STATISTICAL AND ANALYSIS PLAN

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

PROTOCOL VERSION AND DATE: FINAL VERSION 6.0 (INCLUDING AMENDMENT #4) – 23 FEBRUARY 2022

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STUDY NUMBER:	F-FR-60000-023
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SAP DATE:	17 August 2023

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Clinical Statistics Manager or designee	Ipsen (PPD , 65 Quai Georges Gorse 92650 Boulogne-Billancourt Cedex, France)	eSignature	
Medical Affairs Director	Ipsen PPD 65 Quai Georges Gorse 92650 Boulogne-Billancourt Cedex, France)	eSignature	

This document has been approved and signed by the following:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study statistician	Parexel PPD 14 rue Jean Antoine de Baif 75013 Paris, France)	N/A	
Interim Statistician	Parexel PPD 15 Talavera Road, Suite B, Level 6, Macquarie Park, Australia NSW 2113)	eSignature	

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
2		08Aug2019	06Oct2021	Updated the Ipsen signature page to reflect change in team
3		08Aug2019	06Oct2021	Updated the Parexel signature page to reflect change in team
8	1.1.2	08Aug2019	06Oct2021	Suppressed "best overall response (BOR)" and added "to assess objective response rate (ORR) by Investigator's review" in the secondary objectives following protocol amendment #1.
8	1.2	08Aug2019	06Oct2021	Suppressed "Belgium" from the countries and updated the 'Pre-treatment Period' paragraph following protocol amendment #1. Updated the study design following protocol amendment #3: updated the wording about the first line combination, updated the treatment period to delete that the date of first dose should occur within 15 days after the Screening visit, updated the post-treatment follow-up period to collect only SAEs related to study treatment or study procedure, and the study design figure.
10	1.2.2	08Aug2019	06Oct2021	Updated study start. Updated following protocol amendment #3: updated from the first cabozantinib administration to the ICF signature for the study start of each subject, and updated the follow-up period to mention that only related SAEs will be collected and Cabometyx® will be supplied.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
11	1.3.1	08Aug2019	06Oct2021	Added details about Subject identification and allocation to study treatment
11	1.3.2.1	08Aug2019	06Oct2021	Updated the Tumour Assessments paragraph following protocol amendment #1. Minor update from "protocol" to "study protocol". Updated from "Overall survival" to "Survival status" to reflect the assessment collected.
12	1.3.2.2	08Aug2019	06Oct2021	Updated following protocol amendment #3: Updated to clarify that AEs will be monitored "during the study treatment" instead of "during the study", and that only related SAEs will be recorded during the follow-up period.
12	1.3.2.2	08Aug2019	06Oct2021	Updated the abnormalities in laboratory test values definition as per Protocol Section 8.1.2.4. Updated following protocol amendment #3: updated from "prior to study entry" to "prior to baseline" for the laboratory tests and from "prior to the screening visit" to "prior to the baseline visit" for β-HCG in the 'Clinical Laboratory Tests' paragraph, and updated the Table 1 to remove "fasted" for glucose, and to remove total cholesterol and triglycerides. Added "normal ranges" also collected in eCRF.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
12	1.3.2.2	08Aug2019	06Oct2021	Updated from "Screening/Baseline" to "Screening" in the 'Physical Examination' paragraph following protocol amendment #1. Added "Any clinically significant physical examination findings (abnormalities) observed during treatment period will be reported as AE" as per Protocol section 8.3. Added that the clinically significant abnormalities in vital signs are as per investigator assessment.
15	1.3.2.4	08Aug2019	06Oct2021	Added 'to assess' following protocol amendment #1.
16	1.3.3	08Aug2019	06Oct2021	Updated the 'Table 2 Study Procedures and Assessments' following protocol amendments #1 and #3.
21	1.3.4	08Aug2019	06Oct2021	Added the reference of the LANCET article used for the sample size calculation assumption, and the definition of the non-evaluable subjects following protocol amendment #3.
21	2.2	08Aug2019	06Oct2021	Added the Included Population and updated the safety population definition following protocol amendment #3.
22, 23, 26, and 31 to 33	2.3, 3.1.3, 3.2.2, and 3.2.4 to 3.2.10	08Aug2019	06Oct2021	Added "For intermediate analysis, in case of significant difference in the number of subjects between the two cohorts, the tables will be presented for each cohort fully separately, with no overall results".

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
22	3.1.1	08Aug2019	06Oct2021	Updated the ORR definition to mention clearly that this is derived from the BOR. Deleted that the response was to be "confirmed by a subsequent visit ≥28 days later" following Protocol amendment#3. Added the estimand definition for the primary efficacy endpoint.
22	3.1.2	08Aug2019	06Oct2021	Suppressed the BOR from the secondary endpoints following protocol amendment #1. Updated the DCR definition to mention clearly that this is derived from the BOR. Updated the DOR definition to delete "subsequently confirmed" and the response confirmation following Protocol amendment#3. Clarified that the ORR, TTR, DOR, DCR and PFS according to local Investigator's review are defined as for the independent central review. Added the reference to the Appendix 1 derived items. Added the estimand definition used for the secondary efficacy endpoint.
23	3.1.4	08Aug2019	06Oct2021	Updated the multiplicity section for more clarity.
23	3.1.5	08Aug2019	06Oct2021	Updated the 'Significance testing and estimation' part following protocol amendment #1.
23	3.2.1	08Aug2019	06Oct2021	Added that additional supportive analysis of PFS, Kaplan-Meier and Waterfall plots will be performed only on efficacy population

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
24	3.2.1.1	08Aug2019	06Oct2021	Updated the ORR definition to mention clearly that this is derived from the BOR. Added the sentence "The statistical testing will only be carried out at the final analysis.".
24	3.2.1.2	08Aug2019	06Oct2021	Suppressed the BOR from the secondary endpoints following protocol amendment #1. Added the ORR tables by subgroup defined in Section 3.2.16. Added clarification for concordance tables, and change in tumour size tables. Added the Tumour response and ORR tables presented for both independent central review and investigator assessments. Moved the censoring rules to Appendix 1. Removed the additional supportive analyses of PFS on Per Protocol population because not needed. Reworded for the second supportive analysis from 'clinical deterioration in absence of progression' to 'non-radiological disease progression' to stick to the CRF wording.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
26	3.2.2.1	08Aug2019	06Oct2021	Adverse events section: Added a table by frequency and preferred term, tables for related TEAEs, a table for TEAEs related to laboratory tests, non-serious TEAEs, and for suspected or confirmed COVID-19 (SARS-CoV-2) infection TEAEs. Removed that when intensity is missing, the worst case is assumed. Added the time-to-event tables and plots, added tables on deaths during study drug and after study drug, suppressed the tables about dose delayed, added a table about adverse events during the post-treatment follow-up period at Ipsen request. Added the reference to Appendix 1 items.
27	3.2.2.2	08Aug2019	06Oct2021	Added the standardisation method because of local laboratories with multiple ranges. Laboratory data section: updated to have shift tables with low/normal/high and with NCI-CTCAE grade depending on the parameters. Added reference to Appendix 1 derived items.
28	3.2.2.3	08Aug2019	06Oct2021	Added a listing and a summary table about Potentially Clinically Significant Abnormalities
29	3.2.2.4	08Aug2019	06Oct2021	Added Table 14.3.6.3
29	3.2.2.5	08Aug2019	06Oct2021	Removed the shift table about Physical examination. Added reference to Appendix 1 derived items. Added weight loss classes.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
30	3.2.3.1	08Aug2019	06Oct2021	Added reference to Appendix 1 derived items.
30	3.2.3.2	08Aug2019	06Oct2021	Clarified rules about derivations in case of partial dates. Added reference to Appendix 1 derived items.
31	3.2.4	08Aug2019	06Oct2021	Added Listings of treatment batch number and of enrolment scheme and codes will be presented by subject for each cohort (Listings 16.1.6 and 16.1.7) following a CRF update with new pages. Updated the exposure definitions accordingly. Added the included population following protocol amendment #3. Added tables about subject disposition, subject enrolment, and analysis population. Clarified last visit definition and study drug exposure. Added that the average daily dose will be calculated. Added reference to Appendix 1 derived items.
31	3.2.5	08Aug2019	06Oct2021	Added the included subjects following protocol amendment #3. Updated from "post-treatment period" to "post-treatment follow-up period". Added withdrawals due to COVID-19. Clarified the definition of subjects having completed the treatment.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
31 and 32	3.2.6 and 3.2.7	08Aug2019	06Oct2021	Removed the listing on Prohibited medications because they will be part of the Protocol deviations. Removed the outputs on screened population in Demographic and baseline characteristics and Medical and surgical history following protocol amendment #3. Added that medical and surgical history listing will present the primary system organ class. Added reference to Appendix 1 derived items.
32	3.2.8	08Aug2019	06Oct2021	Updated the 'Subject compliance' section following the addition of a page in CRF about compliance. Added reference to Section 3.2.4 for summary tables of study drug dose reduction and interruption, and to Section 3.2.2.1 for summary tables of AEs leading to dose modification.
32	3.2.9	08Aug2019	06Oct2021	Moved the Protocol deviation sections from 3.2.9 to 3.2.6 to follow the analysis outputs numbering. Updated from "impacting inclusion in the PP population" to "impacting inclusion in the analysis populations" following protocol amendment #3. Updated the listing and table to present only the major protocol deviations (the minor protocol deviations will not be listed or tabulated). Added protocol deviation due to COVID-19.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
33	3.2.10	08Aug2019	06Oct2021	Removed the outputs on screened population in Concomitant section. Updated that medications starting after the last dose of study drug will only be listed. Updated the list of prohibited therapies following protocol amendment #3.
34	3.2.12	08Aug2019	06Oct2021	Updated the visit mappings. Added reference to Appendix 1 for the study day calculation.
36	3.2.15	08Aug2019	06Oct2021	Updates from one to two intermediate analyses following protocol amendment #1. Updated the final analysis definition.
36	3.2.16	08Aug2019	06Oct2021	Deleted 'will be converted from ECOG status' for ECOG (0,1) following protocol amendment #1. Added reference to Appendix 1 for age and treatment duration calculation. Updated to state that MET status and PD-L1 status will be part of a sub-study and a separate SAP.
37	4.2	08Aug2019	06Oct2021	Updated the SAS version from 9.3 to 9.4
37	5	08Aug2019	06Oct2021	Added the changes from protocol needed.
37	6	08Aug2019	06Oct2021	Added references for the article used for the sample size, the laboratory data normalization, and the questionnaire scoring guideline

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
38	Appendix 1	08Aug2019	06Oct2021	Reordered and renumbered to follow the core SAP order. Updated the derivation for the TTR, DoR, PFS and OS. Added the derivation for FKSI-DRS Total Score to provide clarifications. Corrected the formula for the Percent reduction from Baseline. Removed the AE duration. Added the time from first study dose for AE. Removed the time since last dose for AE. Added urinalysis derivation. Updated the derivation for NCI-CTC AE grades. Updated the derivation for Study exposure to consider the Informed Consent and not the Screening as starting point. Updated the derivations for Study drug exposure and Compliance due to CRF update. Added the treatment duration on 1st anti-cancer therapy. Removed Concomitant therapy duration. Updated the derivation for Study day.
41	Appendix 2	08Aug2019	06Oct2021	Updated the List of Tables, Figures and Listings due to updates in the Core SAP.
16	List of Abbreviations	06Oct2021	28Jun2022	Deleted MET (Hepatocyte Growth Factor Receptor Protein) and PD-L1 (Programmed Death-ligand 1 protein)

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
19	1.1.1	06Oct2021	28Jun2022	Added in cohort A to remove cohort B from the primary objective following protocol amendment #4.
19	1.1.2	06Oct2021	28Jun2022	Added ORR evaluated by independent central review in cohort B following protocol amendment #4. Added Investigator review of ORR and PFS and added OS assessment for cohorts A and B following protocol amendment #4.
19	1.2	06Oct2021	28Jun2022	Updated the number of subjects in study design following protocol amendment #4.
21	1.2.1	06Oct2021	28Jun2022	Updated the study population to stick to protocol Section 1.6. Updated the number of subjects to be included following protocol amendment #4.
21	1.2.2	06Oct2021	28Jun2022	Updated study exposure period following protocol amendment #4.
21	1.3.1	06Oct2021	28Jun2022	Updated from anonymise to pseudonymise
27	1.3.3	06Oct2021	28Jun2022	Updated the schedule of assessments to delete the tumour assessments following protocol amendment #4.
32	1.3.4	06Oct2021	28Jun2022	Updated the planned sample size following protocol amendment #4.
32	2	06Oct2021	28Jun2022	Updated the included population because of subjects who did not fulfill the inclusion and exclusion criteria but were treated.
33	2.3	06Oct2021	28Jun2022	Updated following protocol amendment #4.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
33, 35, 38, and 44 to 47	2.3, 3.1.3, 3.2.2, and 3.2.4 to 3.2.10	06Oct2021	28Jun2022	Deleted "For intermediate analysis, in case of significant difference in the number of subjects between the two cohorts, the tables will be presented for each cohort fully separately, with no overall results".
33	3.1.1	06Oct2021	28Jun2022	Added in cohort A from the primary efficacy endpoint, and removed cohort B in the definition of estimand, following protocol amendment #4.
34	3.1.2	06Oct2021	28Jun2022	Added ORR in cohort B determined by independent central review, added ORR and PFS according to local Investigator's review presented in the overall population, added OS presented in the overall population, and removed cohort B in the definition of estimand, following protocol amendment #4.
35	3.1.4 and next	06Oct2021	28Jun2022	Updated wording from intermediate analysis to interim analysis
35	3.1.4	06Oct2021	28Jun2022	Deleted that each cohort will be tested separately as only cohort A will be tested following protocol amendment #4. Updated from analyses to analysis, and removed safety endpoint because only efficacy endpoints are tested at final analysis timepoint
36	3.2.1	06Oct2021	28Jun2022	Updated following protocol amendment #4.
36	3.2.1.1	06Oct2021	28Jun2022	Removed cohort B following protocol amendment #4.
36	3.2.1.2	06Oct2021	28Jun2022	Added cohort B for ORR assessed by independent central review following protocol amendment #4.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
43	3.2.3.2	06Oct2021	28Jun2022	Added the time from diagnosis to screening because the derivation was added in Appendix 1.
46	3.2.7	06Oct2021	28Jun2022	Added the time from diagnosis to screening because the derivation was added in Appendix 1 and imputation rules are defined.
51	3.2.13	06Oct2021	28Jun2022	Added the 95% CI of the mean for the final analysis for continuous data. Updated from two more decimal places to one more decimal place for SD. Added the 95% CI of the mean for the final analysis for proportions. Updated the rule for percentages calculations.
52	3.2.15	06Oct2021	28Jun2022	Updated the interim analysis scope following protocol amendment #4.
52	3.2.16	06Oct2021	28Jun2022	Added clarification about the presentation to be consistent with the other sections (i.e. in each cohort separately, and in overall population for the ORR according to local Investigator's review). Deleted MET and PD-L1 as the substudy is cancelled following protocol amendment #4.
54	5	06Oct2021	28Jun2022	Added that the sample size may exceed the targeted number of subjects. Suppressed the sentence about the interim analysis display because the overall column will be presented.
55	Appendix 1	06Oct2021	28Jun2022	Added the derivation about time from diagnosis to screening.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
62	Appendix 2	06Oct2021	28Jun2022	Added List of Tables, Figures and Listings for Interim Analysis, and renumbered Appendix 2 to Appendix 3.
18	List of Abbreviations	28Jun2022	05Jun2023	Added AESI, ETM, NAP and PRES.
All	All Sections	28Jun2022	05Jun2023	Updated the Appendix 1 references due to renumbering.
38	3.2.1.2	28Jun2022	05Jun2023	Updated 'percent reduction from Baseline' to 'percent change from Baseline'. Added reference to 'percent change from nadir' in Appendix 1.
41	3.2.2.1	28Jun2022	05Jun2023	Added reference to Section 3.2.3.2 in case of missing or partial dates and to Appendix 1 for the imputation rules. Added tables for Adverse Events of Special Interest.
43	3.2.2.2.1	28Jun2022	05Jun2023	Added tables about the changes in toxicity grading.
45	3.2.3.2	28Jun2022	05Jun2023	Added reference to Appendix 1 for prior/concomitant medication flag and TEAE flag.
48	3.2.10	28Jun2022	05Jun2023	Added reference to Appendix 1 for the imputation rules in case of missing or partial dates.
50	3.2.12	28Jun2022	05Jun2023	Added about the use of the screening assessment, when the baseline assessment was missing.
54	3.2.15	28Jun2022	05Jun2023	Added the cut-off for the final analysis.
55	5	28Jun2022	05Jun2023	The Adverse Events of Special Interest are added.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
57	Appendix 1	28Jun2022	05Jun2023	Suppressed the derivation about percent reduction from Baseline. Added the derivation about percent change from Baseline, about percent change from nadir, about algorithm prior/concomitant flag, and about algorithm for TEAE flag. Moved a few derivations to follow the order of the first reference in SAP.
65	Appendix 3	28Jun2022	05Jun2023	Updated the list of Tables, Figures and Listings for Final Analysis. Added tables for Adverse Events of Special Interest. Added tables about the changes in toxicity grading.
NAP	Appendix 4	28Jun2022	05Jun2023	Added an appendix for the list of Tables, Figures and Listings for Follow-up Analysis.
2	Signature Page	05Jun2023	26Jun2023	Removed the Parexel Statistician reviewer.
44	2.1	05Jun2023	26Jun2023	Split Efficacy and Per Protocol populations for IRC and investigator assessments.
45	2.3	05Jun2023	26Jun2023	Clarified the Primary population following the Efficacy and Per Protocol population updates.
48	3.2.1.2	05Jun2023	26Jun2023	Moved the paragraph about the concordance in ORR. Clarified that the concordance will be on subjects with assessments in both populations.
54	3.2.2.3	05Jun2023	26Jun2023	Updated listing numbers.
55	3.2.2.4	05Jun2023	26Jun2023	Updated listing number.
55	3.2.2.5	05Jun2023	26Jun2023	Updated listing numbers.

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
68	5	05Jun2023	26Jun2023	Added the change from protocol about the split of Efficacy and Per Protocol populations.
78	Appendix 3	05Jun2023	26Jun2023	Updated the Efficacy and Per Protocol populations.
86	Appendix 4	05Jun2023	26Jun2023	Updated the Efficacy and Per Protocol populations.
87	3.2.2.2	26Jun2023	16Aug2023	Updated the text from “standardisation” to “normalisation”

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	Adverse Event/Experience
AESI:	Adverse Event of Special Interest
ALP:	Alkaline Phosphatase
ALT (SGPT):	Alanine Aminotransferase
ANC:	Absolute Neutrophil Count
AST (SGOT):	Aspartate Aminotransferase
ATC:	Anatomic Therapeutic Class
BMI:	Body Mass Index
BOR:	Best Overall response
BP:	Blood Pressure
BUN:	Blood Urea Nitrogen
C/A/P:	Chest, Abdomen, and Pelvis
CI:	Confidence Interval
CPI:	Checkpoint Inhibitors
CR:	Complete Response
CRF:	Case Report Form
CRO:	Clinical Research Organisation
CT:	Contrast Tomography
DCR:	Disease Control Rate
DOR:	Duration of Response
e:	Electronic
ECG:	Electrocardiogram
ETM:	Event to Monitor
FKSI-DRS:	Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index
FT4:	Free Thyroxine 4
GGT:	Gamma-Glutamyl Transferase
HRQOL:	Health-related Quality of Life
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio

IRC:	Independent Radiology Committee
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	Magnetic Resonance Imaging
MSKCC:	Memorial Sloan Kettering Cancer Center
n:	Number of values
NAP:	Not Applicable
NCI-CTCAE:	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NPACT:	Non-Protocol Anti-Cancer Therapy
ORR:	Objective Response Rate
OS:	Overall Survival
PCSA:	Potentially Clinically Significant Abnormalities
PD:	Progressive Disease
PFS:	Progression-Free Survival
PO	Per Os (orally)
PP:	Per Protocol
PR:	Partial Response
PRES:	Posterior reversible encephalopathy syndrome
PT:	Preferred Term
PTT:	Partial thromboplastin time
q.d.:	Once Daily (in Latin: quaque die)
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
SAP:	Statistical and Analysis Plan
SOC:	System Organ Class
SOP:	Standard Operating Procedure
RCC:	Renal Cell Carcinoma
RECIST:	Response Evaluation Criteria in Solid Tumours
SAE:	Serious Adverse Event/Experience
SAS®:	Statistical Analysis System®
SD:	Stable Disease
SI:	Standard International

SOP:	Standard Operating Procedure
TEAE:	Treatment-Emergent Adverse Event/Experience
TFLs:	Tables, Figures and Listings
TSH:	Thyroid-stimulating hormone
TTR:	Time to Response
UPCR	Urine Protein-to-Creatinine Ratio
VGEF:	Vascular Endothelial Growth Factor
WBC:	White Blood Cell
WHODD:	World Health Organization Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 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 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.

1.1.1 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.

1.1.2 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.

1.2 Study design

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.):

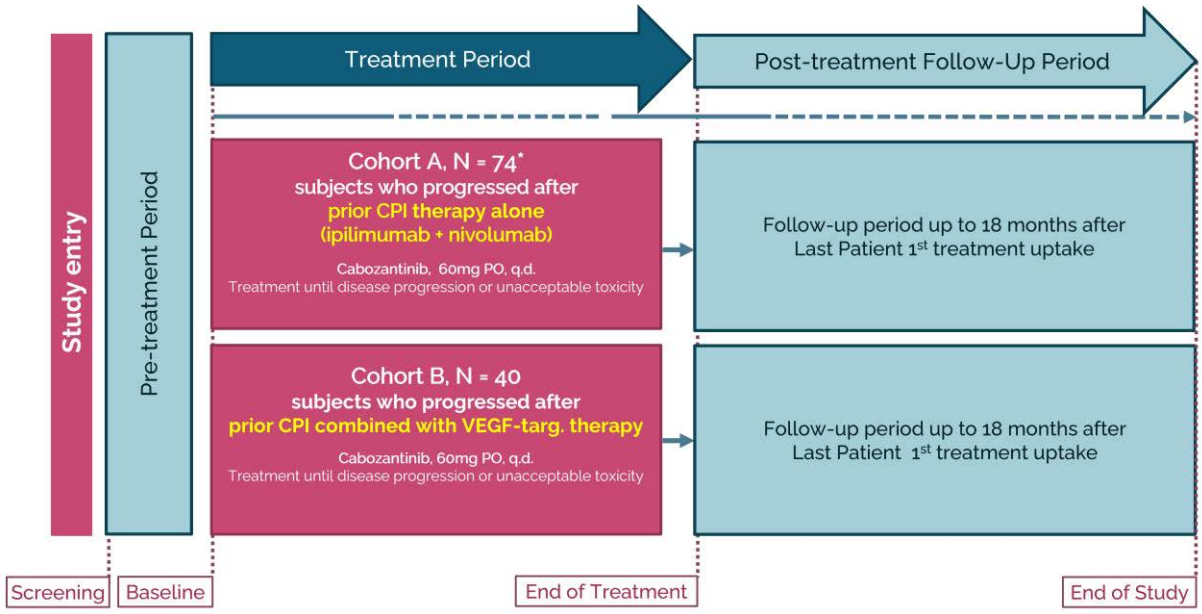
Cohort A: 74 subjects
Cohort A will be composed of subjects who radiographically progressed after one prior line by CPI therapy with ipilimumab and nivolumab.

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 1.3.3 (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, 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 1.3.2.1 (see Table 2 for schedule of assessments). These include radiographic tumour assessments which will be blindly reviewed by a central independent radiology committee (IRC) to evaluate efficacy endpoints (Sections 3.1.1 and 3.1.2).
Safety assessments will start on the date of the Screening visit and will be continued throughout the study as described in Section 1.3.2.2 (see Table 2 for schedule of assessments). Unscheduled safety evaluations are allowed at any time throughout the study.
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 to 45 days after the last dose of cabozantinib). Subjects who prematurely stop the study 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 serious AEs (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.

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.

1.2.1 Study population

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. In this study, 74 subjects need to be included with CPI alone (cohort A) and approximately 40 subjects with CPI combined with VEGF-targeted therapy (cohort B).

1.2.2 Study exposure

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

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

In this study, data will be collected through an eCRF. Once the subject has provided his/her informed consent, the eCRF will provide a numeric subject identifier to pseudonymise the data within eCRF. Only investigating sites will be able to link to numeric identifier to the subject.
Each subject will only be given the study treatment if they carry his/her registration number. 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).

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

The timing of efficacy assessments is provided in Table 2.
The primary and secondary efficacy endpoints are detailed in Section 3.1.1 and Section 3.1.2, and the statistical methods to be used in the analysis of these efficacy endpoints are provided in Section 3.2.1.

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.
C/A/P CT/MRI will be performed at Screening/Baseline (within 28 days prior start of study treatment) and then every 12 weeks (±10 days) while on study protocol treatment beginning at Week 12 (i.e. Week 12, Week 24, Week 36, etc) until the end of study. There could be additional assessments if clinically indicated. Follow-up for radiographic progression, tumour assessment should be performed until radiographic progression confirmed by the Investigator for subjects who have discontinued

cabozantinib treatment before radiographic disease progression and who have not withdrawn consent.
Brain CT/MRI and Bone scintigraphy scan will be performed at Screening/Baseline (within 28 days prior start of study treatment) only if they are indicative of metastases. Then they will be performed at same timepoints only if there are brain and/or bone metastases at screening or if there are signs or symptoms suggesting that metastases develop.
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 by batch using RECIST 1.1 (any additional details will be found in the IRC charter). 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 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.

Overall Survival
Survival status will be assessed during the Post-treatment Follow-up period 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 (NPACT) will also be collected at the same time as this assessment.

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.

1.3.2.2 Safety assessments

The timing of safety assessments is provided in Table 2.
The safety endpoints are detailed in Section 3.1.3, and the statistical methods to be used in the analysis of these safety endpoints are provided in Section 3.2.2.

Adverse Events
Adverse events (AEs) will be monitored from the time the subject gives informed consent and throughout the study treatment (see Section 1.2.2 for a definition of study

duration) and will be assessed by direct, nonleading questioning. All adverse events are to be reported during the treatment period, which includes 30 days after the date of the last cabozantinib dose. 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 cabozantinib or study procedures will also be collected and followed until resolution or stability according to the Investigator. In case of screen failure, AEs will be recorded until the date the subject is deemed to be a screen failure.

Adverse events will be recorded and graded according to the National Cancer Institute for Adverse Events (NCI-CTCAE) version 5.0.
The relationship of an AE to investigational medicinal product (IMP) administration will be classified into Related or Not Related.
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.

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.
Any other abnormal test findings judged by the Investigator as clinically significant (e.g. electrocardiogram [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 also be recorded as AEs.

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 electronic case report form (eCRF).

Clinical Laboratory Tests

Blood and urine samples will be collected at the frequency indicated in Table 2 and as detailed below for the evaluation of haematology, blood biochemistry, urinalysis, pregnancy tests and other clinical laboratory tests as safety measurements.
All laboratory tests to establish eligibility must be done within 15 days prior to baseline. Then, Haematology, blood biochemistry and urinalysis will be collected at Baseline, Week 2, Week 4, Week 8 and every 4 weeks until the End of Study Treatment visit or Early Study Withdrawal visit. Thyroid function test will be collected at Baseline and every 4 weeks.
A β-human chorionic gonadotrophin (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. Any subject becoming pregnant during the study will be withdrawn from the study.

A list of all laboratory analyses that will be measured in this study is provided in Table 1.

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 and normal ranges will be recorded on the eCRF and provided by the Investigator.

Table 1 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.

Vital Signs

Vital signs (BP [blood pressure] and heart rate) will be assessed as indicated in Table 2 as safety measures.

Vital signs will be measured at the Screening visit, Baseline, Week 2, Week 4, Week 8 and every 4 weeks until the End of Study Treatment visit or Early Study Withdrawal visit.

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 as per investigator assessment in the vital signs will be reported as an AE.

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.

Physical Examination

Physical examinations will be conducted as indicated in Table 2 as a safety measure. This assessment will be performed at the Screening visit, Baseline, Week 2, Week 4, Week 8 and every 4 weeks until the End of Study Treatment visit or Early Study Withdrawal visit. And 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, gastrointestinal (GI) system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

The Eastern Cooperative Oncology Group (ECOG) performance status of the subject will be assessed at each scheduled safety assessment starting at Screening.

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

Any clinically significant physical examination findings (abnormalities) observed during treatment period will be reported as AE. 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.

1.3.2.3 Other assessments

Demographic and Baseline Characteristics

Demographic and Baseline characteristics (year of birth, age, sex, race, medical history, RCC history, prior surgery/radiotherapy/chemotherapy/medications related to RCC) will be collected at Screening.

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.

1.3.2.4 Withdrawal/discontinuation

Each subject may discontinue study treatment or withdraw their consent to participate in the study at any time for any reason. 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.

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 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 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.

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.

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. A complete final evaluation at the time of the subject's withdrawal should be made.

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.

1.3.3 Schedule of assessments

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

Table 2 Study Procedures and Assessments

	Pre-treatment Period	Treatment Period						Post-treatment Follow-up Period [d]
Assessment	**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						
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)	X	X	X	Every 4 weeks	X	
Weight	≤15 Days prior to baseline	X (prior to first dose)	X	X	X	Every 4 weeks	X	
Vital signs	≤15 Days prior to baseline	X (prior to first dose)	X	X	X	Every 4 weeks	X	
ECOG performance status	≤15 Days prior to baseline	X (prior to first dose)	X	X	X	Every 4 weeks	X	

	Pre-treatment Period	Treatment Period						Post-treatment Follow-up Period [d]
Assessment	**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)**
12-lead ECG	≤15 Days prior to baseline	X (prior to first dose) [f]		X		Every 12 weeks	X	
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)

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)**
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]	≤15 Days prior to Screening	X	X	X	X	X	X	X [k]
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 tests or urine protein/creatinine ratio [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.

[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.

1.3.4 Planned sample size

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 [1, 2], 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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

The Screened population is all subjects screened (i.e. who signed the informed consent).
The Included population is all screened subjects who fulfilled the inclusion and exclusion criteria. In case a subject did not fulfil the inclusion and exclusion criteria but received at least one dose of study medication, this subject will be considered as part of the included population.

2.1 Efficacy

2.1.1 Efficacy population - IRC

The Efficacy population - IRC is 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, i.e. reporting at least one target lesion at baseline based on IRC assessment.

2.1.2 Efficacy population - investigator

The Efficacy population – investigator is 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, i.e. reporting at least one target lesion at baseline based on investigator assessment.

2.1.3 Per Protocol (PP) population - IRC

The Per Protocol population - IRC is all subjects in the efficacy population – IRC who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the subject).
Criteria for exclusion from the Per Protocol population will be provided in the Protocol Deviation Specifications. Listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed by the study team.

Reasons for exclusion from Per Protocol population will be presented in a summary table by cohort.

2.1.4 Per Protocol (PP) population - investigator

The Per Protocol population – investigator is all subjects in the efficacy population – investigator who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the subject).
Criteria for exclusion from the Per Protocol population will be provided in the Protocol Deviation Specifications. Listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed by the study team.
Reasons for exclusion from Per Protocol population will be presented in a summary table by cohort.

2.2 Safety

The safety population is all included subjects who received at least one dose of study medication.

2.3 Primary population

In the rest of the SAP, we used the generic name efficacy population and PP population but it is implicit that efficacy population - investigator and PP population - investigator will be applicable for all analyses based on investigator assessment and efficacy population - IRC and PP population - IRC for all analyses based in IRC assessment.
Analysis based on the primary efficacy endpoint will be performed on the efficacy population in cohort A. Analyses based on the secondary efficacy endpoints will be performed on the efficacy population 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).
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 difference will be checked for each cohort separately. In case the difference is greater than 15% for one cohort only, only this cohort will be presented in both efficacy population and PP population.
The analyses of safety data will be performed based on the safety population in each cohort separately and overall.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guideline and will be based on the pooled data from the individual study sites for each cohort separately, unless otherwise stated.
Statistical analyses will be performed by Parexel, managed by the Sponsor’s biometry department.

3.1.1 Primary efficacy endpoint

The primary efficacy endpoint is:

- ORR defined as the proportion of subjects with a best overall response (BOR) of 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.

The BOR will be derived as defined in Appendix 1 (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 (i.e. up to 30 days after the discontinuation of Cabozantinib) 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%.

3.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

(a) 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) (see Appendix 1 (2), for the derivation and censoring rules).

(b) 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. Censoring rules will be similar to those applied for progression-free survival (PFS) (see Appendix 1 (3)).

(c) DCR defined as the proportion of subjects with a BOR of a PR, CR or SD as determined by independent central review per RECIST 1.1

(d) 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 (see Appendix 1 (4)).

(e) ORR in cohort B defined as the proportion of subjects with a BOR of a PR or CR at any timepoint as determined by independent central review per RECIST 1.1

(f) OS defined as the time from the start of treatment until death due to any cause (see Appendix 1 (5)).

(g) ORR, TTR, DOR, DCR and PFS according to local Investigator's review per RECIST 1.1 and defined as for the independent central review,

(h) Change in disease-related symptoms as assessed by the FKSI-DRS questionnaire.

The endpoints of ORR, TTR, DOR, DCR and PFS will be evaluated by tumour assessments (see Section 1.3.2.1). The OS will be assessed as described in Section 1.3.2.1.

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.

3.1.3 Safety endpoints

Safety endpoints are adverse events, clinical laboratory test results, vital signs measurements, ECG and physical examination results, and use of concomitant medication.

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.

3.1.4 Multiplicity

No multiple testing will be performed in this study as no statistical testing will be carried out at the interim analysis for efficacy endpoints.

3.1.5 Significance testing and estimation

ORR (primary endpoint) will be tested at the final analysis as described in Section 3.2.1.1 using the one-sided significance level (alpha) of 0.025. No statistical testing will be carried out at the interim analysis for efficacy endpoints.

3.2 Analysis methods

3.2.1 Efficacy

Analysis based on the primary efficacy endpoint will be performed on the efficacy population in cohort A. Analyses based on the secondary efficacy endpoints will be performed on the efficacy population as defined in Section 2.1.1 and 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).

Sensitivity efficacy analyses will be based on PP population as defined in Sections 2.1.3 and 2.3. Efficacy analyses in the PP population will be presented if there is a difference greater than 15% between efficacy population and PP population. The difference will be checked for each cohort separately. In case the difference is greater than 15% for one cohort only, only this cohort will be presented in both efficacy population and PP population.

Additional supportive analysis of PFS, Kaplan-Meier and Waterfall plots will be performed only on efficacy population.

Subject data listings (Listings 16.2.6.1 to 16.2.6.8) will be based on Efficacy Population.

3.2.1.1 Primary efficacy analysis

The ORR defined as the proportion of subjects with a best overall response (BOR) of a partial response (PR) or complete response (CR) as assessed by independent central review will be estimated in Cohort A 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 statistical testing will only be carried out at the final analysis.

The ORR estimates will be presented in statistical tables with their associated 2-sided 95% CIs using Clopper-Pearson exact method (Tables 14.2.1.1 based on Efficacy population and 14.2.1.2 based on Per Protocol population).

The SAS code below will be used:

```
proc freq data=<dataset>;
  [by <cohort>;]
   tables <response> / binomial (level='1' p=0.10) alpha=0.05;
  exact binomial;
run;
```

3.2.1.2 Secondary efficacy analysis

The secondary efficacy endpoints will be analysed as below.

(a) Time-to-event endpoints such as TTR (Table 14.2.1.3 and 14.2.1.4, and Figure 14.2.1.5) 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, as well as 25th and 75th percentiles. Event rates at timepoints will also be estimated with associated 2-sided 95% CIs.

(b) DOR will be analysed using the Kaplan-Meier method (Tables 14.2.1.3 and 14.2.1.4, and Figure 14.2.1.6).

(c) DCR estimates will be presented in statistical tables with associated 2-sided 95% CIs (Tables 14.2.1.3 and 14.2.1.4).

(d) PFS will be analysed using the Kaplan-Meier method (Tables 14.2.2.1 and 14.2.2.2, and Figure 14.2.2.3).

(e) OS will also be analysed using the Kaplan-Meier method (Tables 14.2.3.1 and 14.2.3.2, and Figure 14.2.3.3).

(f) 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 (Table 14.2.4.1). TTR, DOR, DCR and PFS according to Investigator's assessment will be analysed in the same way as these endpoints assessed by independent central review (Tables 14.2.4.5 and 14.2.4.6, Figures 14.2.4.8 and 14.2.4.9, Tables 14.2.5.1 and 14.2.5.2, and Figures 14.2.5.3 and 14.2.5.4).

(g) 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. Baseline will be defined as the last questionnaire answered prior to the first dose of study drug. Subject will rate each question from 0 to 4. Total score will be calculated as the sum of the item responses divided by the number of items completed and multiplied by the total number of items in the scale. Completion score will be defined as answering at least 5 of 9 items i.e. total score will be derived only if at least 5 items were answered. Total score ranges will be from 0 to 36 (see Appendix 1 (6)). Descriptive statistics will be performed at each timepoint and change from Baseline (Tables 14.2.6.1 and 14.2.6.2). Comparisons between Baseline and post-Baseline scores will be performed using paired Student t-tests. The proportion of subjects with at least one increase of 1 point, 3 points and 5 points from Baseline will also be reported. The graph of change from Baseline over time will be presented (Figure 14.2.6.3).

Change from baseline in tumour size over time will be summarized (Tables 14.2.1.7 and 14.2.1.8 for independent review, and Tables 14.2.4.10 and 14.2.4.11 for investigator assessments). The tumour size will be the sum of diameters of target lesions measured by independent review, or by investigators. The change from baseline will be calculated as defined in Appendix 1 (7), and the percent change from baseline as defined in Appendix 1 (8). The best percentage change from baseline (biggest decrease, or smallest increase if no decrease) will be presented by waterfall plots (Figure 14.2.1.9 for independent review, and Figure 14.2.4.12 for investigator assessments). The nadir and percent change from nadir will be calculated as defined in Appendix 1 (9) and listed.

The ORR will also be presented by subgroup defined in Section 3.2.16 (Tables 14.2.1.10 and 14.2.1.11 for independent review, and Tables 14.2.4.13 and 14.2.4.14 for investigator assessments).

ORR and tumour response (TTR, DoR and DCR) will also be presented for both independent central review and investigator assessments (Tables 14.2.4.2 and 14.2.4.7). The results are available but on different tables (Tables 14.2.1.1 and 14.2.4.1, and Tables 14.2.1.3 and 14.2.4.5, respectively), this is only a different presentation.

Concordance in Overall Response Rate and BOR assessed by independent central review and by Investigator will be described using shift tables for each cohort separately (Tables 14.2.4.3 and 14.2.4.4). The concordance will be presented for the subjects with assessments in both populations i.e. from both IRC and investigator assessments.

General censoring rules for the analysis of PFS are described in Appendix 1 (4).

Additional supportive analyses of PFS below will be performed 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. This is applicable for PFS only. These additional supportive analyses will be performed on the Efficacy population only.

- The primary PFS analyses described above will be repeated with the same general censoring rules, except that the progression or death will be considered a PFS event regardless of when it occurs during the study i.e. the event will be considered a PFS event even if the subjects missed two or more scheduled tumour assessment prior this event and/or even if the subjects received NPACT prior the event (Table 14.2.2.4, Figure 14.2.2.5, Table 14.2.5.5 and Figure 14.2.5.6).;
- The primary PFS analyses described above will be repeated with the same general censoring rules, except that non-radiological disease progression will also be considered a PFS event (Table 14.2.2.6, Figure 14.2.2.7, Table 14.2.5.7 and Figure 14.2.5.8).
- The primary PFS analyses described above will be repeated with the same general censoring rules, with additional censoring at last tumour assessment prior to treatment discontinuation for subjects who discontinued study treatment due to reasons other than PD or death (Table 14.2.2.8, Figure 14.2.2.9, Table 14.2.5.9 and Figure 14.2.5.10).

3.2.2 Safety

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population as defined in Section 2.2 and will be presented in each cohort separately and overall.

3.2.2.1 Adverse events

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 version 5.0.

Adverse event listings (Listings 16.2.7.1 to 16.2.7.9) will be presented by cohort, subject id, SOC and PT. Listings of serious adverse events (SAEs), adverse events leading to withdrawal and listings of deaths will also be presented. Treatment-emergent AEs (TEAEs) will be flagged (*) in the AEs listings and will be summarized.

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.

If AE start and/or stop dates are missing or partial, the rules mentioned in Section 3.2.3.2 will be applied, and the algorithm for imputation is defined in Appendix 1 (10).

A summary table of overall counts will include the number of subjects with: any AE, any TEAE, any TEAE of Grade 3 or 4, any study drug related TEAE, any study drug related TEAE of Grade 3 or 4, any serious TEAE, any study drug related serious TEAE, any TEAE leading to study drug withdrawal, any TEAE leading to study drug interruption, any TEAE leading to a dose reduced, any TEAE leading to death (Table 14.3.1.1). TEAEs associated with change of schedule of administration will be defined as those with an action taken with study drug as dose reduced or study drug interrupted.

The incidence of all TEAEs will be tabulated by cohort and overall, with the number and percentage of subjects with adverse events classified by SOC (ordered alphabetically) and PT (in descending order of overall PT incidence) (Table 14.3.1.2). The number of occurrences of a TEAE will also be presented. Summary of TEAEs with incidence rate above or equal 10% will also be presented (Table 14.3.1.3).

In addition, summary tables will be presented for TEAEs of Grade 3 or 4 (Table 14.3.1.4), by worst reported severity (Table 14.3.1.7), by investigator causality (Table 14.3.1.8), for related TEAEs of Grade 3 or 4 (Table 14.3.1.9), by decreasing frequency (Tables 14.3.1.10 and 14.3.1.11), for TEAEs related to Laboratory Tests (Table 14.3.1.12), and for non-serious TEAEs with incidence rate above or equal 5% (Table 14.3.1.13).

The incidence of all SAEs will also be tabulated with similar presentation (Table 14.3.2.1).

In addition, summary tables will be presented for SAEs with incidence rate above or equal 5% (Table 14.3.2.2), related SAEs (Table 14.3.2.3), TEAEs associated with premature study drug withdrawal (Table 14.3.2.4), related TEAEs associated with premature study drug withdrawal (Table 14.3.2.7), TEAEs associated with study drug interruption (Table 14.3.2.8), related TEAEs associated with study drug interruption (Table 14.3.2.9), TEAEs associated with dose reduction of study medication (Table 14.3.2.10), related TEAEs associated with dose reduction of study medication (Table 14.3.2.11), and suspected or confirmed COVID-19 (SARS-CoV-2) infection TEAEs (Table 14.3.2.12).

In the event of multiple occurrences of the same adverse events being reported by the same subject, the maximum intensity grade (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related > not related) will be chosen and used in the summaries. So, the adverse event will be counted only once with the worst intensity and worst causality. If causality is missing, the worst case will be assumed.

Time-to-event plots will also be presented using the Kaplan-Meier method for time from first study dose to any TEAE of Grade 3 or 4 (Table 14.3.1.5 and Figure 14.3.1.6), and time to any TEAE leading to drug withdrawal (Table 14.3.2.5 and Figure 14.3.2.6).

The time from first dose will be calculated as defined in Appendix 1 (11).

Summary tables of related SAEs reported in post-treatment follow-up period (i.e. starting more than 30 days after the date of the last cabozantinib dose) will also be presented (Table 14.3.2.13). During the Post-treatment Follow-up period, only SAEs assessed as related to cabozantinib or study procedures, will be collected.

Summary tables of TEAEs leading to death, and of AEs occurring during post-treatment follow-up period and leading to death, will also be presented (Table 14.3.2.14 and 14.3.2.15), as well as by causality (Table 14.3.2.16 and 14.3.2.17). AEs leading to death are AEs with an outcome of death and/or an NCI-CTCAE Grade 5. All subject deaths reported on the death form will be summarised (Table 14.3.2.18). Subject deaths under treatment with study drug (i.e. deaths until 30 days after the date of the last cabozantinib dose) and after treatment with study drug will also be presented separately (Tables 14.3.2.19 and 14.3.2.20).

The incidence of Adverse Events of Special Interest (AESI)/Events to Monitor (ETM) will be tabulated by cohort and overall, with the number and percentage of subjects with adverse events classified by type of event (ordered alphabetically) and PT (in descending order of overall PT incidence) (Table 14.3.2.21). A summary table will be presented for AESIs of Grade 3-4, Grade 4 and Grade 5 (Table 14.3.2.22).

The list of AESI/ETM will be as below:

- Gastrointestinal perforation
- Gastrointestinal and non-gastrointestinal fistula
- Thromboembolic events
- Haemorrhage (Grade ≥3)
- Wound complications
- Posterior reversible encephalopathy syndrome (PRES)
- Osteonecrosis
- Renal failure
- Hepatotoxicity
- Embryotoxicity
- Carcinogenicity.

3.2.2.2 Laboratory data

Laboratory data (haematology, coagulation, thyroid function, blood chemistry and urinalysis) will be listed in standard international (SI) units (Listings 16.2.8.1.1 to 16.2.8.1.7). Any unscheduled laboratory assessments will be flagged in the listings.
A list of clinically significant abnormal values will be presented (Listing 16.2.8.1.8). This listing will present all laboratory values of the laboratory parameter for a subject with at least one clinically significant abnormal value for a laboratory parameter. The abnormality will be as per reported in eCRF.

For all laboratory parameters, the Baseline will be defined as the last measurement collected prior to the first dose of study drug.
As more than one laboratory will be involved in the study for the measurement of laboratory values, a normalisation method will be required in order to take into account the multiple reference ranges [3] for haematology, biochemistry, and urinalysis parameters. The site which has analysed the largest number of blood samples will be used as the reference site. The following formula will be used:

$$Normalised\ value = L_R + (x - L_X)\frac{U_R - L_R}{U_X - L_X}$$

With LR the reference site lower limit, UR the reference site upper limit, LX the local site lower limit, UX the local site upper limit and x the non normalised value assessed in the local laboratory. Reference site lower/upper limits, local site lower/upper limits and local value are converted in the SI unit.
If a normalised value is negative it will be replaced by 0.

The neutrophils values will be imputed as defined in Appendix 1 (12).

3.2.2.2.1 Haematology and Biochemistry

For haematology, coagulation, thyroid function, and blood chemistry parameters, summary statistics (number of values [n], mean, median, standard deviation and range) will be presented, by cohort and overall, at each scheduled assessment for actual values and changes from Baseline (Tables 14.3.4.1.1 to 14.3.4.1.4).

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria version 5.0 (see Appendix 1 (13)). The NCI-CTCAE grade (1 to 4) of haematology and biochemistry by visit and by subject will be listed in Clinical Study Report (CSR) Section 16.2.8 (Listing 16.2.8.1.9). Shift tables in toxicity grading will be presented for haematology and biochemistry parameters (Tables 14.3.4.2.1.1 and 14.3.4.2.4.1). Shift tables for haematology, coagulation, thyroid function, and biochemistry parameters with no NCI-CTCAE grading will also be presented of the number and percentage of subjects with low, normal or high values (Tables 14.3.4.2.1.2, 14.3.4.2.2, 13.3.4.2.3 and 14.3.4.2.4.2).

Changes in toxicity grading will be presented for haematology and biochemistry parameters (Tables 14.3.4.2.5.1 and 14.3.4.2.5.2) in terms of number and proportion of subjects:

- With normal value at baseline and at least one change to grade ≥1
- With normal / G1 value at baseline and at least on change to grade ≥2
- With normal /G1/G2 value at baseline and at least one change to grade 3 or 4.

Listings of the laboratory parameters in CSR Section 14.3.4 will include listings of NCI-CTC Grade 3 and 4 haematological toxicities, listings of NCI-CTC Grade 3 and 4 biochemical toxicities and listings of out-of-range parameters that could not be graded using NCI-CTC grade (below LLN or above ULN) (Tables 14.3.4.3.1 to 14.3.4.3.3).

3.2.2.2.2 Urinalysis

For categorical urinalysis data (absent/trace/positive and normal/abnormal for protein, glucose and blood parameters), frequency tables will be presented, by cohort and overall, at each scheduled assessment as well as the change from Baseline with the following categories: improved, stable, worsened and abnormal worsening (Table 14.3.4.4.1) (see Appendix 1 (14) for the derivation rules). Shift tables may be presented for the number and percentage of subjects with [normal, abnormal] (Table 14.3.4.4.3).

For continuous urinalysis data (pH parameter, 24-hour urine protein, and UPCR), summary statistics (n, mean, median, standard deviation and range), by cohort and overall, will be presented at each scheduled assessment for actual values and changes from Baseline (Tables 14.3.4.4.2 and 14.3.4.4.4). Shift tables may be presented for the number and percentage of subjects with [normal, abnormal NCS, abnormal CS] (Table 14.3.4.4.5).

3.2.2.2.3 Serum and Urine Pregnancy Test

The pregnancy results based on serum and urine tests will also be presented (Table 14.3.4.5) and listed (Listing 16.2.8.1.7).

3.2.2.3 Vital signs

Vital signs (systolic BP, diastolic BP and heart rate in sitting and standing position) will be listed at each assessment by cohort and subject (Listing 16.2.9.1.1). Any unscheduled vital signs will be flagged [U] in the listing.

A listing of Potentially Clinically Significant Abnormalities (PCSA) will also be presented (Listing 16.2.9.1.2). All data for a vital sign parameter will be displayed for a subject having at least one post-baseline PCSA (with flag indicating PCSA). PCSA criteria are defined in Table 3.

Summary statistics (n, mean, median, standard deviation and range) will be presented by cohort and overall, at each scheduled assessment for actual values and changes from Baseline for each vital sign (Table 14.3.5.1). Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug.

A summary of the number and percentage of subjects experiencing PCSA will also be presented (Table 14.3.5.2).

Table 3 PCSA for Vital Signs

Parameter	PCSA
Systolic Blood Pressure	≤ 90 mmHg and change from baseline ≤ -20 mmHg ≥ 180 mmHg and change from baseline ≥ 20 mmHg
Diastolic Blood Pressure	≤ 50 mmHg and change from baseline ≤ -15 mmHg ≥ 105 mmHg and change from baseline ≥ 15 mmHg
Heart Rate	≤ 50 bpm and change from baseline ≤ -15 bpm ≥ 120 bpm and change from baseline ≥ 15 bpm

3.2.2.4 ECG

ECG results will be listed at each assessment by cohort and subject (Listing 16.2.9.2). Any unscheduled ECG will be flagged [U] in the listings.

For continuous ECG parameters (i.e. heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, corrected QT interval), summary statistics (n, mean, median, standard deviation and range), by cohort and overall, will be presented at each scheduled assessment for actual values and changes from Baseline (Table 14.3.6.1). Baseline will be defined as the last ECG measurement collected prior to the first dose of study drug.

For interpretation of clinical significance assessed by the investigator (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by cohort and overall, at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable > within normal limits) (Tables 14.3.6.2 and 14.3.6.3).

3.2.2.5 Physical Examination

Abnormalities identified from physical examination will be listed (Listing 16.2.9.3), as well as ECOG, Height at Baseline, Weight and BMI over time will be listed (Listing 16.2.9.4). BMI will be derived as defined in Appendix 1 (15).

Baseline will be defined as the last available examination performed prior to the first dose of study drug.

A shift table from Baseline to post-Baseline ECOG status will be produced, as well as the Baseline status versus worst post-Baseline status (Table 14.3.7.1).

Summary statistics (n, mean, median, standard deviation and range), by cohort and overall, will be presented at each scheduled assessment for actual values and changes from Baseline for weight and Body Mass Index (BMI) over time (Table 14.3.7.2). A summary of subjects with a weight loss from baseline will be presented (Table 14.3.7.3). Following NCI-CTC AE grading, weight loss from baseline will be breakdown as below: ≤5%, [5 to 10%[, [10 to 20%[and ≥20%.

3.2.3 Missing data and incomplete dates

3.2.3.1 Missing data

If a value required a retest (for laboratory values, vital signs and ECG), the first closest non-missing value to the scheduled visit will be used in the summary tables.
If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries.
Any repeat or additional assessments performed will be included in the individual subject data listings.

Missing tumour assessment data will be handled as defined in Appendix 1 (1).

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

For study drug, no imputation will be used.

For TTR, DOR, PFS and OS, the imputation rules in case of partial dates are defined in Appendix 1 (2), (3), (4) and (5), respectively.

The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase [i.e. a TEAE for AEs] except if the partial onset date or other data [stop date, …] indicates differently).
A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly, a medication with partial start and stop dates could be considered as prior and concomitant treatment).
Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in APR2004 after the administration performed on 31MAR2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates.).

For TEAE flag, the algorithm is defined in Appendix 1 (10) in case of partial start or stop dates. For time from first dose for adverse events, the imputation rules in case of partial dates are defined in Appendix 1 (11).

For prior/concomitant medication flag, the algorithm is defined in Appendix 1 (16) in case of partial start or stop dates.

For time from diagnosis to screening, the imputation rules in case of partial dates are defined in Appendix 1 (17).

For treatment duration on 1st anti-cancer therapy for subgroup analysis (see Section 3.2.16), the imputation rules in case of partial dates are defined in Appendix 1 (18). In case, the duration treatment cannot be derived as <6 months, or ≥6 months based on the available data, the subgroup ≥6 months will be considered by default.

3.2.4 Subject disposition

Listings of treatment batch number and of enrolment scheme and codes will be presented by subject for each cohort (Listings 16.1.6 and 16.1.7).

Listings of eligibility details, and of dates of assessments and visits (relative day) and their study drug exposure and study exposure will be presented by subject for each cohort (Listings 16.2.1.1 to 16.2.1.3).

The numbers and percentages of subjects in the screened, included, safety, efficacy and PP populations will be tabulated by cohort and overall (Table 14.1.1). The reasons for subject exclusions from each of the populations will also be tabulated. Subject disposition by visit (Table 14.1.2), the subject enrolment by country and site (Table 14.1.3), and the sample size of analysis populations by country and site (Table 14.1.4) will also be tabulated.

Summary tables will present the extent of subject exposure in the study and the extent of subject study drug exposure for each cohort and overall (Tables 14.1.5 and 14.1.6). The study exposure is from date of consent to the last study visit (see Appendix 1 (19)). The last visit will be during the post-treatment follow-up period (if a post-treatment follow-up period took place). The total study drug exposure is from study drug first intake to last study drug intake (see Appendix 1 (20)). The actual study drug exposure excludes the study drug interruptions. The average daily dose will also be calculated (see Appendix 1 (21)). Study drug dose reduction, interruption, and escalation will also be presented (Table 14.1.7).

3.2.5 Withdrawals

Discontinued subjects will be listed (Listing 16.2.1.4) and a summary table (Table 14.1.8) of the number and percentage of subjects who were screened, screened failed, included, 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, as well as Primary reasons for discontinuation of study. Primary reasons for discontinuation of study due to COVID-19 will be also tabulated. The subjects who did not discontinue the study treatment prematurely and completed the study (i.e. 18 months after the last subject received the first cabozantinib administration) will be considered as having completed the treatment.

3.2.6 Protocol deviations

The impact of major protocol deviation on the efficacy analysis will be investigated by comparing the results of the Efficacy and PP population analyses (see Section 3.2.1).
Any major protocol deviation 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 analysis populations.

The measurements on the day of first dose will not be considered as the baseline measurement, if a protocol deviation states that measurement was after the first dose.

All the major protocol deviations identified will be also listed by subject for each cohort (Listing 16.2.2). Subjects excluded from the Efficacy population, the Per Protocol population, and the Safety population will be listed (Listing 16.2.3). Subjects excluded from the Per Protocol population due to receiving prohibited concomitant medication will be flagged (+).

A summary table of major protocol deviations will be produced by cohort and overall, for the Included population (Table 14.1.9) including major protocol deviations due to COVID-19.

3.2.7 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by cohort and subject (Listings 16.2.4.1 to 16.2.4.2).
Descriptive summary statistics (n, mean, standard deviation, median and range) or frequency counts will be provided for demographic and Baseline characteristics (sex, age, race, height, weight and BMI at Baseline, ECOG at Baseline, substance use, RCC history, independent tumour assessment at Baseline, investigator tumour assessment at Baseline), by cohort and overall, for the safety population as defined in Section 2.2 (Tables 14.1.10 to 14.1.15).
Age will be derived as defined in Appendix 1 (22), BMI in Appendix 1 (15), time from diagnosis to screening Appendix 1 (17), and treatment duration on first anti-cancer therapy in Appendix 1 (18).
No statistical comparison between the cohorts will be performed and only 95% Confidence Intervals (CIs) will be reported.

3.2.8 Medical and surgical history

Medical and surgical history will be coded using MedDRA most recent version.
Listings will present the primary system organ class, preferred term and verbatim text (Listing 16.2.4.3). The listings will be sorted by cohort, subject, primary system organ class, preferred term and verbatim text.
A frequency table of the number and percentage of subjects will be provided for all / active medical and surgical history by primary system organ class and preferred term for each cohort and overall, for the safety population (Table 14.1.16).

3.2.9 Subject compliance

A listing will be presented for drug administration (dose, quantity, date, reason for change) by subject for each cohort (Listing 16.2.5.1), and for drug dispensation and compliance (Listings 16.2.5.2 and 16.2.5.3). Deviations from number of tablets and dosage taken and scheduled intake will be presented.
A summary table of compliance expressed in percentage and by category (<80% / >120%) will be produced by cohort and overall, for the safety population (Table 14.1.17). The compliance will be calculated as the number of tablets taken divided by the number of tablets planned to be taken multiplied by 100 (see Appendix 1 (23)).

Summary tables of study drug dose reduction and interruption are planned in Section 3.2.4. Summary tables of AEs leading to dose modification are also planned in Section 3.2.2.1.

3.2.10 Prior and concomitant therapies

Prior and ongoing medications started before the study and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) most recent version. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, that is, corresponding to the first 3 figures.

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the last dose of study drug will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the rules mentioned in Section 3.2.3.2 will be applied, and the algorithm for imputation is defined in Appendix 1 (16).

Listings of prior and concomitant therapies will be presented (Listings 16.2.4.4 to 16.2.4.11). For coded medications, the listings will be sorted by cohort, subject, chronological start date, therapeutic class, preferred name and verbatim name. For non-coded therapies, the listings will be sorted by cohort, subject, chronological start date and procedures by alphabetical order.

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications (Tables 14.1.18 and 14.1.19), prior non-drug therapies and concomitant non-drug therapies (Tables 14.1.20 and 14.1.21), prior systemic therapies (Table 14.1.22), prior radiotherapies (Table 14.1.23), prior surgical procedures (Table 14.1.24) and concomitant surgical procedures (Table 14.1.25), subsequent anticancer therapies (Table 14.1.26), subsequent anticancer radiotherapies (Table 14.1.27) and subsequent surgical procedures (Table 14.1.28). Coded medications will be summarized by therapeutic class and preferred name. These summary tables will be presented for each cohort and overall. They will be based on the safety population for prior therapies, and for concomitant 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 anti-cancer treatment 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 (29);
- 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;
- 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.

3.2.11 Derived data

Derived data are detailed in Appendix 1: Derived Data.

3.2.12 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the first closest non-missing result to the scheduled visit should be used.

Baseline will be defined as the last non-missing result prior to the first dose of study drug. As the time of first dose is not planned to be collected, assessments on the day of first dose will be considered prior to first dose if such procedures are required by

the protocol to be conducted before first dose, except if a protocol deviation states that the assessment was collected after the first dose.

The study day will be calculated as defined in Appendix 1 (24).

For tumour assessment, the following visit mapping will be performed:

Study phase	Scheduled visit	Protocol Time Interval	Analysis Time Interval (days)
Pre treatment	Visit 1 - Pre study		-20 to –1
Active phase	Visit 2 - Baseline	Day 1	0 (prior to first dose)
	Visit 6 - Week 12 (Day 85)	Day 85 (±10 Days)	71 to 98
	Visit 9 - Week 24 (Day 169)	Day 169 (±10 Days)	155 to 182
	Visit 12 - Week 36 (Day 253)	Day 253 (±10 Days)	239 to 266
	Etc. (every 12 weeks until the End of Study)	Day XXX = number of weeks * 7 +1	XXX -14 to XXX +13
Follow-up	Follow-up	Every 12 weeks (±15 Days)	after last dose of treatment

For Questionnaires, the following visit mapping will be performed:

Study phase	Scheduled visit	Protocol Time Interval	Analysis Time Interval (days)
Active phase	Visit 2 - Baseline	Day 1	Prior to first dose
	Visit 6 - Week 12 (Day 85)	Day 85 (±5 Days)	71 to 98
	Visit 9 - Week 24 (Day 169)	Day 169 (±5 Days)	155 to 182
	Visit 12 - Week 36 (Day 253)	Day 253 (±5 Days)	239 to 266
	Etc. (every 12 weeks until the End of Study Treatment visit or Early Study Withdrawal visit)	Day XXX = number of weeks * 7 +1	XXX -14 to XXX +13

We may need to extend the interval in case some assessments are out of the windows. The last questionnaires collected at the end of the study will also be summarized.

For laboratory data (including thyroid function test collected every 4 weeks after Baseline), vital signs, physical examination and ECOG status, the following visit mapping will be performed:

Study phase	Scheduled visit	Protocol Time Interval	Analysis Time Interval (days)
Pre treatment	Visit 1 - Pre study		-20 to –1
Active phase	Visit 2 - Baseline	Day 1	0 (prior to first dose)
	Visit 3 - Week 2 (Day 15)	Day 15 (±2 Days)	1 to 21
	Visit 4 - Week 4 (Day 29)	Day 29 (±2 Days)	22 to 42
	Visit 5 - Week 8 (Day 57)	Day 57 (±2 Days)	43 to 70
	Visit 6 - Week 12 (Day 85)	Day 85 (±5 Days)	71 to 98
	Visit 7 - Week 16 (Day 113)	Day 113 (±5 Days)	99 to 126
	Visit 8 - Week 20 (Day 141)	Day 141 (±5 Days)	127 to 154
	Etc. (every 4 weeks until the End of Study Treatment visit or Early Study Withdrawal visit)	Day XXX = number of weeks * 7 +1	XXX -14 to XXX +13

In case the assessment was performed at Screening visit, and there was no assessment at Baseline visit, the following rules will be applied. The assessment will be tabulated both at Screening and at Baseline, as Baseline will be defined as the last non-missing result prior to the first dose of study drug. The assessment at Screening visit will be considered as a Baseline record, but not mapped to Baseline visit.

For ECG, the following visit mapping will be performed:

Study phase	Scheduled visit	Protocol Time Interval	Analysis Time Interval (days)
Pre treatment	Visit 1 - Pre study		-20 to –1
Active phase	Visit 2 - Baseline	Day 1	0 (prior to first dose)
	Visit 4 - Week 4 (Day 29)	Day 29 (±2 Days)	22 to 42
	Visit 6 - Week 12 (Day 85)	Day 85 (±5 Days)	71 to 98
	Visit 9 - Week 24 (Day 169)	Day 169 (±5 Days)	155 to 182
	Etc. (every 12 weeks until the End of Study Treatment visit or Early Study Withdrawal visit)	Day XXX = number of weeks * 7 +1	XXX -14 to XXX +13

In case the assessment was performed at Screening visit, and there was no assessment at Baseline visit, the following rules will be applied. The assessment will be tabulated both at Screening and at Baseline, as Baseline will be defined as the last non-missing result prior to the first dose of study drug. The assessment at Screening visit will be considered as a Baseline record, but not mapped to Baseline visit.

3.2.13 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

Continuous data will be summarized in terms of the number of observations, arithmetic mean, standard deviation, 95% CI of the mean (for final analysis only), median and the range (minimum, maximum), unless otherwise stated.
Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations.
The mean, median and standard errors of the mean (SE) will be reported to one more decimal place than the raw/derived data recorded in the database. The SD will be reported to one more decimal place than the raw data that they summarise.
Minimum and maximum values will be reported with the same precision as the raw data. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts, percentages and when appropriate 95% CIs (for the final analysis only, see in the table shells). Any planned collapsing of categories might be detailed in this SAP text and the data displays. Changes from Baseline in categorical data will be summarized using shift tables where appropriate.
Percentages will be reported to one decimal place and 0% will not be presented. For disposition tables, percentages will be calculated using a denominator of all subjects in a specified population and in each cohort. For other tables, percentages will be calculated based on non-missing data. The denominator will be specified in a footnote to the tables for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Lower and upper CI values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.
P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.
All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm] in 24-hour time format.

3.2.14 Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.15 Interim analysis

An interim and purely descriptive analysis will be conducted when 80% of subjects (i.e. 59 subjects) of the 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. A subset of Tables, Figures and Listings (TFLs) will be produced for this interim analysis. 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, i.e. as soon as all subjects have discontinued study treatment or at the latest 12 months after the last subject received the first cabozantinib administration whichever occur first. A cut-off will be performed considering the date when last subject received the first cabozantinib administration plus 12 months.
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.

3.2.16 Covariates and analysis of subgroups

Subgroup analyses will be conducted by presenting the primary analysis of ORR (with point estimates and 95% CIs) for both independent central review (Tables 14.2.1.10 based on Efficacy population and 14.2.1.11 based on Per Protocol population) and Investigator's assessment (Tables 14.2.4.13 and 14.2.4.14) in the following subgroups:

- Age (<65 years, ≥65 years);
- Gender (female, male);
- Memorial Sloan Kettering Cancer Center (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).

Subgroup analyses will be presented in each cohort separately. In addition, ORR according to local Investigator's review per RECIST 1.1 will be presented in the overall population (cohort A + cohort B).

The age will be calculated as defined in Appendix 1 (22), and the treatment duration in Appendix 1 (18).

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using UNIX operating system.

4.2 Software

All tables, listings and figures will be produced, and statistical analysis performed using SAS® version 9.4 or a later version in a secure and validated environment. All outputs will be produced in Microsoft Word Format (RTF format) and will be combined into a PDF file(s).

4.3 Validation programs

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.
Program validation (including any macros) will be in accordance with Parexel's SOPs referenced in Project Specific SOP list.
Copies of the internal QC forms produced for the validation process and the Clinical Research Organisation (CRO)'s sign-off forms will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs developed for this study for producing the analysis datasets, tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

The end of the recruitment being driven by the approval of the protocol amendment by competent authorities and/or ethics committees in each country, the sample size in cohort A exceeds the target of 74 subjects (see Section 1.2).

The included Population definition is revised to include the subjects who did not fulfil the inclusion and exclusion criteria (e.g. if non-compliance to inclusion or exclusion criteria is identified after inclusion in the study), but nevertheless received at least one dose of study medication (see Section 2).

Efficacy and Per Protocol populations are split for IRC assessments and investigator assessments (see Section 2.1).

Change from baseline in tumour size summaries (Tables 14.2.1.7, 14.2.1.8, 14.2.4.11 and 14.2.4.12) and corresponding waterfall plots (Figure 14.2.1.9 and Figure 14.2.4.12) are added for exploratory purpose (see Section 3.2.1.2).

The Adverse Events of Special Interest are added for exploratory purpose (see Section 3.2.2.1).

6 REFERENCES

1. Choueiri, Toni K., et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. New England Journal of Medicine 373.19, 2015: 1814-1823.
2. 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.
3. Karvanen, J. The Statistical Basis of Laboratory Data Normalization. Ther Innov Regul Sci 37, 101–107 (2003). https://doi.org/10.1177/009286150303700112.
4. Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS) Scoring Guidelines (Version 4); downloaded from https://www.facit.org/measures/FKSI-DRS).

7 APPENDICES

Appendix 1: Derived Data

The following derived data will be calculated and included in the listings:

(1) **Tumour assessments and best overall response (BOR)**
In case of missing tumour assessment at visit n, it should be kept missing as long as the next evaluation at visit n+1 is a Progressive Disease (PD). The best overall response (BOR) in this case is 'not evaluable' if there are no previous assessments. Otherwise, the best overall response will be assessed by using tumour assessments up to visit n-1.
On the other hand, if the assessment at visit n+1 does not show any progression, this missing assessment (at visit n) will be derived by using the assessment from previous visit n-1 (last observation carried forward method). In this case the BOR will be assessed as defined.

(2) **Time-to-response (TTR)**
TTR is defined as the time from start of study treatment to the date of first evidence of response (PR or CR). For subjects with no evidence of response, the TTR will be censored at the last tumour assessment and considering the censoring rules defined in the table below.

Event	Decision	Date of event or censoring
Response to treatment (PR or CR) with no more than one missing scheduled tumor assessment before the event and without NPACT before the event.	Not censored	Earliest date between: - date of PR - date of CR
Response to treatment (PR or CR) with two or more missing scheduled tumor assessments before the event	Censored	Date of the last tumor assessment prior to the missing assessment.
Response to treatment (PR or CR) with NPACT after the start of cabozantinib and before the event	Censored	Date of the last tumor assessment prior to the date of initiation of NPACT.
No response (no PR and no CR) with at least one radiological or assessment after the initiation of study treatment.	Censored	Date of last radiological assessment
No response (no PR and no CR) without any radiological assessment after the initiation of study treatment.	Censored	Date of first cabozantinib intake

TTR will be calculated as:
TTR (months) = round ((date of initial response or date of last tumour assessment – date of first study drug intake +1) / (30.4375), .01)

In case of incomplete date of first study drug intake, no imputation will be used.

In case of response and a partial initial response date, missing day will be imputed by the last day of the month. This will be the most conservative approach considering the latest date for the response. It will be imputed by the first study drug intake in case the first study drug intake is earlier than the imputed date.

In case of censoring and a partial last tumour assessment date, missing day will be imputed by the first day of the month. It will be imputed by the first study drug intake in case the first intake is later than the imputed date. The censoring may occur earlier than the exact date.

(3) **Duration of response (DOR)**
DOR is defined as the time from first documented response (PR or CR) to either disease progression or death due to any cause, whichever occurs first. DOR will be analysed for responding subjects only. For responding subjects (i.e. subjects with a PR or CR) who are not known to be dead or progressed at the time of data cut-off for DOR analysis, the DOR will be censored at the last tumour assessment and considering the censoring rules defined in the table below.

Event	Decision	Date of event or censoring
Progressive disease with no more than one missing scheduled tumor assessment before the event and without NPACT before the event.	Not censored	Date of first progressive disease
Death with no more than one missing scheduled tumor assessment before the event and without NPACT before the event.	Not censored	Date of death
PD or death with two or more missing scheduled tumor assessments before the event	Censored	Date of the last tumor assessment prior to the missing assessment.
PD or death with NPACT after the start of cabozantinib and before the event	Censored	Date of the last tumor assessment prior to the date of initiation of NPACT.
No event (no PD, no death) with at least one radiological assessment after the first response to treatment.	Censored	Date of last radiological assessment

No event (no PD, no death) without any radiological assessment after the first response to treatment.	Censored	Date of first response to treatment

DOR will be calculated as:
DOR(months) = round ((progression date or death date or date of last tumour assessment – date of initial response+1) / (30.4375),0.01)

In case of non-censoring and a partial progression/death date, missing day will be imputed by the first day of the month. This will be the most conservative approach considering that the earliest date for progression/date. It will be imputed by the date of initial response in case the date of initial response is later than the imputed date.

In case of censoring and a partial last tumour assessment date, missing day will be imputed by the first day of the month. It will be imputed by the date of initial response in case the initial response is later than the imputed date. The censoring may occur earlier than the exact date.

(4) **Time-to-Progression for Progression-Free Survival (PFS) analysis**
PFS is 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. For subjects who are not known to have died or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the last tumour assessment and considering the censoring rules defined in the table below.

Event	Decision	Date of event or censoring
Progressive disease with no more than one missing scheduled tumor assessment before the event and without NPACT before the event.	Not censored	Date of first progressive disease
Death with no more than one missing scheduled tumor assessment before the event and without NPACT before the event.	Not censored	Date of death
PD or death with two or more missing scheduled tumor assessments before the event	Censored	Date of the last tumor assessment prior to the missing assessment.
PD or death with NPACT after the start of cabozantinib and before the event	Censored	Date of the last tumor assessment prior to the date of initiation of NPACT.
No event (no PD, no death) with at least one radiological	Censored	Date of last radiological assessment

assessment after the initiation of study treatment.		
No event (no PD, no death) without any radiological assessment after the initiation of study treatment.	Censored	Date of first cabozantinib intake

PFS will be calculated as:
PFS (months) = round ((date of progression or date of death or date of last tumour assessment – date of first study drug intake+1) / (30.4375), .01).

In case of incomplete date of first study drug intake, no imputation will be used.

In case of non-censoring and a partial progression/death date, missing day will be imputed by the first day of the month. This will be the most conservative approach considering that the earliest date for progression/death. It will be imputed by the first study drug intake in case the first study drug intake is later than the imputed date.

In case of censoring and a partial last tumour assessment date, missing day will be imputed by the first day of the month. It will be imputed by the first study drug intake in case the first intake is later than the imputed date. The censoring may occur earlier than the exact date.

(5) **Time-to-death for Overall Survival (OS) analysis**
OS is defined as the time from the start of treatment until death due to any cause. For subjects who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they were last known to be alive. OS will be calculated as:
OS (months) = round ((date of last known alive or death date – date of first study drug intake +1) / (30.4375), .01).

Event	Decision	Date of event or censoring
Death	Not censored	Death date
No event (no death)	Censored	Date of last known alive

In case of incomplete date of first study drug intake, no imputation will be used.

In case of non-censoring and a partial death date, missing day will be imputed by the first day of the month. This will be the most conservative approach considering the earliest date for the death. It will be imputed by the first study drug intake in case the first study drug intake is later than the imputed date.

In case of censoring and a partial last know alive date, missing day will be imputed by the first day of the month. It will be imputed by the first study drug intake in case the first intake is later than the imputed date. The censoring may occur earlier than the exact date.

(6) **FKSI-DRS Total Score**

Following the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS) Scoring Guidelines Version 4 [4], the 9 item answers will be coded as: "Not at all" = 0, "A little bit" = 1, "Some-what" = 2, "Quite a bit" = 3, and "Very much" = 4.

When at least 50% of items (i.e. 5 items) were answered in the subject questionnaire, the FKSI-DRS Total Score will be calculated as follows.
First, each item will be reversed by doing 4 minus the answer. Then, these individual reversed items will be summed to obtain a score. In last step, this score will be prorated by multiplying by the total number of items in the subscale (i.e. 9) and by dividing by the number of items answered in the questionnaire. This will produce the symptom index score.
The score ranges from a minimum possible score of 0 to a maximum possible score of 36.
As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic subject and the highest possible score is an asymptomatic subject.

(7) **Changes from Baseline**

Changes from Baseline will be calculated as a difference from Baseline (e.g. assessment at the visit – assessment at Baseline).

(8) **Percent change from Baseline**

Percent change from Baseline will be calculated as a percentage of change from Baseline (e.g. 100*((assessment at the visit - assessment at Baseline) / (assessment at Baseline))).

(9) **Percent change from nadir**

Nadir is the smallest sum of measurements at prior timepoints (including baseline).
Percent change from nadir will be calculated as a percentage of change from nadir (e.g. 100*((assessment at the visit - assessment at nadir) / (assessment at nadir))).

(10) **Algorithm for TEAE flag**

An AE will be classified as a TEAE in case AE start date is between the first dose of study drug and the last study drug administration plus 30 days.

In case of an incomplete AE start date, an AE start date imputation algorithm will be implemented as described in the Table below. Classification of adverse event according to its treatment-emergent status is then performed using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose first dose of study drug is equal to 2002-08-11 and several AEs have incomplete start dates.

Description of incomplete AE start date	Imputed numeric date	Example	
		Character date	Imputed AE start date
Day is missing			
YYYY-MM < YYYY-MM of first dose of study drug	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of first dose of study drug	Min (first dose of study drug, AE end date) or first dose of study drug in case AE end date is missing	2002-08-XX	Min (2002-08-11, AE end date) or 2022-08-11 in case AE end date is missing
YYYY-MM > YYYY-MM of first dose of study drug	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY of first dose of study drug	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY of first dose of study drug	Min (first dose of study drug, AE end date) or first dose of study drug in case AE end date is missing	2002-XX-XX	Min (2002-08-11, AE end date) or 2022-08-11 in case AE end date is missing
YYYY > YYYY of first dose of study drug	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min (first dose of study drug, AE end date) or first dose of study drug in case AE end date is missing		Min (2002-08-11, AE end date) or 2022-08-11 in case AE end date is missing

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

In case the AE start date is missing, the most conservative approach will be systematically considered and the AE will be considered as a TEAE, except if other data (e.g. end date) indicates differently.

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

(11) **Time from first study dose for adverse event**

If the start date of the adverse event is identical to the date of first administration, then "<1" day will be presented.

The time will be calculated as (AE start date – first administration date)+1 and presented in days.

If the AE start date is partial due to missing day, the time from first dose will be presented as a superior inequality (e.g.: for an AE started in FEB2004 after the first administration performed on 31JAN2004, the time from first dose will be as "≥2" days).

If the first administration date is partial due to missing day, the time from first dose will be presented as a superior inequality (e.g. for an AE started on 01FEB2004 after the first administration performed in JAN2004, the time from first dose will be as "≥2" days).

If both the AE start day and the first administration day are missing, the time from first dose will not be presented.

If the AE start month is missing or the first administration month is missing, the time from first dose will not be presented.

If the AE start date is missing or the first administration date is missing, the time from first dose will not be presented.

(12) **Neutrophils values**

In some cases, laboratory data may not be reported as they may be difficult to detect. When the White Blood Cells counts (WBC) are recorded, and if WBC < $0.5*10^9$/L, then neutrophils value will be imputed as zero and thus will be considered to be in NCI grade 4.

(13) **NCI-CTC AE grades for laboratory parameters**

For NCI/CTC gradable laboratory parameters, appropriate grades should be attributed according to the coding rules specified in the National Cancer Institute for Adverse Events (NCI-CTCAE) version 5.0 if this grade is not present in the database.

(14) **Urinalysis**

Improved is Positive to Trace or Negative, and Trace to Negative. Worsened is Negative to Trace or Positive, and Trace to Positive, with the result classified as Normal. Abnormal worsening is Negative to Trace or Positive, and Trace to Positive, with the result classified as Abnormal.

(15) **BMI**

BMI (kg/m^2) will be derived as Weight (kg)/[Height at Baseline (cm)/100]^2 and rounded to the nearest decimal.

(16) **Algorithm for Prior/ Concomitant flag**

Medication, therapies and procedures start and stop dates will be compared to the date of the first dose of study drug to allow classification as either Prior only, Prior and Concomitant, or Concomitant only.

In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be performed to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, the most conservative approach will be systematically considered and the medication will be classified as prior and concomitant.

(17) **Time from Diagnosis to Screening**

Time from Diagnosis to Screening will be calculated as (date of screening – date of diagnosis). It will be then divided by 30.4375 to be presented in months.
In case of missing screening day, the day will be imputed to 15. In case of missing screening month, the month will not be imputed.
In the same way, in case of missing diagnosis day, the day will be imputed to 15. In case of missing diagnosis month, the day and month will be imputed to 01JUL.
No imputation will be performed for missing year.

(18) **Treatment duration on 1st anti-cancer therapy**

Treatment duration on 1st anti-cancer therapy will be calculated as (latest stop date – earliest start date)+1. It will be then divided by 30.4375 to be presented in months.
In case of missing drug start day, the day will be imputed to 15. In case of missing drug start month, the month will not be imputed.
In the same way, in case of missing drug stop day, the day will be imputed to 15. In case of missing drug stop month, the month will not be imputed.
No imputation will be performed for missing year.
In case, the duration treatment cannot be derived as <6 months, or ≥6 months based on the available data, the subgroup ≥6 months will be considered by default.

(19) **Study exposure**

Study exposure will be calculated as:
Study exposure (days) = last visit attended – informed consent date +1. It will be then divided by 30.4375 to be presented in months.

(20) **Study drug exposure**

a) Total study drug exposure will be calculated as:
Total study drug exposure (days) = last study drug intake date – first study drug intake date +1. It will be then divided by 30.4375 to be presented in months.
b) Actual study drug exposure will exclude the study drug interruptions.
For interim analysis, the last attended visit date will be considered as the last study drug intake date, in case the subject has not ended the treatment prior to this visit.

(21) **Average daily dose**

Average daily dose in mg/day will be calculated as the number of tablets taken multiplied by the corresponding dosage in mg from each kit, and divided by the total study drug exposure in days (i.e. including the study drug interruptions).

(22) **Age**

Subject age (years) will be derived as (screening year – birth year).

(23) **Compliance**

The compliance will be calculated as :
Total number of tablets taken divided by Total number of tablets planned to be taken multiplied by 100.
Total number of tablets planned to be taken will be calculated as (last study drug intake date – first study drug intake date)+1, as the planned intake is one tablet per day.

(24) **Study day**

Study day will be defined as ‘-1’ for the day prior to treatment and as ‘1’ for the day of the first intake of study treatment (i.e. day 0 does not exist).

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