CABOCARE: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT

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Final Version 1.1: 05 September 2018

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the prospective non-interventional study (protocol number: A-DE-60000-009) to evaluate the use of cabozantinib and cabozantinib-nivolumab combination in adult patients with advanced renal cell carcinoma according to licensed indications in 1st line treatment.

I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices (GPP), 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.

Investigator

NAME : _____

TITLE : (Prinicipal) Investigator SIGNATURE : _____

DATE : _____

OFFICE : _____

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

On behalf of the Sponsor:

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SUMMARY OF CHANGES

The current version of the protocol was released on 27 November 2023 and includes Amendment #3. The amendment form was prepared and is provided in Appendix 6 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	09 April 2021	Appendix 4
2	05August 2022	Appendix 5
3	27 November 2023	Appendix 6

SYNOPSIS

Study Title:	**CABOCARE**: Prospective non-interventional study of **CABO**zantinib as monotherapy or in combination with nivolumab in patients with advan**C**ed or metastatic ren**A**l cell carcinoma under **RE**al-Life clinical setting in 1st line treatment
Study Objectives:	Primary objective • To describe the use of Cabometyx™ (cabozantinib) tablets as monotherapy and the use of Cabometyx™ and Opdivo™ combination (cabozantinib-nivolumab combination) including the number of dose reductions, dose interruptions and terminations due to SAEs/AEs in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score. Secondary objectives • To describe the effectiveness of cabozantinib tablets as monotherapy and the effectiveness of cabozantinib-nivolumab combination in advanced or metastatic RCC in real-life in terms of progression free survival (PFS) and best overall response (Objective Response Rate [ORR] & Disease Control Rate [DCR]); • To describe the use of cabozantinib tablets as monotherapy and the use of cabozantinib-nivolumab combination in real-life clinical setting in 1st line treatment split by histological subtype; • To describe all non-serious and serious adverse events (AEs / SAEs) and fatal outcomes per drug cohort; • To describe the impact of the activity level at baseline on the occurrence of adverse events (AEs). Exploratory objectives • To describe the use of preventative and accompanying measures to cope with treatment related adverse events using quality of life, activity measurement and concomitant medications.
Rationale	Cabozantinib is a new oral inhibitor of receptor tyrosine kinases including c-MET, VEGFR and AXL. Cabozantinib has shown to provide significantly prolonged PFS and OS as well as better ORR in subjects with progressive advanced RCC if compared to (previous) standard 2nd line treatment with the mTOR (mammalian target of rapamycin) inhibitor everolimus. Convincing data from the international multicenter trial METEOR revealed a gain of nearly 4 and 5 months of PFS and OS, respectively, and already led to a change of international and national guideline recommendations for the treatment of advanced RCC [I]. Cabozantinib as well as nivolumab (an anti-PD1 checkpoint inhibitor) are now recommended as primary options after progressive disease in advanced RCC subjects initially treated with targeted anti-VEGF therapy [II].

	In patients with no prior systemic treatment, cabozantinib monotherapy has shown to significantly prolong PFS and increase ORR compared to the current standard of care, sunitinib (CABOSUN study; subjects with intermediate or poor risk according to IMDC only). Recently published analyses by an independent IRC confirmed the superiority of cabozantinib over sunitinib concerning PFS in all pre-specified subgroups as well as confirmed a more than doubled ORR (20 vs. 9% for cabozantinib and sunitinib, respectively) [III]. With regards to the above-mentioned METEOR and CABOSUN studies the safety profile of cabozantinib was acceptable and tolerability was similar to other VEGFR TKIs used in this patient population. Main adverse events of low grade (>25% of subjects treated with cabozantinib) were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia, vomiting, decreased weight and constipation, while hypertension (15% and 28%), diarrhea (13% and 10%) and fatigue (11% and 6%) were detected as main serious adverse events respectively, in METEOR and CABOSUN (grade 3 only) [I], [III]. Since the start of the CABOCARE study in 2018 the landscape of treatment options for advanced and metastatic RCC has changed as new drugs and drug combinations are available. Due to these new options guidelines recommend only restrictively and no longer as treatment of first choice cabozantinib monotherapy for medium-to-high risk patients as 1st line treatment in mRCC. The efficacy and safety of cabozantinib in combination with nivolumab (an anti-PD1 checkpoint inhibitor) as first line therapy in mRCC patients was investigated in the phase 3 CheckMate 9ER study. The combination met all efficacy endpoints and demonstrated superiority over sunitinib in PFS (median PFS 16.6 vs 8.3 month), OS and ORR [IV]. The combination of cabozantinib plus nivolumab was generally well tolerated, with a low rate of treatment-related discontinuations. Furthermore, patients had significantly better quality of life with cabozantinib-nivolumab combination versus sunitinib. [IV] The cabozantinib-nivolumab combination was submitted for regulatory approval to EMA. A positive CHMP opinion occurred in February 2021 and the Approval and Marketing Authorization by the European Commission was given on 31.03.2021. Now as the cabozantinib-nivolumab combination is authorized for the European market, patients treated with this combination can be included in the Cabocare study as second treatment group. Outside the setting of strictly controlled clinical studies there is only limited information about the efficacy and safety of cabozantinib or cabozantinib-nivolumab combination in the treatment of patients with advanced or metastasized renal cell carcinoma. Therefore, this non-

	interventional study is planned to collect data of cabozantinib and cabozantinib-nivolumab combination usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria. [I] T. K. Choueiri *et al.*, "Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial," *Lancet Oncol.*, vol. 17, no. 7, pp. 917–927, 2016. [II] T. Powles *et al.*, "European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor–Targeted Therapy," *Eur. Urol.*, vol. 70, no. 5, pp. 705–706, 2016. [III] T. K. Choueiri *et al.*, "Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial," *J. Clin. Oncol.*, vol. 35, no. 6, pp. 591–597, 2017. [IV] T. K. Choueiri *et al.,* ESMO 2020; oral presentation.
Study Timelines	Expected median duration of cabozantinib treatment is approx. 8-9 months, expected median duration of cabozantinib-nivolumab treatment is approximately. 14 months, for 1st line treatment (IV). Study duration including a 2-year follow-up was from Q3 2018 – Q2 2026 and will be extended. This extension includes a 1-year-enrollment phase (Q2 2024 – Q2 2025) and 2-year follow-up (Q2 2025 - Q2 2027).
Study Design:	Prospective German and Austrian multicenter non-interventional study (NIS) with approximately 50 centers in Germany and Austria.
Study Population:	Inclusion Criteria (1) Males or females aged 18 years and older with capacity to consent. (2a) Subjects receiving cabozantinib or cabozantinib-nivolumab combination as a first line treatment for advanced or metastatic renal cell carcinoma. (3a) Subjects with the intention to be treated with cabozantinib or cabozantinib-nivolumab combination according to the current SmPC; decision has to be taken before entry in the study. (4) Signed written informed consent. Exclusion Criteria (1) Participation in an interventional study at the same time and/or within 3 months before baseline. (2) Previous participation in this study.
Study Treatment:	In this non-interventional study, cabozantinib or cabozantinib-nivolumab combination are to be administered as directed by the investigator according to the current SmPCs and the study site´s usual clinical practice. The physician should refer to the SmPCs of the study medications for any information on the treatment prescribed.
Study Evaluations:	- **Treatment characteristics:** starting dose, dose reductions, dose interruptions, dose delay, treatment discontinuation; - **Demographic and baseline characteristics:** medical history and baseline characteristics of RCC and demographics;

	- **Effectiveness:** including overall response assessed by RECIST 1.1 and vital status; - **Safety:** clinical parameter (i.e. ECOG performance status, weight, blood pressure), as routinely assessed by the investigator, as well as occurrence of all serious and non-serious AEs as well as fatal outcomes and special situations will be captured in the eCRF; - **Exploratory**: data of activity level and quality of life will be collected as routinely assessed; inflammatory blood markers, as routinely assessed by the investigator, will be captured.
Statistical Methods:	A formal sample size calculation was not done. We intended to include 100 1st line subjects in the analyses, assuming a drop-out rate due to lost to follow-up of 5% 105 subjects had to be enrolled. In the open-label METEOR (cabozantinib), any dose reduction due to an AE occurred in 59.8% of subjects and the study drug was interrupted in 70% of subjects. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval would have been respectively 5.9%, 9.6% and 9.0% for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption. Up to 28 February 2021, 31 subjects were enrolled in the cabozantinib monotherapy group. The landscape of treatment options for advanced and metastatic RCC having changed, cabozantinib monotherapy is only restrictively recommended in guidelines for first line treatment in mRCC patients. Consequently, the treatment group with cabozantinib monotherapy will not be closed but only a limited number of subjects are further expected in this group. In the second treatment group with cabozantinib-nivolumab combination, the intent is to include 167 subjects. Assuming a drop-out rate due to lost to follow-up of 5%, 175 subjects have to be enrolled. In the interventional Checkmate 9ER study, dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of 167 subjects, the precision of 2- sided 95% confidence interval (based on simple asymptotic method) will be respectively 5.4% and 7.5% for proportions of 15% of discontinuation and 55% of dose reduction. **Data Analysis** At least 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) / Safety population: all included subjects who have taken at least one dose of study treatment.

	As this is a non-interventional 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, quartiles, maximum when appropriate for continuous variables; • Frequency count and percentage for categorical nominal variables; • Both the above for categorical ordinal variables. All the analyses will be presented separately for each group, cabozantinib monotherapy and cabozantinib in combination with nivolumab. Primary endpoint will be the descriptive analysis of the use of cabozantinib and the use of cabozantinib-nivolumab combination. Secondary endpoints will be effectiveness (ORR, DCR and PFS). For secondary endpoints, the Kaplan-Meier method will be used to obtain the estimates of median PFS time and their associated 2-sided 95% CIs. For all other secondary objectives and safety events a descriptive analysis will be used. Analyses by risk groups will be performed for all endpoints where appropriate.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CRO	Contract Research Organisation
CRP	C-reactive protein
CSR	Clinical Study Report
DCR	Disease Control Rate
ECOG	Eastern Co-operative of Oncology Group
EU	European Union
FAS	Full Analysis Set
FSA	Freiwillige Selbstkontrolle für die Arzneimittelindustrie
FSI	First Subject In
GEP	Guidelines for the Proper Conduct in Epidemiologic Research
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
hsCRP	High-sensitive C-reactive protein
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IRB	Institutional Review Board
IRC	Independent Review Committee
LSI	Last Subject In
LSV	Last Subject Visit
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastatic RCC
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NFKSI-19	National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy–Kidney Symptom Index with 19 questions
NIS	Non-Interventional Study

ORR	Overall Response Rate
PD-1	Programmed cell death protein
PFS	Progression Free Survival
PT	Preferred Term
Q	Quartal
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
RCC	Renal Cell Carcinoma
RTK	Receptors of tyrosine kinases
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TD	Treatment discontinuation
TEAEs	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitor
TNM	Tumor node metastasis (classification of malignant tumors)
TFL	Tables, Figures and Listings
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor

2 INTRODUCTION

2.1 Background

Renal cell carcinoma (RCC) is diagnosed in about 16,500 individuals in Germany and Austria each year and results in over 5,500 deaths [1], [2].

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor (TKI) with potent activity against c-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 c-MET and VEGFR signaling, rapidly inducing apoptosis of endothelial and tumour cells, resulting in tumour regression in a variety of xenograft models [3].

Cabozantinib has shown to provide significantly prolonged progression free survival (PFS) and overall survival (OS) as well as a better overall response rate (ORR) in subjects with progressive advanced RCC if compared to (previous) standard 2nd line treatment with the mTOR (mammalian target of rapamycin) inhibitor everolimus. Convincing data from the international multicenter trial METEOR revealed a gain of nearly 4 and 5 months of PFS and OS, respectively, and already led to a change of international and national guideline recommendations for the treatment of advanced RCC [4]. Cabozantinib as well as nivolumab (an anti-PD1 checkpoint inhibitor) are now recommended as primary options after progressive disease in advanced RCC subjects initially treated with targeted anti-VEGF therapy [5].

In subjects with no prior systemic treatment cabozantinib monotherapy has shown to significantly prolong PFS and increase ORR compared to the current standard of care, sunitinib (CABOSUN study; subjects with intermediate or poor risk according to IMDC only). Recently published analyses by an independent review committee (IRC) confirmed the superiority of cabozantinib over sunitinib concerning PFS in all pre-specified subgroups as well as confirmed a more than doubled ORR (20 vs. 9% for cabozantinib and sunitinib, respectively) [6].

With regards to the above-mentioned METEOR and CABOSUN studies the safety profile of cabozantinib was acceptable and tolerability was similar to other VEGFR TKIs used in this patient population. Main adverse events of low grade (>25% of subjects treated with cabozantinib) were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia, vomiting, decreased weight and constipation, while hypertension (15% and 28%), diarrhea (13% and 10%) and fatigue (11% and 6%) were detected as main serious adverse events respectively, in METEOR and CABOSUN (grade 3 only) [4], [6].

Since the start of the CABOCARE study in 2018 the landscape of treatment options for advanced and metastatic RCC has changed as new drugs and new drug combinations are available. Due to these new treatment options guidelines recommend only restrictively and no longer as treatment of first choice cabozantinib monotherapy for medium-to-high risk patients as 1st line treatment in mRCC. [16] Therefore, the recruitment of patients with advanced or metastatic RCC who are intended to be treated with Cabozantinib is rare. Based on the current recommendation for the first line treatment of mRCC the planned 100 patients cannot be achieved.

The phase 3 CheckMate 9ER study that compared cabozantinib-nivolumab combination with sunitinib monotherapy, demonstrated superiority over sunitinib in PFS, OS and ORR and met all efficacy endpoints [17].

The cabozantinib-nivolumab combination was generally well tolerated, with a low rate of treatment-related discontinuations. Furthermore, patients had significantly better quality of life with cabozantinib-nivolumab combination versus sunitinib. [17]

The cabozantinib-nivolumab combination was submitted for regulatory approval to the EMA. Approval and Marketing Authorization was given on 31.03.2021. As soon as the cabozantinib-nivolumab combination is authorized for the European market, patients who are treated with or intended to be treated with the combination can be included in the Cabocare study as second treatment group.

With the inclusion of patients on cabozantinib-nivolumab combination therapy the Cabocare study fulfills state-of-the-art treatment in advanced and metastatic RCC and is enabled to be continued.

2.2 Rationale

Outside the setting of strictly controlled clinical studies there is only limited information about the effectiveness and safety of cabozantinib as monotherapy or in combination with nivolumab in the treatment of subjects with advanced or metastasized renal cell carcinoma. Therefore, this non-interventional study is planned to collect data of cabozantinib/ cabozantinib-nivolumab combination usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria. Furthermore, no data is available for the activity profile of the patients with RCC. Therefore, this non-interventional study will collect data of the activity status from the physicians as well as the patient's view in centers where this is part of the clinical routine. This data together with an objective measurement method will help to analyze the status quo of activity profile of RCC patients.

3 STUDY OBJECTIVES

3.1 Primary Objective

To describe the use of Cabometyx™ (cabozantinib) tablets as monotherapy and the use of Cabometyx™ and Opdivo™ combination (cabozantinib-nivolumab combination) including the number of dose reductions, dose interruptions and terminations due to SAEs/AEs in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score

3.2 Secondary Objectives

- To describe the effectiveness of cabozantinib tablets as monotherapy and the effectiveness of cabozantinib-nivolumab combination in advanced or metastatic RCC in real-life in terms of progression free survival (PFS) and best overall response (Objective Response Rate [ORR] & Disease Control Rate [DCR])
- To describe the use of cabozantinib tablets as monotherapy and the use of cabozantinib-nivolumab combination in real-life clinical setting in 1st line treatment split by histological subtype
- To describe all non-serious and serious adverse events (AEs / SAEs) and fatal outcomes per drug cohort
- To describe the impact of the activity level at baseline on the occurrence of adverse events (AEs)

3.3 Exploratory objectives

To describe the use of preventative and accompanying measures to cope with treatment related adverse events using quality of life, activity measurement and concomitant medications in centers where this is part of the clinical routine.

4 STUDY DESIGN

As this is a non-interventional study, the decision to prescribe the product must be taken prior to, and independently from the decision to enrol the subject. This decision should be made in accordance with routine clinical practice at the clinical site with the concerned physician.

4.1 Overview

This is an international, multicentre, non-interventional prospective study. Data will be collected via electronic case report form (eCRF) by the sites.

This study will be conducted in Germany and Austria, which have a cabozantinib tablets Marketing Authorisation (MA) for first line use. MA for the cabozantinib-nivolumab combination as first line treatment in advanced or metastatic RCC was in March 2021. Patients intended to be treated with this combination can be enrolled as soon as the MA is in place for use of these products in the European Union.

Investigators will follow their individual therapeutic concept for the treatment with cabozantinib or cabozantinib-nivolumab combination in accordance with the current SmPC.

No out-of-routine diagnostic or therapeutic intervention is allowed during this study. All data recorded in this study originate from routine diagnostic and therapeutic procedures.

The investigator needs to inform the subject that personal and medical data will be recorded for this study. The subject has to give written informed consent for data collection, data processing and for monitoring purposes.

Data will be collected at the described visits:

- Visit 1 (baseline): enrolment visit,
- Visit 2 (approximately 4 weeks after baseline),
- Visit 3 (approximately 8 weeks after baseline),
- Visit 4 (approximately 12 weeks after baseline),
- Visit 5 (approximately 16 weeks after baseline),
- Visit 6 (approximately 24 weeks after baseline),
- Visit 7 (approximately 32 weeks after baseline),
- Visit 8 (approximately 40 weeks after baseline),
- Visit 9 (approximately 48 weeks after baseline),
- Visit 10 (approximately 56 weeks after baseline),
- Follow-up 1 (30 days after treatment discontinuation),
- Follow-up 2 (1 year after treatment discontinuation or 24 months after baseline if subjects reached visit 10).

The timing of the visits according to routine clinical practice is assumed to be close to the proposed schedule. If the timing does not meet the schedule, entries should be made at the visit nearest in time to the proposed schedule.

If a subject discontinues the intake of cabozantinib or of cabozantinib-nivolumab combination at any visit before Visit 10, the follow-up period starts, and the next visit will be Follow-up 1. Discontinuation of the cabozantinib-nivolumab combination is defined as the permanent discontinuation of both study medications. i.e. as soon as one of the treatments is still ongoing the combination is not considered as discontinued. The Follow-up period can only start once both treatments have been permanently discontinued.

4.2 Population Characteristics

Treatment-naïve advanced or metastatic renal cell carcinoma patients in Germany or Austria will be included in this study: males and females aged 18 years and older, with the intention to be treated with cabozantinib or cabozantinib-nivolumab combination according to the current local SmPCs taken prior to the entry in the study.

4.3 Data Collection

Data from subjects suffering from advanced or metastatic renal cell carcinoma and treated first line with cabozantinib or cabozantinib-nivolumab combination will be collected.

Subjects will be treated in accordance with current local SmPCs during their participation in this study. No additional assessment or test will be required.

Relevant data collected as part of routine medical care will be captured in an eCRF. These data will be transmitted to the data management vendor managed by the sponsor for analysis. The data transmitted will be pseudonymised and will be identified by a numeric identifier.

All the collected data will be in accordance with the daily practice of medical doctors dedicated to treatment of subjects suffering from advanced or metastatic renal cell carcinoma. If some data is not collected, he/she will mark the corresponding sections in the eCRF as not done.

4.4 Study Duration

The study will be considered to have started when the first subject has signed informed consent (first subject in).

The study will be considered to be completed after the last subject has had its last visit (LSV).

Planned duration:

- First subject in (FSI): Q3 2018
- Last subject in (LSI): Q2 2025
- Time for recruitment: approx. 7years
- Last subject last visit (LSLV): Q2 2027
- Final clinical study report (CSR): Q2 2028
- Total study duration: 10 years
- Subject participation duration: 2 years

4.5 Subject Information

Prior to enrolment of a subject in this study, the investigator, or a person designated by the investigator, will explain the nature and purpose of this data collection to each subject, or each subject's legally acceptable representative. As all assessments and procedures will be conducted in accordance with routine medical practice, participation in the study does not convey any additional risks or burdens for the subject. However, the subject will be required to provide written informed consent to confirm that they allow their medical data to be collected and analysed. For data privacy reasons, the subject must give his consent that his contact data will be given out to the vendor (German Sportsuniversity Cologne) who is in charge of the handling of questionnaires and actigraphs.

This must be obtained prior to subject enrolment and prior to any data being entered in the study database. Sufficient time should be allowed to discuss any questions raised by the subject. The subject should be allowed as much time as they need to consider their decision.

The sponsor will provide an informed consent form, in German language readily understood by the subject. Each subject's original consent form personally signed and dated by the subject or

by the subject's legally acceptable representative, and by the physician, who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled subjects with a copy of their signed informed consent. None of these informed consents will be collected by the sponsor.

The consent form will be revised during the study if important new information becomes available.

5 STUDY POPULATION

Eligible subjects for this study are systemic treatment-naïve adult subjects with advanced or metastatic renal cell carcinoma, scheduled to be treated with cabozantinib or Cabozantinib-nivolumab combination prior to entry in the study. Currently 35 subjects are treated with cabozantinib in monotherapy. It is planned to include 175 subjects treated with cabozantinib-nivolumab combination.

It is planned to recruit up to 50 sites in Germany and Austria, both practices and hospitals.

5.1 Inclusion Criteria

All subjects must fulfil the following:

(1) Males or females aged 18 years and older with capacity to consent.

(2a) Subjects receiving cabozantinib or cabozantinib-nivolumab combination as a first line treatment for advanced or metastatic renal cell carcinoma.

(3a) Subjects with the intention to be treated with cabozantinib or cabozantinib-nivolumab combination according to the current SmPC; decision has to be taken before entry in the study.

(4) Signed written informed consent.

5.2 Exclusion Criteria

Subjects will not be included in the study if the following apply:

(1) Participation in an interventional study at the same time and/or within 3 months before baseline.

(2) Previous participation in this study.

5.3 Subject Withdrawal Criteria

As this is a non-interventional study, no specific withdrawal criteria are specified. Subjects are free to withdraw consent at any time. Data will be collected up to the time of withdrawal, but no additional information will be collected after this time.

When a subject is withdrawn from the study, the primary reason should be recorded in the eCRF. The reason can be adverse event, withdrawal by subject or guardian, lost to follow-up, protocol deviation, physician decision, site terminated by sponsor, study terminated by sponsor, pregnancy, death or other.

6 STUDY ASSESSMENTS

Study Flow Chart Table 2 shows the data that can be recorded in the eCRF at each of these visits.

Table 2 Flowchart

Visit Assessment / Procedure	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Follow-up (FU) 1	FU 2
Week	**Day 1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	**30 days after TD**	**1 year after TD or 24 months after V1**
Signature of informed consent	✓	informed consent must be signed prior to any documentation of data										
Visit date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Eligibility	✓											
Demographics (gender, year of birth)	✓											
Significant Medical or Surgical History	✓											
Disease history	✓											
Prior nephrectomies	✓											
Overall response		✓	✓	✓	✓	✓	✓	✓	✓	✓		
ECOG Performance Status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Cabozantinib / cabozantinib-nivolumab regimen	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓*
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Inflammatory markers	✓			✓		✓		✓		✓		
Occupational status and smoking status	✓			✓		✓		✓		✓		
Quality of life questionnaire°	✓			✓		✓		✓		✓		
Activity questionnaire°	✓			✓		✓		✓		✓		
Actigraph measurement (1 week) °†	✓			✓		✓		✓		✓		
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication for AEs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study discontinuation or completion form		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Post cabozantinib / cabozantinib-nivolumab systemic treatment for RCC											✓	✓

All data will be recorded as applicable and available: if a specific diagnostic procedure is done according to clinical routine the corresponding data should be recorded in the eCRF, otherwise the corresponding part of the eCRF will be marked as not done. TD: Treatment discontinuation, *: only for subjects who have performed visit 10, °: not collected in eCRF, collected from patient by German Sport University Cologne; † only in centres where activity measurement is part of clinical routine

6.1 Study Assessments

All data will be recorded as applicable and available. In other words, if a specific diagnostic procedure is done according to clinical routine, the corresponding data should be recorded in the eCRF, otherwise the corresponding part of the eCRF will be marked as not done.

The timing of the visits according to routine clinical practice is assumed to be close to the proposed schedule. If the timing does not meet the schedule, entries should be made at the visit nearest in time to the proposed schedule.

The following data will be collected at the following visits:

Visit 1, baseline (enrolment):

- Date of informed consent signature
- Visit date
- Eligibility (verification of in- and exclusion criteria)
- Demographics (gender, year of birth)
- Significant Medical or Surgical History
- Disease history (date of renal cell carcinoma diagnosis, RCC stage at diagnosis, RCC stage at baseline (TNM), cancer histology, risk score either by IMDC or MSKCC)
- Prior Nephrectomies (occurrence and date)
- ECOG Performance Status
- Smoking status and Occupational status
- Vital Signs (Height and body weight, blood pressure)
- Inflammatory blood markers (hsCRP or CRP, as available, no safety marker)
- Quality of life questionnaire (NFKSI-19) after Visit 1 (within 2 weeks)
- Activity questionnaire after Visit 1 (within 2 weeks)
- Actigraph measurement (1 week) after Visit 1 (within 2 weeks) [only in centres where activity measurement is part of clinical routine]

Visits 2/3/5/7/9 - (about 4, 8, 16, 32 and 48 weeks, respectively, after baseline)

- Visit date
- Evaluation of tumour (Overall response)
- ECOG Performance Status
- Vital Signs (Body weight, blood pressure)
- Adverse Events
- Concomitant medication for AEs
- Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation)
- Nivolumab regimen (dose and date of injection, reason for injection delayed if any and primary reason for nivolumab discontinuation)
- Study discontinuation or completion form (in case of discontinuation: reason for premature withdrawal)

Visits 4/6/8/10 - (about 12, 24, 40 and 56 weeks, respectively, after baseline):

- Visit date

- Evaluation of tumour (Overall response)
- ECOG Performance Status
- Adverse Events
- Concomitant medication for AEs
- Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation).
- Nivolumab regimen (dose and date of injection, reason for injection delayed if any and primary reason for nivolumab discontinuation)
- Smoking status and Occupational status
- Vital Signs (Body weight, blood pressure)
- Inflammatory blood markers (hsCRP or CRP, as available, no safety marker)
- Quality of life questionnaire (NFKSI-19) after the visit
- Activity questionnaire after the visit
- Actigraph measurement (1 week) after the visit [only in centres where activity measurement is part of clinical routine]
- Study discontinuation or completion form (in case of discontinuation: reason for premature withdrawal)

Follow-up visit (FU) 1 - (about 30 days after treatment discontinuation):

- Visit date
- Adverse Events
- Concomitant medication for AEs
- Post Cabozantinib / cabozantinib-nivolumab combination systemic treatment for RCC
- Study discontinuation or completion form (in case of discontinuation: reason for premature withdrawal)

Follow-up visit (FU) 2 - (1 year after treatment discontinuation or 24 months after visit 1):

- Visit date
- Adverse Events
- Concomitant medication for AEs
- Post Cabozantinib /cabozantinib-nivolumab combination systemic treatment for RCC
- Cabozantinib regimen (dose and date for last cabozantinib intake; only for patients who continued until visit 10)
- Cabozantinib-nivolumab combination regimen (dose and date for last cabozantinib and nivolumab intake; only for patients who continued until visit 10)
- Study discontinuation or completion form (in case of discontinuation: reason for premature withdrawal)

6.2 Methods

6.2.1 Quality of life questionnaire

The quality of life questionnaire is the NFKSI-19 questionnaire (see Appendix 1). It will be provided to the subjects in paper form. The handling is described in 6.3.4.

6.2.2 Activity questionnaire

The activity questionnaire is a questionnaire asking for the activity of the patients using boxes to provide time of activity and visual analogue scales (VAS) (see Appendix 2 and 3). It was designed by PPD (German Sport University Cologne) for this study. There is a longer version for Visit 1 (see Appendix 2) and a shorter version for the following visits (see Appendix 3). It will be provided to the subjects in paper form. The handling is described in 6.3.4.

6.2.3 Actigraph measurement

The Actigraph is the most frequently used tool to objectively assess physical activity in clinical and non-clinical studies. In detail, the Actigraph GT9X Link device will record raw data on physical activity (acceleration), steps, intensity of physical activity and body position.

The device will be worn by all subjects up to five times (less in case of early treatment discontinuation) for one week (seven days) after the respective visits. After wearing the device for one week, patients will complete the questionnaires listed under 6.3.1 and 6.3.2. After completing Visit 10 or after cabozantinib treatment discontinuation, subjects and the respective treating physician will receive a detailed report on their physical activity behaviour together with exercise recommendations. The Actigraph will only be used in centres where activity measurement is part of clinical routine.

6.2.4 Handling of device and questionnaires

The device (Actigraph) and the questionnaires will be sent to the subjects first after informed consent (Visit 1) and thereafter at the respective weeks of Visit 4, 6, 8 and 10 (see Table 2). The subjects will receive a package from the researcher (German Sport University Cologne) including the device with an instruction and a help desk number, as well as the two questionnaires and a return package. After one week the subject will fill out the questionnaire and send the device and the questionnaires in the provided return package back to the vendor. The researcher will follow up with the subject if package is not received. Data handling is described in 12.3.

7 STUDY EVALUATIONS

7.1 Endpoints & Evaluations

In the framework of this non-interventional study, the nature and timing of subject assessments will be in accordance with routine medical practice.

7.1.1 Primary Endpoints & Evaluations

The primary endpoints are to describe the use of cabozantinib /cabozantinib-nivolumab combination in terms of:

- number and proportion of subjects with dose reduction of cabozantinib due to SAEs/AEs,
- number and proportion of subjects with dose interruption of cabozantinib and/or nivolumab due to SAEs/AEs,
- number and proportion of subjects with termination of cabozantinib /cabozantinib-nivolumab combination due to SAEs/AEs,
- injection delayed of nivolumab due to SAE/AE,

in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score

7.1.2 Secondary Endpoints & Evaluations

- To describe the effectiveness of cabozantinib /cabozantinib-nivolumab combination in advanced or metastatic RCC in real-life in terms of progression free survival (PFS), and best overall response (ORR & DCR).

  - Progression free survival is defined as the time between the start date of cabozantinib /cabozantinib-nivolumab combination and the date of progression or death from any cause. Disease progression is defined as either radiological progression assessed by the investigator using RECIST 1.1 [7] or clinical progression.
  - The best overall response is the best response assessed by investigator recorded during the treatment period.
  - ORR is defined as the proportion of subjects achieving complete or partial response.
  - DCR is defined as the proportion of subjects achieving a complete response, partial response or stable disease.

- To describe the impact of the activity level at the beginning of the treatment (within the first 2 weeks of cabozantinib /cabozantinib-nivolumab combination intake) on the occurrence of adverse events (AEs) using the actigraph and questionnaires
- To describe the use of cabozantinib /cabozantinib-nivolumab combination in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment split by histological subtype (clear cell and non-clear cell) in terms of:
  - Number and proportion of subjects with dose reductions of cabozantinib due to SAEs/AEs
  - Number and proportion of subjects with dose interruption of cabozantinib and/or nivolumab due to SAEs/AEs
  - Number and proportion of subjects with termination of cabozantinib /cabozantinib-nivolumab combination due to SAEs/AEs
  - Number and proportion of subjects with injection delayed of nivolumab due to SAEs/AEs

7.1.3 Exploratory endpoints

To describe the use of preventative and accompanying measures to cope with treatment related adverse events by evaluating:

- physical activity overall and throughout therapy by questionnaire and actigraph.
- occupational status and smoking status
- influence of inflammation measured by inflammatory blood markers on activity level
- quality of life by questionnaire: total score and the four subscores (disease related symptoms – physical and emotional score, treatment side effects, and well-being)
- concomitant medications to cope with related adverse events

7.2 Safety Evaluations

In this prospective non-interventional study, investigators will collect and report all serious and non-serious adverse events, deaths, and all instances of 'special situations' as described in Section 10, starting at the time from signature of ICF up to Follow-up 1. The description of this safety evaluation is a secondary endpoint of this study. The adverse events will be described overall and also according to level of physical activity assessed by questionnaire and actigraph.

8 STUDY TREATMENTS

The decision to prescribe cabozantinib /cabozantinib-nivolumab combination will be made prior to and independently from the decision to enrol the subject in this non-interventional study and the treatment should follow the current local SmPC.

9 STATISTICAL CONSIDERATIONS

9.1 Subject Classification and Definitions

- **Enrolled subject:** Subject who has signed informed consent to participate.
- **Treated subject:** Enrolled subject who received study treatment at least once during the study.

9.2 Analysis Population Definitions

At least, the following populations will be used during the statistical analyses:

- **Enrolled population:** All subjects for whom the informed consent has been signed.
- **Full Analysis Set (FAS) / Safety population:** All enrolled subjects who have received at least one dose of study treatment (cabozantinib for mono or cabozantinib and nivolumab for combination treatment).

9.2.1 Populations Analysed

All analyses will be performed on the FAS / Safety population.

9.2.2 Subject Allocation and Reasons for Exclusion from the Analyses

The rules for allocation of subjects to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock. An interim data review meeting will be held prior to the planned interim analysis.

9.3 Sample Size Determination

A formal sample size calculation is not done. We intended to include 100 1st line subjects in the analyses, assuming a drop-out rate of 5% 105 subjects had to be enrolled. 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. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval would have been respectively 5.9 %, 9.6 % and 9.0 % for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption. With 100 evaluable subjects the expected 12-months progression-free survival rate of 35% can be estimated with a 95% confidence interval of [0.257; 0.452] and the expected ORR of 20% with one of [0.127; 0.292].

Up to 28 February 2021, 31 subjects were enrolled in the cabozantinib monotherapy group. The landscape of treatment options for advanced and metastatic RCC having changed, cabozantinib monotherapy is no longer recommended as treatment of choice for 1st line treatment in mRCC patients. Consequently, only a limited number of subjects are further expected in this group.

In the second treatment group with cabozantinib-nivolumab combination, the intent is to include 167 subjects. Assuming a drop-out rate due to lost to follow-up of 5%, 175 subjects have to be enrolled. In the interventional Checkmate 9ER study dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of 167 subjects, the precision of 2- sided 95% confidence interval (based on simple asymptotic method) will be respectively 5.4% and 7.5% for proportions of 15% of discontinuation and 55% of dose reduction.

Furthermore, with 167 subjects adverse events occurring with a probability of at least 1% will be detected with a probability of at least 81%.

9.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the sponsor's Medical Affairs Biometrics Department.

A Statistical Analysis Plan (SAP) describing the planned statistical analyses in detail with Tables, Figures and Listings (TFLs) templates will be developed as a separate document. This SAP will detail the rules and conventions used to compute the derived analysis variables and to handle missing data.

Statistical evaluation will be performed using Statistical Analysis System® (SAS®) (version 9.3 or higher).

Due to the non-interventional character of this study the analysis will be mainly based on descriptive methods. Descriptive statistics will be presented as follows:

- Continuous variables: number of observations, number of missing values, mean, 95% CI of the mean, standard deviation (SD), median, quartiles, minimum and maximum.
- Dichotomous or categorical variables: number of observations, number of missing values, frequency and percentage of each of the categories.

Statistical testing will only be carried out for exploratory purposes. Unless otherwise stated, testing will be performed 2-sided with a type 1 error rate set at 5%.

All study data will be presented in listings.

All the analyses will be presented separately for each group, cabozantinib monotherapy and cabozantinib in combination with nivolumab.

9.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, 95 % CI of the mean, SD, median, quartiles, minimum, maximum) or frequency counts of demographic and baseline data will be presented for the enrolled population.

9.4.2 Homogeneity of Groups

The risk score as part of the primary endpoint will split up the population in the following categories: favourable, intermediate and poor risk. This will be done either by IMDC [8] or MSKCC [9] risk score in the decision of the investigator. Description of demographic and baseline characteristics by risk group will be used to assess homogeneity. No comparison test will be performed.

9.4.3 Subject Disposition and Withdrawals

The number of subjects included, and number and percentage of subjects included but not part of the FAS / Safety population will be provided in total.
The numbers and percentages of subjects included in each of the FAS and in each class of the risk for the FAS population will be tabulated by country, study site and in total. The reasons for subject exclusions will also be tabulated by subgroups and in total. In addition, the numbers of subjects who discontinued and completed the study treatment will be tabulated for the FAS by subgroups and in total. Primary reasons for discontinuation of study treatment will also be tabulated for FAS by subgroup and in total.

9.4.4 Primary and Secondary Evaluations

9.4.4.1 Primary Endpoint Analysis

The proportion of subjects with ≥1 dose reduction of cabozantinib due to AE will be described with its 95% confidence interval, by risk group and overall.
The same analysis will be presented for the proportion of subjects with ≥1 dose interruption of cabozantinib and/or nivolumab, delayed dose injection of nivolumab and discontinuation of cabozantinib and/or nivolumab due to AE.

9.4.4.2 Secondary Endpoint Analysis

The secondary endpoints will be analysed descriptively by risk group and overall.
ORR and DCR will be described at each time point (W8, W16, W24, W32, W40, W46 and W52). The progression free survival, defined as time from cabozantinib /cabozantinib-nivolumab combination initiation to disease progression or death will be analysed using standard survival analysis methods including Kaplan-Meier product-limit survival curve. The median time to event will be estimated and presented with its 95% confidence interval.
The subjects still alive without disease progression at the end of the follow-up will be censored at their last assessment date.

9.4.4.3 Exploratory Endpoint Analysis

The evolution of activity level and quality of life between baseline and each time point (W12, W24, W40 and W56) will be described overall and also according to occupational and smoking status at initiation of Cabozantinib /cabozantinib-nivolumab combination in centers where this is part of the clinical routine.
Concomitant medications to cope with treatment related adverse event will be presented by therapeutic group and preferred name.

9.4.5 Adjustment for Country/Centre effect

No adjustment for country/centre effect is planned.

9.4.6 Safety Evaluation

Analyses and summary tables will be presented on the Safety population (by cabozantinib monotherapy and cabozantinib-nivolumab combination therapy).

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, treatment emergent AEs (TEAEs), SAEs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum grading and drug relationship. Treatment emergent AEs associated with dose modification (temporary interruption, reduction or discontinuation) of cabozantinib and TEAEs leading to cabozantinib temporary dose interruption, reduction or discontinuation will also be summarised separately. Similarly, TEAEs associated with delayed dose injection, temporary interruption or discontinuation of nivolumab will be presented. Adverse events will also be described by level of physical activity.

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

- It was not present prior to receiving the first dose of cabozantinib /cabozantinib-nivolumab combination; or

- It was present prior to receiving the first dose of cabozantinib /cabozantinib-nivolumab combination but the intensity increased during treatment with cabozantinib /cabozantinib-nivolumab combination.

Summary statistics will be presented for ECOG performance status and weight at each visit. Changes from baseline to each postbaseline assessment will be summarised similarly.

9.5 Subgroup Analyses

All the analyses will be provided by risk score. Primary endpoint will be presented by risk score and histological subtype. All analyses will be performed by treatment cohort.

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

9.6 Interim Analysis

One interim analysis is planned and will be performed, when the first 50 subjects have completed cabozantinib-nivolumab combination treatment. This interim analysis will present the results of the cabozantinib-nivolumab combination and the until this timepoint available cabozantinib monotherapy patient data.

The results of the interim analyses will not have any impact on the conduct of the study.

9.7 Final Analysis

The final analysis will be performed after the end of the study, once all data are collected and cleaned, after the final data review and the database lock.

10 DEFINITIONS, MONITORING, AND REPORTING

10.1 *Definitions*

10.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be the development of a new medical condition, or the deterioration of a pre-existing medical condition. This includes any 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, electrocardiogram) temporally associated with the use of a medicinal product, whether or not considered related.

10.1.2 Special Situations

This is any incidence of drug exposure during pregnancy or breast-feeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic 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 (see Section 10.2).

10.1.2.1 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.

AEs that occur in infants following exposure to a medicinal product from breast milk should also be reported.

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

10.1.2.3 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 recommend per the product labelling.

10.1.2.4 Medication error

Medication error refers to any unintentional error in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product while in the control of the healthcare professional or consumer that leads to, or has the potential to lead to harm to the patient.

For example:

- Pharmacist dispenses the incorrect drug due to confusion concerning the drug name;
- Patient swallows a tablet rather than taking sublingually.

10.1.2.5 Occupational exposure

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

For example:

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

10.1.2.6 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.

10.1.2.7 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.

10.1.3 Serious Adverse Event (SAE)

An SAE is any AE occurring at any dose that:

- results in death;
- is life-threatening, defined as any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death;
- results in hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons;
    - Hospitalisation is defined as any inpatient admission (even if less than 24 hours) (unless it occurs to ensure treatment compliance). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.

- Prolongation of hospitalisation is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.
- Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae that 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.

10.1.4 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 events having fatal **outcomes** should be considered 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 adverse event term may be 'Death' or 'Sudden death'.

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

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

10.2.1 Collection of Safety Reports

All safety reports, whether they are serious/nonserious, related/not related, should be **collected** separately for carbozantinib and nivolumab monotherapy and for combination therapy by the investigator in the study source document during the course of the study. The safety data will be collected in the eCRF which triggers automated alerts providing the information corresponding to AE Report Form for Non-Interventional Studies ([CCI]) and/or corresponding information from the eCRF to Ipsen according to the timelines set out in Section 10.2.2. Providing the information on the AE Report Form ([CCI]) is used as back-up when eCRF is not available.

10.2.2 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 7 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.

Reporting Information for safety reports
For SAEs and Special Situations, to report initial or follow-up information to Ipsen, the eCRF must be completed with information corresponding to Adverse Event Report Form for Non-Interventional Studies (CCI) within 24 hours of becoming aware of the event which triggers automated alerts to: Email: PPD and PPD As back-up when eCRF is not available information can be provided to Ipsen on AE Report Form (CCI) which can be either e-mailed to the above-mentioned addresses or Fax: PPD . If the back-up option was used for initial or follow-up reporting, the information should be recorded as soon as possible in the corresponding eCRF section. ***For nonserious adverse events,*** to report initial or follow-up information to Ipsen, the same applies as above for SAEs and Special Situations with the only exception being a deadline within 7 calendar days of becoming aware of the event.

All safety reports will be processed by Ipsen according to their relevant Standard Operating Procedures (SOP). This includes the follow-up of safety reports with the investigator, as required.

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

10.2.3 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 each AE:

- Patient identifier;
- Product name;
- AE description including assessment of causal relationship (see Section 10.3.1) and seriousness (see Section 10.1.3);
- 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.

The investigator should report a diagnosis or a syndrome, if known, 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.

10.3 Safety Classifications

10.3.1 Relationship of Events to the Medicinal Product

The following definitions should be considered when evaluating a causal relationship between the study treatment and an AE, assessed separately for each product:

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

10.3.2 Severity of Events

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 adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event
4	Life-threatening or disabling adverse event
5	Death related to adverse event

10.3.3 Expectedness of Events

Expectedness of all AEs will be determined by Ipsen according to the local SmPC [10] for investigators.

11 MONITORING PROCEDURES

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

11.1 Routine Monitoring

A risk-based approach to monitoring will be applied to this non-interventional 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.

It is planned to perform monitoring visits in about 10% of the sites, chosen based on the results of remote data review. The scope of source data verification will be defined in the monitoring guidelines. The investigator will allow direct access to all relevant files (for all subjects) and for the purpose of verifying entries made in the eCRF and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs within 7 days of the subject's visit and on an ongoing basis to allow review by the study monitor, both remotely via the internet and during site visits.

Whenever a subject name is revealed on a document required by the sponsor, the name must be blacked out permanently by the site personnel and annotated with the subject number as identification.

12 STUDY MANAGEMENT

12.1 Data Recording of Study Data

In compliance with Good Pharmacoepidemiology Practices (GPP), the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in this study.

An eCRF will be utilised for collecting subject data. The sponsor will ensure that the entrusted CRO uses adequate technology to ensure data security transfer and backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. In order to ensure the confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, or from Ipsen or third parties.

Data entry in the eCRF should be performed by the investigator or by the designated person from his/her team within 7 days of the subject's visit and on an ongoing basis.

Subject questionnaires will be printed and provided to the subjects. The completed questionnaires will be electronically processed by the German Sport University Cologne using single data entry with verification. The sponsor will ensure that the entrusted vendor uses adequate technology and storing to ensure data security. The device will be programmed by the vendor (German Sport University Cologne). Data obtained by the device can only be read out by a special software at the vendors site. The device will not transfer data over the internet. The software will be installed only on password secured computers using local secured connection and handled by authorised and trained personnel to ensure data security and confidentiality. The data from the questionnaires will be transferred pseudonymised (i.e. using a patient identifier number) between the German Sport University Cologne and the data management of the CRO in secured manner according to written data transfer protocol.

12.2 Data Verification on site

Definition 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, subject's 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 medico-technical departments involved in the clinical study).

The sponsor-assigned monitor must verify, by direct reference to the medical records/medical notes, that the data required by the protocol are accurately reported on the eCRF.

The medical records/medical notes must, as a minimum, contain the following: a statement that the subject is included in the study (with the corresponding study number) and has provided written informed consent to study participation.

The subject must have consented to their medical records being viewed by sponsor-authorised personnel. This information is included in the informed consent form.

12.3 Data Quality

The eCRF data will be reviewed for completeness, consistency and protocol compliance.

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

The investigator must, as a minimum, provide an electronic signature (e-signature) for each subject 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.

12.4 Data Management

Data management will be conducted by a CRO, directed by the sponsor's Medical Affairs Biometry department. All data management procedures will be completed in accordance with Ipsen's and the contracted CRO's SOPs.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately. At the end of the study, the Investigator will receive their data, from the clinical study in an electronic format (PDF files stored on a CD/DVD) which will be an exact copy of the eCRF for archiving purposes and future reference. Data from the patient's questionnaires and the device will be handled by the German Sport University Cologne and transferred to the sponsored assigned CRO according to pre-agreed data transfer specifications. No private or patient identifying data known by the university for management purposes will be transferred to the sponsor. Only pseudo anonymized data will be transferred.

12.5 Record Archiving and Retention

Study documents will be retained by the investigator in a secure place for 10 years after completion of the final CSR.

13 ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES

13.1 Ethical Considerations

NIS falls outside of the scope of the European Union (EU) Directive 2001/20/EC and the EU Directive 2005/28/EC.

This study must be conducted in compliance with the recommendations of the Declaration of Helsinki (2013) [11] and the International Ethical Guidelines for Epidemiological Studies, CIOMS, February 2008 [12].

This study should also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP), November 2007 [13] and the International Society for Pharmacoepidemiology (ISPE) Good Pharmaco Epidemiological Practices (GPP) Guidelines, April 2007 [14].

Safety data collection and reporting should be consistent with EU Good Pharmacovigilance Practice (GVP) [15] unless dictated by relevant local legislation for safety reporting in which case that must be followed instead.

In addition, this study will adhere to all local regulatory requirements applicable to non-interventional studies.

Before initiating the study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB (Independent Ethics Committee/Institutional Review Board), as applicable.

13.2 Regulatory Approval

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

This study is non-interventional and falls outside the scope of the EU Directive 2001/20/EC, the EU Directive 2005/28/EC and International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines.

This study complies with the EU Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

13.3 Publication Policy

In line with the Freiwillige Selbstkontrolle für die Arzneimittelindustrie (FSA)-Codex this NIS will be posted on a public open internet-platform and the results will be posted within the stipulated timeframe.

The publication will follow the IPSEN publication policy, which is available on the IPSEN Internet website:

https://www.ipsen.com/commitments/transparency-and-trust/clinical-trials/

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 upon and implemented by the study investigators or a Steering Committee. 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 study agreements, governing the relationship between the sponsor and the author (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 study agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including study agreements, governing the relationship between the sponsor and the author (or the author's 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.

13.4 Study Report

A CSR will be prepared in compliance with any applicable regulatory requirements and national laws in force within 12 months after last subject last visit. It should be written in English.

13.5 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per documentation in the eCRF of included subject, and the specified terms of payment will be described in the contract.

14 PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required:

As required by local regulations, the sponsor's Regulatory Affairs group will ensure that all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies.

15 BIBLIOGRAPHIC REFERENCES

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[10] IPSEN, "Cabometyx SmPC German Version."

[11] "Declaration of Helsinki," 2013.

[12] CIOMS, "International Ethical Guidelines for Epidemiological Studies."

[13] "International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP)."

[14] "International Society for Pharmacoepidemiology (ISPE) Good PharmacoEpidemiological Practices (GPP) Guidelines."

[15] "EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)."

[16] Escudier B et al.: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 30: 706 – 720, 2019 + eUpdates

[17] T. K. Choueiri et al., ESMO 2020; oral presentation

16 LIST OF APPENDICES

Appendix 1 NCCN-FACT FKSI-19 questionnaire

CABG CARE
BEWEGUNG IN DER 1. LINIE

NCCN-FACT FKSI-19 (Version 2) **Date:** _____

Patient ID: **Signature:** _____

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	H7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	H12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	GF1	I am able to work (include work at home)	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
Page 1 of 1

permission. If any changes are made to the wording or phrasing of any FACIT item without permission, the document cannot be considered the FACIT, and subsequent analyses and/or comparisons to other FACIT data will not be considered appropriate.

Permission to use the name "FACIT" will not be granted for any unauthorized translations of the FACIT or FACIT items. Any analyses or publications of unauthorized changes or translated versions may not use the FACIT name. Any unauthorized translation will be considered a violation of copyright protection.

The FACIT copyright information provided on these documents must be included on every page of a FACIT questionnaire in study documents, and in any reproductions for manuscript or other publication purposes.

If there are issues of scientific or copyright misconduct in using the FACIT system of questionnaires, Dr. Cella reserves the right to withdraw permission for use and seek damages to the full extent provided by international copyright law.

Translation and linguistic validation of all FACIT scales must be performed by FACITtrans.

NCCN/FACT Kidney Symptom Index-19 (FKSI-19)
Scoring Guidelines (Version 2)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Scale	Item Code	Reverse item?		Item response	Item Score
FKSI-19	GP1	4	-	_____	=_____
Total	GP4	4	-	_____	=_____
	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
Score range: 0-76	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GP2	4	-	_____	=_____
	C5	4	-	_____	=_____
	GP5	4	-	_____	=_____
	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 19: _____
Divide by number of items answered: _____**=FKSI-19 score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FKSI-DRS-P (Disease Related Symptoms-Physical) *Score range:* 0-48	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____

Sum individual item scores: _____
Multiply by12: _____
Divide by number of items answered: _____**=FKSI-DRS-P score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FKSI-DRS-E (Disease Related Symptoms-Emotional) score *Score range:* 0-4	GE6	4	-	_____	=_____**=FKSI-DRS-E**
FKSI-TSE (Treatment Side Effects) *Score range:* 0-12	GP2	4	-	_____	=_____
	C5	4	-	_____	=_____
	GP5	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 3: _____
Divide by number of items answered: _____**=FKSI-TSE score**

FKSI-F/WB (Function/ Well-Being) *Score range:* 0-12	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____**=FKSI-F/WB score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix 2 Activity questionnaire Visit 1

CABG CARE
BEWEGUNG IN DER 1. LINIE

Activity Questionnaire
Visit 1

Date: _____

Patient ID:

Signature: _____

Please enter the number of hours you were physically active last week in the box beneath (everyday activities, e.g.; gardening, shopping, travelling on foot or by bike, Sports):

☐ **Hours**

Please enter the number of minutes you spent engaged in sports last week in the box beneath:

☐ **Minutes**

How many of these minutes were...

...Slightly exhausting (possible to talk without any problem while exercising) ☐ **Minutes**

...Somewhat exhausting (partly possible to talk while exercising) ☐ **Minutes**

...Very exhausting (not possible to talk while exercising) ☐ **Minutes**

Please indicate, with a vertical line along the black scale (bar), the place where you assess your level of activity to be. To give an example: A person is asked about their level of activity in the last four weeks. They assess themself as being averagely active. Consequently, they mark an area in the middle of the scale.

Now it is your turn. How do you assess your overall level of physical activity (everyday activity, physical activity at work and sporting activity)...

a)...based on the last week? Not active ——— Very active

b)...based on the last four weeks? Not active ——— Very active

c)...directly before your diagnosis? Not active ——— Very active

d)...directly after your diagnosis? Not active ——— Very active

e)...based on your whole life? Not active ——— Very active

Appendix 3 Activity questionnaire Visit 4, 6, 8 and 10

CABG CARE
BEWEGUNG IN DER 1. LINIE

Activity Questionnaire
Visit 4,6,8,10
Patient ID:

Date: _____
Signature: _____

Please enter the number of **hours** you were physically active last week in the box beneath (everyday activities, e.g.; gardening, shopping, travelling on foot or by bike, Sports):

☐ **Hours**

Please enter the number of **minutes** you spent engaged in sports last week in the box beneath:

☐ **Minutes**

How many of these minutes were...

...Slightly exhausting (possible to talk without any problem while exercising) ☐ **Minutes**

...Somewhat exhausting (partly possible to talk while exercising) ☐ **Minutes**

...Very exhausting (not possible to talk while exercising) ☐ **Minutes**

Please indicate, with a vertical line along the black scale (bar), the place where you assess your level of activity to be. To give an example: A person is asked about their level of activity in the last four weeks. They assess themself as being averagely active. Consequently, they mark an area in the middle of the scale.

Not active — Very active

a)...based on the last week? Not active — Very active

b)...based on the last four weeks? Not active — Very active

c)...based on your whole life? Not active — Very active

Appendix 4 Amendment Form #1

STUDY NUMBER:	A-DE-60000-009
PROTOCOL TITLE:	*CABOCARE*: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #1): 09 April 2021

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**05 SEPTEMBER 2018**	**09 APRIL 2021**
Page	**Section**	**WAS**	**IS**
1	Cover Page	*CABOCARE*: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT **Sponsor's Medically Responsible Person:** PPD IPSEN Pharma GmbH ~~Willy-Brandt-Str. 3~~ ~~76275 Ettlingen~~ – Germany Tel: PPD ~~Fax:~~ PPD **Study Sponsor:** IPSEN Pharma GmbH	*CABOCARE*: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB **AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB** IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT **Sponsor's Medically Responsible Person:** PPD IPSEN Pharma GmbH **Einsteinstrasse 174** **81677 München** – Germany Tel: PPD **Study Sponsor:** IPSEN Pharma GmbH **Einsteinstrasse 174**

		~~Willy Brandt Str. 3~~ ~~76275 Ettlingen~~ Germany Tel: PPD ~~Fax:~~ PPD **Sponsor's Co-ordinating Office/Monitoring Office:** PPD IPSEN Pharma GmbH ~~Willy Brandt Str. 3~~ ~~76275 Ettlingen~~ Germany Tel: PPD ~~Fax:~~ PPD **Pharmacovigilance / Emergency Contact:** PPD IPSEN Pharma GmbH ~~Willy Brandt Str. 3~~ ~~76275 Ettlingen~~ Germany Tel: PPD (24/7 Emergency Mobile Phone) ~~Fax:~~ PPD E-mail: PPD	**81677 München** – Germany Tel: PPD **Sponsor's Co-ordinating Office/Monitoring Office:** PPD IPSEN Pharma GmbH **Einsteinstrasse 174** **81677 München** – Germany Tel: PPD **Pharmacovigilance / Emergency Contact:** IPSEN Pharma GmbH **Einsteinstrasse 174** **81677 München** – Germany 24/7 Emergency Mobile Phone : PPD E-mail: PPD
2	Protocol Signatures	**Investigator Signature:** I have read and agree to the prospective non-interventional study (protocol number: A-DE-60000-009) to evaluate the use of cabozantinib ~~tablets~~ in adult patients with advanced renal cell carcinoma according to licensed indications in 1st line treatment. […] **On behalf of the Sponsor:** NAME: PPD OFFICE: IPSEN Pharma GmbH ~~Willy Brandt Str. 3~~ ~~76275 Ettlingen~~ Germany	**Investigator Signature:** I have read and agree to the prospective non-interventional study (protocol number: A-DE-60000-009) to evaluate the use of cabozantinib **and cabozantinib-nivolumab combination** in adult patients with advanced renal cell carcinoma according to licensed indications in 1st line treatment. […] **On behalf of the Sponsor:** NAME: PPD PPD **OFFICE:** IPSEN Pharma GmbH **Einsteinstrasse 174** **81677 München** – Germany

4	Synopsis (Study Title)	**CABOCARE**: Prospective non-interventional study of **CABO**zantinib in patients with advan**C**ed or metastatic ren**A**l cell carcinoma under **RE**al-Life clinical setting in 1st line treatment	**CABOCARE**: Prospective non-interventional study of **CABO**zantinib **as monotherapy or in combination with nivolumab** in patients with advan**C**ed or metastatic ren**A**l cell carcinoma under **RE**al-Life clinical setting in 1st line treatment
4 and 16	Synopsis (Study Objectives), Section 3.1 and 3.2	Primary objective • To describe the use of Cabometyx™ (cabozantinib) tablets including the number of dose reductions, dose interruptions and terminations due to SAEs/AEs in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score Secondary objectives • To describe the effectiveness of ~~Cabometyx™~~ (cabozantinib tablets in advanced or metastatic RCC in real-life in terms of progression free survival (PFS) and best overall response (Objective Response Rate [ORR] & Disease Control Rate [DCR]) • To describe the use of cabozantinib tablets in real-life clinical setting in 1st line treatment split by histological subtype	Primary objective • To describe the use of Cabometyx™ (cabozantinib) tablets **as monotherapy and the use of Cabometyx™ and Opdivo™ combination (cabozantinib-nivolumab combination)** including the number of dose reductions, dose interruptions and terminations due to SAEs/AEs in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score Secondary objectives • To describe the effectiveness of cabozantinib tablets **as monotherapy and the effectiveness of cabozantinib-nivolumab combination** in advanced or metastatic RCC in real-life in terms of progression free survival (PFS) and best overall response (Objective Response Rate [ORR] & Disease Control Rate [DCR]) • To describe the use of cabozantinib tablets **as monotherapy and the use**

		• To describe all non-serious and serious adverse events (AEs / SAEs) and fatal outcomes	**of cabozantinib-nivolumab combination** in real-life clinical setting in 1st line treatment split by histological subtype • To describe all non-serious and serious adverse events (AEs / SAEs) and fatal outcomes **per drug cohort**
5-6	Synopsis (Rationale)	[…] Outside the setting of strictly controlled clinical studies there is only limited information about the efficacy and safety of cabozantinib in the treatment of ~~subjects~~ with advanced or metastasized renal cell carcinoma. Therefore, this non-interventional study is planned to collect data of cabozantinib usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria.	[…] **Since the start of the CABOCARE study in 2018 the landscape of treatment options for advanced and metastatic RCC has changed as new drugs and drug combinations are available. Due to these new options guidelines recommend only restrictively and no longer as treatment of first choice cabozantinib monotherapy for medium-to-high risk patients as 1st line treatment in mRCC.** **The efficacy and safety of cabozantinib in combination with nivolumab (an anti-PD1 checkpoint inhibitor) as first line therapy in mRCC patients was investigated in the phase 3 CheckMate 9ER study. The combination met all efficacy endpoints and demonstrated superiority over sunitinib in PFS (median PFS 16.6 vs 8.3 month), OS and ORR [IV].** **The combination of cabozantinib plus nivolumab was generally well tolerated, with a low rate of treatment-related discontinuations.** **Furthermore, patients had significantly better quality of life with cabozantinib-nivolumab combination versus sunitinib. [IV]** **The cabozantinib-nivolumab combination was submitted for**

			regulatory approval to EMA. A positive CHMP opinion occurred in February 2021 and the Approval and Marketing Authorization by the European Commission was given on 31.03.2021. **Now as the cabozantinib-nivolumab combination is authorized for the European market, patients treated with this combination can be included in the Cabocare study as second treatment group.** Outside the setting of strictly controlled clinical studies there is only limited information about the efficacy and safety of cabozantinib **or cabozantinib-nivolumab combination** in the treatment of **patients** with advanced or metastasized renal cell carcinoma. Therefore, this non-interventional study is planned to collect data of cabozantinib **and cabozantinib-nivolumab combination** usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria. […] **[IV] T. K. Choueiri *et al.,* ESMO 2020; oral presentation**
6	Synopsis (Study Timelines)	~~It is expected that 105 subjects will be enrolled within a 2-year timeframe.~~ Expected median duration of cabozantinib treatment is approx. 8-9 months for 1st line treatment. Study duration including a 2-year follow-up: ~~Q3 2018 – Q2 2022~~	Expected median duration of cabozantinib treatment is approximately 8-9 months, **expected median duration of cabozantinib-nivolumab treatment is approximately 14 months,** for 1st line treatment **(IV).** Study duration including a 2-year follow-up **was from Q3 2018 – Q2**

			2022 and will be extended. This extension includes a 1-year-enrollment phase (Q2 2021 – Q2 2022) and 2-year follow-up (Q2 2022 - Q2 2024).
6	Synopsis (Study Design)	Prospective German and Austrian multicenter non-interventional study (NIS)	Prospective German and Austrian multicenter non-interventional study (NIS) **with approx. 50 centers in Germany and Austria.**
6 and 20	Synopsis (Study Population) and Section 5.1	Inclusion Criteria (1) Males or females aged 18 years and older with capacity to consent. (2) Subjects receiving cabozantinib as a first line treatment for advanced or metastatic renal cell carcinoma (3) Subjects with the intention to be treated with cabozantinib ~~tablets~~ according to the current ~~local~~ SmPC (~~Germany, Austria~~); decision has to be taken before entry in the study. (4) Signed written informed consent. […] ~~Sample size: 105 subjects from approx. 50 centers in Germany and Austria.~~	Inclusion Criteria (1) Males or females aged 18 years and older with capacity to consent. (2**a**) Subjects receiving cabozantinib **or cabozantinib-nivolumab combination** as a first line treatment for advanced or metastatic renal cell carcinoma (3**a**) Subjects with the intention to be treated with cabozantinib **or cabozantinib-nivolumab combination** according to the current SmPC; decision has to be taken before entry in the study. (4) Signed written informed consent.
6	Synopsis (Study Treatment)	In this non-interventional study, cabozantinib ~~is~~ to be administered as directed by the investigator according to the ~~local SmPC~~ and the study site´s usual clinical practice. The physician should refer to the ~~Cabometyx™ SmPC~~ for any information on the treatment prescribed.	In this non-interventional study, cabozantinib **or cabozantinib-nivolumab combination are** to be administered as directed by the investigator according to the **current SmPCs** and the study site´s usual clinical practice. The physician should refer to the **SmPCs of the study medications** for any information on the treatment prescribed.
6	Synopsis (Study Evaluations)	- **Treatment characteristics:** starting dose ~~of cabozantinib~~, dose reductions, dose	- **Treatment characteristics:** starting dose, dose reductions, dose interruptions, **dose delay**, treatment discontinuation

		interruptions, treatment discontinuation	
7-8	Synopsis (Statistical Methods)	A formal sample size calculation was not done. We ~~intend~~ to include 100 1st line subjects in the analyses, assuming a drop-out rate due to lost to follow-up of 5% 105 subjects ~~have~~ to be enrolled. 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. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval ~~will be~~ respectively 5.9%, 9.6% and 9.0% for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption.	A formal sample size calculation was not done. We **intended** to include 100 1st line subjects in the analyses, assuming a drop-out rate due to lost to follow-up of 5% 105 subjects **had** to be enrolled. In the open-label METEOR **(cabozantinib),** any dose reduction due to an AE occurred in 59.8% of subjects and the study drug was interrupted in 70% of subjects. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval **would have been** respectively 5.9%, 9.6% and 9.0% for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption. **Up to 28 February 2021, 31 subjects were enrolled in the cabozantinib monotherapy group. The landscape of treatment options for advanced and metastatic RCC having changed, cabozantinib monotherapy is only restrictively recommended in guidelines for first line treatment in mRCC patients. Consequently, the treatment group with cabozantinib monotherapy will not be closed but only a limited number of subjects are further expected in this group.** **In the second treatment group with cabozantinib-nivolumab combination, the intent is to include 100 subjects. Assuming a drop-out rate due to lost to follow-up of 5%, 105 subjects have to be enrolled. In the interventional Checkmate 9ER study, dose reduction occurred in**

			56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. **With a sample of 100 subjects, the precision of 2- sided 95% confidence interval will be respectively 7.0% and 9.7% for proportions of 15% of discontinuation and 55% of dose reduction.**
		Data Analysis […] • Full Analysis Set (FAS) / Safety population: all included subjects who have taken at least one dose of ~~cabozantinib~~. […] Primary endpoint will be the descriptive analysis of the use of cabozantinib.	Data Analysis […] • Full Analysis Set (FAS) / Safety population: all included subjects who have taken at least one dose of **study treatment.** […] **All the analyses will be presented separately for each group, cabozantinib monotherapy and cabozantinib in combination with nivolumab.** Primary endpoint will be the descriptive analysis of the use of cabozantinib **and the use of cabozantinib-nivolumab combination.**
12	List of Abbreviations and definition of terms		**MA: Marketing Authorisation**
14-15	2.1		[…] **Since the start of the CABOCARE study in 2018 the landscape of treatment options for advanced and metastatic RCC has changed as new drugs and new drug combinations are available. Due to these new treatment options guidelines recommend only restrictively and no longer as treatment of first choice cabozantinib**

			monotherapy for medium-to-high risk patients as 1st line treatment in mRCC. [16] Therefore, the recruitment of patients with advanced or metastatic RCC who are intended to be treated with Cabozantinib is rare. Based on the current recommendation for the first line treatment of mRCC the planned 100 patients cannot be achieved. **The phase 3 CheckMate 9ER study that compared cabozantinib-nivolumab combination with sunitinib monotherapy, demonstrated superiority over sunitinib in PFS, OS and ORR and met all efficacy endpoints [17].** **The cabozantinib-nivolumab combination was generally well tolerated, with a low rate of treatment-related discontinuations. Furthermore, patients had significantly better quality of life with cabozantinib-nivolumab combination versus sunitinib. [17]** **The cabozantinib-nivolumab combination was submitted for regulatory approval to the EMA. Approval and Marketing Authorization was given on 31.03.2021. As soon as the cabozantinib-nivolumab combination is authorized for the European market, patients who are treated with or intended to be treated with the combination can be included in the Cabocare study as second treatment group. With the inclusion of patients on cabozantinib-nivolumab combination therapy the Cabocare study fulfills state-of-the-art treatment in advanced**

			and metastatic RCC and is enabled to be continued.
15	2.2	Outside the setting of strictly controlled clinical studies there is only limited information about the effectiveness and safety of cabozantinib in the treatment of subjects with advanced or metastasized renal cell carcinoma. Therefore, this non-interventional study is planned to collect data of cabozantinib usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria.	Outside the setting of strictly controlled clinical studies there is only limited information about the effectiveness and safety of cabozantinib **as monotherapy or in combination with nivolumab** in the treatment of subjects with advanced or metastasized renal cell carcinoma. Therefore, this non-interventional study is planned to collect data of cabozantinib/ **cabozantinib-nivolumab combination** usage in a real-life clinical setting taking into account the different prescribing physician groups (clinical oncologists and urologists as well as registered oncologists and urologists) in Germany and Austria.
17	4.1	[…] This study will be conducted in Germany and Austria, which have a cabozantinib tablets Marketing Authorisation ~~for first line use~~. Investigators will follow their individual therapeutic concept for the treatment with cabozantinib ~~tablets~~ in accordance with the current ~~local~~ SmPC. […] If a subject discontinues the intake of cabozantinib ~~tablets~~ at any visit before Visit 10, the follow-up	[…] This study will be conducted in Germany and Austria, which have a cabozantinib tablets Marketing Authorisation **(MA) for first line use. MA for the cabozantinib-nivolumab combination as first line treatment in advanced or metastatic RCC is expected in May 2021. Patients intended to be treated with this combination can be enrolled as soon as the MA is in place for use of these products in the European Union.** Investigators will follow their individual therapeutic concept for the treatment with cabozantinib **or cabozantinib-nivolumab combination** in accordance with the current SmPC. […] If a subject discontinues the intake of cabozantinib **or of cabozantinib-nivolumab**

		period starts and the next visit will be Follow-up 1. ~~If subjects continue until Visit 10, only~~ Follow-up ~~2 has to be performed~~.	**combination** at any visit before Visit 10, the follow-up period starts, and the next visit will be Follow-up 1. **Discontinuation of the cabozantinib-nivolumab combination is defined as the permanent discontinuation of both study medications. i.e. as soon as one of the treatments is still ongoing the combination is not considered as discontinued. The** Follow-up **period can only start once both treatments have been permanently discontinued.**
18	4.2	~~A total of 105 systemic treatment-~~ naïve advanced or metastatic renal cell carcinoma patients ~~in up to 50 study sites~~ in Germany or Austria will be included in this study: males and females aged 18 years and older, with the intention to be treated with cabozantinib ~~tablets~~ according to the current local ~~SmPC~~ taken prior to the entry in the study.	**Treatment**-naïve advanced or metastatic renal cell carcinoma patients in Germany or Austria will be included in this study: males and females aged 18 years and older, with the intention to be treated with cabozantinib **or cabozantinib-nivolumab combination** according to the current local **SmPCs** taken prior to the entry in the study.
18	4.3	Data from ~~105~~ subjects suffering from advanced or metastatic renal cell carcinoma and treated first line with cabozantinib ~~tablets~~ will be collected. Subjects will be treated in accordance with current local ~~SmPC~~ during their participation in this study. No additional assessment or test will be required.	Data from subjects suffering from advanced or metastatic renal cell carcinoma and treated first line with cabozantinib **or cabozantinib-nivolumab combination** will be collected. Subjects will be treated in accordance with current local **SmPCs** during their participation in this study. No additional assessment or test will be required.
18	4.4	[…] - Last subject in (LSI): ~~Q3 2020~~ - Time for recruitment: approx. ~~2~~ years - Last subject visit (~~LSV): Q3 2022~~ - Final clinical study report (CSR): ~~Q3 2023~~	[…] - Last subject in (LSI): **Q2 2022** - Time for recruitment: approx. **4** years - Last subject **last** visit (**LSLV): Q2 2024** - Final clinical study report (CSR): **Q2 2025**

		- Total study duration: ~~5~~ years	- Total study duration: **7** years
20	5	Eligible subjects for this study are systemic treatment-naïve adult subjects with advanced or metastatic renal cell carcinoma, scheduled to be treated with cabozantinib ~~tablets~~ prior to entry in the study. It is planned to include ~~a total of~~ 105 subjects ~~in this study~~.	Eligible subjects for this study are systemic treatment-naïve adult subjects with advanced or metastatic renal cell carcinoma, scheduled to be treated with cabozantinib **or Cabozantinib-nivolumab combination** prior to entry in the study. **Currently 31 subjects are treated with cabozantinib in monotherapy.** It is planned to include 105 subjects **treated with cabozantinib-nivolumab combination**.
22	6.1	*[Table 1 updated]* **Assessment / Procedure column:** Cabozantinib regimen Concomitant medication Post Cabozantinib systemic treatment for RCC	*[Table 1 updated]* **Assessment / Procedure column:** Cabozantinib **/ cabozantinib-nivolumab** regimen Concomitant medication **for AEs** Post cabozantinib **/ cabozantinib-nivolumab** systemic treatment for RCC
24-25	6.2	Visits 2/3/5/7/9 - (about 4, 8, 16, 32 and 48 weeks, respectively, after baseline) • Visit date • ~~First intake of cabozantinib (Dose and date; only at Visit 2)~~ • Evaluation of tumour (Overall response~~, not at Visit 2~~) • ECOG Performance Status • Vital Signs (Body weight, blood pressure) • Adverse Events • Concomitant medication • Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation)	Visits 2/3/5/7/9 - (about 4, 8, 16, 32 and 48 weeks, respectively, after baseline) • Visit date • Evaluation of tumour (Overall response) • ECOG Performance Status • Vital Signs (Body weight, blood pressure) • Adverse Events • Concomitant medication **for AEs** • Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation) • **Nivolumab regimen (dose and date of injection, reason for injection delayed if any and primary reason for nivolumab discontinuation)**

		[…] Visits 4/6/8/10 - (about 12, 24, 40 and 56 weeks, respectively, after baseline): • Evaluation of tumour (Overall response, ~~not at visit 4~~) • ECOG Performance Status • Adverse Events • Concomitant medication for AEs • Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation). […] Follow-up visit (FU) 1 - (about 30 days after treatment discontinuation): • Visit date • Adverse Events • Concomitant medication for AEs • Post Cabozantinib systemic treatment for RCC […] Follow-up visit (FU) 2 - (1 year after treatment discontinuation or 24 months after visit 1): • Visit date • Adverse Events	[…] Visits 4/6/8/10 - (about 12, 24, 40 and 56 weeks, respectively, after baseline): • Evaluation of tumour (Overall response) • ECOG Performance Status • Adverse Events • Concomitant medication for AEs • Cabozantinib regimen (Start date, stop date, dose, frequency, time of day of intake, primary reason for dose change or discontinuation). • **Nivolumab regimen (dose and date of injection, reason for injection delayed if any and primary reason for nivolumab discontinuation)** […] Follow-up visit (FU) 1 - (about 30 days after treatment discontinuation): • Visit date • Adverse Events • Concomitant medication for AEs • Post Cabozantinib / **cabozantinib-nivolumab combination** systemic treatment for RCC […] Follow-up visit (FU) 2 - (1 year after treatment discontinuation or 24 months after visit 1): • Visit date • Adverse Events • Concomitant medication for AEs

		• Concomitant medication for AEs • Post Cabozantinib systemic treatment for RCC • Cabozantinib regimen (dose and date for last cabozantinib intake; only for patients who continued until visit 10)	• Post Cabozantinib **/cabozantinib-nivolumab combination** systemic treatment for RCC • Cabozantinib regimen (dose and date for last cabozantinib **intake; only for patients who continued until visit 10)** • **Cabozantinib-nivolumab combination regimen (dose and date for last cabozantinib and nivolumab** intake; only for patients who continued until visit 10)
26	7.1.1	The primary endpoints are to describe the use of cabozantinib ~~tablets~~ in terms of: - number and proportion of subjects with dose reduction due to SAEs/AEs, - number and proportion of subjects with dose interruption due to SAEs/AEs - number and proportion of subjects with termination of Cabozantinib due to SAEs/AEs in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score.	The primary endpoints are to describe the use of cabozantinib **/cabozantinib-nivolumab combination** in terms of: - number and proportion of subjects with dose reduction **of cabozantinib** due to SAEs/AEs, - number and proportion of subjects with dose interruption **of cabozantinib and/or nivolumab** due to SAEs/AEs - number and proportion of subjects with termination of cabozantinib **/cabozantinib-nivolumab combination** due to SAEs/AEs - **injection delayed of nivolumab due to SAE/AE** in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment overall and split by risk score.
27	7.1.2	• To describe the effectiveness of cabozantinib ~~tablets~~ in advanced or metastatic RCC in real-life in terms of progression free survival	• To describe the effectiveness of cabozantinib **/cabozantinib-nivolumab combination** in advanced or metastatic RCC in real-life in terms of progression

		(PFS), and best overall response (ORR & DCR). - Progression free survival is defined as the time between the start date of cabozantinib and the date of progression or death from any cause. Disease progression is defined as either radiological progression assessed by the investigator using RECIST 1.1 [7] or clinical progression.	free survival (PFS), and best overall response (ORR & DCR). - Progression free survival is defined as the time between the start date of cabozantinib **/cabozantinib-nivolumab combination** and the date of progression or death from any cause. Disease progression is defined as either radiological progression assessed by the investigator using RECIST 1.1 [7] or clinical progression.
		[…] • To describe the impact of the activity level at the beginning of the treatment (within the first 2 weeks of Cabozantinib intake) on the occurrence of adverse events (AEs) using the actigraph and questionnaires • To describe the use of cabozantinib ~~tablets~~ in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment split by histological subtype (clear cell and non-clear cell) in terms of: o Number and proportion of subjects with dose reductions due to SAEs/AEs o Number and proportion of subjects with dose	[…] • To describe the impact of the activity level at the beginning of the treatment (within the first 2 weeks of cabozantinib **/cabozantinib-nivolumab combination** intake) on the occurrence of adverse events (AEs) using the actigraph and questionnaires • To describe the use of cabozantinib **/cabozantinib-nivolumab combination** in subjects with advanced or metastatic renal cell carcinoma (mRCC) treated in real-life clinical setting in 1st line treatment split by histological subtype (clear cell and non-clear cell) in terms of: o Number and proportion of subjects with dose reductions **of**

		interruption due to SAEs/AEs o Number and proportion of subjects with termination of cabozantinib due to SAEs/AEs	**cabozantinib** due to SAEs/AEs o Number and proportion of subjects with dose interruption **of cabozantinib and/or nivolumab** due to SAEs/AEs o Number and proportion of subjects with termination of cabozantinib **/cabozantinib-nivolumab combination** due to SAEs/AEs**Number and proportion of subjects with injection delayed of nivolumab due to SAEs/AEs**
28	8	The decision to prescribe cabozantinib ~~tablets~~ will be made prior to and independently from the decision to enrol the subject in this non-interventional study and the treatment should follow the current local SmPC.	The decision to prescribe cabozantinib **/cabozantinib-nivolumab combination** will be made prior to and independently from the decision to enrol the subject in this non-interventional study and the treatment should follow the current local SmPC.
28	9.1	• **Enrolled subject:** Subject who has signed informed consent to participate. • **Treated subject:** Enrolled subject who received ~~cabozantinib tablets~~ at least once during the study. • ~~**Withdrawn subject:** Subject who did not complete the Follow-up 2 visit.~~	• **Enrolled subject:** Subject who has signed informed consent to participate. • **Treated subject:** Enrolled subject who received **study treatment** at least once during the study.
28	9.2	• **Full Analysis Set (FAS) / Safety population:** All enrolled subjects who have	• **Full Analysis Set (FAS) / Safety population:** All enrolled subjects who have received at least one dose of **study treatment**

		received at least one dose of ~~cabozantinib tablets~~.	**(cabozantinib for mono or cabozantinib and nivolumab for combination treatment).**
28	9.3	A formal sample size calculation was not done. We ~~intend~~ to include 100 1st line subjects in the analyses, assuming a drop-out rate due to lost to follow-up of 5% 105 subjects ~~have~~ to be enrolled. 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. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval ~~will be~~ respectively 5.9%, 9.6% and 9.0% for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption.	A formal sample size calculation was not done. We **intended** to include 100 1st line subjects in the analyses, assuming a drop-out rate due to lost to follow-up of 5% 105 subjects **had** to be enrolled. In the open-label METEOR **(cabozantinib),** any dose reduction due to an AE occurred in 59.8% of subjects and the study drug was interrupted in 70% of subjects. The rate of treatment discontinuation due to an AE was 9.7% for subjects treated with cabozantinib. With a sample of 100 subjects, the precision of 2-sided 95% confidence interval **would have been** respectively 5.9%, 9.6% and 9.0% for proportions of 10% of discontinuation, 60% of dose reduction and 70% of interruption. **Up to 28 February 2021, 31 subjects were enrolled in the cabozantinib monotherapy group. The landscape of treatment options for advanced and metastatic RCC having changed, cabozantinib monotherapy is only restrictively recommended in guidelines for first line treatment in mRCC patients. Consequently, the treatment group with cabozantinib monotherapy will not be closed but only a limited number of subjects are further expected in this group.** **In the second treatment group with cabozantinib-nivolumab combination, the intent is to include 100 subjects. Assuming a drop-out rate due to lost to follow-up of 5%, 105 subjects have to be enrolled. In the**

			interventional Checkmate 9ER study, dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. **With a sample of 100 subjects, the precision of 2- sided 95% confidence interval will be respectively 7.0% and 9.7% for proportions of 15% of discontinuation and 55% of dose reduction.**
29	9.4	[…]	[…] **All the analyses will be presented separately for each group, cabozantinib monotherapy and cabozantinib in combination with nivolumab.**
30	9.4.4.1	The proportion of subjects with ≥1 dose reduction due to AE will be described with its 95% confidence interval, by risk group and overall. The same analysis will be presented for the proportion of subjects with ≥1 dose interruption and discontinuation due to AE.	The proportion of subjects with ≥1 dose reduction **of cabozantinib** due to AE will be described with its 95% confidence interval, by risk group and overall. The same analysis will be presented for the proportion of subjects with ≥1 dose interruption **of cabozantinib and/or nivolumab, delayed dose injection of nivolumab** and discontinuation **of cabozantinib and/or nivolumab** due to AE.
30	9.4.4.2	[…] The progression free survival, defined as time from cabozantinib initiation to disease progression or death will be analysed using standard survival analysis methods including Kaplan-Meier product-limit survival curve.	[…] The progression free survival, defined as time from cabozantinib **/cabozantinib-nivolumab combination** initiation to disease progression or death will be analysed using standard survival analysis methods including Kaplan-Meier product-limit survival curve.
30	9.4.4.3	The evolution of activity level and quality of life between baseline and each time point (W12, W24, W40 and W56) will be described overall and also according to occupational and smoking status at initiation of	The evolution of activity level and quality of life between baseline and each time point (W12, W24, W40 and W56) will be described overall and also according to occupational and smoking status at initiation of

		cabozantinib in centers where this is part of the clinical routine.	Cabozantinib **/cabozantinib-nivolumab combination** in centers where this is part of the clinical routine.
30-31	9.4.6	Analyses and summary tables will be presented on the 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, treatment emergent AEs (TEAEs), SAEs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum grading 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. Adverse events will also be described by level of physical activity. 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. Summary statistics will be presented for ECOG performance status and weight at each visit.	Analyses and summary tables will be presented on the Safety population **(by cabozantinib monotherapy and cabozantinib-nivolumab combination therapy)**. 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, treatment emergent AEs (TEAEs), SAEs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum grading and drug relationship. Treatment emergent AEs associated with dose modification (temporary interruption, reduction or discontinuation) of **cabozantinib** and TEAEs leading to cabozantinib temporary dose interruption, reduction or discontinuation will also be summarised separately. **Similarly, TEAEs associated with delayed dose injection, temporary interruption or discontinuation of nivolumab will be presented.** Adverse events will also be described by level of physical activity. A TEAE is defined as any AE that occurs during the administration of cabozantinib **/cabozantinib-nivolumab combination** if**:** • It was not present prior to receiving the first dose of cabozantinib **/cabozantinib-**

		Changes from baseline to each postbaseline assessment will be summarised similarly.	**nivolumab combination;** or • It was present prior to receiving the first dose of cabozantinib /**cabozantinib-nivolumab combination** but the intensity increased during treatment with cabozantinib /**cabozantinib-nivolumab combination**. Summary statistics will be presented for ECOG performance status and weight at each visit. Changes from baseline to each postbaseline assessment will be summarised similarly.
31	9.5	All the analyses will be provided by risk score. Primary endpoint will be presented by risk score and histological subtype.	All the analyses will be provided by risk score. Primary endpoint will be presented by risk score and histological subtype. **All analyses will be performed by treatment cohort.**
31	9.6	One interim analysis is planned and will be performed, when 50% of the ~~enrolled~~ subjects have completed cabozantinib treatment.	One interim analysis is planned and will be performed, when 50% of the **targeted (100)** subjects have completed cabozantinib-**nivolumab combination** treatment. **This interim analysis will present the results of the cabozantinib-nivolumab combination and the until this timepoint available cabozantinib monotherapy patient data.**
34	10.2.1	All safety reports, whether they are serious/nonserious, related/not related, should be collected by the investigator in the study source document during the course of the study.	All safety reports, whether they are serious/nonserious, related/not related, should be collected **separately for carbozantinib and nivolumab and for combination therapy** by the investigator in the study source document during the course of the study.
35	10.2.2	As back-up when eCRF is not available information can be provided to Ipsen on AE Report Form ([redacted]) which can be	As back-up when eCRF is not available information can be provided to Ipsen on AE Report Form ([redacted]) which can be

		either e-mailed to the above-mentioned addresses or Fax: PPD […] 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 of the suspected medicinal product, but not both (to avoid duplicate reporting).	either e-mailed to the above-mentioned addresses or Fax: PPD […] If related AEs (i.e. adverse reactions) occur with "non Ipsen products" **(except Nivolumab)**, the investigator should inform the competent authority in the Member State where the reactions occurred or the marketing authorisation holder of the suspected medicinal product, but not both (to avoid duplicate reporting).
36	10.3.1	The following definitions should be considered when evaluating a causal relationship between the study treatment and an AE	The following definitions should be considered when evaluating a causal relationship between the study treatment and an AE, **assessed separately for each product**
44	15		**[16] Escudier B et al. : Renal cell carcinoma : ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 30: 706 – 720, 2019 + eUpdates** **[17] T. K. Choueiri et al., ESMO 2020; oral presentation**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	A-DE-60000-009	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final (including Amendment #1): 09 April 2021	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	- Main change of the protocol amendment #1 is linked to the extention of study population (to include patients treated on combination of Cabozantinib and Nivolumab following marketing authorisation) and extension of recruitment period.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 5 Amendment Form #2

STUDY NUMBER:	A-DE-60000-009
PROTOCOL TITLE:	*CABOCARE*: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT
AMENDED PROTOCOL VERSION NUMBER & DATE	**Final Version 3.0 (including Amendment #2): 05 August 2022**

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date	**09 APRIL 2021**	**05 AUGUST 2022**	**Brief Rationale**
Section	**Was**	**Is**	
1 Cover Page	Sponsor's Medically Responsible Person: PPD IPSEN Pharma GmbH Einsteinstrasse 174 81677 München – Germany Tel: PPD **Study Sponsor:** IPSEN Pharma GmbH ~~Willy Brandt Str. 3~~ ~~76275 Ettlingen~~ Germany Tel: PPD ~~Fax:~~ PPD	Sponsor's Medically Responsible Person: PPD IPSEN Pharma GmbH Einsteinstrasse 174 81677 München – Germany Tel: PPD **Study Sponsor:** IPSEN Pharma GmbH **Einsteinstrasse 174** **81677 München – Germany** Tel: PPD	Change of the sponsor's medically responsible person and sponsor signatory (name and address)
Synopsis (Study Timelines)	Expected median duration of cabozantinib treatment is approximately 8-9 months,	Expected median duration of cabozantinib treatment is approximately 8-9 months,	Extension of the recruitment period to allow appropriate

	expected median duration of cabozantinib-nivolumab treatment is approximately 14 months, for 1st line treatment (IV). Study duration including a 2-year follow-up was from Q3 2018 – Q2 2022 and will be extended. This extension includes a ~~1~~-year-enrollment phase (Q2 ~~2021~~ – Q2 ~~2022~~) and 2-year follow-up (Q2 ~~2022~~ - Q2 ~~2024~~).	expected median duration of cabozantinib-nivolumab treatment is approximately 14 months, for 1st line treatment (IV). Study duration including a 2-year follow-up was from Q3 2018 – Q2 2022 and will be extended. This extension includes a **2**-year-enrollment phase (Q2 **2022** – Q2 **2024**) and 2-year follow-up (Q2 **2024** - Q2 **2026**).	recruitment of patients treated with the combination of Cabozantinib and Nivolumab
Section 4.4 Study Duration	[…] - Last subject in (LSI): Q2 ~~2022~~ - Time for recruitment: approx. ~~4~~ years - Last subject last visit (LSLV): Q2 ~~2024~~ - Final clinical study report (CSR): Q2 ~~2025~~ Total study duration: ~~7~~ years	[…] - Last subject in (LSI): Q2 **2024** - Time for recruitment: approx**. 6** years - Last subject last visit (LSLV): Q2 **2026** - Final clinical study report (CSR): Q2 **2027** Total study duration: **9** years	Updated to reflect the extension of the recruitment period
Section 10.2.1 Collection of Safety reports	All safety reports, whether they are serious/nonserious, related/not related, should be **collected** separately for carbozantinib and nivolumab and for combination therapy by the investigator in the study source document during the course of the study.	All safety reports, whether they are serious/nonserious, related/not related, should be **collected** separately for carbozantinib and nivolumab **monotherapy** and for combination therapy by the investigator in the study source document during the course of the study.	Updated to provide clarification

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	A-DE-60000-009	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Final (including Amendment #2): 05 August 2022**	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	This amendment aimed to: Extend the study recruitment for another 24 months, until April 2024	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*
	LOCAL INFORMED CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 6 Amendment Form #3

STUDY NUMBER:	A-DE-60000-009
PROTOCOL TITLE:	*CABOCARE*: PROSPECTIVE NON-INTERVENTIONAL STUDY OF CABOZANTINIB AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA UNDER REAL-LIFE CLINICAL SETTING IN 1ST LINE TREATMENT
AMENDED PROTOCOL VERSION NUMBER & DATE	**Final Version 4.0 (including Amendment #3): 27 November 2023**

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date	**05 AUGUST 2022**	**27 NOVEMBER 2023**	**Brief Rationale**
Section	**Was**	**Is**	
Cover Page	Sponsor's Medically Responsible Person: PPD IPSEN Pharma GmbH Einsteinstrasse 174 81677 München – Germany Tel: PPD	Sponsor's Medically Responsible Person: PPD IPSEN Pharma GmbH Einsteinstrasse 174 81677 München – Germany Tel: PPD	Change of the sponsor's medically responsible person
Protocol Signatures	On behalf of the Sponsor: NAME : PPD PPD TITLE : PPD	On behalf of the Sponsor: NAME : PPD TITLE : PPD	Change of the sponsor signatory (name and address)
Synopsis (Study Timelines)	[…]	[…]	Extension of the recruitment period to

	Study duration including a 2-year follow-up was from Q3 2018 – Q2 202~~2~~ and will be extended. This extension includes a ~~2~~-year-enrollment phase (Q2 202~~2~~ – Q2 202~~4~~) and 2-year follow-up (Q2 202~~4~~ - Q2 202~~6~~).	Study duration including a 2-year follow-up was from Q3 2018 – Q2 202**6** and will be extended. This extension includes a **1**-year-enrollment phase (Q2 **2024** – Q2 **2025**) and 2-year follow-up (Q2 **2025** - Q2 **2027**).	allow appropriate recruitment of patients treated with the combination of Cabozantinib and Nivolumab and increase statistic power
Synopsis (Statistical Methods)	[…] In the second treatment group with cabozantinib-nivolumab combination, the intent is to include ~~100~~ subjects. Assuming a drop-out rate due to lost to follow-up of 5%, ~~105~~ subjects have to be enrolled. In the interventional Checkmate 9ER study, dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of ~~100~~ subjects, the precision of 2- sided 95% confidence interval will be respectively ~~7.0~~% and ~~9.7~~% for proportions of 15% of discontinuation and 55% of dose reduction.	[…] In the second treatment group with cabozantinib-nivolumab combination, the intent is to include **167** subjects. Assuming a drop-out rate due to lost to follow-up of 5%, **175** subjects have to be enrolled. In the interventional Checkmate 9ER study, dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of **167** subjects, the precision of 2- sided 95% confidence interval **(based on simple asymptotic method)** will be respectively **5.4**% and **7.5**% for proportions of 15% of discontinuation and 55% of dose reduction.	Updated to reflect the planned study population

Section 4.4 Study Duration	Planned duration: First subject in (FSI): Q3 2018 Last subject in (LSI): Q2 ~~2024~~ Time for recruitment: approx. ~~6~~ years Last subject last visit (LSLV): Q2 ~~2026~~ Final clinical study report (CSR): Q2 ~~2027~~ Total study duration: ~~9~~ years Subject participation duration: 2 years	Planned duration: First subject in (FSI): Q3 2018 Last subject in (LSI): Q2 **2025** Time for recruitment: approx. **7** years Last subject last visit (LSLV): Q2 **2027** Final clinical study report (CSR): Q2 **2028** Total study duration: **10** years Subject participation duration: 2 years	Updated to reflect the expanded study duration
Section 5 Study Population	Eligible subjects for this study are systemic treatment-naive adult subjects with advanced or metastatic renal cell carcinoma, scheduled to be treated with cabozantinib or Cabozantinib-nivolumab combination prior to entry in the study. Currently ~~31~~ subjects are treated with cabozantinib in monotherapy. It is planned to include ~~105~~ subjects treated with cabozantinib-nivolumab combination.	Eligible subjects for this study are systemic treatment-naive adult subjects with advanced or metastatic renal cell carcinoma, scheduled to be treated with cabozantinib or Cabozantinib-nivolumab combination prior to entry in the study. Currently **35** subjects are treated with cabozantinib in monotherapy. It is planned to include **175** subjects treated with cabozantinib-nivolumab combination.	Updated to reflect the current and planned study population

Section 9.3 Sample Size Determination	[…] In the second treatment group with cabozantinib-nivolumab combination, the intent is to include ~~100~~ subjects. Assuming a drop-out rate due to lost to follow-up of 5%, ~~105~~ subjects have to be enrolled. In the interventional Checkmate 9ER study dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of ~~100~~ subjects, the precision of 2- sided 95% confidence interval will be respectively ~~7.0~~% and ~~9.7~~% for proportions of 15% of discontinuation and 55% of dose reduction. Furthermore, adverse events occurring with a probability of at least 1% will be detected with a probability of at least ~~63~~%.	[…] In the second treatment group with cabozantinib-nivolumab combination, the intent is to include **167** subjects. Assuming a drop-out rate due to lost to follow-up of 5%, **175** subjects have to be enrolled. In the interventional Checkmate 9ER study dose reduction occurred in 56.3% of the subjects. The rate of treatment discontinuation of cabozantinib or nivolumab due to an AE was 15.3%. With a sample of **167** subjects, the precision of 2- sided 95% confidence interval **(based on simple asymptotic method)** will be respectively **5.4**% and **7.5**% for proportions of 15% of discontinuation and 55% of dose reduction. Furthermore, **with 167 subjects** adverse events occurring with a probability of at least 1% will be detected with a probability of at least **81**%.	Updated to reflect the planned study population
Section 9.6 Interim Analysis	One interim analysis is planned and will be performed, when 50% of the targeted (100) subjects have completed cabozantinib-nivolumab	One interim analysis is planned and will be performed, when **the first** 50 subjects have completed cabozantinib-nivolumab combination treatment. This interim analysis will present the results of the cabozantinib-nivolumab	Updated to reflect the planned study population

	combination treatment. This interim analysis will present the results of the cabozantinib-nivolumab combination and the until this timepoint available cabozantinib monotherapy patient data.	combination and the until this timepoint available cabozantinib monotherapy patient data.	

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	A-DE-60000-009	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Final (including Amendment #3): 27 November 2023**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	This amendment aimed to: • Increase the study population within the Cabozantinib + Nivolumab combination arm to 175 subjects. • Extend the study recruitment for another 12 months, until April 2025	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*
	LOCAL INFORMED CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*