TITLE:
CABOLIFE: A PROSPECTIVE NON-INTERVENTIONAL STUDY ON EFFECTIVENESS AND SAFETY OF CABOZANTINIB IN REAL-LIFE SETTING FOR PREVIOUSLY TREATED PATIENTS WITH NEUROENDOCRINE TUMOURS

STUDY PROTOCOL
STUDY NUMBER: CLIN-60000-467

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the CLIN-60000-467 entitled "CaboLife: A Prospective Non-Interventional Study on effectiveness and safety of Cabozantinib in Real-Life setting for previously treated patients with Neuroendocrine Tumours". I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices, any regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: 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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DATE : 05-Aug-2025

SYNOPSIS

Study Title	**CaboLife**: A Prospective Non-Interventional Study on effectiveness and safety of **Cabo**zantinib in Real-**Life** setting for previously treated patients with Neuroendocrine Tumours
Study Objectives	Primary objective • To describe the effectiveness of cabozantinib tablets in participants with previously treated neuroendocrine tumours (NET) in real-life in terms of disease control rate (DCR) at 6 months of cabozantinib treatment as investigated by the treating physician. Secondary objectives • To describe the objective response rate (ORR) as assessed by the treating physician. • To describe health-related quality of life (hrQoL) over the course of cabozantinib treatment. • To describe the safety of cabozantinib by review of all non-serious, drug-related and serious adverse events (AEs). • To describe cabozantinib dosage adjustment and schedule. • To describe the duration of treatment (DoT) with cabozantinib. • To describe subsequent therapies following cabozantinib. • To describe the potential impact of cabozantinib treatment on NET biomarkers. • To describe the time to next treatment (TTNT) for cabozantinib. • To describe the progression free survival (PFS). Exploratory objectives • To describe supporting measures. • To describe potential correlations between effectiveness outcomes or quality of life and occurrence of AEs, dose reduction or supportive measures.
Rationale	Neuroendocrine tumours (NETs) are rare, heterogeneous neoplasms originating from cells of the diffuse neuroendocrine system. They can arise in various organs, most commonly in the gastrointestinal tract, pancreas, and lungs. Based on differentiation and proliferation rate, NETs are classified into grades 1 to 3, with grade 3 tumours showing higher proliferative activity. Gastroenteropancreatic NETs (GEP-NETs) account for the majority of cases, while lung-NETs are the most frequent non-GEP-NETs. Treatment strategies vary depending on tumour location, grade, and other clinical factors, and include somatostatin analogues, targeted therapies, peptide receptor radionuclide therapy (PRRT), and chemotherapy. Cabozantinib is a multi-tyrosine kinase inhibitor targeting mesenchymal-epithelial transition

	factor (c-MET), vascular endothelial growth factor receptor (VEGFR), AXL (from Greek *anexelekto* ≙ uncontrolled), and other kinases involved in tumour progression. It has been approved in the European Union (EU) for several indications, including renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid carcinoma. In 2025, cabozantinib received EU approval for the treatment of unresectable or metastatic, well differentiated pancreatic (pNET) and extra-pancreatic NET (epNET) who have progressed following at least one prior systemic therapy other than somatostatin analogues. In the phase III CABINET trial, cabozantinib significantly prolonged progression-free survival (PFS) compared to placebo in patients with advanced, well-differentiated pNET and epNET, with median PFS of 13.8 and 8.4 months, respectively. This non-interventional study aims to evaluate the real-world effectiveness and safety of cabozantinib in patients with NETs. It will also assess the impact of dose modifications on treatment duration, explore quality of life outcomes, and collect data on prior and subsequent therapies.
Study Timelines	Expected median duration of cabozantinib treatment derives from mPFS in the CABINET trial with 8.4 months for epNET patients and 13.8 months for pNET patients. It is expected that patients visit their physician approximately every 3 months as standard of care. All recruited patients are planned to enter an 18-month observational phase: • For participants who stop cabozantinib treatment during the first 15 months of the observational period, a follow-up visit will be conducted 3 months after the stop of cabozantinib. • For participants without discontinuation of cabozantinib, study will be completed after 18 months of observational period. Study will be conducted from Q4 2025 until Q4 2028. Recruitment period will be 18 months from Q4 2025 until Q2 2027. Planned First Participant First Visit: Q4 2025. Planned Last Participant Last Visit: Q4 2028. Planned final report: Q4 2029. Three interim analyses are planned for this non-interventional study: 1. Interim analysis 1 (IA1): The first interim analysis is planned to be conducted in Q3 2026, expecting about one third of the target sample size (~ 50 participants) to be enrolled. It will evaluate data from Visit 1 (Baseline) with a focus on participant characteristics and NETs medical history. 2. Interim analysis 2 (IA2): The second interim analysis is planned to be conducted in Q2 2027, expecting about half of the target sample size (~ 75 participants) to be enrolled. It will evaluate data based on Visit 5 (Month 6) and will focus on effectiveness data, Quality of Life (QoL) and safety.

	3. Interim analysis 3 (IA3): The third interim analysis is planned to be conducted in Q1 2028, when full recruitment is expected. Updates on IA2 evaluations will be given as well as analyses on later endpoints and will focus on effectiveness data and post-cabozantinib therapies.
Study Design:	International, multicentre, non-interventional, prospective, single-arm study conducted at up to 50 sites in Germany and Austria.
Study Population:	150 adult participants in Austria and Germany who are prescribed cabozantinib tablets for unresectable or metastatic, well-differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues prior to entry into the study will be included. **Inclusion Criteria** 1. Aged ≥18 years with capacity to consent. 2. Physician-initiated decision to treat with cabozantinib for NET (prior to study enrolment) according to Summary of product characteristics (SmPC). 3. Signed written informed consent. **Exclusion Criteria** 1. Participation in an interventional trial at the same time and/or within 3 months before baseline. 2. Contraindication for cabozantinib treatment according to SmPC.
Study Treatment:	This is a non-interventional study. The medicinal product cabozantinib is prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a study protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and good pharmaco-epidemiological practices and statistical principles for clinical trials (ICH E9) are used for the analysis of collected data.

Study Evaluations:	All endpoints will be assessed under real-world conditions. Primary endpoint • DCR: proportion of participants who within 6 months achieve complete response (CR), partial response (PR) or stable disease (SD) determined based on radiographic assessments between the date of the first dose of cabozantinib until the date of progressive disease (PD) or date of subsequent therapy. Disease response definitions: **CR**: Complete resolution of all visible disease. **PR**: Partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease. Captures a decrease in disease volume even though disease is still present. **SD**: No change in overall size of visible disease. Also includes cases where some lesions increased in size and some lesions decreased in size. **PD**: Increase in visible disease and/or presence of any new lesions. Includes cases where the clinician indicates PD or progression of disease as the overall assessment. Secondary Endpoints • ORR: proportion of participants who achieve CR or PR determined based on radiographic assessments between the date of the first dose of cabozantinib and the date of PD or date of subsequent therapy. • Patient-reported outcome questionnaire (EORTC QLQ-C30) QLQ-C30 global and subscale scores for each visit at which hrQoL was assessed. • QLQ-GINET21 subscale scores for each visit at which hrQoL was assessed for GI-NET participants. • Incidence of all AEs, all nonserious, drug-related AEs and all serious AEs, overall and by grade and causality. • Frequency of dose interruptions, dose reductions and treatment discontinuations, specifically due to AEs. • DoT: defined as the time from first dose until last dose of cabozantinib. • Frequency overall and by type of therapy switch (defined as permanent discontinuation of cabozantinib treatment within the cabozantinib treatment phase and start of a next line of treatment (LoT) as well as nature of next LoT). . • DCR of next LoT: proportion of participants who achieve CR, PR or SD determined based on routine radiographic response assessments approx. 3 months after switch to next line of therapy after cabozantinib. • Evolution of NET biomarkers such as Chromogranin A (CgA) and Neuron-Specific Enolase (NSE) during the treatment period.

	• TTNT, defined as time from first dose of cabozantinib until first dose of subsequent therapy. • PFS during cabozantinib treatment phase, defined as time from first intake of cabozantinib until PD (as assessed by the investigator per radiological and/or clinical tumour assessment) or death from any cause, whichever occurs first. • Rate of progression-free survival at 12 months and 18 months. <u>Exploratory endpoints</u> • Assessment of nature and proportion of participants receiving the different measures at each visit these measures were assessed.. • Assessment of a potential correlation between the investigated parameters, specifically: - Effectiveness outcomes and occurrence of AEs. - Effectiveness outcomes and dose reduction. - HrQoL and dose reduction. - HrQoL and supporting measures. - Supportive measures and DoT/treatment discontinuation due to AEs. - Dose reduction and DoT. - HrQoL and DoT.
Statistical Methods:	Based on the feasibility evaluation, it was estimated that 150 participants in approximately 50 sites could be enrolled in this study. No power calculations have been performed since this is a non-interventional study with a descriptive objective. Assuming a dropout rate of 10%, 135 patients will be evaluable for the primary endpoint (DCR). With a sample size of 135 participants, a two-sided 95% confidence interval (CI) for a sample proportion using the normal approximation will extend to ±7.5% from the observed proportion for an expected DCR of 73% (145/198), based on the CABINET study with both pNET (51/64) and epNET (94/134) cohorts pooled. In this 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, two-sided 95% CI 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 (StD), minimum, median, quartiles, maximum for continuous variables, and counts and percentages of each category for categorical nominal variables. The primary endpoint will be DCR of cabozantinib-treated NET participants; the rate of disease control will be presented with the 95% CI. Secondary endpoints, i.e. ORR, QoL, safety and DCR of

	subsequent treatment, and DoT (time from the first to the last day of treatment with cabozantinib), as well as TTNT will be presented descriptively. The Kaplan-Meier method will be used to obtain the estimates of median PFS (time between the start of treatment with cabozantinib until progression assessed clinically or via imaging as observed by the treating physician or death from any cause) and their associated two-sided 95% CIs or landmark 12-month and 18-month PFS. Descriptive summary statistics of demographic and baseline data (including NET medical history, characteristics of NET at start of cabozantinib, NET-specific concomitant medication and previously received therapies for NET) will be presented for the Full Analysis Set population. Subgroup analyses are only performed if data permit. Subgroups may be merged into larger subgroups if deemed necessary. The following subgroups are defined: Subgroups NET localisation • LungNET. • GI-NET. • pNET. • Other NET.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (classification)
CA	Competent Authorities
CgA	Chromogranin A
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DoT	Duration of Treatment
DTC	Differentiated Thyroid Carcinoma
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
epNET	Extra Pancreatic Neuroendocrine Tumour
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organisation for Research and Treatment of Cancer
EoS	End of Study
ESMO	European Society For Medical Oncology
EU	European Union
FAS	Full Analysis Set
FU	Follow-Up
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumour
GI	Gastrointestinal
GI-NET	Gastrointestinal Neuroendocrine Tumour
GPP	Good Pharmacoepidemiology Practices
HCC	Hepatocellular Carcinoma
HrQoL	Health-related Quality of Life
ICF	Informed Consent Form
IEC	Independent Ethics Committees
LoT	Line of Treatment
MedDRA	Medical Dictionary for Regulatory Activities
NEC	Neuroendocrine Carcinoma

NEN	Neuroendocrine Neoplasm
NET	Neuroendocrine Tumour
NSE	Neuron-specific Enolase
Non-GEP-NET	Non Gastroenteropancreatic Neuroendocrine Tumour
ORR	Objective Response Rate
pNET	Pancreatic Neuroendocrine Tumour
PFS	Progression-Free Survival
PI	Package Insert
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
PSP	Patient Support Program
PT	Preferred Term
QLQ-C30	Core Quality of Life Questionnaire (EORTC)
QLQ-GINET	Quality of Life Questionnaire module for GI-NET patients (EORTC)
QoL	Quality of Life
RECIST 1.1	Response Evaluation Criteria in Solid Tumours 1.1
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI-NET	Small Intestine Neuroendocrine Tumour
SAS®	Statistical Analysis System®
SSA	Somatostatin Analogue
SD	Stable Disease
StD	Standard Deviation
SmPC	Summary of Product Characteristics
SP	Service Provider
SOP	Standard Operating Procedure
SOC	System Organ Class
SS	Special Situation
TA	Tumour assessment
TFL	Tables, Figures and Listings
TTNT	Time To Next Treatment
VEGFR	Vascular endothelial growth factor receptor

2 INTRODUCTION

2.1 Disease Review

Neuroendocrine neoplasms (NEN) are rare neoplasms with an estimated incidence of about 3,000 patients and a prevalence of about 22,500 to 40,000 patients in Germany [1]. However, the incidence is steadily increasing worldwide [2], and NENs are potentially losing their status of a rare disease in the future [3]. NENs can be subdivided according to their status of differentiation into well differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinoma (NEC) with NETs accounting for about 90% of all NENs. Whereas NETs are classified according to their proliferation rate into grade 1 (slow), grade 2 (intermediate) and grade 3 (high) tumours, NEC are always classified as grade 3 as they are characterized by fast growth with >20 % proliferating cells [4].

NETs derive from disseminated cells of the diffuse neuroendocrine system and can originate from endocrine glands, endocrine islets or endocrine cells which are dispersed through the digestive system or respiratory tract. About 60% of all NETs arise from the gastrointestinal (GI) tract (~53%) or pancreas (~7%) and are referred to as gastroenteropancreatic NETs (GEP-NETs). All other NETs are referred to as non-GEP-NETs with lung-NETs being the most frequent non-GEP-NETs, accounting for about 27% of all non-GEP-NETs. The remaining non-GEP-NETs (~12%) arise from other organs [5,6].

The European Society For Medical Oncology (ESMO) guideline and the European Neuroendocrine Tumor Society (ENETS) consensus guideline provide treatment algorithms for the management of GEP-NETs, i.e. small intestine NETs (SI-NETs) and pNETs [7-11]. Depending on factors like the primary tumour location, differentiation, grade and other factors, different therapy strategies are provided including surgical resection or initiation of specific treatment sequences with approved antineoplastic drugs, i.e. somatostatin analogue (SSA), peptide receptor radionuclide therapy (PRRT), targeted therapies with everolimus and sunitinib or chemotherapeutic approaches.

2.2 Compound Review

Cabozantinib (anatomic therapeutic chemical (ATC) code: L01EX07) is a low molecular weight small molecule which inhibits multiple receptor tyrosine kinases (RTKs). It has potent activity against mesenchymal-epithelial transition factor (c-MET), AXL (from Greek *anexelekto* ≙ uncontrolled), and vascular endothelial growth factor receptors (VEGFRs) as well as various other RTKs involved in tumour pathogenesis, including rearranged during transfection (RET), KIT and Fms like tyrosine kinase (FLT) [12]. The mode of action of cabozantinib is the suppression of RTK signalling thereby interfering with the respective downstream signal transduction cascade leading to reduced angiogenesis, motility and invasiveness of tumour cells.

Cabozantinib was approved in the European Union (EU) as first-line treatment of advanced renal cell carcinoma (RCC) and second-line treatment after sorafenib therapy for the treatment of hepatocellular carcinoma (HCC). It is also approved for the treatment of differentiated thyroid carcinoma (DTC) after prior systemic therapy [13]. Cabozantinib was approved in the EU in July 2025 for the treatment of unresectable or metastatic, well differentiated pancreatic NET (pNET) and extra-pancreatic NET (epNET) who have progressed following at least one prior systemic therapy other than somatostatin analogues.

2.3 Study Rationale

Cabozantinib showed efficacy and safety in the phase III randomised controlled trial (RCT) CABINET (NCT01466036) in patients with well-differentiated grade 1-3 pNET and epNET [14]. A median (95% Confidence Interval [CI]) progression-free survival (PFS) of 13.8 (9.2; 18.5) months for pNET and 8.4 (7.6; 12.7) months for epNET was observed. The median (range) duration of treatment (DoT) was 8.3 (0.5; 39.6) months for pNET and 5.5 (0.2; 32.4) months for epNET and the objective response rate (ORR) (95% CI) for pNET was 19% (10; 30) and 5% (2; 10) for epNET.

The aim of the CABOLIFE study is to collect clinical effectiveness and safety data for patients with pNET/epNET who are treated with cabozantinib under real-world conditions.

The results of the study are expected to add important real-world evidence of the effectiveness and safety of cabozantinib to the already existing data obtained under the stringent conditions of a RCT.

The primary endpoint of the study is the disease control rate (DCR), which is a reasonable variable to address the effectiveness of a drug targeting slow to intermediate growing tumours, i.e. acting tumouristatic rather than tumouricidal [15,16]. The duration of the study is set to 15 months of observation (plus a 3-month follow-up period for participants discontinuing cabozantinib within the 15-month observation period and switching to a new LoT) and aligned with the median PFS with cabozantinib in the CABINET trial (8.4 months for epNET patients and 13.8 months for pNET patients) [14].

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To describe the effectiveness of cabozantinib tablets in participants with previously treated neuroendocrine tumours (NETs) in real-life in terms of disease control rate (DCR) at 6 months of cabozantinib treatment as assessed by the treating physician.	• The primary endpoint is the DCR defined as proportion of participants who within 6 months achieve complete response (CR), partial response (PR) or stable disease (SD) determined based on radiographic assessments between the date of the first dose of cabozantinib until the date of progressive disease (PD) or date of subsequent therapy.
Secondary	
• To describe the objective response rate (ORR) as investigated by the treating physician.	• ORR defined as proportion of participants who achieve CR or PR determined based on radiographic assessments between the date of the first dose of cabozantinib and the date of PD or date of subsequent therapy.
• To describe health-related quality of life (hrQoL) over the course of cabozantinib treatment.	• QLQ-C30 global and subscale scores for each visit at which hrQoL was assessed. • QLQ-GINET21 subscale scores for each visit at which hrQoL was assessed for GI-NET participants.
• To describe the safety of cabozantinib by review of all nonserious, drug-related and serious adverse events (AEs).	• All AEs assessed according to incidence, intensity/grade, causality, outcome, action taken and seriousness, specifically: a) Frequency of serious AEs (SAEs). b) Frequency of drug-related non serious AEs (nsAEs). c) Frequency of drug-related SAEs.

Objectives	Endpoints
• To describe cabozantinib dosage adjustment and schedule.	• All dose modifications according to frequency, timing, reason for adjustment, type of adjustment and duration of modified dosing, specifically: (a) Frequency of dose reductions due to AEs. (b) Frequency of dose interruptions due to AEs. (c) Frequency of treatment discontinuations due to AEs.
• To describe the duration of treatment (DoT) with cabozantinib.	• DoT during cabozantinib treatment phase, defined as the time from first dose until last dose of cabozantinib.
• To describe subsequent therapies following cabozantinib.	• Frequency overall and by type of therapy switch. • DCR of next line of treatment (LoT): proportion of participants who achieve CR, PR or SD determined based on routine radiographic response assessments approximately 3 months after switch to next line of therapy after cabozantinib.
• To describe the potential impact of cabozantinib treatment on NET biomarkers .	• Chromogranin A (CgA) levels at each visit. • Neuron-Specific Enolase (NSE) levels at each visit.
• To describe the time to next treatment (TTNT) for cabozantinib.	• TTNT, defined as time from first dose of cabozantinib until first dose of subsequent therapy.
• To describe the progression free survival (PFS).	• PFS during cabozantinib treatment phase, defined as time from first intake of cabozantinib until PD (as assessed by the investigator per radiological and/or clinical tumour assessment) or death from any cause. • Rate of progression-free survival at 12 months and 18 months.
Exploratory	
• To describe supporting measures.	• Assessment of nature and proportion of participants receiving the different measures at each visit these measures were assessed.

Objectives	Endpoints
• To describe potential correlations between effectiveness outcomes or quality of life and occurrence of AEs, dose reduction or supportive measures.	• Assessment of a potential correlation between the investigated parameters, specifically: - Effectiveness outcomes and occurrence of AEs. - Effectiveness outcomes and dose reduction. - HrQoL and dose reduction. - HrQoL and supporting measures. - Supportive measures and DoT/treatment discontinuation due to AEs. - Dose reduction and DoT. - HrQoL and DoT. *see related secondary safety, effectiveness and hrQoL endpoints.*

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 participant. This decision should be made in accordance with the Summary of product characteristics (SmPC) and routine/standard clinical practice at the investigational site. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician.

4.1 Overview

This is an international, multicentre, non-interventional, prospective, single-arm study. This study will be conducted in up to 50 centres in Austria and Germany. A total of 150 participants will be included in the study. Participants will be treated and monitored in accordance with usual medical practice during their participation in this study.

The expected duration of the recruitment period will be 18 months. Participants will be followed for a maximum of 18 months (observation period) while they receive cabozantinib as per the SmPC.

Participants prematurely discontinuing cabozantinib (i.e. within the first 15 months of observation period) and initiating a subsequent treatment will be followed up approximately 3 months after the treatment switch to collect effectiveness data for the new LoT. Enrolment in the study is possible if cabozantinib treatment started up to 4 weeks prior to enrolment. The data for Visit 1 will be captured retrospectively and starting at Visit 2 data will be collected prospectively including hrQoL baseline assessment.

To avoid selection bias in participant recruitment, investigators will offer enrolment to all eligible participants consecutively to achieve their recruitment target during a restricted and defined period. This includes patients who have stopped cabozantinib treatment within their first 4 weeks to avoid selection bias. But, if consecutive enrolment is not feasible (e.g. administrative constraints), an alternate enrolment schedule will be permitted and will have to be documented before the first participant is enrolled. The investigators will have to follow the same recruitment pace until achievement of his/her recruitment target.

4.2 Population Characteristics

One hundred and fifty (150) adult participants with unresectable or metastatic, well -differentiated epNET and pNET who have progressed following at least one prior systemic therapy other than SSA, and who are prescribed cabozantinib tablets according to the SmPC prior to entry into the study will be included in Austria and Germany.

Further details of the study population are provided in Section 5.

4.3 Study Data Collection

Participants will be treated in accordance with usual medical practice during their participation in this study. No additional assessments or tests will be required by this protocol. This study is non-interventional, thus if some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the eCRF.

Relevant data collected as part of routine medical care will be captured on an electronic Case Report Form (eCRF). These data will be transmitted to the sponsor for analysis. Data transmitted will be pseudonymized and will be identified by a participant number.

4.4 Study Data Collection Flow

As this is a non-interventional study, treatment with cabozantinib, the nature and timing of study visits and assessments, and data collection at each visit will be conducted as per routine/clinical practice at each clinical site and the SmPC for cabozantinib tablets.

The assessments relevant to this study are presented in Table 4-1. No additional assessments or tests will be required for the purpose of this study.

Table 4-1 Data to be collected in the eCRF

Collected data	Collection timepoints (visits)									
									EoS Visit	
	Visit 1 (Day 1)	Visit 2 (Month 1)	Visit 3 (Month 2)	Visit 4 (Month 3)	Visit 5 (Month 6)	Visit 6 (Month 9)	Visit 7 (Month 12)	Visit 8 (Month 15)	Visit 9[a] (Month 18)	VISIT FU[b] (approximately 3 months after cabozantinib treatment discontinuation)
Signature of informed consent[c]	X	*informed consent must be signed prior to any documentation of data*								
Visit Date	X	X	X	X	X	X	X	X	X	X
Eligibility	X	-	-	-	-	-	-	-	-	-
Demographic and baseline characteristics	X	-	-	-	-	-	-	-	-	-
Significant medical and surgical history	X									
NETs diagnosis	X	-	-	-	-	-	-	-	-	-
Prior systemic treatment for NETs	X	-	-	-	-	-	-	-	-	-
Prior NETs related radiotherapies	X	-	-	-	-	-	-	-	-	-
Prior NETs related surgeries	X	-	-	-	-	-	-	-	-	-
Tumour assessment[d]	X[e]			X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
ECOG Performance Status	X	X	X	X	X	X	X	X	X[f]	X
Cabozantinib regimen[g]	X	X	X	X	X	X	X	X	X	
Clinical characteristics	X	X	X	X	X	X	X	X	X	
NETs biochemical markers	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30 and QLQ-GINET21	X	(X)[h]		X	X	X	X	X	X	
Supporting measures[i]	X	X	X	X	X	X	X	X	X	
Concomitant medication for NETs (including concomitant medications for AEs)	X	X	X	X	X	X	X	X	X	X
Concomitant non-drug NETs therapy		X	X	X	X	X	X	X	X	
Post-cabozantinib treatment for NETs[j]	-	-	-	-	-	-	-	-	-	X
AEs and Special Situations	X	X	X	X	X	X	X	X	X	X[k]
Study Discontinuation/Completion	-	X								
Death information form	-	X								

Abbreviations: AE=Adverse Event; CR=Complete Response; DCR=Disease control rate; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EORTC=European Organisation for Research and Treatment of Cancer; EoS=End of Study; FU=Follow-Up; HrQoL=Health-related Quality of Life; NETs=Neuroendocrine tumours; PD=Progressive Disease; PR=Partial Response; PSP=Patient Support Program; QLQ-C30=Core Quality of Life Questionnaire; QLQ-GINET21= Quality of Life Questionnaire module for GI-NET patients; SD=Stable Disease; TA=Tumour Assessment.

All data will be recorded as applicable and available during standard of care routine: 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.

[a] EoS visit for participants still on cabozantinib treatment after 18 months.

[b] Combined FU/EoS visit for participants who discontinued cabozantinib early (up to 15 months after Visit 1) and subsequent therapy switch.

[c] Enrolment in the study is possible if cabozantinib treatment started up to 4 weeks prior to enrolment. See Section 4.1.

[d] Clinical and/or TA via imaging to determine SD, PR, CR and PD. The type of assessment must be recorded in the eCRF.

[e] The baseline radiological tumour assessment should be the most recent TA prior to enrolment.

[f] In case of PD and cabozantinib treatment discontinuation and subsequent therapy switch, only the FU visit must be performed 3 months after end of cabozantinib treatment. Of note, cabozantinib treatment beyond progress is possible; in this case the participant is not passed over to the FU period but remains in the 18-month observation period. In addition, also other reasons e.g. drug intolerability or adverse events might lead to cabozantinib treatment discontinuation and switch to subsequent treatment; in these cases, also only the FU visit must be performed 3 months after end of cabozantinib treatment.

[g] Including recording of dose modifications, overdoses, treatment interruptions and permanent study discontinuations along with the reason for discontinuation.

[h] Performed if participant was enrolled up to 4 weeks after first dose of cabozantinib and Visit 1 was captured retrospectively. HrQoL baseline will then be taken.

[i] Supporting measures include the recording of participation in a PSP, use of psycho-oncological support or nutritional advice.

[j] In particular, start of new treatment, type of treatment, treatment line and DCR within 12 weeks. For the determination of the DCR after therapy switch, the last TA prior to therapy switch serves as the baseline TA.

[k] Only AEs related to cabozantinib as assessed by investigator.

4.5 Study Data Collection Timing and Methods

The expected duration of the study is maximum of 36 months. The expected duration of recruitment is 18 months. Participants will be followed-up for up to 18 months of cabozantinib treatment. If cabozantinib is discontinued during the first 15 months of observation, and a subsequent therapy is started, a follow-up visit will be performed approximately 3 months after discontinuation of cabozantinib. Enrolment in the study is possible if cabozantinib treatment started up to 4 weeks prior to enrolment. The data for Visit 1 will be captured retrospectively. Starting at Visit 2 data will be collected prospectively including hrQoL baseline assessment. Patients who have started cabozantinib treatment up to 4 weeks before giving informed consent but stopped treatment during the 4 weeks may be included.

Three visit types will be performed:

- Baseline Inclusion/ Treatment Initiation Visit (Visit 1)
- Regular visit during the observational period (Visits 2 to 9) approximately every month until Month 3 and every 3 months afterwards
- Follow-up visit for participants discontinuing cabozantinib treatment during the 15-month observational period

All data will be recorded as applicable and available during standard of care routine. If a specific diagnostic procedure or assessment 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 / not available.

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.

For regular visits during the observation period the minimum information that must be recorded is the most recent result of the tumour assessment at/before Visit 1 to obtain a baseline value required for determination of the primary endpoint, DCR. Minimum required information for follow up visits after therapy switch, i.e. starting a new LoT includes the start date of new treatment (partial dates are allowed) and the type of treatment.

Adverse events (including treatment-emergent nonserious AEs and serious adverse events (SAEs)) and Special Situations (SS) including pregnancy will be collected during the observation period, see Section 9.

Inclusion/Treatment Initiation (Visit 1)

The following data will be collected:

- Date of signed informed consent.
- Date of visit.
- Eligibility (verification of the inclusion and exclusion criteria, see Section 5.1 and Section 5.2.
- Demographic and baseline characteristics:
  - Year of birth and gender.

- Baseline clinical characteristics:
  - Height (centimetres), Weight (kilograms).
  - Systolic and diastolic blood pressure (mmHg).
  - Heart frequency (bpm).
- Significant medical and surgical history.
- NET diagnosis:
  - Date of initial diagnosis.
  - Primary tumour location.
  - Grade (at first diagnosis and at baseline).
  - Stage (at first diagnosis and at baseline).
  - Ki67 Index (at first diagnosis and at baseline).
  - Hormone secretion.
- Prior systemic NET therapies. For each LoT:
  - Drug name.
  - Start and stop date.
  - Reason for discontinuation.
  - LoT.
- Prior NET related radiotherapies:
  - Start and Stop date.
  - Duration.
- Prior NET related surgeries:
  - Location.
  - Date.
- Baseline tumour assessment:
  - Date of last imaging (reference images).
  - Type.
- Eastern Cooperative Oncology Group (ECOG) performance status:
- Cabozantinib regimen:
  - Start date.
  - Dose.
- NET biochemical markers:
  - Chromogranin A (CgA).
  - Neuron-specific Enolase (NSE).
- EORTC QLQ-C30 and QLQ-GINET21 questionnaire every 3 months until the last visit while taking cabozantinib.
- Supporting measures:
  - participation in a patient support program (PSP).
  - psycho-oncological support.
  - special skin care.
  - special mouth care.

- nutritional advice.
- nutritional substitution.
  - high calorie drinks.
  - parenteral nutrition.
- Vitamin substitution for NET, NET-therapy or symptoms:
  - Vitamin C.
  - Lipid soluble vitamins.
  - Combination vitamins.
  - Other.

- Concomitant NET medication (including concomitant medications for AEs).
- All AEs and SS will be collected from the first intake of cabozantinib.

Treatment Period visits (Visit 2 to Visit 9)

As this is a non-interventional study, no formal schedule for Treatment Period visits could be planned. During the Treatment Period, data of interest will be collected at visits occurring as per routine/ standard clinical practice approximately every month until Month 3, and then approximately every 3 months onwards. If two visits or more occur within a 3-month window, only the visit closest to the time point should be reported with most relevant information.

The following data will be collected:

- Date of visit.
- Tumour assessment (TA):
  - by the investigator (clinical and radiographic). If radiological assessment is performed, it should be indicated whether the assessment of progression is based on Response Evaluation Criteria in Solid Tumours 1.1 guidelines (RECIST 1.1) or local standard of care. The most recent radiographic assessment performed before the visit is to be reported with the date and overall response. If clinical assessment is performed, the date of progression is to be provided if applicable. An assessment via imaging is expected approximately every 3 months as per standard of care.
- ECOG performance status.
- Cabozantinib regimen:
  - (Start date, stop date, administered dose, frequency, primary reason for dose change or discontinuation).
- Clinical characteristics:
  - weight, systolic and diastolic blood pressure; heart frequency.
- NET biochemical markers:
  - CgA.
  - NSE.
- EORTC QLQ-C30 and QLQ-GINET21 questionnaire every 3 months until the last visit while taking cabozantinib.
- Supporting measures (see Visit 1).
- Concomitant NET medication (including concomitant medications for AEs).
- Concomitant non-drug NET therapy.
- Adverse Events and Special Situations:

- From Visit 1 onwards until the End of Study (EoS), treatment-emergent nonserious AEs and SAEs and SS including pregnancy occurring during the data reporting period at each visit will be reported. Any clinically significant (CS) findings (as assessed by the investigator) on physical examination, laboratory values and electrocardiograms (ECGs) performed as per routine/ standard clinical practice will be reported as AEs.

If a participant withdraws consent, data will be collected up to the time of withdrawal, with no additional information collected thereafter.

Post-cabozantinib Treatment Follow-up Period:

For participants who discontinued cabozantinib during the first 15 months of observation, a follow-up visit at approximately 3 months after discontinuation should be documented, as the next standard of care visit for the next LoT is expected.

The following data will be collected:

- Date of visit/contact.
- ECOG Performance Status.
- Subsequent treatment following cabozantinib discontinuation including sequences of treatment, drug names and DoT, and reasons for end of treatment line.
- New nonserious AEs and SAEs assessed as related to cabozantinib (Adverse Drug Reactions (ADRs)) that start during the Post-Treatment Follow-up Period.
- Tumour assessment by the investigator (clinical and radiographic). If radiological assessment is performed, it should be indicated whether the assessment of progression is based on RECIST 1.1 or local standard of care. The most recent radiographic assessment performed before the visit is to be reported with the date and overall response. If clinical assessment is performed, the date of progression is to be provided if applicable.
- Concomitant medications for treatment of ADRs and changes to concomitant medications for treatment of pre-existing medical and surgical conditions (i.e. medical/ surgical history) at the time of occurrence of ADRs. Only AEs related to cabozantinib as assessed by the investigator will be collected, see above.
- Any further follow-up information for ongoing AEs (until resolution or stabilisation) and SS including pregnancy that occur during the Treatment Period.

If a participant is lost to follow-up during the Post-treatment Follow-up Period, multiple attempts should be made to contact the participant or designee, which should be documented in the participant's records.

4.6 Data Sources

Data for this study will be obtained via the following sources:

- Patient medical file: The investigator or authorised medical staff will record clinical and treatment data (if applicable) from patients' medical files into the eCRF at each collection time point, specified in Table 4-1.
- Tumour assessments: All tumour assessments are based on investigator's clinical and/or assessments by imaging. For radiological assessments tumour imaging data is provided by the radiologists. Data is recorded in the eCRF at each collection time point, specified in Table 4-1.

- Quality of Life (QoL) questionnaire: EORTC QLQ-C30 (Version 3, German language) and QLQ-GINET21 (2006, German language) questionnaire data will be collected on paper-based questionnaires or electronic version if used per treatment routine in the site and completed by the participant at each collection time point. The investigator or authorised medical staff will record the data into the eCRF at each collection time point, specified in Table 4-1.
- NET Biomarkers: NET Biomarker data for CgA and NSE are provided by the centre's local laboratory and recorded in the eCRF at collection time points when available, specified in Table 4-1.

4.7 Study Duration/Observation Period

The expected study duration is 3 years, with an 18-month enrolment period from first participant, first visit. The EoS is expected to be a maximum 18 months after the last participant has been enrolled.

The study will be considered to have started when the first participant has signed informed consent.

The study will be considered to have ended after the last participant's data has been collected.

The study observation period starts from participants signing the informed consent and continues until Visit 9 (Month 18). Participants discontinuing cabozantinib treatment and starting a new LoT during the first 15 months of cabozantinib treatment are passing over into the follow-up, which is approximately 3 months after discontinuation of cabozantinib.

Participants will be followed until the end of observational period (i.e. a maximum of 18 months after Visit 1) or withdrawal of consent, or death, whichever occurs first.

4.8 Participant Information

Prior to enrolment of a participant in this study, the investigator, or a person designated by the investigator, will explain the nature and purpose of this data collection to each participant. As all assessments and procedures will be conducted in accordance with routine/standard clinical practice, participation in the study does not convey any additional risks or burdens for the participant. However, the participant will be provided with information on the benefits and risks of their medical treatment.

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

The sponsor will provide an informed consent form (ICF), in German language easily understood by the participant. Each participant's original consent form, personally signed and dated by the participant, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled participants 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

Study sites will include oncology practices, hospitals, and Academic Medical Centres as well as ENETS Centres of Excellence. This prospective study will include participants who meet all eligibility criteria.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1. Participant aged ≥8 years with capacity to consent.
2. Physician-initiated decision to treat with cabozantinib for NET (prior to study enrolment) according to SmPC.
3. Signed written informed consent.

5.2 Exclusion Criteria

Patients will not be included in the study if they meet any of the following criteria:

1. Participation in an interventional trial at the same time and/or within 3 months before baseline.
2. Contraindication for cabozantinib treatment according to SmPC.

5.3 Participant Withdrawal Criteria

As this is a non-interventional study, participants will be managed according to each clinical site's medical routine/standard practice, therefore no specific withdrawal criteria are specified.

Participants are free to withdraw consent at any time. The investigator may withdraw a participant from the study at any time for safety reasons or at his/her discretion. Data will be collected up to the time of withdrawal, with no additional information collected thereafter.

For participants who withdraw from the study, withdrawal details are recorded in the specific section of the eCRF of the next planned collection time point. Any AEs collected/reported will, however, be followed-up until resolved or stabilised or until the participant is lost to follow up (a participant is considered lost to follow-up if the centre was repeatedly unable to contact the participant e.g. by phone or email).

In case the participant is withdrawn from the study, the primary reason for withdrawal should be recorded in the eCRF.

6 STUDY ENDPOINT AND EVALUATIONS

6.1 Effectiveness Endpoints and Evaluations

All effectiveness data are collected as per local routine. Effectiveness assessments are based on clinical and/or tumour assessment via imaging of the disease status.

6.1.1 Primary Effectiveness Endpoint

Disease control rate (DCR):

DCR is defined as proportion of participants who within 6 months achieve complete response (CR), partial response (PR) or stable disease (SD) determined based on radiographic assessments between the date of the first dose of cabozantinib until the date of progressive disease (PD) or date of subsequent therapy.

Table 6-1 Disease response definitions

Disease response definitions:		
CR	Complete response	Complete resolution of all visible disease.
PR	Partial response	Partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease. Captures a decrease in disease volume even though disease is still present.
SD	Stable disease	No change in overall size of visible disease. Also includes cases where some lesions increased in size and some lesions decreased in size.
PD	Progressive disease	Increase in visible disease and/or presence of any new lesions. Includes cases where the clinician indicates PD or progression of disease as the overall assessment.

6.1.2 Secondary Effectiveness Endpoints

Objective response rate (ORR):

ORR is defined as proportion of participants who achieve CR or PR determined based on radiographic assessments between the date of the first dose of cabozantinib and the date of PD or date of subsequent therapy.

Quality of life (hrQoL):

See Section 6.3.

Cabozantinib dosage adjustment and schedule:

- Starting dose, all dose modifications according to frequency, timing, reason for adjustment, type of adjustment and duration of modified dosing, specifically:
  - Frequency of dose reductions and reason (specifically adverse events).
  - Frequency of dose interruptions and reason (specifically adverse events).
  - Frequency of treatment discontinuations and reason (specifically adverse events).

Duration of treatment (DoT):

DoT during cabozantinib treatment phase, defined as time from first intake of cabozantinib until date of permanent cabozantinib treatment discontinuation.

Frequency of therapy switch and subsequent therapy:

Frequency of therapy switch is defined as permanent discontinuation of cabozantinib treatment within the cabozantinib treatment phase and start of a next LoT as well as nature of next LoT.

Disease control rate (DCR) after switch to next LoT:

DCR is defined as proportion of participants who within 3 months after switch to next LoT achieve CR, PR or SD determined based on radiographic assessments between the date of the first dose of new treatment until the date of progressive disease (PD) or date of further subsequent therapy.

Time to next treatment (TTNT):

Time from the first dose of cabozantinib to the first dose/administration of the subsequent therapy.

Landmark PFS at 12 months and 18 months:

PFS during cabozantinib treatment phase is defined as time from first intake of cabozantinib until PD (as assessed by the investigator per radiological and/or clinical tumour assessment) or death from any cause. Landmark PFS will be determined at 12 and 18 months and if the number of events allows, the median PFS will be presented.

Biomarker assessments:

Determination of CgA and NSE levels by local labs as per local routine.

- CgA-levels at each visit, CgA was assessed.
- NSE-levels at each visit, NSE was assessed.

6.2 Safety Endpoints and Evaluations

Safety assessments comprise the collection of data on adverse events, dose reductions, overdoses, dose interruptions and treatment discontinuations.

6.2.1 Adverse Events and Special Situations

The collection and reporting of AEs and Special Situations (SS) will follow regulations related to non-interventional studies.

The definition of AEs and SAEs can be found in Section 9.1. For the management and reporting of the AEs and SS, please refer to Section 9.

All AEs, whether they are serious/nonserious, related/unrelated, and all SS should be collected throughout the observation period of cabozantinib treatment. After cabozantinib treatment has ended, only serious/nonserious AEs that are related to cabozantinib, as assessed by the investigator, that occur during the 3-month follow-up period are collected. All AEs will be assessed according to incidence, intensity/grade, causality, outcome, action taken and seriousness.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up any AEs or SAEs.

6.2.2 Other Safety Endpoints

Not applicable.

6.2.2.1 Physical Examination

Not applicable.

6.2.2.2 Vital Signs

Evolution of weight and blood pressure over time.

6.2.2.3 Clinical Safety Laboratory Assessments

Not applicable.

6.3 Quality of Life/Standardised Questionnaires

Patient reported outcomes on hrQoL are assessed with the validated 30-item EORTC QLQ-C30 (28 questions with a 4-point Likert scale and two questions with a 7-point Likert scale) and 21-item QLQ-GINET21 questionnaires (21 questions with a 4-point Likert scale). Global and subscale scores are determined by the official scoring algorithm.

QoL-related endpoints are:

- QLQ-C30 global and subscale scores for each visit at which hrQoL was assessed.
- QLQ-GINET21 subscale scores for each visit at which hrQoL was assessed.

6.4 Medical Resource Utilisation

Not applicable.

6.5 Exploratory Endpoints

Supporting measures:

Frequency and type of supporting measures at each visit these measures were assessed.

Correlation analyses:

Assessment of a potential correlation between the investigated parameters, specifically:

- Effectiveness outcomes and occurrence of AEs.
- Effectiveness outcomes and dose reduction.
- HrQoL and dose reduction.
- HrQoL and supporting measures.
- Supportive measures and DoT/treatment discontinuation due to AEs.
- Dose reduction and DoT.
- HrQoL and DoT.

See more details in Section 8.4.3.3.

7 TREATMENTS OF INTEREST

This is an observational study designed to collect data on the use of Cabometyx® (cabozantinib) in real-world clinical practice.

The decision to prescribe cabozantinib will be made prior to and independently of the decision to enrol the patient in this non-interventional study.

8 STATISTICAL CONSIDERATIONS

The information provided in this section may be subject to changes that will be indicated in the final Statistical Analysis Plan (SAP) of this study. The SAP will be developed as a separate document and approved prior to database lock, containing a description of the planned statistical analysis in detail with Tables, Figures and Listings (TFLs) templates.

8.1 Participant Classification and Definitions

Enrolled participant:	Eligible participant who is fully informed about the study and who has given written informed consent to participate (before any study data is collected).
Treated participant:	Enrolled participant who received at least one intake of cabozantinib during the study.
Switched participant:	Treated participant who permanently discontinued cabozantinib treatment and switched to a subsequent LoT.
Withdrawn participant:	Participant who ceased participation in the study prior to the planned follow-up of the study.

8.2 Definition of Analyses Populations

Enrolled population:	All participants enrolled.
Full Analysis Set (FAS) / Safety population	All eligible participants treated with cabozantinib within this non-interventional study.

8.2.1 Populations Analysed

The primary and secondary effectiveness analyses will be based on the FAS population.

8.2.2 Participant Allocation and Reasons for Exclusion from the Analyses

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

During the data review meeting, based on minor or major protocol deviations recorded, participants may be excluded from the safety/FAS population.

8.3 Sample Size Determination

As this is a non-confirmatory, exploratory, non-interventional study, no formal sample size calculation was performed.

Based on the feasibility evaluation, it was estimated that 150 participants in approximately 50 sites could be enrolled in this study. No power calculations have been performed since this is a non-interventional study with a descriptive objective.

Assuming a dropout rate of 10%, 135 participants will be evaluable for the primary endpoint (DCR). With a sample size of 135 participants, a two-sided 95% CI for a sample proportion using the normal approximation will extend to ±7.5% from the observed proportion for an expected DCR of 73% (145/198), based on the Cabinet study [14] with both pNET (51/64) and epNET (94/134) cohorts pooled.

8.4 Statistical and Analytical Methods

Statistical analyses will be performed using Statistical Analysis System (SAS)® (Version 9.4 or higher).

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, two-sided 95% CIs will be displayed. If p-values are presented, this will be for exploratory purposes only.

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

- Mean, Standard Deviation (StD), minimum, median, maximum, first and third quartiles and 95% CIs for means;
- Counts and percentages of each category for categorical nominal variables with 95% CIs.

Percentages will be based on the number of non-missing observations.

Missing data will not be replaced. Imputation rules will be detailed in the SAP, as appropriate (e.g. for incomplete dates).

8.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics of demographic and baseline data (including NET medical history, characteristics of NET at start of cabozantinib, NET-specific concomitant medication and previously received therapies for NET) will be presented for the FAS population.

8.4.2 Participant Disposition and Withdrawals

The numbers and percentages of participants in the FAS population will be tabulated by country and centre. The reasons for participant exclusions from each of the populations will also be tabulated. In addition, the number of participants who were treated and withdrawn will be tabulated. Primary reasons for withdrawal from the study will be tabulated.

8.4.3 Effectiveness Analysis

8.4.3.1 Primary Effectiveness Analysis

The primary endpoint is the DCR at 6 months, defined as the proportion of participants who, within 6 months achieve CR, PR or SD determined based on radiographic assessments between the date of the first dose of cabozantinib until the date of progressive disease (PD) or date of subsequent therapy.

The proportion of participants with DCR will be calculated by counting all participants who have SD, PR or CR at any post-baseline TA and dividing them by the number of participants in the FAS with at least one post-baseline TA. Participants who are treated with cabozantinib beyond progression but have not had SD, PR or CR prior to disease progression, will be considered to have no SD, PR or CR, even if they achieve SD, PR or CR after PD. DCR will be provided with the corresponding 95% CI.

In a secondary analysis, the DCR will be calculated similarly except that the count of participants who have SD, PR or CR at any post-baseline TA will be divided by the number of participants in the FAS.

8.4.3.2 Secondary Effectiveness Analysis

Objective response rate (ORR):

ORR is defined as the proportion of participants who achieve CR or PR determined based on radiographic assessments between the date of the first dose of cabozantinib and the date of PD or date of subsequent therapy.

The proportion of participants with ORR will be calculated by counting all participants who have PR or CR at any post-baseline TA and dividing them by the number of participants in the FAS with at least one post-baseline TA. Patients who are treated with cabozantinib beyond progression but have not had PR or CR prior to disease progression, will be considered to have no PR or CR, even if they achieve PR or CR after PD. ORR will be provided with the corresponding 95% CI.

In a secondary analysis, the ORR will be calculated similarly except that the count of participants who have PR or CR at any post-baseline TA will be divided by the number of participants in the FAS.

QLQ-C30 global and subscale scores for each visit at which hrQoL was assessed:

See Section 8.4.5.

QLQ-GINET21 subscale scores for each visit at which hrQoL was assessed:

See Section 8.4.5.

Duration of treatment (DoT) and time to next treatment (TTNT):

Both DoT and TTNT will be presented descriptively as quantitative parameters. TTNT will be presented for the subgroup of participants with a subsequent therapy.

Progression-free survival:

PFS will be estimated on the FAS, using the Kaplan-Meier method and plotted as a survival curve.

The survival rates at 12-month follow-up and 18-month follow-up will be estimated and presented with their 95% CIs.

If the number of events allows, the median PFS, first and third quartiles with their two-sided 95% CIs will be presented.

Biomarker assessments:

CgA levels at each visit where CgA was assessed will be summarised for each visit by descriptive statistics providing n, mean, 95% CI of the mean, StD, median, minimum, and maximum.

NSE levels at each visit where NSE was assessed will be summarised for each visit by descriptive statistics providing n, mean, 95% CI of the mean, StD, median, minimum, and maximum.

Switch to subsequent therapy:

The proportion of participants who permanently discontinued cabozantinib and started a new LoT will be described, as well as the types of therapies in this subsequent line.

The DCR at 3 months after the switch to the next LoT will be analysed similarly to the primary endpoint, except that the population of analysis will be the FAS for participants who switched to the next LoT.

8.4.3.3 Exploratory Effectiveness Analysis

Supporting measures:

Frequency and type of supporting measures (e.g. PSP, psycho-oncological support, nutritional advice etc.) will be summarised for each visit by descriptive statistics providing counts and percentages of each category for categorical nominal variables with 95% CIs.

Exploratory correlation analyses:

Details of exploratory correlation analyses assessing the following correlations will be provided in the SAP. The exploratory analyses will mainly focus on the description of:

- DCR and ORR depending on the number and grade of treatment-related AEs (ADRs).
- DCR and ORR depending on the implementation of dose reductions of cabozantinib.
- The evolution of the hrQoL assessed by EORTC QLQ-C30 and additionally QLQ-GINET 21 for GI-NET participants depending on the occurrence of ADRs and dose reductions.
- The DoT and treatment discontinuation due to AEs in regard to supportive measures the participants received.
- The DoT in regard to dose reduction.
- The DoT in regard to hrQoL.

8.4.4 Safety Analysis

Safety analyses will be performed on the Safety population.

During the Treatment Period (Visit 2 to Visit 9), all treatment-emergent AEs including non-serious AEs and SAEs and SS including pregnancy will be collected.

Analysis of AEs

A treatment-emergent AE is defined as any AE that occurs after the first dose of study treatment if:

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

The focus of analysis of this study will be the duration of the Treatment Period, i.e. up to 30 days after the permanent discontinuation of cabozantinib.

An overall summary table of all AEs (including fatal events) will be presented with the number and proportion of participants and the number of events, including frequency of SAEs, drug-related AEs and drug-related SAEs. Summary incidence tables of all AEs, SAEs and AEs by relationship and intensity/grade to study drug will be provided, classified by primary System Organ Class (SOC) and Preferred Term (PT).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA PT and SOC.

All safety data will be included in the participant data listings, such as listings of all AEs, SAEs, AEs leading to study drug withdrawal, AEs leading to dose reduction or interruption and listings of deaths.

Analysis of "Special Situation"

SSs will be listed separately, and summary incidence tables will be provided. The AEs associated with SSs will be described.

8.4.5 Quality of Life Analysis

QLQ-C30 global and subscale scores for each visit at which hrQoL was assessed:

Scoring of EORTC QLQ-C30 global and subscale scores is performed by using the official scoring manual for the questionnaire. Global and subscale scores are analysed by descriptive statistics at each visit with the change from baseline.

QLQ-GINET21 subscale scores for each visit at which hrQoL was assessed:

Scoring of EORTC QLQ-GINET21 global and subscale scores is performed by using the official scoring manual for the questionnaire. Global and subscale scores are analysed by descriptive statistics at each visit with the change from baseline on the subgroup of participants with GI NET.

8.4.6 Medical Resource Utilisation Analysis

Not applicable.

8.5 Subgroup Analyses

Subgroup analyses are only performed if data permit. Subgroups may be merged into larger subgroups if deemed necessary. The following subgroups are defined:

Subgroups NET localisation:

NET-I	LungNET (27.3%)
NET-II	GI-NET (53.2%)
NET-III	pNET (7.3%)
NET-IV	Other NET (12.2%)

Estimation for subgroup sample size: The breakdown into subgroups follows the distribution described in the literature for NET [4,6]. Due to the difference in treatment sites for LungNET and other NETs in Germany and Austria the LungNET cohort is estimated to be approx. 20% and the other NETs make up approx. 80% of the sample size. All endpoints will be analysed for the subgroups if participant collective allows it.

Feasibility of subgroup assessment will be completed following the enrolment of all participants in this study. If necessary, these subgroups may be combined to make larger groups.

8.6 Interim Analysis

Three interim analyses are planned:

1. Interim analysis 1 (IA1): The first interim analysis is planned to be conducted in Q3 2026, expecting about one third of the target sample size (~ 50 participants) to be enrolled. It will evaluate data from Visit 1 (Baseline) with a focus on participant characteristics and NET medical history.
2. Interim analysis 2 (IA2): The second interim analysis is planned to be conducted in Q2 2027, expecting about half of the target sample size (~ 75 participants) to be enrolled. It will evaluate data based on Visit 5 (Month 6) and will focus on effectiveness data, QoL and safety.
3. Interim analysis 3 (IA3): The third interim analysis is planned to be conducted in Q1 2028, when full recruitment is expected. Updates on IA2 evaluations will be given as well as analyses on later endpoints and will focus on effectiveness data and post-cabozantinib therapies.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS

9.1 Definition

9.1.1 Adverse Event

AE Definition
An Adverse Event (AE) is any untoward medical occurrence in a patient/participant, administered a medicinal product (cabozantinib) and which does not necessarily have a causal relationship with this treatment. NOTE: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events Meeting the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For studies involving marketed products in established indications include: The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of effectiveness" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgement should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

9.1.3 "Special Situations"

Special situation (SS) is any incidence of drug exposure during pregnancy (i.e. drug exposure to a fetus in utero (whether the fetus is exposed via the mother taking the product or transmission via semen following paternal exposure)) or breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic effectiveness whilst using the medicinal product. A SS should be collected by the investigator and reported to Ipsen whether or not these SS are associated with an AE.

9.1.3.1 Pregnancy or Breastfeeding

Pregnancy

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.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the ICF and until at least 5 months after EoS.

The investigator is to report to the Sponsor if they become aware of a pregnancy occurring in the partner of a participant participating in the study. If the female partner gives her consent, the pregnancy outcome should be followed up and reported.

Information regarding any pregnancies must be collected on the SS section of eCRF, including those with normal progress and throughout the Drug exposure for Pregnancy form (080479-FOR).

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to a marketed Ipsen product, attempt to follow-up until one month after delivery.

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

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

Breastfeeding

Any use of an IPSEN product during lactation/breastfeeding must be collected on the SS eCRF.

9.1.3.2 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC, or in the protocol. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labelling text will be assessed as 'overdose'. Overdoses should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All overdoses should be reported to Ipsen within 7 calendar days.

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Off-label use should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All Off-label use should be reported to Ipsen within 7 calendar days.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Misuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All misuse should be reported to Ipsen within 7 calendar days.

Abuse

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

Abuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All abuse should be reported to Ipsen within 7 calendar days.

Occupational exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported as AEs in the AE eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days.

Medication error

Medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant.

Medication error should be reported as AEs in the AE eCRF whether or not they were associated with a clinical event. All medication error should be reported to Ipsen within 7 calendar days.

9.1.4 Adverse Events of Special Interest

Not applicable

9.2 Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information

For the definition of the AEs and SS, please refer to Section 9.1.

During the Treatment Period, (i.e. from Day 1 until 30 days after discontinuation of cabozantinib treatment or EoS), all AEs including nonserious AEs and SAEs, and SS will be collected. During the Post-treatment Follow-up Period (i.e. from 30 days after discontinuation of cabozantinib treatment until the EoS), only new AEs assessed as related to cabozantinib that start during this period will be collected. Incidence of pregnancy will be collected until 5 months after EoS. If possible, pregnancy should be followed up until the outcome is known. Any further follow-up information on ongoing AEs (until resolution or stabilisation) and SS including pregnancy that occurred during the Treatment Period will be collected.

From this point onwards, the term 'Safety Report' will collectively refer to all reports of non-serious related AEs, SAEs, fatal outcomes and SS.

9.2.1 Collection of the AEs/SAEs/SS in the eCRF

The collection and reporting of AEs will follow regulations related to non-interventional studies.

All AEs, whether they are serious/nonserious, related/unrelated, and all SS should be collected in the eCRF during the course of the study. Adverse events will be assessed according to incidence, intensity/grade, causality, outcome, action taken and seriousness.

All AEs will be collected in the eCRF from the first intake of cabozantinib until study completion, i.e. EoS or the EoS/follow-up visit, as specified in Table 4-1.

9.2.2 Reporting of SAEs, nonserious ADRs and SS to Sponsor Pharmacovigilance

In order to adhere to all applicable laws and regulations for reporting of a Safety Report, the investigator must report to Ipsen Pharmacovigilance all the following events using the eCRF:

- All serious adverse events (SAEs) – related and non-related;
- All related nonserious AEs (ADRs));
- Any SS (see definitions in Section 9.1).

Primary Data Collection NIS		
Safety Event	**Collected on the eCRF (observation period)**	**Reported to Ipsen Global Pharmacovigilance**
Non serious adverse event (AE)	All AEs related or not	Only the **Related** AEs - within 7 calendar days of awareness
Serious adverse event (SAE)	All SAEs related or not	All - within 24 hours of awareness
Pregnancy (as an SS)	All pregnancies	All - within 24 hours of awareness
Special Situations (SS)	All SS related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) - within 7 calendar days of awareness

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

All nonserious related AEs and SS will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

SAE Reporting to Ipsen Pharmacovigilance via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Ipsen Pharmacovigilance will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE form "Adverse Event and Special Situation Reporting Form for non-interventional Studies" (134232-FOR) (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Ipsen Pharmacovigilance department by telephone.
- Contacts for SAE reporting:
  E-mail: PPD
  PPD

  Telephone: PPD

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

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

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 a SAE and within 7 days for a nonserious related AE of awareness for each adverse event:

- Participant identifier
- Product name
- Adverse Event description including assessment of causal relationship and seriousness (See Section 9.3)
- Investigator name and contact details

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

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

9.3 Method of Detecting AEs and SAEs

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/related AE reports are provided below.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to Ipsen Pharma GmbH in lieu of completion of the Ipsen Pharma GmbH AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Ipsen Pharma GmbH. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Ipsen Pharma GmbH. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Grade
The investigator will make an assessment of intensity for each AE and SAE reported during the study using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) grading system Version 5.0 (2017).
Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgement to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Ipsen Pharma GmbH. However, it is

very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Ipsen Pharma GmbH.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 5.3). Further information on follow-up procedures is provided below.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

9.5 Regulatory Reporting Requirements for SAEs/Related AEs

- Prompt notification by the investigator to the sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it in the investigator's site folder and will notify the IRB/IEC, if appropriate according to local requirements.

9.6 Expectedness of Events

The expectedness of an AE shall be determined by the sponsor according to the SmPC) or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation. If the product has marketing authorisations in several countries with different SmPCs or PIs, one will be selected by the study team as the reference document for assessing expectedness and agreed by the pharmacovigilance Ipsen representative.

The reference document for assessing expectedness of AEs/event in this study will be the current EU SmPC.

10 STUDY MANAGEMENT

10.1 Monitoring Procedures

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

Ipsen or Service provider (SP)-assigned monitors may conduct site visits. The investigator will allow direct access to all relevant files (for all participants) 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 CRFs within 14 days of the participant'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 participant name is revealed on a document required by the sponsor, the name must be blacked out permanently by the site personnel annotated with the participant number as identification.

10.2 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 participant's participation in this study.

Participant-completed questionnaires will be completed on a paper questionnaire or electronically as per treatment routine at Visits 1, 4, 5, 6, 7, 8 and 9 and captured in the eCRF by the investigator or delegate. Electronic Case Report Form (eCRF) will be utilised for collecting participant data. The sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer & backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. To ensure 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, Ipsen or third parties.

Data entry in the eCRF will be performed by the investigator or by the designated person from his/her team.

10.3 Data Verification on Site

Within the framework of a non-interventional study, only the following source data verification will be performed by the sponsor or SP:

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, participant'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, participant 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 participant is included in the study (with corresponding study number).

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

10.4 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 not adequately explained will require additional queries to be raised to the investigator for clarification/correction. The investigator must ensure that queries are dealt with promptly. All corrections on the eCRF data will be automatically tracked and a reason for 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) to each eCRF to attest to the accuracy and completeness of all the data. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature.

10.5 Data Management

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

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately. At the study end, the investigator will receive their data, from the clinical study, in an electronic format which will be an exact copy of the eCRF for archiving purposes and future reference.

10.6 Record Archiving and Retention

Study documents will be retained by the investigator in a secure place for 10 years after EoS (defined as the Last Participant Last Visit).

11 ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES

11.1 Ethical and Regulatory Considerations

This study is non-interventional and falls outside the scope of the EU Directive 2001/20/EC [17], the EU Directive 2005/28/EC [18] and International Council for Harmonisation-Good Clinical Practice guidelines.

This study must be conducted in compliance with the recommendations of the Declaration of Helsinki [19] and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences, 2009 [20].

This study complies with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regards to the processing of personal data and on the free movement of such data [21].

This study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research [22] and the International Society for Pharmacoepidemiology (ISPE) GPP Guidelines [23].

Safety data collection and reporting should be consistent with EU Good Pharmacovigilance Practice [24] 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 Independent Ethics Committee/Independent Review Board as applicable.

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

11.2 Publication Policy

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

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

Authorship should be based on:

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

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

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

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

11.3 Study Report

A study report will be prepared in compliance with any applicable regulatory requirements, national laws in force. It should be written in English.

11.4 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 included participant, and the specified terms of payment will be described in the contract.

12 PROTOCOL AMENDMENTS

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

As required by local regulations, the sponsor will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies.

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