3.4%), portal vein thrombosis (1.3%, 0%) and hepatic pain (0%, 1.3%).

Grade 3 or 4 AEs in the hepatobiliary disorders SOC were reported for 6.2% of subjects in the cabozantinib and 8.4% of subjects in the placebo arm. The most frequent Grade 3 or 4 AEs (≥ 1% incidence, either arm) were hyperbilirubinemia (cabozantinib 1.3%, placebo 2.1%), portal vein thrombosis (1.1%, 0%) and hepatic failure (0.4%, 2.5%).

In the cabozantinib arm, 11 subjects (2.4%) experienced Grade 5 AEs from the hepatobiliary disorders SOC: hepatic failure (6 subjects), portal vein thrombosis, hepatorenal syndrome, hepatic cirrhosis, ischemic hepatitis, and liver disorder (1 subject each). Three were considered related to study treatment (hepatic failure, hepatorenal syndrome and portal vein thrombosis, as described previously) and 8 were considered unrelated. These subjects had extrahepatic tumour spread and/ or macrovascular invasion (n=8), had been heavily pre-treated [multiple TACE (n=4); SIRT (n=1); RFA (n=1); hepatectomy/ lobectomy/ segmentectomy (n=3)] and/ or had an ECOG PS of 1 (n=3).

In the placebo arm, 4 subjects (1.7%) experienced Grade 5 hepatobiliary events: hepatic failure (2 subjects), hepatorenal syndrome and chronic hepatic failure (1 subject each). One hepatic failure AE was considered treatment related, as described previously.

AEs of hepatic encephalopathy and oesophageal varices haemorrhage are associated with progression of liver disease but are not reported in the primary SOC of hepatobiliary disorders.

Hepatic Encephalopathy

Hepatic encephalopathy (any grade) was reported for 19 subjects (4.1%) in the cabozantinib and 3 subjects (1.3%) in the placebo arm. Most events were not considered to be related to study treatment by the Investigator: related AEs of hepatic encephalopathy occurred in 8 (1.7%) and 1 (0.4%) subjects, respectively.

All-causality Grade 3 or 4 events were reported for 13 subjects (2.8%) and 2 subjects (0.8%), respectively. In addition, one subject in the cabozantinib arm had a Grade 5 event (4403-3510) 43 days after last dose of study drug, which the Investigator considered was due to progressive disease.

All 19 subjects in the cabozantinib arm with treatment-emergent hepatic encephalopathy had predisposing baseline and/or postbaseline factors that potentially contributed to the occurrence of hepatic encephalopathy:

- 11 had a history of cirrhosis prior to enrolment (baseline cirrhosis status was not solicited per CRF)

- 2 were Child-Pugh B at baseline

- 2 had a prior history of hepatic encephalopathy

- 3 had hepatic encephalopathy onset more than 30 days after their last dose of study treatment

- 5 had hepatic encephalopathy onset before steady-state cabozantinib plasma concentrations were likely to have been reached (i.e. 15 days from first dose of study treatment)

- 1 had hepatic encephalopathy onset the same day that the subject “abused alcohol”

- 12 had AEs or laboratory abnormalities that could contribute to the development of hepatic encephalopathy per AASLD guidelines (constipation, electrolyte disorders, GI haemorrhage and infection) within 14 days before the first onset of hepatic encephalopathy

- 10 had AEs that could contribute to the development of electrolyte imbalances or fluid shifts (vomiting, diarrhoea or decreased appetite) within 14 days before the first onset of hepatic encephalopathy

Seven of the 19 subjects continued to receive cabozantinib at a reduced dose for at least 30 days after the initial onset of hepatic encephalopathy.

Encephalopathy AEs of any grade were reported at a higher incidence in the cabozantinib compared with the placebo arm (8 subjects [1.7%] and 1 subject [0.4%], respectively). Encephalopathy was considered related in 4 (0.9%) and 0 subjects, respectively. All-causality Grade 3 events were reported for 3 (0.6%) and 1 subject (0.4%), respectively; no Grade 4 or 5 events were reported. Encephalopathy as an SAE was reported for 1 subject (0.2%) in the cabozantinib arm and no subjects in the placebo arm.

All 8 subjects in the cabozantinib arm, who had treatment-emergent encephalopathy, had predisposing baseline and/or postbaseline factors that potentially contributed to the development of encephalopathy, including: a history of cirrhosis (n=3); a gastric ulcer bleed with a ligation procedure (n=1); concomitant CNS depressants, lorazepam and oxycodone (n=1); “massive” tumour progression (n=1); potentially contributory AEs or laboratory abnormalities within 14 days before the first onset of encephalopathy - constipation, electrolyte disorders, GI haemorrhage and infection (n=7) or AEs possibly leading to electrolyte imbalances or fluid shifts within 14 days before the first onset of encephalopathy - vomiting, diarrhoea or decreased appetite (n=6).

Three of the 8 cabozantinib subjects who experienced treatment- emergent encephalopathy continued to receive study treatment for at least 30 days after AE onset.

Events to Monitor (ETMs)

A series of ETMs were defined based on groupings of AE PTs known to be associated with VEGFR-TKIs

Table 50: XL184-309: Incidence of Events to Monitor (Safety Analysis Set)

	Cabozantinib N=467 n (%)			Placebo N=237 n (%)		
	Grade			Grade		
ETM	Any	3/4	5	Any	3/4	5
GI perforation	4 (0.9)	4 (0.9)	0	2 (0.8)	1 (0.4)	1 (0.4)
Fistula	7 (1.5)	2 (0.4)	1 (0.2)	1 (0.4)	1 (0.4)	0
Abscess—all	18 (3.9)	9 (1.9)	0	2 (0.8)	0	0
Intra-abdominal and pelvic abscess	5 (1.1)	3 (0.6)	0	0	0	0
Haemorrhage (≥ Grade 3)	34 (7.3)[a]	29 (6.2)	5 (1.1)	17 (7.2)[a]	17 (7.2)	0
Arterial thrombotic events	12 (2.6)[b]	7 (1.5)[b]	2 (0.4)[b]	3 (1.3)	1 (0.4)	0
Venous and mixed/unspecified thrombotic events	23 (4.9)	16 (3.4)	2 (0.4)	6 (2.5)	4 (1.7)	0
Wound complications	4 (0.9)	1 (0.2)	0	0	0	0
Hypertension	138 (30)	75 (16)	0	14 (5.9)	4 (1.7)	0
Osteonecrosis	0	0	0	0	0	0
PPES[c]	217 (46)	79 (17)	NA	12 (5.1)	0	NA
Proteinuria[d]	17 (3.6)	7 (1.5)	NA	1 (0.4)	1 (0.4)	NA
RPLS	0	0	0	0	0	0
Diarrhoea	251 (54)	46 (9.9)	0	44 (19)	4 (1.7)	0
QT prolongation	3 (0.6)	1 (0.2)	0	0	0	0

PPES, palmar-plantar erythrodysesthesia syndrome; RPLS, reversible posterior leukoencephalopathy syndrome (preferred term: posterior reversible encephalopathy syndrome [PRES]).
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.
[a] Only Haemorrhage ETM events with severity ≥ Grade 3 are summarized.
[b] The following were not captured as arterial thrombotic events: ischaemic hepatitis (Grade 5), intestinal ischaemia (Grade 4) and peripheral ischaemia (Grade 4) in the cabozantinib arm (one subject each); ischaemic hepatitis (Grade 4) and myocardial ischaemia (Grade 3) in the placebo arm (one subject each). Including these subjects, the overall incidence of all-grade ATEs was 15 (3.2%) in the cabozantinib arm and 5 (2.1%) in the placebo arm; Grade ≥ 3 ATEs was 12 (2.6%) vs 3 (1.3%).
[c, d] Per CTCAE v4, there are no events of PPES or proteinuria with severity > Grade 3.

Most ETMs occurred at a higher incidence in the cabozantinib arm compared to the placebo arm, except osteonecrosis and RPLS, which did not occur in either treatment arm.

In line with what is known about the safety profile of cabozantinib in approved indications, the incidences of grade 3/4 thromboembolic events, hypertension, PPES, and diarrhoea, were higher in the cabozantinib arm of Study XL184-309 compared to placebo.

Grade ≥ 3 Haemorrhage:

Clinically relevant haemorrhage events occurred at a similar frequency in both treatment arms (7.3% cabozantinib vs 7.2% placebo). The incidence of ≥Grade 3 AEs of oesophageal varices haemorrhage was also similar in each arm (1.5% vs 2.1%). However, five subjects in the cabozantinib arm had a Grade 5 haemorrhage event. One event (upper GI haemorrhage, as discussed in the section on deaths) was assessed as related to treatment by the Investigator. Median time to onset was 9.1 weeks.

Venous Thromboembolism (VTE):

VTE (all grades) occurred in 4.9% of subjects in the cabozantinib arm compared with 2.5% in the placebo arm, including portal vein thrombosis (1.3% vs 0%), deep vein thrombosis (0.9% vs 0%) and pulmonary embolism (1.5% vs 2.1%).

Two subjects in the cabozantinib arm had a Grade 5 VTE (pulmonary embolism and portal vein thrombosis); both events were deemed related to study treatment by the Investigator.

The incidence of VTEs in the cabozantinib arm was higher in subjects that had extrahepatic spread and/or macrovascular invasion at baseline than in subjects that did not (5.6% vs 1.4%), which was mainly due to the incidence of portal vein thrombosis (3.2% vs 0.6%). Among the 6 cabozantinib subjects who experienced portal vein thrombosis, 4 had a history of portal vein tumour invasion prior to randomization. In the placebo arm, no notable difference in the incidence of VTEs was observed based on whether the subjects had extrahepatic spread and/or macrovascular invasion at baseline.

Arterial Thromboembolism (ATE):

If all events, including ischaemic events were captured, the incidence of ATE (all grades) in the cabozantinib and placebo arms was 3.2% vs 2.1%; the incidence of ≥ Grade 3 ATEs was 2.6% vs 1.3%. Two subjects in the cabozantinib arm had Grade 5 ATEs, neither of which was deemed related to study treatment by the Investigator:

ischemic stroke; 66-year-old male with a history of smoking, hypertension and sleep apnoea,

cerebrovascular accident; 57-year-old male who was hospitalized in a confusional state following an overdose of zolpidem; the subject experienced “inhalation bronchopneumopathy” and, on Study Day 43, developed secondary hepatic failure followed by the cerebrovascular accident on Study Day 68, approximately 38 days after last dose of study drug.

In addition, one subject had Grade 5 ischaemic hepatitis deemed related to study treatment by the Investigator; 66-year-old male with a history of smoking, alcoholic liver cirrhosis, chronic gastritis, hypertension and diabetes mellitus. The subject had undergone prior segmentectomy and Cyberknife to liver; the subject was hospitalized due to gastric varices haemorrhage and ischaemic hepatitis, an increased risk for bleeding was evidenced by elevated PT and INR values; the subject died three days later. This was not captured in the section on deaths. The applicant confirmed that this was erroneously attributed to study therapy when the investigator assessed the haemorrhage and ischaemic hepatitis as due to underlying cirrhosis.

QT Prolongation:

A non-serious Grade 3 AE of QT prolongation occurred in one subject in the cabozantinib arm concurrent with Grade 2 hypokalaemia; the subject had Investigator-assessed triplicate average QTcF of > 500 ms, but, per independent central review, was determined to not exceed a triplicate average of 440 ms.

In addition, one subject had a Grade 1 AE of QT prolongation and another subject had Grade 1 AE of QT abnormal.

Events of Torsades de pointes have not been reported in any cabozantinib study, or in the post-marketing setting. The potential risk of QT prolongation is unlikely to be clinically significant.

Time to Event

There was a relatively early median onset for the more frequent ETMs: hypertension (2.1 weeks), PPES (3.1 weeks) and diarrhoea (4.1 weeks). The median time to first occurrence was longer for

clinically significant but less frequent events: approximately 6 weeks for intra-abdominal and pelvic abscesses and GI perforations; 7 weeks for wound complications; and 9 weeks for VTEs, ATEs and ≥ Grade 3 haemorrhages and 14 weeks for fistulas.

Gastrointestinal perforation, fistulas, haemorrhage, thromboembolic events, wound complications, hypertension, PPES, proteinuria and RPLS are described in the Warnings and Precautions section of the Cabometyx SmPC.

Table 51: **Pooled Studies XL184-309, XL184-308, and A031203: Incidence of Events to Monitor (Safety Population) Study XL184-309**

	Cabozantinib N = 876 n (%)		
	Grade		
ETM	**Any**	**3/4**	**5**
GI perforation	9 (1.0)	7 (0.8)[a]	1 (0.1)[a]
Fistula	11 (1.3)	3 (0.3)	1 (0.1)
Abscess—all	25 (2.9)	13 (1.5)	0
Intra-abdominal and pelvic abscess	9 (1.0)	7 (0.8)	0
Haemorrhage (≥ Grade 3)	45 (5.1)[b]	38 (4.3)	7 (0.8)
Arterial thrombotic events	20 (2.3)[c]	12 (1.4)[c]	3 (0.3)[c]
Venous and mixed/unspecified thrombotic events	58 (6.6)[d]	36 (4.1)[d]	2 (0.2)
Wound complications	12 (1.4)	2 (0.2)	0
Hypertension	318 (36)	149 (17)	0
Osteonecrosis	2 (0.2)	1 (0.1)	0
PPES[e]	389 (44)	112 (13)	NA
Proteinuria[e]	63 (7.2)	17 (1.9)	NA
RPLS	0	0	0
Diarrhoea	553 (63)	92 (11)	0
QT prolongation	7 (0.8)	1 (0.1)	0

[a] One subject in Study A031203 experienced a Grade 4 AE of jejunal perforation; follow-up information indicated that the Investigator later re-assessed the cause of death as jejunal perforation (Grade 5 AE). This subject is counted in the "Grade 5" and excluded from the "Grade 3/4" column.
[b] For the Haemorrhage ETM, this cell summarizes subject-incidence of events of ≥ Grade 3 only.
[c] Count includes 5 additional subjects who experienced the following events that were not captured as arterial thrombotic events in SCS, ISS Table 6.1: Study XL184-309 (1 subject each): ischemic hepatitis (Grade 5); intestinal ischemia (Grade 4); and peripheral ischemia (Grade 4). Study A031203 (1 subject): stroke, thrombosis of axillary artery, and thrombosis of the left internal carotid artery (unknown grades; counted in "Any Grade" column). Study XL184-308 (1 subject): peripheral ischemia (Grade 3).
[d] Count includes 10 additional subjects in Study A031203 who experienced events that were not captured as a VTE in SCS, ISS Table 6.1: 2 subjects had Grade 4 events, 5 subjects had Grade 3 events, and 3 subjects had Grade 2 events.
[e] Per CTCAE v4, there are no events of PPES or proteinuria with severity > Grade 3.

Laboratory findings

Serum Chemistry

The most frequent (≥40%) treatment-emergent serum chemistry laboratory abnormalities (all grades) reported in the cabozantinib arm by decreasing frequency were increased lactose dehydrogenase

(LDH), increased ALT, increased AST, decreased albumin, increased glucose, increased alkaline phosphatase (ALP) and decreased sodium. Abnormalities with a ≥5% higher per-subject incidence in the cabozantinib compared with the placebo arm were: LDH increased (84% vs 29%), ALT increased (73% vs 37%), AST increased (73% vs 46%), albumin decreased (51% vs. 32%), ALP increased (43% vs. 38%), phosphate decreased (25% vs. 8.4%), potassium decreased (23% vs. 6.3%), magnesium decreased (22% vs. 2.5%), amylase increased (16% vs. 8.9%), and corrected calcium decreased (7.7% vs. 0%).

The incidence of all-grade increases in ALT and AST was higher in the cabozantinib arm relative to placebo; however, there was a similar incidence of increased bilirubin (38% vs 34%; Grade 3/4 6.9% vs 7.6%) and ALP (43% vs 38%) and a lower incidence of increased GGT (28% vs 40%).

The incidence of electrolyte abnormalities, often associated with diarrhoea and vomiting, was higher in the cabozantinib arm relative to placebo including decreases in phosphate, potassium, magnesium and corrected calcium. The difference in the incidence of Grade 3-4 laboratory abnormalities was less marked: decreased phosphate (8.8% vs 3.8%), potassium (5.6% vs 1.3%), magnesium (3.2% vs 0%) and calcium (1.7% vs 0%).

There was a similar incidence of all-grade creatinine elevations in either arm (8.6% vs 7.2%).

Haematology

The most frequent (≥ 40%) treatment-emergent haematology abnormalities (all grades) reported in the cabozantinib arm by decreasing frequency were decreased platelets, white blood cell count (WBC) and absolute neutrophil count (ANC).

Haematology abnormalities (all grades) that had a ≥ 5% higher per-subject incidence in the cabozantinib compared with the placebo arm were decreased platelets (54% vs 16%), decreased WBC (51% vs 13%), decreased ANC (43% vs 8.4%) and increased haemoglobin (7.7% vs 0.8%). The corresponding Grade 3 or 4 incidence was decreased platelets (cabozantinib 10% vs placebo 1.3%), decreased WBC (4.9% vs 0.8%), decreased ANC (6.9% vs 1.3%) and increased haemoglobin (0% in each arm). The incidence of decreased haemoglobin was similar in both arms (32% vs 29%) and Grade 3/4 (4.1% vs 4.2%).

The incidence of all-grade haematology abnormalities in the cabozantinib arm of Study XL184-309 was generally consistent with that observed in the pooled population; however, the incidence of decreased platelets was somewhat higher in the cabozantinib arm of Study XL184-309 than the pooled population (54% vs 42%).

Thyroid Function

Of the subjects with normal baseline thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels, 15% (52/350) in the cabozantinib arm and 3% (5/191) in the placebo arm had post-baseline increased TSH with normal FT4 (subclinical hypothyroidism). A further 1.4% (5/350) in the cabozantinib arm and 0% (0/191) in the placebo arm had post-baseline increased TSH with FT4 decreased (clinical hypothyroidism).

The effect of concomitant thyroid hormone replacement therapy has not been evaluated, so AE reporting may better reflect the incidence of hypothyroidism. Hypothyroidism as an AE was reported in 8.1% of subjects in the cabozantinib arm and in 0.4% in the placebo arm. In addition, two subjects in the cabozantinib arm had related AEs of thyroiditis (Grades 1 and 2); both had received prior sorafenib.

The incidence of subclinical and clinical hypothyroidism was similar in the cabozantinib arm of Study XL184-309 and in the pooled population (11% and 1.4%).

Urine Protein/Creatinine Ratio (UPCR)

Sponsor-defined UPCR grades were: Grade 1 (≥ 0.15 to ≤ 1.0 mg/mg), Grade 2 (> 1.0 to ≤ 3.5 mg/mg) and Grade 3 (> 3.5 mg/mg).

Treatment-emergent UPCR laboratory abnormalities, mostly Grade 1 or 2, occurred in 45% of subjects in the cabozantinib arm and 30% in the placebo arm; Grade 3 abnormalities occurred in 2.6% of cabozantinib-treated subjects (1.7% placebo).

A ≥ 2-grade postbaseline worsening from Grade 0 at baseline occurred in 26 (5.6%) of subjects in the cabozantinib arm and 2 (0.8%) in the placebo arm. A 2-grade postbaseline worsening from Grade 1 at baseline occurred in 7 (1.5%) of subjects in the cabozantinib arm and 3 (1.5%) in the placebo arm.

The most frequent corresponding AE was proteinuria (also documented via dipstick), which occurred in 3.6% of cabozantinib-treated subjects (0.4% placebo); 1.5% of cabozantinib-treated subjects (0.4% placebo) had Grade 3 AEs. The incidence of proteinuria may have been affected by subjects' prior treatment with sorafenib. Cases meeting screening criteria for potential drug-related renal dysfunction

The incidence of UPCR abnormalities in the cabozantinib arm of XL184-309 was similar to that in the pooled population.

Screening for Potential Drug-Induced Liver Injury (DILI)

Blinded laboratory data listings were reviewed by the Sponsor quarterly for potential cases of DILI as identified by ALT, AST and bilirubin levels (Hy's Law laboratory criteria). Elevated ALP levels were not used to rule out DILI in cases where the baseline ALP was high or confounding factors were present (e.g. bone metastases). The study IDMC reviewed unblinded safety data and was asked to assess for potential DILI in the context of baseline reduced liver function.

Table 52: Summary of Treatment-Emergent Liver Function Test Abnormalities (Safety Population)

Laboratory Parameter	Cabozantinib (N = 467)	Placebo (N = 237)
ALT (all subjects), n/N (%)		
> 3 × ULN	90/451 (20)	25/230 (11)
> 5 × ULN	49/451 (11)	15/230 (6.5)
> 10 × ULN	9/451 (2.0)	1/230 (0.4)
> 20 × ULN	1/451 (0.2)	0/230
AST (all subjects), n/N (%)		
> 3 × ULN	135/451 (30)	40/229 (17)
> 5 × ULN	94/451 (21)	34/229 (15)
> 10 × ULN	19/451 (4.2)	10/229 (4.4)
> 20 × ULN	6/451 (1.3)	2/229 (0.9)
Alkaline phosphatase (all subjects), n/N (%)		
> 1.5 × ULN	84/451 (19)	30/230 (13)
> 2 × ULN	148/451 (33)	91/230 (40)
Total bilirubin (all subjects), n/N (%)		
> 1.5 × ULN	49/451 (11)	15/230 (6.5)
> 2 × ULN	59/451 (13)	35/230 (15)
(> 3 × ULN ALT or AST) AND > 2 × ULN total bilirubin AND < 2 × ALP (all subjects), n (%)	20 (4.3)	8 (3.4)
(> 3 × ULN ALT or AST) AND > 2 × ULN total bilirubin AND ≥ 2 × ALP (all subjects), n (%)	37 (7.9)	25 (11)

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

In total, 79 subjects (49 in the cabozantinib arm, 30 in the placebo arm) met the laboratory screening criteria (concurrent ALT or AST > 3 × ULN, total bilirubin > 2 × ULN). Of these, the proportion with ALP < 2 × ULN was similar in both treatment arms (cabozantinib, 20 subjects [4.3%]; placebo, 8 subjects [3.4%]). No subjects identified through laboratory screening were deemed to be potentially indicative of DILI following medical review.

There were no confirmed cases of DILI in Study XL184-308.

Laboratory Screening Criteria for Potential Drug-Related Renal Dysfunction

The proportion of subjects who met routine screening criteria for potential drug-related renal dysfunction was similar in both treatment arms of Study XL184-309.

Table 53: Study XL184-309: Summary of Treatment-Emergent Renal Function Test Abnormalities (Safety Population)

	Cabozantinib (N = 467)	Placebo (N = 237)
Met screening criteria for renal failure, n (%)	13 (2.8)	6 (2.5)
Serum creatinine ≥ 3 × ULN and ≥ 2 × baseline value	1 (0.2)	1 (0.4)
eGFR < 30 mL/min/1.73 m^2 and ≥ 25% reduction from baseline	6 (1.3)	3 (1.3)
eGFR ≤ 50% baseline value	13 (2.8)	5 (2.1)

The following relevant SAEs occurred:

- cabozantinib arm: Grade 5 renal failure; Grade 5 prerenal failure; Grade 3 acute renal failure and Grade 1 acute renal failure
- placebo arm: Grade 3 renal failure; Grade 4 acute renal failure and Grade 2 acute renal failure

There were no nephrotic syndrome events in either arm.

Transfusions

Fifty-two subjects (11%) in the cabozantinib arm and 20 subjects (8.4%) in the placebo arm had at least one transfusion, most frequently packed red blood cells (cabozantinib 8.4%, placebo 5.9%).

Weight Loss

In Study XL184-309, 28% of subjects in cabozantinib arm had ≥10% weight loss from baseline compared with 4.6% of subjects in the placebo arm. The incidence of the corresponding AE of weight decreased was 17% and 5.9%, respectively. The mechanism is unknown, but the higher incidence of GI events seen with cabozantinib treatment may contribute.

Safety in special populations

The incidence of AEs and ETMs in Study XL184-309 was summarized by subgroups based on intrinsic factors (sex, age group, race, weight, aetiology, extent of extrahepatic disease and baseline ECOG status) and extrinsic factors (number of prior systemic anticancer agents, geographic region).

There were no marked treatment differences in safety noted for most subgroups. However, the small number of subjects in the Black/African American (1.7% cabozantinib, 4.6% placebo) and Other (8.4%, 5.9%) racial categories did not allow meaningful safety conclusions to be drawn for these subgroups.

Table 54: XL184-309: ETMs by Age Group (Safety Population)

ETM	Cabozantinib N=467 n (%)			Placebo N=237 n (%)		
	< 65 (N=239)	65 < 75 (N=156)	75 < 85[a] (N=67)	< 65 (N=124)	65 < 75 (N=75)	75 < 85 (N=35)
GI perforation	3 (1.3)	0	1 (1.5)	1 (0.8)	1 (1.3)	0
Fistula	7 (2.9)	0	0	1 (0.8)	0	0
Abscess–all	11 (4.6)	6 (3.8)	1 (1.5)	2 (1.6)	0	0
Intra-abdominal and pelvic abscess	4 (1.7)	1 (0.6)	0	0	0	0
Haemorrhage (≥ Grade 3)	24 (5.1)	9 (1.9)	1 (0.2)	10 (4.2)	4 (1.7)	3 (1.3)
Arterial thrombotic events	5 (2.1)	5 (3.2)	2 (3.0)	1 (0.8)	1 (1.3)	1 (2.9)
Venous and mixed/unspecified thrombotic events	12 (5.0)	7 (4.5)	4 (6.0)	1 (0.8)	3 (4.0)	2 (5.7)
Wound complications	2 (0.8)	1 (0.6)	1 (1.5)	0	0	0
Hypertension	65 (27)	54 (35)	18 (27)	8 (6.5)	4 (5.3)	2 (5.7)
Osteonecrosis	0	0	0	0	0	0
PPES	127 (53)	63 (40)	25 (37)	6 (4.8)	5 (6.7)	1 (2.9)
Proteinuria	8 (3.3)	7 (4.5)	2 (3.0)	1 (0.8)	0	0
RPLS	0	0	0	0	0	0
Diarrhoea	124 (52)	88 (56)	37 (55)	27 (22)	11 (15)	6 (17)
QT prolongation	0	2 (1.3)	1 (1.5)	0	0	0

[a] There were 5 subjects ≥ 85 years old at baseline (cabozantinib arm). These subjects are not summarized in this table.

Safety data were also summarized by age per EMA recommendations. No notable age-related differences in related AEs were observed for cabozantinib-treated subjects.

Table 55: XL184-309: Related Adverse Events by Age Group in Cabozantinib- Treated Subjects (Safety Population)

	Cabozantinib N=467			
	< 65 (N=239)	65 < 75 (N=156)	75 < 85 (N=67)	≥ 85 (N=5)
Number of events, n				
Total Related AEs[a]	2547	1716	728	36
Total Related SAEs	51	45	34	0
Fatal	2	2	2	0
Hospitalization	45	41	27	0
Life-threatening	3	0	0	0
Disability	0	1	0	0
Medically Significant	5	3	8	0
Subject Incidence [b], n (%)				
AEs Leading to Dropout [c]	23 (9.6)	15 (9.6)	12 (18)	3 (60)
Psychiatric Disorders (SOC)	47 (20)	21 (14)	14 (21)	0
Nervous System Disorders (SOC)	98 (41)	66 (42)	36 (54)	2 (40)
Accidents and Injuries (SMQ)	19 (7.9)	12 (7.7)	9 (13)	0
Cardiac Disorders (SOC)	14 (5.9)	6 (3.8)	2 (3.0)	0
Vascular Disorders (SOC)	81 (34)	61 (39)	26 (39)	1 (20)
Cerebrovascular Disorders (SMQ)	2 (0.8)	4 (2.6)	2 (3.0)	0
Infections and Infestations (SOC)	89 (37)	51 (33)	29 (43)	2 (40)

Anticholinergic syndrome (SMQ)	23 (9.6)	22 (14)	12 (18)	0
Quality of Life Decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures (PTs)	25 (11)	27 (17)	13 (19)	0
Drug Withdrawal (SMQ)	0	0	0	0

[a] These data represent an over-estimate of related AE episodes because a unique record is documented for every change in severity grade, up or down, even within a single AE episode.
[b] Each subject is counted only once at each level of summarization.
[c] Excludes AEs related to disease progression.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

The overall incidence of study treatment discontinuation due to an AE regardless of causality (excluding AEs due to PD) was 98 subjects (21%) in the cabozantinib arm and 11 subjects (5%) in the placebo arm.

The overall incidence of study treatment discontinuation due to a treatment-related AE (excluding AEs due to PD) was 76 subjects (16%) in the cabozantinib arm and 7 subjects (3%) in the placebo arm.

Table 56: Adverse Events Not Related to Disease Progression that Led to Study Treatment Discontinuation in ⩾ 1% of Subjects in Either Treatment Arm (Safety Population)

	Cabozantinib N=467 n (%)		Placebo N=237 n (%)	
Preferred Term	All Causality	Related	All Causality	Related
Subjects with an AE[a]	96 (21)	74 (16)	10 (4.2)	6 (2.5)
Palmar-plantar erythrodysaesthesia syndrome	11 (2.4)	11 (2.4)	0	0
Fatigue	7 (1.5)	6 (1.3)	1 (0.4)	1 (0.4)
Decreased appetite	5 (1.1)	5 (1.1)	0	0
Diarrhoea	5 (1.1)	4 (0.9)	0	0
Nausea	5 (1.1)	5 (1.1)	1 (0.4)	1 (0.4)

At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events.
[a] In the subject disposition table, three subjects (two cabozantinib and one placebo) were summarized as discontinuing study treatment due to AE who were not summarized as having AEs leading to treatment discontinuation (not related to disease progression) in this table:
Cabozantinib arm: Subject (blood bilirubin increased, Grade 2) and Subject (fatigue, Grade 3).
Placebo arm: Subject (pulmonary haemorrhage, Grade 2).

Adverse events leading to study treatment discontinuation that were related to disease progression occurred in 17% and 16% of subjects in the cabozantinib and placebo arms, respectively (per Investigator as indicated on the AE CRF). Most frequently these were general physical health deterioration (cabozantinib 3.6%, placebo 1.7%), HCC (1.7%, 3.4%), ascites (1.3%, 1.7%) and fatigue (1.3%, 0.8%).

Safety in the HCC Cohort of Study XL184-203 RDT

Subjects received starting cabozantinib doses of 100 mg qd (freebase equivalent, development stage capsule formulation), and treatment-emergent toxicities were managed with dose interruptions and reductions. The permitted dose reduction levels were to 60 mg (first reduction) and 40 mg (second reduction).

All subjects experienced at least one AE of any grade, and 78% of subjects experienced at least one ≥ Grade 3 AE. The most frequent ≥ Grade 3 AEs (≥10% incidence) were diarrhoea (22.0%), thrombocytopenia (17.1%), PPES (14.6%) and increased AST (12.2%). Grade 4 AEs were experienced by four subjects (9.8%): acute pancreatitis, hypoglycaemia, hyponatremia and back pain (1 subject each). One Grade 5 AE of hepatic failure (not related to study treatment) was reported. Two subjects met the screening criteria for Hy's Law (including the subject that had the Grade 5 AE of hepatic failure), but medical review determined that neither case was clearly indicative of DILI.

Table 57: XL184-203 RDT: Summary of Frequent Adverse Events (≥ 20%) for HCC Subjects (Continuous Cabozantinib Data Set, N=41)

Preferred Term	Any Grade n (%)	≥ Grade 3 n (%)
Subjects with at least one adverse event	41 (100)	32 (78.0)
Diarrhoea	28 (68.3)	9 (22.0)
Fatigue	24 (58.5)	1 (2.4)
Palmar-plantar erythrodysaesthesia syndrome	22 (53.7)	6 (14.6)
Vomiting	17 (41.5)	1 (2.4)
Nausea	16 (39.0)	1 (2.4)
Thrombocytopenia	15 (36.6)	7 (17.1)
Rash	13 (31.7)	0
Decreased appetite	13 (31.7)	0
Asthenia	11 (26.8)	4 (9.8)
Aspartate aminotransferase increased	11 (26.8)	5 (12.2)
Oedema peripheral	10 (24.4)	2 (4.9)
Weight decreased	10 (24.4)	2 (4.9)
Hypertension	10 (24.4)	4 (9.8)
Stomatitis	10 (24.4)	0
Dysgeusia	9 (22.0)	0
Constipation	9 (22.0)	1 (2.4)

Three deaths were reported up to 30 days after last dose of study treatment for HCC subjects in the Continuous Cabozantinib Data Set; all were attributed to PD per Investigator, including a Grade 5 AE of hepatic failure.

Fifteen subjects experienced 37 SAEs irrespective of causality; all the SAE PTs were reported for 1 or 2 subjects and none led to study treatment discontinuation. The SAEs experienced by more than one subject were: asthenia, diarrhoea, hypoglycaemia and urinary tract infection.

Overall, there were no additional safety signals observed in Phase 2 Study XL184-203 RDT compared with Phase 3 Study XL184-309.

Post marketing experience

The post-marketing population for cabozantinib (Cabometyx and Cometriq combined) up until 28 November 2017 comprised a total of 10,565 patients exposed, including approximately 7507 in the US, 2873 in the EU (946 marketed, 1927 named patient use [NPU] or managed access program [MAP]) and 167 from other countries (NPU/MAP and a global access program).

Patients in the US received cabozantinib for treatment of RCC (n= 4232) and thyroid cancer (n= 878) as well as malignancies other than the approved indications, including HCC, prostate, lung, bone and brain. In the EU, information on treated indication is not available.

Post-marketing serious adverse reactions (SARs) reported up to 28 November 2017:

In 603 patients who received Cabometyx on-label for renal cancer 901 post-marketing SARs were received. The most frequent nonfatal SARs (excluding hospitalization) were diarrhoea (n=26), pneumonia (n=22), pulmonary embolism (n=21), thrombosis (n=19), nausea (n=15), dehydration, vomiting (each n=13), dyspnoea, hypertension, fatigue (each n=10), asthenia (n=9), malaise (n=8), decreased appetite, pain, cerebrovascular accident (each n=7), atrial fibrillation, myocardial infarction, and rash (each n=6).

In the US 1739 patients received Cabometyx for a non-approved indication, including 20 for HCC; one of these HCC patients died due to an unknown cause of death.

In 157 patients who received Cometriq on-label for the indication of thyroid cancer, 286 post-marketing SARs were received. The most frequent non-fatal SARs included dehydration (n= 12), pneumonia (n=8), diarrhoea (n=7), dyspnoea (n=6), asthenia, pancreatitis, vomiting, hypotension and hypertension (each n=5).

In the US 1283 patients have received Cometriq for a non-approved indication, including 25 for HCC; 4 of these HCC patients experienced at least one SAR. The most frequent non-fatal SAR was chest pain (n=2). One patient reported SARs of portal vein thrombosis, sepsis, hypocalcaemia, pancytopenia, malnutrition and chest pain; one patient reported SARs of pulmonary embolism and decreased platelet count; one patient reported a single event of chest pain; and one patient reported an SAR of muscle spasms.

2.5.1. Discussion on clinical safety

Exposure

Safety data were primarily from the placebo-controlled Phase 3 XL184-309 study in subjects with previously treated advanced HCC up to 01 June 2017, the data cut-off for the primary OS analysis.

The median duration of exposure (including dose interruptions) was longer in the cabozantinib arm compared with the placebo arm (3.8 [1.1, 60.0] vs 2.0 [0.0, 27.2months], respectively), but shorter than the RCC population in trial XL184-308 (5.6 months). As discussed in the efficacy section, median cabozantinib exposure was shorter than the median PFS in the cabozantinib arm (5.2 months).

The median dose intensity in HCC patients was 60%, corresponding to a median daily dose of 36 mg cabozantinib, lower than in the RCC trial population (45mg), and notably lower than the starting dose

of 60mg. The recommended Cabometyx dose for patients with hepatic impairment prior to the current Phase 3 HCC study was 40mg.

Dose modifications and Discontinuations

Dose modifications were commonly required in conjunction with supportive care to manage AEs and occurred in 88% of cabozantinib – treated subjects (vs. 39% of placebo subjects), with dose reductions in 62% and dose interruptions in 84%. The median time to first cabozantinib dose modification was short – 38 days for dose reduction and 28 days to first dose interruption. The median time to the second dose reduction/ modification was longer (83 and 70 days, respectively), suggesting that AEs could be managed with dose modifications. The median number of dose interruptions per patient was 2 and the median duration was 9 days.

The incidence of subjects with AEs leading to dose modification per AE CRF was higher and occurred earlier in the cabozantinib arm of Study XL184-309 than the cabozantinib arm of Study XL184-308 (76% with a median time to first dose modification of 36 days).

The most frequent AEs leading to dose modification (PPES, diarrhoea, fatigue, hypertension, and AST increased), largely reflect the most frequently observed AEs for cabozantinib. Incidence of PPES and liver enzyme elevations (AST and ALT) leading to dose modification were higher in the cabozantinib arm of Study XL184-309 (28%, 10% and 6%, respectively) than in the cabozantinib arm of Study XL184-308 (16%, 3.0% and 3.9%, respectively).

In the CELESTIAL study, thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia.

Dose modification did allow most patients to continue treatment; 21% discontinued due to an AE (excluding disease progression) compared with 4.2% in the placebo arm. The AEs generally responsible for treatment discontinuation were PPES (2.4%), fatigue (1.5%), decreased appetite, diarrhoea and nausea (1.1% each).

Therefore, the starting dose of 60mg, although it appears excessive from a safety viewpoint, does provide flexibility in terms of individual patient dosing.

Adverse Events

The most frequently reported AEs (≥ 20% incidence) were consistent with the known safety profile of cabozantinib and included diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension, vomiting, increased AST and asthenia. The most frequent AEs (≥ 20% incidence) in the placebo arm were fatigue and abdominal pain.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite hypertension and nausea (see section 4.8 of the SmPC).

Similarly, the most frequently reported Grade 3/4 AEs were consistent with the known cabozantinib safety profile i.e. PPES, hypertension, increased AST, fatigue, diarrhoea, asthenia and decreased appetite. Of these Grade 3/4 events, PPES, AST increased, and decreased appetite occurred at a higher frequency in the HCC trial compared to the RCC trials XL184-308 and A031203, and more frequently in the cabozantinib arm compared to the placebo arm.

In line with the patient population, there was a high overall incidence of SAEs; 50% in the cabozantinib arm and 37% in the placebo arm. The most common serious adverse drug reactions in the HCC

population (≥1% incidence) are hepatic encephalopathy, palmar-plantar erythrodysaesthesia syndrome, asthenia and diarrhea (see section 4.8 of the SmPC). For comparison, the most common serious adverse drug reactions in the RCC population (≥1% incidence) are diarrhoea, hypertension, dehydration, hyponatraemia, nausea, decreased appetite, embolism, fatigue, hypomagnesaemia, palmar-plantar erythrodysaesthesia syndrome (PPES).

Consistent with advanced HCC and underlying liver disease, Grade 3/4 liver – related AEs were reported frequently for both treatment arms; Grade 3/4 AEs in the primary SOC of hepatobiliary disorders were reported for 6.2% of cabozantinib and 8.4% of placebo subjects. The incidence of Grade 3/4 AEs of ascites (3.9% vs. 4.6%) and increased blood bilirubin (3.0% vs 1.7%) were generally similar for cabozantinib and placebo-treated subjects as were Grade ≥ 3 oesophageal varices haemorrhage (1.1% cabozantinib, 2.1% placebo). Grade 3/4 hepatic failure was reported with a higher incidence in the placebo arm (cabozantinib 0.4% vs placebo 2.5%).

In the CELESTIAL study, hepatic encephalopathy was reported more frequently in the cabozantinib than the placebo arm. Cabozantinib has been associated directly or indirectly with diarrhoea, vomiting, decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy (see sections 4.4 and 4.8 of the SmPC). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment.

The incidence of GI toxicity with cabozantinib was very high in comparison to placebo. Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI adverse reactions. Prompt medical management, including supportive care with antiemetics, antidiarrhoeals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant GI adverse reactions (see sections, 4.2, 4.4 and 4.8 of the SmPC).

In addition, diarrhoea was a major cause of dose interruption (15%) and dose reduction (10%), second only to PPES. It also caused treatment discontinuations (1.1%), suggesting that diarrhoea was difficult to manage adequately with supportive care alone. It is noted that the risk of diarrhoea and PPES was concentration-dependent in the exposure-response analysis.

Deaths and Events to monitor

There was a high proportion of deaths up to the 01 June 2017 data cut-off: 314 (67%) in the cabozantinib arm and 167 (70%) in the placebo arm. Most deaths occurred more than 30 days after last dose of study (257 [55%] of subjects in the cabozantinib arm and 139 [59%] in the placebo arm); these deaths were primarily attributed to PD (228 [49%] cabozantinib, 119 [50%] placebo).

Deaths up to 30 days after the last dose occurred at a similar frequency in both arms; 57 (12%) subjects in the cabozantinib arm and 28 (12%) in the placebo arm. Over half of the deaths were attributed to PD, more in the placebo arm (cabozantinib 30 [6.4%] and placebo 21 [8.9%]); the most frequent Grade 5 AE was HCC (cabozantinib 5.1%, placebo 7.6%). More subjects died of other causes in the cabozantinib than the placebo arm (5.8 % vs 3.0%).

A large proportion of the other Grade 5 events were hepatobiliary. In the cabozantinib arm, 11 subjects (2.4%) experienced Grade 5 hepatobiliary events: hepatic failure (6 subjects), portal vein thrombosis, hepatorenal syndrome, hepatic cirrhosis, ischemic hepatitis and liver disorder (1 subject each). In the placebo arm, 4 subjects (1.7%) experienced Grade 5 hepatobiliary events: hepatic failure (2 subjects), hepatorenal syndrome, and chronic hepatic failure (1 subject each). Six Grade 5 AEs up

to 30 days after last dose were assessed as treatment-related in the cabozantinib arm (PTs of hepatic failure, hepatorenal syndrome, oesophagobronchial fistula, portal vein thrombosis, pulmonary embolism, and upper GI haemorrhage), and one was assessed as treatment-related in the placebo arm (PT of hepatic failure).

Events to monitor (ETMs) that are known to be associated with TKIs or VEGF pathway inhibition and have potentially serious consequences were defined. These comprised GI perforation, fistula, abscess [all, intra-abdominal and pelvic], ≥ Grade 3 haemorrhage, venous thromboembolic events (VTEs), arterial thromboembolic events (ATEs), wound complications, hypertension, osteonecrosis, PPES, proteinuria, reversible posterior leukoencephalopathy syndrome (RPLS), diarrhoea and QT prolongation.

Diarrhoea was experienced by 54% of cabozantinib-treated subjects with 9.9% of patients having G3-4 events. Most patients (82%) experienced 1 to 3 episodes of diarrhoea. Dose modification was required in 47/ 251 (18.7%) subjects with diarrhoea and dose interruption in 69/251 (27.4%). The toxicity grade post dose modification generally reflected the initial grade, although with no Grade 4 events.

PPES was experienced by 46% of cabozantinib-treated subjects with 17% of patients having G3 events. Most patients (85%) experienced 1 to 4 episodes of PPES. Dose modification was required in 119/ 217 (54.8%) subjects with PPES and dose interruption in 54.8%. The toxicity grade post dose modification generally reflected the initial grade.

Over half of subjects were receiving 20mg cabozantinib daily prior to treatment discontinuation. Diarrhoea and PPES were generally manageable with dose adjustments.

The incidence of Grade 3/4 fistula ETMs was similar between treatment arms. The single Grade 5 oesophagobronchial fistula was reported for a cabozantinib-treated subject who had radiation induced esophagitis following recent prior radiotherapy to mediastinum and lung.

In the CELESTIAL study, fatal haemorrhagic events were reported at a higher incidence with cabozantinib than placebo. Predisposing risk factors for severe haemorrhage in the advanced HCC population may include tumour invasion of major blood vessels and the presence of underlying liver cirrhosis resulting in oesophageal varices, portal hypertension, and thrombocytopenia. The CELESTIAL study excluded patients with concomitant anticoagulation treatment or antiplatelet agents. Subjects with untreated, or incompletely treated, varices with bleeding or high risk for bleeding were also excluded from this study (see sections 4.2, 4.4, 4.8 of the SmPC).

The most frequently reported VTEs in the cabozantinib arm were pulmonary embolism and portal vein thrombosis; only portal vein thrombosis was reported in higher incidence in the cabozantinib compared with the placebo arm (1.3% vs 0), including one fatal event. Patients with a history of portal vein invasion appeared to be at higher risk of developing portal vein thrombosis. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant thromboembolic complication (see sections 4.2, 4.4, 4.8 of the SmPC).

Most patients (~80%) will have underlying cirrhosis. Cirrhosis increases the baseline risk for a patient entering the study, and there is potential for overlap between the cirrhosis-related risks and the toxicities of the agent under study. This is highlighted by the high level of SAEs (36%) in the placebo arm. Particularly, there is an increased risk of bleeding in this patient population, due to portal hypertension, varices and thrombocytopenia. The AEs were as seen with cabozantinib in other indications, exacerbated by the patient population, namely Grade 5 haemorrhage and episodes of portal vein (PV) thrombosis, including fatal events, particularly in patients with PV invasion at baseline. All fatal haemorrhagic (n=5) and thromboembolic events (n=2) occurred in the cabozantinib arm. The

increased incidence of encephalopathy with cabozantinib, attributable to GI toxicity has been detailed in the SmPC.

Laboratory abnormalities

There was higher post-baseline incidence of increased ALT (73% vs 37%) and AST (73% vs. 46%) in the cabozantinib arm relative to placebo; however, there was a similar incidence of increased bilirubin (38% vs 34%) and increased ALP (43% vs 38%) and a lower incidence of increased GGT (28% vs 40%). Cases meeting Hy's Law screening criteria were examined, and none were clearly indicative of DILI.

It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests considered related to cabozantinib treatment (i.e. where no alternative cause is evident), dose modification advices should be followed (see sections 4.2, 4.4, 4.8 of the SmPC).

Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatremia). It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities (see sections 4.2, 4.4, 4.8 of the SmPC).

There was a similar incidence of all-grade creatinine elevations in both arms (8.6% vs 7.2%). There was a higher incidence of all-grade haematology abnormalities, specifically decreased platelets, WBCs and ANCs with cabozantinib. Still, the incidence of the corresponding Grade 3-4 laboratory abnormalities was low; decreased platelets (cabozantinib 10%, placebo 1.3%), WBCs (4.9%, 0.8%) and ANCs (6.9%, 1.3%).

Marked weight loss of ≥ 10% from baseline at any post-baseline visit was recorded for 28% of subjects in the cabozantinib arm compared with 4.6% in the placebo arm. The incidence of the corresponding AE of decreased weight was 17% vs 5.9% (Grade 3/4: 1.1% vs 0%). Weight loss could be attributed to gastrointestinal (GI) toxicity of cabozantinib. GI AEs were frequent with cabozantinib (≥ 20% incidence), particularly diarrhoea, but also decreased appetite, nausea and vomiting. Hypokalaemia and hypomagnesemia in the cabozantinib arm may be associated with the frequent occurrence of diarrhoea. GI toxicity and its effects have been included in Sections 4.4 and 4.8 of the SmPC.

Subgroups, post-marketing and pooled analysis

Analyses of AEs and ETMs did not show a notable difference in safety between subgroups for intrinsic factors (sex, age group, race, weight group, ECOG PS, aetiology, extrahepatic spread and/or macrovascular invasion) or extrinsic factors (number of prior systemic anticancer therapy agents, region).

There were no additional safety signals identified in the HCC cohort of Study XL184-203 RDT. Safety observations in the post-marketing setting through 28 November 2017 were also consistent with the known profile of cabozantinib.

The safety profile of cabozantinib in HCC Study XL184-309 was generally in line with the pooled analysis of safety data incorporating XL184-309 and previously submitted RCC Studies XL184-308 and A031203 (AE data only); except certain events associated with HCC in the context of underlying liver disease originated only from study XL184-309.

2.5.2. Conclusions on clinical safety

The safety of cabozantinib in advanced HCC reflects the known safety profile, however new ADRs have been identified such as hepatic encephalopathy. Grade 3/4 AEs associated with HCC occurred more frequently with cabozantinib, such as hepatic encephalopathy, increased liver enzymes and thrombocytopenia. The MAH should thoroughly review the ADRs included in the SmPC in the context of the next PSUR.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The important identified and potential risk should focus on the safety concerns that could potentially impact the risk- benefit balance of the product and would usually warrant further evaluation as part of the pharmacovigilance plan or additional risk minimisation activities. The MAH is requested to consider this issue in future updates of the Cabometyx and Cometriq RMPs.

The CHMP endorsed the Risk Management Plan version 4.2 (6 September 2018) with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Gastrointestinal perforation Gastrointestinal and non-gastrointestinal fistula Thromboembolic events Haemorrhage (Grade ≥3) Wound complications Reversible posterior leukoencephalopathy syndrome (RPLS) Osteonecrosis
Important potential risks	Renal failure Hepatotoxicity Embryotoxicity Carcinogenicity
Missing information	None

Pharmacovigilance plan

Category 3 Study				
Study/status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**

Category 3 Study				
Study / status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy/planned	**Primary:** To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy. **Secondary:** To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings To describe all treatment-emergent nonserious and serious AEs To describe the effectiveness of cabozantinib in RCC in real-life in terms of progression-free survival and best overall response To describe the health care resource utilisation associated with the management of treatment-related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays; concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).	To assess the risk-benefit profile of Cabometyx with respect to identified and potential risks	1. Protocol submission to PRAC 2. PRAC approval 3. Study start 4. Study finish 5. Progress report 6. Interim report 7. Final report	1. Submitted 24 April 2017 2. 12 October 2017 3. Planned March 2018 (FPI) 4. Planned December 2020 (LPO) 5. Planned December 2018 6. Planned December 2019 7. Planned December 2021

Risk minimisation measures

Routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures

Routine risk minimisation measures are proposed for all the safety concerns. This is sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

In the current variation, for the addition of the proposed indication in HCC, the design, layout and format of the leaflet are not impacted. The modifications relate to slight changes in the safety profile to include the safety profile in HCC and the current writing style has been respected. In the context of user testing, the updates are considered non-significant and the evidence from user testing previously performed on the Cabometyx leaflet is considered relevant and applicable to this application.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cabometyx is proposed as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib.

3.1.2. Available therapies and unmet medical need

Surgical resection, liver transplantation, or percutaneous ablation are potentially curative in patients with early stage disease. However, these are not appropriate for most patients because of tumour size or location. Palliative TACE is a widely-used option for patients with unresectable disease without extrahepatic involvement. However, patients who present with advanced disease or those with recurrence after locoregional therapy have a very poor prognosis without further treatment: the expected median survival time is 6 months for patients with cancer-related symptoms, macrovascular invasion or extrahepatic spread.

The standard treatment for patients with advanced HCC is sorafenib, a small molecule VEGF pathway inhibitor. Disease progression usually occurs due to acquired resistance to these therapies and more therapeutic options are needed in advanced HCC.

Regorafenib received approval in the EU in 2017 for the treatment of patients with HCC who have been previously treated with sorafenib.

3.1.3. Main clinical studies

The pivotal study was XL 184 309, a randomised double-blind, placebo-controlled evaluation of cabozantinib in previously treated subjects with advanced HCC who had received prior sorafenib and progressed on at least one prior systemic treatment for HCC.

3.2. Favourable effects

Subjects in the cabozantinib 60mg qd arm had a statistically significant improvement in OS compared with placebo. There was a 2.2-month difference in the median OS, as estimated by KM analysis; median duration of OS were 10.2 vs 8.0 months in the cabozantinib and placebo arms respectively (stratified HR 0.76, 95% CI: 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value = 0.021). The landmark estimate of the proportion of subjects that were event-free at 12 months was 46% compared with 34%.

The primary analysis of Investigator- determined PFS (PFS1) yielded a median duration of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors (per IxRS), was 0.44 (95% CI: 0.36, 0.52, stratified log-rank p-value < 0.0001).

Results of additional sensitivity analyses of PFS (PFS2 and PFS3) were consistent with the primary PFS1 analysis. For PFS3 treatment discontinuation due to clinical deterioration was also an event. In addition, further systemic or local therapy or surgery were events for PFS2.

PFS in the cabozantinib arm was similar in the full trial population and those who had received only prior sorafenib (5.2 vs. 5.5 months).

Subgroup analyses of the primary OS showed consistent efficacy favouring cabozantinib across the majority of prespecified baseline and demographic subgroups, including subjects who had HBV aetiology and regardless of baseline AFP level (< or ≥ 400ng/mL). In an ad hoc subgroup analysis, subjects whose only prior therapy for HCC was sorafenib also showed an OS benefit. For subjects who received 1 prior regimen the OS HR was 0.74 (95% CI 0.59, 0.92), whilst for subjects who received 2 prior regimens the unstratified OS HR was 0.90 (95% CI 0.63, 1.29).

3.3. Uncertainties and limitations about favourable effects

Recruited patients were a selected group with Child Pugh A and ECOG PS 0 or 1 so cabozantinib has not been investigated in patients with more advanced liver disease or poor performance status. This has been reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite hypertension and nausea.

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, palmar-plantar erythrodysaesthesia syndrome, asthenia and diarrhoea.

The incidence of SAEs was 50% in the cabozantinib arm and 37% in the placebo arm.

3.5. Uncertainties and limitations about unfavourable effects

Due to the dose modifications for toxicity, the median daily dose in HCC patients was 36 mg cabozantinib, lower than in the pooled population (41mg) and notably lower than the starting dose of 60mg.

3.6. Effects Table

Table 58: Effects table for Cabometyx in the treatment of hepatocellular carcinoma following prior treatment with sorafenib (data cut-off: 1 June 2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	time from randomization to death due to any cause.	months	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)	Minimal uncertainty HR 0.76 (0.63, 0.92) 2-sided p=0.0049	CSR
PFS	time from randomization to the earlier of the following events: progressive disease (PD) or death due to any cause.	months	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)	Placebo probably shorter than 1.9 (1st visit) HR 0.44 (0.36, 0.52) 2-sided p<0.0001	
Unfavourable Effects						
G3/4		%	68	36		
PPES	G 3/4	%	17	0		
HTN	G 3/4	%	16	1.7		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AST inc.	G 3/4	%	12	6.8		
diarrhoea	G 3/4	%	9.9	1.7		
asthenia	G 3/4	%	6.9	1.7		
HE	G 3/4	%	2.8	0.8		

Abbreviations: mon = months; C= cabozantinib; P = placebo; OS = overall; G 3/4 = Grade 3/4; SAE = serious adverse event; HTN = hypertension; inc. = increased; HF = hepatic failure; HE = hepatic encephalopathy; AST = aspartate aminotransferase

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Cabometyx has demonstrated a clinically significant improvement in overall survival compared to placebo in the proposed population of patients with hepatocellular carcinoma who have previously been treated with sorafenib. This is remarkable given the poor prognosis of these patients and the relatively few treatment options available. Secondary endpoints support the primary outcome.

The safety profile appears similar to the known profile of cabozantinib except certain events associated with HCC in the context of underlying liver disease originated only from study XL184-309. These appear to be managed with appropriate monitoring and dose modifications.

3.7.2. Balance of benefits and risks

The benefit-risk balance of cabozantinib as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The prognosis of patients with advanced HCC is poor, as evidenced by the 8-month median OS in the placebo arm of the submitted Phase 3 study. There are relatively few treatment options for patients who progress on first line systemic therapy (currently sorafenib) – the median OS for regorafenib in this patient population post sorafenib in the RESORCE study was 10.6 months.

The median improvement in OS with regorafenib compared to placebo (RESORCE study) was 2.8 months. This was in a similarly restricted population (Child Pugh A 98%, ECOG PS 0 66% or 1 34%; BCLC stage B 13%, Stage C 87%). The additional 0.6 months with regorafenib over cabozantinib is likely not relevant in a cross-trial comparison. Overall, the trial populations were similar. The main differences between the CELESTIAL and RESORCE studies concerned prior HCC therapy. In RESORCE patients had received only sorafenib as systemic therapy for advanced disease, whilst in CELESTIAL patients had received sorafenib but could also have received 1 other systemic therapy for advanced disease; 28% (n=130) patients in the cabozantinib arm had received 2 prior regimens, mainly cytotoxic chemotherapy (n=41), other TKIs (n=19) or antibodies (n=25), with the additional treatment in 45 patients not described.

In RESORCE, patients had to have 'tolerated' sorafenib (at least 50% of the recommended daily dose for 20/28 days prior to discontinuation). There was no such stipulation for cabozantinib, but it is not known if patients intolerant of sorafenib were recruited; 69% patients (n=322) had progressed whilst receiving sorafenib as their most recent prior systemic agent and 96% (n=452) had progressed on sorafenib. Therefore, it seems unlikely that many sorafenib-intolerant patients were recruited. Median

duration of prior sorafenib treatment in RESORCE was 7.8 months and 5.3 months in the cabozantinib arm of CELESTIAL.

Therefore, there are no important differences between the two trial populations that may have impacted efficacy or would allow a broader indication.

However, most important in the benefit risk assessment will be the safety profile. Overall the safety profiles of regorafenib (from the EPAR) and cabozantinib were similar: including median duration of treatment, TEAEs, Grade 3-4 AEs, Grade 5 AEs and ETM/ AESI. There appeared to be marginally more SAEs (50 vs. 44.4%) and treatment related SAEs (18 vs 10.4%) with cabozantinib vs regorafenib. Most of the common AEs were reported at a similar frequency, although those with >10% difference were mainly GI and all occurred with cabozantinib (diarrhoea, decreased appetite, fatigue, nausea and vomiting). Encephalopathy was more frequently reported with cabozantinib (5.6%) than regorafenib (1.9%) and at a higher incidence than placebo. LFT abnormalities (increased ALT/ AST) were similar for the 2 treatments.

From the information available, cabozantinib appears to be more toxic than regorafenib.

On the one-hand, cabozantinib efficacy may not vary according to the specific first line VEGF targeted therapy administered. However, the efficacy of cabozantinib after first-line treatment other than sorafenib cannot be extrapolated directly from that observed after sorafenib failure. This would require at least a further discussion on differences in targets and potencies and how these differences would contribute to anticancer activity in vivo in 2nd line treatment. It is questionable whether this can be based on in vitro data only.

3.8. Conclusions

The overall B/R of Cabometyx for treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib is positive.

4. Recommendations

Outcome

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

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

Extension of indication to add Cabometyx as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the risk management plan (version 4.2) are updated accordingly.

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

5. EPAR changes

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

Scope

Extension of indication to add Cabometyx as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the risk management plan (version 4.2) are updated accordingly.

Summary

Please refer to the scientific discussion Cabometyx EMEA/H/C/004163/II/0005.