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PASS Information

Title	Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy
Protocol version identifier	3.0
Date of last version of protocol	2.0 (dated 26 June 2017)
European Union electronic register of postauthorisation studies (EU PAS register) number	Not registered yet
Active substance	CABOZANTINIB S-MALATE Pharmacotherapeutic group: Other antineoplastic agents, protein kinase inhibitors ATC code: L01XE26
Medicinal product	Cabometyx™ tablets
Product reference	EU/1/16/1136
Procedure number	EMEA/H/C/004163
Marketing authorisation holder (MAH)	Ipsen Pharma
Joint PASS	No
Research question and objectives	For this prospective study, the objective is to understand the utilisation of cabozantinib in subjects with advanced renal cell carcinoma (RCC) following prior VEGF-targeted therapy in real-life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy. Other patterns of use of cabozantinib will also be described as listed in the study objectives. Primary objective: • To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy. Secondary objectives: • To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings; • To describe all treatment-emergent nonserious and serious AEs; • To describe the effectiveness of cabozantinib in RCC in real-life in terms of progression-free survival and best overall response; • To describe the health care resource utilisation associated with the management of treatment-related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays; concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).
Countries of study	The study will be conducted in countries where cabozantinib is marketed at the time of the study. It is anticipated that there will be approximately 100 study centres in 10 to 15 European countries.
Author	PPD Global Medical Affairs Director, Uro-oncology Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne-Billancourt Paris, France

Marketing Authorisation Holder

MAH	Ipsen Pharma 65, quai Georges Gorse 92100 Boulogne-Billancourt Paris, France
MAH contact person	PPD PPD Ipsen Biopharm Ltd 102, Park Drive Milton Park, Abingdon Oxfordshire OX14 4RY United Kingdom Serious Adverse Event (SAE) form(s) to be submitted to: Email: PPD or Fax: PPD

PROTOCOL SIGNATURES

Investigator Agreement and Signature

I have read and agree to the postauthorisation safety study (PASS) protocol N° F-FR-60000-001 entitled "Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy". I am aware of my responsibilities as an investigator under the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), the European Medicines Agency (EMA) guidelines for good pharmacovigilance practices (GVP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: (Principal) Investigator: SIGNATURE: _____

DATE: _____

OFFICE: _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

Coordinating Investigator Agreement and Signature:

NAME: PPD

TITLE: Coordinating Investigator SIGNATURE: _____

DATE: _____

OFFICE: _____

On behalf of the sponsor:

NAME: PPD

TITLE: Global Medical Affairs Director, Uro-oncology SIGNATURE: _____

DATE: _____

OFFICE: _____

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2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AXL	AXL receptor tyrosine kinase
CI	Confidence interval
CRO	Contract Research Organisation
CSR	Clinical study report
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS register	European Union electronic register of postauthorisation studies
FAS	Full Analysis Set
FLT	Fms related tyrosine kinase
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HR	Hazard ratio
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
ISPE	International Society for Pharmacoepidemiology
KIT	KIT proto-oncogene receptor tyrosine kinase
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene, receptor tyrosine kinase
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
OS	Overall survival
PASS	Postauthorisation Safety Study

ABBREVIATION	Wording Definition
PFS	Progression-free survival
PT	Preferred term
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumours
RET	Ret proto-oncogene
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SIS-ICF	Subject Information Sheet and Informed Consent Form
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHODRUG	World Health Organization Drug Dictionary

3 RESPONSIBLE PARTIES

The coordinating investigator of the protocol is PPD :

PPD

4 ABSTRACT

Study Title:	Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy
Study Number:	F-FR-60000-001
Protocol Version N°:	Final version 3.0
Date	21 July 2017
Date of the Last Version of the Protocol:	26 June 2017
Author:	PPD Global Medical Affairs Director, Uro-oncology Ipsen Pharma

Rationale and Background

Renal cell carcinoma (RCC) is diagnosed in about 330,000 individuals worldwide each year and results in over 140,000 deaths [Ferlay et al, 2015]. Up to 30% of patients present with metastatic disease at initial diagnosis [Gupta et al, 2008].

In advanced stages, despite an increasing number of available systemic therapies such as immunotherapies, VEGF-targeted therapies and mammalian target of rapamycin (mTOR) inhibitors for this malignancy, virtually all patients eventually relapse.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor (TKI) with potent activity against MET, VEGF receptors (VEGFRs) and AXL as well as a number of other receptors of tyrosine kinases (RTKs) that have also been implicated in tumour pathobiology, including RET, KIT and FLT. Cabozantinib suppresses MET and VEGFR signalling, rapidly inducing apoptosis of endothelial and tumour cells, resulting in tumour regression in a variety of xenograft models [Sennino and McDonald, 2012; Yakes et al, 2011].

In the pivotal phase 3 METEOR study, cabozantinib (tablets) has been shown to significantly improve progression-free survival (PFS), overall response rate and overall survival (OS) as compared with everolimus in subjects with previously treated advanced RCC with clear cell component [Chouieri et al, 2015; Chouieri et al, 2016].

In the METEOR study, the starting dose of cabozantinib was 60 mg daily. If a subject experienced an unacceptable study treatment-related adverse event (AE), study treatment interruption or a dose reduction was allowed at the investigator's discretion. Following a treatment interruption, the subject could have resumed treatment if the AE resolved to ≤ grade 1 or to baseline values within 6 weeks. The study treatment could have been restarted at a reduced dose to avoid worsening AEs, if the AE was related to treatment or dose reduction was otherwise deemed clinically necessary.

Although AEs were most often manageable in the METEOR study, cabozantinib treatment was interrupted in 70% of subjects and dose reduction due to an AE occurred in 59.8% of subjects in the cabozantinib arm. Overall, at least one dose modification (i.e. interruption or reduction) was reported for 76% of subjects treated with cabozantinib in this study.

Subjects in the METEOR study were included under controlled conditions (strict inclusion and exclusion criteria, guidelines for therapy management, monitoring of compliance). In the

real-world setting, the same criteria will not apply and the utilisation pattern of cabozantinib is unknown.

Research Question and Objectives

For this prospective study, the objective is to understand the utilisation of cabozantinib in subjects with advanced RCC following prior VEGF-targeted therapy in real-life settings in terms of dose modifications due to AEs when used as a second line therapy or third and later line therapy. Other patterns of use of cabozantinib will also be described as listed in the study objectives.

Primary objective:

- To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy.

Secondary objectives:

- To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings;
- To describe all treatment-emergent nonserious and serious AEs (SAEs);
- To describe the effectiveness of cabozantinib in RCC in real-life in terms of PFS and best overall response;
- To describe the health care resource utilisation associated with the management of treatment-related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays, concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).

Study Design

This is a prospective, international, multicentre, noninterventional study.

Study Setting

To be included in the study, the subject should fulfil all the following inclusion criteria:

(1) Age ≥18 years old;
(2) Has a diagnosis of advanced RCC;
(3) Has received at least one prior VEGF-targeted therapy;
(4) For whom the treating physician has decided to start treatment with cabozantinib tablets prior to inclusion;
(5) No previous exposure to cabozantinib prior to inclusion;
(6) Not concurrently involved in an interventional study;
(7) Consents to participate in this noninterventional study.

There are no exclusion criteria for this study.

A total of 680 subjects are planned to be included: 340 subjects receiving second line therapy and 340 subjects receiving third and later line therapy.

The study population will consist of subjects diagnosed with advanced RCC, having received at least one prior VEGF-targeted therapy, who are starting cabozantinib tablets at the discretion of the treating physician and who consent to participate in the study. In order to avoid bias, participating physicians will be asked to include all successive eligible subjects except those who refuse the collection of and/or access to their data until 340 subjects have been included in each subgroup (second and third and later line therapy).

Cabozantinib is to be administered as directed by the investigator according to the study site's clinical practice and the Cabometyx™ Summary of Product Characteristics (SmPC).

In the METEOR study, the median duration of exposure in subjects receiving cabozantinib was 8.3 months (Inter-Quartile Range 4.2 to14.6). Subjects will be followed up to 30 days after discontinuation of cabozantinib with a maximum follow-up per subject of 12 months from treatment initiation, even if the subject continues to receive cabozantinib.

The end of the study will be the date of the last study visit for the last subject in the study.

The study will be conducted in countries where cabozantinib is marketed at the time of the study. It is anticipated that there will be approximately 100 study centres in 10 to 15 European countries.

Visits will take place according to the study site's clinical practice. During each data reporting period, the investigator will report data for the study endpoint assessments (see Table 1).

Variables

Only available evaluations as decided by the investigator based on local clinical practice will be collected in the study. See Table 1 for the schedule of assessments to be reported.

The data that will be collected are summarised below.

Demographic and baseline characteristics:

- Baseline demography: year of birth, gender;
- Use of tobacco, occupational status, sick leave status;
- Presence of significant medical history including hypertension, diabetes, hypercholesterolemia, gastrointestinal (GI) diseases (e.g. inflammatory bowel disease), complication from prior GI surgery, dermatologic diseases, endocrine diseases, thromboembolism, myocardial infarction, stroke, risk of severe bleeding, renal and hepatic function impairment;
- History and baseline characteristics of RCC including: date of first diagnosis, stage at first diagnosis, stage at initiation of treatment with cabozantinib, histology, number and locations of metastatic sites, risk group category (International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) scores);
- Previous treatment for RCC including surgery of the primary tumour and of metastatic sites, type and number of systemic treatment lines for advanced disease including date of first and last dose, reason for discontinuation, best response, time to progression;
- Baseline clinical parameters (Eastern Cooperative Oncology Group (ECOG) performance status, weight, height, blood pressure) and electrocardiograms (ECGs); If clinically significant abnormal ECGs findings, as assessed by the investigator, are observed, further details will be collected (ie, heart rate, RR, PR, QRS, QT, and QTc durations).
- Planned frequency of radiological assessments during cabozantinib treatment.

Cabozantinib pattern of use:

- Date of cabozantinib treatment initiation, line of treatment, cabozantinib starting dose and schedule, date of the last dose of cabozantinib, any modification in the dose (reduction, increase, temporary interruption or discontinuation) with date and reason for the modification and schedule;

- Concomitant radiotherapies;
- Systemic therapy planned following cabozantinib discontinuation.

Safety:

- During each data reporting period after Day 1 until the end of the study: clinical parameters (ECOG performance status, weight, blood pressure) and clinically significant results observed, as assessed by the investigator, for clinical laboratory tests and ECGs. Any clinically significant abnormality observed for laboratory tests and ECGs will be reported as AEs or SAEs. The investigator assessment of ECG findings (normal/abnormal) will be recorded. In case of clinically significant abnormal ECG findings, the investigator will report heart rate, RR, PR, QRS, QT, and QTc durations. In case of clinically significant abnormal laboratory parameters, the corresponding values will be reported in the AE Form in the eCRF.
- Occurrence of all serious and nonserious AEs.
- Effectiveness:
- Date of clinical and radiographic progression or death and overall response (based on Response Evaluation Criteria In Solid Tumours (RECIST 1.1)) as per investigator assessment.

Health care resource utilisation during treatment with cabozantinib:

- Assessment of health care resource utilisation associated with the prophylaxis or management of treatment-related AEs (as assessed by the investigator as certain, probable, possible or unlikely) during the treatment period: hospitalisation, surgical procedures, emergency room visits, intensive care unit stays, concomitant medications (initiation or change to manage AEs), physician visits and homecare visits by nurse, unplanned laboratory tests.

Endpoints:

Primary endpoint:

- Proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation) when cabozantinib is used as a second line therapy or third and later line therapy;

Secondary endpoints:

- Description of the pattern of use of cabozantinib in real-life clinical settings:
- starting dose and schedule
- duration of cabozantinib treatment
- treatment line
- dose reductions and reasons
- treatment interruption and reasons
- treatment discontinuation and reasons
- changes in the dose and schedule and reasons
- concomitant radiotherapies
- planned systemic therapy following cabozantinib discontinuation
- median time to first dose modification due to AEs based on the investigator's decision (reduction, temporary interruption or discontinuation) together and for

each component separately • mean and median daily dose of cabozantinib received, and dose intensity (average daily dose compared to starting dose) • mean and median number of any dose modification (reduction, temporary interruption, increase or discontinuation) • median time to any first dose modification (reduction, temporary interruption, increase or discontinuation) together and for each component separately • median time to end of treatment;
• Effectiveness assessment: • overall best response per investigator assessment • clinical and radiographic (assessed by the investigator based on RECIST 1.1) median PFS time defined as the time between the start date of cabozantinib and the date of progression or death • OS rate at the end of the study; • Description of health care resource utilisation associated with the management of treatment-related AEs (as assessed by the investigator as certain, probable, possible or unlikely) during the treatment period: • number and duration of hospitalisations • number of surgical procedures • number of emergency room visits and intensive care unit stays • number of physician visits • number of homecare visits by nurse • concomitant medication (initiation or change to manage AEs) • number of unplanned laboratory tests.
Data Sources Source documents will include medical records and workup results. The source data will be collected by the investigator in the subject file and captured in an electronic case report form (eCRF).

Study Size

Sample size justification:

The sample size is based on the primary endpoint which is the proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation) assessed for each line of treatment (second line therapy or third and later line therapy).

In the open-label METEOR Study, any dose reduction due to an AE occurred in 59.8% of subjects and the study drug was interrupted in 70% of subjects. Overall, at least one dose modification (i.e. reduction or interruption) was reported for 76% of subjects treated with cabozantinib. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib.

Assuming a dose modification proportion of 75%, a sample size of 289 subjects is required to estimate a 2-sided 95% level of confidence of the dose modification proportion with a precision of ±5%. To have a precision of at least 5% in second line therapy and third and later line therapy, a minimum of 289 subjects must be included in each line of treatment (second line and third and later line).

Assuming that up to 15% subjects will start the treatment with cabozantinib using scheduled regimens different from the recommended regimen at initiation (60 mg/day) [Bradley et al, 2014; Bracarda et al, 2015], the total included population will represent 680 subjects.

The recruitment of subjects in the concerned subgroup will be closed as soon as the 340 subjects are reached.

Data Analysis

The following populations will be used during the statistical analyses:

- **Included population:** all subjects who signed the informed consent form (ICF);
- **Full Analysis Set (FAS):** all included subjects who have taken at least one dose of cabozantinib;
- **Safety population:** all included subjects who have taken at least 1 dose of cabozantinib and have a follow-up of safety;
- **Primary Safety population:** all subjects from the Safety population who started cabozantinib at the prescribed recommended dose.

As this is a noninterventional study, no formal statistical testing will be performed and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% confidence interval (CIs) will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive statistics will include number of available data, number of missing data and the following:

- Mean, standard deviation (SD), minimum, median, maximum when appropriate for continuous variables;
- Frequency count and percentage for categorical nominal variables;
- Both the above for categorical ordinal variables.

Missing data will not be replaced.

The primary endpoint is the proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation).

The primary analysis of the primary endpoint will be summarised descriptively for each line of treatment (second line or third and later line) and in total with their associated 2-sided 95% CIs based on the Clopper Pearson method and using the Primary Safety population.

A proportion of missing data (ie, dose modification of cabozantinib due to AE) up to 20% is deemed acceptable in terms of precision of the estimation, meaning that, a proportion of more than 20% of missing data might impact the ability to assess the primary endpoint.

A secondary analysis of the primary endpoint will be performed in a similar way and using the Safety population.

The secondary endpoints will be summarised descriptively using the FAS or the Safety populations, as appropriate, by line of treatment and in total.

In addition, the Kaplan-Meier method will be used to obtain the estimates of median PFS time, OS rate, median time to end of treatment, median time to first dose modification due to AEs based on the investigator's decision (temporary interruption, reduction or discontinuation) together and for each component separately median time to any first dose modification (temporary interruption, reduction, increase or discontinuation) together and for each component separately and their associated 2-sided 95% CIs.

An interim analysis will be performed and an interim report will be provided when at least 340 included subjects complete a study follow-up of at least 3 months. This analysis will be conducted so that preliminary results can be provided to local health authorities, where required. There will be no change in the study design or conduct based on the results of this interim analysis.

Milestones

Expected study duration: 36 months

Expected duration of recruitment period: 24 months

Expected subject participation duration: up to12 months

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

Milestone	Planned date
Registration in the EU PAS register	September 2017
Start of data collection	December 2017
Progress report	December 2018
Interim report	December 2019
End of data collection	December 2020
Final report of study results	December 2021

EU PAS register=**European Union electronic register of postauthorisation studies**

7 RATIONALE AND BACKGROUND

7.1 Background

Renal cell carcinoma (RCC) is diagnosed in about 330,000 individuals worldwide each year and results in over 140,000 deaths [1]. Up to 30% of patients present with metastatic disease at initial diagnosis [2].

In advanced stages, despite an increasing number of available systemic therapies such as immunotherapies, vascular endothelial growth factor (VEGF)-targeted therapies and mammalian target of rapamycin (mTOR) inhibitors for this malignancy, virtually all patients eventually relapse.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor (TKI) with potent activity against MET, VEGF receptors (VEGFRs) and AXL as well as a number of other receptors of tyrosine kinases (RTKs) that have also been implicated in tumour pathobiology, including RET, KIT and FLT. Cabozantinib suppresses MET and VEGFR signalling, rapidly inducing apoptosis of endothelial and tumour cells, resulting in tumour regression in a variety of xenograft models [3, 4].

The randomised, pivotal phase 3 METEOR trial compared the efficacy and safety of cabozantinib versus the mTOR inhibitor everolimus in subjects with advanced RCC with a clear cell component who progressed after previous VEGFR TKI treatment [5, 6]. Subjects (N=658) were randomised (1:1) to receive cabozantinib (N=330) or everolimus (N=328). Cabozantinib (tablets) significantly improved progression-free survival (PFS), overall response rate and overall survival (OS) as compared with everolimus in this study.

The primary endpoint was PFS as assessed by an independent radiology review committee in the first 375 randomly assigned subjects [5]. The results of the analysis demonstrated a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the everolimus arm: the hazard ratio (HR) for progression or death was 0.58 (95% confidence interval (CI): 0.45, 0.75; $p<0.001$). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm versus 3.8 months in the everolimus arm, an estimated 3.6 months difference in the medians.

The objective response rate was 17% with cabozantinib and 3% with everolimus ($p<0.0001$) [6]. A best response of stable disease occurred in 65% of subjects in the cabozantinib arm compared with 62% of subjects in the everolimus arm. Progressive disease occurred in 12% of subjects assigned to cabozantinib and 27% of subjects assigned to everolimus.

A planned interim analysis of OS conducted at the time of the PFS analysis [5] demonstrated a trend for longer OS for subjects in the cabozantinib arm compared with the everolimus arm: the HR for death was 0.67 (unadjusted 95% CI: 0.51, 0.89; $p=0.005$). The p-value of ≤ 0.0019 required to achieve statistical significance at the time of the interim analysis was not reached. In a subsequent unplanned interim analysis of OS [6], a statistically significant difference in duration of OS for subjects in the cabozantinib arm compared with the everolimus arm was demonstrated (critical p-value from the alpha spending function of ≤ 0.0163): the HR was 0.66 (95% CI: 0.53, 0.83; stratified logrank $p=0.00026$). Kaplan-Meier estimates of median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm, an estimated 4.9 month difference in the medians.

In the METEOR study, cabozantinib was initiated at 60 mg/day. If a subject experienced an unacceptable study treatment-related adverse event (AE), study treatment interruption or a dose reduction was allowed at the investigator's discretion. Following a treatment interruption, the subject could have resumed treatment if the AE resolved to $\leq$ grade 1 or to

baseline values within 6 weeks. The study treatment could have been restarted at a reduced dose to avoid worsening AEs, if the AE was related to treatment or dose reduction was otherwise deemed clinically necessary.

Treatment with cabozantinib was associated with a significant rate of treatment-emergent AEs (TEAEs) in the METEOR study: 100% of subjects presented with at least one TEAE. The most common grade 3 or 4 TEAEs with cabozantinib were hypertension (15%), diarrhoea (11%) and fatigue (9%) and with everolimus were anaemia (16%), fatigue (7%) and hyperglycaemia (5%). The most common TEAEs (any grade) leading to dose reductions with cabozantinib were diarrhoea (16%), the palmar-plantar erythrodysesthesia syndrome (11%) and fatigue (10%) and the most common with everolimus were pneumonitis (4%), fatigue (3%) and stomatitis (3%) (data cut-off 21 May 2015).

Although AEs were most often manageable in the METEOR study, treatment with cabozantinib was interrupted in 70% of subjects. The median time to treatment interruption was 38.0 days. Any dose reduction due to an AE occurred in 59.8% of subjects in the cabozantinib arm; a second-level dose reduction due to an AE occurred in 19.3% of subjects. The median times to the first and second dose reduction were 55.0 and 93.0 days, respectively. The median daily dose was 45 mg and the rate of cabozantinib discontinuation due to AEs not related to RCC was 9.7%. Overall, at least one dose modification (i.e. interruption or reduction) was reported for 76% of subjects treated with cabozantinib in this study [7].

Cabometyx™ (cabozantinib) tablets have been approved for the treatment of advanced RCC in adults following prior VEGF-targeted therapy in the European Union (09 September 2016). The product is also approved in the United States of America (April 2016) for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy.

7.2 Rationale

Subjects in the METEOR study were included under controlled conditions (strict inclusion and exclusion criteria, guidelines for therapy management, monitoring of compliance). In the real-world setting, the same criteria will not apply and the utilisation pattern of cabozantinib is unknown. Prevalent practice patterns may call for implementation of new measures to optimise the use of cabozantinib in RCC.

Published data with VEGFR-targeted therapies reported that a number of subjects start the treatment with doses or regimens that are different from the standard dosing [8, 9]. The rate of subjects using cabozantinib with schedules or dosing different from the recommended regimen at initiation (60 mg/day) and the tolerability of cabozantinib in second versus third and later lines in the real-life setting are unknown.

For this prospective study, the primary endpoint is to describe the proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation) when cabozantinib is used as a second line therapy or third and later line therapy.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

For this prospective study, the objective is to understand the utilisation of cabozantinib in subjects with advanced RCC following prior VEGF-targeted therapy in real-life settings in terms of dose modifications due to AEs when used as a second line therapy or third and later line therapy. Other patterns of use of cabozantinib will also be described as listed in the study objectives.

8.2 Objectives

8.2.1 Primary Objective:

- To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy.

8.2.2 Secondary Objectives:

- To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings;
- To describe all treatment-emergent nonserious and serious AEs;
- To describe the effectiveness of cabozantinib in RCC in real-life in terms of PFS and best overall response;
- To describe the health care resource utilisation associated with the management of treatment-related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays, concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).

9 RESEARCH METHODS

9.1 Study Design

This is a prospective, international, multicentre, noninterventional study.

9.2 Setting

The study will include subjects diagnosed with advanced RCC, having received at least one prior VEGF-targeted therapy, who are starting treatment with cabozantinib tablets at the discretion of the treating physician in the clinical setting (not as part of an interventional clinical study).

A total of 680 subjects are to be included in the study in countries where cabozantinib is marketed at the time of the study. It is planned to include equal numbers of subjects receiving second line therapy and third and later line therapy.

The study will follow the real-life management of patients in clinical practice. Visits will take place according to the study site's clinical practice. Cabozantinib is to be administered as directed by the investigator according to the study site's usual clinical practice and the Cabometyx™ Summary of Product Characteristics (SmPC). Only available evaluations as decided by the investigator based on local clinical practice will be collected. The investigator will report data for study endpoint assessments during the study data reporting periods (see Table 1 for a summary of the schedule of assessments to be reported).

9.2.1 Inclusion Criteria

To be included in the study, the subject should fulfil all the following inclusion criteria:

(1) Age ≥18 years old;

(2) Has a diagnosis of advanced RCC;

(3) Has received at least one prior VEGF-targeted therapy;

(4) For whom the treating physician has decided to start treatment with cabozantinib tablets prior to inclusion;

(5) No previous exposure to cabozantinib prior to inclusion;

(6) Not concurrently involved in an interventional study;

(7) Consents to participate in this noninterventional study.

9.2.2 Exclusion Criteria

There are no exclusion criteria for this study.

9.2.3 Study Population

The study population will consist of subjects diagnosed with advanced RCC, having received at least one prior VEGF-targeted therapy, who are starting cabozantinib tablets at the discretion of the treating physician and who consent to participate in the study.

In order to avoid bias related to physician-led subject selection, participating physicians will be asked to include all successive eligible subjects except those who refuse the collection of and/or access to their data until 340 subjects have been included in each subgroup (second and third and later line therapy).

9.2.4 Study Duration

In the METEOR study, the median duration of exposure in subjects receiving cabozantinib was 8.3 months (Inter-Quartile Range 4.2 to 14.6).

Subjects will be followed up to 30 days after discontinuation of cabozantinib with a maximum follow-up per subject of 12 months from treatment initiation, even if the subject continues to receive cabozantinib.

The end of the study will be the date of the last study visit for the last subject in the study.

9.2.5 Study Place

Subjects will be recruited in countries where cabozantinib is marketed at the time of the study.

It is anticipated that there will be approximately 100 study centres in 10 to 15 European countries. The number of sites in each country will be decided according to the size of the country.

Study centres will be proposed by the sponsor's local medical teams. Successive proposed sites that meet the feasibility criteria will be selected.

9.2.6 Study Schedule

The schedule of assessments to be reported is presented in Table 1.

In this noninterventional study, cabozantinib is to be administered as directed by the investigator according to the study site's usual clinical practice. The physician should refer to the Cabometyx™ SmPC for any information on the treatment prescribed.

Only available evaluations as decided by the investigator based on local clinical practice will be collected in the study. The most recent assessments available before each visit (including the inclusion visit if applicable) will be reported for 12-lead electrocardiograms (ECGs) and radiographic tumour assessments.

Table 1 Schedule of Assessments to be Reported

	Inclusion visit/ Treatment initiation Visit 1[a]	Visit 2[a]	Visit 3[a]	Visit 4[a]	Visit 5[a]	Visit 6[a]	Visit 7[a]	Visit 8[a]	End of study visit Visit 9[a]
Data reporting period (1 month=30 days)	**D1**	**From D2 up to D30**	**Any time point from D31 up to D60**	**Any time point from D61 up to D90 (Month 3)**	**Any time point during Month 4 or Month 5**	**Any time point during Month 6 or Month 7**	**Any time point during Month 8 or Month 9**	**Any time point during Month 10 or Month 11**	**Any time point after Month 11[b]**
Assessments									
Signed informed consent	x								
Eligibility criteria	x								
Demographics, tobacco, occupational status, sick leave status	x								
Medical history, RCC cancer history and previous anticancer therapy	x								
Planned frequency of radiological assessments	x								
ECOG performance status, height[c], weight, vital signs	x	x	x	x	x	x	x	x	x
12-lead ECG[d]	As available[e]	ECG performed according to local standards of care as clinically indicated[f]							
Clinical laboratory tests by local laboratory[d]		Clinical laboratory test to assess safety performed according to local standards of care as clinically indicated[f]							
Radiographic tumour assessment	As available[e]	Radiographic assessment performed according to local standards of care as clinically indicated[f]							
Concomitant medication	x	x	x	x	x	x	x	x	x
Radiotherapy/surgery	x[g]	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x
Dose and schedule of cabozantinib prescribed	x	x	x	x	x	x	x	x	x[h]
Cabozantinib dose modifications		x	x	x	x	x	x	x	x[h]
Health care resource utilisation	x	x	x	x	x	x	x	x	x

	Inclusion visit/ Treatment initiation Visit 1[a]	Visit 2[a]	Visit 3[a]	Visit 4[a]	Visit 5[a]	Visit 6[a]	Visit 7[a]	Visit 8[a]	End of study visit Visit 9[a]
Data reporting period (1 month=30 days)	**D1**	**From D2 up to D30**	**Any time point from D31 up to D60**	**Any time point from D61 up to D90 (Month 3)**	**Any time point during Month 4 or Month 5**	**Any time point during Month 6 or Month 7**	**Any time point during Month 8 or Month 9**	**Any time point during Month 10 or Month 11**	**Any time point after Month 11[b]**
Assessments									
Study discontinuation or completion form		In case of permanent treatment discontinuation (approximately 30 days after the last dose of cabozantinib) [i]							x

Abbreviations: AE=adverse event, D=day, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, RCC=renal cell carcinoma, SAE=serious adverse event

a. Visits will take place according to the study site's clinical practice. The investigator will report data for study endpoint assessments during each data reporting period. Only available evaluations as decided by the investigator based on local clinical practice will be collected. Where there are no data to report, this should be indicated in the applicable section(s) of the eCRF. In the case of more than one visit occurring during the data reporting period, the visit closest to the end of the period should be used for reporting purposes.

b. The closest visit to Month 12 should be recorded as End of study Visit

c. Height will be recorded at Visit 1 only.

d. Any clinically significant abnormal value observed for laboratory tests and ECGs will be collected and reported as AEs or SAEs

e. The most recent evaluations performed before initiation of treatment.

f. The most recent assessment available before each visit.

g. Only concomitant radiotherapy will be collected (i.e., prior radiotherapy will not be collected).

h. If applicable.

i. In case of permanent treatment discontinuation between Visit 2 and Visit 8, the next visit should be completed along with the Study discontinuation form, approximately 30 days after the last dose of cabozantinib.

9.2.7 Study Visits

Visits will take place according to the study site's clinical practice.

The investigator will report data for study endpoint assessments during each data reporting period (see Table 1 and Section 9.3). In the case of more than one visit occurring during the data reporting period, the visit closest to the end of the period should be used for reporting purposes.

The data reporting periods are:

- Visit 1 (inclusion visit/treatment initiation) on Day 1;
- Visit 2: any time point from Day 2 up to Day 30;
- Visit 3: any time point from Day 31 up to Day 60;
- Visit 4: any time point after Day 61 up to Day 90 (Month 3);
- Visit 5: any time point during Month 4 or Month 5;
- Visit 6: any time point during Month 6 or Month 7;
- Visit 7: any time point during Month 8 or Month 9;
- Visit 8: any time point during Month 10 or Month 11;
- Visit 9 (End of study visit): any time point after Month 11 (ie, the closest visit to Month 12).

9.2.8 Study Discontinuation/Withdrawal

If the subject permanently discontinues cabozantinib before Month 12, he/she will be withdrawn from the study.

The investigator may withdraw the subject from the study at any time for safety reasons or at his/her discretion. A subject may withdraw consent to participate in the study at any time.

In case of permanent treatment discontinuation between Visit 2 and Visit 8, the next visit should be completed along with the Study discontinuation form, approximately 30 days after the last dose of cabozantinib (see Table 1 and Section 9.2.7).

9.2.9 Early Study Termination

The sponsor can decide at any time to discontinue the study for any reason. Investigators will be informed of the decision. Ethics committees and competent authorities will also be informed if required by local regulations.

9.3 Variables

Only available evaluations as decided by the investigator based on local clinical practice will be collected in the study. Where there are no data to report, this will be indicated in the applicable section(s) of the electronic case report form (eCRF). See Table 1 for the schedule of assessments to be reported.

9.3.1 Demographic and Baseline Characteristics

- Baseline demography: year of birth, gender;
- Use of tobacco, occupational status, sick leave status;
- Presence of significant medical history including hypertension, diabetes, hypercholesterolemia, gastrointestinal (GI) diseases (e.g. inflammatory bowel disease), complication from prior GI surgery, dermatologic diseases, endocrine diseases, thromboembolism, myocardial infarction, stroke, risk of severe bleeding, renal and hepatic function impairment;

- History and baseline characteristics of RCC including: date of first diagnosis, stage at first diagnosis, stage at initiation of cabozantinib, histology, number and locations of metastatic sites, risk group category (International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [11] and MSKCC (Memorial Sloan Kettering Cancer Center) scores [12]);
- Previous systemic treatment for RCC including surgery of the primary tumour and of metastatic sites, type and number of systemic treatment lines for advanced disease including date of first and last dose, reason for discontinuation, best response, time to progression;
- Baseline clinical parameters (Eastern Cooperative Oncology Group (ECOG) performance status, weight, height, blood pressure) and electrocardiograms (ECGs); If clinically significant abnormal ECGs findings, as assessed by the investigator, are observed, further details will be collected (ie, heart rate, RR, PR, QRS, QT, and QTc durations).
- Planned frequency of radiological assessments during cabozantinib treatment.

9.3.2 Cabozantinib Pattern of Use

- Date of cabozantinib initiation, line of treatment, cabozantinib starting dose and schedule, date of the last dose of cabozantinib, any modification in the dose (reduction, increase, temporary interruption or discontinuation) with date and reason for the modification and schedule;
- Concomitant radiotherapies;
- Systemic therapy planned following cabozantinib discontinuation.

9.3.3 Safety

- During each data reporting period after Day 1 until the end of the study: clinical parameters (ECOG performance status, weight, blood pressure) and clinically significant results observed, as assessed by the investigator, for clinical laboratory tests and ECGs. Any clinically significant abnormality observed for laboratory tests and ECGs will be reported as AEs or SAEs. The investigator assessment of ECG findings (normal/abnormal) will be recorded. In case of clinically significant abnormal ECG findings, the investigator will report heart rate, RR, PR, QRS, QT, and QTc durations. In case of clinically significant abnormal laboratory parameters, the corresponding abnormal values will be reported in the AE Form in the eCRF.
- Occurrence of all serious and nonserious AEs.

9.3.4 Effectiveness

- Date of clinical and radiographic progression or death, and overall response (based on Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 [10]) as per investigator assessment.

9.3.5 Health Care Resource Utilisation During Treatment with Cabozantinib

- Assessment of health care resource utilisation associated with the prophylaxis or management of treatment-related AEs (as assessed by the investigator as certain, probable, possible or unlikely) during the treatment period:
  - hospitalisation
  - surgical procedures
  - emergency room visits

- intensive care unit stays
- concomitant medications (initiation or change to manage AEs)
- physician visits and homecare visits by nurse
- unplanned laboratory tests.

9.4 Data Sources

Source documents will include medical records and workup results (refer to Section 9.8.3 for definitions of source data and source documents). The source data will be collected by the investigator in the subject file and captured in an eCRF.

9.5 Study Size

The sample size is based on the primary endpoint which is the proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation) assessed for each line of treatment (second line therapy or third and later line therapy). In the open-label METEOR Study, any dose reduction due to an AE occurred in 59.8% of subjects and the study drug was interrupted in 70% of subjects. Overall, at least one dose modification (i.e. reduction or interruption) was reported for 76% of subjects treated with cabozantinib. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib.

Assuming a dose modification proportion of 75%, a sample size of 289 subjects is required to estimate a 2-sided 95% level of confidence of the dose modification proportion with a precision of ±5%. To have a precision of at least 5% in second line therapy and third and later line therapy, a minimum of 289 subjects must be included in each line of treatment (second line and third and later line).

Assuming that up to 15% subjects will start the treatment with cabozantinib using scheduled regimens different from the recommended regimen at initiation (60 mg/day) [8, 9], the total included population will represent 680 subjects.

The recruitment of subjects in the concerned subgroup will be closed as soon as the 340 subjects are reached.

9.6 Data Management

9.6.1 Data Collection

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 anonymise the data within the eCRF. Only investigating sites will be able to link to numeric identifier to the subject.

The sponsor and the Contract Research Organisation (CRO) will ensure that an appropriate eCRF is developed to capture the data as required by the protocol.

Each site is required to have a computer and internet connection available for site entry of clinical data. All entries on the eCRF will be made under the electronic signature of the person performing the action (username and password). Only sponsor authorised users will be given access to the eCRF as appropriate for their study responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

Data will be monitored by a monitoring CRO according to an agreed Monitoring Plan. Any queries generated during the data management process will be tracked by the contracted data management CRO.

Data consistency and accuracy will be ensured by running real-time checks at time of data entry in the eCRF. Any queries and items not adequately explained will require additional queries to be raised to the investigator by the Data Management group for clarification/correction. The investigator must ensure that queries are dealt with promptly. All corrections to the eCRF data will automatically be tracked and a reason for the change will always be required. In the eCRF, the audit trail function will allow the changes and clarifications made to be viewed.

The investigator must, at a minimum, provide an electronic signature to each eCRF to attest to the accuracy and completeness of all the data. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature.

Data management will be conducted by a CRO, under the supervision of the sponsor's Global Medical Affairs Clinical Operations. All data management procedures will be completed in accordance with Ipsen and the contracted CROs standard operating procedures (SOPs).

9.6.2 Data Archiving and Retention

After the study has been completed and clinical study report (CSR) approved, data will be stored in the Ipsen data repository.

Study documents will be archived in accordance with applicable regulatory requirements for a minimum of 10 years following study completion.

9.7 Data Analysis

9.7.1 Analysis Population Definitions

The following populations will be used during the statistical analyses:

- **Included population:** all subjects who signed the informed consent form (ICF);
- **Full Analysis Set (FAS):** all included subjects who have taken at least one dose of cabozantinib;
- **Safety population:** all included subjects who have taken at least one dose of cabozantinib and have a follow-up of safety;
- **Primary Safety population:** all subjects from the Safety population who started cabozantinib at the prescribed recommended dose.

9.7.2 Statistical and Analytical Methods

9.7.2.1 Statistical Analyses

The statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A statistical analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9 or higher).

As this is a noninterventional study, no formal statistical testing will be performed and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% CIs will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive statistics will include number of available data, number of missing data and the following:

- Mean, standard deviation (SD), minimum, median, maximum and 95% CIs for means when appropriate for continuous variables;
- Frequency count and percentages for categorical nominal variables;
- Both the above for categorical ordinal variables.

Missing data will not be replaced but they will be displayed in all relevant tables (see Section 9.7.2.5.1).

9.7.2.2 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics including disease characteristics will be listed for the FAS.

Demographics and baseline characteristics will include, age, age group (<65 years, ≥65 years), gender, use of tobacco, occupational status and sick leave status, weight, height, country and blood pressure, duration since disease diagnosis, stage at first diagnosis, stage at initiation of cabozantinib, IMDC and MSKCC risk group categories, therapy line (second line therapy or third and later line therapy), regimen at initiation (60 mg/day, other regimens), baseline bone metastasis (yes, no), ECOG performance-status score, number of prior VEGF-targeted therapies (1, 2, 3, 4 and >4), previous systemic therapy and planned frequency of radiological assessments during cabozantinib treatment.

Descriptive summary statistics for demographic and baseline characteristics will be presented by therapy line (second line or third and later line) and in total for the Primary Safety population and the FAS population. In addition, summaries will also be provided for the Safety population if it differs from the FAS population by at least 10% in total.

9.7.2.3 Subject Disposition and Withdrawals

The number of subjects included and number and percentage of subjects included but not part of the FAS will be provided in total.

The numbers and percentages of subjects included in each of the FAS, Primary Safety, and Safety populations will be tabulated by country, centre, therapy line and in total. The reasons for subject exclusions from each of the populations will also be tabulated by therapy line and in total. In addition, the numbers of subjects who discontinued and completed the study treatment will be tabulated for the FAS by therapy line and in total. Primary reasons for discontinuation of study treatment will also be tabulated for FAS by therapy line and in total.

9.7.2.4 Safety Evaluation

All safety data will be included in the subject data listings using the Safety population. Analyses and summary tables will be presented by therapy line and in total based on the Safety population and also on the Primary Safety population.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term (PT) and system organ class (SOC). Adverse event listings will be presented by subject, SOC and PT.

The incidence of all reported AEs, TEAEs, SAEs, and treatment-emergent serious and nonserious AEs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity and drug relationship. Treatment emergent AEs associated with dose modification (temporary interruption, reduction or discontinuation) of study medication and TEAEs leading to cabozantinib temporary dose interruption, reduction or discontinuation will also be summarised separately.

A TEAE is defined as any AE that occurs during the administration of cabozantinib if:

- It was not present prior to receiving the first dose of cabozantinib; or
- It was present prior to receiving the first dose of cabozantinib but the intensity increased during treatment with cabozantinib.

All TEAEs will be flagged in the AE listings.

Summary statistics (mean, median, SD and range, as appropriate) will be presented for ECOG performance status, vital signs (blood pressure), and weight at each assessment. Changes from baseline to each postbaseline assessment will be summarised similarly.

Counts and percentages of normal and abnormal ECG findings will be presented at each assessment. In addition, shift from baseline to postbaseline assessments in ECG findings will also be presented.

9.7.2.5 Endpoints and Evaluations

9.7.2.5.1 Primary Endpoint and Evaluations

The primary endpoint is the proportion of subjects with dose modifications due to AEs based on the investigator's decision (temporary interruption, dose reduction or discontinuation).

The primary analysis of the primary endpoint will be summarised descriptively for each line of treatment (second line or third and later line) and in total with their associated 2-sided 95% CIs based on the Clopper Pearson method using the Primary Safety population.

The impact of missing data on the analysis of the primary endpoint has been assessed. The precision of the proportion of subjects with dose modification due to AE has been calculated on different scenarios:

% of missing data	Number of evaluable subjects[a]	Precision[b]
5%	274	5.1%
10%	260	5.3%
15%	245	5.4%
20%	231	5.6%

a From 289 subjects per line of treatment of the Primary Safety population

b For a 95% CI and a proportion of subjects with dose modification of 75%

A proportion of missing data (ie, dose modification of cabozantinib due to AE) up to 20% is deemed acceptable in terms of precision of the estimation, meaning that, a proportion of more than 20% of missing data might impact the ability to assess the primary endpoint.

The proportion of missing data will be evaluated at time of the progress report and at time of the interim and final analyses.

A secondary analysis of the primary endpoint will be performed in a similar way and using the Safety population.

The proportion of subjects with dose modifications due to AEs related to cabozantinib (assessed by the investigator as certain, probable, possible or unlikely) will be described for the Safety population and for the Primary Safety population.

Additionally, this analysis will be repeated per AE relationship categories (certain/probable/possible/unlikely/not related/unassessable) (see definitions in Section 11.3.1).

The data for the primary endpoint will be listed using the Safety population.

9.7.2.5.2 Secondary Endpoints and Evaluations

The secondary endpoints include the following:

- Description of the pattern of use of cabozantinib in real-life clinical settings:
  - starting dose and schedule
  - duration of cabozantinib treatment
  - treatment line
  - dose reductions and reasons
  - treatment interruption and reasons
  - treatment discontinuation and reasons
  - changes in the dose and schedule and reasons
  - concomitant radiotherapies
  - planned systemic therapy following cabozantinib discontinuation
  - median time to first dose modification due to AEs based on the investigator's decision (reduction, temporary interruption or discontinuation) together and for each component separately
  - mean and median daily dose of cabozantinib received, and dose intensity (average daily dose compared to starting dose)
  - mean and median numbers of any dose modification (reduction, temporary interruption, increase or discontinuation)
  - median time to any first dose modification (reduction, temporary interruption, increase or discontinuation) together and for each component separately
  - median time to end of treatment;
- Effectiveness assessment:
  - overall best response per investigator assessment
  - clinical and radiographic (assessed by the investigator based on RECIST 1.1 [10]) median PFS time defined as the time between the start date of cabozantinib and the date of progression or death
  - OS rate at the end of the study;
- Description of health care resource utilisation associated with the management of treatment-related AEs (as assessed by the investigator as certain, probable, possible or unlikely) during the treatment period:
  - number and duration of hospitalisations
  - number of surgical procedures
  - number of emergency room visits and intensive care unit stays
  - number of physician visits
  - number of homecare visits by nurse
  - concomitant medication (initiation or change to manage AEs)

- number of unplanned laboratory tests.

The secondary endpoints will be provided in listing format using the FAS and summarised descriptively using the FAS or the Safety populations, as appropriate, by line of treatment and in total.

In addition, the Kaplan-Meier method will be used to obtain the estimates of median PFS time, OS rate, median time to end of treatment, median time to first dose modification due to AEs based on the investigator's decision (temporary interruption, reduction or discontinuation) together and for each component separately and median time to any first dose modification (temporary interruption, reduction, increase or discontinuation) together and for each component separately and their associated 2-sided 95% CIs.

Concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODRUG) and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

9.7.3 Subgroup Analyses

All the analyses will be provided by therapy line (second line or third and later line).

Descriptive statistics for the primary endpoint will be provided within each category of the following variables using the Primary Safety population and the Safety population: gender, age group (<65 years, ≥65 years), baseline bone metastasis (yes, no) and country.

Additional subgroup analyses may be planned in the SAP according to clinical interest.

9.7.4 Interim Analyses

An interim analysis will be performed and an interim report will be provided when at least 340 included subjects complete a study follow-up of at least 3 months. This analysis will be conducted so that preliminary results can be provided to local health authorities, where required. There will be no change in the study design or conduct based on the results of this interim analysis.

9.8 Quality Control

The investigator is responsible for the validity of all data collected at his/her site.

9.8.1 Routine Monitoring and Monitoring Procedures

A risk-based approach to monitoring will be applied to this noninterventional study to ensure that the rights and welfare of the subjects are respected and that the data are of an appropriate quality. Sponsor-assigned monitors will conduct a combination of remote data reviews and periodic site visits to address specific site requirements and data quality.

Unscheduled on-site monitoring will be triggered according to predefined criteria stipulated in the study-specific monitoring plan e.g. sustained inability to contact the investigator or research team, suspected fraud, incomplete ICFs and missing eCRFs.

9.8.2 Inspections and Auditing Procedures

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

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 9.8.3 and to any other locations used for the purpose of the study in question.

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor representative as soon as possible, to assist with preparations for the inspection.

9.8.3 Source Data Verification

Within the framework of a noninterventional study, the source data verification will be done by a CRO contracted by the sponsor.

The source documents must, as a minimum, contain the following:

- A statement that the subject is included in a noninterventional study;
- The identity of the study;
- The date(s) and doses of cabozantinib intake as prescribed by the investigator;
- The dates and reasons for cabozantinib dose reductions, interruptions and modifications in the dose due to AE;
- The date that the written informed consent was provided by the subject;
- Previous VEGF-targeted therapy received;
- The date of study discontinuation/completion;
- The date of clinical and radiographic progression and the best overall response as assessed by the investigator;
- Subject demographics;
- All AE related information with start and end dates.

Definitions for source data and source documents are given below:

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

The subject must have consented to their medical records being viewed by sponsor-authorised personnel and by local and possibly foreign competent authorities. This information is included in the ICF.

9.8.4 Data Quality

The investigator is responsible for protocol compliance, completeness and accuracy of the data. Online checks will be programmed to ensure consistency of reported data and data will be monitored according to a risk-based monitoring plan. The eCRF is a validated system with restricted access to study staff only with a personal username and password. All data changes are recorded in the system audit trail tracing the data changes, the user, the time and the reason. Inadequate data can be queried for clarification by the monitors and/or the data management group.

9.9 Limitations of the Research Methods

This prospective, international, multicentre, noninterventional study will follow the real-life management of subjects in clinical practice.

The study will include subjects diagnosed with advanced RCC, having received at least one prior VEGF-targeted therapy, who are starting cabozantinib at the discretion of the treating physician. The decision to start treatment with cabozantinib will be taken prior to inclusion in the study. In order to avoid bias related to physician-led subject selection, participating physicians will be asked to include all successive eligible subjects except those who refuse the collection of and/or access to their data until 340 subjects have been included in each subgroup (second and third and later line therapy). Study centres will be proposed by the local medical teams. Successive proposed sites that meet the feasibility criteria will be selected.

The study will involve collection of primary data directly from health care professionals. The data collected are expected to provide real-world evidence of the use of cabozantinib in subjects with RCC. Only available evaluations as decided by the investigator based on local clinical practice will be collected. Where there are no data to report there will be no information recorded in the applicable section(s) of the eCRF. Therefore, the assessments performed and data provided from different study sites may vary depending on local clinical practice.

The outcome measures recorded will be as assessed by physicians in clinical practice. The effectiveness of treatment will be determined by investigators' assessment based on the methods available at their centres, rather than centrally by an independent radiology committee. Therefore, there may be inconsistency in the assessment of effectiveness between study sites and/or study physicians.

As this is a noninterventional study, no formal statistical testing will be performed and all the analyses will be primarily descriptive in nature.

9.10 Other Aspects

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Regulatory Approval

The protocol will be submitted to the national competent authority of participating countries in accordance with local applicable regulatory requirements.

10.2 Independent Ethics Committees

The protocol, Subject Information Sheet and ICF (SIS-ICF) and any related documents will be submitted for approval by the Independent Ethics Committee (IEC) if required by local applicable regulatory requirements.

10.3 Compliance with Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices and Ethical Considerations

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki, 1964 and all subsequent amendments).

Where applicable, this study will follow the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) [13], the European Medicines Agency (EMA) guidelines for good pharmacovigilance practices (GVP) [14, 15] and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [16].

This study will be conducted in compliance with the ENCePP Code of Conduct [17] and Ipsen Code of Ethical Conduct.

10.4 Informed Consent

A SIS-ICF will be used as required by local applicable regulatory requirements. Subject informed consent will be obtained before the start of data collection.

Participants will be informed that they may withdraw from the study at any time and that this will not affect their subsequent medical treatment or relationship with the treating physician.

10.5 Data Protection

This study will be conducted in compliance with the European Union data protection requirements. As the data controller (study sponsor) is located in France, the study will comply with the French requirements for data protection (Deliberation no 2016-263 dated 21 July 2016 accrediting a methodology of reference relative to personal data processing implemented within human research which does not need informed consent (MR-003)). Additionally, the sponsor will ensure that all applicable local regulatory requirements for data protection are met.

10.6 Study Team Training

The study teams at participating centres will be trained on all applicable SOPs and protocol specific tasks before beginning any study-related activities.

10.7 Insurance

Insurance may be contracted according to local regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All AEs observed during the study are to be recorded on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the ICF until the end of the study (see Table 1).

11.1 Definitions

11.1.1 Adverse Event

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

Progression of the RCC is not to be reported as an AE.

11.1.2 Special Situations

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

11.1.2.1 Pregnancy and Breastfeeding

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

Information regarding any pregnancies must be collected on the AE report form, including those with normal progress and outcome.

The investigator must instruct all female subjects to inform them immediately should they become pregnant whilst using the study medication.

Adverse events which occur in infants following exposure to a medicinal product from breast milk should be reported.

11.1.2.2 Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied. Overdose can be intentional or accidental.

For example:

- A subject taking twice the recommended dose than as described in the authorised product information;
- A subject taking the recommended dose more frequently than as recommended in the authorised product information.

11.1.2.3 Off-label Use

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.

For example:

- Prescribed use for an unlicensed indication;
- Prescribed use of an unlicensed dose, dosing schedule or route of administration;
- Prescribed use when contraindicated. Contraindications may include past medical history or treatment emergent with clinical consequences where product use is not discontinued;
- Prescribed use for an unlicensed population (e.g. paediatric use when not recommended per the product labelling.

11.1.2.4 Medication Error

Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care professional or consumer.

For example:

- Pharmacist dispenses the incorrect drug due to a confusion with drug name;

11.1.2.5 Occupational Exposure

This refers to the exposure to a medicinal product, as a result of one's professional or nonprofessional occupation.

For example:

- While preparing the injection, the investigator splashed the drug solution in his eye;
- In the manufacturing plant, an employee inhales some micronised product.

11.1.2.6 Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

For example:

- Persistent use of opiates to achieve a euphoric effect;
- Chronic use of steroids to enhance sporting performance.

11.1.2.7 Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.

For example:

- Prophylactic use of antibiotics approved only for treatment.

11.1.3 Serious Adverse Event

An SAE is any AE occurring at any dose that:

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

11.1.4 Death

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

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

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

11.2 Collection and Reporting of Adverse Events, Fatal Outcomes and Special Situations

11.2.1 Collection of Safety Reports

The term 'safety report' refers to all AEs, fatal outcomes and special situations. All safety reports, whether they are serious/nonserious, related (as assessed by the investigator as certain, probable, possible or unlikely)/not related/unassessable, should be **collected** by the investigator in the study source document during the course of the study.

The investigator should record a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

The investigator should provide an assessment of whether there is a causal relationship between the study treatment and the AE (see Section 11.3.1 below).

11.2.2 Reporting of Safety Reports

In order to adhere to all applicable laws and regulations for reporting of a safety report, the investigator should notify Ipsen within 24 hours of the study site staff becoming aware of the safety report for SAEs and Special Situations, and up to 10 calendar days for nonserious adverse events. It is the investigator's responsibility to ensure that the reporting information and procedures are used and followed appropriately.

For SAEs and Special Situations, to report initial or follow up information to Ipsen, a completed Adverse Event Report Form for Non-Interventional Studies (134232-FOR) should be sent to the following within 24 hours of becoming aware of the event:

Email: PPD

Fax: PPD

For nonserious adverse events, to report initial or follow up information to Ipsen, a completed Adverse Event Report Form for Non-Interventional Studies (134232-FOR) and/or information from the eCRF should be sent to Ipsen (see above) up to 10 calendar days of becoming aware of the event.

All AEs will be processed by Ipsen according to relevant SOPs. This includes the follow-up of AE reports with the investigator, as required.

If related AEs (i.e. adverse reactions) occur with "non Ipsen products", the investigator should inform the competent authority in the Member State where the reactions occurred or the marketing authorisation holder (MAH) of the suspected medicinal product but not both (to avoid duplicate reporting).

11.2.3 Mandatory Information for Reporting an Adverse Event

The following information is the minimum that must be provided to Ipsen's Pharmacovigilance contact within 24 hours for SAEs and Special Situations, and up to 10 calendar days for nonserious AEs:

- Subject identifier;
- Product name;
- Adverse Event description including assessment of causal relationship (see Section 11.3.1) and seriousness (see Section 11.1.3);
- Investigator name and contact details.

NOTE: The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

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

11.3 Safety Classifications

11.3.1 Relationship of Events to the Medicinal Product

The following definitions should be considered by the investigator when evaluating a causal relationship between cabozantinib and an AE:

Causality term	Assessment criteria*
Related/Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Related/Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Related/Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Related/Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Source: Uppsala Monitoring Centre (UMC). The use of the WHO-UMC system for standardised case causality assessment [18].

Causality term	Assessment criteria
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: • a temporal relationship between administration of the drug and the event that makes the relationship impossible (e.g. the event occurred before administration of drug); • the presence of a biologically implausible relationship between the product and the AE; • the convincing presence of a more likely alternative explanation for the AE.

Ipsen definition for the purposes of this study

11.3.2 Severity of Events

Please use the severity definition relevant to the event.

The following definitions should be considered when evaluating the severity of oncology events using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0:

Severity of Event	
Grade	**Definition**
1	Mild AE
2	Moderate AE
3	Severe and undesirable AE
4	Life-threatening or disabling AE
5	Death related to AE

11.3.3 Expectedness of Events

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

11.4 Reporting to Competent Authorities

Reporting of serious and nonserious suspected adverse reactions will be done in accordance with the applicable regulatory requirements including Module VI of the EMA GVP guidelines [15].

12 PLANS FOR COMMUNICATING STUDY RESULTS

12.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a study coordinator. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

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

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

12.2 Clinical Study Report

Progress and interim reports will be prepared according to Section 6. A progress report will be submitted one year after the first subject is enrolled and an interim report will be submitted at time of the interim analysis.

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

The CSR will be prepared, reviewed and approved within 12 months of the last subject's last visit.

13 REFERENCES

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15. Guidelines on Good Pharmacovigilance Practices: Module VI - Management and Reporting of Adverse Reactions to Medicinal Products (Rev 1). European Medicines Agency EMA/873138/2011 from 08 September 2014.
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LIST OF APPENDICES

Appendix 1 LIST OF STANDALONE DOCUMENTS

None.

Appendix 2 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy

Study reference number
F-FR-60000-001

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6, 12.2
1.1.4 Interim progress report(s)	☒	☐	☐	6, 9.7.4, 12.2
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6, 12.2
Comments: A progress report will be submitted one year after the first subject is enrolled. An interim analysis is planned when at least 50% of included subjects complete a study follow-up of at least 3 months and an interim report will be provided.				

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2 and 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	NA
Comments: This is a descriptive study with no a priori hypothesis.				

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2, 9.3, 9.4, 9.9
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	NA
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11
Comments: This is a descriptive study therefore no formal statistical testing will be performed and the analyses will be primarily descriptive.				

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.4
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☐	☒	☐	9.2.5
4.2.4 Disease/indication?	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1
Comments: The study will be conducted in 10 to 15 European countries where cabozantinib is marketed at the time of the study.				

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	NA
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	NA
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA
Comments: This study will report the use of cabozantinib in real-life settings with descriptive results only.				

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3, 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.1, 9.2
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3, 9.7
Comments: NA				

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	NA
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	NA
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2.3
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	NA
Comments: Confounding and covariates do not apply to this study.				

Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	NA
Comments: Effect modifiers are no applicable to this study.				

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4, 9.8.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4, 9.8.3
9.1.3 Covariates?	☐	☐	☒	NA
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	NA
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates?	☐	☐	☒	NA
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6
Comments: Covariates do not apply to this study.				

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☐	☒	NA
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	NA

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5
Comments: This study will report descriptive results only.				

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	NA
Comments: There is no plan for an independent review of the study results.				

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	NA
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5
Comments: Confounding does not apply to this study.				

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	NA
13.3 Have data protection requirements been described?	☒	☐	☐	10
Comments: There have been no ethical review applications to date.				

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5
Comments: NA				

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12
Comments: NA				

Name of the main author of the protocol: PPD
Date: / /
Signature: _____