HUTCHMED

Clinical Study Protocol

An Open-Label Phase 2 Study of Surufatinib in Patients with Neuroendocrine Tumors in Europe

Investigational Product(s):	Surufatinib
Protocol Number:	2020-012-00EU1
Clinical Phase:	2
Issue Date:	01 December 2023
Amendment:	6
Sponsor:	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
Regulatory Agency Identifier Number (s)	IND [redacted] EudraCT 2020-006118-19 NCT04579679

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by the International Council for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Re-consent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Patients Protection and GCP training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	An Open-Label Phase 2 Study of Surufatinib in Patients with Neuroendocrine Tumors in Europe
Protocol Number	2020-012-00EU1
Amendment	6

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature table below.

Name:	**Title:**
PPD	HUTCHMED International Corp.
Signature: *See appended signature page*	**Date:** [DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2020-012-00EU1 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight of all personnel to whom study activities have been delegated
- To control all study drugs provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and GCP as outlined by ICH E6(R2)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent—and updated consent, in the event of new information or amendments—from all participants enrolled at my study site prior to initiating any study-specific procedures or administering study drugs to those participants
- To maintain records of each patient's participation and all data required by the protocol

Name: [Last name, first name]	**Title:** [Title at institution]	**Institution:** [Address]
Signature:		**Date:** [DD Month YYYY]

DOCUMENT HISTORY

Amendment	Date of Issue
Original	27 Aug 2020
0.1	12 Jan 2021
1	07 Feb 2021
2	23 Jun 2021
3	12 Aug 2021
4	01 March 2022
5	05 December 2022

AMENDMENT SUMMARY

This 2020-012-00EU1 Amendment 6 replaces Amendment 5 (05 December 2022). This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

The primary purpose of Amendment 6 is to provide notification of termination of this study based upon the strategic re-evaluation of the clinical development program for surufatinib in Europe and the United States. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. CCI [redacted] The major changes incorporated in Amendment 6 relative to Amendment 5 are summarized below. Editorial and formatting changes are not included in this summary.

Details of changes made in prior amendments are summarized in Appendix 9.

Section Number	Summary of Change	Rationale for Change
Cover page, Header, Sponsor's Approval, and Document History	Language was updated to reflect Amendment 6.	Information was updated to acknowledge this document as Protocol Amendment 6.
Synopsis, Section 1.2 Schedule of events, Section 4.1 Study Design, Section 6.1.6.4 End of Treatment/Early Termination, Section 6.3 Study Termination	Language was added detailing the updated timeline for the last day to initiate a new cycle, treatment discontinuation and follow-up visit.	These updates were made to accommodate the process of study termination.
Section 2.1.5 Benefit/Risk Assessment	Table 4 was removed, and a reference was added to the current Investigator's Brochure for details of identified risks	The surufatinib Investigator Brochure is updated annually and the table was no longer current.
Section 4.1 Study Design, Section 9.2.1 Sample Size Rationale	Number of enrolled patients per cohort were updated	These updates were made to reflect the current status of the study.
Section 7.3.2 Prohibited Therapies Appendix 5 Prohibited Concomitant Medications That Have a Known Risk of QT Prolongation and /or Torsades de Pointes	Added a reference to http://www.crediblemeds.org.	This reference was added to guide the study personnel to the most updated and complete source of information.
Appendix 5 Prohibited Concomitant Medications That Have a Known Risk of QT Prolongation and /or Torsades de Pointes	Updated the list of medications based on http://www.crediblemeds.org.	Updates made to align with the most updated and complete source of information.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to time of last measurable concentration
BCRP	Breast cancer resistance protein
BML	Below measurable limit
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CSF-1R	Colony stimulating factor-1 receptor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed analyte concentration just prior to the beginning or at the end of a dosing interval
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day(s)
DCR	Disease control rate

Abbreviation	Definition
DDI	Drug-drug interaction
DIC	Disseminated intravascular coagulation
DILI	Drug-induced liver injury
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
epNET	Extrapancreatic neuroendocrine tumor
EU	European Union
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FGFR-1	Fibroblast growth factor receptor-1
γ-GGT	gamma-glutamyl transferase
GCP	Good Clinical Practice
h	Hour(s)
HR	Hazard ratio
HUVEC	Human umbilical vein endothelial cell
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute(s)
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCI	National Cancer Institute
NE	Not evaluable
NET	Neuroendocrine tumors

Abbreviation	Definition
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
pNET	Pancreatic neuroendocrine tumor
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QTc	Corrected QT interval(s)
QTcF	Corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMQ	Standardized MedDRA Queries
SRC	Safety Review Committee
SSA	Somatostatin analogues
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
t_{max}	Time to reach the maximum plasma concentration
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1 SYNOPSIS

Title	An Open-Label Phase 2 Study of Surufatinib in Patients with Neuroendocrine Tumors in Europe
Short Title	Open-Label Surufatinib in European Patients with NET
Acronym	Not applicable
Phase	2
Study Status as of Protocol Amendment 6	The primary purpose of Amendment 6 is to provide notification of termination of this study based upon the strategic re-evaluation of the clinical development program for surufatinib in Europe and the United States. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. CCI [redacted]
Rationale	Neuroendocrine tumors (NETs) are highly vascularized tumors with overexpression of angiogenic markers, including vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor (FGFR). Current therapies are not highly selective and result in 'off-target' toxicities. Surufatinib, a small molecule selective inhibitor of VEGF receptors 1, 2, and 3; fibroblast growth factor receptor 1 (FGFR-1), and colony stimulating factor-1 receptor (CSF-1R), has demonstrated efficacy in 2 randomized, double-blind, placebo-controlled studies in NETs of extrapancreatic origin and pancreatic origin, SANET-ep and SANET-p, respectively, which were prematurely terminated due to surufatinib demonstrating superior efficacy over placebo in terms of the primary endpoint of progression-free survival (PFS). This study aims to evaluate the antitumor activity of surufatinib in patients with locally advanced or metastatic, well-differentiated, low- to intermediate-grade NETs.
Target Population	Adult patients ≥18 years of age who have histologically or cytologically documented locally advanced or metastatic low- to intermediate- grade (grade 1 or 2) NET and have progressed on at least 1 prior line of therapy, but no more than 3 therapies: Cohort A, NET of lung origin; Cohort B, NET of small bowel origin; Cohort C, NET of non-small bowel, non-pancreas, and non-lung origin; and Cohort D, NET of any origin.
Intervention	**Cohorts A, B, and C:** Oral surufatinib 300 mg **Cohort D:** Oral surufatinib 300 mg and a drug cocktail of midazolam 2.5 mg, fexofenadine 30 mg, and rosuvastatin 10 mg
Number of Sites	18 investigational sites in Europe Approximately 4 investigational sites in the US to enroll patients in Cohort D

Objectives and Endpoints

Objectives	**Corresponding Endpoints**
Primary • To evaluate the antitumor activity of surufatinib in patients with low- to intermediate-grade (grade 1 or grade 2), well-differentiated NETs	**Primary** • Disease control rate (DCR) at 6 months
Secondary • To characterize the pharmacokinetics (PK) of surufatinib in patients with NET	**Secondary** • Observed plasma concentrations, estimated population PK, and exposure parameters of surufatinib

• To evaluate the effect of surufatinib on cardiac repolarization, as detected by changes in electrocardiogram (ECG) corrected QT intervals (QTc), and the potential relationship with surufatinib plasma concentrations	• QTc and plasma concentrations of surufatinib at specified time points
• To further characterize the antitumor activity of surufatinib in patients with NET	• Objective response rate (ORR), time to response, duration of response (DoR), and PFS
• Cohort D only: To evaluate the effects of repeat dosing of surufatinib on the single-dose PK of cytochrome P450 (CYP)3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) substrates in patients with NET	• Exposure parameters of CYP3A4, P-gp, and BCRP substrates
• To evaluate the safety and tolerability of surufatinib in patients with NET	• Frequency and severity of adverse events (AEs), physical examination findings, vital signs, laboratory tests, ECG, and echocardiogram/multigated acquisition

Brief Summary

This is a phase 2, open-label, multicenter study of surufatinib in patients with locally advanced or metastatic, low- to intermediate-grade (grade 1 or grade 2), well-differentiated NETs. The study will enroll 4 cohorts of varying NETs, as follows:

- Cohort A – NET of lung origin
- Cohort B – NET of small bowel origin
- Cohort C – NET of non-small bowel, non-pancreas, and non-lung origin
- Cohort D – NET of any origin (drug-drug interaction [DDI] substudy)

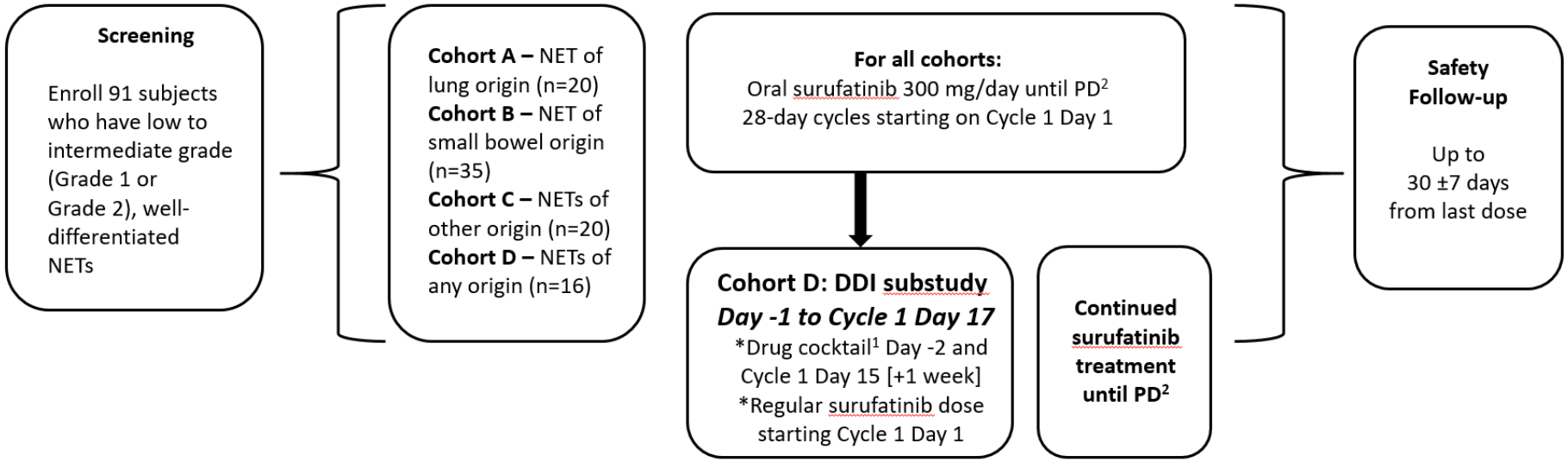
Condition/Disease	NETs
Study Duration	18 months (including 12 months of enrollment)
Treatment Duration	Until disease progression or other discontinuation criteria are met
Health Measurement/Observation	DCR at 6 months
Visit Frequency	Cycle 1: Every week (±1 day, except days 1 and 2) Cycle 2: Every 2 weeks (±3 days) Cycle 3 and onwards: Every 4 weeks (±3 days) End of Treatment: 30±7 days after the last dose
Number of Participants	Total: Approximately 91 patients Per cohort: Approximately 20 patients in Cohorts A and C, approximately 35 patients in Cohort B, and 16 patients in Cohort D
Intervention Groups and Duration	On study duration (including screening and follow-up): treatment until disease progression plus 4-week screening period and 30-day (±7 days) follow-up **Cohorts A, B, and C:** oral surufatinib 300 mg once daily (QD) in treatment cycles of 28 days starting on cycle 1 day 1 **Cohort D:** • Day -2: A single dose of drug cocktail consisting of midazolam 2.5 mg, fexofenadine 30 mg, and rosuvastatin 10 mg • Cycle 1 day 1 to cycle 1 day 14: Oral surufatinib 300 mg QD • Cycle 1 day 15 (+1 week): Oral surufatinib 300 mg QD and a single dose of the drug cocktail

	• Cycle 1 day 16 and beyond: Oral surufatinib 300 mg QD in treatment cycles of 28 days In general, dose modification is allowed no more than twice, from 300 mg QD to 250 mg QD and then to 200 mg QD. Full details for individual toxicities are provided in the protocol.
Independent Monitoring	The sponsor will review study safety data every 6 months or more frequently if safety concerns arise.

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Schematic of Study 2020-012-00EU1



DDI=drug-drug interaction; NET=neuroendocrine tumor; PD=progressive disease.

1. Single dose of drug cocktail consisting of midazolam 2.5 mg, fexofenadine 30 mg, and rosuvastatin 10 mg.
2. Patients will continue to receive surufatinib treatment until disease progression, death, unacceptable toxicity, withdrawal of consent, lost to follow-up, the patient is no longer receiving clinical benefit in the opinion of the investigator, the start of subsequent anticancer therapy, or the sponsor ends the study.

1.2 Schedule of Events

The schedule of events is presented in Table 1.

Table 1 Schedule of Events

Study Visit / Procedure	Screening		Pretreatment[1]		Treatment[2]							Treatment Completion[3]
					Cycle 1				Cycle 2		Cycle 3 and Onward	
	Day -28 to Day -1	Day -7 to Day -1	Day -2	Day -1	Day 1	Day 8 (±1 D)	Day 15 (±1 D)[4]	Day 22 (±1 D)	Day 1 (±3 D)	Day 15 (±3 D)	Day 1 (±3 D) and Then Every 4 Weeks	30±7 D After Completion
Informed consent[5]	X											
Medical and surgical history	X											
Demographics	X											
ECOG performance status	X				X		X		X	X	X	X
Vital signs[6]	X		X		X	X	X	X	X	X	X	X
Height	X											
Complete physical examination[7]	X											
Limited physical examination[7]			X		X	X	X	X	X	X	X	X
Hematology[8]		X[9]				X	X	X	X	X	X	X
Coagulation assay (aPTT, PT/INR)		X[9]					X		X		X	
Serum chemistry[10]		X[9]				X	X	X	X	X	X	X

Study Visit / Procedure	Screening		Pretreatment[1]		Treatment[2]							Treatment Completion[3]
					Cycle 1				Cycle 2		Cycle 3 and Onward	
	Day -28 to Day -1	Day -7 to Day -1	Day -2	Day -1	Day 1	Day 8 (±1 D)	Day 15 (±1 D)[4]	Day 22 (±1 D)	Day 1 (±3 D)	Day 15 (±3 D)	Day 1 (±3 D) and Then Every 4 Weeks	30±7 D After Completion
Lipid panel[11]	X										X	
Pregnancy tests[12]		X[9]							X		X	X
Urinalysis[13]		X[9]				X	X	X	X	X	X	X
Thyroid function test[14]	X								X		X	X
Echocardiogram/MUGA	X					Every 12 weeks (±7 D) after the first dose						
12-lead ECG[15]		X[9]			Refer to Table 2 for Cohorts A, B, and C and Table 3 for Cohort D				X		X	X
Tumor assessment[16]	X				Every 8 weeks for the first 24 weeks from C1D1 (±7 D), then every 12 weeks thereafter (±14 D)							
Meal			X[17]		X		X[17,]					
PK plasma sampling			X[17]	X[17]	Refer to Table 2 for Cohorts A, B, and C and Table 3 for Cohort D							
Surufatinib administration					X							
Cocktail drug administration[1]			X				X					
Prior and concomitant medications[19]	X				X	X	X	X	X	X	X	X
Adverse events		X										

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=cycle; CT=computed tomography; D=day(s); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; INR=international normalized ratio; IV=intravenous; MUGA=multigated acquisition; PD=progressive disease; PK=pharmacokinetic; PT=prothrombin time; QTc=corrected QT interval;

RECIST=Response Evaluation Criteria in Solid Tumors.

1. Day -2 and day -1 and corresponding assessments are only applicable for patients in Cohort D.
2. During C1, the visit window will be ±1 day (unless otherwise noted). From C2 onward, the visit window will be ±3 days (unless otherwise noted).
3. All patients on active treatment at the time of Amendment 6 are required to return to the study site for a follow-up within 30 ±7 days after the last dose of surufatinib received. Treatment with surufatinib should be discontinued on Day 28 of the last cycle that can be fully completed no later than CCI . All treatment completion assessments described in the above table should be followed, including the final collection of patient drug diaries/final drug accountability review. Patients who discontinue study treatment for any reason need to return to the study site for a follow-up within 30±7 days after the last dose of surufatinib. An ongoing AE related to surufatinib will be followed until the event has resolved to baseline grade , the investigator evaluates the AE as stable, or new antitumor treatment is initiated , the patient is lost to follow-up, the patient withdraws informed consent, or it is determined that the study treatment or participation is not the cause of the event.
4. For the first approximately 40 patients of Cohorts A, B, and C and all patients in Cohort D, visits for C1D15 may be scheduled up to 1 week **after** but not before C1D15. This is to ensure that surufatinib reaches steady state (14 days after first dose).
5. A signed ICF should be obtained prior to any protocol-specific procedure or test. Tests completed within 28 days prior to enrollment can be used for screening and do not need to be repeated, with the exception of certain laboratory tests.
6. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. For patients receiving antihypertensive medications with either a baseline history of hypertension or new onset of hypertension during the study, blood pressure should be monitored per institutional standard practice.
7. Complete physical examination refers to the examination of all body systems, including weight. Limited physical examination includes vital signs, any change from baseline abnormalities, any new abnormalities, weight, and evaluation of patient-reported symptoms. In order to assess changes from baseline and screen for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, hepatomegaly, and splenomegaly.
8. The set hematology assessments at these visits consist of complete blood count, including hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count.
9. These tests are to be completed within 7 days before the start of surufatinib treatment.
10. The chemistry panel includes blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, total bilirubin, direct bilirubin, ALT, AST, ALP, lactic dehydrogenase, amylase, total protein, albumin, and uric acid.
11. Lipid panel includes total cholesterol and triglycerides and is to be obtained during screening, C3D1 (±3 days), then every 4 weeks (±3 days).

12. Women of childbearing potential will receive a serum pregnancy test during screening within 7 days prior to surufatinib treatment and within 30±7 days after treatment completion. In addition, serum or urine pregnancy tests will be performed on C2D1 (±3 days) and continue on D1 (±3 days) at each 4-week cycle thereafter. If pregnancy is suspected, additional tests should be completed. In the case of menopausal women, the date of menopause onset should be recorded.
13. Urinalysis includes pH, glucose, protein, and blood. If protein is ≥2+ during screening and/or the period of study treatment, a 24-hour urine test should be conducted within 1 week. If 24-hour urine is required at screening, protein must be ≤1g to be eligible.
14. Includes free triiodothyronine, free thyroxine, and thyroid-stimulating hormone. In the absence of symptoms, the investigator may determine if assessing thyroid function every 2 to 3 cycles is sufficient.
15. Triplicate ECGs (using Holter monitor) will be collected in patients enrolled in cohorts A, B, and C on C1D1 and C1D15 (+1 week) in for QTc evaluation according to the time points outlined in Table 2. Safety ECG will be conducted on C2D1 and C3D1. From C4 onward, ECG will only be performed as clinically indicated.
16. The baseline tumor assessment can be completed within 28 days prior to enrollment. All measurable and evaluable lesions should be assessed and documented at this visit, using physical examination and image-based evaluation. Screening assessments include CT scans with oral and IV contrast of the chest, abdomen, and pelvis. Bone scans and CT scan of the neck should also be performed if clinically indicated. Tumor response will be assessed using RECIST version 1.1 (Appendix 2 [Section 15]). The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST version 1.1 (Appendix 2 [Section 15]) may be used. Patients discontinuing surufatinib for reasons other than PD are to continue tumor assessments until documented disease progression, start of new antitumor therapy, or withdrawal of informed consent.
17. Meals are applicable for all patients in Cohort D; refer to Table 3 for specific details and time points.
18. Concomitant medication includes any prescribed or over-the-counter medicines. All medication used by patients within 7 days before screening and 30 days after study completion should be recorded. At each visit, all medication used since the last record should be recorded.

Table 2 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations (Cohorts A, B, and C)

Study Visit	Time Relative to Dosing	Study Drug Intake[1]	Patients Assigned to Holter Monitoring				All Other Patients	
			Meal	PK Samples[2]	Triplicate ECG for QTc Evaluation (Holter Monitor)	Safety ECG (Standard Equipment)	PK Samples[2]	Safety ECG (Standard Equipment)
C1D1	-30 min		X[5]					
	Predose[3]				X			X
	0 h	X						
	1 h (±5 min)			X	X		X (anytime between 1 and 4 h)	
	2 h (±5 min)			X	X			
	3 h (±5 min)			X	X			
	3.5 h		X[6]					
	4 h (±5 min)			X	X			
C1D8	Predose[3]			X			X	
	0 h	X						
C1D15 (+1 week window)[4]	-30 min		X[5]					
	Predose[3]			X	X		X	
	0 h	X						
	1 h (±5 min)			X	X			
	2 h (±5 min)			X	X		X	X
	3 h (±5 min)			X	X			
	3.5 h		X[6]					
	4 h (±5 min)			X	X			
C1D22	Predose[3]			X			X	
	0 h	X						
C2D1	Predose[3]			X			X	
	0 h	X						
	2 h (±5 min)			X		X	X	X
C3D1[7]	Predose[3]			X			X	
	0 h	X						

	2 h (±5 min)			X		X	X	X
C4D1 and every other cycle thereafter[7]	Predose[3]			X			X	
	0 h	X						

C=Cycle; D=Day; ECG=electrocardiogram; eCRF=electronic case report form; h=hour; min=minute; PK=pharmacokinetic(s); QTc=corrected QT interval.

1. On PK sampling days, study drug must be taken at the investigative site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered on the day of PK collection and 1 day before PK collection must be recorded on the eCRF.
2. The actual date and time of the PK samples must be recorded on the eCRF.
3. Predose PK and ECG must be performed within 30 minutes **before** study drug administration.
4. Visits for C1D15 may be scheduled up to 1 week **after** but not before C1D15. This is to ensure that surufatinib reaches steady state (14 days after first dose).
5. Breakfast should be consumed within 30 minutes. Dosing should occur within 5 minutes after completion of breakfast but no more than 30 minutes after the start of breakfast.
6. Lunch to be given at 3.5 hours.
7. PK samples will no longer be required on C3D1 and beyond. Refer to Section 6.1.4.1 for more details.

Table 3 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations (Cohort D)

Phase	Cycle Day	Time Relative to Dosing	Study Drug Intake[1]		PK Samples[2,3]				Meal	ECG
			Drug Cocktail[4]	Surufatinib	Midazolam	Fexofenadine	Rosuvastatin	Surufatinib		
Pretreatment	D -2	-30 min							X[5]	
		Predose[6]			X	X	X			
		0	X							
		15 min (±2 min)			X					
		30 min (±2 min)			X	X				
		1 h (±5 min)			X	X	X			
		2 h (±10 min)			X	X	X			
		3 h (±10 min)			X	X	X			
		4 h (±10 min)			X	X	X		X[7]	
		5 h (±20 min)			X	X	X			
		6 h (±20 min)			X	X	X			
		8 h (±20 min)			X	X	X			
		10 h (±20 min)			X	X	X			
	D -1	24 h (±30 min)			X	X	X			

Table 3 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations (Cohort D)

Phase	Cycle Day	Time Relative to Dosing	Study Drug Intake[1]		PK Samples[2,3]				Meal	ECG
			Drug Cocktail[4]	Surufatinib	Midazolam	Fexofenadine	Rosuvastatin	Surufatinib		
		36 h (±30 min)					X			
Treatment	C1D1	48 h/ predose[6]					X			X
		0 h		X						
	C1D15 (+1 week window)[8]	-30 min							X[5]	
		Predose[6]			X	X	X	X		X
		0	X[9]	X[9]						
		15 min (±2 min)			X					
		30 min (±2 min)			X	X		X		
		1 h (±5 min)			X	X	X	X		
		2 h (±10 min)			X	X	X	X		X
		3 h (±10 min)			X	X	X	X		
		4 h (±10 min)			X	X	X	X	X[7]	
		5 h (±20 min)			X	X	X	X		
		6 h (±20 min)			X	X	X	X		
		8 h (±20 min)			X	X	X	X		

Table 3 Schedule of Events for Pharmacokinetic and Electrocardiogram Evaluations (Cohort D)

Phase	Cycle Day	Time Relative to Dosing	Study Drug Intake[1]		PK Samples[2,3]				Meal	ECG
			Drug Cocktail[4]	Surufatinib	Midazolam	Fexofenadine	Rosuvastatin	Surufatinib		
		10 h (±20 min)			X	X	X	X		
	C1D16	24 h/ predose[6] (±30 min)		X	X	X	X	X[6]		
		36 h (±30 min)					X			
	C1D17	48 h/ predose[6] (±30 min)					X			
		0 h		X						
	C2D1	Predose[6]						X		
		0 h		X						
		2 h						X		X
	C3D1[10]	Predose[6]						X		
		0 h		X						
		2 h						X		X
	C4D1 and every other cycle thereafter[10]	Predose[6]						X		
		0 h		X						

C=cycle; D=day; ECG=electrocardiogram; eCRF=electronic case report form; h=hour(s); min=minute(s); PK=pharmacokinetic(s).

1. On PK sampling days, study drug must be taken at the investigative site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered on the day of PK collection must be recorded on the eCRF.
2. The actual date and time of the PK samples must be recorded on the eCRF.
3. Relative to drug cocktail administration.
4. Dosing of the cocktail components will be done sequentially in the following order: midazolam, fexofenadine, and rosuvastatin.
5. Breakfast should be consumed within 30 minutes. Dosing should occur within 5 minutes after completion of breakfast but no more than 30 minutes after the start of breakfast.

6. Predose PK blood sample and ECG (when required) must be taken within 15 minutes **before** surufatinib administration.
7. Lunch to be given after the 4-hour PK blood sample.
8. Visits for C1D15 may be scheduled up to 1 week **after** but not before C1D15. This is to ensure that surufatinib reaches steady state (14 days after first dose).
9. Surufatinib and the drug cocktail should be taken at approximately the same time. Surufatinib should be taken prior to intake of the drug cocktail.
10. PK samples will no longer be required on C3D1 and beyond. Refer to Section 6.1.4.1 for more details

2 INTRODUCTION

2.1 Background

2.1.1 Target Indication and Population

Upon implementation of this protocol amendment, CCI [redacted] The termination of this study is based upon the strategic re-evaluation of the clinical development program for surufatinib in Europe and the United States. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment.

Angiogenesis plays a key role in the pathogenesis of neuroendocrine tumors (NETs) (Terris et al 1998), which are rare, highly vascular tumors with overexpression of angiogenic markers, including vascular endothelial growth factor (VEGF) and fibroblast growth factor. The prognosis of patients with NETs varies according to a number of different factors, including location of the primary tumor, histological grade, and tumor stage at diagnosis, with patients with NETs originating in the pancreas having the worst prognosis and 5-year survival at 8.7% for those with poorly differentiated high-grade tumors at diagnosis (Halfdanarson et al 2008, Man et al 2018). Treatment options for managing locoregional and metastatic NETs consist primarily of cytoreductive surgery and systemic antitumor therapy (NCCN 2019, Pavel et al 2020, Shah et al 2018). Small molecule drugs, including sunitinib and sorafenib, targeting the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase signaling pathway have contributed significantly to treating cancer (Escudier et al 2007, Motzer et al 2007). However, most of the early generation small molecule VEGFR tyrosine kinase inhibitors (TKIs) inhibit many kinases other than VEGFR, resulting in 'off-target' toxicities. AntiVEGFR agent sunitinib and mammalian target of rapamycin inhibitor everolimus, approved for the treatment of pancreatic neuroendocrine tumor (pNET-) in the United States (US) and the European Union (EU), have shown improvement in progression-free survival (PFS), with an objective response rate (ORR) of just under 10% in patients with pNETs (Raymond et al 2011, Yao et al 2013). Currently, there is no approved targeted therapy for other types of NETs besides pNETs and extrapancreatic neuroendocrine tumor (epNETs) (nonfunctioning) in the US and the EU.

2.1.2 Description of Surufatinib

Surufatinib is a small molecule kinase inhibitor that primarily targets tumor angiogenesis. It potently inhibits VEGFR1, 2, and 3, fibroblast growth factor receptor 1 (FGFR-1), and colony stimulating factor-1 receptor (CSF-1R) kinase with half maximal inhibitory concentration (IC_{50}) of 1 to 24 nM. Surufatinib was found to have higher kinase selectivity than sunitinib and showed a similar inhibitory effect on VEGFR2 (KDR) but a weaker effect on other kinases, such as PDGFRβ, FLT3, and YES, compared with sunitinib. For further details, refer to the Investigator's Brochure (IB).

The dosing regimen for this study is orally administered surufatinib 300 mg once daily (QD). See Section 7.1.2 for further details. The optimal dose and dosing schedule for surufatinib were determined in 2 phase 1 studies; 1 conducted in China CCI [redacted] and the other is being conducted in the US (2015-012-00US1). A food-effect study CCI [redacted] was also

conducted to guide dosing in clinical studies. Additionally, a phase 1b/2 CCI and phase 3 (2015-012-00CH4, known as SANET-ep, and 2015-012-00CH3, known as SANET-p) studies further evaluated the recommended phase 2 dose and confirmed that surufatinib 300 mg QD provided safe and effective therapy in patients with advanced NETs. This is also the standard dose and dosing schedule in all other completed, ongoing, and planned studies in patients with advanced cancer. Refer to the IB for full details on dosing determination.

2.1.3 Supportive Nonclinical Data

In vitro assays demonstrated that CCI In vivo data on VEGFR2 phosphorylation have indicated that if the coverage on complete target inhibition lasted for more than 8 hours, surufatinib could significantly suppress tumor growth, and if the coverage lasted for more than 16 hours, surufatinib might induce tumor regression. In safety pharmacology studies, the results showed surufatinib had low risk in the cardiovascular, respiratory, and central nervous systems.

In vitro results suggest that CCI

CCI

Refer to the IB for full details on nonclinical findings.

2.1.4 Supportive Clinical Data

Surufatinib is currently in clinical development in multiple cancer indications at various stages. As of 11 February 2020, 8 clinical studies have been completed (including 3 in healthy volunteers and 5 in patients with cancer); 5 clinical studies in patients with cancer are ongoing. Refer to the IB for further information.

2.1.4.1 Clinical Pharmacokinetics

In Chinese patients with cancer, surufatinib was absorbed rapidly, with concentration reaching maximum level after 1.0 to 2.0 hours of dosing. Mean plasma half-life ranging from 14.9 to 20.2 hours was observed. Following multiple doses of surufatinib QD, plasma surufatinib concentration reached steady state by 14 days after dosing, with exposure accumulating 1.2- to 2.4-fold at steady state compared to day 1 (Studies CCI). Preliminary pharmacokinetic (PK) results from the US patient population (Study 2015-012-00US1 [ongoing]) showed that surufatinib exposure, in general, increased proportionally with an increasing dose from 50 to 400 mg QD. There were no meaningful differences in surufatinib exposure between Chinese and US patients.

A study for a single oral dose of surufatinib 250 mg under fasting or fed conditions indicated that the absorption extent of surufatinib was not affected by food intake, but the absorption rate was affected, as demonstrated by the significant difference in time to reach the maximum plasma concentration (t_{max}).

2.1.4.2 Clinical Efficacy

Surufatinib has demonstrated statistically significant and clinically meaningful efficacy in 2 completed phase 3, randomized, double-blind, placebo-controlled studies in China in patients with advanced epNET (SANET-ep) and patients with advanced pNET (SANET-p) and has shown promising antitumor activity in the US (Study 2015-012-00US1). The SANET-ep study met its primary endpoint at the planned interim analysis, with significantly improved PFS in surufatinib-treated patients compared with placebo-treated patients (median PFS of 9.2 months surufatinib versus 3.8 months placebo; hazard ratio [HR] of 0.334; p<0.0001). Similarly, surufatinib-treated patients in the SANET-p study showed a statistically significant improvement in PFS compared with placebo-treated patients (median PFS of 10.9 months in surufatinib versus 3.7 months placebo; HR of 0.491; p=0.0011). In addition to the primary PFS endpoint, SANET-ep and SANET-p demonstrated meaningful improvements in other important efficacy measures, such as ORR, disease control rate (DCR), duration of response (DoR), and time to response (TTR). In the ongoing Study 2015-012-00US1, a total of 32 patients with progressive NETs were enrolled (16 pNET and 16 epNET). In the pNET cohort, 3 patients achieved a confirmed partial response (PR), and 1 patient achieved unconfirmed PR, and an ORR of 18.8% was observed. In the epNET cohort, 1 patient achieved an unconfirmed PR. All patients had previously received everolimus and/or sunitinib (Dasari et al 2020). As the treatment of advanced NETs in China generally follows the same paradigm as that in Western countries, supported by emerging Study 2015-012-00US1 data, the patient populations in SANET-ep and SANET-p received prior therapies that were consistent with contemporaneously available treatments in the EU, and the efficacy data are applicable to EU populations.

2.1.4.3 Clinical Safety

As of 30 June 2020, the safety database includes 955 patients (792 in monotherapy and 163 in combination therapy) and 128 healthy patients who received surufatinib as monotherapy or combination therapy in completed or ongoing studies. Refer to the IB for full safety information. Of the 792 patients who received at least 1 dose of monotherapy of surufatinib, 781 (98.6%) patients reported treatment-emergent adverse events (TEAEs), and 757 (95.6%) patients reported treatment-related TEAEs. Treatment-related TEAEs reported in ≥20% of patients included, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, proteinuria, hypertension, diarrhoea, blood bilirubin increased, blood thyroid-stimulating hormone increased, aspartate aminotransferase (AST) increased, hypertriglyceridemia, occult blood positive, and alanine aminotransferase (ALT) increased. A total of 568 (71.7%) patients reported TEAEs of grade ≥3 regardless of causality, of which hypertension and proteinuria occurred in >10% of patients. Approximately one-third of patients experienced a serious adverse event (SAE), and the most common (frequency of ≥1%) were gastrointestinal hemorrhage, intestinal obstruction, hepatic function abnormal, proteinuria, pneumonia, acute kidney injury, jaundice cholestatic, abdominal pain, and anaemia. The reported fatal SAEs that were considered related to study treatment (31 patients) included hypovolaemic shock, diarrhoea, gastrointestinal haemorrhage,

disseminated intravascular coagulation (DIC) and hepatic encephalopathy, liver injury, cerebral haemorrhage, and death. A total of 142 (17.9%) patients reported TEAEs leading to drug discontinuation, of which proteinuria and hepatic function abnormal were reported in ≥1% of patients.

2.1.5 Benefit/Risk Assessment

2.1.5.1 Risk Assessment

Overall, nonclinical and clinical study results have demonstrated that surufatinib has an acceptable safety profile and is well tolerated. Identified risks for surufatinib are hepatic disorder, hemorrhage, hypertension, and acute kidney injury.

Details regarding identified risks for surufatinib can be found in the current Investigator's Brochure.

2.1.5.2 Benefit Assessment

Surufatinib is a selective, small molecule, kinase inhibitor of VEGFR1, 2, and 3; FGFR-1, and CSF-1R kinase that may fulfill a critical unmet need for patients with NETs. Efficacy data from the randomized, double-blind, placebo-controlled, phase 3 studies SANET-ep and SANET-p have demonstrated encouraging antitumor activity in terms of PFS, ORR, DCR, DoR, and TTR. The primary endpoint of PFS showed clinically meaningful and statistically significant improvement in both studies (SANET-ep: HR 0.334, $p<0.0001$; and SANET-p: HR 0.491, $p=0.0011$). The favorable data resulted in early termination of SANET-ep- and SANET-p at the interim analysis upon recommendation of their respective, independent data monitoring committees. Surufatinib can provide another treatment option to patients with NETs who have poor prognosis and few treatment options available.

2.1.5.3 Overall Benefit/Risk Conclusion

Based on the summary of efficacy and safety data, the proposed safety management actions, the limited life expectancy of patients with advanced malignancies, and the lack of effective alternative treatments, the overall benefit/risk assessment supports the administration of surufatinib to patients with NETs as an investigational treatment.

2.2 Study Rationale

This study primarily aims to demonstrate similar efficacy of surufatinib as seen in SANET-ep and SANET-p in European patients with locally advanced or metastatic, well-differentiated, low- to intermediate-grade NETs reflective of the tumor types seen in the European population. Current NET therapies are not highly selective and result in unintended 'off-target' toxicities. Improving kinase selectivity is a key focus for newer generation TKIs. Surufatinib, a small molecule, selective inhibitor of VEGFR1, 2, 3, FGFR-1, and CSF-1R, has demonstrated efficacy in 2 randomized, double-blind, placebo-controlled studies in NETs of extrapancreatic origin and pancreatic origin (Section 2.1.4.2), which were prematurely terminated by their respective, independent data monitoring committees following a preplanned interim analysis due to surufatinib demonstrating superior efficacy over placebo in terms of the primary endpoint of PFS.

In vitro studies indicated that surufatinib has the potential to inhibit CYP3A4 in a time-dependent manner and cause reversible inhibition of P-glycoprotein (P-gp) and BCRP at clinically relevant concentrations (see the IB for details). In addition to the overall study purpose, the present study aims to further assess the in vivo significance of these nonclinical findings in European and US patients with NETs of any origin using a cocktail approach in a specific drug-drug interaction (DDI) cohort.

3 OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the antitumor activity of surufatinib in patients with locally advanced or metastatic, well-differentiated, low- to intermediate-grade NETs as determined by DCR at 6 months.

Table 4 describes the study objectives and endpoints.

Table 4 Objectives and Endpoints for Study 2020-012-00EU1

Tier	Objectives	Endpoints
Primary	• To evaluate the antitumor activity of surufatinib in patients with low- to intermediate-grade (grade 1 or grade 2), well-differentiated NET	• DCR at 6 months
Secondary	• To characterize the PK of surufatinib in patients with NET	• Observed plasma concentrations, estimated population PK, and exposure parameters of surufatinib
	• To evaluate the effect of surufatinib on cardiac repolarization, as detected by changes in ECG QTc, and the potential relationship with surufatinib plasma concentrations	• QTc and plasma concentrations of surufatinib at specified time points
	• To further characterize the antitumor activity of surufatinib in patients with NET	• Additional efficacy endpoints ○ ORR ○ TTR ○ DoR ○ PFS
	• **Cohort D only:** To evaluate the effects of repeat dosing of surufatinib on the single-dose PK of CYP3A4, P-gp, and BCRP substrates in patients with NET	• **Cohort D only:** Exposure parameters of CYP3A4, P-gp, and BCRP substrates
	• To evaluate the safety and tolerability of surufatinib in patients with NET	Safety assessments include the following: • Frequency and severity of AEs • Physical examination findings • Vital signs • Laboratory tests • ECG • Echocardiograms/MUGA

AEs=adverse events; BCRP=breast cancer resistance protein; CYP=cytochrome P450; DCR=disease control rate; DoR=duration of response; ECG=electrocardiogram; MUGA=multigated acquisition; NET=neuroendocrine tumor; ORR=objective response rate; PFS=progressive-free survival; P-gp=P-glycoprotein; PK=pharmacokinetic; QTc=corrected QT interval; TTR=time to response.

4 STUDY PLAN

4.1 Study Design

This is a phase 2, open-label, multicenter study of surufatinib in patients with locally advanced, or metastatic low- to intermediate -grade (grade 1 or grade 2), well-differentiated NETs. The study will enroll 4 cohorts of varying NETs, as follows:

- Cohort A – NET of lung origin
- Cohort B – NET of small bowel origin
- Cohort C – NET of non-small bowel, non-pancreas, and non-lung origin
- Cohort D – NET of any origin (DDI substudy)

The study planned to enroll approximately 20 patients each in Cohorts A and C, approximately 35 patients in Cohort B, and 16 patients in Cohort D respectively. At the time of protocol amendment preparation (16 November 2023), Cohort B had enrolled 32 patients and Cohort D had enrolled 6 patients. Cohort A had enrolled 20 patients and Cohort C had enrolled 32 patients.

All patients will be treated with a dose of oral surufatinib 300 mg QD in treatment cycles of 28 days starting on cycle 1 day 1. All patients will undergo continuous safety monitoring and tumor assessment on a routine basis. Patients enrolled to Cohorts A, B, and C only will undergo electrocardiogram (ECG) monitoring via a Holter monitor on day 1 and day 15 (+1 week) of the first cycle of treatment. The goal will be to obtain complete Holter monitor data for approximately 40 patients. The number of subjects undergoing Holter assessments may be increased to ensure full, usable data is available. Patients will continue to receive surufatinib treatment until disease progression, death, unacceptable toxicity, withdrawal of consent, lost to follow-up, the patient is no longer receiving clinical benefit in the opinion of the investigator, the start of subsequent anticancer therapy, or the sponsor ends the study.

Based upon the strategic re-evaluation of the clinical development program for surufatinib in Europe and the United States, the study will be terminated. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. CCI [redacted].

DDI substudy (Cohort D): Patients with NETs of any origin

Approximately 16 additional patients with NETs of any origin will be enrolled to Cohort D for the DDI substudy at study sites selected by the sponsor. The primary objective of this cohort is to investigate the potential DDI between surufatinib and a drug cocktail containing selective probes of CYP3A4 (midazolam), P-gp (fexofenadine), and BCRP (rosuvastatin) substrates. Treatment cycles for Cohort D are outlined in Table 3. The DDI drug cocktail will be given on day -2 during the pretreatment phase, and assessment of PK profiles of the probe substrates will be conducted at baseline on days -2 and -1 (ie, during the 48-hour period before starting treatment with surufatinib) and after repeated dosing with surufatinib at a dose of 300 mg QD for at least 14 days (surufatinib steady state on cycle 1 day 15 [+1 week]). Patients enrolled to this cohort will not have to undergo Holter monitoring.

For this DDI cohort, the most critical question will be answered with the completion of cycle 1 day 17. Therefore, once all patients in this cohort have completed the required study procedures

up to cycle 1 day 17, an interim data cutoff is planned to evaluate the short-term safety and the PK profile. An interim PK report for Cohort D will be written on the basis of this data cutoff date.

Table 5 Cohort D Treatment Overview

Phase	Cycle Day	Dose Regimen
Pretreatment	D -2	A single dose of drug cocktail consisting of the following: • Midazolam 2.5 mg • Fexofenadine 30 mg • Rosuvastatin 10 mg
Treatment	C1D1 to C1D14	Surufatinib 300 mg QD
Treatment	C1D15 (+1 week)	A single dose of surufatinib 300 mg **and** a single dose of drug cocktail consisting of the following: • Midazolam 2.5 mg • Fexofenadine 30 mg • Rosuvastatin 10 mg
Treatment	C1D16 and beyond	Surufatinib 300 mg QD

C=cycle; D=day(s); QD=once daily.

The safety of all enrolled patients will be closely and continuously monitored from the time of informed consent until 30±7 days after the last dose. Any SAEs that occur after the informed consent form (ICF) is signed, but before the first dose of study drug is taken, should also be reported. All adverse events (AEs) will be graded in accordance with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In addition, safety will be monitored by a Safety Review Committee (SRC), as described in Section 11.1.1.

Tumor assessments will be conducted according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (Appendix 2 [Section 15]) at screening, every 8 weeks for the first 24 weeks from cycle 1 day 1 (±7 days), and then every 12 weeks thereafter (±14 days). Confirmation of complete response (CR) and PR is required at least 4 weeks after the criteria for response are first met.

See Section 1.1 for the study schematic.

4.2 Design Rationale

The open-label design of Cohorts A, B, and C was chosen to confirm that the safety and efficacy seen in a Chinese patient population (established in 2 randomized, double-blind, placebo controlled studies [SANET-p and SANET-ep]) can be demonstrated in European subjects. Because surufatinib has already proven to be a valid treatment option for NETs and no other treatment options are available to patients, an open-label design was appropriate for this study. Introducing a placebo control group would raise problems of ethics, acceptability, and feasibility.

In this study, the drug interaction potential of surufatinib will be assessed in Cohort D using a cocktail containing selective probes of CYP3A, P-gp, and BCRP. This cocktail approach is considered an advantageous strategy to obtain actual and reliable information on multiple enzyme and transporter protein activities within 1 study and minimize intra-individual variability. The probe drugs are selected in accordance with the existing guidelines (EMA 2012, FDA 2020) and

drug interaction studies reported in the literature. The absence of any in vivo interaction between the individual cocktail probes is crucial. The combination of midazolam and fexofenadine in a cocktail for DDI assessment has been reported (Bosilkovska et al 2014, Duran et al 2020). Although rosuvastatin (BCRP) has not been evaluated in a cocktail, co-administration of rosuvastatin is not expected to interact with midazolam and fexofenadine based on their well characterized DDI profiles. To date, none of the drugs are reported to have the propensity to significantly affect the PK of other drugs via interaction with metabolic enzyme or transporter.

To evaluate the effect of surufatinib as a time-dependent inhibitor of CYP3A, multiple doses of surufatinib to reach a clinically relevant concentration are necessary in order to achieve full effects on enzyme inhibition. The need for repeat-dose administration to reach steady state conditions for surufatinib precludes the conduct of this study in healthy subjects because of potential tolerability concern in healthy volunteers. Therefore, this study will be conducted in patients with NETs.

The surufatinib dose selected for this study is 300 mg QD, the therapeutic dose demonstrated to be efficacious and have good tolerability in patients with NETs. The doses of the drug cocktail proposed in this study are similar to those used by other cocktail drug interaction studies in the literature. The drug cocktail will be administered after intake of a light breakfast, which should be completed within approximately 30 minutes (see Section 7.1.2). This provision is not expected to affect the PK results as conditions will be maintained across the 2 treatment periods, and most of these probe drugs can be given with or without food, or exhibit no significant food effect, according to the literature.

5 POPULATION

5.1 Recruitment

This study will enroll approximately 91 patients from 18 investigational sites in Europe and approximately 4 investigational sites in the US. The US sites will enroll patients to Cohort D only.

Upon implementation of Protocol Amendment 5 (05 December 2022), the enrollment was halted.

Upon implementation of this protocol amendment, CCI [redacted]

5.2 Definitions

Patients enter the screening period following provision of informed consent either directly or via a legally authorized representative.

A screen failure is a consented patient who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may be rescreened once.

An enrolled patient is one who has been deemed eligible and has been assigned to a treatment group.

5.3 Inclusion Criteria

To be included in this study, each patient must satisfy all the following criteria:

1. Has histologically or cytologically documented, locally advanced, or metastatic low- to intermediate-grade (grades 1 to 2) NETs and has progressed on at least 1 prior line of therapy but no more than 3 therapies:
    a. Cohort A: NET of lung origin
    b. Cohort B: NET of small bowel origin
    c. Cohort C: NET of non-small bowel, non-pancreas, and non-lung origin
    d. Cohort D (DDI substudy): NET of any origin
2. Has radiologic evidence of progressive tumor within 12 months of study enrollment
3. Is willing and able to provide informed consent
4. Is ≥18 years of age
5. Has measurable lesions according to RECIST version 1.1 (Appendix 2 [Section 15])
6. Has absolute neutrophil count of $\geq 1.5\times10^9$/L, platelet count of $\geq 100\times10^9$/L, and hemoglobin of ≥9 g/dL
7. Has serum total bilirubin of <1.5 times the upper limit of normal (ULN)
8. Has proteinuria of <2+ by urinalysis, or 24-hour urine collection of ≤1 g of protein, or urine protein: urine-creatinine ratio of ≤1.9
9. Has ALT, AST, or alkaline phosphatase (ALP) levels of ≤2.5 times the ULN
    e. Patients with known liver metastases may have ALT, AST, and ALP of ≤3× the ULN

10. Has serum creatinine of <1.5 times ULN **or** creatinine clearance of ≥60 mL/min as estimated by the Cockcroft-Gault formula
11. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 1 [Section 15])
12. Female patients of childbearing potential and male patients with partners of childbearing potential agree to use a highly effective form(s) of contraception that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include oral, progestogen-only, hormonal contraception (combined estrogen/progestogen should be avoided) or highly effective non-oral hormonal contraception (eg, Depo-Provera and Implanon) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or sexual abstinence in line with the preferred and usual lifestyle of the subject. Oral and non-oral hormonal contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. The same criteria are applicable to male patients involved in this clinical study if they have a partner of childbearing potential, and male patients must always use a condom.
    A female is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (ie, ≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of the ovaries and/or uterus).

5.4 Exclusion Criteria

If a patient meets any of the following criteria, he or she is ineligible for this study:

1. Has an AE due to previous antitumor therapy that has not recovered to CTCAE grade ≤1, except alopecia and peripheral neurotoxicity with CTCAE grade ≤2 caused by platinum chemotherapy
2. Major surgery within previous 4 weeks or radiation therapy within 2 weeks prior to the start of treatment (prior palliative radiotherapy for metastatic lesions is permitted if there is at least 1 measurable lesion that has not been irradiated)
3. Prior VEGF/VEGFR-targeted therapy, including, but not limited to sunitinib, axitinib, and cabozantinib
4. Has uncontrollable hypertension, defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, despite antihypertensive medication
5. Prothrombin time (PT)/International normalized ratio (INR) of >1.5 or activated partial thromboplastin time (aPTT) of >1.5×ULN (for patients on Coumadin or Coumadin-like products, please refer to Section 7.3.3)
6. Has gastrointestinal disease or condition within 6 months prior to first dose that investigators suspect may affect drug absorption, including, but not limited to, active gastric and duodenal ulcers, ulcerative colitis and other digestive disease, gastrointestinal tumor with active bleeding, or other gastrointestinal conditions that could, in the investigators' judgment, result in bleeding or perforation

7. Has a history or presence of a serious hemorrhage (>30 mL within 3 months) or hemoptysis (>5 mL of blood within 4 weeks) within 6 months of first dose of study drug
8. Has clinically significant cardiovascular disease, including, but not limited to, acute myocardial infarction within 6 months prior to enrollment, severe/unstable angina pectoris or coronary artery bypass grafting, congestive heart failure of ≥2 according to the New York Heart Association classification, ventricular arrhythmia that needs drug treatment, and left ventricular ejection fraction (LVEF) of <50%
9. Has a mean corrected QT interval by Fridericia (QTcF) of ≥480 ms
10. Has used medication known to cause QT prolongation or torsades de pointes within 2 weeks of screening (see Appendix 5 [Section 15])
11. Has brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease (SD) for 14 days or longer (patients requiring steroids within 4 weeks prior to start of study treatment will be excluded)
12. Has a high risk of bleeding at screening due to tumor invasion into major vessels, such as pulmonary artery, the superior vena cava, or the inferior vena cava, as determined by investigators
13. Has arterial thrombosis or deep venous thrombosis within 6 months prior to first dosing, or thromboembolic events (including stroke and/or transient ischemic attack) within 6 months prior to the first dose of study drug
14. Use of strong or moderate inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of surufatinib (see Appendix 3 [Section 15] for examples)
15. For Cohort D, use of medications that are known substrates, inhibitors, or inducers of CYP3A or substrates of P-gp or BCRP within 3 weeks before the first dose of the drug cocktail (see Appendix 3 [Section 15] for examples)
16. Prior history of other cancers, except those treated with curative intent for in situ non-melanoma skin cancer, breast or cervical cancer, or those treated with curative intent and no evidence of disease in the last 5 years prior to enrollment in the study
17. Has a clinically meaningful ongoing infection (eg, requiring intravenous treatment with anti-infective therapy)
    a. See Appendix 8 (Section 15)for procedures specific to subjects with suspected or confirmed coronavirus disease 2019 (COVID-19)
18. Has clinical symptoms consistent with pancreatitis
19. Has a history of allergies to any ingredient of surufatinib or its capsule shell, including tartrazine (E 102)
20. Pregnant or breastfeeding females will not be entered into this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies (pregnancy tests must be obtained in females who are of reproductive potential)

5.5 Exceptions to Eligibility Criteria

Exceptions to the eligibility criteria will not be permitted.

5.6 Lifestyle Restrictions

Patients must follow the contraception requirements outlined in the inclusion criteria (Section 5.3).

6 STUDY CONDUCT

The following procedures will be performed according to the schedule in Table 1. During cycle 1, the visit window will be ±1 day (unless otherwise noted). From cycle 2 onward, the visit window will be ±3 days (unless otherwise noted).

6.1 Study Procedures

6.1.1 Screening

6.1.1.1 Informed Consent

All patients (or legally authorized representative; see Section 10.3) must sign the ICF prior to any study-related examinations or protocol procedures. All patients who sign ICF are to be entered into the Interactive Web Response System. The system will generate a patient identification number, which will be assigned to the patient. ICFs for patients who are not subsequently enrolled will be maintained at the study site.

6.1.1.2 Medical and Surgical History

A complete medical and surgical history, including the patient's medical history, surgical history, disease history, and prior therapies for disease prior to signing of the ICF, should be recorded at screening. Comorbidities that began prior to signing the ICF should be recorded and followed as medical history.

6.1.1.3 Demographics

Demographic characteristics, including year of birth, sex, ethnic group, and any relevant lifestyle habits, should be recorded at screening and in the applicable electronic case report form (eCRF) (as permitted by local regulations).

6.1.1.4 Eastern Cooperative Oncology Group Performance Status

Patient performance status will be graded according to the ECOG performance status scale at study visits as detailed in Table 1. It is recommended that ECOG performance status scores be evaluated by the same investigator throughout the study. Details on the ECOG assessment and grading scale are available in Appendix 1 (Section 15).

6.1.2 Safety Assessments

6.1.2.1 Vital Signs Assessment

Vital signs will include measurements of body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position. The patient should be seated for approximately 5 minutes before the measurement of the blood pressure.

For patients receiving antihypertensive medications with either a baseline history of hypertension or a new onset of hypertension during the study, blood pressure should be monitored per institutional standard practice.

6.1.2.2 Physical Examination

A complete physical examination at screening should include the evaluation of head, eye, ear, nose, and throat; and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems as well as weight. Height will be measured at screening only.

At subsequent visits, a limited physical examination will be performed to assess vital signs, weight, any changes from baseline abnormalities, any new abnormalities, and evaluation of patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate. In order to assess changes from baseline and screen for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, hepatomegaly, and splenomegaly. Patient-reported symptoms require a physical examination directed to address the symptoms.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, skin lesions, hepatomegaly, and splenomegaly.

6.1.2.3 Laboratory Test Evaluations

Samples for hematology, serum chemistry, urinalysis, and pregnancy testing will be evaluated at the study site's local laboratory. Laboratory assessments will include the following:

- **Hematology:** Complete blood count, including red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, and platelet count
- **Coagulation assay:** (PT/INR and aPTT)
- **Serum chemistry:** Blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, total bilirubin, direct bilirubin, ALT, AST, ALP, lactic dehydrogenase, amylase, total protein, albumin, and uric acid
- **Lipid panel:** Total cholesterol and triglycerides
- **Pregnancy tests:** Serum pregnancy test at screening (within 7 days before the start of surufatinib treatment) and within 30±7 days after treatment completion for all women of childbearing potential, including those who have had a tubal ligation; in addition, serum or urine pregnancy tests will be performed on day 1 of cycle 2 and each subsequent cycle
- **Urinalysis:** Urinalysis includes pH, glucose, protein, and blood. If there is a result of ≥2+ protein on urinalysis, then a 24-hour urine protein test should be done within 1 week; for urinalysis results conversions, please refer to Appendix 7 (Section 15).
- **Thyroid function:** Thyroid-stimulating hormone, free triiodothyronine, and free thyroxine. In the absence of symptoms, the investigator may determine if assessing thyroid function every 2 to 3 cycles is sufficient.

6.1.2.4 Cardiac Monitoring

LVEF is assessed via echocardiogram or multigated acquisition (MUGA) at screening and every 12 weeks (±7 days) thereafter. The modality of the cardiac function assessments must be consistent within a patient, that is, if the echocardiogram is used for the screening assessment, then the echocardiogram should also be used for subsequent scans, if required. The patients should also be examined using the same machine and operator whenever possible.

6.1.2.5 Electrocardiogram Monitoring

Twelve-lead ECGs should be performed according to the time points in Table 2 for Cohorts A, B, and C and Table 3 for Cohort D. The QTcF will be closely monitored.

In addition, a continuous 12-lead Holter monitor will be used for corrected QT interval (QTc) evaluation during cycle 1 in patients enrolled across Cohorts A, B, and C. The results will be sent for central reading (see below in Continuous 12-Lead Holter Monitor for QTc Evaluation for details). Vital signs will be measured (Section 6.1.2.1), a symptom-directed physical examination will be conducted (Section 6.1.2.2), and safety -related blood samples (Section 6.1.2.3) will be collected as per the time points in Table 1; these should always be completed before the start of any ECG recordings.

Continuous 12-Lead Holter Monitor for QTc Evaluation

Continuous ECG recordings using 12-lead Holter monitoring will be collected to evaluate the effects of surufatinib on ventricular repolarization. The assessments will be conducted at predose and postdose on cycle 1 day 1 and cycle 1 day 15 (+1 week) at specific time points summarized in Table 2.

Patients should reside in a quiet setting without distractions (eg, television, cell phones, and staff talking) at each scheduled time point for ECG measurements. Patients should rest in a supine position for at least 10 minutes before and 5 minutes after the scheduled time point and should refrain from talking or moving their arms or legs. Skin preparation should be optimal to obtain high quality ECGs; if deemed appropriate, the chest should be shaved and prepared with light abrasion.

Continuous digital 12-lead Holter ECGs will be recorded as described in the ECG/Holter manual. Good quality 12-lead ECG selection and extraction will occur during a 10-minute timeframe, starting 5 minutes before and ending 5 minutes after the scheduled ECG time point. All Holter recorder devices (as supplied by the central ECG laboratory) will be of the same brand and model with the same software and will have been recently serviced and calibrated. Documentation describing the brand, type, software, and service/calibration history of Holter recorders will be provided by the central ECG laboratory and archived at the site as well as in the sponsor's study file. Transfer of the Holter recordings and extraction of the ECG tracings will be performed as described in the ECG/Holter manual.

Ten-second digital ECG tracings will be extracted from the Holter device in triplicate by the central ECG laboratory according to the following principles:

- The actual time of dosing will be communicated to the central ECG laboratory on the Holter acquisition form completed by the site.
- Using visual inspection or automated tools, as appropriate, the central ECG laboratory will identify a period of stable heart rate on the continuous Holter tracing within ±5 minutes of the nominal ECG time point (determined relative to the actual dosing time for an individual patient). Three 10-second ECGs will be extracted in close succession from this identified segment.
- The scheduled time points for triplicate ECG extraction are summarized in Table 2.

Unless warranted by a specific safety endpoint of the study, the Holter tracings will not be routinely analyzed for rhythm and conduction abnormalities. These analyses will only be performed on individual patient's Holter if warranted by TEAEs (eg, syncope).

6.1.3 Efficacy Assessments

Tumor evaluation of disease for all patients will be done during the screening period, every 8 weeks for the first 24 weeks from cycle 1 day 1 (±7 days) and then every 12 weeks thereafter (±14 days) until disease progression, death, unacceptable toxicity, withdrawal of consent, lost to follow-up, the patient is no longer receiving clinical benefit in the opinion of the investigator, the start of subsequent anticancer therapy, or the sponsor ends the study (Section 6.2.1.1).

At screening, patients will have radiological assessments by cross-sectional imaging of the chest, abdomen, and pelvis (computed tomography [CT], magnetic resonance imaging [MRI], or a combination of CT/MRI) in order to identify lesions. Using CT scans with oral or intravenous (IV) contrast (unless contraindicated) is preferred; MRI scans are allowed if CT contrast is contraindicated. Bone scans and CT scan of the neck should also be performed if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease (PD) is suspected. In addition, other radiographic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. Assessments throughout the study should be made using the same modality as that used at screening. Tumor response will be evaluated locally using physical examination and image-based evaluation by the investigator to support treatment decisions, as well as the primary endpoint of antitumor activity. Tumor response will be evaluated using RECIST version 1.1 (Appendix 2 [Section 15]). Confirmation of CR and PR is required at least 4 weeks after the criteria for response are first met.

Investigators will assign target and nontarget lesions in accordance with RECIST version 1.1 guidelines (Appendix 2 [Section 15]) at screening. These lesions will be followed locally throughout the study to determine continuation of treatment.

6.1.4 Pharmacokinetic Assessments

6.1.4.1 Sample Collection and Handling

For Cohorts A, B, and C, PK samples for measurement of plasma concentrations of surufatinib will be collected according to the schedule in Table 2.

For Cohort D, PK samples will be collected according to the schedule in Table 3. Separate blood samples will be collected for measurement of plasma concentrations of each probe substrate (plus metabolite, where applicable) and surufatinib.

For all cohorts, the exact times and dates of PK blood sampling should be recorded on the eCRF. In addition, the dates and times of surufatinib administered on the day of PK sample collection and 1 day before PK sample collection must be recorded on the eCRF. For Cohort D, the dates and times of the drug cocktail administered on the day of PK sample collection must be recorded on the eCRF.

Detailed information regarding collection, handling, storage, and shipment of plasma samples is provided in the laboratory manual.

Upon implementation of Protocol Amendment 5, for all cohorts, PK samples for measurement of plasma concentrations of surufatinib will not be collected on C3D1 and beyond. For Cohort D, PK samples for measurement of plasma concentrations of each probe substrate (plus metabolite, where applicable) and surufatinib up to C2D1 will remain unchanged. For all cohorts, PK samples for measurement of plasma concentrations of surufatinib were not to be collected on C3D1 and beyond.

6.1.4.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of surufatinib, midazolam, 1-OH-midazolam, fexofenadine, rosuvastatin, and N-desmethyl rosuvastatin, as appropriate, using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry method.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. If conducted, metabolite analysis will be reported outside of the clinical study report.

6.1.5 Pharmacodynamic Assessments

Continuous ECG recordings using 12-lead Holter monitoring will be collected from patients enrolled in the study (excluding Cohort D) to evaluate the effects of surufatinib on ventricular repolarization. Details are described in Section 6.1.2.5.

6.1.6 Study Visits and Assessments

6.1.6.1 Screening

Followed informed consent, all screening evaluations must be completed and reviewed by the investigator and Clinical Monitor to confirm that patients meet all eligibility criteria before the first administration of surufatinib.

Screening will be performed within 28 days of the first dose day of study drug. Results of standard-of-care tests performed prior to obtaining informed consent and within 28 days prior to study entry may be used (except hematology, coagulation test, clinical chemistry, and urinalysis); such tests do not need to be repeated for screening.

6.1.6.2 Pretreatment (Cohort D Only)

Day -2 and day -1 and corresponding assessments of the pretreatment phase are only applicable for patients in Cohort D. Patients will be given a breakfast meal to consume within 30 minutes of dosing. Predose baseline PK samples will be taken before the patient receives the drug cocktail of DDI substrates. Postdosing samples will be taken at the time points described in Table 3, and a second meal (lunch) will be given 4 hours postdose, after collection of the 4-hour PK blood sample.

6.1.6.3 Treatment Period

All visits beyond cycle 1 must occur within ±3 days from the scheduled date, unless otherwise noted (see Table 1). All assessments will be performed on the day of the specified visit, unless a time window is specified. If scheduled study assessments cannot be obtained because of a holiday, these assessments should be obtained at the soonest following date, unless the soonest following date is within 7 days of other regularly scheduled study assessments.

6.1.6.4 End of Treatment/Early Termination

Patients who discontinue study treatment for any reason need to return to the clinic at 30±7 days after the last dose of surufatinib for a follow-up visit. Ongoing AEs thought to be related to surufatinib will be followed until 1 of the criteria in Section 8.3.3 are met.

Upon implementation of this Protocol Amendment 6, treatment with surufatinib for all patients on active treatment should be discontinued on Day 28 of the last cycle that can be fully completed no later than CCI

6.1.6.5 End of Study

A patient is considered to have completed the study once he or she has completed the last visit or the last scheduled procedure as outlined in Table 1.

The study will be considered completed once the last patient has completed the last visit or last scheduled procedure.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Patients

6.2.1.1 Treatment Discontinuation

The investigator has the right to discontinue a patient from treatment for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study and for reasons of noncompliance (eg, missed doses, visits), pregnancy, or if the investigator determines it is in the best interest of the patient.

Any patient who discontinues treatment but does not withdraw informed consent should be encouraged to return to the study site for a treatment completion visit. See Table 1 for the assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period. The primary reason for discontinuation must be recorded on the appropriate eCRF. Patients discontinuing surufatinib for reasons other than progression of the underlying malignancy are to continue tumor assessments per Table 1 until documentation of disease progression, start of new antitumor therapy, or withdrawal of informed consent.

Patients may be discontinued from treatment for any of the following reasons:

1. Disease progression (according to RECIST version 1.1; Appendix 2 [Section 15]). If the patient is experiencing a treatment benefit in the opinion of the investigator, the patient may continue study treatment beyond radiographic progression until clinical progression. Determination of clinical progression is at the discretion of the investigator and may include both objective and subjective data. The continuation decision should be made by the investigator in consultation with the sponsor.
2. Death
3. Unacceptable toxicity
4. Withdrawal of consent
5. Patient is lost to follow-up
6. The investigator or sponsor determines it is in the best interest of the patient
7. Use of other antitumor treatment during the study

8. Study is terminated by the sponsor
9. Pregnancy
10. Poor patient compliance at the investigator's discretion
11. End of this study

Patients must be discontinued if they experience certain high-grade AEs, recurrent AEs, or AEs that warrant withdrawal of study treatment as determined by the Principal Investigator, as outlined in Section 7.1.3

6.2.1.2 Withdrawal from Study

All patients have the right to withdraw from the study at any time. During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on patients who discontinue study treatment but who do not withdraw consent to continue participation in the study. If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.2.1.3 Replacement of Patients

Patients who are not eligible for response assessment (defined as those subjects who have at least one post-baseline assessment unless any clinical PD or death occurred before the first assessment) may be replaced.

6.2.1.4 Patients Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he or she will be considered to be withdrawn from the study or lost to follow-up.

6.3 Study Termination

The sponsor has the right to stop the study at any time. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

The reasons for stopping the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.

- In the case of patient enrollment being unsatisfactory, the enrollment of new patients will be stopped. Patients already enrolled will be treated and followed in accordance with the protocol.
- Any other reason consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

As of the implementation of Protocol Amendment 6, CCI [redacted] and have a follow up visit 30±7 days after last dose of surufatinib as described in Section 6.1.6.4. The study will be terminated either 30 ±7 days after the last patient has received surufatinib, or at the point at which all AEs considered by the Investigator to be related to surufatinib have resolved or are no longer being followed.

7 STUDY INTERVENTIONS

7.1 Description of Products

Surufatinib is a study drug formulated as an off-white powder in a capsule with a strength of 50 mg per capsule (Table 6).

Table 6 Investigational Treatment Used in This Study

Product	Dosage Form	Strength	Dose	Frequency	Route
Surufatinib	Capsule	50 mg	300 mg	Daily	Oral

The drug cocktail (midazolam, fexofenadine, and rosuvastatin) for Cohort D will be provided by the sponsor. The description of the individual products used in the cocktail is summarized in Table 7.

Table 7 Cohort D: Drug Cocktails

Product	Dosage Form	Dose	Frequency	Route
Midazolam	Oral liquid	2.5 mg	Single dose	Oral
Fexofenadine	Tablet or oral suspension	30 mg	Single dose	Oral
Rosuvastatin	Tablet	10 mg	Single dose	Oral

7.1.1 Formulation, Storage, Preparation, and Handling

The surufatinib 50-mg strength is presented as a size 3, hard gelatin capsule. The capsules are packaged in white, high-density polyethylene bottles. Refer to the IB and pharmacy manual for further details.

Study drugs should be sealed and stored in a secure, limited access area between 10°C and 30°C, protected from light and moisture. Midazolam, fexofenadine, and rosuvastatin should be stored as directed by the label. The temperature log should be recorded and filed in the study binder. Surufatinib capsules should not be used beyond the expiration date provided by the manufacturer.

All study drugs required for this study will be provided by the sponsor. The recipient will acknowledge receipt of the study drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug received at, dispensed from, returned to, and disposed by the study site should be recorded by using the Drug Inventory Log.

The study drugs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the sponsor with the appropriate documentation, as determined by the study site. If the study site chooses to destroy the study drug, the method of destruction must be documented.

7.1.2 Dosing and Administration

The starting dose of surufatinib is 300 mg QD, which is the maximum tolerated dose and recommended phase 2 dose determined by the 2015-012-00US1 study, same as the dose used in 2 phase 3 randomized trials conducted in China. There is no dose escalation in this study. The dose may be reduced as described in Section 7.1.3.

It is recommended that surufatinib be taken with approximately 240 mL water within 1 hour after breakfast. Patients will take six 50-mg capsules for the 300-mg QD dose. When predose PK blood samples need to be collected on the days of PK sample collection, patients must take the study drug after sampling.

If patients miss a dose in the morning, a replacement dose can be taken before 10:00 PM on the same day. Otherwise, the patients should not make up the missed dose but should resume scheduled doses the next day per the protocol. The missed dose should be reported to investigators and recorded on the eCRF.

On the day of PK sampling during cycles 1 to 3, patients should avoid high-fat, high-calorie meals for the entire day. No caffeine-containing foods or drinks, grapefruit, starfruit, Seville oranges or their products, tobacco and tobacco-containing products, or alcohol will be allowed.

Special instructions for the patients in Cohorts A, B, and C assigned to Holter monitoring:

- On cycle 1 day 1 and cycle 1 day 15 (+1 week), intake of surufatinib must occur at the study site under overnight fasted conditions at the morning appointment under supervision of site personnel.
- A light breakfast (ie, a low-fat meal [eg, 2 slices of white bread, 2 tablespoons of jam, and 1 cup of low-fat milk]) will be given on cycle 1 day 1 and cycle 1 day 15 (+1 week). Breakfast should be consumed within 30 minutes. Surufatinib will be given within 5 minutes after completion of breakfast but no more than 30 minutes after the start of breakfast.
- A lunch of approximately 500 to 600 calories (eg, turkey sandwich or chicken and vegetable soup with 2 slices of bread plus 1 cup of decaffeinated tea or coffee) will be given on cycle 1 day 1 and cycle 1 day 15 (+1 week) approximately 3.5 hours postdose.
- On other days up to cycle 1 day 14, surufatinib should be taken between 8:00 AM and 10:00 AM.
- From cycle 1 day 16 onwards, surufatinib will be taken following the usual instructions.

Special instructions for Cohort D

- The dose and schedule for administration of surufatinib and drug cocktail is provided in Table 5.
  - On day -2 and cycle 1 days 1, 15, and 16, study drugs must be taken at the investigative site under the supervision of the investigator or designee.
  - On day -2 and cycle 1 day 15 (+1 week), times of intake of study drugs and meals (start and stop times of breakfast and start time of lunch consistent across dosing days) must be recorded on the eCRF.
- No fruit juice (including apple juice) will be allowed on day -2 and cycle 1 day 15 (+1 week).
- On day -2 and cycle 1 day 15 (+1 week), the patient must fast overnight for at least 10 hours before the morning when safety laboratory tests and PK blood samples are collected.
  - Intake of water is allowed until 2 hours before surufatinib/drug cocktail intake. From 2 hours after dosing, intake of water is allowed.

– A light breakfast (ie, a low-fat meal [eg, 2 slices of white bread, 2 tablespoons of jam, and 1 cup of low-fat milk]) will be given at the site. Breakfast should be consumed within 30 minutes.
– Surufatinib and the drug cocktail will be given within 5 minutes after completion of breakfast but no more than 30 minutes after the start of breakfast.

- Surufatinib and the drug cocktail should be taken at approximately the same time. They will be taken orally with a small amount of noncarbonated water, approximately 240 mL in total for surufatinib/the drug cocktail. If needed, an additional 120 mL of water may be consumed.

– Predose PK and ECG (when required) samples must be collected **within 15 minutes** before dosing.
– Surufatinib should be taken prior to intake of the drug cocktail. Dosing of the cocktail components will be done sequentially in the following order: midazolam, fexofenadine, and rosuvastatin. On cycle 1 day 15 (+1 week).

- Patients will fast until approximately 4 hours postdose, followed by a standard lunch of approximately 500 to 600 calories (eg, turkey sandwich or chicken and vegetable soup with 2 slices of bread plus 1 cup of decaffeinated tea or coffee). After that, patients may resume their usual diet.
- From cycle 1 day 16 onwards, surufatinib will be taken following the usual instructions.
- When surufatinib is self-administered at home (ie, cycle 1 day 2 through cycle 1 day 14 and cycle 1 day 17 onwards), it should be taken within 1 hour after breakfast during the morning hours.
- In case of severe sedation by oral midazolam, the benzodiazepine antagonist flumazenil may be used by the IV route.

7.1.3 Dose Modification

The dose modification sequence by starting dose is shown in Table 8. A patient is normally allowed to have dose reductions no more than twice; ie, dose reductions from 300 mg QD to 250 mg QD and then to 200 mg QD. However, if the investigator judges that a dose lower than 200 mg QD is required for safety reasons and that the patient could still benefit from study drug treatment at such a lower dose, then the dose may be further lowered to 200 mg QD, 3 weeks on and 1 week off, during each subsequent 4-week cycle.

The severity of AEs will be graded according to the NCI CTCAE version 5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded on the eCRF.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade if the investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline that increases to grade 2 during treatment, this will be considered a shift of 1 grade and treated as grade 1 toxicity for dose modification purposes.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment will be continued at the same dose without reduction or

interruption. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) because it can be satisfactorily managed.

- To recover from acute toxicity, unless otherwise indicated, the treatment can be delayed for up to 21 days. If a treatment delay longer than 21 days is required, the patient should be discontinued from the study treatment. Continuation/resumption of surufatinib treatment after an interruption of more than 21 days must be discussed with the medical monitor or his or her designee.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

Table 8 Dose Modification Sequence

Daily Starting Dose	**300 mg**
-1 dose	250 mg
-2 dose	200 mg
-3 dose	200 mg on reduced schedule[1]

QD=once daily.

1. Dosing schedule 200 mg QD, 3 weeks on/1 week off, every 4-week cycle.

Dose reduction guidelines for hematologic and nonhematologic toxicities other than hypertension, proteinuria, liver function impairment, and hemorrhage are shown in Table 9. In principle, treatment should be held until the AE/toxicity resolves or improves to ≤grade 1. If a patient has a grade 3 toxicity that is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves to ≤grade 1. Patients with a grade 3 nonhematologic toxicity that does not resolve to ≤grade 1 within 14 days should permanently discontinue the study drug.

Table 9 Dose Modification for Hematologic and Nonhematologic Toxicity

NCI CTCAE Version 5.0 Toxicity Grading	**Action**
Grade 1 or 2	None
Grade 3 or 4	
Expected manageable/reversible with dose reduction	Hold[1]
Toxicity remains grade 3 >14 days	Discontinue treatment
Toxicity lasts ≤14 days and resolves to ≤grade 1	Reduce 1 dose level
Reoccurrence of grade 3 toxicity	Reduce 1 dose level or discontinue treatment[1]
Reoccurrence of grade 4 toxicity	Discontinue treatment
Not expected manageable/irreversible with dose reduction	Discontinue treatment

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.

Note: Patients who experience gastrointestinal perforation should be permanently discontinued from study treatment.

1. Treatment should be withheld until toxicity recovers to ≤grade 1. For patients who cannot recover within 21 days, the study treatment should be discontinued permanently.

7.1.4 Dose Modification for Important Identified Risks

Dose modifications for important identified risks are provided in Table 10 (hypertension), Table 11 (proteinuria), Table 12 (liver function impairment), and Table 13 (hemorrhage).

Table 10 Dose Modification for Hypertension

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: Pre-hypertension (systolic blood pressure 120 to 139 mmHg or diastolic blood pressure 80 to 89 mmHg)	None	None
Grade 2: Stage 1 hypertension (systolic blood pressure 140 to 159 mmHg or diastolic blood pressure 90 to 99 mmHg); medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously within normal range; monotherapy indicated	None	Treatment target: control blood pressure to below 140/90 mmHg. If patient has already received antihypertensive treatment at baseline, the dose should be increased or treatment changed. If patient did not receive treatment at baseline, monotherapy should be administered. Refer to relevant antihypertensive treatment guidelines for dose administration and modification and consult cardiologist if necessary.
Grade 3: Stage 2 hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated	If blood pressure >160/100 mmHg lasts for >3 days after initiation of antihypertensive treatment or modification of current antihypertensive treatment, surufatinib treatment should be held. If hypertension resolves to grade 1 or baseline level within 21 days, surufatinib treatment could be restarted at a lower dose level.	Treatment target: control blood pressure below 140/90 mmHg Initiate antihypertensive treatment, increase dose of current treatment, or add other treatments. For use and adjustment of antihypertensive treatment, refer to relevant treatment guidelines or consult cardiologist if necessary.
Grade 4: Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Discontinue surufatinib treatment	Emergency medical intervention

Table 11 Dose Modification for Proteinuria

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: 1+ proteinuria; urinary protein <1.0 g/24 hours	None	Follow-up per planned schedule
Grade 2: 2+ or 3+ proteinuria; urinary protein 1.0 to 2.0 g (excluding 2.0 g)/24 hours	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary
Grade 2: Proteinuria ≥2+; urinary protein 2.0 to 3.5 g (excluding 3.5 g)/24 hours	Hold surufatinib treatment and resume treatment at the same dose level if proteinuria resolves to ≤grade 1 within 21 days	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary
Grade 3: Urinary protein ≥3.5 g/24 hours	Hold surufatinib. If test results resolve to ≤grade 1 within 21 days, resume at a lower dose.	Provide supportive treatment and increase the frequency of urine monitor to once or twice a week; consult nephrologist if necessary

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; QD=once daily.
Note: If urine dipstick reveals 2+ proteinuria, 24-hour urine collection should be performed for determination of total protein within 1 week. The CTCAE grade recorded for proteinuria should be determined by the 24-hour urine collection; however, the start date of the AE will be recorded as the first instance of proteinuria (ie, urine dipstick). If surufatinib dose has been reduced to 200 mg QD and a further dose reduction is required for recurrent proteinuria, keep the same daily dose of 200 mg QD of surufatinib for 3 consecutive weeks followed by a 1-week drug holiday and repeat for each treatment cycle, (ie, 3 weeks on and 1 week off; every 4 weeks constitutes a treatment cycle). If proteinuria cannot resolve to ≤grade 1 after a dose interruption of 21 days, continuation/resumption of surufatinib treatment should be discussed with the medical monitor. Surufatinib treatment should be discontinued if a patient develops nephrotic syndrome.

Table 12 Dose Modification for Liver Function Impairment

Grade and Definitions	Dose Adjustment	Suggested Actions
Grade 1: ALT >1 to 3×ULN or AST >1 to 3×ULN	None	Follow-up per planned schedule. Check total bilirubin.[1]
Grade 2: ALT >3 to 5×ULN or AST >3 to 5×ULN	Maintain the original dose, provide supportive care of complications of liver impairment, and observe for 1 week. If the ALT and AST is stable or declining, continue with the original dose treatment. If the ALT and/or AST continue to rise significantly, then interrupt surufatinib; resume treatment at a lower dose if transaminase elevation resolves to ≤grade 1 within 21 days; otherwise, discontinue treatment.	Check total bilirubin.[1] Provide supportive care and increase the frequency of liver function monitoring to 1 to 2 times a week

Table 12 Dose Modification for Liver Function Impairment

Grade and Definitions	Dose Adjustment	Suggested Actions
Grade 3: ALT >5×ULN or AST >5×ULN	Hold surufatinib; resume treatment at the lower dose if resolves to ≤grade 1 within 21 days; otherwise, discontinue treatment.	Check total bilirubin.[1] Provide supportive care and increase the frequency of liver function monitor to twice a week; consult expert if necessary.
Grade 4: ALT >20×ULN or AST >20×ULN	Discontinue treatment	Check total bilirubin.[1] Urgent medical intervention indicated

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

1. If ALT or AST escalates to 3 times baseline level with bilirubin >2×ULN, the biochemical criteria for Hy's law have been met, surufatinib should be discontinued immediately, and the event should be reported to the sponsor within 24 hours. See Appendix 6 (Section 15) for important additional information.

Table 13 Dose Modification for Hemorrhage

Grade and Definitions	Dose Modification	Suggested Actions
Grade 1	None	Follow-up per planned schedule
Grade 2	Hold surufatinib treatment; resume at a lower dose if resolves to ≤grade 1 within 21 days	Active management
Grade 3 or higher	Discontinue treatment	Immediate medical intervention to identify and treat the source of bleeding

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

All patients in this study will receive surufatinib 300 mg QD. Patients will be assigned to 1 of the 4 cohorts as determined by NET origin.

7.2.2 Randomization Strategy and Procedure

This is not a randomized study.

7.2.3 Extent and Maintenance of Blinding

Not applicable to this open-label study.

7.3 Assessment and Verification of Compliance

The investigator is responsible for ensuring the patient's treatment compliance. The sponsor will provide supervision through on-site or remote monitoring visits made by its representatives. The investigators should maintain complete and accurate records of drug use. The dosing regimen and patient's actual dosing should be recorded in the original treatment records as well as on the eCRF. At each treatment visit, the investigators or study staff should comprehensively assess the patient's treatment compliance according to the drug dispensing and return status at each visit and the actual

dosing conditions, such as missed doses and overdosing reported by the patient. The patient must return all drug bottles and remaining capsules at the end of the study. The investigational sites must return all remaining supplies and drugs to the sponsor or provide evidence of destruction at the conclusion of the study.

7.3.1 Prior and Concomitant Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient within 7 days before screening and 30 days after study completion should be recorded. At each visit, all medication used since the last record should be recorded.

7.3.2 Prohibited Therapies

Any therapy intended for the treatment of cancer (with the exceptions noted in Section 7.3.3), whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Concomitant use of somatostatin analogues (SSAs) by patients with nonfunctioning NETs is not permitted and must have been discontinued before administration of the first dose of the study drug.

Medications that are strong or moderate inhibitors or inducers of CYP3A are prohibited and should not be administered concomitantly with surufatinib during the course of the study. Examples of these medications are listed in Appendix 3 (Section 15).

Concomitant use of medications that are known to cause QT prolongation and/or torsades de pointes is not permitted. See Appendix 5 (Section 15) for a table of current medications in this category and also consult the current list at http://www.crediblemeds.org, which is updated continuously, for the most complete information.

Palliative radiation for symptom control is allowed provided it does not compromise tumor assessments of target lesions. However, surufatinib treatment should be suspended during the radiation period and resumed at least 7 days after radiation and only after meeting the following criteria:

- Radiation related toxicities resolves to ≤grade 2
- No disease progression observed

7.3.3 Permitted Therapies

Patients who use hormonal therapy with gonadotropin-releasing hormone agonists for oral contraceptives, hormone replacement therapy, or other allowed maintenance therapy should continue their use.

Prophylactic use of anticoagulation for the maintenance of patency of permanent indwelling central venous access devices or for patients at high risk of venous thromboembolism is permitted during study treatment. If patients are receiving low-dose anticoagulation at study entry:

- Patients who are receiving Coumadin or Coumadin-like products should have their PT/INR monitored and maintained at the lower end of the therapeutic range (eg, close to 2.0 if the therapeutic range is 2.0 to 3.0).

- Patients who require low-molecular-weight heparin should receive the prophylactic dose and monitoring as specified by the appropriate product information label.

Patients who develop arterial thromboembolic events should discontinue the study treatment. If a patient experiences a venous thromboembolic event while still receiving study treatment, it may still be possible for him or her to remain on study treatment under adequate monitoring and dose modification.

- Patients who have functioning NETs and have been on a stable dose of a SSA for a minimum of 2 months prior to the first dose of study drug for control of their secretory symptoms will be permitted to enroll.

All supportive measures consistent with optimal patient care will be given throughout the study.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

7.3.4 Drug-Drug Interactions

In vitro metabolism data indicate that CYP3A plays an important role in the metabolism of surufatinib. The potential effects of medications that can affect the PK of surufatinib via the CYP3A pathway have not been tested in the clinic. Therefore, medications that are strong or moderate inhibitors or inducers of CYP3A are prohibited and should not be administered concomitantly with surufatinib during the course of the study. Examples of these medications are listed in Appendix 3 (Section 15).

In vitro, surufatinib is shown to have the potential to inhibit CYP3A, P-gp, and BCRP (refer to the IB). Patients should avoid concomitant use of medications that are sensitive substrates of CYP3A, P-gp, or BCRP where possible. If used together, patients should be monitored more frequently for adverse reactions, and dose reduction of the CYP3A, P-gp, or BCRP substrate medication should be considered. Examples of the medications that are sensitive substrates of CYP3A, P-gp, and BCRP are listed in Appendix 3 (Section 15).

For patients who participate in Cohort D, medications known to induce or inhibit CYP3A, P-gp, or BRCP must be discontinued or substituted 3 weeks prior to study visit day -2 until after cycle 1 day 17. Examples of these medications are listed in Appendix 3 (Section 15). Moreover, patients should not use midazolam, fexofenadine, rosuvastatin, and any acid-reducing agents from 1 week before day -2 until after the last PK sample is collected on cycle 1 day 17. All fruit juice is temporally disallowed on day -2 and cycle 1 day 15 (+1 week) as clinically relevant juice-drug interactions have been reported (Chen et al 2018).

8 SAFETY MONITORING

Safety will be monitored through continuous reporting of AEs and SAEs, laboratory abnormalities, and incidence of patients experiencing dose modifications (including dose reductions and dose delays) and/or dose discontinuation of the study drug (and reason for discontinuation).

These safety evaluations will be performed from the time of ICF signature throughout the treatment phase and up to 30±7 days after the last study treatment administration. AEs and SAEs ongoing at the end of treatment will be followed until resolution. Any new SAE possibly related to the study treatment occurring any time after the end of treatment should be reported. The NCI CTCAE (version 5.0) will be used to grade all AEs and laboratory abnormalities.

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence in a clinical study patient temporally associated with the use of a study intervention, whether or not considered related to the intervention. An AE can therefore be any of the following:
  - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study intervention, whether or not considered related to the study intervention
  - Any new disease or exacerbation of an existing disease (a worsening in the frequency or severity of a known condition). Recurrence of an intermittent medical condition (eg, headache) not present at baseline
  - Any deterioration in a laboratory value or other clinical test (eg, ECG, x-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
  - AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies)
  - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug 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.
- **Serious adverse event** – An event is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (an event is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Adverse event of special interest** – An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

8.2 Documenting Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the appropriate AE/SAE form.

A consistent methodology of nondirective questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of nondirective questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

When documenting an AE or SAE, the preferred medical terminology or concept should be used. Abbreviations and spoken language should be avoided. Only 1 medical concept should be recorded in the event field on the eCRF. All AEs (including SAEs) should be recorded on the eCRF on the AE page.

All AEs (including SAEs) should be recorded on the AE eCRF, and the check box for 'Serious' should be ticked for entries that fit the criterion of serious. The investigator should also complete an SAE report and submit this to the sponsor or its designee within 24 hours of knowledge of the event.

8.2.1 Assessment of Events

8.2.1.1 Severity

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of severity through clinical description by referring to the 5-grade determination standard in the NCI CTCAE version 5.0. The NCI CTCAE version 5.0 shows specific criteria for a large number of commonly reported specific AEs by MedDRA preferred term. If a specific AE cannot be found in the NCI CTCAE version 5.0, then the investigator should name the AE and report the severity based on the general guideline shown in the list below.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Activities of daily living

- *Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
- **Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

8.2.1.2 Causality

A guideline to the interpretation of the causality question is found in Appendix 4 (Section 15) to the clinical study protocol.

The investigator will assess a causal relationship between the study drug and each AE and will answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?"

For SAEs, a causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied to be "yes."

8.2.2 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.2.3 Adverse Event Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated from the initiating event in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

8.2.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless the severity changes. If a persistent AE becomes more or less severe, it should be recorded again on an AE/SAE eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an AE/SAE eCRF.

8.2.5 Previously Existing Medical Condition

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE/SAE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.2.6 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

8.2.7 Worsening of Solid Tumor

Worsening and/or progression of the patient's solid tumor should not be recorded as an AE or SAE unless it resulted in death within the AE reporting period. These data will be captured as efficacy assessment data only.

8.2.8 Death

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, should be recorded on an AE/SAE eCRF and expeditiously reported to the sponsor or its designee. This includes death attributed to tumor progression.

When recording a death event, the underlying condition that caused or primarily contributed to the fatal outcome should be reported as an AE with death being the outcome of the event on the AE/SAE eCRF. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, record "Unknown Death" on the AE/SAE eCRF.

If the death is attributed to progression of cancer, record "Cancer Progression" as the AE term on the eCRF.

8.3 Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

All AEs that occur after informed consent is signed and through 30±7 days following the last administration of study treatment will be collected. After this period, investigators should report only SAEs that are thought to be related to prior study treatment.

8.3.2 Reporting Requirements for Serious Adverse Events

Investigators will submit reports of all SAEs, regardless of attribution, to the sponsor or its designee within 24 hours of learning of the events.

For initial SAE reports, investigators should record all case details that can be gathered on the SAE report form. Relevant follow-up information should be submitted to the sponsor or its designee as soon as it becomes available and/or upon request.

Any life-threatening (ie, imminent risk of death) or fatal AE that is attributed by the investigator to the study drug will be telephoned to the medical monitor immediately, followed by submission of written case details on the SAE report form within 24 hours.

8.3.3 Adverse Event Follow-Up Duration

The investigator should follow-up all unresolved AEs and SAEs until the events are resolved or stabilized, new antitumor treatment is initiated, the patient is lost to follow-up, the patient withdraws informed consent, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE/SAE eCRF and in the patient's medical record to facilitate source data verification. For SAEs, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the AE eCRF.

For some SAEs, additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report) may be followed up by telephone, fax, email, and/or a monitoring visit to obtain.

8.3.4 Post-Study Adverse Events

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the sponsor or its designee of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if it is felt to be related to prior study treatment. The sponsor or its designee should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

8.4 Adverse Events of Special Interest

The AEs of special interest for surufatinib include hepatic disorder, proteinuria, hypertension, thyroid dysfunction, hemorrhage, and acute renal failure. Depending on the nature of the event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted.

8.5 Clinical Laboratory Findings

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (eg, abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, or further diagnostic investigation).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5×ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the AE/SAE eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mmol/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

8.5.1 Liver Function Abnormality

The finding of an elevated ALT or AST (>3×baseline value) in combination with either an elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury; these findings meet the definition for Hy's law and are associated with an increased risk of drug-induced liver injury (DILI). Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST >3×baseline value in combination with total bilirubin >2×ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST >3×baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF and reported to the sponsor or its designee within 24 hours after learning of the event as an SAE. See Appendix 6 (Section 15) for important additional information.

8.6 Pregnancy

A female patient must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies related to maternal or paternal exposure within 24 hours to the sponsor or its designee. The investigator should counsel the patient and discuss the risks of continuing with the pregnancy

and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the sponsor considers these medically significant), recorded on an AE/SAE eCRF and expeditiously reported to the sponsor or its designee.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the study drug should be recorded and reported as an SAE.

8.7 Overdose

For this study, any dose of surufatinib greater than 400 mg daily will be considered an overdose. No specific information is available on the treatment of overdose of surufatinib. In the event of overdose, further surufatinib administration should be held, and the patient should be observed closely for signs of toxicities. Appropriate supportive treatment should also be provided if clinically indicated. In the event of accidental or intentional overdose, the investigator or other site personnel should inform sponsor study representatives immediately or no later than 24 hours.

An overdose with associated AEs/SAEs should be recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the eCRF and on the study drug eCRF module.

An overdose with no associated signs or symptoms should only be reported on the study drug eCRF module.

9 ANALYSIS

All statistical analysis will be performed under the direction of the sponsor's personnel. Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to the database lock.

The timing of analysis for each cohort may be different depending on completion of each cohort, and the final analysis of the study will be conducted at the time of analysis of the last cohort. An interim analysis is planned for Cohort D only. However, the accrued data from any cohort may be analyzed for internal decision-making purposes; for example, to provide information for a potential phase 3 study design.

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and PK measurements. Time to event variables will be summarized descriptively using Kaplan-Meier medians and quartiles. Analyses will be performed using SAS® (Version 9.1 or higher).

9.1 Hypothesis

No formal hypothesis testing is planned for this study. For efficacy endpoints DCR and ORR, the study will provide the estimates and the associated 95% confidence interval (CI) for precision.

9.2 Population

9.2.1 Sample Size Rationale

Taking into account study feasibility, given that these tumors are relatively rare, it is planned to enroll approximately 20 patients each in Cohorts A and C and approximately 35 patients in Cohort B. Twenty patients in Cohorts A and C and 35 patients in Cohort B can provide adequate precision for the estimate of DCR at a specific time point.

Table 14 shows the range of DCR and the corresponding 95% CIs for a sample size of 20 patients. Table 15 shows the range of DCR and the corresponding 95% CIs for a sample size of 35 patients.

Table 14 Estimated Disease Control Rate and 2-Sided 95% Confidence Intervals for N=20 Patients

Number of Cases	Estimated DCR	95% CI Lower Limit	95% CI Upper Limit
0	0	0.00	0.17
5	0.25	0.09	0.49
10	0.50	0.27	0.73
12	0.60	0.36	0.80
14	0.70	0.46	0.88
16	0.80	0.56	0.94
18	0.90	0.68	0.99
20	1.0	0.83	1.0

CI=confidence interval; DCR=disease control rate.
95% Clopper-Pearson Interval for binomial distribution.

Table 15 Estimated Disease Control Rate and 2-Sided 95% Confidence Intervals for N=35 Patients

Number of Cases	Estimated DCR	95% CI Lower Limit	95% CI Upper Limit
0	0.00	0.00	0.10
5	0.14	0.05	0.30
10	0.29	0.15	0.46
15	0.43	0.26	0.61
20	0.57	0.39	0.74
25	0.71	0.54	0.85
30	0.86	0.70	0.95
35	1.00	0.90	1.00

CI=confidence interval; DCR=disease control rate.
95% Clopper-Pearson Interval for binomial distribution.

Cohort D: Previously published clinical data indicate that the intra-patient coefficient of variation (CV) ranges from approximately 16% to 22% for area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) with respect to the probe drugs to be investigated in the study (Haberer 2014). Assuming an intra-patient CV of 22% among the probe drugs for $AUC_{0-\infty}$, a sample size of 14 patients would be sufficient for the point estimate of the geometric mean ratio of $AUC_{0-\infty}$ of test versus reference to fall within 87% and 115% of the true value with 90% confidence. Assuming a 15% dropout rate, approximately 16 patients will be enrolled to ensure a minimum of 14 completers.

At the time of this protocol amendment preparation (16 November 2023), Cohort B had enrolled 32 patients and Cohort D had enrolled 6 patients. Cohort A had enrolled 20 patients and Cohort C had enrolled 32 patients.

9.2.2 Analysis Subsets

The following analysis populations have been defined for the study:

- **Safety Analysis Set – All Treated Population**: This population includes all patients who have received at least 1 dose of surufatinib. Safety data will be evaluated based on the actual dose initially received. PFS will also be analyzed based on this population.
- **PK Analysis Set**: This population will include all patients who received at least 1 dose of surufatinib and have at least 1 PK sample obtained and analyzed.
  - **PK Population**: all patients who received at least 1 dose of the study drug and have at least 1 measurable plasma concentration data point
  - **PK Evaluable Population**: all patients who received at least 1 dose of the study drug and have a sufficient PK profile to derive at least 1 PK parameter
- **Pharmacodynamic (ECG) Set**: This population will include all patients who received at least 1 dose of study drug and have baseline and at least 1 postdose ECG measurement.
- **Efficacy Analysis Set**: This population includes all patients who have received at least 1 dose of surufatinib and have had at least 1 post-baseline tumor assessment unless death occurs before first post-baseline assessment. All efficacy endpoints will be analyzed based on this analysis set except PFS, which will be analyzed based on the safety analysis set.

Additional populations may be defined in the SAP.

9.3 Testing Procedures

9.3.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint of DCR at 6 months is defined as the proportion of patients at 6 months whose best overall response from baseline is either a CR, PR, or SD per RECIST version 1.1 (Appendix 2 [Section 15]). To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments performed at least 4 weeks after the criteria for response are first met. The estimated DCR and the corresponding 95% CIs based on the Clopper-Pearson method will be provided for each cohort.

9.3.2 Analysis of Secondary Efficacy Endpoints

The ORR is defined as the proportion of patients with a best overall response or CR or PR per RECIST version 1.1 (Appendix 2 [Section 15]). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed at least 4 weeks after the criteria for response are first met. The estimated ORR and the corresponding 95% CIs based on the Clopper-Pearson method will be provided for each cohort.

The TTR is defined as the time between the start date of study drug until first documented response (CR or PR) according to RECIST version 1.1 (Appendix 2 [Section 15]). Time to response will be summarized for patients with best overall response of CR or PR.

The DoR is defined as the time from the first time that the objective response reaches CR or PR, whichever comes first, until the occurrence of PD or death (if the death of the patient occurs before recording the PD). Duration of response will be summarized for patients with best overall response of CR or PR.

The PFS is defined as the time from the start of study drug to date of objective disease progression as defined by RECIST version 1.1 or death, whichever comes first.

The TTR, DoR, and PFS will be summarized using the Kaplan-Meier method, including estimated median (in months) with 95% CI, 25th, and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-defined landmark times as defined in the SAP. Censoring reasons for PFS and DoR will be summarized.

9.3.3 Safety Analysis

An AE is considered a TEAE if the onset date is on or after the start of study treatment or if the onset date is missing, or if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment. After this period, treatment-related SAEs will also be considered as TEAEs.

TEAEs, TEAEs leading to drug modification or discontinuation, changes in laboratory results, changes in ECGs/echocardiograms and MUGA, and changes in vital signs will be summarized by disease cohort. Exposure to study drug will be summarized. Physical examination findings will be listed.

All AE data will be listed by individual patient and cohort. All AEs will be coded with MedDRA and graded using the NCI CTCAE (version 5.0) severity grading system. The frequency of AEs

will be summarized by MedDRA System Organ Class and Preferred Term, and NCI CTCAE grade.

Changes in laboratory data will be summarized by grade for each visit using the NCI CTCAE version 5.0. Selected vital signs and selected laboratory data may be plotted over time for each patient.

9.3.4 Pharmacokinetics Analysis

9.3.4.1 Pharmacokinetic Analysis for Cohorts A to C

Descriptive statistics (including, but not limited to, arithmetic mean, standard deviation, CV, median, minimum, maximum, and geometric mean) will be provided for the observed concentration for surufatinib.

9.3.4.2 Pharmacokinetic Analysis for Drug Interaction Evaluation (Cohort D)

The following PK parameters will be determined:

Surufatinib:

Cycle 1 day 15 (+1 week):

- Maximum plasma concentration (C_{max}), t_{max}, area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{024h}), observed analyte concentration just prior to the beginning or at the end of a dosing interval (C_{trough})

Midazolam and its metabolite 1-OH-midazolam, fexofenadine, and rosuvastatin and its metabolite N-desmethyl rosuvastatin:

Day -2 and cycle 1 day 15 (+1 week):

- C_{max}, t_{max}, area under the plasma concentration-time curve from time 0 to time of the last measurable concentration ($AUC_{0\text{-last}}$), $AUC_{0\text{-}\infty}$, elimination half-life
- Total apparent clearance (only for parent compounds midazolam, fexofenadine, and rosuvastatin)
- Ratio $C_{max,\ metabolite/parent}$, Ratio $AUC_{0\text{-last},\ metabolite/parent}$, Ratio $AUC_{0\text{-}\infty,\ metabolite/parent}$ (metabolite/parent=1-OH-midazolam/midazolam, N-desmethyl rosuvastatin/rosuvastatin; not for fexofenadine)
- Ratio $C_{max,\ test/reference}$, Ratio $AUC_{0\text{-last},\ test/reference}$, Ratio $AUC_{0\text{-}\infty,\ test/reference}$ (test/reference=probe drug in presence of surufatinib/probe drug alone)

Additional PK parameters may be included if deemed appropriate. PK analysis will be performed using actual blood collection times relative to dosing times recorded in the raw data. If an actual blood collection time or a dosing time is missing, the nominal time may be used. Details of the PK analysis, including data handling rules and software used to perform the PK analysis, will be provided in the SAP.

Descriptive statistics will be calculated for the plasma concentrations of surufatinib and for the probe drugs and their metabolites (midazolam and its metabolite 1 OH-midazolam, fexofenadine, rosuvastatin and its metabolite N-desmethyl rosuvastatin) and for the derived PK parameters, as

applicable. Statistics include sample size (n), arithmetic mean, standard deviation, CV, geometric mean, median, minimum, and maximum.

For each patient, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. PK parameters will be subjected to an exploratory graphical analysis, including various transformations in order to obtain a general overview.

Statistical analysis will be performed for the PK parameters (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$) of each of the following analytes of the drug cocktail:

- midazolam and its metabolite 1-OH-midazolam
- fexofenadine
- rosuvastatin and its metabolite N-desmethyl rosuvastatin

The test/reference treatments are defined as cycle 1 day 15 (+1 week; the drug cocktail in the presence of surufatinib at steady state)/day -2 (the drug cocktail alone).

The primary PK parameters of interest for statistical analysis are C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ of the parent compounds of the drug cocktail. For each analyte, all patients who have the primary PK parameters of interest from both pretreatment and treatment phases will be included in the statistical analysis.

Linear mixed-effects models will be applied to log-transformed PK parameters data with treatment as the fixed effect and patient as the random effect. The least square means and intra-patient coefficients of variation will be derived from the model. The geometric mean ratios and the 90% CI of the PK parameters of each probe drug with and without coadministration of surufatinib will then be constructed through back-transformed results based on the model.

The PK parameters of the metabolites of the compounds and the ratios of metabolite to parent for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ will be analyzed in a similar way as planned above.

Additional statistical analysis will be performed if deemed appropriate and will be addressed in the SAP.

9.3.5 Pharmacodynamic (Electrocardiogram) Analysis

Patients who 1) receive at least 1 dose of study drug and 2) have baseline and at least 1 postdose ECG measurement will be evaluable for pharmacodynamic (ECG) evaluation. Patients who had reduced dosage, prolonged dose interruption of >2 days in cycle 1, any dose interruption within 7 days before cycle 1 day 15 (+1 week), or were discontinued from the study prior to the completion of ECG data collection (cycle 1 day 15 [+1 week]) will be excluded. For each of the ECG parameters, the average values from the 3 readings of a triplicate ECG set will be used in the analysis.

For all ECG parameters, the baseline will be defined as the mean values of the triplicate ECG measurements taken at predose on cycle 1 day 1.

9.3.5.1 Corrected QT Intervals

The terminology QTc is used in this section as a general notation for QTc using any of the specified methods.

The QT interval data will be corrected for heart rate using 2 correction methods (Fridericia – QTcF and Bazett – QTcB). For each QTc correction method, the relationship between QTc and RR interval at baseline will be evaluated graphically by plotting the logarithm of baseline QTc values against the logarithm of corresponding RR intervals. Fridericia will be used as the primary correction method for statistical analysis. If the correlation between QTc and RR intervals remains significant using the Fridericia correction method, an alternative correction method may be considered for statistical analysis in addition to QTcF.

For the statistical analysis based on the primary correction method (QTcF), the mean changes from baseline (ΔQTc) at each time point will be summarized (mean, standard deviation, median and range, and 2-sided 90% CI). Mean values for the difference and 2-sided 90% CI for mean difference will be calculated at each time point.

The primary analysis will focus on the maximum mean change from baseline in QTc (ΔQTc) on cycle 1 day 15 (+1 week), which will be estimated by the mean QTc change at around t_{max}, the time when the C_{max} is reached (ie, steady state). The same analysis will be performed for ΔQT data using other correction methods if data warrant. The mean change from baseline in QTc (±standard deviation) over time will be plotted.

In addition, QTc will be categorized based on International Council for Harmonisation (ICH) E14 guidelines. Tables will present the number and percentage of patients meeting or exceeding the following categories:

- QTc prolongation:
  - Absolute values >450 to ≤480 msec
  - Absolute values >480 to ≤500 msec
  - Absolute values >500 msec
- QTc change from baseline:
  - Increase from baseline >30 to ≤60 msec
  - Increase from baseline >60 msec

9.3.5.2 Heart Rate, QRS, and PR Intervals

For each treatment and time point of measurement, heart rate, QRS interval, and PR interval, as well as the change from baseline in heart rate, QRS, and PR (Δheart rate, ΔQRS, ΔPR), will be summarized using descriptive statistics (mean, standard deviation, median, range, and 90% CI). The number and percentage of patients with heart rate >100 bpm will be tabulated for each time point. The number and percentage of patients with QRS >110 msec will be tabulated for each time point. The number and percentage of patients with PR >200 msec will be tabulated for each time point.

9.3.5.3 T-wave and U-wave Morphology

The number and percentage of patients having T-wave morphology changes from baseline and/or the occurrence of abnormal U-waves that represent the appearance or worsening of the morphological abnormality will be summarized. Patients with abnormal ECG findings will be listed. Additional analyses will be performed if deemed necessary.

9.4 Planned Interim Analysis

For Cohort D only, once the last patient enrolled to this cohort has completed the required study procedures up to Cycle 1 Day 17, an interim analysis is planned to evaluate the short-term safety and the PK profile. An interim PK report for Cohort D will be written on the basis of this data cutoff date.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol; consensus ethics principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines; applicable ICH GCP guidelines; and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The Independent Ethics Committee/Institutional Review Board (IEC/IRB) must review the protocol and amendments, IB, ICF, study-relevant materials (such as advertisements for patient recruitment), and any other essential documents. IEC/IRB approval is to be obtained prior to the start of the study at the investigator site.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. The IRB/IEC will be notified of SAEs or other significant safety findings by IEC/IRB procedures. During the study, protocol deviations that may increase a patient's risk should be reported to the IEC/IRB in a timely manner.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB
- Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.3 Informed Consent

- Investigators or designees must obtain the signed ICF from patients prior to conducting any study-related procedures.
- The investigator or his or her representative will explain the nature of the study to the participant or to their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IEC/IRB or study center.

- Patients must be informed that they may withdraw consent to participate in the study without any limitations. If the patient cannot sign the ICF, a legally acceptable representative of the patient must sign the ICF.
- If the patient and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the patient and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the patient and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.
- Informed consent should be recorded on the eCRF.
- The investigator is responsible for answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- If the benefit/risk assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to patients (including patients who have already received the study drug).
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.4 Data Privacy

All information about the study drug (such as patent application, formulation, manufacturing process, and basic study information) is considered confidential as long as it is unpublished.

All information obtained in the study is considered confidential. The sponsor will open the information to investigational personnel and any other regulatory authority when necessary. To ensure the completeness of the study analysis data, investigational personnel are accountable for providing all results and data to the sponsor.

Investigators must guarantee the privacy of patients by not disclosing patient-related information to third parties without authorization. eCRFs and other documents submitted to the sponsor should not contain the patient's name.

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- Patients are identified only by unique identifier. Investigators may retain the identification forms, which include patient numbers, names, and addresses. ICFs and other documents should be documented properly and should not be given to the sponsor.
- The patient must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for his or her data to be used as described in the informed consent.
- The patient must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

10.5 Disclosure

Final study results will be published on a public clinical study website according to applicable local guidelines and regulations.

10.6 Data Quality Assurance

- To ensure the safety of patients in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.
- All patient data relating to the study will be recorded on printed case report forms (CRFs) or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of case report forms (CRFs) will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).

11 OVERSIGHT

11.1 Independent Monitoring

The sponsor will review study safety data every 6 months, or more frequently, if safety concerns arise. In addition, a SRC will monitor patient safety as described below.

11.1.1 Safety Review Committee

Patient safety will be monitored by a SRC. The SRC is charged with evaluating safety data and determining if enrollment may continue as planned. The SRC membership will be comprised of sponsor medical representative(s), CRO medical representative(s), and investigators. The details of roles and responsibilities will be outlined in the SRC Charter. Safety review meetings will be conducted at least once every 6 months, but may be conducted more frequently if safety concerns arise.

11.2 Quality Control and Assurance

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements, and applicable standard operating procedures, including quality control of documents.

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site. The sponsor and investigator will ensure that any individual or party who performs study-related duties or functions on behalf of the sponsor/investigator is qualified to perform the study-related duties or functions.

The overall procedures for quality assurance of clinical study data are described in the sponsor or designee's standard operational procedures. The planned quality assurance and quality control procedures for the study are described in the following sections.

11.2.1 Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the sponsor's personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site or remotely monitor regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence of the protocol to GCP, and the progress of enrollment and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel including the investigator must be available to assist the field monitor during these visits.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The sponsor's monitoring standards require full verification of the informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.2.2 Audits

Authorized representatives of the sponsor, a regulatory/competent authority, and/or an IEC/IRB representative may visit the site to perform audits or inspections, including source data verification. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection
- Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IEC/IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

11.2.3 Records

11.2.3.1 Data Capture and Management

The term eCRF refers to the electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all patients, including screen failures, data will be collected on source documents first. The Principal Investigator is responsible for assuring that the data entered into eCRFs is complete and accurate and that entry and updates are performed in a timely manner.

At all times, the Principal Investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Patient source documents are the investigator's/physician's patient records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts.

The completed pages of the EDC system are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

11.2.3.2 Source Documentation

- The investigator/institution should maintain accurate source documents and study records for all patients that support the information entered in the CRF.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry. All

information recorded on eCRFs must be traceable to source documents in the patient's file. Any changes should be explained if necessary (eg, via an audit trail).

11.2.3.3 Records Retention

Records and documents, including signed ICFs, source documents, study drug documents, monitoring visit records, regulatory documents, and all other correspondence and documents pertaining to the conduct of this study must be retained by the investigator for at least 5 years after study completion, unless local regulations or institutional policies require a longer retention period.

If the documents cannot be stored properly at the investigational site, the documents can be transferred by the investigator and sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. No records may be transferred to another location or party without written notification to the sponsor.

No records may be destroyed during the retention period following study completion or discontinuation without the written approval of the sponsor. Records must be destroyed in a manner that ensures confidentiality.

11.3 Study Termination or Study Site Closure

The sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study but has not enrolled any patient within a reasonable period of time.
- The investigator has violated any fundamental obligation in the study agreement, including, but not limited to, a breach of this protocol (and any applicable amendments), a breach of the applicable laws and regulations, or a breach of any applicable ICH guidelines.
- The total number of patients required for the study is enrolled earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

12 PUBLICATION POLICY

The study results may be published in scientific journals. The names of investigators who make an important contribution to the study implementation and management and personnel who make an important contribution to the study design, analysis, and interpretation (such as the sponsor's staff or consultants) will be listed in the publication. The sponsor will provide the article to investigators for review prior to publishing any study results. Investigators must obtain approval from the sponsor before contributing to any related articles or abstracts.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13 FINANCING AND INSURANCE

Financing and insurance information will be addressed in a separate agreement.

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