A PHASE II, MULTICENTRE, OPEN-LABEL STUDY OF CABOZANTINIB AS 2ND LINE TREATMENT IN SUBJECTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA WITH A CLEAR-CELL COMPONENT WHO PROGRESSED AFTER 1ST LINE TREATMENT WITH CHECKPOINT INHIBITORS

STUDY PROTOCOL
STUDY NUMBER: F-FR-60000-023
CABOZANTINIB/XL184
EudraCT number: 2018-002820-18

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol F-FR-60000-023 entitled "A Phase II, Multicentre, Open-Label Study of Cabozantinib as 2nd Line Treatment in Subjects with Unresectable, Locally Advanced or Metastatic Renal Cell Carcinoma with a Clear-Cell Component Who Progressed After 1st Line Treatment with Checkpoint Inhibitors" with Amendment #4. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control involved in the study.

NAME:

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

Sponsor's Representative Signature:

NAME: PPD

TITLE: PPD SIGNATURE: PPD

PPD

DATE:

OFFICE:

SUMMARY OF CHANGES

The current version of the protocol was released on 23 February 2022 and includes Amendment #4. The amendment forms were prepared and are provided in Appendix 8 to Appendix 11 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	28 November 2019	Appendix 8
2	24 January 2020	Appendix 9
3	03 March 2021	Appendix 10
4	23 February 2022	Appendix 11

SYNOPSIS

Name of Sponsor/company: Ipsen Pharma	
Name of finished product: Cabometyx **Name of active ingredient(s)**: cabozantinib	
Title of study: A Phase II, Multicentre, Open-Label Study of Cabozantinib as 2nd Line Treatment in Subjects with Unresectable, Locally Advanced or Metastatic Renal Cell Carcinoma with a Clear-Cell Component Who Progressed After 1st Line Treatment with Checkpoint Inhibitors **Study number**: F-FR-60000-023	
Number of planned centres: approximately 50 active centres	
Planned study period: Q1 2020 to Q4 2023	**Phase of development**: Phase II
Study type: Efficacy and Safety	

Objectives:

The overall objective of this study is to evaluate the efficacy and safety of cabozantinib as 2nd line treatment in subjects with unresectable, locally advanced or metastatic renal cell carcinoma (RCC) with a clear-cell component, who progressed after prior checkpoint inhibitors (CPI) therapy with ipilimumab and nivolumab in combination or CPI combined with vascular endothelial growth factor (VEGF)-targeted therapy.

Primary Study Objective:

- To assess the efficacy of cabozantinib by the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review in cohort A.

Secondary Study Objectives:

- To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent central review and Investigator's review;
- To assess objective response rate (ORR) by independent central review and Investigator's review in cohort B;
- To assess ORR by Investigator's review in cohort A;
- To assess overall survival (OS);
- To assess the ORR and PFS by Investigator's review and OS in overall population (cohorts A+B);
- To assess the change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS) questionnaire;
- To assess the safety and tolerability of cabozantinib.

Study hypothesis:

The hypothesis for the two cohorts of this study is that cabozantinib as 2nd line treatment will demonstrate a clinically significant increase of response rate as compared to historical control in subjects previously treated with CPI therapy. A therapy will be considered clinically meaningful if it provides a significant benefit in ORR (primary endpoint) over a standard rate of 10% (conservative threshold in reference to the response rate of everolimus in the METEOR study (exact 95% confidence interval (CI): 1.7-5.9)).

Methodology:

This is a Phase II, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib 60 mg once daily (q.d.) in adults with unresectable, locally advanced or metastatic RCC with a clear-cell component that progressed, according to Investigator's judgement, after prior CPI therapy (ipilimumab and nivolumab) alone or CPI combined with VEGF-targeted therapy. Approximately 114 eligible subjects will receive cabozantinib (two independent cohorts with 74 subjects* in cohort A and approximately 40 subjects in cohort B).

*The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.

Each subject's study participation will consist of the following periods:

Pre-treatment Period: Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments will be performed within 15 days prior to first cabozantinib dose except when otherwise specified (detailed in study schedule).

Treatment Period: Subjects who meet all eligibility criteria will be included in one of the two following cohorts based on their 1st line treatment and both cohorts will receive the same open-label treatment with cabozantinib (60 mg q.d.):

- **Cohort A: 74 subjects**

Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.

- **Cohort B: approximately 40 subjects**

Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.

In both cohorts, subjects can receive study treatment up to a maximum of 18 months after the last subject included in the study received the first cabozantinib dose (end of the study), but subjects may terminate study treatment earlier due to reasons such as disease progression, unacceptable toxicity or withdrawal of consent.

Subjects who discontinue treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 to 45 days after the last dose of cabozantinib). Subjects who prematurely stop the study due to withdrawal of consent will be invited to attend the Early Study Withdrawal visit.

Post-treatment Follow-up Period: Subjects who discontinue study treatment will be contacted during the Post-treatment Follow-up visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy. During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator. These assessments will be continued until the subject expires or until the end of the study (18 months after the last subject included in the study started cabozantinib treatment), whichever occurs first. Every effort will be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Number of subjects planned: approximately 114 subjects: 74 subjects* in Cohort A and approximately 40 subjects in Cohort B

* The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.

Diagnosis and criteria for inclusion:

Inclusion criteria:

All subjects must fulfil all the following criteria to be included in the study:

(1) Subjects must provide a signed informed consent prior to any study-related procedures;

(2) Male or female subjects must be aged ≥18 years on the day the informed consent is signed;

(3) Subjects must have histologically confirmed unresectable, locally advanced (defined as disease not eligible for curative surgery or radiation therapy) or metastatic RCC with a clear-cell carcinoma component;

(4) Subjects must have radiographic disease progression, according to Investigator's judgement, following 1st line treatment with CPI (ipilimumab plus nivolumab) (Cohort A) or CPI in combination with VEGF-targeted therapy (Cohort B);

(5) Subjects present ≥1 target lesion according to RECIST 1.1 per Investigator;

(6) Subjects should have Eastern Cooperative Oncology Group (ECOG) status 0-1;

(7) Subjects with treated brain metastases are eligible if metastases have been shown to be stable as per Investigator's judgement;

(8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 15 days before baseline:

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

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

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

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

(e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L).
(f) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation
(g) Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g.

(9) Subject must have recovered to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless adverse event(s) (AE(s)) are clinically nonsignificant and/or stable on supportive therapy as determined by the Investigator;

(10) Subjects must have completed a steroid taper, if he/she experienced an immune-related adverse event associated with previous CPI treatment;

(11) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) must provide a negative pregnancy test within 7 days prior to the start of study treatment. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required;

(12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and for 120 days after the last dose of study treatment;

(13) All male participants must agree to refrain from donating sperm and unprotected sexual intercourse with female partners during the study and for 120 days after the last dose of study treatment;

(14) Subjects must be willing and able to comply with study requirements, remain at the investigational site for the required duration of each study visit and be willing to return to the investigational site for the follow-up evaluation, as specified in the protocol.

(15) Subjects must be covered by social security or be the beneficiary of such a system (only applicable for French subjects).

Exclusion criteria:

Subjects will not be included in the study if the subject:

(1) Inability to swallow tablets;

(2) Was treated with any other investigational medicinal product (IMP) during a clinical study within the last 30 days before baseline;

(3) Was previously treated with cabozantinib;

(4) Has a contraindication to Magnetic Resonance Imaging (MRI) or contrast medium used for Contrast Tomography (CT)-scan;

(5) Presents untreated brain or leptomeningeal metastases, or current clinical or radiographic progression of known brain metastases;

(6) Has a diagnosis of a serious cardiovascular disorder:
(a) Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, or serious cardiac arrhythmias;

(b) Uncontrolled hypertension, defined as sustained blood pressure (BP) (>140 mm Hg systolic or >90 mm Hg diastolic pressure) despite optimal antihypertensive treatment;

(c) Stroke (including transient ischaemic attack (TIA)), myocardial infarction (MI) or other ischaemic event, or thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism) within 6 months before screening;

(d) History of risk factors for torsades de pointes (e.g., long QT syndrome);

(7) Is receiving a concomitant anticoagulation with coumarin agents (e.g. warfarin), direct thrombin inhibitor dabigatran, direct Factor Xa inhibitor betrixaban or platelet inhibitors (e.g. clopidogrel).

Note: The following are allowed anticoagulants: prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose of low molecular weight heparin (LMWH). Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in patients without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before baseline without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.

(8) Has a gastrointestinal (GI) disorder including those associated with a high risk of perforation or fistula formation:

(a) Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction;

(b) Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before screening;

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

(9) Presents a corrected QT (QTc) interval calculated by the Fridericia formula (QTcF) > 500 msec within 1 month prior to baseline;

Note: If a single electrocardiogram (ECG) shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility

(10) Presents clinically significant haematuria, hematemesis, or haemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g. pulmonary haemorrhage) within 3 months before screening;

(11) Presents cavitating pulmonary lesion(s) or known endobronchial disease manifestation;

(12) Presents lesions invading major pulmonary blood vessels;

(13) Has been diagnosed with other clinically significant disorders such as:

(a) Serious nonhealing wound/ulcer/bone fracture;

(b) Malabsorption syndrome;

(c) Uncompensated/symptomatic hypothyroidism (subject with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study);

(d) Moderate to severe hepatic impairment (Child-Pugh B or C);

(e) Requirement for haemodialysis or peritoneal dialysis;

(f) History of solid organ transplantation;

(14) Has a predicted life expectancy of less than 3 months;

(15) Has had prior surgery within 4 weeks prior to baseline. Note: If the subject has undergone major surgery, complete wound healing must have occurred 1 month prior to baseline.

(16) Has had palliative radiation therapy for bone within 2 weeks or for radiation fields including viscera within 4 weeks prior to baseline. Note: Resolution/healing of side effects must be complete prior to baseline;

(17) Has a history of another active malignancy within 3 years from screening except for locally curable cancers that have been apparently cured, such as low-grade thyroid carcinoma, prostate cancer not requiring treatment (Gleason Grade ≤6), basal or squamous cell skin cancer, superficial bladder cancer, *in situ* melanoma, *in situ* prostate, cervix or breast carcinoma or other treated malignancies with <5% chance of relapse according to the Investigator;

(18) Has a history of allergy to study treatment components or agents with a similar chemical structure or any excipient used in the formulation as listed in the Summary of Product Characteristics (SmPC) document;

(19) Has rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption;

(20) Has a serious medical or psychiatric condition that render the subject unable to understand the nature, scope and possible consequences of the study, and/or presents an uncooperative attitude;

(21) Is pregnant or breastfeeding. A β-human chorionic gonadotrophin (HCG) serum pregnancy test will be performed up to 7 days prior to baseline for all female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile);

(22) Is likely to require treatment during the study with drugs that are not permitted by the study protocol;

(23) Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety.

Test product, dose, mode of administration:

All subjects will be treated with oral cabozantinib 60 mg q.d. In case of treatment-emergent toxicity, the Investigator may decide to reduce the dose to 40 mg or 20 mg according to the instructions specified in this protocol.

The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) and screening and baseline visits can take place the same day as long as all eligibility criteria/parameters are available and checked prior to the first dose of cabozantinib. Doses will be self-administered at home by taking cabozantinib q.d. at the same time each day

(preferably at bedtime). Cabozantinib should not be taken with food. The subject should not eat anything for at least 2 hours before and 1 hour after taking cabozantinib. If a dose is missed, the missed dose should not be taken less than 12 hours before the next one.
Duration of treatment: Subjects will receive study treatment, even after radiographic progression per RECIST 1.1, as long as the Investigator believes they continue to experience clinical benefit from study treatment and that this benefit outweighs potential risks, and up to the end of the study, defined as 18 months after the last subject included in the study received the first cabozantinib dose. Subjects may discontinue treatment due to disease progression, unacceptable toxicity, need for subsequent systemic anti-cancer treatment or any other reasons for treatment discontinuation listed in this protocol.
Reference therapy, dose and mode of administration: No reference therapy.

Criteria for evaluation (endpoints):

Efficacy:

Primary Endpoint and Evaluation:

- Objective response rate (ORR) in cohort A per RECIST 1.1 evaluated by independent central review.

Secondary Endpoints and Evaluations:

- Time to response (TTR) per RECIST 1.1 evaluated by independent central review;
- Duration of response (DOR) per RECIST 1.1 evaluated by independent central review;
- Disease control rate (DCR) per RECIST 1.1 by independent central review;
- Progression-free survival (PFS) per RECIST 1.1 by independent central review;
- Objective response rate (ORR) in cohort B per RECIST 1.1 evaluated by independent central review;
- Overall survival (OS);
- ORR, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review;
- Change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS) questionnaire.

Safety:

Safety assessments will start on the day of the Screening visit and will be carried out at minimum at every visit (every 2 weeks) up to Week 4 (Visit 4), and every 4 weeks thereafter. Safety will also be assessed at the End of Study Treatment visit (30 to 45 days after the last study treatment dose) and during the Post-treatment Follow-up period (every 12 weeks (±15 days) by telephone call) up to 18 months after the last subject included in the study started cabozantinib treatment. Unscheduled visits for safety evaluations are allowed at any time.

Routine safety evaluations throughout the study treatment period will include the recording of AEs, clinical laboratory (serum chemistry, haematology and urinalysis) test results, serum pregnancy tests (in females of childbearing potential), thyroid function tests, vital signs (BP and heart rate), ECG findings, physical examination findings and body weight measurements, and use of concomitant medication throughout the study treatment period.

Information on new or worsening AEs and serious AEs (SAEs) will be collected from the date the informed consent is signed until the End of Study Treatment visit. This information will be collected at study visits, by telephone call to the subject or by spontaneous report by the subject. At baseline, AEs will be documented before and after cabozantinib dosing. Certain AEs and all SAEs that are ongoing 30 days after the date of the last cabozantinib dose are to be followed until resolution or until the Investigator considers the event is stable or irreversible. During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator.

Statistical Methods:

Sample size:

With a true ORR proportion of 23%, a sample size of 68 subjects in cohort A will provide a statistical power of 80% to reject the null hypothesis of 10%, using a one-sample exact test for binomial distribution with a significance level of 0.025 (one-sided). Assuming approximately 7% non-evaluable subjects (i.e. subject who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1), up to a total of 74 subjects in cohort A will be included in the study.

For cohort B, no formal sample size determination was performed as the enrolment will stop when the recruitment in cohort A will be reached. We anticipate approximately 40 subjects recruited in cohort B.

Statistical Methods:

An interim and purely descriptive analysis will be conducted when 80% of the subjects (i.e. 59 subjects) of cohort A will be treated for at least 3 months. Both cohorts will be analysed at this cut-off date. The final analysis based on the primary endpoint (ORR) will be performed 12 months after the last subject received the first cabozantinib administration. A follow-up analysis based on OS will be conducted 18 months after the last subject received the first cabozantinib administration. The statistical testing will be carried out at the final analysis.

The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review will be tested in cohort A using a one-sample exact test for binomial distribution. The proportion of subjects achieving ORR will be presented with their two-sided 95% CI using the Clopper-Pearson exact method. DCR estimates will be described with associated 2-sided 95% CIs.

Time-to-event endpoints (TTR, DOR, PFS and OS) will be analysed using the Kaplan-Meier method. Median durations and associated 2-sided 95% CIs will be provided. Event rates at timepoints from either first dose of study treatment or first documented response will also be estimated with associated 2-sided 95% CIs.

The FKSI-DRS score will be described at corresponding visits with associated change from baseline. The proportion of subjects with at least an increase of 1 point from baseline will also be reported. Comparisons between baseline and post-baseline scores will be performed using paired Student t-tests.

All AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by preferred term (PT) and system organ class (SOC). AEs will be graded according to the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (NCI-CTCAE). The incidence of all reported AEs will be tabulated by cohort and overall. Summary tables will be presented by Grade 3 or 4, worst reported severity, drug relationship and AEs associated with premature withdrawal or dose modification of study medication. Subject deaths will be summarised, and primary cause of death will be reported by PT and SOC using MedDRA. Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables, clinical laboratory tests at each assessment. For laboratory data, abnormal values

will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

Concomitant medications will be standardised using the World Health Organization drug dictionary and summarised by SOC and PT.

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
1st line	First line
2nd line	Second line
ADL	Activities of Daily Living
AE	Adverse Event
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AXL	Tyrosine-protein Kinase Receptor UFO
b.i.d.	Twice daily (in Latin: *bis in die*)
BoD	baseline sum of diameters
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C/A/P	Chest/Abdomen/Pelvis
CA	Competent Authorities
ccRCC	Clear-Cell Renal Cell Carcinoma
CFR	Code of Federal Regulations (United States of America)
chRCC	Chromophobe Renal Cell Carcinoma
CI	Confidence Interval
CNS	Central Nervous System
CPI	Checkpoint Inhibitor
CR	Complete Response
CRO	Contract Research Organisation
CSR	Clinical Study Report
CT	Contrast Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
CYP1A2	Cytochrome P450 Family 1 Subfamily A Member 2

ABBREVIATION	Wording Definition
CYP2B6	Cytochrome P450 Family 2 Subfamily B Member 6
CYP2C19	Cytochrome P450 Family 2 Subfamily C Member 19
CYP2C8	Cytochrome P450 Family 2 Subfamily C Member 8
CYP2C9	Cytochrome P450 Family 2 Subfamily C Member 9
CYP2D6	Cytochrome P450 Family 2 Subfamily D Member 6
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
CYP450	Cytochrome P450
DILI	Drug Induced Liver Injury
DCR	Disease Control Rate
DOR	Duration of Response
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FKSI-DRS	Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index
FT4	Free Thyroxine 4
GB	Glioblastoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GGT	γ-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony-stimulating Factor
HCG	Human Chorionic Gonadotrophin
HR	Hazard Ratio

ABBREVIATION	Wording Definition
HRQOL	Health-related Quality of Life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMDC	International Metastatic RCC Database Consortium
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
IRC	Independent Radiology Committee
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MET	Hepatocyte Growth Factor Receptor Protein
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MRP2	Multidrug Resistance-associated Protein 2
MSKCC	Memorial Sloan Kettering Cancer Center
MTC	Medullary Thyroid Cancer
mTOR	Mammalian Target of Rapamycin
NA	Not Applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NOS	Not Otherwise Specified
NPACT	Non-protocol Anti-cancer Therapy
NSAID	Non-steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
ONJ	Osteonecrosis of The Jaw

ABBREVIATION	Wording Definition
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death-1 protein
PD-L1	Programmed Death-ligand 1 protein
PEG	Percutaneous Endoscopic Gastrostomy
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI3K	Phosphoinositide 3-kinase
PO	Per Os (orally)
PP Population	Per Protocol Population
PPES	Palmar-Plantar Erythrodysaesthesia Syndrome
PPI	Proton Pump Inhibitor
PR	Partial Response
pRCC	Papillary Renal Cell Carcinoma
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
PTT	Partial Thromboplastin Time
q.d.	Once Daily (in Latin: *quaque die*)
QTc	Corrected QT Interval
QTcF	Fridericia's Correction of QT Interval
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Proto-oncogene
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure

ABBREVIATION	Wording Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TIA	Transient Ischaemic Attack
TKI	Tyrosine Kinase Inhibitor
TPR	Time Point Response
TSH	Thyroid-stimulating Hormone
TTF	Time to Treatment Failure
TTR	Time to Response
UE	Unable to Evaluate
ULN	Upper Limit of Normal
UPCR	Urine Protein-to-Creatinine Ratio
uRCC	Unclassified Renal Cell Carcinoma
VEGF	Vascular Endothelial Growth Factor
VEGFR2	VEGF Receptor 2
VHL	von Hippel-Lindau
WHODRUG	World Health Organization Drug

1 BACKGROUND INFORMATION

1.1 Renal Cell Carcinoma

Renal cell carcinoma (RCC) comprises a heterogeneous group of kidney cancers and is one of the ten most common cancers worldwide, with more than 300,000 new cases each year (1). The most common subtypes (≥5% incidence) include clear-cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC). The other subtypes are either very rare (each with ≤1% total incidence) or designated as unclassified RCC (uRCC, approximately 4% total incidence) when it is not possible to diagnose the tumour according to any other subtype. The ccRCC subtype is associated with most kidney cancer deaths and is predominant in metastatic disease (83-88%) (2).

It is estimated that around 25-50% of subjects with localised disease eventually develop metastatic RCC (3) and that up to 30% of subjects considered disease-free after curative treatment for localised RCC will relapse (1).

1.1.1 Pathogenic Mechanisms in RCC

Previous studies have contributed to a better understanding of the pathogenic mechanisms underlying RCC, which has not only helped explain why certain subjects with this disease become resistant to chemotherapy but has also provided relevant information to improve the median overall survival (OS) (4).

The hepatocyte growth factor receptor protein (MET) and the vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2) are receptor tyrosine kinases involved in tumour cell growth, invasiveness, metastasis and/or angiogenesis in multiple tumour types including RCC (5). Clear-cell renal carcinomas, which are defined by the presence of malignant epithelial cells with clear cytoplasm, commonly contain mutations in a gene whose activity controls the expression of both MET and VEGFR2, called the tumour suppressor von Hippel-Lindau (VHL) gene (6, 7). These mutations trigger an increase in the expression of VEGF and MET, thereby promoting increased angiogenesis, tumour cell proliferation, invasive growth and, ultimately, tumourigenesis (8). Indeed, high MET expression is associated with poor prognosis in subjects with RCC (9). VHL-deficient renal carcinoma cells have been shown to be more sensitive to MET targeting than similar cells in which VHL function has been restored (10). Moreover, circulating proteases that positively or negatively regulate the activation of the hepatocyte growth factor (a MET ligand) are frequently upregulated or downregulated, respectively, in RCC (7).

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway also contributes to the pathology of RCC by stimulating the expression of proangiogenic factors such as VEGF.

1.1.2 Approved Treatments for RCC

Antiangiogenic therapies have been shown to have clinical benefit in subjects with advanced RCC. Several new marketed antiangiogenic agents are available as first line (1st line) treatments, such as the anti-VEGF antibody bevacizumab, tyrosine kinase inhibitors (TKIs) that target the VEGF pathway (sorafenib, sunitinib, pazopanib, axitinib) and mTOR inhibitors (temsirolimus and everolimus) (4). Cabozantinib, a multitarget antiangiogenic TKI that inhibits the VEGFR pathway (VEGFR-TKI), is also available as a 1st line treatment for intermediate- and poor-risk subjects with advanced RCC (11).

Checkpoint inhibitor (CPI) therapy with ipilimumab and nivolumab is also an approved treatment for advanced RCC. Indeed, in January 2019, the European Medicines Agency (EMA)

granted ipilimumab and nivolumab Marketing Authorisation for 1st line treatment of intermediate- and poor-risk subjects with advanced RCC. European Commission approved pembrolizumab in combination with axitinib in August 2019 and for avelumab plus axitinib as first-line treatment for patients with advanced RCC in September 2019.

There are also agents approved as second line (2nd line) treatment for RCC. These include multitarget antiangiogenic TKIs such as cabozantinib, lenvatinib and everolimus, and the CPI nivolumab.

1.2 Cabozantinib

Cabozantinib (XL184) is a multitarget TKI that inhibits several proteins involved in the pathology of RCC, such as MET, VEGFR2, the tyrosine-protein kinase receptor UFO (AXL) and the proto-oncogene (RET). Cabozantinib is provided as both capsules and tablets, but the two formulations are not interchangeable.

Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the EMA as a 2nd line treatment for subjects with advanced RCC previously treated with VEGF-targeted therapy, and as a 1st line treatment for adults with advanced RCC with intermediate and poor risk. Cabometyx™ (cabozantinib tablets 40 mg) in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.

Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the Food and Drug Administration (FDA) for the treatment of all subjects with advanced RCC regardless of previous therapies received.

A more detailed description of the product is provided in the Summary of Product Characteristics (SmPC) document (11).

1.2.1 Known and Potential Risks and Benefits of Cabozantinib to Human Subjects

A summary of the pharmacology of cabozantinib is provided in the Investigator's Brochure supplied by the Sponsor (or designee). The Investigator's Brochure should be reviewed in conjunction with this study protocol.

In clinical studies, cabozantinib has been evaluated in multiple tumour types including MTC, castration-resistant prostate cancer, ovarian cancer, breast cancer, hepatocellular carcinoma, non-small cell lung cancer (NSCLC), melanoma, differentiated thyroid cancer, RCC and glioblastoma (GB) multiforme (for details, please see the Investigator's Brochure).

1.2.1.1 METEOR Study

The safety and efficacy of cabozantinib were evaluated in a randomised, open-label, multicentre Phase III study (METEOR study) (12). In this study, 658 subjects with advanced RCC with a clear-cell component who had received prior treatment with at least one VEGFR-TKI were randomised (1:1) to receive cabozantinib (N = 330) or everolimus (N = 328). The included subjects could have received other prior therapies, including cytokines and antibodies against VEGF and the programmed death-1 (PD-1) receptor, or its ligands. Subjects with treated brain metastases were also allowed to enrol in the study. The primary endpoint was progression-free survival (PFS) assessed by a blinded independent radiology committee (IRC) among the first 375 subjects randomised. Secondary efficacy endpoints were objective response rate (ORR) and OS. Tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the cabozantinib and everolimus arms. Most subjects were male (75%), with a median age of 62 years. Seventy-one percent received only one prior VEGFR-TKI therapy; 41% of subjects received sunitinib as their only prior VEGFR-TKI therapy. According to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria for prognostic risk category (see Appendix 1), 46% of subjects had favourable prognostics (0 risk factors), 42% had intermediate prognostics (1 risk factor), and 13% had poor prognostics (2 or 3 risk factors). Fifty-four percent of subjects had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%). The median duration of treatment was 7.6 months (range 0.3 - 20.5) in the cabozantinib arm and 4.4 months (range 0.21 – 18.9) in the everolimus arm. A statistically significant improvement in PFS was demonstrated for cabozantinib compared to everolimus in the primary PFS analysis population: 7.4 months *versus* 3.8 months, respectively (stratified hazard ratio (HR) 0.58, 95% confidence interval (CI): 0.45, 0.75; stratified log-rank p-value<0.0001). Similar results were observed in the intention-to-treat (ITT) population (658 subjects): 7.4 months *versus* 3.9 months, respectively (stratified HR 0.51, 95% CI: 0.41, 0.62).

A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (202 events, unadjusted 95% CI: 0.51, 0.90, p = 0.006) (12). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for subjects randomised to cabozantinib compared to everolimus (320 events, median of 21.4 months *versus* 16.5 months, respectively; HR 0.66, 95% CI: 0.53, 0.83, p = 0.0003). Similar OS results were observed in a follow-up analysis (descriptive) at 430 events.

Exploratory analyses of PFS and OS in the ITT population have also shown consistent results in favour of cabozantinib compared to everolimus across different subgroups, such as age (<65 *versus* ≥65, sex, MSKCC risk group (favourable, intermediate, poor), Eastern Cooperative Oncology Group (ECOG) status (0 *versus* 1), time from diagnosis to randomisation (<1 year *versus* ≥1 year), tumour MET status (high *versus* low *versus* unknown), bone metastases (absence *versus* presence), visceral metastases (absence *versus* presence), visceral and bone metastases (absence *versus* presence), number of prior VEGFR-TKI therapies (1 *versus* ≥2), duration of first VEGFR-TKI therapy (≤6 months *versus* >6 months).

The primary ORR analysis conducted by the IRC in the ITT population at the time of the primary analysis of PFS showed that the ORR for the cabozantinib and everolimus arms were 17% (95% CI: 13, 22) and 3% (95% CI: 2, 6), respectively (unstratified p-value<0.0001).

More details about the results obtained in this study can be found in the SmPC document (11).

1.2.1.2 CABOSUN Study

The safety and efficacy of cabozantinib in treatment-naïve subjects with advanced or metastatic RCC were evaluated in a randomised, open-label, multicentre Phase II study (CABOSUN study) (13). In this study, 157 subjects with previously untreated locally advanced or metastatic RCC with a clear-cell component were randomised (1:1) to receive cabozantinib (N = 79) or sunitinib (N = 78). Included subjects had intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories (see Appendix 2). Subjects were stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of subjects had a nephrectomy prior to onset of treatment.

For intermediate risk disease, one or two of the following risk factors were met, while for poor risk, three or more factors were met: time from diagnosis of RCC to systemic treatment <1 year,

Hgb below the lower limit of normal (LLN), corrected calcium above the upper limit of normal (ULN), Karnofsky Performance Status (KPS) lower than 80%, and neutrophil and platelet counts above the ULN.

The primary endpoint was PFS. Secondary efficacy endpoints were ORR and OS. Tumour assessments were conducted every 12 weeks.

The baseline demographic and disease characteristics were similar between the cabozantinib and sunitinib arms. Most subjects were male (78%) with a median age of 62 years. Subject distribution by IMDC risk groups included 81% of subjects with intermediate prognosis (1-2 risk factors) and 19% of subjects with poor prognosis (≥3 risk factors). Most subjects (87%) had ECOG performance status of 0 or 1, whereas 13% of subjects had an ECOG performance status of 2. Thirty-six percent of subjects had bone metastases.

A statistically significant improvement in PFS was demonstrated for cabozantinib compared to sunitinib, as retrospectively assessed by a blinded IRC (14). Median PFS was 8.6 months (95% CI: 6.8, 14) in the cabozantinib arm and 5.3 months (95% CI: 3, 8.2) in the sunitinib arm (HR 0.48, 95% CI: 0.31, 0.74, p = 0.0008). These results were consistent with those obtained in the Investigator analysis (13).

Subjects with both positive and negative MET status experienced a favourable PFS effect with cabozantinib compared to sunitinib. Cabozantinib had greater antitumour activity in subjects with a positive MET status than in subjects with a negative MET status (HR 0.32 (0.16, 0.63) *versus* 0.67 (0.37, 1.23)) respectively.

Cabozantinib treatment was associated with a trend for longer survival compared to sunitinib: median OS was 30.3 months (95% CI: 14.6, not estimable) in the cabozantinib arm and 21.0 months (95% CI: 16.3, 27.0) in the sunitinib arm (HR 0.74, 95% CI: 0.47, 1.14). However, the CABOSUN study was not powered for the OS analysis and the data is immature.

More details about the results obtained in this study can be found in the SmPC document (11).

1.3 Checkpoint Inhibitor Therapy Alone and CPI Combined with Antiangiogenic Therapies as 1st Line Treatment in Renal Cell Carcinoma

While cabozantinib has provided strong positive results in multiple settings in metastatic RCC (12, 14), recent trials have demonstrated that CPI therapy alone or with different combinations of antiangiogenic agents have a beneficial effect in subjects with advanced or metastatic RCC. Therefore, treatment landscape has evolved, this raises the need to evaluate clinical benefit of subsequent VEGF targeted therapies to be used in 2nd line after 1st line systemic treatment containing CPI.

Treatment with CPIs alone

The Phase III Checkmate 214 study compared the effect of treatment with CPIs ipilimumab and nivolumab in combination *versus* sunitinib in untreated subjects with advanced or metastatic RCC. The co-primary endpoints were the ORR, PFS and OS among subjects with intermediate- and poor-prognosis.

Treatment with ipilimumab and nivolumab in combination demonstrated superior ORR (42% (95% CI 37-47%) *versus* 27% (95% CI 22-31%), p<0.0001) and PFS (11.6 *versus* 8.4 months, HR 0.82, p = 0.0331) compared to sunitinib. The median OS was not reached in subjects treated with the combination therapy but reached 26 months in subjects treated with sunitinib (p<0.0001). The complete response (CR) rate was 9% in the combination therapy arm compared to 1% in the sunitinib arm (15).

Treatment-related adverse events (AEs) occurred in 93% of subjects treated with ipilimumab and nivolumab and in 97% of subjects treated with sunitinib. Grade 3-5 AEs were less frequent among subjects treated with the combination therapy (46%) than those treated with sunitinib (63%). The most frequent AEs reported in the combination therapy arm were fatigue (37%), pruritus (28%) and diarrhoea (27%), whereas the most frequent AEs in the sunitinib arm were diarrhoea (52%), fatigue (49%) and palmar plantar erythema (43%). Treatment-related AEs leading to discontinuation were more frequent with ipilimumab and nivolumab (22%) than with sunitinib (12%). Importantly, the health-related quality of life was superior in the combination therapy arm (15).

Although VEGFR-TKIs remain the current 1st line treatment for metastatic RCC, as defined by the principal expert committees in Europe and the United States, the recent approval of CPI therapy with ipilimumab and nivolumab in combination will likely become the new standard of care for subjects with metastatic RCC with intermediate- and poor-prognosis (16).

Treatment with CPIs combined with antiangiogenic agents

Interestingly, treatments that combine CPIs with antiangiogenic therapies may also provide a strong benefit to subjects with advanced or metastatic RCC. Firstly, these combination treatments allow a dual/multifaceted manipulation of the pathways involved in the development of RCC, which strengthens the anti-cancer strategy. Secondly, previous studies suggest that, in addition to their direct effect, antiangiogenic TKIs may enhance the effectiveness of CPI agents when administered concurrently (17, 18).

As such, two new therapeutic options axitinib plus pembrolizumab and axitinib plus avelumab showed the efficacy and safety of combination therapy with CPI and TKI in untreated subjects with advanced RCC have been approved by EMA in August 2019 and in September 2019, respectively. Some clinical trials are ongoing:

- A study evaluating the combination of lenvatinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02811861);
- A study of cabozantinib in combination with nivolumab and ipilimumab in patients with previously untreated advanced or metastatic RCC (NCT03937219).

Results from the study (NCT0314177) that assessed the combination of nivolumab (a programmed death-ligand 1/ PD-1 protein inhibitor) with cabozantinib *versus* sunitinib in untreated subjects with metastatic RCC (CkeckMate 9ER trial) showed that cabozantinib and atezolizumab in combination improved PFS and OS compared to sunitinib in subjects with untreated metastatic or advanced RCC (20).

Together, the clinical trials mentioned in this section represent the evolution of the treatment landscape for 1st line treatment of subjects with advanced or metastatic RCC. The choice of 1st line treatment may impact on tumour growth and may therefore play a role on subsequent treatment activity, thus the results obtained in these trials provide valuable information to help establish the best therapeutic sequence to treat disease progression for subjects with this disease.

1.4 Rationale for Study Design

Multitarget antiangiogenic TKI and CPI therapies represent two systemic treatment modalities that have been instrumental in the recent advances of anti-cancer treatment over the past several years. Studies with cabozantinib (Section 1.2) and CPI alone or in combination with different antiangiogenic inhibitors (Section 1.3) contribute to help determine the best treatment option for subjects with RCC.

Antiangiogenic agents currently represent the preferable 1st line treatment option for patients with advanced and metastatic RCC with intermediate and poor prognosis. However, according to the European Association of Urology Guidelines Recommendations and European Society for Medical Oncology (ESMO) guidelines (21, 22) and based on recent approvals, CPI therapy with ipilimumab and nivolumab is likely to become the new standard of care for subjects with RCC with poor and intermediate prognosis and pembrolizumab and axitinib is likely to become the new standard of care for subjects with favourable prognosis.

Importantly, the choice of 1st line treatment may impact on tumour growth and may therefore play a role on subsequent treatment activity, thus more trials are warranted to investigate the optimal treatment sequence for advanced and metastatic RCC (16). As such, as the pivotal clinical trials of VEGFR-TKIs in advanced or metastatic RCC in 2nd line were conducted before the availability of CPI therapies, there is an unmet need to assess the efficacy and safety of antiangiogenic therapies in subjects treated in 1st line with CPIs.

Cabozantinib may be a potential 2nd line treatment for these subjects. In fact, preliminary data from retrospective analyses assessing the role of VEGFR-TKIs, including cabozantinib, given as early as 2nd line treatment after previous CPI therapy have shown promising results:

- Powles et al. 2018 (23): this study reported outcomes based on prior therapy in the Phase III METEOR trial of cabozantinib *versus* everolimus in advanced RCC (12), including 5% of subjects who had received prior CPI therapy. In the prior anti-PD-1/PD-L1 subgroup, cabozantinib treatment was associated with improved PFS (HR 0.22, 95% CI 0.07-0.65), OS (HR 0.56, 95% CI 0.21-1.52) and ORR, as well as a higher rate of durable responses compared with everolimus;
- Shah A. et al. 2018: this study assessed the effect of VEGFR-TKIs in 43 subjects with metastatic RCC after disease progression with CPI therapy. The authors reported an ORR of 42%, a median PFS of 10 months, an estimated 1-year OS of 87.5% (95% CI 74.6-100) and a disease control rate (DCR) of 100%. In this study, 15 subjects (35%) received cabozantinib: 8 subjects presented stable disease, 6 subjects experienced partial response and 1 subject showed complete response (unpublished data);
- McGregor B. et al. 2018: this study assessed the effect of cabozantinib in 69 subjects previously treated with CPI therapy with or without VEGF-targeted therapy. Overall, the authors reported an ORR of 36%, a median time to treatment failure (TTF) of 6.5 months and improved 1-year OS in subjects with favourable/intermediate risk compared to subjects with poor risk (67% (95% CI 50-80) *versus* 14% (95% CI 1-44)) (unpublished data). According to the authors, response rates were comparable to those in the METEOR trial (Section 1.2.1.1);
- Graham J. et al. 2018: this study assessed the effect of several VEGFR-TKIs (including cabozantinib) *versus* mTOR inhibitors in 184 subjects previously treated with CPIs. In this study, cabozantinib was given as 2nd line treatment (6 subjects) or further (27 subjects). The authors reported significantly longer median times to treatment discontinuation in subjects treated with VEGFR-TKIs compared to those treated with mTOR inhibitors (5.3 *versus* 2.5 months, p = 0.002). The ORR was numerically higher in the VEGFR-TKIs group (19.8%) than in the mTOR inhibitors group (5.0%) (unpublished data);
- Barata P. et al. 2018 (24): this study evaluated the effect of VEGFR-TKIs (including cabozantinib) in 28 subjects with metastatic RCC who progressed after CPI therapy. This

analysis included 3 subjects who received cabozantinib: 1 subject presented an ORR of 33% and the other 2 subjects presented stable disease;

- Auvray M. et al. 2019 (16): this study assessed the effect of VEGFR-TKIs in 33 subjects treated with CPIs ipilimumab and nivolumab, as part of the Checkmate 214 trial (15). In the overall population, median PFS from start of VEGFR-TKI therapy was 8 months (95% CI 5-13). Interestingly, PFS in 2nd line was significantly longer in subjects with a long 1st line duration of response (DOR) to ipilimumab and nivolumab in combination (≥6 months) than in short responders to CPI (<6 months): 8 versus 5 months (p = 0.03). The OS rate was 54% at 12 months. These results suggest a sustained benefit of VEGFR-TKI treatment in subjects who progressed after CPI therapy.
- Kalirai A. 2019 (27): reported results from the Canadian Kidney Cancer Information System: real world analysis of 102 patients treated with targeted therapy post CPI. Those who received first-line ipilimumab + nivolumab versus a VEGFi + CPI combination prior to second-line treatment had a median time to treatment failure of 8.0 vs 5.2 months (m) (HR=0.43, 95% CI: 0.13-1.44) and median OS of 16.5 m vs not reached (HR=0.76, 95% CI: 0.11-5.24). Patients who received a VEGFi versus a mammalian target of rapamycin inhibitor (mTORi) as third-line TT had a median TTF of 7.6 vs 4.4 m (HR=0.52, 95% CI: 0.24-1.10) and median OS of 21.7 vs 16.2 m (HR=0.41, 95% CI: 0.16-1.08). All third-line treatment patients received first-line VEGFi and second-line nivolumab. Of the third-line VEGFi treatment patients, 24 received axitinib (TTF 7.1 m, OS 21.7 m) and 22 received cabozantinib (data immature). Authors concluded that these results support the use of VEGFi after CPI in mRCC patients.
- Ornstein MC 2018 (28) reported the results of a phase 2 Study of the Efficacy and Safety of axitinib given on an individualized schedule for mRCC, after treatment with PD-1 or PD-L1 Inhibitors: the study included 38 patients whose most recent therapy was anti PD-1 (89%) or anti PD L1 (11%). In evaluable patients, the estimated median PFS is 9.2 months, with 54% of patients still on axitinib. The ORR is 38.7%. The median highest dose per patient was 6mg BID (range, 5-9) and 44% of patients required dose reduction to < 5mg BID. There were no unexpected toxicities related to axitinib.

Importantly, the safety profile observed in these studies was considered acceptable, which supports the positive effect of VEGFR-TKIs such as cabozantinib in subjects with advanced RCC who progressed after CPI therapy. However, the available data is still limited and validation of these promising findings in prospective clinical trials is thus required to confirm the key role of cabozantinib in a post-CPI setting. To generate the prospective data of cabozantinib in subjects who have been treated with CPI or CPI plus VEGF therapies for advanced or metastatic RCC, the Sponsor proposes to conduct a Phase II study in subjects with this disease.

This is an international, multicentre, open-label Phase II trial of cabozantinib in subjects with advanced or metastatic RCC with a clear-cell component who progressed after 1st line treatment with CPI alone (ipilimumab and nivolumab in combination) or CPI combined with VEGF-targeted therapy.

The primary endpoint is ORR, defined as the proportion of subjects with CR or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, as determined by an independent central review in cohort A.

Secondary endpoints are time to response (TTR), duration of response (DOR), DCR and PFS per RECIST 1.1 assessed both by independent central review and by local Investigator, ORR

per RECIST 1.1 also assessed by both independent central review (cohort B) and by local Investigator (cohort A and cohort B), OS and change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS). Safety and tolerability of cabozantinib will also be monitored throughout the study.

1.5 Selection of Cabozantinib Dose and Formulation

All approvals of cabozantinib (Cabometyx™) as a treatment for subjects with RCC include the 60 mg dose as the recommended dose.

Details on administration procedures and dosage are provided in Section 6.2.

1.6 Population to be Studied

The study will include adult subjects with unresectable, locally advanced or metastatic RCC with a clear-cell component who progressed after 1st line treatment with CPI alone (ipilimumab and nivolumab in combination) or CPI combined with VEGF-targeted therapy.

1.7 Compliance Statement

The study will adhere to all local regulatory requirements and relevant company policies. The Sponsor will ensure that the countries where the data are transferred provide an adequate level of data protection.

In case of data transfer outside the European Union (EU), the Sponsor will either ensure that the countries where data are transferred provide an adequate level of data protection or that the company receiving data has joined the EU-United States of America Privacy Shield Framework or will put in place a contract including standard contractual clauses adopted by the European Commission to ensure that the transfer of study information complies with applicable data protection legislation. Such a contract can be made available upon request.

Before initiating the study, the Investigator/institution will have the following documents: written and dated approval/favourable opinion from the Independent Ethics Committee (IEC)/institutional review board (IRB) for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with Good Clinical Practice (GCP) requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Cabozantinib is currently approved in the United States as a treatment for adults with advanced RCC regardless of previous therapies received. In the EU, cabozantinib is approved for the treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk and following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Recent EMA approvals and several clinical trials are currently ongoing to investigate the effect of new treatment regimens containing CPI for patients with RCC (Section 1.3). These changes potentially transformed the treatment landscape and the available options for 1st line treatment of RCC. However, some of the patients may be refractory to these treatments, thus it is increasingly important to find potential 2nd line therapies for such patients.

To date, no prospective clinical trial has tested the role of cabozantinib as a 2nd line treatment of subjects with advanced RCC who progressed after treatment with CPI therapy. Thus, the overall objective of this study is to evaluate the efficacy and safety of cabozantinib as 2nd line treatment in subjects with unresectable, locally advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination or CPI combined with VEGF-targeted therapy.

2.2 Study Objectives

The overall objective of this study is to evaluate the efficacy and safety of cabozantinib as 2nd line treatment in subjects with unresectable, locally advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination or CPI combined with VEGF-targeted therapy.

2.2.1 Primary Objective

- To assess the efficacy of cabozantinib by the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review in cohort A.

2.2.2 Secondary Objectives

- To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent central review and Investigator's review;
- To assess objective response rate (ORR) by independent central review and Investigator's review in cohort B;
- To assess ORR by Investigator's review in Cohort A;
- To assess overall survival (OS);
- To assess the ORR and PFS by Investigator's review and OS in overall population (cohorts A+B);
- To assess the change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS) questionnaire.
- To access the safety and tolerability of cabozantinib.

2.3 Study Hypothesis

The hypothesis for the two cohorts of this study is that cabozantinib as 2nd line treatment will demonstrate a clinically significant increase of response rate as compared to historical control

in subjects previously treated with CPI therapy. A therapy will be considered clinically meaningful if it provides a significant benefit in ORR (primary endpoint) over a standard rate of 10% (conservative threshold in reference to the response rate of everolimus in the METEOR study (12), exact 95% CI: 1.7-5.9).

3 STUDY DESIGN

3.1 General Study Design and Study Schema

This study will be conducted in approximately 50 active investigational sites across Germany, Switzerland, the Netherlands, France, UK, Austria and Spain. The list of countries and the number of investigational sites may change during the study depending on recruitment and availability of the first line combination therapies in each country.

This is a Phase II, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib 60 mg once daily (q.d.) in adults with unresectable, locally advanced or metastatic RCC with a clear-cell component who progressed after 1st line treatment with CPI alone (ipilimumab and nivolumab in combination) or CPI combined with VEGF-targeted therapy. Approximately 114 eligible subjects will receive cabozantinib (two independent cohorts with 74 subjects* in cohort A and approximately 40 subjects in cohort B) (Figure 1).

* The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.

Each subject's study participation will consist of the following periods:

Pre-treatment Period: Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments will be performed within 15 days prior to first cabozantinib dose except when otherwise specified (detailed in study schedule in Table 2).

Treatment Period: Subjects who meet all eligibility criteria will be included in one of the two following cohorts based on their 1st line treatment and both cohorts will receive the same open-label treatment with cabozantinib (60 mg q.d.):

- **Cohort A: 74 subjects**

Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.

- **Cohort B: approximately 40 subjects**

Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.

The timing of visits to the investigational site to perform all planned assessments is fixed from baseline and will be conducted as described in Section 5 (see Table 2 for schedule of assessments).

The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2). In both cohorts, subjects can receive study treatment up to the end of the study, defined as 18 months after the last subject included in the study started cabozantinib treatment (Section 5.6), but subjects may terminate treatment earlier due to reasons such as disease progression, unacceptable toxicity or withdrawal of consent.

Efficacy evaluations will be performed as described in Section 7.3 (see Table 2 for schedule of assessments). These include radiographic tumour assessments which will be blindly reviewed by a central IRC (see Section 3.8) to evaluate efficacy endpoints (Section 7).

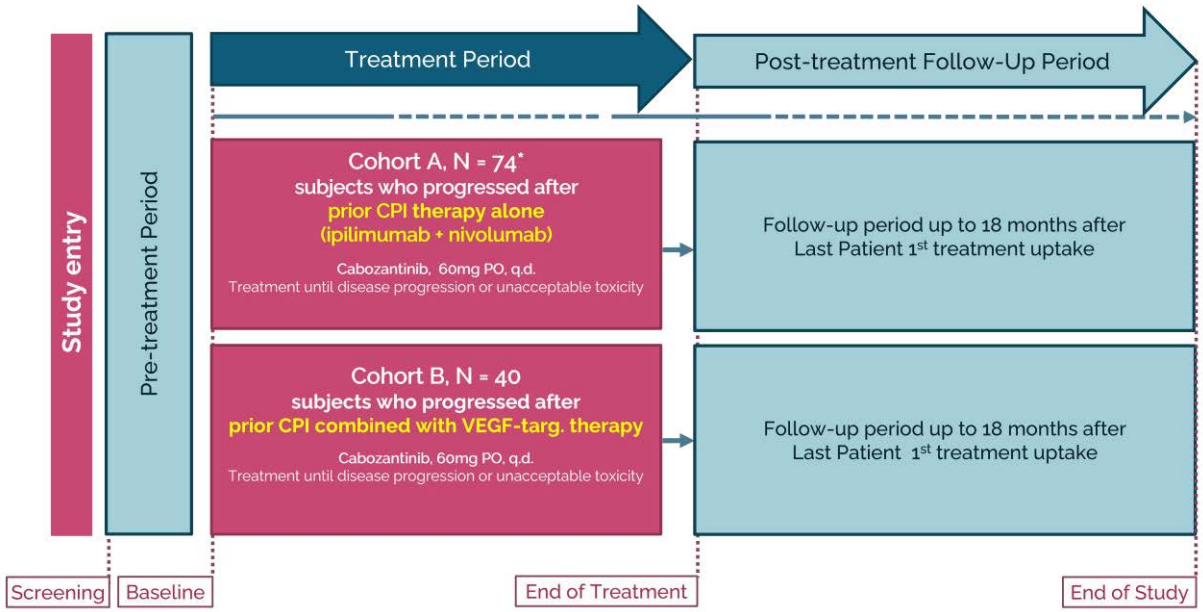
Safety assessments will start on the date of the Screening visit and will be continued throughout the study as described in Section 8 (see Table 2 for schedule of assessments). Unscheduled safety evaluations are allowed at any time throughout the study (Section 5.3).

Subjects who discontinue study treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 to 45 days after the last dose of cabozantinib) (Section 5.2.2.1). Subjects who prematurely stop the study will be invited to attend the Early Study Withdrawal visit (Section 5.2.2.2).

Post-treatment Follow-up Period: Subjects who discontinue study treatment will be contacted during the Post-treatment Follow-up visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy. During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator. These assessments will be continued until the subject expires or until the end of the study (18 months after the last subject included in the study started cabozantinib treatment, Section 5.6), whichever occurs first. Every effort will be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Specific details of study procedures are provided in Section 5. Details for treatment with cabozantinib are provided in Section 6.

Figure 1 Study Design



Abbreviations: CPI = Checkpoint inhibitor; PO = Orally; q.d. = Once daily; VEGF = Vascular endothelial growth factor

*The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.

3.2 Endpoints

3.2.1 Primary Efficacy Endpoint and Evaluation

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review in cohort A.

3.2.2 Secondary Efficacy Endpoints and Evaluation

- Time to response (TTR) per RECIST 1.1 evaluated by independent central review;
- Duration of response (DOR) per RECIST 1.1 evaluated by independent central review;
- Disease control rate (DCR) per RECIST 1.1 by independent central review;
- Progression-free survival (PFS) per RECIST 1.1 by independent central review;
- Objective response rate (ORR) in cohort B per RECIST 1.1 evaluated by independent central review;
- Overall survival (OS);
- ORR, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review;
- Change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS) questionnaire.

The endpoints of ORR, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.

3.2.3 Safety Endpoints and Evaluation

The safety and tolerability of cabozantinib will be assessed throughout the study treatment period by evaluating AEs, clinical laboratory test results, vital signs measurements, electrocardiogram (ECG) and physical examination results, and use of concomitant medication (see Section 8).

Summaries of AEs and SAEs will be tabulated by cohort and overall according to system organ class (SOC) and preferred term (PT) by overall incidence, worst reported severity, and relationship to study treatment. Selected laboratory test results will be summarised by cohort to evaluate worst post-baseline Common Terminology Criteria for Adverse Events (CTCAE) grade, as well as shifts or changes from baseline.

3.3 Randomisation and Blinding

Not applicable.

3.4 Maintenance of Randomisation and Blinding

Not applicable.

3.5 Study Treatments and Dosage

The study treatment cabozantinib will be administered at a dose of 60 mg q.d. A subject's daily dose may be reduced to 40 mg or 20 mg according to the Investigator's clinical judgement as to whether this procedure will decrease the incidence or severity of AEs associated with cabozantinib (see Section 6.2.2). A detailed description of administration procedures is given in Section 6.2.1.

Subjects will receive study treatment until discontinuation due to reasons such as disease progression, unacceptable toxicity, withdrawal of consent (see Section 5.2.2) or until the end of the study (18 months after the last subject included in the study started cabozantinib treatment, Section 5.6).

Cabozantinib will be packaged at Dreux, France. A sufficient quantity of cabozantinib and an acknowledgement of receipt form will be supplied to each investigational site.

The Sponsor's representative will receive a Certificate of Analysis for each batch of cabozantinib used in the study and Material Data Safety Sheets.

The core label texts for all packaging units will be translated and/or adjusted to be in compliance with the applicable local regulatory requirements (e.g. Good Manufacturing Practice guidelines (Volume 4 Annex 13), national laws in force and in accordance with local languages.

The Investigator or designee will only dispense cabozantinib to subjects included in this study. Each subject will only be given the study treatment if they carry his/her registration number. Dispensations for each subject will be documented in the electronic case report form (eCRF).

At each cabozantinib dispensation (at scheduled and unscheduled visits, if applicable), treatment number(s) will be assigned by the Interactive Web Response System (IWRS), according to the appropriate dose (dose adaptation). The IWRS will also manage all logistical aspects of the study treatment (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the Investigator, investigational site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available (see supporting information in the Investigational Site File). If a subject discontinues the study before any intake of study treatment, his/her assigned treatment number(s) will not be reused.

In addition to the information provided in the IWRS, drug accountability records documenting that each subject received the allocated study treatment will be maintained by the Investigator or delegate.

3.6 Study Duration

The study is planned to start in the first quarter of 2020 and will start when the first subject provides a signed informed consent form. The inclusion period will stop either when the number of 74 enrolled subjects in Cohort A is reached or at the latest on 30 June 2022, whichever is reached first. For each subject, the study will start from the ICF signature and may last until the end of the study (18 months after the last subject included in the study received first cabozantinib dose). The period between the start and end of study will include both treatment and post-treatment follow-up periods, regardless of the duration of treatment (e.g. if a subject stops study treatment after 2 months, he/she will be followed-up for the remaining time up to the end of the study).

It is estimated that subjects will receive study treatment for an average of 8 months. However, there is no minimum treatment duration for each subject. Study treatment may be discontinued due to several reasons, such as disease progression (i.e. a subject can discontinue study treatment after 2 weeks if disease has progressed), unacceptable toxicity or withdrawal of consent.

The study will end 18 months after the last subject included in the study received the first cabozantinib dose. However, subjects who continue to benefit from the treatment after the end of the study will be supplied with Cabometyx® free of charge from Ipsen, according to local regulations and as long as there is safety and efficacy evidence to support the continuation of this treatment. Such subjects will be followed until at least 30 days after their last study treatment with cabozantinib administration. Information about cabozantinib administration and

any related SAEs will be collected during the period when Cabometyx® is supplied free of charge from Ipsen.

3.7 Source Data Recorded on The Electronic Case Report Form (eCRF)

Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. As required by GCP guidelines, the monitor assigned by the Sponsor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF as defined in the monitoring plan.

Source documents must, as a minimum, state that the subject is included in the clinical study, the date when the informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates with subject status, cabozantinib administration, any AEs and associated concomitant medication.

As required by Section 6.4.9 of the International Conference on Harmonisation (ICH-E6), if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the Investigator and the Sponsor.

The definitions of source data and source documents are given below:

- **Source data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to his/her medical records being viewed by the Sponsor's authorised personnel and by local and possibly foreign, competent authorities. This information is included in the informed consent.

3.8 Independent Radiology Committee

An IRC will be established to evaluate tumour scans and prior radiation history data of study subjects in a central, blinded and independent fashion. The IRC will be comprised of board-certified radiologists who will evaluate prior radiation history to validate the identification of target lesions, as well as determine radiographic response and progression after screening. All IRC assessments will be performed by batch (any additional details will be found in the IRC charter).

Additional imaging results may be requested by the Sponsor for IRC review.

Details regarding IRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRC Charter.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

This study will include subjects with locally advanced or metastatic RCC with a clear-cell component that have progressed after 1st line CPI alone or CPI combined with VEGF-targeted therapy. The eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that all subjects fully meet all inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

All subjects must fulfil all the following criteria to be included in the study:

(1) Subjects must provide a signed informed consent prior to any study-related procedures;

(2) Male or female subjects must be aged ≥18 years on the day the informed consent is signed;

(3) Subjects must have histologically confirmed unresectable, locally advanced (defined as disease not eligible for curative surgery or radiation therapy) or metastatic RCC with a clear-cell carcinoma component;

(4) Subjects must have radiographic disease progression, according to Investigator's judgement following 1st line treatment with CPI (ipilimumab plus nivolumab) (Cohort A) or CPI in combination with VEGF-targeted therapy (Cohort B);

(5) Subjects present ≥1 target lesion according to RECIST 1.1 per Investigator;

(6) Subjects should have ECOG status 0-1;

(7) Subjects with treated brain metastases are eligible if metastases have been shown to be stable as per Investigator's judgement;

(8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 15 days before baseline:

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

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

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

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

  (e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L).

  (f) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation

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

(9) Subject must have recovered to baseline or ≤ Grade 1 per CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy as determined by the Investigator;

(10) Subject must have completed a steroid taper if he/she experienced an immune-related adverse event associated with previous CPI treatment;

(11) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) must provide a negative pregnancy test within 7 days prior to the start of study treatment. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required;

(12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) and their partners must agree to highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix 3) during the course of the study and for 120 days after the last dose of study treatment;

(13) All male participants must agree to refrain from donating sperm and unprotected sexual intercourse with female partners during the study and for 120 days after the last dose of study treatment;

(14) Subjects must be willing and able to comply with study requirements, remain at the investigational site for the required duration of each study visit and be willing to return to the investigational site for the follow up evaluation, as specified in the protocol.

(15) Subjects must be covered by social security or be the beneficiary of such a system (only applicable for French subjects).

4.2 Exclusion Criteria

Subjects will not be included in the study if the subject:

(1) Inability to swallow tablets;

(2) Was treated with any other investigational medicinal product (IMP) during a clinical study within the last 30 days before baseline;

(3) Was previously treated with cabozantinib;

(4) Has a contraindication to Magnetic Resonance Imaging (MRI) or contrast medium used for Contrast Tomography (CT)-scan;

(5) Presents untreated brain or leptomeningeal metastases, or current clinical or radiographic progression of known brain metastases;

(6) Has a diagnosis of a serious cardiovascular disorder:

  (a) Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, or serious cardiac arrhythmias;

  (b) Uncontrolled hypertension, defined as sustained blood pressure (BP) (>140 mm Hg systolic or >90 mm Hg diastolic pressure) despite optimal antihypertensive treatment;

  (c) Stroke (including transient ischaemic attack (TIA)), myocardial infarction (MI) or other ischaemic event, or thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism) within 6 months before screening;

  (d) History of risk factors for torsades de pointes (e.g., long QT syndrome);

(7) Is receiving concomitant anticoagulation with coumarin agents (e.g. warfarin), direct thrombin inhibitor dabigatran, direct Factor Xa inhibitors betrixaban or platelet inhibitors (e.g. clopidogrel);

  Note: The following are allowed anticoagulants: prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose of low molecular weight heparin (LMWH). Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in patients without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before baseline without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.

(8) Has a gastrointestinal (GI) disorder including those associated with a high risk of perforation or fistula formation:
   (a) Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction;
   (b) Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before screening;

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

(9) Presents a corrected QT (QTc) interval calculated by the Fridericia formula (QTcF) > 500 msec within 1 month prior to baseline;

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility

(10) Presents clinically significant haematuria, hematemesis, or haemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g. pulmonary haemorrhage) within 3 months before screening;

(11) Presents cavitating pulmonary lesion(s) or known endobronchial disease manifestation;

(12) Presents lesions invading major pulmonary blood vessels;

(13) Has been diagnosed with other clinically significant disorders such as:
   (a) Serious nonhealing wound/ulcer/bone fracture;
   (b) Malabsorption syndrome;
   (c) Uncompensated/symptomatic hypothyroidism (subject with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study);
   (d) Moderate to severe hepatic impairment (Child-Pugh B or C);
   (e) Requirement for haemodialysis or peritoneal dialysis;
   (f) History of solid organ transplantation;

(14) Has a predicted life expectancy of less than 3 months;

(15) Has had prior surgery within 4 weeks prior to baseline. Note: If the subject has undergone major surgery, complete wound healing must have occurred 1 month prior to baseline;

(16) Has had palliative radiation therapy for bone within 2 weeks or for radiation fields including viscera within 4 weeks prior to baseline. Note: Resolution/healing of side effects must be complete prior to baseline;

(17) Has a history of another active malignancy within 3 years from screening except for locally curable cancers that have been apparently cured, such as low-grade thyroid carcinoma, prostate cancer not requiring treatment (Gleason Grade ≤6), basal or squamous cell skin cancer, superficial bladder cancer, in situ melanoma, in situ prostate, cervix or breast carcinoma or other treated malignancies with <5% chance of relapse according to the Investigator;

(18) Has a history of allergy to study treatment components or agents with a similar chemical structure or any excipient used in the formulation as listed in the SmPC document;

(19) Has rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded;

(20) Has a serious medical or psychiatric condition that renders the subject unable to understand the nature, scope and possible consequences of the study, and/or presents an uncooperative attitude;

(21) Is pregnant or breastfeeding. A β-human chorionic gonadotrophin (HCG) serum pregnancy test will be performed up to 7 days prior to baseline for all female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile);

(22) Is likely to require treatment during the study with drugs that are not permitted by the study protocol;

(23) Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety.

4.3 Stopping Rules, Discontinuation and Withdrawal Criteria and Procedures

4.3.1 Treatment Discontinuation and Study Withdrawal

In accordance with the Declaration of Helsinki (and with the applicable country's acceptance of this declaration), each subject may discontinue study treatment or withdraw their consent to participate in the study at any time for any reason without prejudice.

The Investigator also has the right to withdraw a subject from the study for any reason concerning the subject's health or wellbeing or in case of lack of cooperation.

Subjects who discontinue the study treatment or withdraw from study will not be replaced.

If a subject fails to return for protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at least a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the investigational site.

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the study drug administration may be temporarily discontinued depending on the subject clinical status. In some cases, the Investigator may request a participant be retested before the study drug administration is resumed.

4.3.1.1 Treatment Discontinuation

If a subject decides to discontinue study treatment or the Investigator decides to discontinue a subject from the study treatment, this subject will be invited to undergo the assessments of the End of Study Treatment/Early Withdrawal visit (see Section 5.2.2) and to attend the Post-treatment Follow-up visits to assess safety, subsequent anti-cancer therapies and survival status assessments, unless the subject withdraws consent to remain in the study and refuses to have his/her data collected. If study treatment discontinuation occurs, the reason and date of this decision must be recorded in the eCRF.

If the reason for study treatment discontinuation is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to a local health care professional, or until the determination of a cause unrelated to cabozantinib or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. If a subject is pregnant, please see Section 8.1.5.

Reasons for **study treatment discontinuation** include:

- The subject no longer experiences clinical benefit as determined by the Investigator;
- The subject requests to discontinue study treatment;
- Unacceptable toxicity that the Investigator feels may be due to study treatment;
- Study treatment needs to be interrupted for more than 6 weeks due to treatment-related AEs;
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilised) to use medically accepted methods of contraception;
- Request by the Sponsor;
- Subject needs treatment with another investigational agent or investigational medical device (not defined in the protocol);
- Pregnancy.

4.3.1.2 Study Withdrawal

If a subject decides to withdraw consent, no further study procedures or assessments will be performed or study data collected for this subject. However, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.2.2) and the date and explanation as to why the subject is withdrawing or being withdrawn from the study must be recorded on the eCRF.

In case of loss to follow-up, public records such as government vital statistics or obituaries will be analysed to assess the subjects' survival status.

Reasons for **study withdrawal** include:

- Withdrawal of consent by the subject;
- Request by the Sponsor or the Investigator;
- Loss to follow-up (confirmed with two documented phone calls and a certified letter (delivery receipt request) without answer;
- Subject's significant noncompliance with protocol schedule (or other protocol violation) in the opinion of the Investigator or the Sponsor;
- Subject's death.

4.3.2 Early Study Termination

There are no formal rules for the early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1) as they are reported by the investigational site to identify safety concerns. A specific investigational site or a given cohort can be discontinued and the entire study may be terminated at any time if the Sponsor considers it necessary for any reason. In such case, only information regarding AEs, other cancer treatments and survival status will be collected for subjects who are still in the study at the time of study termination. Some possible reasons for the closure of an investigational site may include:

- failure of the Investigator staff to comply with the protocol or with the GCP guidelines;
- safety concerns;
- inadequate subject recruitment.

In case of premature discontinuation of an investigational site or the complete study, depending on the reason(s) for discontinuation, the Sponsor will notify the Investigator(s) affected in writing as to whether the ongoing subjects should continue the remaining cabozantinib dose administration(s).

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 2.

Table 2 Study Procedures and Assessments

Assessment	Pre-treatment Period	Treatment Period						Post-treatment Follow-up Period [d]
	Screening	Baseline [a]	Week 2	Week 4	Week 8	Every 4 weeks	End of Study Treatment Visit [b] or Early Study Withdrawal Visit [c]	Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 to Visit X	30 days after the last dose of treatment	Every 12 weeks
	Before first cabozantinib intake	Day 1	Day 15 (±2 Days)	Day 29 (±2 Days)	Day 57 (±2 Days)	Day 85 to Day X (±5 Days)	(+15 Days)	(±15 Days)
Informed consent form	X [e]							
Eligibility Criteria	X	X [f]						
Demography	X							
Medical history	X							
RCC history	X							
Prior surgery/radiotherapy/ chemotherapy/medications related to RCC	X							
Smoking habits/status	X							
Physical examination	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
Weight	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
Vital signs	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
ECOG performance status	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
12-lead ECG	≤15 Days prior to baseline	X (prior to first dose) [f]		X		Every 12 weeks	X	

Assessment	Pre-treatment Period	Treatment Period						Post-treatment Follow-up Period [d]
	Screening	**Baseline [a]**	**Week 2**	**Week 4**	**Week 8**	**Every 4 weeks**	**End of Study Treatment Visit [b] or Early Study Withdrawal Visit [c]**	**Follow-Up**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6 to Visit X**	**30 days after the last dose of treatment**	**Every 12 weeks**
	Before first cabozantinib intake	**Day 1**	**Day 15 (±2 Days)**	**Day 29 (±2 Days)**	**Day 57 (±2 Days)**	**Day 85 to Day X (±5 Days)**	**(+15 Days)**	**(±15 Days)**
Haematology and blood biochemistry	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
Coagulation assessments	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks		
Urinalysis, microscopic urine examination and urine chemistry (including UPCR) [g]	≤15 Days prior to baseline	X (prior to first dose) [f]	X	X	X	Every 4 weeks	X	
Pregnancy test (female subjects only, if applicable)	≤7 days prior to baseline	X (prior to first dose) [f]	Urinary and/or pregnancy blood tests are mandatory at every visit				X	
Thyroid function test (FT4, TSH)	≤15 days prior to baseline	X (prior to first dose) [f]	Every 4 weeks				X	
Chest/Abdomen/Pelvis (C/A/P) CT/MRI	≤28 days prior to baseline	X [f]	Every 12 weeks (±10 days) while on protocol treatment beginning at Week 12 (i.e. Week 12, Week 24, Week 36, etc) until the end of study and additionally if clinically indicated					X [h]
Brain CT/MRI and Bone scintigraphy scan (only if indicative of metastases)	≤28 days prior to baseline	Only if indicative of brain and/or bone metastases at screening or if signs or symptoms suggestive of metastases develop						X [h] (only if indicative of metastases)
Cabozantinib intake [i]		All subjects will be treated with oral cabozantinib 60 mg once daily (q.d.). In case of treatment-emergent toxicity, the Investigator may decide to reduce the dose to 40 mg or 20 mg						
Dispense/return of oral study drug and compliance accounting		X		X	X	X	X	
AEs [j, k]	X	X	X	X	X	X	X	X [k]

Assessment	Pre-treatment Period	Treatment Period						Post-treatment Follow-up Period [d]
	Screening	Baseline [a]	Week 2	Week 4	Week 8	Every 4 weeks	End of Study Treatment Visit [b] or Early Study Withdrawal Visit [c]	Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 to Visit X	30 days after the last dose of treatment	Every 12 weeks
	Before first cabozantinib intake	Day 1	Day 15 (±2 Days)	Day 29 (±2 Days)	Day 57 (±2 Days)	Day 85 to Day X (±5 Days)	(+15 Days)	(±15 Days)
Prior and concomitant therapies [l]	≤30 Days prior to baseline	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	
Other cancer treatment								X
Survival status								X
HRQOL (FKSI-DRS) [m]		X (prior to first dose)	Every 12 weeks while on protocol treatment beginning at Week 12 (i.e. Week 12, Week 24, Week 36, etc) until the End of Study Treatment visit or Early Study Withdrawal visit.					

Abbreviations: AEs = Adverse events; CT = Contrast tomography; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic case report form; FKSI-DRS = Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease-Related Symptoms; FT4 = Free thyroxine 4; HRQOL = Health-related quality of life; MRI = Magnetic Resonance Imaging; RCC = Renal cell carcinoma; SAE = Serious adverse event; TSH = Thyroid-stimulating hormone

[a] Screening and baseline visits can take place the same day as long as all eligibility criteria/parameters are available and checked prior to the first dose of cabozantinib.

[b] This visit will be held for subjects who have discontinued study treatment whatever the reason (e.g. disease progression or unacceptable toxicity).

[c] All included subjects who prematurely stopped the study due to withdrawal of consent during study treatment period will attend the Early Study Withdrawal visit.

[d] During the Post-treatment Follow-up period, subjects will be contacted every 12 weeks (±15 days) starting after the End of Study Treatment visit to assess survival status and document receipt of subsequent anti-cancer therapy. These assessments will be continued until the subject expires or the end of the study (18 months after the last subject included in the study received the first cabozantinib dose), whichever occurs first.

[e] Informed consent must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be used as Screening evaluations if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC) policies of the investigational site.

[f] These assessments are intended to confirm suitability for treatment after the Screening visit. There is no need to perform them again at baseline, unless the subject's clinical status has changed (e.g. onset of new symptoms indicative of clinical deterioration). If these assessments are performed at screening and baseline visits, results must be available to be reviewed by the Investigator prior to first dose.

[g] Microscopic urine examination to be performed at baseline and after that only at the discretion of the Investigator (results are not to be collected in the eCRF except in case of clinically abnormal findings, which are to be reported as an AE). Urine chemistry (24-hour urine protein or UPCR) may be performed at any scheduled or unscheduled visit at the discretion of the Investigator and based on results of routine urinalysis or as clinically indicated.

[h] Follow-up for radiographic progression, tumour assessment should be performed until radiographic progression confirmed by the Investigator only for subjects who have discontinued cabozantinib treatment before radiographic disease progression and who have not withdrawn consent.

[I] Cabozantinib will be self-administered at home until study treatment is discontinued.

[j] Information on new or worsening AEs will be collected from date of the signed informed consent until the end of study treatment, at each study visit, by telephone call or by spontaneous report by the subject. Any AEs and SAEs that are ongoing 30 days after the date of the last cabozantinib dose are to be followed until resolution or until the Investigator considers the event is stable or irreversible (see Section 8.1.3).

[k] During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator.

[l] Information on prior and concomitant medication will be collected up to 30 days before baseline until 30 days after the date of the last cabozantinib dose.

[m] *The FACIT and all related works are owned and copyrighted by, and the intellectual property of David Cella, Ph.D. Permission for use of the FKSI-DRS questionnaire is obtained by contacting Dr. Cella at information@facit.org.*

Based on an average treatment duration of 8 months and 12 visits, the total volume of blood drawn for all evaluations throughout this study will be approximately 144 mL for each subject (12 mL of blood per visit, this volume may depend on the laboratory used, treatment duration and number of visits).

5.2 Study Visits

5.2.1 Procedures Before Study Treatment

All efficacy and safety assessments to be performed during the pre-treatment period are indicated in Table 2 (please see footnotes in the table for details) and described in Section 7 and Section 8, respectively.

A signed and dated informed consent form may be obtained more than 15 days prior screening but must be provided before any study-specific procedures are performed. However, evaluations performed as part of routine care prior to the date of the signed informed consent form can be used as Screening evaluations if permitted by the IRB/Ethics Committee (EC) policies of the investigational site. Subjects will acknowledge and agree to the possible use of these data in the study by signing the informed consent form.

All screened subjects will be allocated a subject number so that they can be identifiable throughout the study. The Investigator will maintain a list of screened subjects (i.e. who signed the informed consent form), subject numbers and names to ensure that all records may be found at a later date if required. In case a subject does not receive cabozantinib after the Screening visit, the primary reason will be recorded.

5.2.2 Procedures During Study Treatment

All efficacy and safety assessments to be performed throughout the treatment period are indicated in Table 2 (please see footnotes in the table for details) and described in Section 7 and Section 8, respectively.

Clinical status will be evaluated by the Investigator at each visit to the investigational site to confirm that the subject is suitable to continue study treatment and to make timely decisions regarding the interruption or restart of cabozantinib dosing. Tumour assessments from imaging visits will be reviewed by central review and by the local Investigator.

Subjects may discontinue study treatment any time during the study due to reasons such as disease progression, intolerance to cabozantinib, need for subsequent systemic investigational drug therapy or other reasons for study treatment discontinuation listed in this protocol (Section 4.3.1). This implies that the duration of cabozantinib treatment may be different for each subject included (see Section 3.6 for details), but the study is planned to follow-up subjects up to 18 months after the last subject included in the study received the first cabozantinib dose.

Subjects with radiographic progression per RECIST 1.1 evaluated by the Investigator may continue study treatment if the Investigator believes that there still is clinical benefit and that it outweighs potential risks. In this case, study treatment can be continued up to the end of the study (Section 5.6), unless the subject or the Investigator decides to discontinue study treatment due to unacceptable toxicity or needs subsequent systemic anti-cancer treatment.

Subjects who discontinue study treatment with cabozantinib (e.g. due to radiographic progression or unacceptable toxicity) will be invited to attend the End of Study Treatment visit (Section 5.2.2.1).

Subjects who discontinue study treatment due to withdrawal of consent will be invited to attend the Early Study Withdrawal visit (Section 5.2.2.2).

5.2.2.1 End of Study Treatment Visit

The End of Study Treatment visit will be carried out 30 to 45 days after the last cabozantinib dose (all necessary assessments to be performed at this visit are indicated in Table 2). After this date, the subject will enter the Post-treatment Follow-up period (Section 5.2.3.1).

The Investigator will ask subjects to return any remaining cabozantinib tablets and check their compliance to study protocol. Efficacy evaluations should not be performed for subjects who do not attend the End of Study Treatment visit within 30 to 45 days after their last dose of cabozantinib. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the Investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.

5.2.2.2 Early Study Withdrawal Visit

All included subjects who prematurely stop the study due to withdrawal of consent will be invited to attend the Early Study Withdrawal visit. Please see the footnotes in Table 2 for details.

5.2.3 Procedures After Study Treatment

Subjects who discontinue study treatment with cabozantinib will be invited to enter the Post-treatment Follow-up period. All necessary assessments performed after treatment are indicated in Table 2.

For subjects who have discontinued cabozantinib treatment before radiographic disease progression and who have not withdrawn consent, tumour assessment should be performed until radiographic progression confirmed by the Investigator.

5.2.3.1 Post-treatment Follow-up Period

During the Post-treatment Follow-up period, subjects will be contacted every 12 weeks (±15 days), starting after the End of Study Treatment visit, to assess survival status and record the receipt of subsequent anti-cancer therapy. During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator. These assessments will be continued until the subject expires or until the end of the study (18 months after the last subject included in the study received the first cabozantinib dose, Section 5.6), whichever occurs first. Every effort will be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn. All AEs will be documented and/or followed as described in Section 8.1.3 and Section 8.1.4.

At each contact, the Investigator (or designee) will determine if the subject has died, and if so, record the date and cause of death as best as can be determined. All efforts must be undertaken by the investigational sites to determine the date of death (or the date the subject was last known to be alive at the time of a data cut-off). This may include, but not necessarily be limited to, telephone calls, registered letters, and reviews of local obituaries and government death records. If a subject is lost to follow-up, multiple attempts to contact study subject or designee must be documented in the subject records.

Every effort will be made to perform protocol-specific evaluations unless consent to participate in the study is withdrawn and the subject no longer allows data collection.

5.3 Unscheduled Visits or Assessments

If the Investigator determines that a subject should be monitored more frequently or with additional laboratory parameter assessments than indicated by the protocol-defined visit

schedule, unscheduled visits or assessments are permitted. All laboratory assessments will be done by the local laboratory. If study treatment is interrupted, during the intervening time between the last dose and the time drug is restarted, the investigational site should perform unscheduled visits to monitor subject safety as needed and appropriateness for re-treatment with study treatment.

5.4 Laboratory Assessments

The complete list of laboratory assessments to be performed in this study are indicated in Section 8.2.

Based on an average treatment duration of 8 months and 12 visits, the total volume of blood drawn for all evaluations throughout this study will be approximately 144 mL for each subject (12 ml at each visit; this volume may depend on the laboratory used, treatment duration and number of visits).

All samples will be analysed locally.

5.5 Imaging

There will be no additional exposure to radiation. The imaging planned in this protocol is comparable to routine practice.

5.6 End of the Study

The study will end 18 months after the last subject included in the study received the first cabozantinib dose.

Subjects who continue to benefit from the treatment after the end of the study will be supplied with Cabometyx® free of charge from Ipsen, according to local regulations and as long as there is safety and efficacy evidence to support the continuation of this treatment. Such subjects will be followed until at least 30 days after their last study drug with cabozantinib administration. Information about cabozantinib administration and any related SAEs will be collected during the period when Cabometyx® is supplied free of charge from Ipsen.

6 TREATMENT OF SUBJECTS

6.1 Investigational Medicinal Product Preparation, Storage, Security and Accountability

6.1.1 Investigational Medicinal Product Storage and Security

The Investigator or an approved representative (e.g. pharmacist) will ensure that all bottles of cabozantinib tablets and any other study-related material is stored in a secured area, in accordance with applicable regulatory requirements. This medicinal product does not require any specific storage conditions.

6.1.2 Investigational Medicinal Product Preparation

The Investigator or an approved representative (e.g. pharmacist) will ensure that all bottles of cabozantinib tablets are dispensed by qualified staff members.

6.1.3 Investigational Medicinal Product Accountability

Cabozantinib tablets and any other study-related material is to be accounted for on the IMP accountability log provided by the Sponsor. It is essential that all unused supplies are retained for verification (by the Sponsor or Sponsor's representative). The Investigator should ensure adequate records are maintained in the IMP accountability log.

6.2 Study Drugs Administered

At the Screening visit, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be included in one of the two following cohorts based on their previous therapy and both cohorts will receive the same open-label treatment with cabozantinib (60 mg q.d.):

- **Cohort A: 74 subjects**

Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.

- **Cohort B: approximately 40 subjects**

Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.

6.2.1 Administration of Cabozantinib

Cabozantinib tablets are meant to be taken orally only and cannot be crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity. This product cannot be taken with food, thus subjects must not eat 2 hours before and 1 hour after taking cabozantinib.

The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2). Subjects will take cabozantinib tablets q.d. at home, at the same time each day, preferably at bedtime. Any unused study treatment must be returned to the investigational site for drug accountability and disposal. If a dose is missed, the missed dose should not be taken less than 12 hours before the next one.

The recommended dose is 60 mg q.d. as indicated in all approvals of cabozantinib (Cabometyx™). A dose of 60 mg should be maintained in the absence of treatment-emergent toxicity; however, management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of cabozantinib therapy (see Table 4). When dose reduction is necessary, it is recommended to reduce to 40 mg q.d. and then to 20 mg q.d. Dose interruptions are recommended for management of CTCAE Grade 3 or greater toxicities or

intolerable Grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (see Section 6.2.2).

The Sponsor will provide each Investigator with adequate supplies of cabozantinib bottles (30 tablets each), which will be supplied as 60 mg, 40 mg and 20 mg yellow film-coated tablets. The 60 mg tablets are oval, the 40 mg tablets are triangle shaped and the 20 mg tablets are round.

Exceptionally, in case there is a stock shortage of 60 mg tablets, the Sponsor will dispense a mix of bottles of cabozantinib in lower dose (e.g. 1 bottle of 20 mg + 1 bottle of 40 mg instead of 1 bottle of 60 mg).

6.2.1.1 First Administration of Cabozantinib (baseline)

The required study assessments and blood collections should be done prior to any study treatment administration. The first intake of cabozantinib will be self-administered at home. On the first day of study treatment (defined as baseline), the subject should be fasted (water is allowed) for at least 2 hours before receiving cabozantinib. Upon completion of the 2-hour fasting, the subject should receive the 60 mg oral dose of cabozantinib with a full glass of water (at least 8 oz 240 mL) and then continue to fast for 1 hour.

6.2.1.2 Subsequent Dose Administration of Cabozantinib

Subjects are to fast (with the exception of water) for at least 2 hours before taking their dose. After the 2-hour fast, subjects are to take cabozantinib with a full glass of water (minimum of 240 mL) with no food intake for one more hour post-dose. If the subject's schedule requires taking cabozantinib during the day, the subject is to be instructed to follow the same fasting recommendations.

Subjects should be instructed to not make up for vomited doses and to maintain the planned dosing schedule. Subjects should not make up for missed doses if more than 12 hours elapse 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 missed one.

Subjects will receive cabozantinib as long as they continue to experience clinical benefit in the opinion of the Investigator and up to a maximum of 18 months after the last subject is included in the study or until unacceptable toxicity, need for subsequent systemic anti-cancer treatment or any other reasons for study treatment discontinuation listed in this protocol (Section 4.3).

Section 6.2.2 provides the instructions for cabozantinib dose modification, interruption, or discontinuation due to AEs.

6.2.2 Cabozantinib Dose Modifications, Interruptions and Discontinuation

Subjects will be monitored for AEs from the time of signing informed consent until 30 days after the date of the last dose of cabozantinib. Any SAE that the Investigator believes to be related to cabozantinib or study procedures can be reported at any time after the last dose with no time limitation during the follow-up period. Subjects will be instructed to notify their physician immediately for any occurring AE and unscheduled safety visits are allowed at any time. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. The severity of all AEs will be graded by the Investigator according to the CTCAE version 5.0.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruptions):

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity considered. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity;
- The assigned dose for cabozantinib is 60 mg/day. Two reductions in dose levels of cabozantinib are permitted but these reductions must be incremental (see Table 3);
- Dose modification criteria for cabozantinib are shown in Table 4. Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Doses may be modified at any time during the study;
- Dose modifications or interruptions may also occur in the setting of lower grade toxicity than that defined in Table 4, if the Investigator feels it is in the interest of a subject's safety and will optimise drug tolerability;
- Interruption of cabozantinib treatment due to AEs may occur at any time per Investigator discretion. If study treatment is interrupted due to AEs for more than 6 weeks, cabozantinib should be discontinued;
- Dose interruptions for reason(s) other than AEs (e.g. surgical procedures) can be longer than 6 weeks but require Sponsor approval. The acceptable length of interruption will depend on agreement between Investigator and the Sponsor.

Warnings, precautions and guidelines for the management of AEs (e.g. GI disorders, hepatobiliary disorders, blood system disorders, constitutional disorders, skin disorders, hypertension, thromboembolic events, proteinuria, QTc prolongation, hypophosphataemia, thyroid function disorders, haemorrhagic events, GI perforation/fistula and non-GI fistula formation and osteonecrosis of the jaw (ONJ)) are provided in Appendix 4.

Table 3 Dose Reductions of Cabozantinib

Assigned dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg cabozantinib orally q.d.	40 mg cabozantinib orally q.d.	20 mg cabozantinib orally q.d.

Abbreviations: q.d. = Once daily

Cabozantinib should be discontinued if a dose of 20 mg q.d. (minimum dose) is not tolerated

Table 4 Dose Modifications of Cabozantinib for Treatment-related AEs

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are intolerable and cannot be adequately managed	At the discretion of the Investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib must be interrupted until the adverse reaction resolves to Grade ≤1. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator; • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Abbreviations: AE = Adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 6.2.4. For reinstitution of cabozantinib after dose interruption, please see Section 6.2.3.

[a] Dose adjustment is only needed if toxicity is considered to be related or has an unclear relationship to cabozantinib treatment.

6.2.3 Cabozantinib Dose Reinstitution and Reescalation

If toxicity decreases to CTCAE version 5.0 Grade ≤1 or to baseline values (or lower) and is considered to be unrelated to study treatment, then subjects may restart cabozantinib with no dose change.

If toxicity decreases to CTCAE version 5.0 Grade ≤1 or to baseline values (or lower) and is considered to be possibly related to study treatment, then subjects may restart cabozantinib at a reduced dose (see Table 3 for dose reduction schedule).

Subjects receiving a dose of 20 mg q.d. may be restarted at the same dose if deemed safe at the discretion of the Investigator. Subjects unable to tolerate a dose of 20 mg q.d. should discontinue study treatment.

Re-escalation to the previous dose (but not higher than 60 mg/day) may be allowed at the discretion of the Investigator but no sooner than 2 weeks beyond resolution of the AEs that led to dose reduction. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (e.g. central nervous system (CNS), cardiac, hepatic, renal).

6.2.4 Cabozantinib Warnings, Precautions and Guidelines for Management of Potential Adverse Events

The side effect profile of cabozantinib includes, in descending order of frequency, diarrhoea, fatigue, decreased appetite, nausea, palmar-plantar erythrodysaesthesia syndrome (PPES), vomiting, weight decreased, hypertension, constipation, dysphonia and asthenia (please refer to the Investigator's Brochure for additional details).

Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g. deep vein thrombosis (DVT), pulmonary embolism, TIA and MI), severe haemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

All AEs associated with laboratory abnormalities experienced by ≥5% of subjects treated with cabozantinib in descending order of frequency were anaemia, AST increased, ALT increased, hypothyroidism, hypokalaemia, hypomagnesaemia, thrombocytopenia, hypocalcaemia, hypophosphataemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, alkaline phosphatase (ALP) increased, hyponatraemia, and leukopenia.

All AEs should be managed with supportive care at the earliest signs of toxicity and dose reductions or study treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. A more detailed approach for management of potential AEs is provided in Appendix 4.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely for all AEs. The plasma effective half-life of cabozantinib is approximately 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 15-21-day 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. The terminal half-life of 120 hours determined in single dose studies is a predictor of drug washout following the last dose which is relevant when interrupting study treatment for AEs management.

For general information regarding study medication error refer to Section 8.1.6.

6.3 Prior and Concomitant Medication/Therapy

Any prior ongoing therapy at baseline and concomitant medications (received during cabozantinib administration) will be indicated on the eCRF, including dose and generic name or trade name.

6.3.1 Allowed Therapies

The following concomitant medications are permitted during this study, but they must be closely monitored and every effort should be made to keep their dose and dose regimen constant throughout the course of the study:

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated;
- Granulocyte colony-stimulating factors (G-CSF) or granulocyte macrophage (GM)-CSF are allowed if used per clinical guidelines (e.g. American Society of Clinical Oncology (ASCO) or ESMO guidelines);

- Drugs used to control bone loss (e.g. bisphosphonates and denosumab) are allowed if started prior to screening activities but may not be initiated or exchanged during the course of the study and require sponsor approval;
- Transfusions, hormone replacement, and short-term higher doses of corticosteroids should be utilised as indicated by standard clinical practice;
- Individualised anticoagulation therapy is allowed if it can be provided safely and effectively under the following circumstances:
  - Prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose of LMWH are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion;
  - Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed in patients without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before baseline without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.
  - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g. due to kidney dysfunction);
  - For restrictions on oral anticoagulants see Section 6.3.2.

Potential drug interactions with cabozantinib are summarised in Section 6.3.3.

6.3.2 Prohibited or Restricted Therapies

The following therapies are prohibited while the subject is on cabozantinib treatment:

- Any investigational agent or investigational medical device;
- Any drug or herbal product used specifically for the treatment of RCC;
- Any coumarin agents (e.g. warfarin), direct thrombin inhibitor dabigatran, direct Factor Xa inhibitors betrixaban or platelet inhibitors (e.g. clopidogrel);
- Any other systemic anti-cancer treatment (e.g. chemotherapy, immunotherapy, radionuclides) and local therapy such as surgery, ablation, or embolisation.

The following therapies should be avoided while the subject is on cabozantinib treatment:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study except if it is clinically unavoidable. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;
- Erythropoietic stimulating agents (e.g. epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumour recurrence/progression associated with erythropoietin (26);
- Chronic co-administration of cabozantinib with strong inducers of the cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4) family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;

- Caution must be used when discontinuing study treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib;
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 6.3.3.

6.3.3 Potential Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) showed that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the curve (AUC) of co-administered rosiglitazone, a cytochrome P450 Family 2 Subfamily C Member 8 (CYP2C8) substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other cytochrome P450 (CYP450) isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e. cytochrome P450 Family 2 Subfamily C Member 9 (CYP2C9), cytochrome P450 Family 2 Subfamily C Member 19 (CYP2C19), cytochrome P450 Family 2 Subfamily D Member 6 (CYP2D6), cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2), and CYP3A4). *In vitro* data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of Cytochrome P450 Family 1 Subfamily A Member 1(CYP1A1) at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, cytochrome P450 Family 2 Subfamily B Member 6 (CYP2B6), or CYP1A2 substrate), based on data from *in vitro* studies.

Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin,rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Protein Binding: Cabozantinib is highly bound (≥99.7%) to human plasma proteins (for details see the SmPC document (11), section 5.2). Therefore, highly protein-bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Multidrug resistance-associated protein 2 (MRP2) inhibitors: *In vitro* data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may lead to increased plasma concentration of cabozantinib.

Bile salt-sequestering agents: Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (for details see the SmPC document (11), section 5.2). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products: The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended (see Appendix 3).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. *In vitro* data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib. Additional details related to these overall conclusions can be found in the Investigator's Brochure.

Concomitant administration of proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma pharmacokinetics in healthy subjects. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

6.4 Lifestyle Restrictions/Recommendations

In addition to the restrictions already presented in the exclusion criteria (see Section 4.2), subjects will also be requested to avoid the following from 48 hours prior to baseline and until discharge from the study:

- Seville oranges (see Section 6.3.3);
- grapefruit (see Section 6.3.3).

A complete list of allowed and prohibited or restricted concomitant medication is provided in Section 6.3.

6.5 Procedures for Monitoring Subject Compliance

The Investigator will be responsible for monitoring subject compliance. Subjects may be withdrawn from the study at any time if the Investigator or Sponsor determines that the subject is not in compliance with the study protocol.

Administration compliance will be assessed at the investigational site using drug dispensing and return records, progress notes about dose reductions/holds and subject interview. These data will not be directly recorded in the eCRF; rather, the eCRF will capture intervals of constant dose and reasons for changes in dose level (e.g. a new record completed each time dose level changes, including periods where no dose was taken, and the reason for a dose level change).

Deviations below 80% of the scheduled amount of cabozantinib intake will be regarded as a major protocol deviation.

Where a subject is consistently noncompliant with cabozantinib intake they should be discontinued from study treatment/withdrawn from the study (see Section 4.3).

7 ASSESSMENT OF EFFICACY

For the timing of efficacy assessments in this study, please refer to the schedule in Table 2.

7.1 Primary Efficacy Endpoint and Evaluation

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review in cohort A.

7.2 Secondary Efficacy Endpoints and Evaluations

- Time to response (TTR) per RECIST 1.1 evaluated by independent central review;
- Duration of response (DOR) per RECIST 1.1 evaluated by independent central review;
- Disease control rate (DCR) per RECIST 1.1 by independent central review;
- Progression-free survival (PFS) per RECIST 1.1 by independent central review;
- Objective response rate (ORR) in cohort B per RECIST 1.1 evaluated by independent central review;
- Overall survival (OS);
- ORR TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review;
- Change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS).

The endpoints of ORR, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.

7.3 Methods and Timing of Assessing, Recording and Analysing Efficacy Data

Methods for assessing efficacy data are described below. The timing of efficacy assessments is provided in Table 2.

Procedures for recording efficacy data are discussed in Section 15.1 and the statistical methods to be used in the analysis of the efficacy endpoints are provided in Section 11.4.3.

7.3.1 Tumour Assessments

Radiographic tumour assessments will include contrast tomography (CT) and/or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis (C/A/P), brain, and bone scintigraphy scans. The same imaging modalities used at the Screening visit should be used for subsequent tumour assessments. For subjects who have discontinued cabozantinib treatment before radiographic disease progression and who have not withdrawn consent, tumour assessment should be performed until radiographic progression is confirmed by the Investigator. (see Table 2 for schedule of assessments).

Tumour assessments will determine the study endpoints of ORR, TTR, DOR, DCR, and PFS. The review of radiographic images will be conducted by a blinded, central IRC (Section 3.8) by batch using RECIST 1.1 (see IRC charter). All radiographic tumour assessments (both scheduled and unscheduled) must be sent to the IRC. Prior radiation history data will also be reviewed by the IRC for selection of target lesions.

Radiographic response and disease progression according to Investigator's assessment will also be assessed by the local Investigator using RECIST 1.1 (see Appendix 5) for subject management and treatment decisions.

All CT/MRI scans (C/A/P, brain) and scintigraphy scans (bone) are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the

imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at the Screening visit should be used for subsequent tumour assessments.

If any doubt or ambiguities exist about radiographic progression, the Investigator is encouraged to continue study therapy if the subject presents acceptable tolerance and repeat the radiographic studies at the next scheduled time, thus delaying the determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the Investigator does not warrant discontinuation of tumour assessments or study treatment (see Section 5.2.2).

7.3.2 Overall Survival

Overall survival will be assessed during the Post-treatment Follow-up period (Section 5.2.3.1) every 12 weeks (±15 days) until the end of the study (18 months after the last subject included in the study started cabozantinib treatment).

Information on subsequent non-protocol anti-cancer therapies will also be collected at the same time as this assessment.

7.3.3 Health-related Quality of Life

Health-related quality of life parameters will be assessed using the paper version of the FKSI-DRS tool during the investigational site visits at baseline and then every 12 weeks beginning at Week 12 until the End of Study Treatment visit or Early Study Withdrawal visit.

The FACIT and all related works are owned and copyrighted by, and the intellectual property of David Cella, Ph.D. Permission for use of the FKSI-DRS questionnaire was obtained by contacting Dr. Cella at information@facit.org. For the questionnaire, please refer to Appendix 6 (25).

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time the subject gives informed consent and throughout the study treatment (see Section 3.6 for a definition of study duration) and will be assessed by direct, nonleading questioning. The Sponsor will be responsible for the collection, assessment and reporting of safety data.

Further details for AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition refers to symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study treatment (as defined in Section 3.6 and Section 5.6).

Natural progression or deterioration of the locally advanced or metastatic RCC with a clear-cell component under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE.

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the clear-cell component RCC.

These signs and symptoms should only be reported as AEs/SAEs (depending on the Investigator's judgement) if they are:

- Judged by the Investigator to be unusually severe or accelerated clear-cell component RCC, or
- If the Investigator considers the deterioration of clear-cell component RCC signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to clear-cell component RCC, it should be reported as an AE/SAE as appropriate.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the National Cancer Institute (NCI)-CTCAE version 5.0 (effective in April 2018). In view of meta-analyses and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling (events qualify as SAEs),
- NCI-CTCAE Grade 5 corresponds to death related to AE (events qualify as SAEs).

Where:

- **Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- **Severe**: or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Life threatening**: urgent intervention indicated (also see Section 8.1.4).

8.1.2.2 Causality Classification

The relationship of an AE to IMP administration will be classified according to the following:

- **Related**: reports include good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports include good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.3 Assessment of Expectedness

The reference document for assessing expectedness of AEs/event in this study will be the current Investigator's Brochure.

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation);
- They require intervention or a diagnosis evaluation to assess the risk to the subject;
- They are considered as clinically significant by the Investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings judged by the Investigator as clinically significant (e.g. ECG changes, thyroid function disturbances) that result in a change in study drug dosage or administration schedule, or in the discontinuation of the study drug, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Recording and Follow-up of Adverse Events

All observed or self-reported AEs, regardless of suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses

with onset during the treatment phase of the study or exacerbations of pre-existing illnesses should be recorded according to the NCI terminology.

Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the Investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification of the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. treatment with cabozantinib or other illness). The Investigator is required to assess causality and record that assessment on the eCRF. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications.

Follow-up of the AE after the date of cabozantinib discontinuation is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

During the follow-up period, any SAE that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator.

Follow-up of SAEs/ Grade 3 and 4 AEs leading to study treatment discontinuation:

All SAEs that are ongoing at 30 days or later after the date of the last dose of study treatment and AEs assessed NCI-CTCAE Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the last dose of study treatment are to be followed until either:

- the AE has resolved;
- the AE has improved to Grade 2 or lower;
- the Investigator determines that the event has become stable or irreversible;

The status of all other AEs that are ongoing 30 days after the last dose will be documented as of the last study visit for the subject.

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below), regardless of suspected relationship to IMP, must be reported immediately (within 24 hours of the Investigator's knowledge of the event) using the email specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

An SAE is any AE that:

(1) Results in death;

(2) Is life-threatening, that is 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;

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see below);

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP;

(6) Is an important medical event that may not immediately result in death, be life-threatening or require hospitalisation but may be considered an SAE when, based upon appropriate medical judgement, it may jeopardise the subject or 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 in-patient hospitalisation, or the development of drug dependency or drug abuse. **A suspected or confirmed coronavirus COVID-19** (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically important serious event" if no other seriousness criteria are present (e.g. hospitalisation)).

In addition to the above criteria, any additional AE that the Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system.

When reporting SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. Signs and symptoms may be described in the event description. The Investigator should also try to separate a primary AE considered as the foremost medical occurrence from secondary AEs which occurred as complications;
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding death is unknown. Terms such as "Unexplained Death" or "Death from Unknown Origin" may be used when the cause is unknown. In these circumstances, the cause of death must be investigated, and the diagnosis amended when the origin has been identified. If an autopsy is performed, the autopsy report should be provided;
- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the anticipated/required stay in relation to the original reason that led to the initial admission, **as determined by the Investigator or treating physician**.
- While most hospitalisations necessitate reporting of an SAE, some hospitalisations do not require SAE reporting, as follows:
  - For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol;
  - Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for seriousness but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor;
  - Pre-planned or elective treatments/surgical procedures should be noted in the subject's Screening documentation. 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. If a new elective treatment/surgical procedure is required for a subject during their participation in the study the elective treatment/surgical procedure should be considered a SAE;

- Events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g. an emergency room visit for haematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics);

• SAEs must be reported for any surgical or procedural complication resulting in prolongation of hospitalisation.

When reporting an SAE, the following information is the minimum that must be provided to the Sponsor for each SAE within 24 hours of its occurrence:

• study number;
• centre number;
• subject number;
• Investigator's name and contact details.

Additional information includes the reason why the event is considered to be serious (i.e. the seriousness criteria), the Investigator's assessment of the relationship of the event to study treatment, medications or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event, which will be recorded on the SAE form.

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. The Investigator should always provide an assessment of causality for each event reported to the Sponsor. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator must also report:

• All SAEs that occur after informed consent and through 30 days after the date of the last cabozantinib dose (or the date the subject is deemed to be a screen failure). This information must be recorded on the AE page of the eCRF;
• Any SAEs assessed as related to study treatment or study procedures.

During the follow-up period, any SAE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study treatment (Section 5.6) must be reported promptly to the sponsor, within 24 hours.

8.1.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will be collected and it will be necessary to discontinue administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the eCRF and should be reported to the Sponsor as an SAE. The Sponsor will request further information from the Investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form, which will be provided to the investigational sites upon request. Any birth defect or congenital anomaly must be reported as an SAE and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

The Investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The Investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.

Pregnancies with a conception date within 120 days after the subject's last dose of cabozantinib must also be reported to the Investigator for onward reporting to the Sponsor.

Use of medically accepted methods of contraception is very important during the study and for 4 months after study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have a follow-up of at least 6 months after birth. If the Investigator becomes aware that the partner of a subject participating in the study is pregnant, this should be reported to the Sponsor. After the partner has given written consent, she should be counselled and followed as described above. Monitoring of the partner should continue until the end of the pregnancy.

Abnormal pregnancy outcome/AE in foetus/neonate/child

If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to cabozantinib, an attempt must be made to follow-up until one month after delivery. The information will be collected in the Clinica1.l Study SAE Report Form (080478-FOR) for the mother and for the foetus/neonate/child.

8.1.6 Study Medication Errors

Medication errors are defined as the administration of study drug medication outside or above the established dosing regimens specified in the protocol.

Any overdose or study medication error that results in an AE or SAE (excluding missed doses) requires reporting within 24 hours to the Sponsor or designee.

Any AEs or SAEs that occur as a result of an overdose have to be treated according to clinical standard practice. Please refer to the Investigator's Brochure for additional management recommendations for an overdose of cabozantinib.

8.1.7 Deaths

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, MI);
- Outcome: fatal.

For AEs leading to death, the NCI-CTCAE Grade 5 is the only appropriate grade (see Section 8.1.2.1). Deaths that cannot be attributed to an NCI-CTCAE term associated with Grade 5 or that cannot be reported within an NCI-CTCAE category as 'Other' have to be reported as one of these four AE options:

- death not otherwise specified (NOS);
- disease progression NOS;
- multi-organ failure;
- sudden death.

8.1.8 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to cabozantinib or other reasons (see Section 4.3).

If cabozantinib treatment is discontinued due to an AE or a clinically significant laboratory test abnormality, it must be reported immediately to the Sponsor's designated representative. Monitoring will continue until the event has resolved or stabilised, until the subject is referred to a local health care professional, or until the determination of a cause unrelated to cabozantinib or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. In

all cases, the Investigator must ensure that the subject receives appropriate medical follow-up (see Section 8.1.3).

8.1.9 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The Sponsor will ensure that processes are in place for the submission of reports of suspected unexpected serious adverse reactions (SUSARs) occurring during the study to the competent authorities, IECs and other Investigators concerned by the IMP. Reporting will be in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected at the frequency indicated in Table 2 for the evaluation of haematology, blood biochemistry, urinalysis, pregnancy tests and other clinical laboratory tests as safety measurements. A list of all laboratory analyses that will be measured in this study is provided in Table 5.

All laboratory tests to establish eligibility must be done within 15 days prior to baseline (Table 2).

All laboratory analyses will be performed and analysed by the local laboratory, including samples that are obtained at unscheduled visits whenever possible. All local laboratory results will be recorded on the eCRF and provided by the Investigator. The Investigator will review the safety laboratory test results, document the review and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

On days when a blood sample is collected, subjects must fast overnight (consumption of water is allowed).

Abnormalities in any clinical laboratory test (including tests not required per protocol) that lead to a change in subject management (e.g. dose withheld or reduced, study treatment discontinued; requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and should be reported as AEs. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 8.1.4).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline levels or to a level deemed acceptable by the Investigator or until the abnormality is explained by an appropriate diagnosis.

Table 5 Laboratory Assessments

Haematology - White blood cells with differential count (absolute neutrophil count (ANC), basophils, eosinophils, lymphocytes and monocytes - Haematocrit - Platelet count - Red blood cell count - Haemoglobin **Coagulation** - Prothrombin time/International normalised ratio (INR) - Partial thromboplastin time (PTT) **Thyroid function** - Thyroid-stimulating hormone (TSH) - Free Thyroxine 4 (FT4)	**Blood Chemistry** - Albumin - Total alkaline phosphatase (ALP) - Alanine aminotransferase (ALT) - Aspartate aminotransferase (AST) - Blood urea nitrogen (BUN) - Chloride - Creatinine (estimation of creatinine clearance by Cockcroft and Gault) - γ-glutamyl transpeptidase (GGT) - Glucose - Potassium - Sodium - Corrected calcium - Total bilirubin (conjugated and unconjugated if total bilirubin is elevated) - Total protein	**Pregnancy Blood/Urine Test** - β-human chorionic gonadotrophin (β-HCG) **Urinalysis** (Dipstick or Routine) [a] - pH - Protein - Glucose - Blood **Microscopic Urine Examination** [a] - At the discretion of the Investigator based on results or routine urinalysis or as clinically indicated **Urine Chemistry** (at the discretion of the Investigator and based on results of routine urinalysis or as clinically indicated) [a] - 24-hour urine protein or urine protein-to-creatinine ratio (UPCR)

[a] Fresh urine samples will be collected to perform these assessments.

8.2.1 Pregnancy Test

A β-HCG serum test and/or an HCG urine test will be performed for all female subjects of childbearing potential within 7 days prior to the baseline visit and at every visit thereafter up to the End of Study Treatment or Early Study Withdrawal visit (Table 2). Any subject becoming pregnant during the study will be withdrawn from the study. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

8.3 Physical Examination

Physical examinations will be conducted as indicated in Table 2 as a safety measure. This assessment will include height (Screening visit only), weight, performance status, and an evaluation of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

The ECOG performance status of the subject will be assessed at each scheduled safety assessment starting at screening (see reference table in Appendix 7).

Any ongoing/intercurrent condition prior to first dose should be recorded in source documents and on the eCRF.

Any clinically significant physical examination findings (abnormalities) observed during the treatment period will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the treatment period will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Vital signs (BP and heart rate) will be assessed as indicated in Table 2 as safety measures. These assessments will be conducted with an automated device so that measurements are independent of the observer. Measurements of BP and heart rate will be performed after a 5-minute rest in sitting position and after standing up for 1 minute. Absolute values and change from baseline will be analysed. Any clinically significant abnormalities in the vital signs will be reported as an AE.

8.5 Electrocardiography

Electrocardiography analyses will be conducted as indicated in Table 2 as a safety evaluation in this study.

The ECGs will be recorded at the Screening visit, baseline and Week 4 (Visit 4). After the first 8 weeks of study treatment, ECGs will be recorded at every 12 weeks up to the End of Study Treatment/Early Study Withdrawal visit.

Twelve-lead ECGs will be recorded so that the different ECG intervals (RR, PR, QRS, QT intervals) can be measured automatically. The ECG will be recorded using a local ECG reader.

Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics will not be assessed in this study.

10 EXPLORATORY BIOMARKERS

Not applicable.

11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the statistical analysis plan (SAP), which will be dated and approved before the first subject is included. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher).

11.1 Analysis Populations

The following populations will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Included population**: All subjects screened who fulfilled the inclusion and exclusion criteria.
- **Safety population**: All included subjects who received at least one dose of study medication.
- **Efficacy population**: All included subjects who received at least one dose of study medication and provided a baseline assessment for the tumour according to RECIST 1.1.
- **Per protocol (PP) population**: All subjects in the efficacy population who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the subject) as described in the protocol deviations document.

11.1.1 Populations Analysed

Analyses based on the primary and secondary efficacy endpoints will be performed on the efficacy population in each cohort separately.

Sensitivity efficacy analyses will be based on PP population. Efficacy analyses in the PP population will be presented if there is a difference greater than 15% between efficacy population and PP population.

The analyses of safety data will be performed based on the safety population in each cohort separately and overall.

11.1.2 Protocol Deviations

Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (efficacy, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, efficacy and PP populations will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the analyses populations.

11.2 Sample Size Determination

For cohort A, the hypothesis for sample size computation is that cabozantinib will demonstrate a clinically significant increase in the response rate as compared to historical control in 2nd line treatment. A therapy will be considered clinically meaningful if it provides a significant benefit in ORR as assessed by independent central review over a standard rate of 10% (conservative threshold in reference to the response rate of everolimus in the METEOR study (12), exact 95% CI: 1.7-5.9). Assuming approximately 7% non-evaluable subjects (i.e. subjects who received at least one dose of study medication but did not provide a baseline for the tumour

according to RECIST 1.1), 74 subjects in cohort A provides at least 80% power (at one-sided significance level (alpha) of 0.025) to reject the null hypothesis of 10% ORR in favour of an alternative hypothesis of 23% ORR.

For cohort B, no formal sample size determination was performed as the enrolment will stop when the recruitment in cohort A will be reached. We anticipate approximately 40 subjects recruited in cohort B.

11.3 Significance Testing and Estimations

ORR (primary endpoint) will be tested at the final analysis as described above using the one-sided significance level (alpha) of 0.025. No statistical testing will be carried out at the interim analysis nor for secondary efficacy and safety endpoints.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external contract research organisation (CRO), managed by the Sponsor's biometry department.

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease and other assessments performed at the Screening visit) will be presented by cohort and overall for the safety population.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects in the screened, included, safety, efficacy and PP populations will be tabulated by cohort and overall. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were screened, screened failed, treated, discontinued and completed each of the study periods (pre-treatment period, treatment period, post-treatment follow-up period) will be tabulated by cohort and overall. Primary reasons for discontinuation of study treatment will be tabulated.

11.4.3 Efficacy Evaluation

11.4.3.1 Primary Efficacy Endpoint

In line with the primary endpoint indicated in Section 7.1 (see also Appendix 5), the primary efficacy endpoint is:

- Objective response rate (ORR) defined as the proportion of subjects who achieved a partial response (PR) or complete response (CR) at any timepoint as determined by independent central review per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 in cohort A.

Details regarding the independent central review will be documented in the IRC charter finalised prior to the enrolment of the first subject.

Below is the definition of the estimand used for the primary efficacy endpoint:

Treatment: Cabozantinib

Population: Subjects with unresectable, locally, advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination (Cohort A).

Endpoint: ORR defined as the proportion of PR and CR at any timepoint during treatment period as determined by independent central review per RECIST1.1.

Intercurrent events:

- Study discontinuation without response (i.e. without PR or CR) during the treatment period (composite strategy)

Subjects withdrawn from the study without response during the treatment period or subjects without any post-baseline tumour assessment are non-responders.

- Treatment discontinuation prior to RECIST 1.1. progression (treatment policy strategy)

The efficacy assessment at any timepoint prior to RECIST 1.1. progression is used regardless of whether the Cabozantinib is discontinued.

- Subjects not treated (while on treatment strategy)

Subjects will not be included in the primary efficacy analysis.

- Subjects receiving non-protocol anti-cancer treatment (while on treatment strategy)

Assessment of the response during the treatment period, i.e. until the initiation of non-protocol anti-cancer treatment.

Population-level summary: ORR compared to the historical control value of 10%.

11.4.3.2 Secondary Efficacy Endpoints

In line with the secondary endpoints indicated in Section 7.2 (see also Appendix 5), the secondary efficacy endpoints are:

- Time to response (TTR) defined as the time from start of study treatment to the date of first evidence of response (PR or CR as determined by independent central review per RECIST 1.1);
- Duration of response (DOR) defined as the time from first documented response (PR or CR as determined by independent central review per RECIST 1.1) to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first. Censoring rules will be similar to those applied for progression-free survival (PFS);
- Disease control rate (DCR), defined as the proportion of subjects who achieved a PR, CR or SD as determined by independent central review per RECIST 1.1;
- PFS defined as the time from start of study treatment to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first;
- Objective response rate (ORR) in cohort B defined as the proportion of subjects who achieved a partial response (PR) or complete response (CR) at any timepoint as determined by independent central review per RECIST 1.1;
- Overall survival (OS) defined as the time from the start of treatment until death due to any cause;
- ORR, TTR, DOR, DCR and PFS according to local Investigator’s review per RECIST 1.1;
- Change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS).

All these secondary endpoints will be presented in each cohort separately. In addition, ORR and PFS according to local Investigator's review per RECIST 1.1 as well as OS will be presented in the overall population (cohort A + cohort B).

Below is the definition of the estimand used for the secondary efficacy endpoint of duration of response:

Treatment: Cabozantinib

Population: Subjects with unresectable, locally, advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination (Cohort A) with a PR or CR at any timepoint during the treatment period.

Endpoint: DOR defined as the time from first documented response (PR or CR as determined by independent central review per RECIST 1.1) to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first.

Intercurrent events:

- Two or more missing scheduled tumour assessment prior to RECIST 1.1. progression (while on treatment strategy)

Subjects will be censored at the date of the last tumour assessment prior to the missing assessment.

- Subjects not treated (while on treatment strategy)

Subjects will not be included in the efficacy analysis.

- Subjects receiving non-protocol anti-cancer treatment prior to RECIST 1.1 progression (while on treatment strategy)

Subjects will be censored at the date of the last tumour assessment prior to the initiation of non-protocol anti-cancer treatment.

- Treatment discontinuation prior to RECIST 1.1. progression (treatment policy strategy)

Subjects will be censored at the date of the last tumour assessment.

- Treatment discontinuation without any post-baseline tumour assessment (treatment policy strategy) after the first response to treatment

Subjects will be censored at the time of first documented response.

Population-level summary: median of DOR 2-sided 95% with CI.

11.4.3.3 Primary Efficacy Endpoint Analysis

The ORR as assessed by independent central review will be estimated in Cohort A and tested *versus* the threshold of 10% using a one-sample exact test for binomial distribution. A higher response rate over 10% will be considered statistically significant if the p-value for the one-sided test is less than 0.025.

The ORR estimates will be presented in statistical tables with their associated 2-sided 95% CIs using Clopper-Pearson exact method.

11.4.3.4 Secondary Efficacy Endpoint Analyses

The ORR according to Investigator's assessment (cohort A and cohort B) and by independent central review (cohort B) will be presented with their associated 2-sided 95% CIs using Clopper-Pearson exact method. Discordance in ORR assessed by independent central review and by Investigator will be described.

DCR estimates will be presented in statistical tables with associated 2-sided 95% CIs.

Time-to-event endpoints (TTR, DOR, PFS and OS) will be analysed using the Kaplan-Meier method. The results will be presented for each Cohort A and B both in summary tables and graphically in Kaplan-Meier plots. Kaplan-Meier methodology will be used to characterise the

distribution of endpoints. Median durations and associated 2-sided 95% CIs will be provided. Event rates at timepoints from either first dose of study treatment or first documented response will also be estimated with associated 2-sided 95% CIs.

General censoring rules for the analysis of PFS are described below:

- Subjects who receive non-protocol anti-cancer therapy (NPACT) after start of cabozantinib and before experiencing an event will be right censored at the date of the last tumour assessment prior to the date of initiation of subsequent therapy;
- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cut-off will be right censored on the date of their last tumour assessment;
- Subjects who miss two or more scheduled tumour assessments followed by an event will be right censored on the date of their most-recent tumour assessment prior to the missing assessments.

Additional supportive analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing assessments, address bias due to tumour assessment timing, evaluate the impact of potentially informative censoring, and to address potential discrepancies between the documentation of progression per the Investigator and per the independent central review.

For the 9-item subset of disease related symptoms of the FKSI-DRS, the total score will be calculated using the number of subjects having a baseline and at least one post-baseline completion score. Completion score will be defined as answering at least 5 of 9 items. Descriptive statistics will be performed at each timepoint and change from baseline. Comparisons between baseline and post-baseline scores will be performed using paired Student t-tests. The proportion of subjects with at least an increase of 1 point from baseline will also be reported.

11.4.4 Safety Evaluation

The safety endpoints are indicated in Section 3.2.3.

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population in each cohort separately and overall.

The number of subjects experiencing dose reduction, delay, and/or discontinuation due to an AE will be provided.

All AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by PT and SOC. AEs will be graded according to the NCI-CTCAE. The incidence of all reported treatment-emergent AEs (TEAEs) and SAEs will be tabulated by cohort and overall.

A TEAE is defined as any AE that occurs after first dose of study drug if:

- it was not present prior to receiving the first dose of study drug, or
- it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study.

The focus of analysis for this study will be the duration of the treatment period and 30 days after the date of last study drug administration.

In addition, summary tables will be presented by Grade 3 or 4, worst reported severity, drug relationship and TEAEs associated with premature withdrawal or dose modification of study medication.

Subject deaths will be summarised, and primary cause of death will be reported by PT and SOC using MedDRA.

Adverse event listings will be presented by subject, SOC and PT. All TEAEs will be flagged in the AEs listings.

Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables and clinical laboratory tests at each assessment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

Concomitant medications will be standardised using the World Health Organization drug dictionary and summarised by anatomic therapeutic class (ATS) and preferred name.

11.5 Subgroup Analyses

Subgroup analyses will be conducted by presenting the primary analysis of ORR (with point estimates and 95% CIs) for both independent central review and Investigator's assessment in the following subgroups:

- Age (<65 years, ≥65 years);
- Gender (female, male);
- MSKCC Risk Factors (favourable [0], intermediate [1], poor [2 or more]);
- Heng criteria (favourable [0], intermediate [1-2], poor [3-6]);
- Number of organs with metastases (1, 2, ≥3);
- ECOG (0, 1);
- Treatment duration on 1st anti-cancer therapy (<6 months, ≥6 months);

11.6 Interim Analyses

An interim and purely descriptive analysis will be conducted when 80% of the subjects (i.e. 59 subjects) of cohort A will be treated for at least 3 months. Both cohorts will be analysed at this cut-off date. The aim of this interim analysis is to describe the baseline characteristics, demographics, ORR as assessed by the Investigator at 3 months and any further efficacy parameters measured at the Month 3 visit. Further details will be provided in the SAP. The results of this interim analysis will not have any impact on the study conduct. A final analysis based on the primary endpoint (ORR) will be performed 12 months after the last subject received the first cabozantinib administration.

A follow-up analysis based on OS will be conducted 18 months after the last subject received the first cabozantinib administration.

The statistical testing will be carried out at the final analysis.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external competent authorities (CAs) and Quality Assurance personnel authorised by the Sponsor may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to study documents and investigational site facilities as specified in Section 13.4 and to any other locations involved in the study (e.g. laboratories).

In the event of the investigational site being notified directly for a regulatory inspection, the Investigator must notify the Sponsor's representative as soon as possible to assist with the preparations for the inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion by the IEC/IRB, except when necessary to eliminate immediate safety concerns for the subjects or when the change involves only logistics or administration.

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***Non-substantial amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- ***Substantial amendments*** are those considered 'substantial' to the conduct of the clinical study and are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the study;
  - the conduct or management of the study;
  - the quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- ***Urgent amendments*** are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent notification of the IECs and regulatory authorities.

The principal Investigator and the Sponsor will sign all protocol amendments.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the Sponsor or Sponsor's representative.

A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the Investigator or the Sponsor to the protocol's specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Generally, a protocol deviation qualifies as major if:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject;

(2) The deviation compromises the scientific integrity of the data collected in the study;

(3) The deviation is a wilful or knowing breach of human subject protection regulations, policies or procedures on the part of the Investigator(s);

(4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies or procedures;

(5) The deviation is inconsistent with the Sponsor's research, medical and/or ethical principles.

See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

As a matter of policy, the Sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular subject, prior approval from the Sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject is allowed to enter the study. If personnel from the investigation centre learns that a subject who did not meet protocol eligibility criteria was included in the study (protocol violation), they must immediately inform the Sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the Sponsor and the responsible IRB/IEC and according to the applicable SOP. The participation of these subjects in the study will be discussed between Sponsor and Investigator, taking into account subject safety and data reliability. The IRB/IEC will be informed if subject safety/protection is inadvertently affected.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the Sponsor or its representatives will provide instructional material to the investigational sites, as appropriate. A study initiation visit will be conducted prior to the Screening visit to instruct the Investigators and study coordinators. This session will comprise instructions on the protocol, completion of the eCRF and all study-related procedures. The Investigator is responsible for providing information about the study to all staff members involved in the study or any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff is involved). The Investigator must assure that all study staff members are qualified (education, experience and training) to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of the responsibilities of each staff member. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the Investigator and for ensuring their compliance with the protocol. Additional information will be made available when new staff becomes involved in the study and as agreed with either the Investigator or the study monitor.

13.3 Study Monitoring

The Investigator is responsible for the validity of all data collected at the investigational site.

The Sponsor is responsible for monitoring these data to verify that the rights and wellbeing of the subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP guidelines and regulatory requirements.

Sponsor-assigned monitors will conduct regular investigational site visits. The Investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the verification of entries made in the eCRF and will assist with the monitor’s activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The investigational site must complete the eCRFs on an ongoing basis to allow regular review by the study monitor, both remotely (internet) and during investigational site visits. The Sponsor’s central study monitor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the investigational site personnel in a timely manner.

Whenever a subject's name is revealed on a document required by the Sponsor (e.g. laboratory printouts) the name must be blacked out permanently by the investigational site personnel and annotated with the subject's number as identification.

A Steering Committee will be composed of Investigator and Sponsor representatives to supervise the overall scientific and operational management of the study.

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP guidelines. This includes that the study may be audited at any time by a quality assurance personnel designated by the Sponsor or inspected by regulatory bodies. The Investigator must adhere to ICH GCP guidelines in addition to any applicable local regulations.

If requested, the Investigator will provide the Sponsor, applicable regulatory agencies and applicable EC with direct access to any original source documents.

The Investigator should demonstrate due diligence in the recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the Sponsor. The Sponsor should be notified of any projected delays that may impact the completion of the study.

This clinical trial will be conducted in compliance with all international laws and regulations and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines.

13.5 Audit and Inspection

Authorised personnel from external CAs and Quality Assurance personnel authorised by the Sponsor may carry out inspections and audits (see Section 12).

13.6 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

14 ETHICS

14.1 Compliance with Good Clinical Practice (GCP) and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP guidelines.

In addition, this study will adhere to all local regulatory requirements.

Before initiating the study, the Investigator/institution should receive written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, cards with study contact in case of subject emergency, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB showing that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval must be sought prior to implementation. Ethical approval on administrative changes will be obtained if required by the local/investigational site IEC/IRB.

14.2 Informed Consent for Participation in the Study

Prior to screening, the Investigator or a person designated by the Investigator will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained before to the subject enters the study (before initiation of any study-related procedure and administration of cabozantinib). Sufficient time will be given to discuss any questions raised by the subject.

The Sponsor will provide a sample informed consent form. The final version-controlled form must be agreed to by the Sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understandable by the subject. The Investigator will keep each subject's original consent form, personally signed and dated by the subject or subject's legally acceptable representative and by the person who conducted the informed consent discussion. The Investigator will provide a copy of their signed informed consent form to each subject.

The informed consent form may need to be revised during the study should important new information become available that may be relevant to the subject's safety or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as described above. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

14.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the Sponsor's Regulatory Affairs group will ensure that all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

The following documents should be submitted to the relevant EC for review and approval to conduct the study (this list may not be exhaustive):

- protocol/amendment(s) approved by the Sponsor;
- currently applicable Investigator's Brochure or package labelling;
- relevant Investigator's curriculum vitae;
- subject information and informed consent document(s) and form(s);
- cards with study contact in case of subject emergency;
- recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required and a written favourable opinion for the conduct of the study should be made available to the Investigator before initiating the study. These documents must be dated, clearly identify the version number(s) and date(s) of the documents submitted/reviewed and include a statement from the EC showing that they comply with GCP requirements.

The study may begin at the investigational site(s) only after receiving this dated and signed documentation containing the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC, either for information or review and approval, depending on how substantial the modifications are: (1) Investigator's Brochure; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about study completion.

14.4 Confidentiality Regarding Study Subjects

The Investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the Sponsor, subjects will be identified not by their names but by an identification code (e.g. identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the Sponsor, the quality assurance unit or regulatory authorities. Personal medical information will always be treated as confidential.

15 DATA HANDLING AND RECORD KEEPING

15.1 Recording of Study Data

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest the accuracy and completeness of all data. If any changes are made to the eCRF after a form has been locked and electronically signed, the Investigator will be required to perform an additional e-signature to show agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and the reason for the change is always required. In the eCRF, the audit trail function will make visible the changes made to each included item.

15.2 Data Management

The EDC system will be utilised for collecting subject data. Each investigational site is required to have a computer and internet connection available for local clinical data entry. All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only Sponsor-authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted either by a CRO directed by the Sponsor's data management department or by the Sponsor's data management department. All data management procedures will be completed in accordance with the Sponsor and the SOPs of the contracted CRO. Prior to data being received in-house by the assigned CRO, they will be monitored at the investigational site (for further details see Section 13.3). The eCRF and other data documentation removed from the investigational site(s) will be tracked by the CRO and the monitor.

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or inconsistent data. The Investigator will receive data from the clinical study in an electronic format (PDF files), which will be an exact copy of the eCRF, and will include the full audit trail for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The Sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the Sponsor's pharmacovigilance department (and vice-versa).

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by the contracted CRO/a CRO directed by the Sponsor's Biometry Group and reviewed and approved by the Sponsor. Prior and ongoing medications started before the study and concomitant medications (started at the time of cabozantinib administration) will be coded using World Health Organization Drug (WHODRUG) and AEs/medical history terms will be coded using MedDRA.

Only data from included subjects will be reported in the eCRFs and collected in the Sponsor's database.

For screening failure subjects, the Unique Subject Identifier, the date of informed consent signature, the reason why the subject failed screening and the potential AEs which occurred during the Screening visit will be reported in the eCRFs and collected in the Sponsor's database

(for complete list of data to be collected for screen failure patients, please refer to eCRF completion Guidelines).

15.3 Record Archiving and Retention

During the initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the investigational site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for the maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

16 FINANCING AND INSURANCE

16.1 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall their specific responsibilities in relation to the study. Financial remuneration will cover the cost per included subject based on the calculated costs to perform the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

16.2 Insurance, Indemnity and Compensation

The Sponsor will provide product liability insurance for all subjects included in the clinical study. Where required, a hospital-specific indemnity agreement will be used.

17 REPORTING AND PUBLICATION OF RESULTS

17.1 Publication Policy

The Sponsor is committed to disclosing information about the clinical trials it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Global Publications Manager and incorporated in the relevant publication plan before initiation. A dedicated Publications Committee, involving interested members of the study Steering Committee as well as the Global Publications Manager, may be established to plan specific publications. As a minimum, summary results of this study should be posted on the relevant clinical trial registry. When the trial has been conducted by a large multicentre group, the principal Investigator, the study steering committee (if applicable) and the Sponsor's responsible physician should discuss and agree the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing Investigators will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). In particular, those named as authors, whether employed by a Sponsor's affiliate or the Sponsor, or external Investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The Sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at the Sponsor, coordinated by the Global Publications team. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The Sponsor's review comments must be answered before a final version for submission can be approved by the author team.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors'

institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

17.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. The final CSR will include data on any subject that has signed the informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate, an abbreviated report may be prepared. The CSR will comply with any applicable regulatory requirements, national laws in force and will be in English.

An analysis will be performed on the final response data 12 months after the last subject received the first cabozantinib administration. This analysis will be included in the final study report. An addendum to the report, including the analysis of data from the follow-up period, will be prepared 18 months after the last subject received the first cabozantinib administration.

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19 LIST OF APPENDICES

Appendix 1 Memorial Sloan Kettering Cancer Center (MSKCC) Criteria for prognostic risk category

The identified prognostic factors include:

- Low Karnofsky performance status (<80%)
- Low serum haemoglobin (<13 g/dL for males and ≤11.5 g/dL for females)
- High corrected calcium (≥10 mg/dL)

Number of risk factors	Risk category
0	Favourable
1	Intermediate
2 or 3	Poor

Appendix 2 International Metastatic RCC Database Consortium (IMDC) risk group category

Risk factors

- Karnofsky performance status <80%
- Haemoglobin <lower limit of normal (<LLN)
- Time from diagnosis to treatment of <1 year
- Corrected calcium above the upper limit of normal (>ULN)
- Platelets greater than the upper limit of normal (>ULN)
- Neutrophils greater than the upper limit of normal (>ULN)

Number of risk factors	Risk category
0	Favourable
1–2	Intermediate
3+	Poor

Appendix 3 Methods of contraception

Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) and their partners must agree to use highly effective methods of contraception (that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly) during the course of the study and for 4 months after the last dose of study treatment.

The interaction of cabozantinib with oral contraceptives has not been investigated and the contraceptive effect may not be guaranteed, therefore it is recommended that an additional contraceptive method such as a barrier method (e.g. condom or diaphragm) is used by your patient if they are using oral combined contraception or progestogen-only contraception.

Effective methods of birth control include:

- Hormonal contraception (oral, injectable, implantable, transdermal) plus a barrier method;
- intrauterine device (IUD) *o*r intrauterine hormone-releasing system (IUS) plus a barrier method;
- bilateral tubal occlusion (females);
- vasectomized partner (males).

Men with partners who can get pregnant will need to use one of the medically accepted methods of birth control listed above while in this study, as will their partner. All male subjects must refrain from donating sperm and sexual intercourse without condoms with female partners for the duration of study and for 120 days after the last dose of study drug.

Appendix 4 Warnings, Precautions and Guidelines for The Management of Potential Cabozantinib Adverse Events

1 GASTROINTESTINAL DISORDERS

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess

Prior to initiation of treatment with cabozantinib, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Tumours invading GI or respiratory tracts
- Active peptic ulcer disease, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Ongoing visceral complications from prior radiation therapy
- Prior GI surgery (particularly when associated with delayed or incomplete healing)

Complete healing following abdominal surgery and radiation therapy and/or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

After starting cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula are present.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhoea

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. Guidelines for the evaluation and management of diarrhoea are shown in Table A1. 1 .

Table A1. 1 Guidelines for Management of Treatment-Emergent Diarrhoea

Status	Management
Tolerable Grade 1-2 (duration <48 hours)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (e.g. loperamide 4 mg followed by 2 mg after each episode of diarrhoea [maximum: 16 mg loperamide per day]) • Dietary modifications (e.g. small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: - Diarrhoea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 hours diarrhoea-free interval - Diarrhoea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 >48 hours, or ≥Grade 3	• Interrupt study treatment • Ask subject to attend investigational site • Rule out infection (e.g. stool sample for culture) - Administer antibiotics as needed (e.g. if fever or Grade 3-4 neutropenia persists >24 hours) • Administer fluids (1-1.5 L/day oral or intravenous (IV), as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhoea consider hospitalisation and IV hydration • Re-assess after 24 hours - Diarrhoea resolving to baseline bowel habits or Grade ≤1: consider restarting study treatment at reduced dose - Diarrhoea not resolving: - Start and or continue antidiarrheal treatment (e.g. loperamide 4 mg followed by 2 mg after each episode of diarrhoea (maximum: 16 mg loperamide per day)) - Consider starting 2nd line antidiarrheal or referral to gastroenterologist

Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhoea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhoea to tolerable levels, study treatment should be temporarily interrupted, or dose reduced. When the diarrhoea is controlled, retreatment with cabozantinib may be acceptable per Investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhoea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasised. Regular examinations of the perianal region should be performed whenever

diarrhoea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions.

2 NON-GASTROINTESTINAL FISTULA

Non-GI fistula formation: Complications from radiation therapy has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (i.e. radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 3 months of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

3 HAEMORRHAGE

Haemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for haemorrhagic events may include (but may not be limited to) the following:

- Tumour of the lung with cavitary lesions or tumour lesions which invade or encase major blood vessels. Non-small cell lung cancer (NSCLC) with squamous cell differentiation is known for significant lung cavitations and centrally located tumours that may invade major blood vessels. Thus, the anatomic location and characteristics of tumour as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, inflammatory GI diseases including Crohn’s disease and ulcerative colitis;
- Underlying medical conditions which affect normal haemostasis (e.g. deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal haemostasis;
- History of clinically significant haemoptysis, hematemesis, or haematuria.

The risk of haemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analysed. Though the incidence of CNS haemorrhage events in a study of subjects with GB was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of haemorrhage in GB translates to a risk of haemorrhage for subjects with brain metastases. Currently, brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS haemorrhage occur.

Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment, and cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent haemoptysis (≥2.5 mL of red blood).

4 VASCULAR DISORDERS

Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anti-cancer therapy. Events of DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment held until therapeutic anticoagulation is established. Refer to the individual protocol for guidance on anticoagulation medication use. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming study treatment per discretion of the Investigator and according to individual protocols. LMWHs are the preferred management agent for thrombotic events; Oral anticoagulants (including warfarin) are not allowed.

Arterial thrombotic events (e.g. TIA, MI) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidaemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Hypertension

Table A1. 2 provides treatment guidelines for hypertension deemed related to cabozantinib. Subjects with known hypertension should be optimally managed prior to entry into clinical trials with cabozantinib according to entry criteria of specific protocols. The subjects' BP should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. 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.

Table A1. 2 Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects NOT receiving optimised anti-hypertensive therapy	
>150 mm Hg (systolic) [a] and <160 mm Hg OR >100 mm Hg (diastolic) and <110 mm Hg	• Optimise antihypertensive medications 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 cabozantinib by one dose level[b] or interrupt study treatment per Investigator's discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimised 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 systolic BP (≥160 mm Hg) are sustained and not adequately manageable or if systolic BP is >180 mm Hg or diastolic BP >110 mm Hg, or if subject is symptomatic • Re-start study treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at <150 mm Hg systolic and <100 mm Hg diastolic
Hypertensive emergency [c]	• Discontinue study treatment

BP = Blood pressure.

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

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g. MI/ischaemia, intracranial haemorrhage, cerebral ischaemia, pulmonary oedema, encephalopathy, kidney damage).

5 STOMATITIS AND MUCOSITIS

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses

(e.g. with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturised with lip balm. The use of lipstick, lip-gloss, and vaseline should be avoided.

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.

6 SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Wound healing and surgery

Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysaesthesia syndrome

Palmar-plantar erythrodysaesthesia syndrome (also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual 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. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarised in Table A1. 3.

Table A1. 3 Dose Modification Criteria and Recommended Guidelines for Treatment-emergent Hand-Foot Syndrome (PPES)

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade	Action to Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily (b.i.d.) AND clobetasol 0.05% cream once daily (q.d). Reassess at least weekly; if PPES 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 PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream b.i.d. AND high potency steroid cream (e.g. clobetasol 0.05%) q.d. and add analgesics (e.g. NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g. clobetasol 0.05%) b.i.d. AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

NSAID = Non-steroidal anti-inflammatory drug; PPES = Palmar-plantar erythrodysaesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

7 ANGIOEDEMA

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

8 OSTEONECROSIS

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ.

Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib therapy. Advise subjects regarding oral hygiene practice and to quickly report symptoms to the Investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be held for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

If ONJ occurs, cabozantinib treatment should be held and should not be restarted until the condition has sufficiently healed and the Sponsor has approved the re-initiation of therapy.

9 PROTEINURIA

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring urine protein/creatinine ratio (UPCR). Table A1. 4 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and oedema).

Table A1. 4 Management of Proteinuria Related to Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤1 mg/mg (≤113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
>1 and <3.5 mg/mg (>113.1 and <395.9 mg/mmol)	• Consider confirming with a 24-hour protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤2 mg/mg or urine protein ≤2 g/24 hours on 24-hour urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR >2 mg/mg on repeat UPCR testing or urine protein >2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to <2 mg/mg. Consider holding cabozantinib treatment if UPCR remains >2 mg/mg despite a dose reduction until UPCR decreases to <2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose hold unless otherwise approved by sponsor. • Repeat UPCR within 7 days and once per week. If UPCR <1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to <2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to <1 mg/mg. If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue all study treatment

UPCR = Urine protein/creatinine ratio.

10 NERVOUS SYSTEM DISORDERS

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia and ataxia have been observed in clinical studies with cabozantinib. In addition, hepatic encephalopathy has been observed in HCC clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported and should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

11 HEPATIC EVENTS

Investigators should monitor for Drug induced lived injury (DILI) diligently and report any potential events.

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (e.g. liver cirrhosis, thrombosis of portal or hepatic vein, HCC, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

If not otherwise specified in individual protocols, cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 × ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g. International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib should be held until the aetiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic metastases 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 bilirubin concentration or coagulation factors. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate DILI. Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.

12 INFECTIONS AND INFESTATIONS

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g. after myelosuppressive anti-cancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal haematopoiesis, as well as the presence of intravenous (IV) devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be held until adequate healing has taken place.

13 BLOOD AND LYMPHATIC SYSTEM DISORDERS

Haematological toxicities (i.e. neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed

with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for haematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anaemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered unless prohibited by a specific protocol. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

14 FATIGUE

Common causes of fatigue, such as anaemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited by a particular protocol.

15 WEIGHT LOSS

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

16 CORRECTED QT PROLONGATION

The effect of orally administered cabozantinib 140 mg q.d. on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase of 10-15 ms in QTcF was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. There were no events of torsades de pointes reported.

Unless otherwise specified in certain protocols, only subjects with a baseline QTcF ≤500 msec are eligible for cabozantinib research studies. Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or other drugs known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value >500 ms or an increase of >60 ms above baseline, two additional 12-lead ECGs must be performed with intervals not less than 3 minutes apart within 30 minutes after the initial ECG.

If the average QTcF from the three ECGs is >500 ms or increased by >60 ms above baseline, the following actions must be taken:

- Withhold study treatment;
- Immediately notify the Sponsor;
- Hospitalise symptomatic subjects (e.g. 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, potassium and calcium; correct abnormalities as clinically indicated;
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org);
- Repeat ECG triplicates hourly until the average QTcF is ≤500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. 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 or increase of >60 ms above baseline is not confirmed according to protocol procedures;
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤500 msec or return to ≤60 ms above baseline;
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved;

Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All 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.
-

17 ENDOCRINE DISORDERS

Treatment-emergent increases in thyroid-stimulating hormone (TSH) have been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (e.g. symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

18 MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when

there are no other clear causes. Re-initiation of cabozantinib treatment must be discussed with and approved by the sponsor. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

19 RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Dyspnoea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnoea given the risk of thrombosis associated with inhibition of VEGF signalling. Furthermore, fistula formation and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

20 ELECTROLYTE ABNORMALITIES

Electrolyte abnormalities, including hypocalcaemia, hypokalaemia, hypomagnesaemia, and hypophosphataemia have been noted in subjects treated with cabozantinib. In some cases, these have been Grade 3 or 4 and/or serious. These laboratory values should be evaluated routinely. Deficits should be corrected when an electrolyte abnormality is noted in order to avoid worsening. Correction of electrolyte abnormalities should be accompanied by increased frequency of monitoring.

Appendix 5 Response Evaluation Criteria in Solid Tumours (RECIST) 1.1

Adapted from (29).

TUMOUR MEASURABILITY

At baseline, tumour lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumour assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumour Lesions

Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumour lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be

considered measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above.

  However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions.

However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrolment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumour type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOUR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumour markers, cytology, and histology cannot be used for objective tumour evaluation.

ASSESSMENT OF TUMOUR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumour. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm (30 mm has a short

axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumour assessment as a measure of tumour burden.

Measuring Lymph Nodes

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 node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is + 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.

Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of nontarget lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumour response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumour response for the group of nontarget lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumour marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumour marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumour 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 progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A5.1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A5.1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR= complete response, NE= not evaluable, PD= progressive disease, PR= partial response, SD= stable disease

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in 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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A5.1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Appendix 6 FKSI-DRS Questionnaire

FKSI –DRS (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		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
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
BRM 3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4

Appendix 7 Performance Status Criteria

Table A1. 1 Performance Status Criteria

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

Appendix 8 Amendment Form #1

STUDY NUMBER:	F-FR-60000-023
PROTOCOL TITLE:	A PHASE II, MULTICENTRE, OPEN-LABEL STUDY OF CABOZANTINIB AS 2ND LINE TREATMENT IN SUBJECTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA WITH A CLEAR-CELL COMPONENT WHO PROGRESSED AFTER 1ST LINE TREATMENT WITH CHECKPOINT INHIBITORS
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #1):28 November 2019

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**26 APRIL 2019**	**28 NOVEMBER 2019**
Page	**Section**	**WAS**	**IS**
1	Cover page	**For serious adverse event (SAE) reporting:** Fax: ~~+ 44 (0)1753 627842~~ E-mail: adverse.events@ipsen.com	**For serious adverse event (SAE) reporting:** Fax: **+44 (0) 1753 627860** E-mail: adverse.events@ipsen.com
5	Synopsis (Objectives)	Secondary Study Objectives: • To assess other efficacy criteria of cabozantinib such as ~~best overall response (BOR),~~ time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent and Investigator's review; […]	Secondary Study Objectives: • To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent and Investigator's review; • **To assess objective response rate (ORR) by Investigator's review;**

			[…]
6	Synopsis (Methodology)	[…] Each subject's study participation will consist of the following periods: **Pre-treatment Period:** Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments ~~at the Screening visit~~ will be performed within 15 days prior to first cabozantinib dose except when otherwise specified. ~~Eligible subjects will be included in the study on the day of the Screening visit.~~ […] Subjects who discontinue treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 days ~~(+15 days)~~ after the last dose of cabozantinib). Subjects who prematurely stop the study due to withdrawal of consent will be invited to attend the Early Study Withdrawal visit.	[…] Each subject's study participation will consist of the following periods: **Pre-treatment Period:** Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments will be performed within 15 days prior to first cabozantinib dose except when otherwise specified **(detailed in study schedule)**. […] Subjects who discontinue treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 **to 45** days after the last dose of cabozantinib). Subjects who prematurely stop the study due to withdrawal of consent will be invited to attend the Early Study Withdrawal visit.
7-8 and 38-39	Synopsis (Inclusion criteria) and Section 4.1	All subjects must fulfil all the following criteria to be included in the study:	All subjects must fulfil all the following criteria to be included in the study:

		[…] (8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within ~~10~~ days before ~~study entry~~: (a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L). (b) Platelets ≥ 100,000/mm3 (≥ 100 GI/L). (c) Haemoglobin ≥ 9 g/dL (≥ 90 g/L). (d) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN). (e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L). (f) Fasting serum triglycerides ≤ 2.5 × ULN AND total cholesterol ≤ 300 mg/dL (≤ 7.75 mmol/L). Lipid-lowering medication is allowed. (g) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation (h) Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g.	[…] (8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within **15** days before **baseline**: (a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L). (b) Platelets ≥ 100,000/mm3 (≥ 100 GI/L). (c) Haemoglobin ≥ 9 g/dL (≥ 90 g/L). (d) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN). (e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L). (f) Fasting serum triglycerides ≤ 2.5 × ULN AND total cholesterol ≤ 300 mg/dL (≤ 7.75 mmol/L). Lipid-lowering medication is allowed. (g) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation (h) Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g. […]

		[…] (12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) must agree to use ~~medically accepted~~ methods of contraception ~~(e.g. 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;	(12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) **and their partners** must agree to use **highly effective** methods of contraception **that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix 3)** during the course of the study and for 4 months after the last dose of study treatment; […] (15) **Subjects must be covered by social security or be the beneficiary of such a system (only applicable for French subjects).**
8-9 and 39-40-41	Synopsis (Exclusion criteria) and Section 4.2	Subjects will not be included in the study if the subject: ~~(1) Has a diagnosis of predominant non clear-cell RCC;~~ (2) Inability to swallow tablets; (3) Was treated with any other investigational medicinal product (IMP) within the last 30 days before ~~study entry~~; (4) Was previously treated with cabozantinib;	Subjects will not be included in the study if the subject: (1) Inability to swallow tablets; (2) Was treated with any other investigational medicinal product (IMP) within the last 30 days before **baseline**; (3) Was previously treated with cabozantinib;

			(4) **Has a contraindication to Magnetic Resonance Imaging (MRI) or contrast medium used for Contrast Tomography (CT)-scan;**
		(5) Presents untreated brain or leptomeningeal metastases, or current clinical or ~~radiological~~ progression of known brain metastases;	(5) Presents untreated brain or leptomeningeal metastases, or current clinical or **radiographic** progression of known brain metastases;
		(6) Has a diagnosis of a serious cardiovascular disorder: (a) Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, or serious cardiac arrhythmias; (b) Uncontrolled hypertension, defined as sustained blood pressure (BP) (>140 mm Hg systolic or >90 mm Hg diastolic pressure) despite optimal antihypertensive treatment; (c) Stroke (including transient ischaemic attack (TIA)), myocardial infarction (MI) or other ischaemic event, or thromboembolic event (e.g. deep venous thrombosis, pulmonary	(6) Has a diagnosis of a serious cardiovascular disorder: (a) Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, or serious cardiac arrhythmias; (b) Uncontrolled hypertension, defined as sustained blood pressure (BP) (>140 mm Hg systolic or >90 mm Hg diastolic pressure) despite optimal antihypertensive treatment; (c) Stroke (including transient ischaemic attack (TIA)), myocardial infarction (MI) or other ischaemic event, or thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism) within 6 months before **screening**;

		embolism) within 6 months before ~~study entry~~; (d) History of risk factors for torsades de pointes (e.g., long QT syndrome);	(d) History of risk factors for torsades de pointes (e.g., long QT syndrome);
		(7) Is receiving a concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g. clopidogrel). Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), ~~low-dose warfarin (<1 mg/day~~), and low dose, low molecular weight heparin (LMWH) are permitted.	(7) Is receiving a concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g. clopidogrel). Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose, low molecular weight heparin (LMWH) are permitted.
			(8) Has a gastrointestinal (GI) disorder including those associated with a high risk of perforation or fistula formation: (a) Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction; (b) Abdominal fistula, GI perforation, bowel obstruction, or intra-

		(8) Has a gastrointestinal (GI) disorder including those associated with a high risk of perforation or fistula formation: (a) Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction; (b) Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before ~~study entry~~; Note: Complete healing of an intra-abdominal abscess must have been confirmed before ~~study entry~~. (9) Presents a corrected QT (QTc) interval calculated by the Fridericia formula	abdominal abscess within 6 months before **screening**; Note: Complete healing of an intra-abdominal abscess must have been confirmed before **screening**. (9) Presents a corrected QT (QTc) interval calculated by the Fridericia formula (QTcF) > 500 msec within 1 month prior to **baseline**; *Note: If a single electrocardiogram (ECG) shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility* (10) Presents clinically significant haematuria, hematemesis, or haemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g. pulmonary haemorrhage) within 3 months before **screening**;

		(QTcF) > 500 msec within 1 month prior to ~~study entry~~; *Note: If a single electrocardiogram (ECG) shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility* (10) Presents clinically significant haematuria, hematemesis, or haemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g. pulmonary haemorrhage) within 3 months before ~~study entry~~; […] (15) Has had prior surgery within 4 weeks prior to ~~study entry~~. Note: If the subject has undergone major surgery, complete wound healing must have occurred 1 month prior to ~~study entry~~.	[…] (15) Has had prior surgery within 4 weeks prior to **baseline**. Note: If the subject has undergone major surgery, complete wound healing must have occurred 1 month prior to **baseline**. (16) Has had palliative radiation therapy for bone within 2 weeks or for radiation fields including viscera within 4 weeks prior to **baseline**. Note: Resolution/healing of side effects must be complete prior to **baseline**; (17) Has a history of another active malignancy within 3 years from **screening** except for locally curable cancers that have been apparently cured, such as low-grade thyroid carcinoma, prostate cancer not requiring treatment (Gleason Grade ≤6), basal or squamous cell skin cancer, superficial bladder cancer, *in situ* melanoma*, in situ* prostate, cervix or breast carcinoma or other treated malignancies with <5% chance of relapse according to the Investigator; […]

		(16) Has had palliative radiation therapy for bone within 2 weeks or for radiation fields including viscera within 4 weeks prior to ~~study entry~~. Note: Resolution/healing of side effects must be complete ~~within 4 weeks~~ prior to ~~study entry~~; (17) Has a history of another active malignancy within 3 years from ~~study entry~~ except for locally curable cancers that have been apparently cured, such as low-grade thyroid carcinoma, prostate cancer not requiring treatment (Gleason Grade ≤6), basal or squamous cell skin cancer, superficial bladder cancer, *in situ* melanoma, *in situ* prostate, cervix or breast carcinoma or other treated malignancies with <5% chance of relapse according to the Investigator; […] (21) Is pregnant or breastfeeding. A β-human chorionic gonadotrophin (HCG) serum pregnancy test will be performed up to 7 days prior to ~~study entry~~ for all female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile);	(21) Is pregnant or breastfeeding. A β-human chorionic gonadotrophin (HCG) serum pregnancy test will be performed up to 7 days prior to **baseline** for all female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile);

11	Synopsis (Criteria for evaluation (endpoints))	**Efficacy**: Secondary Endpoints(s) and Evaluation(s): • ~~Best overall response (BOR) per RECIST 1.1 evaluated by independent central review;~~ • Time to response (TTR) per RECIST 1.1 evaluated by independent central review; […] • ORR, ~~BOR,~~ TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; **Safety**: Safety assessments will start on the day of the Screening visit and will be carried out at minimum at every visit (every 2 weeks) up to Week 4 (Visit 4), and every 4 weeks thereafter. Safety will also be assessed at the End of Study Treatment visit (30 days ~~(±15 days))~~ after the last study treatment dose) and during the Post-treatment Follow-up period (every 12 weeks (±15 days) by telephone call) up to 18 months after the last subject included in the study started cabozantinib treatment. Unscheduled visits for safety evaluations are allowed at any time.	**Efficacy**: Secondary Endpoints(s) and Evaluation(s): • Time to response (TTR) per RECIST 1.1 evaluated by independent central review; […] • ORR, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; **Safety**: Safety assessments will start on the day of the Screening visit and will be carried out at minimum at every visit (every 2 weeks) up to Week 4 (Visit 4), and every 4 weeks thereafter. Safety will also be assessed at the End of Study Treatment visit (30 **to 45** days after the last study treatment dose) and during the Post-treatment Follow-up period (every 12 weeks (±15 days) by telephone call) up to 18 months after the last subject included in the study started cabozantinib treatment. Unscheduled visits for safety evaluations are allowed at any time.
12	Synopsis (Statistical methods)	Statistical Methods: ~~Analyses will be performed at two~~ intermediate ~~data cut-offs: 1)~~ when 60% of subjects (i.e. 75 subjects)	Statistical Methods: **An** intermediate **analysis will be conducted** when 60% of subjects (i.e. 75 subjects) of the

		of the first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up. ~~2) when 60% of subjects (i.e. 75 subjects) of the second recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow up. In addition,~~ at this cut-off date~~, all subjects at 12 months of study follow up in the first recruiting cohort will be analysed.~~ ~~A~~ final analysis will be performed ~~after database lock, i.e.~~ 18 months after the last subject received the first cabozantinib administration. At intermediate analysis, no statistical testing ~~with alpha spending approach~~ will be performed. The statistical testing will only be carried out at the final analysis. The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review and confirmed by a subsequent visit ≥28 days later, will be tested in each cohort using a one-sample exact test for binomial distribution. The proportion of subjects achieving ORR will be presented with their two-sided 95% CI using the Clopper-Pearson exact method. ~~Best overall response (BOR) will be descriptively summarised and~~ DCR estimates will be described with associated 2-sided 95% CIs. […]	first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up. **Both cohorts will be analysed** at this cut-off date. **The** final analysis **based on the primary endpoint (ORR)** will be performed **12 months after the last subject received the first cabozantinib administration. A follow-up analysis based on OS will be conducted** 18 months after the last subject received the first cabozantinib administration. At **the** intermediate analysis, no statistical testing will be performed. The statistical testing will only be carried out at the final analysis. The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review and confirmed by a subsequent visit ≥28 days later, will be tested in each cohort using a one-sample exact test for binomial distribution. The proportion of subjects achieving ORR will be presented with their two-sided 95% CI using the Clopper-Pearson exact method. DCR estimates will be described with associated 2-sided 95% CIs. […]

19-20	LIST OF ABBREVIATIONS	[…] ~~BOR: Best Overall Response~~ […]	[…] **DILI: Drug Induced Liver Injury** […]
24-25	1.1.2	[…] Checkpoint inhibitor (CPI) therapy with ipilimumab and nivolumab is also an approved treatment for advanced RCC. Indeed, in January 2019, the European Medicines Agency (EMA) granted ipilimumab and nivolumab Marketing Authorisation for 1st line treatment of intermediate- and poor-risk subjects with advanced RCC.	[…] Checkpoint inhibitor (CPI) therapy with ipilimumab and nivolumab is also an approved treatment for advanced RCC. Indeed, in January 2019, the European Medicines Agency (EMA) granted ipilimumab and nivolumab Marketing Authorisation for 1st line treatment of intermediate- and poor-risk subjects with advanced RCC. **In September 2019, European Commission approved pembrolizumab in combination with axitinib and CHMP adopted positive opinion for avelumab plus axitinib as first-line treatment for patients with advanced RCC.**
28	1.3	[…] As such, several clinical trials have been underway to determine the efficacy and safety of a combination therapy with CPI and antiangiogenic TKI agents in untreated subjects with advanced RCC (19). These clinical trials include several Phase III trials, as follows: • An ongoing study evaluating the combination of cabozantinib and nivolumab *versus*	[…] As such, several clinical trials have been underway to determine the efficacy and safety of a combination therapy with CPI and antiangiogenic TKI agents in untreated subjects with advanced RCC (19). These clinical trials include several Phase III trials, as follows: • An ongoing study evaluating the combination of cabozantinib and

		sunitinib monotherapy in subjects with RCC (NCT03141177); • ~~A study that assessed the combination of axitinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02853331);~~ • An ongoing study evaluating the combination of lenvatinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02811861); • ~~A study that assessed the combination of axitinib and avelumab *versus* sunitinib monotherapy in subjects with RCC (NCT02684006);~~ • A study that assessed the combination of atezolizumab with or without an anti-VEGF agent (bevacizumab) *versus* sunitinib in untreated subjects with metastatic RCC (NCT02420821). ~~Some of these studies have already provided promising results for the treatment of advanced RCC. The study that assessed axitinib plus pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (KEYNOTE-426 trial) showed that subjects treated with the combination therapy experienced significantly longer OS and PFS and higher ORR compared to those treated with sunitinib (20).~~	nivolumab *versus* sunitinib monotherapy in subjects with RCC (NCT03141177); • An ongoing study evaluating the combination of lenvatinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02811861); • A study that assessed the combination of atezolizumab with or without an anti-VEGF agent (bevacizumab) *versus* sunitinib in untreated subjects with metastatic RCC (NCT02420821).

		~~The assessment of axitinib and avelumab *versus* sunitinib monotherapy in untreated subjects with RCC (JAVELIN Renal 101) showed that PFS was significantly longer in the combination therapy arm compared to the sunitinib arm (21).~~	
29	1.4	[…] Antiangiogenic agents currently represent the preferable 1st line treatment option for patients with advanced and metastatic RCC with intermediate and poor prognosis. However, according to the European Association of Urology Guidelines Recommendations and European Society for Medical Oncology (ESMO) guidelines (22, 23) and based ~~on the results of the Phase III Checkmate-214 study (15)~~, CPI therapy with ipilimumab and nivolumab is likely to become the new standard of care for subjects with RCC with poor and intermediate prognosis	[…] Antiangiogenic agents currently represent the preferable 1st line treatment option for patients with advanced and metastatic RCC with intermediate and poor prognosis. However, according to the European Association of Urology Guidelines Recommendations and European Society for Medical Oncology (ESMO) guidelines (22, 23) and based on **recent approvals**, CPI therapy with ipilimumab and nivolumab is likely to become the new standard of care for subjects with RCC with poor and intermediate prognosis **and pembrolizumab and axitinib is likely to become the new standard of care for subjects with favourable prognosis.**
30-31	1.4	[…]	[…] • **Kalirai A. 2019 (28): reported results from the Canadian Kidney Cancer Information System: real world analysis of 102 patients treated with targeted therapy post CPI. Those who**

			received first-line ipilimumab + nivolumab versus a VEGFi + CPI combination prior to second-line treatment had a median time to treatment failure of 8.0 vs 5.2 months (m) (HR=0.43, 95% CI: 0.13-1.44) and median OS of 16.5 m vs not reached (HR=0.76, 95% CI: 0.11-5.24). Patients who received a VEGFi versus a mammalian target of rapamycin inhibitor (mTORi) as third-line TT had a median TTF of 7.6 vs 4.4 m (HR=0.52, 95% CI: 0.24-1.10) and median OS of 21.7 vs 16.2 m (HR=0.41, 95% CI: 0.16-1.08). All third-line treatment patients received first-line VEGFi and second-line nivolumab. Of the third-line VEGFi treatment patients, 24 received axitinib (TTF 7.1 m, OS 21.7 m) and 22 received cabozantinib (data immature). Authors concluded that these results support the use of VEGFi after CPI in mRCC patients. • **Ornstein MC 2018 (29) reported the results of a phase 2 Study of the Efficacy and Safety of axitinib given on an individualized schedule for mRCC, after treatment with PD-1 or PD-L1 Inhibitors: the study included 38**

			patients whose most recent therapy was anti PD-1 (89%) or anti PD L1 (11%). In evaluable patients, the estimated median PFS is 9.2 months, with 54% of patients still on axitinib. The ORR is 38.7%. The median highest dose per patient was 6mg BID (range, 5-9) and 44% of patients required dose reduction to < 5mg BID. There were no unexpected toxicities related to axitinib. […] Secondary endpoints are time to response (TTR), duration of response (DOR), DCR and PFS per RECIST 1.1 assessed both by independent central review and by local Investigator, ORR per RECIST 1.1 assessed by local Investigator, OS and change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS). Safety and tolerability of cabozantinib will also be monitored throughout the study.

		[…] Secondary endpoints are ~~best overall response (BOR),~~ time to response (TTR), duration of response (DOR), DCR and PFS per RECIST 1.1 assessed both by independent central review and by local Investigator, ORR per RECIST 1.1 assessed by local Investigator, OS and change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS). Safety and	

		tolerability of cabozantinib will also be monitored throughout the study.	
32	2.1	[…] Several clinical trials are currently ongoing to investigate the effect of new treatment regimens containing CPI for patients with RCC (Section 1.3). ~~If positive, the results from these trials will change~~the available options for 1st line treatment of RCC. However, some of the patients may be refractory to these treatments, thus it is increasingly important to find potential 2nd line therapies for such patients.	[…] **Recent EMA approvals and** several clinical trials are currently ongoing to investigate the effect of new treatment regimens containing CPI for patients with RCC (Section 1.3). **These changes potentially transformed the treatment landscape and** the available options for 1st line treatment of RCC. However, some of the patients may be refractory to these treatments, thus it is increasingly important to find potential 2nd line therapies for such patients.
32	2.2.2	• To assess other efficacy criteria of cabozantinib such as ~~best overall response (BOR),~~ time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent and Investigator's review; […]	• To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent and Investigator's review; • **To assess objective response rate (ORR) by Investigator's review;** […]
33-34	3.1	This study will be conducted in approximately 50 active investigational sites across Germany, Switzerland, the Netherlands, France, UK, ~~Belgium,~~ Austria and Spain. The list of countries and the number of investigational sites may change during the study depending on recruitment and	This study will be conducted in approximately 50 active investigational sites across Germany, Switzerland, the Netherlands, France, UK, Austria and Spain. The list of countries and the number of investigational sites may change during the study depending on recruitment and

		availability of the CPI combination (ipilimumab and nivolumab) in each country. […] **Pre-treatment Period:** Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments ~~at the Screening visit~~ will be performed within 15 days prior to first cabozantinib dose except when otherwise specified. ~~Eligible subjects will be included in the study on the day of the Screening visit.~~ […]Subjects who discontinue study treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 days ~~(+15 days))~~ after the last dose of cabozantinib) (Section 5.2.2.1). Subjects who prematurely stop the study will be invited to attend the Early Study Withdrawal visit (Section 5.2.2.2). […]	availability of the CPI combination (ipilimumab and nivolumab) in each country. […] **Pre-treatment Period:** Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying assessments will be performed within 15 days prior to first cabozantinib dose except when otherwise specified **(detailed in study schedule in Table 2)**. […] Subjects who discontinue study treatment with cabozantinib due to disease progression or unacceptable toxicity will be invited to attend the End of Study Treatment visit (30 **to 45** days after the last dose of cabozantinib) (Section 5.2.2.1). Subjects who prematurely stop the study will be invited to attend the Early Study Withdrawal visit (Section 5.2.2.2). […] [*Figure 1 updated*]
34-35	3.2.2	• ~~Best overall response (BOR) per RECIST 1.1 evaluated by independent central review;~~	• Time to response (TTR) per RECIST 1.1 evaluated by independent central review;

		• Time to response (TTR) per RECIST 1.1 evaluated by independent central review; […] • ORR, ~~BOR~~, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; […] The endpoints of ORR, ~~BOR,~~ TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.	[…] • ORR, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; […] The endpoints of ORR, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.
35	3.2.3	Summaries of AEs and SAEs will be tabulated by cohort according to system organ class (SOC) and preferred term (PT) by overall incidence, worst reported severity, and relationship to study treatment.	Summaries of AEs and SAEs will be tabulated by cohort **and overall** according to system organ class (SOC) and preferred term (PT) by overall incidence, worst reported severity, and relationship to study treatment.
36	3.6	The study is planned to start in the ~~third~~ quarter of 2019 and will start when the first subject provides a signed informed consent form.	The study is planned to start in the **fourth** quarter of 2019 and will start when the first subject provides a signed informed consent form.
37	3.8	An IRC will be established to evaluate tumour scans and prior radiation history data of study subjects in a central, blinded and independent fashion. The IRC will be comprised of board-certified radiologists who will evaluate prior radiation history to validate the identification of target lesions, as well as determine radiographic response and progression after ~~study entry~~.	An IRC will be established to evaluate tumour scans and prior radiation history data of study subjects in a central, blinded and independent fashion. The IRC will be comprised of board-certified radiologists who will evaluate prior radiation history to validate the identification of target lesions, as well as

			determine radiographic response and progression after **screening**.
41	4.3.1.1	If a subject decides to discontinue study treatment or the Investigator decides to discontinue a subject from the study treatment, this subject will be invited to undergo the assessments of the End of Study Treatment/Early Withdrawal visit (see Section 5.2.2) and to attend the Post-treatment Follow-up visits safety, subsequent anti-cancer therapies and survival status assessments, unless the subject withdraws consent to remain in the study and refuses to have his/her data collected. If study treatment discontinuation occurs, the reason and date of this decision must be recorded in the eCRF.	If a subject decides to discontinue study treatment or the Investigator decides to discontinue a subject from the study treatment, this subject will be invited to undergo the assessments of the End of Study Treatment/Early Withdrawal visit (see Section 5.2.2) and to attend the Post-treatment Follow-up visits **to assess** safety, subsequent anti-cancer therapies and survival status assessments, unless the subject withdraws consent to remain in the study and refuses to have his/her data collected. If study treatment discontinuation occurs, the reason and date of this decision must be recorded in the eCRF.
44-45-46-47	Table 2	Assessment column: • Urinalysis, microscopic urine examination and urine chemistry[g] • Brain CT/MRI Bone ~~CT~~ scan (only if indicative of metastases)	*[Table 2 updated]* Footnote [f] added at baseline column for eligibility criteria, physical examination, weight, vital signs and ECOG performance status assessments. Assessment column: • Urinalysis, microscopic urine examination and urine chemistry **(including UPCR)**[g] • Brain CT/MRI **and** Bone **scintigraphy** scan (only if indicative of metastases)

		Pre-treatment Period column for Prior and concomitant therapies line: ≤~~15~~ Days prior to Screening Footnote: [e] Informed consent may be obtained more than 15 days prior to ~~study entry~~ but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be used as Screening evaluations if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC) policies of the investigational site. [f] These assessments are intended to confirm suitability for treatment after the Screening visit. ~~If these assessments have been performed during the Screening visit and within 15 days (or ≤7 days for pregnancy test and ≤28 days for CT/MRI scans) prior to first cabozantinib dose (baseline/Day 1),~~ there is no need to perform them again at baseline, unless the subject's clinical status has changed (e.g. onset of new symptoms indicative of clinical	Pre-treatment Period column for Prior and concomitant therapies line: ≤**30** Days prior to Screening Footnote [e] Informed consent may be obtained more than 15 days prior to **screening** but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be used as Screening evaluations if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC) policies of the investigational site. [f] These assessments are intended to confirm suitability for treatment after the Screening visit. There is no need to perform them again at baseline, unless the subject's clinical status has changed (e.g. onset of new symptoms indicative of clinical deterioration). If these assessments are performed at **screening and** baseline **visits**, results must be available to be reviewed by the Investigator prior to first dose. [g] Microscopic urine examination to be performed at baseline and after that only at the discretion of the Investigator (results are not to

		deterioration). If these assessments are performed at baseline, results must be available to be reviewed by the Investigator prior to first dose. [g] Microscopic urine examination to be performed at baseline and after that only at the discretion of the Investigator (results are not to be collected in the eCRF except in case of clinically abnormal findings, which are to be reported as an AE). Urine chemistry (24-hour urine protein) may be performed at any scheduled or unscheduled visit at the discretion of the Investigator and based on results of routine urinalysis or as clinically indicated. [i] Follow-up for ~~radiological~~ progression, tumour assessment should be performed until ~~radiological~~ progression confirmed by the Investigator only for subjects who have discontinued cabozantinib treatment before ~~radiological~~ disease progression and who have not withdrawn consent. [m] Information on prior and concomitant medication will be collected up to 30 days before ~~study entry~~ until 30 days after the date of the last cabozantinib dose.	be collected in the eCRF except in case of clinically abnormal findings, which are to be reported as an AE). Urine chemistry (24-hour urine protein **or UPCR)** may be performed at any scheduled or unscheduled visit at the discretion of the Investigator and based on results of routine urinalysis or as clinically indicated. [i] Follow-up for **radiographic** progression, tumour assessment should be performed until **radiographic** progression confirmed by the Investigator only for subjects who have discontinued cabozantinib treatment before **radiographic** disease progression and who have not withdrawn consent. [m] Information on prior and concomitant medication will be collected up to 30 days before **screening** until 30 days after the date of the last cabozantinib dose.
48	5.2.1	[…] A signed and dated informed consent form may be obtained more than 15 days prior ~~study entry~~ but must be provided before any study-specific	[…] A signed and dated informed consent form may be obtained more than 15 days prior **screening** but must be provided before any study-specific

		procedures are performed. However, evaluations performed as part of routine care prior to the date of the signed informed consent form can be used as Screening evaluations if permitted by the IRB/Ethics Committee (EC) policies of the investigational site. Subjects will acknowledge and agree to the possible use of these data in the study by signing the informed consent form. ~~After informed consent is obtained, subjects that meet all the inclusion criteria and none of the exclusion criteria will be included in the study. Included subjects will be assigned to Cohort A or Cohort B according to their 1st line therapy to treat RCC (Section 3.1). Subjects will undergo the required screening assessments outlined in Table 2 to determine eligibility (see Section 4 for inclusion and exclusion criteria). Screening assessments must be performed within 15 days prior to first dose unless otherwise stated (as indicated in Table 2, certain assessments must be obtained closer to study entry).~~	procedures are performed. However, evaluations performed as part of routine care prior to the date of the signed informed consent form can be used as Screening evaluations if permitted by the IRB/Ethics Committee (EC) policies of the investigational site. Subjects will acknowledge and agree to the possible use of these data in the study by signing the informed consent form.
49	5.2.2.1	The End of Study Treatment visit will be carried out 30 days ~~(+15 days)~~ after the last cabozantinib dose (all necessary assessments to be performed at this visit are indicated in Table 2). After this date, the subject will enter the Post-treatment Follow-up period (Section 5.2.3.1). The Investigator will ask subjects to return any remaining cabozantinib tablets and check their compliance to study protocol. Efficacy evaluations	The End of Study Treatment visit will be carried out 30 **to 45** days after the last cabozantinib dose (all necessary assessments to be performed at this visit are indicated in Table 2). After this date, the subject will enter the Post-treatment Follow-up period (Section 5.2.3.1). The Investigator will ask subjects to return any remaining cabozantinib tablets and check their compliance to study protocol. Efficacy

		should not be performed for subjects who do not attend the End of Study Treatment visit within 30 days ~~(+15 days)~~ after their last dose of cabozantinib. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the Investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.	evaluations should not be performed for subjects who do not attend the End of Study Treatment visit within 30 **to 45** days after their last dose of cabozantinib. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the Investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.
49	5.2.3	[…] For subjects who have discontinued cabozantinib treatment before ~~radiological~~ disease progression and who have not withdrawn consent, tumour assessment should be performed until ~~radiological~~ progression confirmed by the Investigator.	[…] For subjects who have discontinued cabozantinib treatment before **radiographic** disease progression and who have not withdrawn consent, tumour assessment should be performed until **radiographic** progression confirmed by the Investigator.
54	6.2.2	Table 4 First column: Common Terminology Criteria for Adverse Events (CTCAE) version ~~4.~~0 Grade	*[Table 4 updated]* First column: Common Terminology Criteria for Adverse Events (CTCAE) version **5**.0 Grade
55	6.2.4	[…] Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g. deep vein thrombosis (DVT), pulmonary embolism, TIA and MI), severe haemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic	[…] Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g. deep vein thrombosis (DVT), pulmonary embolism, TIA and MI), **aneurysms and artery dissections,** severe haemorrhagic events, proteinuria, wound healing complications, GI

		abscess, GI and non-GI fistulae formation, ONJ, and reversible posterior leukoencephalopathy syndrome (RPLS) also known as Posterior Reversible Encephalopathy Syndrome (PRES).	perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, ONJ, and reversible posterior leukoencephalopathy syndrome (RPLS) also known as Posterior Reversible Encephalopathy Syndrome (PRES).
60	7.2	• ~~Best overall response (BOR) per RECIST 1.1 evaluated by independent central review;~~ • Time to response (TTR) per RECIST 1.1 evaluated by independent central review; […] • ORR, ~~BOR~~, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; […] The endpoints of ORR, ~~BOR~~, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.	• Time to response (TTR) per RECIST 1.1 evaluated by independent central review; […] • ORR, TTR, DOR, DCR and PFS per RECIST 1.1 according to local Investigator's review; […] The endpoints of ORR, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 7.3.1). The OS will be assessed as described in Section 7.3.2.
60	7.3.1	Radiographic tumour assessments will include contrast tomography (CT) and/or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis (C/A/P), brain, bone scans. The same imaging modalities used at the Screening visit should be used for subsequent tumour assessments.	Radiographic tumour assessments will include contrast tomography (CT) and/or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis (C/A/P), brain, **and** bone **scintigraphy** scans. The same imaging modalities used at the Screening visit should be

		For subjects who have discontinued cabozantinib treatment before ~~radiological~~ disease progression and who have not withdrawn consent, tumour assessment should be performed until ~~radiological~~ progression is confirmed by the Investigator. (see Table 2 for schedule of assessments). […] All CT/MRI scans (C/A/P, brain) and ~~CT~~ scans (bone) are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at the Screening visit should be used for subsequent tumour assessments.	used for subsequent tumour assessments. For subjects who have discontinued cabozantinib treatment before **radiographic** disease progression and who have not withdrawn consent, tumour assessment should be performed until **radiographic** progression is confirmed by the Investigator. (see Table 2 for schedule of assessments). […] All CT/MRI scans (C/A/P, brain) and **scintigraphy** scans (bone) are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at the Screening visit should be used for subsequent tumour assessments.
63-64	8.1.3	All observed or self-reported AEs, regardless of ~~treatment group or~~ suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study or exacerbations of pre-existing illnesses should be recorded according to the NCI terminology. […]	All observed or self-reported AEs, regardless of suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study or exacerbations of pre-existing illnesses should be recorded according to the NCI terminology. […]

		Follow-up of the AE after the date of cabozantinib discontinuation is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.	Follow-up of the AE after the date of cabozantinib discontinuation is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative. **Any AE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study (Section 5.6) must be reported promptly, within 24 hours.** **<u>Follow-up of SAEs/ Grade 3 and 4 AEs leading to study treatment discontinuation:</u>** **All SAEs that are ongoing at 30 days or later after the date of the last dose of study treatment and AEs assessed NCI-CTCAE Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the last dose of study treatment are to be followed until either:** • **the AE has resolved;** • **the AE has improved to Grade 2 or lower;** • **the Investigator determines that the event has become stable or irreversible;** **The status of all other AEs that are ongoing 30 days after the last dose will be**

			documented as of the last study visit for the subject.
66	8.1.4	[…] Any ~~AE/~~SAE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study must be reported promptly, within 24 hours.	[…] Any SAE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study **(Section 5.6)** must be reported promptly, within 24 hours.
67	8.1.5		[…] **Abnormal pregnancy outcome/AE in foetus/neonate/child** **If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to cabozantinib, an attempt must be made to follow-up until one month after delivery. The information will be collected in the Clinica1.l Study SAE Report Form (080478-FOR) for the mother and for the foetus/neonate/child.**
68	8.2	[…] All laboratory tests to establish eligibility must be done within 15 days prior to ~~study entry~~ (Table 2).	[…] All laboratory tests to establish eligibility must be done within 15 days prior to **screening** (Table 2).
69	8.2	Table 5 Blood Chemistry column: […]	*[Table 5 updated]* Blood Chemistry column: […]

		- Triglycerides (fasted) ~~- Lactate Dehydrogenase (LDH)~~	- Triglycerides (fasted)
69	8.3	[…] The ECOG performance status of the subject will be assessed at each scheduled safety assessment starting at baseline (see reference table in Appendix 7).	[…] The ECOG performance status of the subject will be assessed at each scheduled safety assessment starting at **screening** (see reference table in Appendix 7).
74	11.3	ORR (primary endpoint) will be tested as described above using the one-sided significance level (alpha) of 0.025. ~~The null hypothesis will be rejected at the final analysis if the result is statistically significant.~~ No statistical testing ~~for statistical comparisons~~ will be carried out at the intermediate analysis nor for secondary efficacy and safety endpoints	ORR (primary endpoint) will be tested **at the final analysis** as described above using the one-sided significance level (alpha) of 0.025. No statistical testing will be carried out at the intermediate analysis nor for secondary efficacy and safety endpoints
74-75	11.4.3.2	In line with the secondary endpoints indicated in Section 7.2 (see also Appendix 5), the secondary efficacy endpoints are: ~~• Best overall response (BOR) defined as the best response among CR, PR, stable disease (SD) or progressive disease (PD) as determined by independent central review per RECIST 1.1;~~ • Time to response (TTR) defined as the time from start of study treatment to the date of first evidence of response (PR or CR as determined by independent central review per RECIST 1.1); […]	In line with the secondary endpoints indicated in Section 7.2 (see also Appendix 5), the secondary efficacy endpoints are: • Time to response (TTR) defined as the time from start of study treatment to the date of first evidence of response (PR or

		• ORR, ~~BOR~~, TTR, DOR, DCR and PFS according to local Investigator's review per RECIST 1.1; […]	CR as determined by independent central review per RECIST 1.1); […] • ORR, TTR, DOR, DCR and PFS according to local Investigator's review per RECIST 1.1; […]
75	11.4.3.4	The ORR according to Investigator's assessment will be analysed in the same way as ORR assessed by independent central review without statistical testing. Discordance in ORR assessed by independent central review and by Investigator will be described. ~~The BOR will be descriptively summarised.~~ DCR estimates will be presented in statistical tables with associated 2-sided 95% CIs.	The ORR according to Investigator's assessment will be analysed in the same way as ORR assessed by independent central review without statistical testing. Discordance in ORR assessed by independent central review and by Investigator will be described. DCR estimates will be presented in statistical tables with associated 2-sided 95% CIs.
76	11.4.4	[…] A TEAE is defined as any AE that occurs after first dose of study drug ~~until 30 days after the date of last study drug administration~~ if: • it was not present prior to receiving the first dose of study drug, or • it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study.	[…] A TEAE is defined as any AE that occurs after first dose of study drug if: • it was not present prior to receiving the first dose of study drug, or • it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study.

			The focus of analysis for this study will be the duration of the treatment period and 30 days after the date of last study drug administration.
77	11.5	[…] • ECOG (0, 1) ~~which will be converted from ECOG status~~; […]	[…] • ECOG (0, 1); […]
77	11.6	There are no formal interim analyses with stopping rules for efficacy or futility planned for this study. However, intermediate analyses ~~are~~ planned as follows: • The ~~first~~ intermediate analysis will be conducted when 60% of subjects (i.e. 75 subjects) of the first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up; • ~~The second intermediate analysis will be conducted when 60% of subjects (i.e. 75 subjects) of the second recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up. In addition, at this cut off date, all subjects in the first recruiting cohort at 12 months of study~~	There are no formal interim analyses with stopping rules for efficacy or futility planned for this study. However, **one** intermediate analys**is** **is** planned as follows: The intermediate analysis will be conducted when 60% of subjects (i.e. 75 subjects) of the first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up; **Both cohorts will be analysed at this cut-off date.**

		~~follow-up will be analysed. A final analysis will be performed after database lock, i.e. 18 months after the last subject received the first cabozantinib administration.~~ A follow-up analysis based on OS will be conducted ~~after database lock, i.e.~~ 18 months after the last subject received the first cabozantinib administration.	A final analysis **based on the primary endpoint (ORR)** will be performed **12 months after the last subject received the first cabozantinib administration.** A follow-up analysis based on OS will be conducted 18 months after the last subject received the first cabozantinib administration. **The statistical testing will only be carried out at the final analysis.**
82	14.2	Prior to ~~study entry~~, the Investigator or a person designated by the Investigator will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally	Prior to **screening**, the Investigator or a person designated by the Investigator will explain the nature, purpose, benefits and risks of participation in the study to each subject,

		acceptable representative or impartial witness. Written informed consent must be obtained before to the subject enters the study (before initiation of any study-related procedure and administration of cabozantinib). Sufficient time will be given to discuss any questions raised by the subject.	subject's legally acceptable representative or impartial witness. Written informed consent must be obtained before to the subject enters the study (before initiation of any study-related procedure and administration of cabozantinib). Sufficient time will be given to discuss any questions raised by the subject.
88	17.2	[…] As indicated in Section 11.6, an analysis will be performed on the final response data after the last subject has completed the treatment period. This analysis will be included in the final study report. An addendum to the report, including the analysis of data from the follow-up period, will be prepared after the last subject completes the follow-up period.	[…] As indicated in Section 11.6, **the intermediate analysis will be conducted when 60% of subjects of the first recruiting cohort reaching the target number of subjects have reached 12 months of study follow-up. This analysis will be included in the interim study report.** An analysis will be performed on the final response data after the last subject has completed the treatment period. This analysis will be included in the final study report. An addendum to the report, including the analysis of data from the follow-up period, will be prepared after the last subject completes the follow-up period.
90	18	***[references deleted]*** ~~20 Rini, Brian I., et al. "Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma." *New*~~	***[references added]*** 28 Kalirai A, Wood L, Lalani A et al. Efficacy of targeted therapy (TT) after checkpoint inhibitors (CPI) in metastatic renal cell carcinoma (mRCC): Results

		~~*England Journal of Medicine* (2019).~~ ~~21 Motzer, Robert J., et al. "Avelumab plus axitinib versus sunitinib for advanced renal cell carcinoma." *New England Journal of Medicine* (2019).~~	from the Canadian Kidney Cancer Information System (CKCis). *Journal of Clinical Oncology* 37, no. 7_suppl (March 1 2019) 568-568. ***29*** Ornstein MC, Pal SK, Wood LS et al. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2019.
92-93	Appendix		***[Appendix 1 Memorial Sloan Kettering Cancer Center (MSKCC) Criteria for prognostic risk category added]***
94-95	Appendix 2		***[Appendix 2 International Metastatic RCC Database Consortium (IMDC) risk group category added]***
96-97	Appendix 3		***[Appendix 3 Methods of contraception added]***
102	Appendix 4 (4 Vascular disorders)	[…]	[…] **Aneurysms and artery dissections** **The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully**

			considered in patients with risk factors such as hypertension or history of aneurysm.
104	Appendix 4 (6 Skin and subcutaneous tissue disorders)	Table A1.3 First column: **Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Grade**	*[Table A1.3 updated]* First column: **Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade**
107	Appendix 4 (11 Hepatic events)	Elevations of aminotransferases when hepatic ~~tumours~~ are present may not require ~~study treatment~~ 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. ~~Subjects with right upper quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.~~	**Investigators should monitor for Drug induced lived injury (DILI) diligently and report any potential events.** **Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (e.g. liver cirrhosis, thrombosis of portal or hepatic vein, HCC, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.** **If not otherwise specified in individual protocols, cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 × ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g. International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib**

			should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic **metastases** 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 bilirubin concentration or coagulation factors. **Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate DILI. Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.**
112	Appendix 5	**Definitions** Baseline: Baseline is defined as the most recent assessment performed prior to study entry. ~~In this study, baseline is equivalent to the Screening visit.~~ Baseline assessments must be performed within the period defined in the protocol eligibility criteria. […]	**Definitions** Baseline: Baseline is defined as the most recent assessment performed prior to study entry. Baseline assessments must be performed within the period defined in the protocol eligibility criteria. […]

121	Appendix 7		*[Appendix 7 updated]*

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	**F-FR-60000-023**	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #1): 28 November 2019	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	- Main changes of the protocol amendment #1 are linked to requests from Regulatory European authorities and ECs. - Correction of minor inconsistencies and typos. - Update of background and rationale parts due to new treatments approved in RCC	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 9 Amendment Form #2

STUDY NUMBER:	F-FR-60000-023
PROTOCOL TITLE:	A PHASE II, MULTICENTRE, OPEN-LABEL STUDY OF CABOZANTINIB AS 2ND LINE TREATMENT IN SUBJECTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA WITH A CLEAR-CELL COMPONENT WHO PROGRESSED AFTER 1ST LINE TREATMENT WITH CHECKPOINT INHIBITORS
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #2): 24 January 2020

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**28 NOVEMBER 2019**	**24 JANUARY 2020**
Page	**Section**	**WAS**	**IS**
97	Appendix 3		[…] **The interaction of cabozantinib with oral contraceptives has not been investigated and the contraceptive effect may not be guaranteed, therefore it is recommended that an additional contraceptive method such as a barrier method (e.g. condom or diaphragm) is used *by your patient* if *they* are *using* oral combined contraception or progestogen-only contraception.** Effective methods of birth control include: • Hormonal contraception (oral, injectable, implantable, transdermal) **plus a barrier method**; • intrauterine device (IUD) *or* intrauterine
		Effective methods of birth control include: • Hormonal contraception (oral, injectable, implantable, transdermal); ~~• 2 effective barrier methods (male or female~~	

		~~condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or~~ • intrauterine device (IUD) *o*r intrauterine hormone-releasing system (IUS) plus a barrier method; • bilateral tubal occlusion (females); • vasectomized partner (males). […] ~~The interaction of cabozantinib with oral contraceptives has not been investigated and *this may mean your oral contraceptive could be ineffective*, therefore it is recommended that an additional contraceptive method such as a barrier method (e.g. condom or diaphragm) is used if *you* are *taking* oral combined contraception or progestogen-only contraception.~~	hormone-releasing system (IUS) plus a barrier method; • bilateral tubal occlusion (females); • vasectomized partner (males).

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	**F-FR-60000-023**	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #2): 24 January 2020	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
Reason(s) for changes	- Main change of the protocol amendment #2 is linked to requests from Regulatory European authorities: re-wording of the contraceptive methods on a precautionary basis.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 10 Amendment Form #3

STUDY NUMBER:	F-FR-60000-023
PROTOCOL TITLE:	A PHASE II, MULTICENTRE, OPEN-LABEL STUDY OF CABOZANTINIB AS 2ND LINE TREATMENT IN SUBJECTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA WITH A CLEAR-CELL COMPONENT WHO PROGRESSED AFTER 1ST LINE TREATMENT WITH CHECKPOINT INHIBITORS
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #3): 03 March 2021

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**24 JANUARY 2020**	**03 MARCH 2021**
Page	**Section**	**WAS**	**IS**
1	Cover Page	**Emergency Contact:** PPD, Ipsen Innovation ZI de Courtaboeuf, 5 Avenue du Canada 91940 Les Ulis, France Mobile: +33 (0) 6 ~~99 40 03 70~~ **For serious adverse event (SAE) reporting:** Fax: ~~+44 (0) 1753 627860~~ E-mail: adverse.events@ipsen.com	**Emergency Contact:** Head Global **Patient Safety**, Ipsen Innovation ZI de Courtaboeuf, 5 Avenue du Canada 91940 Les Ulis, France Mobile: +33 (0) 6 **43 53 35 70** **For serious adverse event (SAE) reporting:** Fax: **+33 (0) 1 60 92 21 19** E-mail: adverse.events@ipsen.com

3	Coordinating investigator's agreement page		*[Page deleted]*
4	Synopsis (number of planned centres)	50 active centres	**Approximately** 50 active centres
5-6	Synopsis (Methodology)	[…]q **Post-treatment Follow-up Period:** Subjects who discontinue study treatment will be contacted during the Post-treatment Follow-up visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy.	[…] **Post-treatment Follow-up Period:** Subjects who discontinue study treatment will be contacted during the Post-treatment Follow-up visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy. **During the follow-up period, any SAEs that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator.**
6-7 and 37-38	Synopsis (Inclusion criteria) and Section 4.1	[…] (8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 15 days before baseline: (a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L). (b) Platelets ≥ 100,000/mm3 (≥ 100 GI/L).	[…] (8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 15 days before baseline: (a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L).

		(c) Haemoglobin ≥ 9 g/dL (≥ 90 g/L). (d) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN). (e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L). ~~(f) Fasting serum triglycerides ≤ 2.5 × ULN and total cholesterol ≤ 300 mg/dL (≤ 7.75 mmol/L). Lipid lowering medication is allowed.~~ (g) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation (h) Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g. […] (12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) and their partners must agree to use highly effective methods of contraception (that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly) during the course of the study and for ~~4 months~~ after the last dose of study treatment;	(b) Platelets ≥ 100,000/mm3 (≥ 100 GI/L). (c) Haemoglobin ≥ 9 g/dL (≥ 90 g/L). (d) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN). (e) Total bilirubin ≤ 1.5 × ULN. For subjects with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L). (f) Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation (g) Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g. […] (12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly) during the course of the study and for **120 days** after the last dose of study treatment;

7-8 and 38-39	Synopsis (Exclusion criteria) and Section 4.2	[…] (2) Was treated with any other investigational medicinal product (IMP) within the last 30 days before baseline; […] (7) Is receiving a concomitant anticoagulation with ~~oral anticoagulants~~ (e.g. warfarin, direct thrombin ~~and~~ Factor Xa ~~inhibitors)~~ or platelet inhibitors (e.g. clopidogrel). Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose, low molecular weight heparin (LMWH) ~~are permitted~~.	[…] (2) Was treated with any other investigational medicinal product (IMP) **during a clinical study** within the last 30 days before baseline; […] (7) Is receiving a concomitant anticoagulation with **coumarin agents** (e.g. warfarin**),** direct thrombin **inhibitor dabigatran, direct** Factor Xa **inhibitor betrixaban** or platelet inhibitors (e.g. clopidogrel). Note: **The following are allowed anticoagulants: prophylactic use of** low-dose aspirin for cardioprotection (per local applicable guidelines), and low dose **of** low molecular weight heparin (LMWH). **Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in patients without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before baseline without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.** […]

		[…] (13) Has been diagnosed with other clinically significant disorders such as: (a) Serious nonhealing wound/ulcer/bone fracture; (b) Malabsorption syndrome; ~~(c) Free thyroxine 4 (FT4) outside the laboratory normal reference range;~~ (d) Uncompensated/symptomatic hypothyroidism; (e) Moderate to severe hepatic impairment (Child-Pugh B or C); (f) Requirement for haemodialysis or peritoneal dialysis; (g) History of solid organ transplantation;	(13) Has been diagnosed with other clinically significant disorders such as: (a) Serious nonhealing wound/ulcer/bone fracture; (b) Malabsorption syndrome; (c) Uncompensated/symptomatic hypothyroidism **(subject with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study);** (d) Moderate to severe hepatic impairment (Child-Pugh B or C); (e) Requirement for haemodialysis or peritoneal dialysis; (f) History of solid organ transplantation;
9	Synopsis (Test product, dose, mode of administration)	[…] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) and ~~should occur within 15 days after the Screening visit~~. Doses will be self-administered at home by taking cabozantinib q.d. at the same time each day (preferably at bedtime). Cabozantinib should not be taken with food. The subject should not eat anything for at least 2 hours before and 1 hour after taking cabozantinib.	[…] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) and **screening and baseline visits can take place the same day as long as all eligibility criteria/parameters are available and checked prior to the first dose of cabozantinib**. Doses

			will be self-administered at home by taking cabozantinib q.d. at the same time each day (preferably at bedtime). Cabozantinib should not be taken with food. The subject should not eat anything for at least 2 hours before and 1 hour after taking cabozantinib.
10	Synopsis (Criteria for evaluation (endpoints))	Safety […] Routine safety evaluations throughout the study will include the recording of AEs, clinical laboratory (serum chemistry, haematology and urinalysis) test results, serum pregnancy tests (in females of childbearing potential), thyroid function tests, vital signs (BP and heart rate), ECG findings, physical examination findings and body weight measurements, and use of concomitant medication throughout the study. Information on new or worsening AEs will be collected from the date the informed consent is signed until the End of Study Treatment visit ~~(treatment related serious AEs (SAEs) are to be reported at any time, including after the study is finished)~~. This information will be collected at study visits, by telephone call to the subject or by spontaneous report by the subject. At baseline, AEs will be documented before and after cabozantinib dosing. Certain AEs and all SAEs that are ongoing 30 days after the date of the last cabozantinib dose are to be followed until resolution or until the Investigator considers the event is stable or irreversible. ~~Any AE/SAEs assessed as related to study treatment or study procedures, even~~ SAEs that occur more than 30 days after the date of the last cabozantinib dose, will also be collected and followed until resolution or stability according to the Investigator.	Safety […] Routine safety evaluations throughout the study **treatment period** will include the recording of AEs, clinical laboratory (serum chemistry, haematology and urinalysis) test results, serum pregnancy tests (in females of childbearing potential), thyroid function tests, vital signs (BP and heart rate), ECG findings, physical examination findings and body weight measurements, and use of concomitant medication throughout the study **treatment period**. Information on new or worsening AEs **and serious AEs (SAEs)** will be collected from the date the informed consent is signed until the End of Study Treatment visit. This information will be collected at study visits, by telephone call to the subject or by spontaneous report by the subject. At baseline, AEs will be documented before and after cabozantinib dosing. Certain AEs and all SAEs that are ongoing 30 days after the date of the last cabozantinib dose are to be followed until resolution or until the Investigator

			considers the event is stable or irreversible. **During the follow-up period, any** SAEs that occur more than 30 days after the date of the last cabozantinib dose, **assessed as related to study treatment or study procedures** will also be collected and followed until resolution or stability according to the Investigator.
11	Synopsis (Statistical Methods)	Sample size: With a true ORR proportion of 19%, a sample size of 117 subjects in each cohort will provide a statistical power of 80% to reject the null hypothesis of 10%, using a one-sample exact test for binomial distribution with a significance level of 0.025 (one-sided). Assuming approximately 7% non-evaluable subjects~~,~~ a total of 125 subjects per cohort will be included in the study. Statistical Methods: […] The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review ~~and confirmed by a subsequent visit ≥28 days later,~~ will be tested in each cohort using a one-sample exact test for binomial distribution.	Sample size: With a true ORR proportion of 19%, a sample size of 117 subjects in each cohort will provide a statistical power of 80% to reject the null hypothesis of 10%, using a one-sample exact test for binomial distribution with a significance level of 0.025 (one-sided). Assuming approximately 7% non-evaluable subjects **(i.e. subject who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1),** a total of 125 subjects per cohort will be included in the study. Statistical Methods: […] The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review will be tested in each cohort using a one-sample exact test for binomial distribution.

		[…] Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables, clinical laboratory tests ~~etc.~~ at each assessment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.	[…] Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables, clinical laboratory tests ~~etc.~~ at each assessment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.
24	1.1.2	[…] Checkpoint inhibitor (CPI) therapy with ipilimumab and nivolumab is also an approved treatment for advanced RCC. Indeed, in January 2019, the European Medicines Agency (EMA) granted ipilimumab and nivolumab Marketing Authorisation for 1st line treatment of intermediate- and poor-risk subjects with advanced RCC. ~~In September 2019,~~ European Commission approved pembrolizumab in combination with axitinib ~~and CHMP adopted positive opinion~~ for avelumab plus axitinib as first-line treatment for patients with advanced RCC.	[…] Checkpoint inhibitor (CPI) therapy with ipilimumab and nivolumab is also an approved treatment for advanced RCC. Indeed, in January 2019, the European Medicines Agency (EMA) granted ipilimumab and nivolumab Marketing Authorisation for 1st line treatment of intermediate- and poor-risk subjects with advanced RCC. European Commission approved pembrolizumab in combination with axitinib **in August 2019 and** for avelumab plus axitinib as first-line treatment for patients with advanced RCC **in September 2019.**
24	1.2	Cabozantinib (XL184) is a multitarget TKI that inhibits several proteins involved in the pathology of RCC, such as MET, VEGFR2, the tyrosine-protein kinase receptor UFO (AXL) and the proto-oncogene (RET). Cabozantinib is provided as both capsules and tablets, but the two formulations are not interchangeable.	Cabozantinib (XL184) is a multitarget TKI that inhibits several proteins involved in the pathology of RCC, such as MET, VEGFR2, the tyrosine-protein kinase receptor UFO (AXL) and the proto-oncogene (RET). Cabozantinib is

		~~Cometriq® (cabozantinib capsules, 20 and 80 mg) was approved as a treatment for subjects with progressive, metastatic medullary thyroid cancer (MTC) on 29 November 2012 by the Food and Drug Administration (FDA), and on 21 March 2014 by the EMA.~~ Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the EMA as a 2nd line treatment for subjects with advanced RCC previously treated with VEGF-targeted therapy, and as a 1st line treatment for adults with advanced RCC with intermediate and poor risk. Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the FDA for the treatment of all subjects with advanced RCC regardless of previous therapies received.	provided as both capsules and tablets, but the two formulations are not interchangeable. Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the EMA as a 2nd line treatment for subjects with advanced RCC previously treated with VEGF-targeted therapy, and as a 1st line treatment for adults with advanced RCC with intermediate and poor risk. Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the **Food and Drug Administration (**FDA**)** for the treatment of all subjects with advanced RCC regardless of previous therapies received.
27	1.3	Treatment with CPIs combined with antiangiogenic agents […] As such, ~~several clinical trials have been underway to determine~~ the efficacy and safety of ~~a~~ combination therapy with CPI and ~~antiangiogenic~~ TKI ~~agents~~ in untreated subjects with advanced RCC ~~(19). These~~ clinical trials include several Phase III trials, as follows: ~~An~~ ongoing ~~study evaluating the combination of cabozantinib and nivolumab *versus* sunitinib monotherapy in subjects with RCC (NCT03141177);~~ • ~~An ongoing~~ study evaluating the combination of lenvatinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02811861);	Treatment with CPIs combined with antiangiogenic agents […] As such, **two new therapeutic options axitinib plus pembrolizumab and axitinib plus avelumab showed** the efficacy and safety of combination therapy with CPI and TKI in untreated subjects with advanced RCC **have been approved by EMA in August 2019 and in September 2019, respectively. Some** clinical trials **are** ongoing: • **A** study evaluating the combination of lenvatinib and pembrolizumab *versus* sunitinib monotherapy in subjects with RCC (NCT02811861);

		• A study ~~that assessed the~~ combination ~~of atezolizumab~~ with ~~or without an anti-VEGF agent (bevacizumab)~~ *versus* ~~sunitinib in~~ untreated ~~subjects with~~ metastatic RCC (~~NCT02420821~~). Results from the study that assessed the combination of ~~atezolizumab~~ (a programmed death-ligand 1 ~~(PD-L1)~~/ PD-1 protein inhibitor) with ~~or without an anti-VEGF agent (bevacizumab)~~ *versus* sunitinib in untreated subjects with metastatic RCC (~~IMmotion151~~ trial) showed that cabozantinib and atezolizumab ~~and bevacizumab~~ in combination improved PFS compared to sunitinib in subjects with untreated metastatic or advanced RCC (20). ~~A recent safety analysis showed that atezolizumab and bevacizumab in combination showed a tolerable safety profile in subjects with metastatic RCC with less toxicity compared to sunitinib. The toxicities observed were consistent with each agent alone, and no new AEs were identified in this analysis (21).~~	• A study **of cabozantinib in** combination with **nivolumab and ipilimumab in patients with previously** untreated **advanced of** metastatic RCC **(NCT03937219).** Results from the study **(NCT0314177)** that assessed the combination of **nivolumab** (a programmed death-ligand 1/ PD-1 protein inhibitor) with **cabozantinib** *versus* sunitinib in untreated subjects with metastatic RCC (**CkeckMate 9ER** trial) showed that **cabozantinib and** atezolizumab in combination improved PFS **and OS** compared to sunitinib in subjects with untreated metastatic or advanced RCC (20).
29	1.4	The primary endpoint is ORR, defined as the proportion of subjects with ~~a confirmed~~ CR or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, as determined by an independent central review.	The primary endpoint is ORR, defined as the proportion of subjects with CR or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, as determined by an independent central review.
30	1.7	[…] In case of data transfer outside the European Union (EU), the Sponsor will either ensure that the countries where data are transferred provide an adequate level of data protection or that the company receiving data ~~has joined the EU-United States of America Privacy Shield Framework or~~ will put in place a contract including standard contractual clauses adopted by the European Commission to ensure that the transfer of study information complies with applicable data	[…] In case of data transfer outside the European Union (EU), the Sponsor will either ensure that the countries where data are transferred provide an adequate level of data protection or that the company receiving data will put in place a contract including standard contractual clauses adopted by the European Commission to ensure

		protection legislation. Such a contract can be made available upon request.	that the transfer of study information complies with applicable data protection legislation. Such a contract can be made available upon request.
31	2.1	Cabozantinib is currently approved in the United States as a treatment for adults with advanced RCC regardless of previous therapies received. In the EU, cabozantinib is approved ~~as a 1st line~~ treatment ~~for adults with~~ advanced RCC with intermediate ~~and~~ poor risk and ~~as a 2nd line treatment for subjects previously treated with (~~VEGF~~)~~ targeted therapy.	Cabozantinib is currently approved in the United States as a treatment for adults with advanced RCC regardless of previous therapies received. In the EU, cabozantinib is approved **for the** treatment **of** advanced **renal cell carcinoma (**RCC**) in treatment-naïve adults** with intermediate **or** poor risk and **following prior vascular endothelial growth factor (**VEGF)-targeted therapy.
32-33	3.1	This study will be conducted in approximately 50 active investigational sites across Germany, Switzerland, the Netherlands, France, UK, Austria and Spain. The list of countries and the number of investigational sites may change during the study depending on recruitment and availability of the ~~CPI~~ combination ~~(ipilimumab and nivolumab)~~ in each country. […] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) ~~and should occur within 15 days after the Screening visit~~. […] <u>Post-treatment Follow-up Period:</u> Subjects who discontinue study treatment will be contacted during the Post-treatment Follow-up	This study will be conducted in approximately 50 active investigational sites across Germany, Switzerland, the Netherlands, France, UK, Austria and Spain. The list of countries and the number of investigational sites may change during the study depending on recruitment and availability of the **first line** combination **therapies** in each country. […] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2). […] <u>Post-treatment Follow-up Period:</u> Subjects who discontinue study treatment will be contacted

		visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy. Any ~~AE/serious AEs (~~SAEs~~)~~ assessed as related to ~~cabozantinib~~ or study procedures, ~~even SAEs that occur more than 30 days after the date of the last cabozantinib dose,~~ will also be collected and followed until resolution or stability according to the Investigator.	during the Post-treatment Follow-up visits every 12 weeks ±15 days to assess survival status and collect information about subsequent anti-cancer therapy. **During the follow-up period,** any SAEs **that occur more than 30 days after the date of the last cabozantinib dose,** assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator. *[Figure 1 updated]*
34	3.2.3	The safety and tolerability of cabozantinib will be assessed throughout the study by evaluating AEs, clinical laboratory test results, vital signs measurements, electrocardiogram (ECG) and physical examination results, and use of concomitant medication (see Section 8).	The safety and tolerability of cabozantinib will be assessed throughout the study **treatment period** by evaluating AEs, clinical laboratory test results, vital signs measurements, electrocardiogram (ECG) and physical examination results, and use of concomitant medication (see Section 8).
35	3.5	[…] In addition to the information provided in the IWRS, drug accountability ~~paper~~ records documenting that each subject received the allocated study treatment will be maintained by the Investigator.	[…] In addition to the information provided in the IWRS, drug accountability records documenting that each subject received the allocated study treatment will be maintained by the Investigator **or delegate**.
35	3.6	The study is planned to start in the fourth quarter of 2019 and will start when the first subject provides a signed informed consent form. The inclusion period is estimated to last approximately 24 months, but this may be extended if necessary. For each subject, the study will start from ~~their first cabozantinib administration~~ and may last until	The study is planned to start in the fourth quarter of 2019 and will start when the first subject provides a signed informed consent form. The inclusion period is estimated to last approximately 24 months, but this may be

		the end of the study (18 months after the last subject included in the study received first cabozantinib dose). […] Such subjects will be followed until at least 30 days after their last study treatment with cabozantinib administration. Information about cabozantinib administration, ~~AEs~~ and any SAEs will be collected during ~~this~~ period.	extended if necessary. For each subject, the study will start from **the ICF signature** and may last until the end of the study (18 months after the last subject included in the study received first cabozantinib dose). […] Such subjects will be followed until at least 30 days after their last study treatment with cabozantinib administration. Information about cabozantinib administration and any **related** SAEs will be collected during **the** period **when Cabometyx® is supplied free of charge from Ipsen**.
35	3.7	Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. As required by GCP guidelines, the monitor assigned by the Sponsor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.	Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. As required by GCP guidelines, the monitor assigned by the Sponsor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF **as defined in the monitoring plan**.
40	4.3.1	[…]	[…] **In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the study drug administration may be temporarily discontinued depending on the subject clinical status. In some cases, the investigator may**

			request a participant be retested before the study drug administration is resumed.
44 to 47	Table 2	Pre-treatment period column: Prior to ~~Screening~~ Pre-treatment period column and Line AEs: ~~≤ 15 Days prior to Screening~~ Footnote: [a] ~~All assessments should be performed~~ and the ~~corresponding results obtained~~ prior to first dose of cabozantinib ~~to ensure subjects meet the eligibility criteria.~~ […]	Assessment column: […] • **Smoking habits/status** Pre-treatment period column and Line 4: **Before first cabozantinib intake** Pre-treatment period column and Smoking habits/status line: **X** Pre-treatment period column: Prior to **baseline** Pre-treatment period column and Line AEs: **X** Footnote: [a] **Screening** and **baseline visits can take place** the **same day as long as all eligibility criteria/parameters are available and checked** prior to **the** first dose of cabozantinib. […]

		[e] Informed consent ~~may be obtained more than 15 days prior to screening but~~ must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be used as Screening evaluations if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC) policies of the investigational site. […] [l] During the Post-treatment Follow-up period, any ~~AE/~~SAEs assessed as related to ~~cabozantinib~~ or study procedures, ~~even SAEs that occur more than 30 days after the date of the last cabozantinib dose,~~ will also be collected and followed until resolution or stability according to the Investigator. [m] Information on prior and concomitant medication will be collected up to 30 days before ~~screening~~ until 30 days after the date of the last cabozantinib dose.	[e] Informed consent must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be used as Screening evaluations if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC) policies of the investigational site. […] [l] During the follow-up period, any SAEs **that occur more than 30 days after the date of the last cabozantinib dose,** assessed as related to **study treatment** or study procedures will also be collected and followed until resolution or stability according to the Investigator. [m] Information on prior and concomitant medication will be collected up to 30 days before **baseline** until 30 days after the date of the last cabozantinib dose.
48	5.2.1	[…] All screened subjects will be allocated a subject number so that they can be identifiable throughout the study. The Investigator will maintain a list of screened subjects (i.e. who signed the informed consent form), subject numbers and names to ensure that all records may be found at a later date if required. ~~Under no circumstances will subjects be screened more than once.~~ In case a subject does not receive cabozantinib after the Screening visit, the primary reason will be recorded.	[…] All screened subjects will be allocated a subject number so that they can be identifiable throughout the study. The Investigator will maintain a list of screened subjects (i.e. who signed the informed consent form), subject numbers and names to ensure that all records may be found at a later date if required. In case a subject does not receive cabozantinib after the

			Screening visit, the primary reason will be recorded.
48	5.2.2	[…] ~~Subjects should receive their first dose of cabozantinib within 15 days after the Screening visit~~. […] Subjects with radiographic progression per RECIST 1.1 evaluated by the Investigator may continue study treatment if the Investigator believes that there still is clinical benefit and that it outweighs potential risks. In this case, study treatment can be continued up to the end of the study (Section 5.6), unless the subject decides to discontinue study treatment due to unacceptable toxicity or needs subsequent systemic anti-cancer treatment.	 […] Subjects with radiographic progression per RECIST 1.1 evaluated by the Investigator may continue study treatment if the Investigator believes that there still is clinical benefit and that it outweighs potential risks. In this case, study treatment can be continued up to the end of the study (Section 5.6), unless the subject **or the investigator** decides to discontinue study treatment due to unacceptable toxicity or needs subsequent systemic anti-cancer treatment.
49	5.2.3.1	[…] Any ~~AE/~~SAEs assessed as related to ~~cabozantinib~~ or study procedures, ~~even SAEs that occur more than 30 days after the date of the last cabozantinib dose,~~ will also be collected and followed until resolution or stability according to the Investigator.	[…] **During the follow-up period,** any SAEs **that occur more than 30 days after the date of the last cabozantinib dose,** assessed as related to **study treatment** or study procedures will also be collected and followed until resolution or stability according to the Investigator.
50	5.6	[…] Such subjects will be followed until at least 30 days after their last study drug with cabozantinib administration. Information about	[…] Such subjects will be followed until at least 30 days after their last study drug with cabozantinib administration. Information about

		cabozantinib administration~~, AEs~~ and any SAEs will be collected during ~~this~~ period.	cabozantinib administration and any **related** SAEs will be collected during **the** period **when Cabometyx® is supplied free of charge from Ipsen**.
51	6.2.1	[…] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) ~~and should occur within 15 days after the Screening visit~~). Subjects will take cabozantinib tablets q.d. at home, at the same time each day, preferably at bedtime. Any unused study treatment must be returned to the investigational site for drug accountability and disposal. If a dose is missed, the missed dose should not be taken less than 12 hours before the next one. The ~~assigned~~ dose is 60 mg q.d. as indicated in all approvals of cabozantinib (Cabometyx™).	[…] The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2). Subjects will take cabozantinib tablets q.d. at home, at the same time each day, preferably at bedtime. Any unused study treatment must be returned to the investigational site for drug accountability and disposal. If a dose is missed, the missed dose should not be taken less than 12 hours before the next one. The **recommended** dose is 60 mg q.d. as indicated in all approvals of cabozantinib (Cabometyx™).
52	6.2.1.1	The required study assessments and blood collections should be done prior to any study treatment administration. ~~Subjects should receive their first dose of cabozantinib within 15 days after the Screening visit.~~	The required study assessments and blood collections should be done prior to any study treatment administration.
52	6.2.1.2	~~After baseline, all subsequent doses of cabozantinib will also be self-administered at home~~. Subjects ~~should~~ fast for at least 2 hours ~~after eating the evening meal (water is allowed)~~ before taking ~~the study treatment.~~ After the 2-hour ~~fasting and before going to bed~~, subjects are to take cabozantinib with a full glass of water (~~at least 8 oz or~~ 240 mL) with no food intake for ~~1~~ hour post-dose. If the subject's schedule requires taking cabozantinib during the day, the subject ~~should~~ be instructed to follow the same fasting recommendations.	Subjects **are to** fast **(with the exception of water)** for at least 2 hours before taking **their dose.** After the 2-hour **fast**, subjects are to take cabozantinib with a full glass of water (**minimum of** 240 mL) with no food intake for **one more** hour post-dose. If the subject's schedule requires taking cabozantinib during the

		~~The subject should take cabozantinib at approximately the same time every day and adhere to the fasting requirements described in this section.~~	day, the subject **is to** be instructed to follow the same fasting recommendations.
52	6.2.2	Subjects will be monitored for AEs from the time of signing informed consent until 30 days after the date of the last dose of cabozantinib. Any SAE that the Investigator believes to be related to cabozantinib or study procedures can be reported at any time after the last dose with no time limitation.	Subjects will be monitored for AEs from the time of signing informed consent until 30 days after the date of the last dose of cabozantinib. Any SAE that the Investigator believes to be related to cabozantinib or study procedures can be reported at any time after the last dose with no time limitation **during the follow-up period**.
55	6.2.4	The side effect profile of cabozantinib includes, in descending order of frequency, diarrhoea, fatigue, decreased appetite, nausea, ~~weight decrease~~, palmar-plantar erythrodysaesthesia syndrome (PPES), vomiting, constipation, ~~hypertension~~, dysgeusia, dysphonia, asthenia, ~~and dyspnoea~~ (please refer to the Investigator's Brochure for additional details). Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g. deep vein thrombosis (DVT), pulmonary embolism, TIA and MI), ~~aneurysms and artery dissections,~~ severe haemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, ~~ONJ~~, and reversible posterior leukoencephalopathy syndrome (RPLS) ~~also known as Posterior Reversible Encephalopathy Syndrome (PRES~~).	The side effect profile of cabozantinib includes, in descending order of frequency, diarrhoea, fatigue, decreased appetite, nausea, palmar-plantar erythrodysaesthesia syndrome (PPES), vomiting, **weight decreased, hypertension**, constipation, dysphonia **and** asthenia (please refer to the Investigator's Brochure for additional details). Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g. deep vein thrombosis (DVT), pulmonary embolism, TIA and MI), severe haemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, **osteonecrosis**, and reversible posterior leukoencephalopathy syndrome (RPLS).

56	6.3.1	[…] • Individualised anticoagulation therapy ~~with heparin~~ is allowed if it can be provided safely and effectively under the following circumstances: - ~~Low~~ dose heparins for ~~prophylactic use~~ are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion; - Therapeutic doses of LMWH ~~at the time of first dose~~ are allowed ~~if the subject has no evidence of~~ brain ~~metastasis, has been~~ on a stable dose of ~~LMWH~~ for at least ~~12 weeks, and has had no~~ complications from ~~a thromboembolic event or~~ the anticoagulation regimen; ~~- Therapeutic doses of LMWH after first dose are allowed if clinically indicated (e.g. for the treatment of deep venous thrombosis) and the benefit outweighs the risk per the Investigator's discretion;~~ - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy ~~with heparins~~ must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g. due to kidney dysfunction);	[…] • Individualised anticoagulation therapy is allowed if it can be provided safely and effectively under the following circumstances: - **Prophylactic use of low** dose heparins for **cardioprotection per local applicable guidelines), and low dose of LMWH** are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion; - Therapeutic doses of LMWH **or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban** are allowed **in patients without known** brain **metastases who are** on a stable dose of **the anticoagulant** for at least **1 week before baseline without clinically significant hemorrhagic** complications from the anticoagulation regimen **or the tumour.** - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation

			therapy must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g. due to kidney dysfunction);
56	6.3.2	[…] • Any ~~oral anticoagulants (e.g. warfarin or other~~ coumarin ~~related~~ agents~~,~~ direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel~~, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines~~); • Any other systemic anti-cancer treatment (e.g. chemotherapy, immunotherapy, radionuclides) and local ~~anti-cancer treatment~~ such as surgery, ablation, or embolisation. […] • Chronic co-administration of cabozantinib with strong inducers of the cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4) family (e.g. ~~dexamethasone,~~ phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;	[…] • Any coumarin agents **(e.g. warfarin),** direct thrombin **inhibitor dabigatran**, direct FXa inhibitors **betrixaban**, or antiplatelet **inhibitor** (**e.g.** clopidogrel); Any other systemic anti-cancer treatment (e.g. chemotherapy, immunotherapy, radionuclides) and local **therapy** such as surgery, ablation, or embolisation. […] • Chronic co-administration of cabozantinib with strong inducers of the cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4) family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease

			cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;
57-58	6.3.3	Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) showed that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the curve (AUC) of co-administered rosiglitazone, a cytochrome P450 Family 2 Subfamily C Member 8 (CYP2C8) substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other cytochrome P450 (CYP450) isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e. cytochrome P450 Family 2 Subfamily C Member 9 (CYP2C9), cytochrome P450 Family 2 Subfamily C Member 19 (CYP2C19), cytochrome P450 Family 2 Subfamily D Member 6 (CYP2D6), cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2), and CYP3A4). *In vitro* data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 µM). […] Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. ~~dexamethasone,~~ phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. […] Protein Binding: Cabozantinib is highly bound (≥99.7%) to human plasma proteins.	Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) showed that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the curve (AUC) of co-administered rosiglitazone, a cytochrome P450 Family 2 Subfamily C Member 8 (CYP2C8) substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other cytochrome P450 (CYP450) isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e. cytochrome P450 Family 2 Subfamily C Member 9 (CYP2C9), cytochrome P450 Family 2 Subfamily C Member 19 (CYP2C19), cytochrome P450 Family 2 Subfamily D Member 6 (CYP2D6), cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2), and CYP3A4). *In vitro* data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of **Cytochrome P450 Family 1 Subfamily A Member 1(**CYP1A1**)** at high cabozantinib concentrations (30 µM).

		[…] Effect of cabozantinib on other medicinal products: The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.	[…] Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. […] Protein Binding: Cabozantinib is highly bound (≥99.7%) to human plasma proteins **(for details see the SmPC document (11), section 5.2).** […] Effect of cabozantinib on other medicinal products: The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended **(see Appendix 3).**
60	7.3.1	[…] Tumour assessments will determine the study endpoints of ORR, TTR, DOR, DCR, and PFS. The review of radiographic images will be conducted by a blinded, central IRC (Section 3.8) by batch (see IRC charter).	[…] Tumour assessments will determine the study endpoints of ORR, TTR, DOR, DCR, and PFS. The review of radiographic images will be conducted by a blinded, central IRC (Section 3.8) by batch **using RECIST 1.1** (see IRC charter).

61	7.3.3	[…] Permission for use of the FKSI-DRS questionnaire ~~is~~ obtained by contacting Dr. Cella at information@facit.org.	[…] Permission for use of the FKSI-DRS questionnaire **was** obtained by contacting Dr. Cella at information@facit.org.
62	8.1	Adverse events will be monitored from the time the subject gives informed consent and throughout the study (see Section 3.6 for a definition of study duration) and will be assessed by direct, nonleading questioning.	Adverse events will be monitored from the time the subject gives informed consent and throughout the study **treatment** (see Section 3.6 for a definition of study duration) and will be assessed by direct, nonleading questioning.
62	8.1.1	[…] This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.6 and Section 5.6). […] Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the ~~baseline~~ clear-cell component RCC.	[…] This definition includes events occurring from the time of the subject giving informed consent until the end of the study **treatment** (as defined in Section 3.6 and Section 5.6). […] Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the clear-cell component RCC.
64	8.1.3	[…] ~~Any AE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study (Section 5.6) must be reported promptly, within 24 hours.~~	[…] **During the follow-up period, any SAE that occur more than 30 days after the date of the last cabozantinib dose, assessed as related to study treatment or study procedures will also be collected and followed until resolution or stability according to the Investigator.**

64- 65-66	8.1.4	All SAEs (as defined below), regardless of ~~treatment group or~~ suspected relationship to IMP, must be reported immediately (within 24 hours of the Investigator's knowledge of the event) using the email specified at the beginning of this protocol. […] (6) Is an important medical event that may not immediately result in death, be life-threatening or require hospitalisation but may be considered an SAE when, based upon appropriate medical judgement, it may jeopardise the subject or 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 in-patient hospitalisation, or the development of drug dependency or drug abuse.	All SAEs (as defined below), regardless of suspected relationship to IMP, must be reported immediately (within 24 hours of the Investigator's knowledge of the event) using the email specified at the beginning of this protocol. […] (6) Is an important medical event that may not immediately result in death, be life-threatening or require hospitalisation but may be considered an SAE when, based upon appropriate medical judgement, it may jeopardise the subject or 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 in-patient hospitalisation, or the development of drug dependency or drug abuse. **A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically important serious event" if no other seriousness criteria are present (e.g. hospitalisation)).**

		[…] • While most hospitalisations necessitate reporting of an SAE, some hospitalisations do not require SAE reporting, as follows: - For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol; - Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for seriousness but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor; - Pre-planned or elective treatments/surgical procedures should be noted in the subject's Screening documentation. 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;	[…] • While most hospitalisations necessitate reporting of an SAE, some hospitalisations do not require SAE reporting, as follows: - For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol; - Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for seriousness but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor; - Pre-planned or elective treatments/surgical procedures should be noted in the subject's Screening documentation. 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. **If a new elective treatment/surgical procedure is required for a subject during their participation in the study the elective treatment/surgical procedure should be considered a SAE;**
		[…] The Investigator must also report: • All SAEs that occur after informed consent and through 30 days after the date of the last cabozantinib dose (or the date	[…] The Investigator must also report: • All SAEs that occur after informed consent and through 30 days after the date of the last cabozantinib dose (or the date the subject is deemed to be a screen failure). This information must be recorded on the AE page of the eCRF; • Any SAEs assessed as related to study treatment or study procedures. **During the follow-up period, any** SAE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study (Section 5.6) must be reported promptly **to the sponsor**, within 24 hours.

		the subject is deemed to be a screen failure). This information must be recorded on the AE page of the eCRF; • Any ~~AE/~~SAEs assessed as related to study treatment or study procedures, ~~including SAEs occurring more than 30 days after the date of the last cabozantinib dose.~~ ~~If the subject does not meet the eligibility criteria during the Screening visit, then SAEs only need to be reported from the time the subject signs the informed consent until the day when the subject has been determined to not be eligible for study participation.~~ ~~Any~~ SAE with a suspected causal relationship to cabozantinib administration occurring at any other time after completion of the study (Section 5.6) must be reported promptly, within 24 hours.	
67	8.1.6	[…] Any overdose or study medication error that results in an AE or SAE (excluding missed doses) requires reporting within 24 hours to the Sponsor or designee. ~~Forms for reporting medication errors will be provided to the investigational sites.~~	[…] Any overdose or study medication error that results in an AE or SAE (excluding missed doses) requires reporting within 24 hours to the Sponsor or designee.
68	8.2	[…] All laboratory tests to establish eligibility must be done within 15 days prior to ~~screening~~ (Table 2). […] On days when a blood sample is collected, subjects must fast overnight (~~no caloric intake for at least 8 hours,~~ consumption of water is allowed).	[…] All laboratory tests to establish eligibility must be done within 15 days prior to baseline (Table 2). […] On days when a blood sample is collected, subjects must fast overnight (consumption of water is allowed)
69	8.2	Table 5	*[Table 5 updated]*

		Blood Chemistry column: […] - Glucose ~~(fasted)~~ […] ~~- Total cholesterol (fasted)~~ ~~- Triglycerides (fasted)~~	Blood Chemistry column: […] - Glucose
69	8.2.1	A β-HCG serum test and/or an HCG urine test will be performed for all female subjects of childbearing potential within 7 days prior to the ~~Screening~~ visit and at every visit thereafter up to the End of Study Treatment or Early Study Withdrawal visit (Table 2).	A β-HCG serum test and/or an HCG urine test will be performed for all female subjects of childbearing potential within 7 days prior to the **baseline** visit and at every visit thereafter up to the End of Study Treatment or Early Study Withdrawal visit (Table 2).
73	11.1	The following populations will be used during statistical analyses: • **Screened population**: All subjects screened (i.e. who signed the informed consent).	The following populations will be used during statistical analyses: • **Screened population**: All subjects screened (i.e. who signed the informed consent). • **Included population: All subjects screened who fulfilled the inclusion and exclusion criteria.**
73	11.1.2	Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (efficacy, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, efficacy and PP populations will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include	Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (efficacy, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, efficacy and PP populations will be reviewed prior to database lock. The list may be updated,

		any additional major protocol deviations impacting inclusion in the ~~PP population~~.	up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the **analyses populations**.
73-74	11.2	[…] Assuming approximately 7% non-evaluable subjects~~,~~ 125 subjects in each cohort provides at least 80% power (at one-sided significance level (alpha) of 0.025) to reject the null hypothesis of 10% ORR in favour of an alternative hypothesis of 19% ORR. In total, 250 subjects need to be included in the study.	[…] Assuming approximately 7% non-evaluable subjects **(i.e. subjects who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1),** 125 subjects in each cohort provides at least 80% power (at one-sided significance level (alpha) of 0.025) to reject the null hypothesis of 10% ORR in favour of an alternative hypothesis of 19% ORR. In total, 250 subjects need to be included in the study.
74	11.4.1	Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease and other assessments performed at the Screening visit) will be presented by cohort and overall for the ~~screened and~~ safety population~~s~~.	Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease and other assessments performed at the Screening visit) will be presented by cohort and overall for the safety population.
74	11.4.2	The numbers and percentages of subjects in the screened, safety, efficacy and PP populations will be tabulated by cohort and overall. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were screened, screened failed, treated, discontinued and completed each of the study periods (pre-treatment period, treatment period, post-treatment period) will be tabulated by cohort and overall.	The numbers and percentages of subjects in the screened, **included,** safety, efficacy and PP populations will be tabulated by cohort and overall. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were screened, screened failed, treated, discontinued and completed each of the study periods (pre-

		Primary reasons for discontinuation of study treatment will be tabulated.	treatment period, treatment period, post-treatment **follow-up** period) will be tabulated by cohort and overall. Primary reasons for discontinuation of study treatment will be tabulated.
74	11.4.3.1	[…] • Objective response rate (ORR) defined as the proportion of subjects who achieved a partial response (PR) or complete response (CR) at any timepoint as determined by independent central review per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, ~~confirmed by a subsequent visit ≥28 days later~~.	[…] • Objective response rate (ORR) defined as the proportion of subjects who achieved a partial response (PR) or complete response (CR) at any timepoint as determined by independent central review per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.
74-75	11.4.3.2	[…] • Duration of response (DOR) defined as the time from first documented response (PR or CR as determined by independent central review per RECIST 1.1 ~~that is subsequently confirmed~~) to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first. ~~If the response is not confirmed, it will not be included.~~ Censoring rules will be similar to those applied for progression-free survival (PFS);	[…] • Duration of response (DOR) defined as the time from first documented response (PR or CR as determined by independent central review per RECIST 1.1) to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first. Censoring rules will be similar to those applied for progression-free survival (PFS);
76	11.4.3.4	[…] Additional supportive analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing assessments, address bias due to tumour assessment timing, evaluate the impact of potentially	[…] Additional supportive analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing assessments,

		informative censoring, and to address potential discrepancies between the documentation of progression per the Investigator and per the independent central review. ~~These analyses will be performed using the same statistical methods described for the primary analysis.~~	address bias due to tumour assessment timing, evaluate the impact of potentially informative censoring, and to address potential discrepancies between the documentation of progression per the Investigator and per the independent central review.
76	11.4.4	[…] Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables, clinical laboratory tests ~~etc.~~ at each assessment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Concomitant medications will be standardised using the World Health Organization drug dictionary and summarised by ~~SOC~~ and ~~PT~~.	[…] Summary statistics (mean, median, standard deviation and range as appropriate) of values and changes or shifts from baseline will be presented by cohort and overall for vital signs, ECG variables, clinical laboratory tests at each assessment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Concomitant medications will be standardised using the World Health Organization drug dictionary and summarised by **anatomic therapeutic class (ATS)** and **preferred name**.
77	11.5	Subgroup analyses will be conducted by presenting the primary analysis of ORR (with point estimates and 95% CIs) for both independent central review and Investigator's assessment in the following subgroups: • Age (<65 years, ≥65 years); • Gender (female, male);	Subgroup analyses will be conducted by presenting the primary analysis of ORR (with point estimates and 95% CIs) for both independent central review and Investigator's assessment in the following subgroups: • Age (<65 years, ≥65 years); • Gender (female, male);

		• MSKCC Risk Factors (favourable [0], intermediate [1], poor [2 or more]); • Heng criteria (favourable [0], intermediate [1-2], poor [3-6]); • Number of organs with metastases (1, 2, ≥3); • ECOG (0, 1); • Treatment duration on 1st anti-cancer therapy (<6 months, ≥6 months); ~~• Tumour MET status (high, low, unknown);~~ ~~• PD-L1 status (negative, positive, unknown).~~	• MSKCC Risk Factors (favourable [0], intermediate [1], poor [2 or more]); • Heng criteria (favourable [0], intermediate [1-2], poor [3-6]); • Number of organs with metastases (1, 2, ≥3); • ECOG (0, 1); • Treatment duration on 1st anti-cancer therapy (<6 months, ≥6 months);
84-85	15.2	[…] For screening failure subjects, ~~only~~ the Unique Subject Identifier, the date of informed consent signature, the reason why the subject failed screening and the potential AEs which occurred during the Screening visit will be reported in the eCRFs and collected in the Sponsor's database.	[…] For screening failure subjects, the Unique Subject Identifier, the date of informed consent signature, the reason why the subject failed screening and the potential AEs which occurred during the Screening visit will be reported in the eCRFs and collected in the Sponsor's database **(for complete list of data to be collected for screen failure patients, please refer to eCRF completion Guidelines).**
85	15.3	During the ~~pre-treatment period and~~ initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.	During the initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.
88	17.2	[…] This analysis will be included in the interim study report. An analysis will be performed on the final response data after the last subject ~~has completed~~ the ~~treatment period.~~ This analysis will be included in the	[…] This analysis will be included in the interim study report. An analysis will be performed on the final response data **12 months** after the last

		final study report. An addendum to the report, including the analysis of data from the follow-up period, will be prepared after the last subject ~~completes~~ the ~~follow-up period~~.	subject **received** the **first cabozantinib administration.** This analysis will be included in the final study report. An addendum to the report, including the analysis of data from the follow-up period, will be prepared **18 months** after the last subject **received** the **first cabozantinib administration**.
89-90	18	11 Cabometyx Product Information. https://www.~~medicines.org.uk/emc/product/7631/smpc~~ 12 Choueiri~~, Toni K.~~, et al ~~"~~Cabozantinib versus everolimus in advanced renal-cell carcinoma.~~"~~ ~~*New England Journal of Medicine* 373.19 (2015): 1814-1823.~~ […] ~~20 Motzer, Robert J., et al. "IMmotion151: a randomized phase III study of atezolizumab plus~~	11 Cabometyx® Product Information, **October 2020**. https://www.**ema.europa.eu** 12 Choueiri **TK, Escudier B**, et al, **for the METEOR investigators.** Cabozantinib versus everolimus in advanced renal cell carcinoma **(METEOR):final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016; published online June 5. http://dx.doi.org/10.1016/S1470-2045(16)30107-3.** […] **20 Choueiri TK, et al. Oral presentation 6960. Presented at ESMO 2020.** […] 22 Escudier, Bernard, et al. "Renal cell carcinoma: ESMO Clinical Practice Guidelines for

		~~bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC).” Journal of Clinical Oncology 2018 36:6_suppl, 578-578.~~ ~~21 Suarez, C., et al. “873P Safety and tolerability of atezolizumab (atezo) plus bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC): Pooled analysis of IMmotion150 and IMmotion151.” *Annals of Oncology* 29. suppl_8 (2018): mdy283.082~~	diagnosis, treatment and follow-up.” *Annals of oncology* (2019**) updated on 30 November 2020.**
107	Appendix 4	10 Nervous system disorders […] RPLS ~~also known PRES~~ has been reported and should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.	10 Nervous system disorders […] RPLS has been reported and should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.
112 to 118	Appendix 5		*[Appendix 5 updated]*

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	**F-FR-60000-023**	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #3): 03 March 2021	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	- Update of inclusion and exclusion criteria - Correction of minor inconsistencies and typos. - Update of background and rationale parts due to new treatments approved in RCC - Update of AE management part due to the availability of new Investigator's Brochure. - Addition of some clarifications	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 11 Amendment Form #4

Amendment 4 (23 February 2022)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for the Amendment:

Since the set-up of Cabopoint study, increasing clinical data is supporting a higher targeted ORR in the post IO 2L setting compared to the initial statistical assumptions for Cabopoint. Beside this increasing supporting data, the evaluation by investigator assessment of the first 21 subjects of cohort A is demonstrating a ORR >30%. Based on the significant underperformance of the study enrolment, an amendment of the study including a new statistical assumption is the only possibility to proceed with Cabopoint, alternative would have been to stop study enrolment due to underperformance.

With an adapted statistical assumption based on latest clinical data, it will be possible to finalize the study in a meaningful scientifically and timeline manner.

Summary change table from previous version of the protocol

Section	WAS (Version 5.0, 03 MARCH 2021)	IS (Version 6.0, Date)	Rationale
Cover Page	Sponsor Signatory: PPD 65 Quai Georges Gorse 92650 Boulogne-Billancourt Cedex,France Tel: +33 (0) 1 58 33 50 00	Sponsor Signatory: PPD 65 Quai Georges Gorse 92650 Boulogne-Billancourt Cedex, France Tel: +33 (0) 1 58 33 50 00	Modification of sponsor's representative
INVESTIGATOR'S AGREEMENT	**Sponsor's Representative Signature:** NAME: PPD	**Sponsor's Representative Signature:** NAME: PPD	Modification of sponsor's representative
Synopsis (Planned study period)	~~Q3 2019~~ to Q~~1~~ 2023	**Q1 2020** to Q**4** 2023	Update of study timelines.

Synopsis (Primary Study Objective) and Section 2.2.1	• To assess the efficacy of cabozantinib by the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review.	• To assess the efficacy of cabozantinib by the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by independent central review **in cohort A**.	Removal of cohort B from the primary objective/endpoint as no more hypothesis is defined for cohort B.

Synopsis (Secondary Study Objective) and Section 2.2.2	• To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent and Investigator's review; • To assess objective response rate (ORR) by Investigator's review; • To assess overall survival (OS)	• To assess other efficacy criteria of cabozantinib such as time to response (TTR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by independent **central review** and Investigator's review; • To assess objective response rate (ORR) by **independent central review and** Investigator's review **in cohort B**; • **To assess ORR by Investigator's review in cohort A** • To assess overall survival (OS) • **To assess the ORR and PFS by Investigator's review and OS in overall population (cohorts A+B)**	Description of cohort B in the secondary objective/endpoint as no more hypothesis is defined for cohort B. To add Investigator review of ORR and PFS and to add OS assessment for cohorts A and B.

Synopsis (Methodology) and Section 3.1	This is a Phase II, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib 60 mg once daily (q.d.) in adults with unresectable, locally advanced or metastatic RCC with a clear-cell component that progressed, according to Investigator's judgement, after prior CPI therapy (ipilimumab and nivolumab) alone or CPI combined with VEGF-targeted therapy. Approximately ~~250~~ eligible subjects will receive cabozantinib (two independent cohorts with ~~125~~ subjects in ~~each~~ cohort). […] **Treatment Period:** […] • **Cohort A: ~~125~~ subjects** Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.	This is a Phase II, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib 60 mg once daily (q.d.) in adults with unresectable, locally advanced or metastatic RCC with a clear-cell component that progressed, according to Investigator's judgement, after prior CPI therapy (ipilimumab and nivolumab) alone or CPI combined with VEGF-targeted therapy. Approximately **114** eligible subjects will receive cabozantinib (two independent cohorts with **74** subjects*** in cohort A and approximately 40 subjects in cohort B**). ***The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.** […] **Treatment Period:** […] • **Cohort A: 74** subjects Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.	Modification of number of eligible subjects to reflect the sample size recalculation performed following the underperformance of the study enrolment.

	• **Cohort B: ~~125~~ subjects** Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.	• **Cohort B: approximately 40** subjects Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.	
Synopsis (Number of subjects planned)	~~250~~ subjects: ~~125~~ subjects in Cohort A and ~~125~~ subjects in Cohort B	**approximately 114** subjects: **74** subjects* in Cohort A and **approximately 40** subjects in Cohort B ***The inclusion period will stop either when 74 subjects have been enrolled in cohort A or at the latest on 30 June 2022, whichever is reached first.**	Modification of number of eligible subjects to reflect the sample size recalculation performed following the underperformance of the study enrolment.
Synopsis (Inclusion criteria) and Section 4.1	(10) Subjects must have completed a steroid taper, if he/she must ~~have had~~ an immune-related adverse event associated with ~~immune~~ CPI;	(10) Subjects must have completed a steroid taper, if he/she **experienced** an immune-related adverse event associated with **previous** CPI **treatment**;	Reworded for better clarity.

Synopsis (Criteria for evaluation (endpoints)), Section 3.2, Section 7.1, Section 7.2, Section 11.4.3.1 and Section 11.4.3.2	Primary Endpoint and Evaluation: • Objective response rate (ORR) per RECIST 1.1 evaluated by independent central review. Secondary Endpoints and Evaluations: […]	Primary Endpoint and Evaluation: • Objective response rate (ORR) **in cohort A** per RECIST 1.1 evaluated by independent central review. Secondary Endpoints and Evaluations: […] • **Objective response rate (ORR) in cohort B per RECIST 1.1 evaluated by independent central review;**	Removal of cohort B from the primary objective/endpoint and description of cohort B in secondary objectives/endpoints as no more hypothesis is defined for cohort B. To add that ORR for cohort B will be assessed by independent review.

Synopsis (Statistical Methods)	Sample size: With a true ORR proportion of ~~19~~%, a sample size of ~~117~~ subjects in ~~each~~ cohort will provide a statistical power of 80% to reject the null hypothesis of 10%, using a one-sample exact test for binomial distribution with a significance level of 0.025 (one-sided). Assuming approximately 7% non-evaluable subjects (i.e. subject who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1), a total of ~~125~~ subjects ~~per~~ cohort will be included in the study. ~~A minimum sample size fixed at 70% for subjects previously treated more than 6 months by first anti cancer therapy will be applied in the study for each cohort. This will provide meaningful descriptive summaries with sufficient accuracy and precision in this subgroup of subjects.~~	Sample size: With a true ORR proportion of **23**%, a sample size of **68** subjects in cohort **A** will provide a statistical power of 80% to reject the null hypothesis of 10%, using a one-sample exact test for binomial distribution with a significance level of 0.025 (one-sided). Assuming approximately 7% non-evaluable subjects (i.e. subject who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1), **up to** a total of **74** subjects **in** cohort **A** will be included in the study. **For cohort B, no formal sample size determination was performed as the enrolment will stop when the recruitment in cohort A will be reached. We anticipate approximately 40 subjects recruited in cohort B.** Statistical Methods:	Modification of number of eligible subjects to reflect the sample size recalculation performed following the underperformance of the study enrolment. The scope of the interim analysis has been revised. Addition of text to describe secondary endpoint analysis of ORR.

	Statistical Methods: ~~An intermediate analysis will be conducted when 60% of subjects (i.e. 75 subjects) of the first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow-up.~~ Both cohorts will be analysed at this cut-off date. The final analysis based on the primary endpoint (ORR) will be performed 12 months after the last subject received the first cabozantinib administration. A follow-up analysis based on OS will be conducted 18 months after the last subject received the first cabozantinib administration. ~~At the intermediate analysis, no statistical testing will be performed.~~ The statistical testing will ~~only~~ be carried out at the final analysis. The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined	**An interim and purely descriptive analysis will be conducted when 80% of the subjects (i.e. 59 subjects) of cohort A will be treated for at least 3 months.** Both cohorts will be analysed at this cut-off date. The final analysis based on the primary endpoint (ORR) will be performed 12 months after the last subject received the first cabozantinib administration. A follow-up analysis based on OS will be conducted 18 months after the last subject received the first cabozantinib administration. The statistical testing will be carried out at the final analysis. The primary endpoint (ORR), defined as the proportion of subjects with complete response (CR) and partial response (PR) per RECIST 1.1 as determined by independent central review will be tested in cohort **A** using a one-sample exact test for binomial distribution. The proportion of subjects achieving ORR will be presented with their two-sided 95% CI using the Clopper-Pearson exact method. DCR estimates will be described with associated 2-sided 95% CIs.	

	by independent central review will be tested in ~~each~~ cohort using a one-sample exact test for binomial distribution. The proportion of subjects achieving ORR will be presented with their two-sided 95% CI using the Clopper-Pearson exact method. DCR estimates will be described with associated 2-sided 95% CIs.		
1.2	Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the EMA as a 2nd line treatment for subjects with advanced RCC previously treated with VEGF-targeted therapy, and as a 1st line treatment for adults with advanced RCC with intermediate and poor risk.	Cabometyx™ (cabozantinib tablets, 20, 40 and 60 mg) is currently approved by the EMA as a 2nd line treatment for subjects with advanced RCC previously treated with VEGF-targeted therapy, and as a 1st line treatment for adults with advanced RCC with intermediate and poor risk. **Cabometyx™ (cabozantinib tablets 40 mg) in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.**	Addition of details regarding indication of Cabometyx™ in combination with nivolumab.

Section 1.4	[…] The primary endpoint is ORR, defined as the proportion of subjects with CR or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, as determined by an independent central review. Secondary endpoints are time to response (TTR), duration of response (DOR), DCR and PFS per RECIST 1.1 assessed both by independent central review and by local Investigator, ORR per RECIST 1.1 assessed by local Investigator, OS and change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI DRS). Safety and tolerability of cabozantinib will also be monitored throughout the study.	[…] The primary endpoint is ORR, defined as the proportion of subjects with CR or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, as determined by an independent central review **in cohort A**. Secondary endpoints are time to response (TTR), duration of response (DOR), DCR and PFS per RECIST 1.1 assessed both by independent central review and by local Investigator, ORR per RECIST 1.1 **also** assessed by **both independent central review (cohort B) and by** local Investigator **(cohort A and cohort B**, OS and change in disease-related symptoms as assessed by the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS). Safety and tolerability of cabozantinib will also be monitored throughout the study.	Removal of cohort B from the primary objective/endpoint and description of cohort B in secondary objectives/endpoints as no more hypothesis is defined for cohort B.
Section 3.1		[Figure 1 updated]	This figure was updated to reflect the changed planned subject numbers for each cohort.

Section 3.6	The study is planned to start in the ~~fourth~~ quarter of ~~2019~~ and will start when the first subject provides a signed informed consent form. ~~The inclusion period is estimated to last approximately 24 months, but this may be extended if necessary~~. For each subject, the study will start from the ICF signature and may last until the end of the study (18 months after the last subject included in the study received first cabozantinib dose). The period between the start and end of study~~ is estimated to be approximately 42 months~~ and will include both treatment and post treatment follow up periods, regardless of the duration of treatment (e.g. if a subject stops study treatment after 2 months, he/she will be followed-up for the remaining time up to the end of the study).	The study is planned to start in the **first** quarter of **2020** and will start when the first subject provides a signed informed consent form. **The inclusion period will stop either when the number of 74 enrolled subjects in Cohort A is reached or at the latest on 30 June 2022, whichever is reached first.** For each subject, the study will start from the ICF signature and may last until the end of the study (18 months after the last subject included in the study received first cabozantinib dose). The period between the start and end of study will include both treatment and post-treatment follow-up periods, regardless of the duration of treatment (e.g. if a subject stops study treatment after 2 months, he/she will be followed-up for the remaining time up to the end of the study).	Update of study timelines.
Section 5.1		*[Table 2 modified]* Tumour tissue line deleted Footnote h deleted	Deletion of tumour tissue analysis because the substudy is cancelled.

Section 6.2	[…] • **Cohort A: ~~125~~ subjects** Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab. • **Cohort B: ~~125~~ subjects** Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.	[…] • Cohort A: **74** subjects Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab. • Cohort B: **approximately 40** subjects Cohort B will be composed of subjects who radiographically progressed after one prior line by CPI therapy combined with VEGF-targeted therapy.	Modification of number of eligible subjects to reflect the sample size recalculation performed following the underperformance of the study enrolment.
Section 10	~~At selected sites, tumour tissue (archived before 1st line treatment) may be obtained at any time (archived biopsy) for a biomarker sub-study (exploratory analysis) of MET and PD-L1 expression (status) associated with RCC prognosis or the mechanism(s) of action of study treatment. Details regarding the preparation, processing, and shipping of samples can be found in the biomarkers manual.~~	**Not applicable.**	Substudy cancelled.

Section 11.2	For ~~each~~ cohort, the hypothesis for sample size computation is that cabozantinib will demonstrate a clinically significant increase in the response rate as compared to historical control in 2nd line treatment. […] Assuming approximately 7% non-evaluable subjects (i.e. subjects who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1), ~~125~~ subjects in ~~each~~ cohort provides at least 80% power (at one-sided significance level (alpha) of 0.025) to reject the null hypothesis of 10% ORR in favour of an alternative hypothesis of ~~19~~% ORR. ~~In total, 250 subjects need to be included in the study.~~ ~~A minimum sample size fixed at 70% for subjects previously treated more than 6 months by first anti-cancer therapy will be~~	For cohort **A**, the hypothesis for sample size computation is that cabozantinib will demonstrate a clinically significant increase in the response rate as compared to historical control in 2nd line treatment. […] Assuming approximately 7% non-evaluable subjects (i.e. subjects who received at least one dose of study medication but did not provide a baseline for the tumour according to RECIST 1.1), **74** subjects in cohort **A** provides at least 80% power (at one-sided significance level (alpha) of 0.025) to reject the null hypothesis of 10% ORR in favour of an alternative hypothesis of **23**% ORR. **For cohort B, no formal sample size determination was performed as the enrolment will stop when the recruitment in cohort A will be reached. We anticipate approximately 40 subjects recruited in cohort B.**	Modification of number of eligible subjects to reflect the sample size recalculation performed following the underperformance of the study enrolment.

	~~applied in the study for each cohort. This will provide meaningful descriptive summaries with sufficient accuracy and precision in this subgroup of subjects.~~		
Section 11.3	ORR (primary endpoint) will be tested at the final analysis as described above using the one-sided significance level (alpha) of 0.025. No statistical testing will be carried out at the ~~intermediate~~ analysis nor for secondary efficacy and safety endpoints.	ORR (primary endpoint) will be tested at the final analysis as described above using the one-sided significance level (alpha) of 0.025. No statistical testing will be carried out at the **interim** analysis nor for secondary efficacy and safety endpoints.	Modification of 'intermediate' to 'interim' analysis.

Section 11.4.3.1		**Below is the definition of the estimand used for the primary efficacy endpoint:** **Treatment: Cabozantinib** **Population: Subjects with unresectable, locally, advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination (Cohort A).** **Endpoint: ORR defined as the proportion of PR and CR at any timepoint during treatment period as determined by independent central review per RECIST1.1.** **Intercurrent events:** **• Study discontinuation without response (i.e. without PR or CR) during the treatment period (composite strategy)** **Subjects withdrawn from the study without response during the treatment period or subjects without any post-baseline tumour assessment are non-responders.** **• Treatment discontinuation prior to RECIST 1.1. progression (treatment policy strategy)**	Addition of estimands to follow ICH E9 guidelines and the addendum on estimands.

		The efficacy assessment at any timepoint prior to RECIST 1.1. progression is used regardless of whether the Cabozantinib is discontinued. **• Subjects not treated (while on treatment strategy)** **Subjects will not be included in the primary efficacy analysis.** **• Subjects receiving non-protocol anti-cancer treatment (while on treatment strategy)** **Assessment of the response during the treatment period, i.e. until the initiation of non-protocol anti-cancer treatment.** **Population-level summary: ORR compared to the historical control value of 10%**	
Section 11.4.3.2		**All these secondary endpoints will be presented in each cohort separately. In addition, ORR and PFS according to local Investigator's review per RECIST 1.1 as well as OS will be presented in the overall population (cohort A + cohort B).**	Clarification of the secondary endpoint analysis.

Section 11.4.3.2		**Below is the definition of the estimand used for the secondary efficacy endpoint of duration of response:** **Treatment: Cabozantinib** **Population: Subjects with unresectable, locally, advanced or metastatic RCC with a clear-cell component who progressed after prior CPI therapy with ipilimumab and nivolumab in combination (Cohort A) with a PR or CR at any timepoint during the treatment period.** **Endpoint: DOR defined as the time from first documented response (PR or CR as determined by independent central review per RECIST 1.1) to either disease progression (as determined by independent central review per RECIST 1.1) or death due to any cause, whichever occurs first.** **Intercurrent events:** • **Two or more missing scheduled tumour assessment prior to RECIST 1.1. progression (while on treatment strategy)**	Addition of estimands to follow ICH E9 guidelines and the addendum on estimands.

		Subjects will be censored at the date of the last tumour assessment prior to the missing assessment. • **Subjects not treated (while on treatment strategy)** **Subjects will not be included in the efficacy analysis.** • **Subjects receiving non-protocol anti-cancer treatment prior to RECIST 1.1 progression (while on treatment strategy)** **Subjects will be censored at the date of the last tumour assessment prior to the initiation of non-protocol anti-cancer treatment.** • **Treatment discontinuation prior to RECIST 1.1. progression (treatment policy strategy)** **Subjects will be censored at the date of the last tumour assessment.** • **Treatment discontinuation without any post-baseline tumour assessment (treatment policy strategy) after the first response to treatment** **Subjects will be censored at the time of first documented response.**	

		Population-level summary: median of DOR 2-sided 95% with CI.	
Section 11.4.3.3	The ORR as assessed by independent central review will be estimated in ~~each~~ Cohort A ~~and B~~ and tested versus the threshold of 10% using a one-sample exact test for binomial distribution. ~~In each cohort, a~~ higher response rate over 10% will be considered statistically significant if the p value for the one-sided test is less than 0.025.	The ORR as assessed by independent central review will be estimated in Cohort A and tested *versus* the threshold of 10% using a one-sample exact test for binomial distribution. A higher response rate over 10% will be considered statistically significant if the p-value for the one-sided test is less than 0.025.	Removal of cohort B from the primary objective/endpoint as no more hypothesis is defined for cohort B.
Section 11.4.3.4	The ORR according to Investigator's assessment will be ~~analysed in the same way as ORR assessed by independent central review without statistical testing~~. Discordance in ORR assessed by independent central review and by Investigator will be described.	The ORR according to Investigator's assessment **(cohort A and cohort B)** will be **presented with their associated 2-sided 95% CIs using Clopper-Pearson exact method.** Discordance in ORR assessed by independent central review and by Investigator will be described.	Description of cohort A and B in secondary objectives/endpoints as no more hypothesis is defined for cohort A and cohort B.

Section 11.6	~~There are no formal interim analyses with stopping rules for efficacy or futility planned for this study. However, one intermediate analysis is planned as follows:~~ ~~The intermediate analysis will be conducted when 60% of subjects (i.e. 75 subjects) of the first recruiting cohort reaching the target number of subjects (either Cohort A or Cohort B) have reached 12 months of study follow up. Both cohorts will be analysed at this cut off date.~~ […] The statistical testing will ~~only~~ be carried out at the final analysis.	**An interim and purely descriptive analysis will be conducted when 80% of the subjects (i.e. 59 subjects) of cohort A will be treated for at least 3 months. Both cohorts will be analysed at this cut-off date. The aim of this interim analysis is to describe the baseline characteristics, demographics, ORR as assessed by the Investigator at 3 months and any further efficacy parameters measured at the Month 3 visit. Further details will be provided in the SAP. The results of this interim analysis will not have any impact on the study conduct.** […] The statistical testing will be carried out at the final analysis.	Revision of the scope of the interim analysis.

Section 17.2	[…] ~~As indicated in Section 11.6, the intermediate analysis will be conducted when 60% of subjects of the first recruiting cohort reaching the target number of subjects have reached 12 months of study follow-up. This analysis will be included in the interim study report.~~		No interim CSR will be provided.

Other documents impacted

Informed consent form	Yes ☒	No ☐
Case report form (CRF)	Yes ☐	No ☒
Statistical analysis plan (SAP)	Yes ☒	No ☐