ACTION Clinical Study Protocol

A phase II triAl of Cabozantinib for hepaTocellular carcInoma patients intOlerant to sorafenib treatment or first line treatment different to sorafeNib. (ACTION trial)

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TITLE PAGE

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Study Sponsor: Fundació Clinic per a la Recerca Biomèdica
Principal Investigators: Maria Reig
Affiliation: BCLC group. Liver Unit. ICMDM. CIBEREHD. IDIBAPS. Hospital Clínic
c/ Villarroel, 170. Escala 11, 4ª planta. 08036. Barcelona. Spain
Tel: 0034 93 227 9803
Fax: +34 932275792
email: mreig1@clinic.cat

SYNOPSIS

Study Title (Full)	
A phase II triAl of Cabozantinib for hepaTocellular carcInoma patients intOlerant to sorafenib treatment or other First-Line treatment different to sorafenib (ACTION trial)	
Related Product	
CABOZANTINIB	
Indication	
Patients with HCC intolerant to sorafenib according to the RESORCE trial definition or those patients who received other first-line treatment.	
Phase of Study	*Phase IIa*
Countries	*Spain*
Retrospective or prospective study	*Prospective*
Planned number of sites/ subjects	*7 sites / 40 patients*
Blinding & Control	*non-randomized, non-blinded*
Study Type and Design	
Single arm, interventional, prospective study.	
Rationale	
Cabozantinib, a small molecule directed to vascular endothelial growth factor receptors, MET, and AXL, has shown to significantly improve the overall survival (OS) over placebo in the randomized phase 3 CELESTIAL trial in patients who had up to two lines of prior systemic therapy (including sorafenib) with progression on at least one in comparison to patients who received best supportive care (1). *Although cabozantinib shares similar targets with sorafenib/regorafenib, they present different toxicity profile. While the most common grade 3-4 AEs reported for sorafenib were fatigue (4%), diarrhea (8%), hand-foot reaction (8%) and hypertension (2%) (2); the most frequent grade 3-4 AEs for cabozantinib were hand-foot reaction (HFSR) (3.6%), hypertension (3.4%) and elevation of AST (2.6%) (1).* *In clinical practice, regorafenib, ramucirumab and cabozantinib are approved by EMA as second-line treatment approved by EMA until now (3). However, more than 40% of candidate patients to 2nd line do not meet the RESORCE criteria or REACH-2 trial and are only candidates to cabozantinib treatment. However, we do not have safety data about those patients who are treated with other treatments than sorafenib in first line neither data about the real impact of sorafenib-intolerant patients according to the RESORCE trial definition.* *For this reason, we propose to explore the role of cabozantinib in patients who were not considered in the CELESTIAL trial.*	

Primary Study Objective(s)

To evaluate the safety profile established by rate of adverse events (AE) with Common Terminology Criteria for Adverse Events (CTCAE)≥3 excluding palmar-plantar erythordysthesia, rate of related-AEs and rate of death. The rate of AEs leading to treatment discontinuation.

Secondary Study Objective(s)

Overall survival (OS), objective response rate (ORR), time to progression (TTP), pattern of progression, post-progression survival (PPS), rate of patients who develop new extra-hepatic spread

Operational/organizational aspects of the Study

Multicenter study conducted by the BCLC in Spain with 7 relevant sites in HCC involved. Some study tasks will be outsourced to a national CRO (regulatory process, EDC system, monitoring plan, analysis, etc.)

Study Population

Patients with HCC intolerant to sorafenib according to the RESORCE trial definition or those patients who received other first-line treatment.

Inclusion Criteria (detailed)

1. *HCC diagnosed according to criteria of American Association for the Study of Liver Diseases (AASLD) definition in 2010.*
2. *Intolerant to sorafenib according to RESORCE trial definition or patients who received treatment different to sorafenib as first-Line treatment .*
3. *The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)*
4. *Recovery to ≤ Grade 1 according to (CTCAE) v.5.0. from toxicities related to any prior treatments, unless the adverse events are clinically non-significant and/or stable on supportive therapy*
5. *Respect the 15 days of first-line treatment washout before starting cabozantinib*
6. *Age ≥ 18 years old on the day of consent*
7. *ECOG performance status of 0 or 1*
8. *Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before starting therapy:*
   a. *absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)*
   b. *platelets ≥ 60,000/mm3 (≥ 60 x 10^9/L)*
   c. *hemoglobin ≥ 8 g/dL (≥ 80 g/L)*
9. *Adequate renal function, based upon meeting the following laboratory criteria within 7 days before starting therapy:*
   a. *Serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum*

Creatinine x72 [mg/dL]) for males. (For females multiply by 0.85).

AND

b. 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. *Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before starting therapy*
12. *Serum albumin ≥ 2.8 g/dL (≥28 g/L) within 7 days before starting therapy*
13. *Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5.0 upper limit of normal (ULN) within 7 days before starting therapy*
14. *Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before starting therapy (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)*
15. *Antiviral therapy per local standard of care if active hepatitis B (HBV) infection*
16. *Capable of understanding and complying with the protocol requirements and signed informed consent*
17. *Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment*
18. *Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression, low body weight, or other reasons.*
19. *Subjects must consent to perform a tumor liver biopsy within 4 weeks before starting cabozantinib, allowing the acquisition of a tumor sample for performance of correlative studies. A formalin-fixed, paraffin embedded (FFPE) tumor tissue block of tumor sample should be stored at local sites for correlative studies. For these biopsies, subjects must have a soft tissue tumor lesion that can be biopsied at acceptable clinical risk, as judged by the investigator. Subjects must consent to the pre-treatment fresh liver biopsy as a condition of protocol participation. If adequate tissue is not obtained during the first procedure then a repeat biopsy should be considered based on the investigator's assessment of clinical risk. However, biopsies at the time of radiological tumor progression are not required to meet eligibility. Tumor biopsy is recommended at the time of tumor progression development. However, patients who develop radiologic tumor progression should have performance status 0/1 and preserved liver function. Finally, patients with symptomatic tumor progression will*

not be biopsied.

Exclusion Criteria

1. *Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma*
2. *Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases or radionuclide treatment within 6 weeks of starting therapy (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)*
3. *Prior cabozantinib treatment*
4. *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 starting therapy. Eligible subjects must be without corticosteroid treatment at the time of starting therapy.*
5. *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 (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low dose LMWH are permitted.*
6. *The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions*
   a. *Cardiovascular disorders including:*
      i. *Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias*
      ii. *Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or 100 mm Hg diastolic despite optimal antihypertensive treatment*
      iii. *Stroke (including TIA), myocardial infarction, or another ischemic event within 6 months before starting therapy*
      iv. *Thromboembolic event within 3 months before starting therapy. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible*

   b. *Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:*
      i. *Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction*
      ii. *Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before starting therapy*
      iii. *Note: Complete healing of an intra-abdominal abscess must be confirmed*

prior to starting therapy

c. Major surgery within 2 months before starting therapy. Complete healing from major surgery must have occurred 1 month before starting therapy. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before starting therapy. Subjects with clinically relevant complications from prior surgery are not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

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

f. Clinically significant bleeding risk including the following within 3 months of starting therapy: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.

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

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis

vi. History of solid organ transplantation

7. *Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.*
8. *Moderate or severe ascites. Note that controlled ascites with stable dose of diuretics in the last month is allowed.*
9. *Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before starting therapy*

Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

10. *Inability to swallow tablets*
11. *Previously identified allergy or hypersensitivity to components of the study treatment formulations*
12. *Pregnant or lactating females*
13. *Diagnosis of another malignancy within 2 years before starting therapy, except for superficial*

skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

14. *History of allergy to study drug components.*
15. *Prisoners or subjects who are involuntarily incarcerated*
16. *Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg. infectious disease) illness*
17. *Inability to comply with restrictions and prohibited activities/treatments.*

Test Treatment(s) (Description)

Cabozantinib will be initiated at full dose (60 mg every day) which will be modified upon development of adverse events according to the manufacturer's recommendations. Treatment will continue until symptomatic tumor progression, unacceptable adverse events, patient decision or death.

Safety reporting

All AEs that occur after the patient has signed informed consent until at least 30 days after the last dose of the study treatment must be recorded in the CRF.

The documentation should be confirmed with a note in the patient's file. An abnormal laboratory result considered clinically significant—e.g. any which causes the patient's withdrawal from the study, requires treatment or causes obvious clinical manifestations, or which is assessed as relevant by the investigator—must be reported as an AE. Each event should be described in detail, together with the start and end dates, severity, relationship to the investigational medicinal product, measures taken and outcome.

All actions taken concerning the study treatment to resolve the AE (drug withdrawal, drug suspension, dose reduction, unchanged dose, dose escalation, not applicable, not known) will be documented.

Notice to the IECs of all relevant events (e.g. SAEs, Suspected Unexpected Serious Adverse Reactions [SUSARs]) will be given by the sponsor and/or investigator in accordance with the applicable regulations.

The processing and communication of all relevant events (SAEs, SUSARs) to the authorities will be carried out by the sponsor in accordance with current legislation.

The sponsor will inform all sites of relevant adverse events (e.g. SUSARs) in accordance with current legislation.

Standard of Reference/Standard of Truth*

Cabozantinib is a second-line treatment approved in HCC. However, in the CELESTIAL trial all patients received sorafenib as first-line treatment.

Rationale for selection of a reference treatment

In clinical practice, regorafenib, ramucirumab and cabozantinib are approved by EMA as second-line treatment until now (3). More than 40% of candidate patients to 2nd line do not meet the RESORCE criteria or REACH-2 trial and are only candidates to cabozantinib treatment. However, we do not have safety data about those patients who are treated with other treatments of sorafenib in first line

neither data about the real impact of sorafenib-intolerant patients according to the RESORCE trial definition.

For this reason, our aim is to explore the role of cabozantinib in intolerant patients to first-line treatments or patients who received first line treatment different to sorafenib.

Blinding

Open-label due to the characteristic of the study. All patients will receive cabozantinib orally.

Primary Outcome(s)

Rate of AEs with CTCAE≥3 excluding palmar-plantar erythordysthesia, rate of AEs, rate of related-AEs and rate of death.

Adverse events will be graded following version 5.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose before discontinuation.

Secondary Outcome(s)

Time to progression, pattern of progression, overall survival, post-progression survival, progression free survival, rate of patients who develop new extrahepatic spread. ORR

Safety Outcomes

Rate of AE, rate of related-AEs and rate of death.

Adverse events will be graded following version 5.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose.

Visit schedule

***Baseline evaluation and Follow-up included**:*

All patients will be biopsied before starting cabozantinib. If the patient has a previous tissue sample, that material will be analyzed. However, this does not exclude the need to perform a biopsy within the month after initiation and at the time of developing radiologic tumor progression.

Follow-up period

Follow-up will include clinical and laboratory assessment every 2 weeks within the first 2 month, then every 4 weeks, tumor evaluation at week 4 and every 8 weeks thereafter. In addition, unscheduled visits will be made should they be needed (adverse events or symptoms). At each time point that the dose is changed we will perform a blood extraction to determine serum biomarkers. Moreover, a second extraction will be done 7 days after modifying the cabozantinib dose. Adverse events will be graded following version 5.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose. Tumor evaluation during follow-up will be evaluated by CT-scan. Response and TP will be defined according to the RECIST criteria v1.1. Outcomes will be measured from the date of starting cabozantinib until the date of death regardless of cause of death. TTP will be defined as the time from the starting date of cabozantinib to disease progression (according to RECISTv1.1). PPS will be measured from the date of detecting progression at radiology until the date of death or

last follow-up. Assessment will be done by radiologists in each center and then a central revision by radiologists with more than 10 years of experience in HCC and blinded to the evolution and outcome of the patients. Disease-control rate (DCR) will be defined as the percentage of patients who had a best-response rating of complete response (CR), partial response (PR) or stable disease (SD) (according to RECIST and BCLC-RECIST) maintained for at least 28 days after the first demonstration of best-response rating as per independent radiologic review.

Statistical & Analytical Plan and Methodology

The study will be analyzed using standard statistical methods to estimate rates and 95%CI (for ORR and other binary variables) by means of the Clopper-Pearson exact method, and the Kaplan-Meier method to describe the survival functions and the median and [95%CI]. A Statistical Analysis Plan, which will include all details regarding all analyses, the interim method, the handling of missing data and any plan for the analysis, will be finalized before the initiation of the study recruitment.

The sample size calculation will be triggered by the primary outcome, i.e, the rate of adverse events (AE) with CTCAE≥3 excluding palmar-plantar erythordysthesia (critical AEs). The expected rate for this outcome was 56% in this population. The Simon's two-stage optimal design will be used to test the alternative hypothesis that with cabozantinib the rate of critical AEs will be reduced at least to 32.5% against the null hypothesis of 56%. In the first stage, 14 patients will be accrued and if there are 8 or more critical AES in these 14 patients, the study will be stopped for futility. Otherwise, 26 additional patients will be accrued for a total of 40. The null hypothesis will be rejected if 23 or fewer critical AEs are observed in 40 patients. This design yields a type I error rate of 2.5% one-sided and power of 80% when the true response rate is 67.5%.

Planned Study Timelines:

1. *Enrolment rate (patients per month): 3*
2. *Planned estimate of treatment(s) duration: **24months***
3. *Submission date to health authority/ethics: Jan 2020*
4. *Start of subject enrolment: March 2020*
5. *End of Subject enrolment: Jul 2022*
6. *All patients completed: **Oct 2023***
7. *End of Study: Jan 2024*
8. *Report**: Q2-Q3 2024***
9. *Planned publication/presentation: Q1 2025*

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1. INTRODUCTION

1.1 HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the third main cause of cancer-related death globally and has an incidence of around 850,000 new cases per year[1] HCC represents nearly 90% of all cases of primary liver cancer and is the first cause of death in cirrhotic patients[2]. In Western countries, leading risk factors for HCC development are well known and include hepatitis B (HBV) and C virus (HCV) infection, alcohol intake and nonalcoholic fatty liver disease (NAFLD) associated with the metabolic syndrome[1]. The Barcelona Clinic Liver Cancer (BCLC) staging classification is the most accepted clinical algorithm for the stratification of patients according to prognosis and treatment allocation[1]. The systemic treatment in hepatocellular carcinoma is quickly evolving since the sorafenib breakthrough in 2007[3], the only available drug for advanced HCC for more than 10 years. New drugs were recently made available for these patients due to their benefit on the overall survival (OS). In first-line therapy, the lenvatinib vs sorafenib (REFLECT) trial[4] was a multicenter, randomized, 1st-line phase 3 trial in HCC demonstrating that both treatments are equally effective but with a different safety profile[4]. Very recently, the combination of atezolizumab (anti-PDL1) and bevacizumab (IMbrave150 phase III trial[5]) has been reported to be superior than sorafenib. The first available second-line treatment with benefits in terms of survival was regorafenib[6] and more recently cabozantinib[7] and ramucirumab (REACH-2 trial[8]), all demonstrated to improve OS as compared to placebo in 3 phase III second-line randomized controlled trials (RCTs). Additionally, nivolumab[9] and pembrolizumab[10] have been granted an accelerated FDA approval in 2nd-line treatment based on radiologic tumor response. However, the phase III trial that compared pembrolizumab vs placebo in second-line is negative[11]. Specifically, the phase III CELESTIAL trial[7] demonstrated that cabozantinib is safe and effective in terms of OS [hazard ratio (HR) for death, 0.76; 95%CI, 0.63 to 0.92] in patients intolerant to sorafenib but there was any definition of intolerance in that trial and also in patients who developed progression under sorafenib.

1.2 CABOZANTINIB: BACKGROUND

A summary of the non-clinical pharmacology, toxicology, pharmaceutical and metabolism data on cabozantinib is provided in this section. Additional information can be found in the Investigator Brochures for cabozantinib.

1.2.1 PHARMACOLOGY AND PHARMACOKINETICS

Cabozantinib shows a potent inhibitory activity against different receptor tyrosine kinases that are known to impact on tumor growth, metastasis, and angiogenesis. The primary targets of cabozantinib are MET, VEGFR2/KDR, and RET with cell-based IC50 (concentration associated with 50% inhibition) values of 8, 2 and 85 nM, respectively[12]. In addition, cabozantinib suppressed phosphorylation of KIT, FLT3, and AXL with IC50 values of 5, 11, and 42 nM, respectively. The IC50 values in biochemical kinase assays do not always translate evenly in vivo. For example, cabozantinib exhibits comparable potency against MET and VEGFR2 in cellular and in vivo assays, in spite of its apparent greater potency for inhibition of VEGFR2 in biochemical kinase assays. Hence, cabozantinib is a balanced inhibitor of MET and VEGFR2 that also

inhibits a number of other receptor tyrosine kinases implicated in tumor pathobiology, including RET, KIT, AXL, and FLT3[12]. Data from pharmacodynamic experiments showed that cabozantinib inhibits MET and VEGFR2 in vivo. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. In addition, oral administration of cabozantinib resulted in blockade of phosphorylation of mutationally activated RET in human medullary thyroid cancer (MTC) xenografts grown in nude mice[13]. Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and glioblastoma[12].

Overall, the preclinical data produced in vivo demonstrate that the target profile of cabozantinib translates into potent anti-angiogenic activity and potent antitumor efficacy both in soft tissue and in bone.

A summary of cabozantinib pharmacology is contained in the Investigator's Brochure, which should be reviewed in conjunction with this study protocol.

A population PK analysis of cabozantinib was performed in using data collected from 289 subjects with solid tumors including metastatic medullary thyroid carcinoma (MTC) following oral administration of 140 mg (FBE) daily doses as capsules[14]. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr. The terminal half-life (for predicting drug washout) is approximately 120 hours. Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%). A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years)[14].

A second PopPK analysis was conducted in subjects with renal cell carcinoma (RCC) who received repeated oral daily cabozantinib tablet dosing at 60 mg (with protocol-permitted dose reductions to 40 mg and 20 mg) combined with healthy subjects who received a single oral tablet dose of 20, 40, or 60 mg. This analysis indicated that for a White male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (Vz) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h. Female gender and Asian race were significant covariates on CL/F, and while the attributes were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. Further evaluation of the differences in the two PopPK analyses revealed that compared with other cancer patient groups (ie, RCC, castration-resistant prostate cancer [CRPC], glioblastoma multiforme [GB]), MTC subjects cleared cabozantinib faster and thus had lower dose-normalized steady-state plasma exposures. Several possible factors may underlie the higher cabozantinib clearance observed in the first PopPK analysis; however, an exact cause has yet to be identified.

Exposure of cabozantinib was assessed in Japanese subjects in capsule and tablet formulations (Study XL184-014)[15]. At steady state, exposure, AUC increased slightly less than dose proportionally from 40 to 80 mg capsule doses and slightly more than dose proportionally from 40 to 60 mg tablet doses. There was no clinically relevant difference in exposure between capsule and tablet formulations. Steady-state plasma exposures in Japanese subjects administered 60-mg tablets were approximately 30% higher than reported in non-Japanese subjects administered 60-mg tablets (Study Report XL184-308)[15]. However, as this difference was within the range of inter-subject variability determined in Japanese (%CV= 34%) and non-Japanese subjects (%CV=48%), no firm conclusions may be drawn regarding differences in cabozantinib exposures between these two subject populations.

In the mass balance study, within a 48-day collection period after a single dose of 14Ccabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. A PK study of cabozantinib in patients with renal impairment is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib. The PK evaluation of cabozantinib has not been completed in patients with hepatic impairment; preliminary data suggest that subjects with mild hepatic function impairment (Child-Pugh A) show a 61% higher plasma AUC0-∞ for cabozantinib as compared with matched healthy subjects (XL184-003)[16].

A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose. Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin.

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsomal (HLM) preparations. IC50 values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems[14]. Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in patients with solid tumors.

Cabozantinib is an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Additional results from this and other clinical PK trials may be found in the Investigator Brochure.

1.2.2 CABOZANTINIB SAFETY SUMMARY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA.

The 41 subjects with advanced HCC treated with cabozantinib in phase II Study XL184-203 RDT[17] received an initial dose of 100 mg/day (FBE). Fifty-nine percent of subjects required at least 1 dose reduction throughout both the Lead-in and Randomized Stages. The most frequently reported AEs during the study were consistent with those in subjects with other tumor types who received single-agent cabozantinib and included diarrhea (68%), fatigue (59%), palmar-plantar erythrodysesthesia (PPE) syndrome (54%), vomiting (42%), and nausea (39%). Common Grade 3 or higher AEs included diarrhea (22%), thrombocytopenia (17%), PPE syndrome (15%), aspartate aminotransferase (AST) increased (12%).

The safety and efficacy were recently evaluated in the randomized, double-blind, placebo-controlled Phase 3 study[7]. The 707 patients with HCC not susceptible to curative treatment and who had received sorafenib were randomized (2: 1) to receive cabozantinib (N = 470) or placebo (N = 237). Patients may have received prior systemic treatment for advanced disease in addition to sorafenib. Randomization was stratified by disease etiology (HBV [with or without HCV), HCV [without HBV] or other), geographic region (Asia, other regions) and by the presence of extrahepatic spread of the disease and / or macrovascular invasions.

In the CELESTIAL study[7] the most frequently reported AEs during the study were consistent with those in subjects with previous data with cabozantinib single-agent and included diarrhea (54%), decreased appetite (48%), PPE syndrome (46%), fatigue (45%), nausea (31%), hypertension (29%) and vomiting (26%). Common Grade 3 AEs included PPE syndrome (17%), hypertension (16%), Increase in AST/ALT level (11%), diarrhea (10%) and fatigue (10%).

1.2.3 SUMMARY OF CABOZANTINIB CLINICAL ACTIVITY IN HEPATOCELLULAR CARCINOMA

The safety and efficacy were recently evaluated in the randomized, double-blind, placebo-controlled Phase 3 study (CELESTIAL)[7]. The 707 patients with HCC not susceptible to curative treatment and who had received sorafenib were randomized (2: 1) to receive cabozantinib (N = 470) or placebo (N = 237). Patients may have received prior systemic treatment for advanced disease in addition to sorafenib. Randomization was stratified by disease etiology (HBV [with or without HCV), HCV [without HBV] or other), geographic region (Asia, other regions) and by the presence of extrahepatic spread of the disease and / or macrovascular invasions.

The main efficacy variable was overall survival (OS). Secondary efficacy variables were progression-free survival (PFS) and objective response rate (ORT), evaluated by the researcher using the criteria for evaluation of solid tumor response (RECIST) 1.1[18]. Tumor evaluations were performed every 8 weeks. The subjects continued the treatment of the blind study after the progression of the radiological disease, while experiencing a clinical benefit or even the need for a local systemic or anticancer therapy directed to the liver. The placebo crossing to cabozantinib was not allowed during the blind treatment phase. The CELESTIAL trial showed significantly longer OS in the cabozantinib arm compared to with placebo. Median OS was 10.2 months with cabozantinib and 8.0 months with placebo (HR for death, 0.76; 95% CI, 0.63 to 0.92; P = 0.005). Median PFS was 5.2 months with cabozantinib and 1.9 months with placebo (HR for disease progression or death, 0.44; 95% CI, 0.36 to 0.52; P<0.001), and the ORR were 4% and less than 1%, respectively (P = 0.009).

1.2.4 RATIONALE FOR THE CURRENT STUDY

The systemic treatment for HCC has rapidly evolved in last years, having available in first-line sorafenib[3] and lenvatinib[4] but very recently the IMbrave150 phase III trial[5] has been presented as positive. Cabozantinib has been shown to be safe and effective in patient who progressed on sorafenib treatment[7]. Here, sorafenib intolerant patients were also included but no clear definition was applied to identify those patients. Therefore, the aim of this study will be to test the safety of cabozantinib in patients sorafenib intolerant according to the RESORCE[6] trial definition and in patients treated with first-line treatments other than sorafenib.

1.2.4.1 TREATMENT SCHEDULE

Cabozantinib will be initiated at full dose (60 mg/day) and this dose will be modified upon development of adverse events according to the manufacturer's recommendations. Cabozantinib will be continued at the dose that the patient can tolerate. Treatment will continue until symptomatic tumor progression, unacceptable adverse events, patient decision or death.

2. STUDY OBJECTIVES

The aim of this study will be to test the safety of cabozantinib in patients sorafenib intolerant according to the RESORE trial[6] definition and in patients treated with first-line treatments other than sorafenib. Indeed, although a phase III trial (CELESTIAL)[7] showed improved OS with acceptable toxicity in sorafenib intolerant patients or in those who progressed on sorafenib, no clear definition was applied to identify those patients. The primary endpoints are the rate and type of AEs leading to treatment discontinuation, the rate and type of AEs, serious AEs (SAEs), rate of related-AE and rate of death. Secondary endpoints are time to progression, pattern of progression, overall survival, post-progression survival, rate of patients who develop new extra-hepatic spread and ORR. Radiologic tumor response will be defined according to the RECIST 1.1[18] and then will be evaluated by BCLC-RECIST[19]. Exploratory objectives are: i) to evaluate the role of tissue biomarkers (see Table 5 for timing-points) in determining the antitumoral activity of cabozantinib; ii) to describe the quality of life and iii) the gut microbiota composition at different time points. This study will collect blood and biopsy samples but the exploratory objectives will be done in a second study only if the study meets the safety end-point.

3. ETHICAL CONSIDERATIONS

3.1 GOOD CLINICAL PRACTICE

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying regulation (EU) Nº536/2014 of the European Parliament and the council of 16 April 2014. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to the

Sponsor. The responsible unit (e.g. EC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 4.1.5

3.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or the sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates. The investigator or the sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 INFORMED CONSENT

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised IC form. Any revised written IC form and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to patients / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

4. STUDY DESIGN AND PLAN

The study is a prospective, multicenter, open-label, non-controlled phase IIa study evaluating cabozantinib for the treatment of patients with unresectable hepatocellular carcinoma sorafenib intolerant according to the RESORCE trial definition or who received other first-line treatments than sorafenib. Treated patients will be followed until death, withdrawal of consent or until the end of the duration of the study.

4.1 TREATMENT PLAN

4.1.1 SCREENING PHASE

Study entry is defined as the date that the Informed Consent has been signed by the patient. No patient may undergo any screening procedures that are not considered standard of care to assess his/her eligibility to receive protocol treatment, or commence protocol treatment, prior to signing the informed consent form. The time period between study entry and the commencement of protocol treatment is not to exceed 28 days. Patients may only commence protocol treatment after all eligibility criteria have been confirmed. After signing the informed consent and upon documentation of eligibility, the patient will be allocated with an enrolment number and registered in an enrolment log. The patient identification number will be multi-digit, to represent the investigational site and an enrolment number that will be unique to each subject. All patients referred for possible participation in this study must be assessed at screening to confirm the patient's eligibility. All documentation supports the inclusion and exclusion criteria and screening investigation results are to be retained by the Investigator and made available for monitoring by the study

Sponsor including source data verification. All patients assessed as ineligible to be enrolled in the study after study entry are considered screening failures. The investigator will have their initials recorded on the Patient Screening Log and no further data will be collected for these patients. The Patient Screening Log will include the reason(s) for the patient not meeting the eligibility criteria and will be maintained by the site and copies retained by the study Sponsor. Patient who withdrew consent after study entry but before treatment for any reason will be considered screening failures and should be registered in the screening log.

The study monitor should be contacted in the event of any query or uncertainty relating to a patient's eligibility to receive protocol treatment:

Dr. Marco Sanduzzi-Zamparelli
BCLC group, Liver Unit, Hospital Clinic de Barcelona
Email: msanduzzi@clinic.cat
Phone: +34 932279803;
Fax:+34 932275792

Dr. Maria Reig
BCLC group, Liver Unit, Hospital Clinic de Barcelona
Email: mreig1@clinic.cat
Phone: +34 932279803;
Fax:+34 932275792

4.1.2 CABOZANTINIB

The choice of dosage (starting dose of 60 mg) and schedule to be used in this trial is based on available data accumulated in previous Phase I, II and III trials and approved to treat HCC with cabozantinib.

The study drug will be administered orally. The investigator or designated study personnel is responsible for dispensing the study drug to patients.

Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking cabozantinib. Subjects should be instructed to not make up vomited doses and to maintain the planned dosing schedule. Subjects should not make up for missed doses if more than 12 hours have elapsed after the time the subject would usually take cabozantinib. In the event of missed doses, subjects should not take 2 doses to make up for the one the subject missed.

Any unused study treatment must be returned to the study site for drug accountability and disposal.

Cabozantinib will be initiated at full dose (60 mg/day) and the dose will be modified upon development of adverse events according to the manufacturer's recommendations. Treatment will be continued until symptomatic tumor progression, unacceptable adverse events, patient decision or death. Criteria for cabozantinib dose reduction or escalation and to resume treatment are described in Section 6.1.4.1

4.1.3 END OF THE STUDY

After discontinuation from study therapy, there is 1 follow-up visit required within seven days of discontinuation (on site visit), and additional survival follow-up (on-site or phone visits). The study will end

when survival follow-up collection has concluded. The last visit will be defined as the latest follow-up Visit. Additional survival follow-up may continue beyond the time of this analysis.

4.1.4 DISCONTINUATION OF CABOZANTINIB

Subjects MUST discontinue study medication:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, abnormal laboratory test results or any illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Clinical deterioration (Section 6.1.7)
- Pregnancy
- Termination of the study by the promoter
- Specific criteria for discontinuation of outlined in (Section 6.1.6)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Protocol defined disease progression unless subject is eligible for treatment beyond progression (Section 6.1.7.1).
- In the case of pregnancy, the investigator must immediately notify the Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Principal Investigator must occur.
- All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in section. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF page.

4.1.5 POST STUDY DRUG STUDY FOLLOW-UP

In this study, overall survival is a secondary endpoint. Subjects who discontinue study drug must continue to be followed for collection of survival follow-up data until death or the conclusion of the study. Survival follow-up visits should be planned every 3 months from Follow-Up Visit-1 and may be performed by phone contact or office visit.

4.1.6 WITHDRAWAL OF CONSENT

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject

specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the Investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The Investigator should explain the withdrawal of consent in detail in the medical records, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

4.1.7 LOST TO FOLLOW-UP

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails or whatsapp messages as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

5. PATIENT POPULATION

For entry into the study, the following criteria MUST be met. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used.

5.1 INCLUSION CRITERIA

5.1.1 SIGNED WRITTEN INFORMED CONSENT

Willing, able and mentally competent to provide written informed consent.

5.1.2 TARGET POPULATION

- HCC diagnosed according to criteria of American Association for the Study of Liver Diseases (AASLD) definition in 2010.
- Intolerant to sorafenib according to RESORCE trial definition or patients who received treatment different to sorafenib as first-Line treatment.
- The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
- Recovery to ≤ Grade 1 according to (CTCAE) v.5.0. from toxicities related to any prior treatments, unless the adverse events are clinically no significant and/or stable on supportive therapy
- Respect the 15 days of first-line treatment washout before starting cabozantinib
- Age ≥ 18 years old on the day of consent
- ECOG performance status of 0 or 1
- Adequate hematologic function, based upon meeting the following laboratory criteria within

7 days before starting therapy:

a. absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)

b. platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)

c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)

- Adequate renal function, based upon meeting the following laboratory criteria within 7 days before starting therapy:

  a. Serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum Creatinine x72 [mg/dL]) for males. (For females multiply by 0.85).

  AND

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

- Child-Pugh Score of A
- Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before starting therapy
- Serum albumin ≥ 2.8 g/dL (≥28 g/L) within 7 days before starting therapy
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5.0 upper limit of normal (ULN) within 7 days before starting therapy
- Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before starting therapy (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)
- Antiviral therapy per local standard of care if active hepatitis B (HBV) infection
- Capable of understanding and complying with the protocol requirements and signed informed consent
- Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
- Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression, low body weight, or other reasons.
- Subjects must consent to perform a tumor liver biopsy within 4 weeks before starting cabozantinib, allowing the acquisition of a tumor sample for performance of correlative studies. A

formalin-fixed, paraffin embedded (FFPE) tumor tissue block of tumor sample should be stored at local sites for correlative studies, as described in Section 7.4. For these biopsies, subjects must have a soft tissue tumor lesion that can be biopsied at acceptable clinical risk, as judged by the investigator. Subjects must consent to the pre-treatment fresh liver biopsy as a condition of protocol participation. If adequate tissue is not obtained during the first procedure then a repeat biopsy should be considered based on the investigator's assessment of clinical risk. However**, biopsies at the time of radiological tumor progression are not required to meet eligibility.** Tumor biopsy is recommended at the time of tumor progression development. However, patients who develop radiologic tumor progression, should have performance status 0/1 and preserved liver function. Finally, patients with symptomatic tumor progression will not be biopsied.

All patients on cabozantinib treatment must stop cabozantinib 5-7 days before performing the biopsy to avoid the risk of bleeding. They will be visited 5-7 days after the biopsy to re-start cabozantinib.

5.2 EXCLUSION CRITERIA

5.2.1 MEDICAL HISTORY AND CONCURRENT DISEASES

- Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
- Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of starting therapy (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)
- Prior cabozantinib treatment
- 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 starting therapy. Eligible subjects must be without corticosteroid treatment at the time of starting therapy.
- 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 (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and lowdose LMWH are permitted.
- The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including:
        i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
        ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or 100 mm Hg diastolic despite optimal antihypertensive treatment
        iii. Stroke (including TIA), myocardial infarction, or another ischemic event within 6 months before starting therapy

iv. Thromboembolic event within 3 months before starting therapy. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible

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

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

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before starting therapy

Note: Complete healing of an intra-abdominal abscess must be confirmed prior to starting therapy

c. Major surgery within 2 months before starting therapy. Complete healing from major surgery must have occurred 1 month before starting therapy. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before starting therapy. Subjects with clinically relevant complications from prior surgery are not eligible

c. Cavitating pulmonary lesion(s) or endobronchial disease

d. Lesion invading a major blood vessel including, but not limited to:, pulmonary artery, or aorta). Subjects with lesions invading the portal vasculature are eligible.

e. Clinically significant bleeding risk including the following within 3 months of starting therapy: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

f. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.

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

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis

vi. History of solid organ transplantation

- Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.
- Moderate or severe ascites. Note that controlled ascites with stable dose of diuretics in the last month is allowed.
- Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before starting therapy

  Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.
- Inability to swallow tablets
- Previously identified allergy or hypersensitivity to components of the study treatment formulations
- Pregnant or lactating females
- Diagnosis of another malignancy within 2 years before starting therapy, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy
- History of allergy to study drug components.
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg. infectious disease) illness
- Inability to comply with restrictions and prohibited activities/treatments.

6. STUDY DRUG(S) AND CONCOMITANT MEDICATIONS

6.1 INVESTIGATIONAL PRODUCTS

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. Authorized personnel according to local regulations must dispense the investigational product only from official study sites. In this protocol, investigational products is cabozantinib.

6.1.1 CABOZANTINIB

Cabozantinib will be initiated at full dose (60 mg/day) and the dose will be modified upon development of adverse events according to the manufacturer's recommendations and continued until symptomatic tumor progression, unacceptable adverse events, patient decision or death.

6.1.2 PACKAGING AND LABELING.

Cabozantinib 60, 40 and 20 mg will be packaged in an open-label fashion and labeled for use in the ACTION clinical trial.

6.1.3 HANDLING AND DISPENSING

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational products are only dispensed to study subjects and only from official study sites by authorized personnel according to local regulations. The product storage manager should ensure that the study drugs are stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the manufacturer. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed. Investigational products documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes.

6.1.4 DOSE MODIFICATIONS

6.1.4.1 CABOZANTINIB DOSE MODIFICATIONS

Cabozantinib dose reduction

Toxicities will be graded using the NCI CTC version 5.0 (see Appendix 4). All dose modifications will follow pre-defined dose levels as indicated below.

The modifications of cabozantinib dosage will follow the following pre-defined dose levels:

Table 1: Cabozantinib dose reduction

Dose level 0 (standard dose)	60 mg po	1 tablet of cabozantinib every day
Dose level -1	40 mg po	1 tablet of cabozantinib every day
Dose level -2	20 mg po	1 tablet of cabozantinib every day
Dose level -3	20 mg po	1 tablet of cabozantinib every 2 or 3 days

If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment, which reduces the dose to the lowest level, should be used.

If a dose reduction has been performed, intra-subject dose re-escalation can be considered (up to the maximum of 60 mg daily dose) at the discretion of the treating investigator provided that the toxicities has resolved to at least CTC-Grade baseline levels.

Table 2 Dose Modification Criteria

Toxicity	Criteria Recommended Guidelines for Management
Grade 1 AEs	Continue study treatment if AE is tolerated
Grade 2 AEs which are intolerable and cannot be adequately managed	At the discretion of the investigator, study treatment should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 (except clinically non-relevant laboratory abnormalities)	Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have their study treatment interrupted immediately. Discontinue study treatment unless the following criteria are met: Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.
[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to study treatment or had an unclear relationship to study treatment.
[b] For dose reduction levels, see Table 1.

6.1.4.2 GENERAL

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including PPE syndrome, elevated liver function tests (including alanine aminotransferase [ALT] and AST), increased pancreatic enzymes with rare cases of overt pancreatitis, hypothyroidism, QTc prolongation, as well as side effects associated with inhibition of VEGF signaling. The latter of these include arterial and venous thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack, and myocardial infarction; hypertension; hemorrhagic events; proteinuria, wound complications, and rare cases of GI perforation, fistulae formation and rectal/perirectal abscess, osteonecrosis, and reversible posterior leukoencephalopathy (RPLS). Please refer to the Investigator's Brochure for additional details. As with all investigational products, unknown AEs may occur. Subjects should be monitored closely throughout their study participation for all AEs. As with other agents in development, additional AEs are unknown. As of 22 October 2013, in studies with cabozantinib,

angioedema has been reported to occur in ~0.1% of subjects treated. The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2-3 weeks to reach steady state after daily dosing. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, since without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE. Management of fatigue, anorexia, diarrhea, nausea, skin disorders, vomiting, rash, hypertension, proteinuria, elevated ALT and AST, myelosuppression, mucositis, hypothyroidism, and cardiac disorders are presented in this section as these have been observed in previous studies with cabozantinib or represent common class effect toxicity. In addition, guidelines to minimize the risk for potential SAEs such as GI and non-GI perforation and fistula formation, hemorrhagic events, and osteonecrosis of the jaw (ONJ) are provided in this section. Please refer to the Investigator's Brochure for additional practice guidelines and management

recommendations for side effects potentially related to cabozantinib treatment; available information on potential risk of congenital, familial, and genetic disorders; and guidelines on management of cabozantinib overdose.

6.1.4.3 GASTROINTESTINAL DISORDERS

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 2.

In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping

lactose-containing products, high fat meals and alcohol. For more information please refer to the current Investigator's Brochure.

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During study

treatment good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of study treatment should be considered.

6.1.4.4 HEPATOBILIARY DISORDERS

Elevations of ALT, AST, and total bilirubin have been observed during treatment with cabozantinib.

A subject who has ALT, AST, and total bilirubin ≤ 3.0 X ULN at baseline and who develops ≥ Grade 3 elevated ALT, AST, or total bilirubin should have study treatment interrupted and the dose reduced as outlined in Tables Table 2.

Subjects on this study may enter the study with elevations of AST/ALT up to 5 X ULN at baseline. Elevations of aminotransferases when hepatic tumors are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum total bilirubin concentration or coagulation factors. Cabozantinib treatment should be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. If hepatic toxicity resolves during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment. Elevations > 3x ULN of ALT or AST concurrent with > 2xULN total bilirubin without other explanation can indicate drug-induced liver injury and drug should be permanently discontinued. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or total bilirubin. Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. AEs which are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions.

6.1.4.5 HEMATOLOGICAL DISORDERS

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion. Complete blood counts with differentials and platelets should be performed during treatment if necessary. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated aggressively

according to institutional guidelines. Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be given as clinically indicated.

6.1.4.6 FATIGUE, ANOREXIA, AND WEIGHT LOSS

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual nonpharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the investigator's discretion. Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for Grade ≥ 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of study treatment may be re-escalated to the previous dose.

6.1.4.7 SKIN DISORDERS

Palmar-plantar erythrodysesthesia (PPE) syndrome PPE syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo). Early signs of PPE syndrome include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study drug (referred to as "study treatment") are presented in Table 3. In the case of study treatment-related skin changes, the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve Wound Healing and Surgery VEGF inhibitors can

cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting study treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with study drug. Study treatment should be stopped at least 28 days prior to scheduled surgery. The decision to resume study treatment after surgery should be based on clinical judgment of adequate wound healing. Study treatment should be interrupted for any wound healing complication. Study treatment should be discontinued in subjects with serious or chronic wound healing complications.

Table 3 Dose Modification Criteria and Recommended Guidelines for Treatment emergent

PPE Syndrome

CTCAE v.5.0 Grade	Action To Be Taken
Grade 1	Study treatment[a] may be continued at the current dose if PPE syndrome is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE syndrome worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPE is tolerated. Study treatment should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily and clobetasol 0.05% cream once daily and add analgesics (eg, gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment[a] until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPE syndrome recovers to

	Grade ≤ 1. Discontinue subject from study if intolerable PPE syndrome recurs at a reduced dose or if PPE syndrome does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; GABA, gamma-amino butyric acid; PPE, Palmar Plantar Erythrodysesthesia.
[a] Study treatment includes both cabozantinib and matched placebo.

6.1.4.8 HYPERTENSION

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported in subjects treated with cabozantinib. Blood pressure (BP) should be monitored in a constant position at each visit (either sitting or supine) and every day at home by the patients himself.

Treatment guidelines for hypertension deemed related to study drug are presented in Table 4. In general, subjects with known hypertension should be optimally managed prior to study entry. Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 4 Guidelines for the Management of Treatment-emergent Hypertension

Criteria for Dose Modification[a]	Dose Modification
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	•Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce study treatment by 1 dose level • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized

	antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if subject is symptomatic. • Restart study treatment at the most tolerable dose and reescalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive emergency[b] or hypertensive encephalopathy	• Discontinue study treatment

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP > 150 mm Hg or diastolic BP > 100 mm Hg based on their clinical judgment and assessment of the individual subject.

[b] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (ie, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage)

6.1.4.9 THROMBOEMBOLIC EVENTS

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. DVT and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins (LMWH) is established. (Note: therapeutic anticoagulation with oral anticoagulants is prohibited.) Study treatment may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated, they are deriving benefit from study treatment, and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as

determined by the investigator. Subjects who develop portal/hepatic vessel thrombosis may not require anticoagulation. The decision regarding anti-coagulation in such cases is at the discretion of the investigator and within the context of standard of care. Arterial thrombotic events (eg, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac or thromboembolic events that occurred prior to initiation of study treatment. Study treatment should be discontinued in subjects who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

6.1.4.10 PROTEINURIA

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. During each safety assessment visit, proteinuria will be quantified by measuring the urine protein-to-creatinine (UPCR) ratio performed by the central lab. In addition, urine dipstick analysis performed by the local lab will be done at least every 8 weeks and more as clinically indicated. Management of proteinuria will be based on UPCR results provided by the central lab. As dipstick results from the local labs may be available prior to the UPCR results from the central lab, they can be used by the investigator for interim management. In the case of proteinuria, if the dipstick analysis shows proteinuria ≥ 3+, study treatment should be interrupted until the UPCR results are available and more definitive management can be applied.

6.1.4.11 CORRECTED QTc PROLONGATION

The effect of orally administered cabozantinib at 140 mg/day (FBE) on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled Phase 3 study in patients with MTC (Study XL184-301). A mean increase in QT interval corrected by Fridericia (QTcF) of 10-15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib treated patients on this study had a QTcF > 500 ms during the QT evaluation period.

Only subjects with a baseline QTcF ≤ 500 ms are eligible for this study. Subjects will have ECGs performed at times designated by the protocol. If at any time on study there is an increase in QTcF interval to an absolute value > 500 ms, within 30 minutes after the initial ECG, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart. If the average QTcF from the 3 ECGs is > 500 ms, the following actions must be taken:

- Withhold study treatment
- Immediately notify the Principal Investigator
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management

- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (see http://www.qtdrugs.org)
- Send ECGs to central ECG laboratory (see ECG study manual)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms Study treatment may be restarted at a reduced dose level if all of the following conditions are met:
- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed by the central ECG laboratory or a QTcF

> 500 ms confirmed by the central laboratory returns to ≤ 500 ms

- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms

Study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study

treatment at a reduced dose

6.1.4.12 HEMORRAGIC EVENTS

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors prior to initiating study treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for study treatment.
- Recent or concurrent radiation
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis

Discontinue study treatment in subjects who experience a severe bleeding complication.

6.1.4.13 GI PERFORATION/FISTULA AND NON-GI FISTULA FORMATION

GI perforation/fistula and non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI perforation/fistula:

- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing).

Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating study treatment.

Additional risk factors include concurrent chronic use of steroid treatment or nonsteroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

- Complications from radiation therapy have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab). Subjects are excluded from this study if there are any clinically relevant ongoing complications from prior radiation therapy (ie, radiation esophagitis or other inflammation of the viscera).

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

6.1.4.14 OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Osteonecrosis has been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary study treatment interruption. If clinically possible, study treatment should be held for approximately 4 weeks prior to a dental procedure and resumed after complete healing has occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by the Principal Investigator of the study.

6.1.5 CRITERIA TO RESUME CABOZANTINIB TREATMENT

Subjects may resume treatment with cabozantinib when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume dosing in the presence of Grade 2 fatigue
- Subjects who delayed dosing due to UPCR ≥ 2.0 or urine dipstick protein ≥ 3+ may resume dosing at one dose level reduction when 24 hours urine protein < 2.0 g or repeat UPCR < 2.0
- Subjects who delayed dosing due to Grade 3 hypertension may resume dosing at the same dose or at one dose level reduction, at the discretion of the investigator, when hypertension has improved to Grade ≤ 2.
- Subjects who delayed dosing due to Grade 4 lipase abnormalities (either asymptomatic or in the absence of radiographic findings) may resume dosing upon resolution to Grade ≤ 2.
- Subjects who delayed dosing due to major surgery should not resume cabozantinib until complete wound healing has taken place. Following cabozantinib resumption, subjects should be monitored for wound dehiscence, wound infections, and other signs of impaired wound healing.

If treatment is delayed 8 weeks for any reason, the participant must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the Medical Monitor or designee.

6.1.6 PERMANENT DISCONTINUATION OF CABOZANTINIB DUE TO ADVERSE EVENTS

Cabozantinib administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date of this decision is to be recorded and every effort should be made to continue safety evaluations and collection of subsequent treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment, including any subject with a GI or non-GI perforation/fistula
- Any adverse event, laboratory abnormality or intercurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continuing study medication.
- Any Grade 3 non-skin, drug-related adverse event lasting > 21 days
  Exception of grade 3 drug-related AE:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
- Any drug-related Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days;

  - Grade 4 lymphopenia or leukopenia;
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis;
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset;
- The investigator feels it is not in the best interest of the subject to continue on study
- Participation in another clinical study using an investigational agent or investigational medical device
- Necessity for treatment with non-protocol systemic anticancer therapy
- Receipt of liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy, including stereotactic radiotherapy, or surgery)
- Necessity for withholding study drug for greater than 8 weeks for AEs, unless continuation of treatment is approved by the Principal Investigator
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
- Pregnancy of a female subject
- Request by the Principal Investigator
- Subject request to discontinue study treatment
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Principal Investigator
- The Principal Investigator should be notified of all discontinuations of study treatment as soon as possible. If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at a minimum, a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the study site.
- For subjects who withdraw or are withdrawn from study treatment, every effort must be made to continue protocol-specified evaluations and procedures through the post-treatment follow-up and extended follow-up visits unless consent to participate in the study is also withdrawn. All subjects will be followed until death, unless consent to do so is specifically withdrawn by the subject or until a decision by the Principal Investigator is made to stop collection of these data.

If the Investigator consider the option of continue with one of the investigations drugs, the decision to continue with one of the drug-study treatments beyond the criteria mentioned in this point of the protocol should be discussed with the Principal Investigator, Medical Monitor and documented in the study records.

6.1.7 STOPPING RULES FOR CLINICAL DETERIORATION

Clinical deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and

therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bisphosphonates, bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the Principal Investigator and Medical Monitor as well as will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline despite transitory cabozantinib interruption for at least 4 weeks
- Skeletal related events defined by spinal cord or nerve root compression.
- Development of new central nervous system metastases or Grade 3 encephalopathy despite transitory cabozantinib interruption for at least 2 weeks
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the patient.

6.1.7.1 TREATMENT WITH CABOZANTINIB BEYOND DISEASE PROGRESSION

In the absence of clinical deterioration, it is thus reasonable that subjects will be allowed to continue study therapy after an initial investigator-assessed RECIST 1.1 defined progression (based on a comparison with baseline or nadir scans or other tumor evaluations) as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- These criteria aim to ensure the risk/benefit of continuing treatment will continue to favor the subjects due to the current data available about the impact of the pattern of progression on post-progression survival[20–24]. The assessment of clinical benefit should consider whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The decision to start or continue with the drug-study treatments beyond initial investigator-assessed progression should be discussed with the Principal Investigator, Medical Monitor and documented in the study records. If the decision is taken to continue cabozantinib treatment beyond progression, the subject will remain on the trial and continue to be treated and monitored according to the Time and Events Schedule in Section 8.

6.2 CONCOMITANT TREATMENTS

6.2.1 PERMITTED TREATMENTS

- Standard therapies for concurrent medical conditions. Prophylactic anti emetics may be administered according to standard practice.
- Antiviral treatment for chronic HBV.
- Megestrol acetate (Megace®) as supportive care
- Bisphosphonates
- Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low dose LMWH are permitted. The protocol does not restrict the use of heparins

at prophylactic doses. Therapeutic doses of heparins are allowed if clinically indicated for supportive treatment and the benefit outweighs the risk per the investigator's discretion. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel) are not allowed.

6.2.2 PROHIBITED TREATMENTS

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, hormonal therapy (unless hormonal replacement therapy was initiated prior the study inclusion) and experimental or approved therapies during this trial or within 30 days before starting to receive study medication, except prior therapy with sorafenib as detailed in the current protocol.
- Any drug that targets angiogenesis, especially VEGF and VEGFR.
- TKIs other than cabozantinib
- Bone marrow transplant or stem cell rescue.
- Patients taking narrow therapeutic index medications (e.g., warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin) should be monitored proactively.
- For anticoagulants and low dose aspirin see 6.2.1 section.

Therapeutic monitoring should be performed consistent with the local clinical standard of care following dose modification of the agent. In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

Additional information on potential drug interactions with cabozantinib is provided in Section 14.7

6.2.3 SUPPORTIVE TREATMENTS

- Subjects may continue to receive hormonal replacement therapy if initiated prior to the study inclusion.
- Bisphosphonates and RANK-L inhibitors are allowed for bone metastases.
- It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

6.2.3.1 PALLIATIVE LOCAL THERAPY

Palliative local therapy for clinically symptomatic tumor sites (eg bone pain) including palliative (limited-field) radiation and palliative surgical resection may be considered if the following criteria are met:

- The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 6.1.7.1).
- The lesion for palliative local therapy is a non-target lesion
- Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy.
- Palliative therapy must be clearly documented in the source records and case report form. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events.

6.2.4 TREATMENT OF HBV VIROLOGICAL BREAKTHROUGH AND ONGOING HCV

Subjects will have ongoing assessments of HBV DNA as per local practice. If a subject has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized guidelines.

Initiation of direct acting antivirals (DAAs) for HCV is not allowed but if the investigator considers this option should discuss it with the Principal Investigator and Medical Monitor.

6.3 TREATMENT COMPLIANCE

Study drug will be administered in the clinical facilities of each center and treatment compliance will be assessed by investigator report on the case report forms and Source Data Verification by Monitors.

6.4 DESTRUCTION OF STUDY DRUG

For this study, study drugs partially used study drug containers and syringes ~~may~~ should be destroyed on site. Cabozantinib containers must be destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures agree with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to the Sponsor upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable national, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Table 5: Study procedures

Each cycle has 28 days.	Screening[1]	Cycles (+/- 72 hours) (Day 15 only for Cycle 1 and 2)			First radiologic progression	EOT (after last dose +7 days)	Follow-up[2]
		Day 1	Day 15 ~~(+/- 24 hours)~~	~~Day 28 (+/- 72 hours)~~			
Demographics	x						
General Informed Consent	x						
Inclusion/Exclusion criteria and Eligibility	x						
		Tumor and disease assessments					
Disease assessment by RECIST v1.1 Every 8 weeks from Day 1 Cycle 2 (+/- 7 days)	X			~~x~~			
Fresh tumor biopsy *(See section 7.4)*	x				x[3]		
		Study procedures and examinations					
Physical examination	x	x	x	~~x~~	x	X	
ECOG performance status	x	x	x	~~x~~	x	X	
12-lead ECG[4]	x					X	
Vital signs[5]	x	x	x	~~x~~	x	X	
Assessment of AEs/SAEs	x	x	x	~~x~~	x	X	
Concomitant medications	x	x	x	~~x~~	x	x	
Diet and gut microbiota	x						
		Laboratory tests					
Serum chemistry[6]	x	x	x	~~x~~	x	x	
Hematology[7]	x	x	x	~~x~~	x	x	
Coagulation (PT, INR, PTT)	x	x	x	~~x~~	x	x	
HBsAg and HBsAb, HBcAb and HCV Ab; HBeAg and HBeAb, HBV DNA and HDV RNA and HDV Ab(HBV+ subjects only); HCV RNA (HCV+ subjects only)	x					x	
Thyroid function tests (TSH, free T3, free T4)	x						
Urinalysis	x	x	x	~~x~~		x	
Urine or serum pregnancy test (WOCBP)	x						
		Other procedures[8]					
Other laboratory blood tests and assays[9]		X	X Only in C1		x		
Other liver tissue analysis[10]	x			~~x~~	x		
Patient-reported Quality of Life (EQ-5D, EORTC-QLQ C30, EORTC-HCC18 and FACT-Hep)[11]		x			x	x	
Other stool tests and assays[12] Day 1		x				x	

Cycle 4 and in case of OR or PD							

EOT: End of Treatment; **OR**: Objective Response; **PD:** Progressive Disease

[1] The time period between study entry and the commencement of protocol treatment is not to exceed 28 days.

[2] Follow-up visits could be on-site or phone visits after the last visit and will include survival data and liver cirrhosis complications evaluation every 3 months. If the patient does not start any other treatment after end of treatment, radiologic follow-up with the same scheduled will be preferred. Laboratory tests will be performed at the discretion of the treating investigator until death or the end of the study.

[3] A biopsy will be performed at the time of progression whenever possible.

[4] Note: The ECG should be performed within the 7 days prior the randomization. If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

[5] Including height (only at screening visit) weight, body temperature, respiratory rate, seated blood pressure, heart rate and oxygen saturation (at rest and after mild exercise)

[6]AST, ALT, GGT, Alkaline Phosphatase alkaline phosphatase, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Albumin, Creatinine, Alpha alpha fetoprotein, Calcium, Sodium, Potassium, Glucose, Uric Acid, triglycerides**,** Total Protein, Lipase, Amylase, Magnesium, Phosphate, lactic dehydrogenase LDH, Chloride, Glomerular filtration rate.

[7]Complete blood count with differential

[8] All the samples included in this section, will be centrally analyzed in a second-study

[9]Other laboratory blood tests will include peripheral Blood Mononuclear Cells (PBMCs) immunophenotyping, serum biomarker analysis, polymorphism detection associated with treatment response/resistance, circulating-free DNA analysis, circulating mRNA/miRNA. In case of any cabozantinib dose reduction a blood sample for PBMCs and serum biomarker analysis is recommended but no mandatory. Serum biomarker will be analyzed at each cabozantinib dose reduction. For details see the laboratory manual.

[10]Other liver tissue analysis will include tumor and non-tumor infiltrated immune cell population characterization (fresh tissue from biopsy analyzed in situ in each recruiting center) and tumor and non-tumor cell transcriptome analysis (samples can be frozen and stored until analysis). Note that these samples will be obtained accordingly to the time point of "fresh tumor biopsy" but all the analysis will be performed in a second-study.

[11] Patient-reported Quality of Life (EQ-5D, EORTC-QLQ C30, EORTC-HCC18 and FACT-Hep) will be administered at Day 1 of Cycle 1 and Cycle 3, then at Day 1 every 3 cycle and at end of treatment s.

[12]Other stool tests and assays will include gut microbiota composition and/or metabolomic analysis.

7. STUDY PROCEDURES

7.1 FLOW CHART/TIME AND EVENTS SCHEDULE

Cabozantinib
Informed consents must be signed to perform the liver biopsy before starting cabozantinib.
Screening before starting: • Clinical and laboratory evaluation to

confirm all the inclusion and exclusion criteria to receive cabozantinib. • Respect the 15 days of first-line treatment washout before starting cabozantinib. • Chest and abdominal CT scan within 4 weeks before starting therapy. • Liver biopsy within 4 weeks before starting therapy.
Drug administration Cabozantinib will be given orally every day. All patients will start with 60 mg/day to be modified upon development of adverse events.
Clinical evaluation at day 1 of every cycle and at day 15 of cycle 1 and 2. **Unscheduled visits** will be made should they be needed (adverse events or symptoms).
Laboratory evaluation at day 1 of every cycle and at day 15 of cycle 1 and 2. **Unscheduled laboratory evaluation** will be made should they be needed (adverse events or symptoms).
Radiological tumor evaluation at tumor evaluation at week 8 according to the RECIST criteria v1.1
Dose modifications: Cabozantinib dose will be modified according to the manufacturer's recommendations.

Serum biomarker determination: At baseline and at each time point accordingly to table 5, serum biomarker will be evaluated.
Liver biopsy will be done if the patient develops radiologic tumor progression, performance status 0/1 and preserved liver function. Patients with symptomatic tumor progression will not be biopsied. **All patients on must stop cabozantinib 5-7 days before performing the biopsy to avoid the risk of bleeding. They will be visited 5-7 days after the biopsy to re-start cabozantinib.**
Patient-reported Quality of Life Questionnaires: The FACT-Hep (Version 4), EORTC- QLQ C30, EORTC-HCC18 and the EQ-5D should be self-administered by the subject at the start of the visit, before the subject sees the investigator and before any study related procedures are done, so that any interaction between the patients and investigator or other health care provider will not influence the responses to the questionnaires. Questionnaires should be administered at Day 1 of Cycle 1 and Cycle 3, then at Day 1 every 3 cycles and at the End of Treatment (EOT) visit. The site personnel should complete the Patient Reported Outcomes Information Sheet.
Diet and gut microbiota: At screening, specific points regarding patient usual diet and other factors potentially impacting on gut microbiota (domestic animals, smoking, medications) should be investigated by the

investigator in detail.

7.2 SAFETY ASSESSMENTS

7.2.1 ASSESSMENTS AND DOCUMENTATION OF ADVERSE EVENTS

All AEs occurring after the subject has signed the informed consent form (IC) up until the end of the safety follow-up period (30 ± 7 days after permanently discontinuing cabozantinib administration) must be fully recorded in the subject's CRF.

Adverse event documentation is event-based (using the NCI-CTCAE version 5.0 guidelines): Adverse events should be collected past 30 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new adverse events that in the opinion of the investigator could be related to study treatment. (Information may be obtained via phone call).

Documentation must be supported by an entry in the subject's file.

Adverse events should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

If any patient dies within 30 days of last dose of study drug, the investigator will inform the sponsor and record the cause of death in detail within 24 hours on a SAE form.

A laboratory test abnormality considered clinically relevant, e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Note that all the patients will receive the "alert card" reporting useful information in case of need such as the name of the clinical trial, the name and contacts of PI or collaborators.

7.2.2 REPORTING OF SERIOUS ADVERSE EVENTS

The definition of SAE is given in Section 8.1.2.

7.2.3 INVESTIGATOR'S NOTIFICATION TO THE SPONSOR

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 8.2 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. A SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

In each case of a fatal or life-threatening reaction, the investigator must seek relevant follow-up information and must complete a follow-up report to be faxed to the sponsor as soon as possible but not later than 8 calendar days after the initial report is sent.

An isolated laboratory abnormality that is assigned Grade 4, according to CTCAE v.5.0 definition, is not reportable as an SAE, unless the investigator assesses that the event meets standard International Conference on Harmonization (ICH) criteria for an SAE. CTC Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he/she should consult with the study monitor for the Sponsor. CTC Grade 4 lab abnormalities will be documented in the laboratory data and will be reviewed on a regular basis.

For all SAEs, the investigator is required to document in full, the course of the SAE and any therapy given, including any relevant findings/records in the report.

It is not mandatory to report SAEs occurring after the protocol-defined observation period, however, at the investigator's discretion these may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

Notification to the IECs / IRBs

Notification of the institutional ethical committees (IECs)/institutional review boards (IRBs) about all relevant events (e.g., SAEs, Suspected Unexpected Serious Adverse Reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification to the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification to the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

7.2.4 EXPECTED ADVERSE EVENTS

For this study, the applicable reference document is the most current version of the IB.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

7.2.5 PREGNANCIES

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

7.2.6 FURTHER SAFETY

7.2.6.1 PHYSICAL EXAMINATIONS

Physical examinations will be performed according to the schedule summarized in the flow chart of Section

For this examination, the investigator will assess/examine the following:

- General appearances
- Skin
- Eyes
- Ears, nose and throat
- Head and neck
- Lungs
- Heart
- Abdomen
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Neurological findings

If indicated by the patient's history, the following will be examined by specialists, if applicable:

- Genito-urinary system
- Gynecological organs
- Rectum

Depending on criteria of relative timing (before or after signing IC), the findings of the physical examination has to be recorded as medical/surgical history or as an AE.

This includes review of all organ systems, examination of pertinent organ systems, vital signs, (heart rate, blood pressure (BP), and temperature). BP measurements (monitored weekly for the first 6 weeks of treatment) must be performed in a consistent manner using a manual cuff on the same arm. Have the subject sit comfortably for 5 minutes with feet on the floor and arm supported at heart level prior to taking the evaluation. The assessment must be made with the patients in the sitting position using the same arm for all evaluations. Two additional measurements, taken 5 minutes apart, should be conducted if the first BP is abnormal.

7.2.6.2 VITAL SIGNS

Body weight/height, temperature, BP, respiratory and heart rate will be assessed according to the schedule summarized in Table the flow chart of Section 7.1 and in table 5 If clinically indicated

(e.g., excessive weight loss), it is at the investigator's discretion to perform these measurements more frequently.

Note that all the patients will receive a *patient diary* to report the dose of cabozantinib, BP, number of bowel movements each day and other additional comment by the patient.

7.2.6.3 12-LEAD ECG

12-lead ECGs will be performed according to the schedule summarized in the Table 5.

The study number, subject number, visit and the date of the ECG are noted on every ECG; all indications, which might lead to the identification of the subject, must be made illegible.

The overall interpretation in ECG (normal/abnormal, clinical relevance) and the ECG diagnosis will be documented in the electronic case report form (eCRF).

7.2.6.4 LABORATORY ASSESSMENTS

Laboratory analyses will be performed locally.

- Complete blood count (CBC) with differential. This will include red blood cell count (RBC), hemoglobin, hematocrit, platelet count and white blood cell count (WBC). WBC must include differential neutrophil, lymphocyte, monocyte, basophil, and eosinophil absolute counts.
- Chemistry and electrolyte panel: This includes sodium, potassium, chloride, AST, ALT, GGT, bilirubin (total and direct), alkaline phosphatase, uric acid, total protein, albumin, calcium, lipase, amylase, triglycerides, phosphate, lactic dehydrogenase (LDH), glucose, creatinine, blood urea nitrogen (BUN).
- Urine analysis.
  - Macroscopic appearance
  - Laboratory analysis: Protein and creatinine on a random urine sample preferably taken at mid-morning for the quantification of proteinuria by urinary protein/creatinine ratio. This should be reported as the ratio of concentrations of total urine protein (in mg/dL) to urine creatinine (in g/dL).
  - Dipstick or laboratory analysis: Bilirubin, erythrocytes or hemoglobin (blood), glucose, ketones, leukocytes, or leukocyte esterase, nitrite, pH.
  - A microscopic analysis should be performed if the appearance is turbid, or if protein, leukocytes, erythrocytes, or nitrite are out of normal range.
- Thyroid function test (thyroid-stimulating hormone [TSH], free triiodothyronine [T3], free thyroxine [T4]).
- Coagulation panel: PT or PT-INR and partial thromboplastin time (PTT).

- Alpha-fetoprotein (AFP)
- Serum pregnancy test in woman of childbearing potential. Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history in the eCRF).

The laboratory evaluations are not required at Day 1 of Cycle1 if these were completed within 7 days of starting study drug treatment.

7.3 EFFICACY ASSESSMENTS

The following parameters will be evaluated: Time to progression, pattern of progression, overall survival, post-progression survival, rate of patients who develop new extra hepatic spread.

7.4 EXPLORATORY BIOMARKER, PERIPHERAL BLOOD AND TUMOR ASSESSMENTS

This study will collect blood and biopsy samples but the analysis will be done in a second study only if the study meets the safety end-point.

Tumor and non-tumor tissue samples should be obtained by expert radiologists with 18 Gauge needle (Monopty, Bard Inc, Covington, UK) and will utilized to analyze tumor and non-tumor infiltrated immune cell population characterization (fresh tissue from biopsy analyzed in situ in each recruiting center) and tumor and non-tumor cell transcriptome analysis (samples can be frozen and stored until analysis).

8. ADVERSE EVENTS

8.1 DEFINITIONS

Investigators should refer to the Safety Information section of the current cabozantinib IB. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

8.1.1 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be the development of a new medical condition, or the deterioration of a pre-existing medical condition. This includes any unfavorable and unintended sign (e.g. tachycardia, enlarged liver), symptom (e.g. nausea, chest pain) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram) temporally associated with the use of a medicinal product, whether or not considered related.

8.1.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is any AE occurring at any dose that:

- results in death;

- Is life threatening, defined as any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death;
- results in hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons;
    - Hospitalisation is defined as any inpatient admission (even if less than 24 hours) (unless it occurs to ensure treatment compliance). For chronic or long term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.
    - Prolongation of hospitalisation is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.
    - Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.
- results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
- results in congenital anomaly/birth defect in the offspring of a subject who received the product;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but that when, based upon appropriate medical judgment, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of product dependency or product abuse.

8.1.3 DEATH

All AEs resulting in death whilst using the medicinal product must be reported to Ipsen within 24 hours of the Investigator's knowledge of the event. All fatal outcomes should be considered as adverse events, even if this fatal outcome is not considered to be related to the medicinal product.

The convention for recording death on the adverse event reporting form is as follows:

- Adverse event term that led to death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.
- The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the adverse event term may be 'Death' or 'Sudden death'.

8.1.4 SPECIAL SITUATIONS

This is any incidence of drug exposure during pregnancy or breast-feeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic effectiveness whilst using the medicinal product. A 'special situation' should be collected by the Investigator and reported to Ipsen whether or not these 'special situations' are associated with an adverse event.

8.1.4.1 PREGNANCY

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference by the medicinal product with a contraceptive method.

Information regarding any pregnancies must be collected on the adverse event report form, including those with normal progress and outcome. The investigator must instruct all female subjects to inform them immediately should they become pregnant whilst using the study medication.

Reports of pregnancy must be reported to Ipsen within 24 hours of the Investigator's knowledge.

8.1.4.2 OVERDOSE

An overdose is any dose of the medicinal product given to a study participant that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be reported to Ipsen within 24 hours. An overdose should be reported even if it does not result in an AE.

8.2 COLLECTION AND REPORTING OF ADVERSE EVENTS, FATAL OUTCOMES AND SPECIAL SITUATIONS

Note
From this point onwards, the term 'Safety Report' will collectively refer to all reports of AE, fatal outcomes and special situations.

8.2.1 COLLECTION OF SAFETY REPORTS

All safety reports, whether they are serious/non-serious, related/unrelated, should be collected by the Investigator in the study source document during the course of the study.

The Investigator must report all safety reports on the Clinical Study Serious Adverse Event (SAE) report form (080478-FOR) (Section 14.8) to Ipsen according to the timelines set out in section 8.2.2.

8.2.2 REPORTING OF SAFETY REPORTS

In order to adhere to all applicable laws and regulations for reporting of a safety report, the Investigator should notify to the sponsor and sponsor will notify Ipsen within 24 hours of the study site staff becoming aware of the safety report. It is the Investigator's responsibility to ensure that the reporting information and procedures are used and followed appropriately.

Reporting Information for safety reports
To report initial or follow-up information to Ipsen, a completed ***Clinical Study Serious Adverse Event (SAE) report form (080478-FOR)*** should be sent to the following within 24 hours of becoming aware of the event: ANNA ROSET DALMAU, Local Pharmacovigilance Manger **Email**: pharmacovigilance.spain@ipsen.com, anna.roset@ipsen.com ***Phone:*** +34 936858153 / +34 617052107 **Fax:** +34 93 685 10 11

All adverse events will be processed by Ipsen according to their relevant Standard Operating Procedures. This includes the follow up of adverse event reports with the Investigator, as required.

If an AE occurs with a "non Ipsen product", the Investigator should consider informing the competent authority in the Member State where the event occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

8.2.3 MANDATORY INFORMATION FOR REPORTING AN ADVERSE EVENT

The following information is the minimum that must be provided to Sponsors and will be provided to Ipsen's Pharmacovigilance contact within 24 hours for each adverse event:

- Patient identifier
- Product name
- Adverse Event description including assessment of causal relationship and seriousness
- Investigator name and contact details

The additional information included in the adverse event report form must be provided to Ipsen as soon as it is available.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary adverse event considered as the foremost untoward medical occurrence from secondary adverse events which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

8.3 SAFETY CLASIFICATIONS

8.3.1 RELATIONSHIP OF EVENTS TO THE MEDICINAL PRODUCT

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Not related	An adverse event will be considered "not related" to the use of the medicinal drug if there is not a possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of the medicinal drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event

8.3.2 SEVERITY OF EVENTS

The following definitions should be considered when evaluating the severity of oncology events:

Severity of Events	
Grade	Definition
1	Mild adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event

4	Life-threatening or disabling adverse event
5	Death related to adverse event

8.3.3 EXPECTEDNESS OF EVENTS

Expectedness of all AEs will be determined by Ipsen according to the SmPC.

8.3.4 SAFETY DATA LISTING

A safety data listing will be obtained from the global safety database and will be included in the clinical study report.

All collected adverse events will be summarized for inclusion as part of any interim safety analysis and in the clinical study report.

9. STATISTICAL METHODS

9.1 END-POINTS

The study will be analyzed using standard statistical methods to estimate rates and 95%CI (for ORR and other binary variables) by means of the Clopper-Pearson exact method, and the Kaplan-Meier method to describe the survival functions and the median and [95%CI]. Indirect comparisons with will conducted with external data by assessing the 95%CI of the study estimates. A Statistical Analysis Plan, which will include all details regarding all analyses, the interim method, the handling of missing data and any plan for the analysis, will be finalized before the initiation of the study recruitment.

Primary Outcome(s)

- Rate of adverse events (AE) with Common Terminology Criteria for Adverse Events (CTCAE)≥3 excluding palmar-plantar erythordysthesia, rate of AEs, rate of related-AEs and rate of death. Rate of AEs leading to treatment discontinuation.
- Adverse events will be graded following version 5.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose.

Secondary Outcome(s)

Time to progression, objective response rate, pattern of progression, overall survival, post-progression survival, rate of patients who develop new extrahepatic spread. Serum and tissue marker characterization.

Safety Outcomes

This is a clinical trial were the main purpose is the assessment of safety, therefore, the primary and secondary outcomes were defined accordingly, as described above.

9.2 SAMPLE SIZE

The sample size calculation will be triggered by the primary outcome, i.e, the rate of adverse events (AE) with CTCAE≥3 excluding palmar-plantar erythordysthesia (critical AEs). The expected rate for this outcome was 56% in this population[1]. The Simon's two-stage optimal design[2] will be used to test the alternative hypothesis that with cabozantinib the rate of critical AEs will be reduced at least to 32.5% against the null hypothesis of 56% as previously observed. In the first stage, 14 patients will be accrued. If there are 8 or more critical AES in these 14 patients, the study will be stopped because of futility. Otherwise, 26 additional patients will be accrued for a total of 40. The null hypothesis will be rejected if 23 or fewer critical AEs are observed in 40 patients. This design yields a type I error rate of 2.5% one-sided and power of 80% when the true response rate is 67.5%.

All patients exposed to the study treatment (regardless of protocol adherence) will count be safety, and thus no need to sample size increases as per potential withdrawals are foreseen.

9.3 INTERIM ANALYSES

We plan to conduct 1 fixed pre-scheduled interim analyses for futility as per the Simon's design as described in section 9.2. The interim analysis will be conducted after follow-up data from the first 14 patients will be available after at least 30 days from study inclusion, or otherwise presenting an occurrence of the primary outcomes. The DSMB will consist of 3 members (2 hepatologists and 1 nurse) and an agreed charter by all members will come into operation before the initiation of the study recruitment. To note, this interim futility analysis will have no impact on the type I error at the end of the trial, and thus alpha adjustment is not needed.

10.STUDY CONDUCT CONFIDENTIAL

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

[1] Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klümpen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul 5;379(1):54-63. doi: 10.1056/NEJMoa1717002.

[2] Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials. Controlled Clinical Trials 1989;10: 1-10

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

10.1 ADHERENCE TO THE PROTOCOL

The study shall be conducted as described in this protocol. The investigators should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment. If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

10.2 DATA SAFETY MONITORING BOARD (DSMB)

A Data Safety Monitoring Board will be instituted in order to ensure ongoing safety of study patients with respect to a risk/benefit assessment during periodic data review meetings, review results from planned interim analyses and provide a formal recommendation for continuation/termination of the study and monitor study conduct to ensure the overall integrity of trial is maintained. One formal interim analysis is planned and will be performed as per separate DSMB charter. Recommendation for trial continuation will be guided by monitoring boundaries at formal interim analyses as well as safety evaluations at all safety data reviews (refer to Section for details on interim analyses). The committee will include at least 2 independent hepatologist and one independent nurse. Data review meetings will be held periodically as per separate DSMB charter. Enrollment to the study will continue throughout the scheduled meetings of the DSMB. Decisions on trial termination, amendment or cessation of patient recruitment based on risk/benefit assessments will be made after recommendations from the DSMB have been assessed by the Sponsor.

11. DATA MANAGEMENT

11.1 Data Source

Each patient is pseudonymized by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code. Uncoded patient data (which allows to directly identify a person) as well as the list allowing to connect the patient with the unique central patient identification code are only stored at the study site. As soon as the site has destroyed that list according to local legal requirements, no data processed within the study can be linked to a patient's identity.

11.2 Confidentiality

Fundació Clinic per a la Recerca Biomèdica (FCRB) as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in pseudonymized form only. The entire documentation made available to FCRB does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

11.3 Withdrawal

Each patient may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. In case a patient would like to withdraw the consent given earlier, he/she should inform his/her doctor and the site should document the withdrawal in the (electronic) Case Report Form as well as in the patient medical records.

12.LIST OF ABBREVIATIONS

AASLSD	American Association for the Study of Liver Diseases
AE	Adverse events
AFP	Alpha-fetoprotein
AHA	Alpha Hydroxy Acids
APCs	Antigen presenting cells
BCLC	Barcelona Clinic Liver Cancer
BP	Blood Pressure
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CL	Clearance
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAAs	Direct acting antivirals
DAMP	Damage associated molecular patterns
DILI	Drug-induced liver injury
DSMB	Data and safety monitoring board
eCRF	Electronic Case Report Form
EDR	Early dermatologic reactions
eGFR	Estimated Glomerular Filtration Rate
EMT	Epithelial mesenchymal transition
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice

GFR	Glomerular filtration rate
GIST	GastroIntestinal Stromal Tumors
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFSR	Hand-foot skin reaction
HIF-1α	Hypoxia-inducible factor 1α
HIV	Human inmunodeficiency virus
HR	Hazard ratio
IC	Informed consent form
ICD	Immunogenic cell death
ICH	International conference on harmonization
IECs	Institutional Ethical Committees
IRBs	Institutional Review Boards
LDH	Lactic dehydrogenase
mAbs	Monoclonal antibodies
mCRC	Metastasic colorectal cancer
MDSC	Myeloid-derived suppressor cells
NAFLD	Nonalcoholic fatty liver disease
NF-κB	Nuclear factor κB
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression free survival
PK	Pharmacokinetics
PPS	Post- Progression Survival

PR	Parcial Response
PTT	Parcial thromboplastin time
RBC	Red blood cell count
RCTs	Randomized controlled trials
SAEs	Serious adverse events
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TAN	Tumor associated neutrophils
TNF-α	Tumor necrosis factor α
TRAEs	Treatment- related AEs
TSH	Thyroid – stimulating hormone
TTP	Time to progression
UPCR	Urine protein/creatinine ratio
VEGFR	Vascular endothelial growth factor receptor

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14.APPENDICES

14.1 APPENDIX 1: ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-diseasese performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

14.2 APPENDIX 2: CHILD-PUGH SCALE

Points Scored for Observed Findings

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy grade [a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, mg/dL	< 2	2 to 3	> 3.0
Serum albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time, sec (prolonged)	< 4	4-6	> 6

a Encephalopathy grades:
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Assessment as good operative risk (A) if 5 or 6 points; moderate risk (B) if 7 to 9 points, and poor operative risk (C) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics).

14.3 APPENDIX 3: RECIST 1.1 CRITERIA

Response and progression will be evaluated in this study using the RECIST criteria version 1.1[18]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used.

Measurable Disease:

Tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest x-ray
- 10 mm calliper measurement by clinical examination (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to < 15mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesion with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the baseline

sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are >5 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions*. including pathological lymph nodes (with short axis ≥10 mm and < 15 mm) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or in rare cases "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg; 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. While some non- target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

All subjects will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute progressive disease. (Note: the appearance of one or more new lesions is also considered progression).

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target

lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm.

To achieve unequivocal progression in patients with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

In the absence of measurable disease, the same general concepts apply here as noted above.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease duration

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Table 8 Response for patients with target and non-target lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented after 8 wks.
Not all evaluated	Non-PD	no	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	
Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.				

Table 9: Response for patients with non-target lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
** Non-CR/non-PD is preferred over "stable disease" for non-target disease.*		

Methods of Measurement

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions - Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10mm diameter as assessed using callipers. For the

case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray - Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, chest CT is preferable.

CT / MRI - CT is the best currently available and reproducible method to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The central revision will be also done based on BCLC-RECIST[19].

14.4 APPENDIX 4: NCI CTCAE V.5.0 RECOMMENDATION FOR GRADING OF ADVERSE EVENTS

The full Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published November 27, 2017can be obtained at the following website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

14.5 APPENDIX 5: MANAGEMENT OF SUSPECTED CABOZANTINIB TOXICITIES

The management will be done according to manufacture recommendation.

14.6 APPENDIX 7: PATIENT-REPORTED QUALITY OF LIFE QUESTIONNAIRES

Patient reported outcome measures

Guidelines for Administration of the patient reported outcomes questionnaires

These guidelines assume that an appropriate person has been designated to facilitate the self-administration of the questionnaires.

When and how should the questionnaire be administered?

The FACT-Hep, EORTC-QLQ C30, EORTC-HCC18 and EQ-5D should be self-administered by the patient alone at the beginning of their scheduled visits at the clinic. These instruments should be administered at the start of the visit, before the patient sees the physician so that any interaction between the patient and physician will not influence the patient's responses to the questionnaire. The questionnaire should also be administered before the patient is asked about adverse experiences and concurrent illnesses, again so that any discussions of health problems do not influence the patient's responses.

A quiet place should be provided for the patient to complete the questionnaire. It is important that the patient completes the questionnaire alone, without any advice from family members or friends who may accompany them. On average, it takes ~~less than 15~~ around 25 minutes to complete the questionnaires.

Foreign speaking patients:

Patients must have basic fluency in the language of their country in order to complete the PRO instruments. If a patient is not able to speak/read the language of his/her country, please check if the patient has basic fluency in any of the languages in which the questionnaire is currently available. Copies of the alternative language questionnaire are available from the study manager. If the patient is illiterate, the person designated to facilitate the questionnaires should read the instructions, questions and answer alternatives to the patient verbatim and without providing interpretation.

How should the Questionnaires be introduced?

A sample script for introducing the questionnaire is given below.

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, please complete this questionnaire about your health. The questionnaire is easy to fill out. The instructions are on the front cover (point to them). You should read (for illiterate patients: listen)1 each question and then circle the appropriate number that matches your answer. Remember that this is not a test and there are no rights or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are done to make sure that all the questions have been answered. You should answer these questions by yourself. Your spouse or other family members should not help you when you answer the questionnaire. I will be

nearby in case you want to ask me any questions. Please return, the questionnaire to me when you have finished".

What to do if the patient asks for clarification?

Some patients may ask the meaning of specific questions. If this happens, the staff member can assist the patient by re-reading the question for them verbatim. If the patient asks what something means, do not try to explain what the question means, but tactfully suggest that the patient use his/her own interpretation of the question. All patients should answer the questions based on what they think the questions mean, or the study results may be biased.

Questionnaires completion:

When the patient returns the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the patient that some of the questions were not answered. If the patient does not quickly volunteer to answer these items, ask him/her whether she had any difficulty completing the questionnaire. If the patient says that he/she had trouble understanding a question, ask him/her why he/she had difficulty with that item. Re-read the question for him/her verbatim, but do not attempt to explain or reword the question, as explained before. If the patient is still unable to answer the question, accept the questionnaire as is.

Some patients may be confused by the response choices. They may want to respond with "I don't know" or some other response choice that is not available. If this happens, try to help the patient choose one of the response categories by saying something like: "I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?" If the patient still cannot select an answer, accept the questionnaire as is.

Occasionally, patients may not report having difficulty with a question or the response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is.

If a patient asks for interpretation of his/her responses or asks for his/her scores on the questionnaire, tell him/her that you are not trained to score or interpret the questionnaire. Emphasize that their answers will be kept confidential.

Completed questionnaires:

Thank the patient once he/she has completed the questionnaire and you have checked it for completeness.

Patient reported outcomes (PRO) Information Sheet

Instructions:

- This information sheet is to be completed by the study nurse/investigator
- This information sheet must be completed for all patients at each visit in which the protocol requires PRO assessment, whether or not the questionnaire has been completed by the patient.
- When the patient returns the questionnaire
  - Please complete this information sheet
  - Please check that the patient has answered all the questions and no more than one answer

Was the questionnaire provided to the patient at this visit ☐ No ☐ Yes

If YES please continue

If NO please go to question 5

Date questionnaire completed _____/_____/____ (dd/mm/yyyy)

Was the questionnaire provided prior to clinical examination? ☐ No ☐ Yes

Were all questions answered? ☐ No ☐ Yes

If YES, please STOP

If NO, specify reason questionnaire/questions were not answered

☐ Patient felt too ill

☐ Patient refused to complete questionnaire for reason other than illness

☐ Patient did not keep appointment

☐ Questionnaire not administered due to institution error

☐ Questionnaire not available in the appropriate language

☐ Other, please specify:_____

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4

C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued 0	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐

Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐

Today's date (Day, Month, Year): 31☐☐☐☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or othe leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4

12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

EQ-5D

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

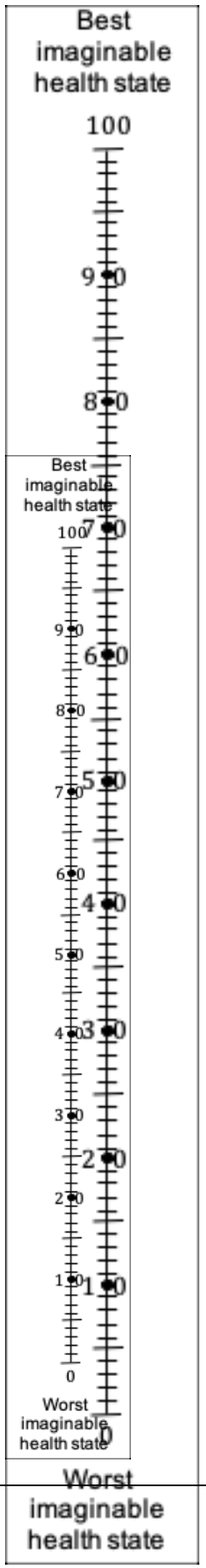
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today

Your own health state today



14.7 CYP3A4 and CYP1A2 Inhibitors/Inducers

http://medicine.iupui.edu/clinpharm/ddis/

Strong inhibitors and inducers (underlined) are not permitted during this study.

CYP3A4 inhibitors	**CYP3A4 inducers**
indinavir	rifampin
nelfinavir	carbamazepine
ritonavir	phenobarbital
saquinavir	phenytoin
clarithromycin	pioglitazone
itraconazole	rifabutin
ketoconazole	St. John's wort
nefazodone (withdrawn in the US)	
erythromycin	
grapefruit juice	
verapamil	
diltiazem	
cimetidine	
amiodarone	
fluvoxamine	
mibefradil (withdrawn in the US)	
troleandomycin	

14.8 CLINICAL STUDY SAE REPORT FORM

Associated Procedure / Instruction Ref:		080493 - Expedited & Periodic Reporting of Suspected Unexpected Serious Adverse Reactions
Version: 9.0	Effective date: 15-Dec-2019	

IPSEN

Clinical Study SAE Report Form

Please complete as many details as possible and forward it to IPSEN contact immediately/within 24 hours

(please choose one): ○ Initial ○ Follow Up **Follow-up No.:** ___

Email to: adverse.events@ipsen.com

PROTOCOL	SITE	SUBJECT NUMBER	COUNTRY
_____	|_|_|_|_|_|	|_|_|_|_|	_____

A – SUBJECT INFORMATION

Birth Date \|_\|_\| \|_\|_\| \|_\|_\|_\|_\| (Day Month Year) Height (cm) \|_\|_\|_\| Weight (kg) \|_\|_\|_\|.\|_\| Sex : M ☐ F ☐

Age: _____ years

Race *(if applicable)*: ☐ Asian ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native

☐ Other *Specify*: ..... ☐ Not Applicable

Pregnant? ☐ Yes ☐ No ☐ Not Applicable **If Yes, please complete Standard Pregnancy Outcome Report Form (Form No.080479)**

Pregnancy in participant's partner? ☐ Yes ☐ No ☐ Not Applicable

B - SERIOUS ADVERSE EVENT DESCRIPTION *(e.g. Diagnosis of SAE(s). If diagnosis is not known, describe symptom(s) in free text section below)*

Serious Adverse Event	.....	
Intensity OR Grade *(1-5 for NCI-CTCAE)*	☐ Mild ☐ Moderate ☐ Severe	Oncology studies - National Cancer Institute Common Toxicity Criteria (NCI – CTCAE) Grade Grade 1-5: |_|
Seriousness Criteria *(Tick all that apply)* *(DD MM YYYY)*	☐ Resulted in death *If yes, Cause of death:* ..... *Date of Death:* |_|_| |_|_| |_|_|_|_| Autopsy : ☐ Yes ☐ No ☐ Congenital abnormality or birth defect ☐ Persistent or significant disability / incapacity ☐ Requires or prolongs hospitalization *If yes, Admission Date:* |_|_| |_|_| |_|_|_|_| *Discharge Date:* |_|_| |_|_| |_|_|_|_| ☐ Life-threatening ☐ Important Medical Event	
Other suspicious causes	☐ Yes ☐ No *If Yes, please complete the information below* ☐ Disease related ☐ Other Medical condition i.e. Other than disease related (See section E) ☐ Procedure related to protocol ☐ Concomitant medication (see Section G) ☐ Unscheduled procedure ☐ Other (specify)	

INVESTIGATOR NAME: **DATE:**

INVESTIGATOR SIGNATURE:

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