PROTOCOL COVER PAGE

Clinical Study Protocol

A Multi-Center, Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Surufatinib (HMPL-012), Previously Named Sulfatinib in Advanced Solid Tumors

Protocol Number:	2015-012-00US1
Study Phase	Phase 1/1b
Investigational Product:	Surufatinib (HMPL-012) previously named Sulfatinib
Sponsor:	Hutchison MediPharma Limited NO.4, Lane 720, Cailun Road, Zhangjiang Hi-tech Park, Shanghai, China Post Code: 201203
Date of Issue:	19 Mar 2021
Amendment:	11
Version:	7
Regulatory Identifier Number (s)	CCI EudraCT 2020-000456-35

Confidential Statement

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Conference on 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. Reconsent 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 Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Multi-Center, Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Surufatinib (HMPL-012), Previously Named Sulfatinib in Advanced Solid Tumors
Protocol Number	2015-012-00US1
Amendment	11
Version	7

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 below.

Name: [last name, first name]	**Title**:
PPD	PPD Hutchison MediPharma International, Inc
Signature: *See appended signature page*	**Date**: [DD Month YYYY]

Name: [last name, first name]	**Title**:
PPD	PPD Hutchison MediPharma Limited
Signature: *See appended signature page*	**Date**: [DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2015-012-00US1 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 to all personnel to whom study activities have been delegated
- To control all investigational products 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 investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name:	**Title:**	**Institution:**
Signature:		**Date:**

DOCUMENT HISTORY

Edition	Amendment	Date
1.0	Original	15 Jan 2015
1.1	1	15 Mar 2015
1.2	2	17 Jun 2015
1.3	3	31 Oct 2016
1.4	4	16 Dec 2016
2.0	5	8 Dec 2017
3.0	6	30 May 2018
4.0	7	25 Jan 2019
5.0	8	4 Sep 2019
5.1	9	27 Sep 2019
6.0	10	28 Feb 2020

PROTOCOL AMENDMENT HISTORY

Amendment 11

Amendment Rationale

This 2015-012-00US1 Amendment 11 replaces 2015-012-00US1 Amendment 10. 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.

The primary purpose of Amendment 11 is to correct text that was erroneously introduced and to update the protocol to match sponsor-approved format and language for clinical study protocols and to revise the protocol to comply with ICH E6(R2) guidance. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary. Previous amendments are detailed below in this section.

Section	Description of Changes	Rationale for Change
First page	Revised Confidentiality Statement	Align with updated sponsor-approved template
Statement of Compliance (section added)	Added Statement of Compliance	To add missing information for International Conference on Harmonisation (ICH) E6(R2) compliance
Sponsor's Approval	Revised Sponsor's Approval page	Align with sponsor's approved template
Investigator's Agreement	Added Investigator's Agreement page	Align with sponsor's approved template
Document History	Relocated and revised Document History to show each protocol amendment	To align with sponsor's approved template language and for compliance with ICH E6(R2) language
Section 1 - Synopsis	Updated Synopsis format and content	To align with sponsor's approved template language and for compliance with ICH E6(R2)
Section 2.3 - Clinical Experience	Updated information in the Background	Align with sponsor's approved template
Section 4.2.3 - Secondary Objectives	Added an efficacy objective to the Expansion Phase Secondary Objectives	To add a secondary objective for efficacy correct a previous oversight and align with existing efficacy endpoints in the Expansion Phase
Section 4.2.4 - Secondary Endpoints	Changed order of Expansion Phase Secondary Endpoints	To align with the order of the Secondary Endpoints in the Expansion Phase
Section 4.2.5 - Exploratory Objectives	Revised Exploratory Objectives in the Expansion Phase from evaluation of anticancer activity to evaluation of overall survival	Clarification
Section 4.2.6 - Exploratory Endpoints	Revised text to state that efficacy would be evaluated in all 3 disease	Clarification

Section	Description of Changes	Rationale for Change
	cohorts to 'the biliary tract cancer (BTC), pancreatic neuroendocrine tumor , and extrapancreatic neuroendocrine tumor disease cohorts'	
Section 5.1.1.2 - Definition of DLT Evaluable Patients	Corrected definition of dose-limiting toxicity (DLT)-evaluable patients as an individual who has not received any preventive treatment during the DLT period	Correction of error
Section 5.1.2 - Dose Expansion Phase	Removed text on Safety Review Committee (SRC) for the Dose Expansion Phase	Text is redundant with Section 5.4
Section 5.3 - Investigational Site	Revised and updated maximum number of study sites to 15 sites	Consistency with the informed consent form
Section 5.4 - Safety Review Committee	Revised text describing the SRC for the Dose Expansion Phase	Clarification
Section 7.1.6 - Dose and Administration	Specified that for patients in the European Union, only 50 mg formulation capsules will be available	Clarification
Section 7.1.7 - Important Safety Risks	Removed table of important identified risks and referred to the current Investigator's Brochure	Remove outdated information
Section 10.1 - Determination of Sample Size (moved section)	Moved section on sample size determination to beginning of Statistical Analysis section	Align with sponsor's clinical study protocol template
Section 10.2 - Analysis Populations	Clarified that efficacy endpoints, progression-free survival and overall survival for the BTC and soft tissue sarcoma cohorts will be analyzed using the Safety Analysis Set.	Clarification
Section 10.3 - Statistics and Analysis Method (revised header)	Revised text in the Statistics and Analysis Method	Revised header for align with sponsor's protocol template. Revised text for improved clarity.
Section 10.4 - Safety Analysis	Specified that SRC decisions for the Dose Expansion cohorts will be based on clinical data presented to SRC members	Clarification
Section 10.6 - Tumor Assessment	Specified that efficacy data from patients enrolled in the expansion phase at the recommended phase 2 dose will be presented by disease cohort	Clarification
Section 10.6.2 - Secondary Efficacy Endpoints Section 10.6.3 - Exploratory Endpoints	Revised text on analysis of efficacy endpoints	Clarification
Section 11 - Ethics Section 12 - Oversight	Revised Sections 11, 12, and 13, including all subsections	Updated to align with sponsor's approved template language and for

Section	Description of Changes	Rationale for Change
Section 13 - Publication Policy		compliance with ICH E6(R2) language
Section 16 - Appendices (section added) Appendix 1 Study Flowcharts (formerly Appendix A) Appendix 2 ECOG Performance Status (formerly Appendix B) Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 (formerly Appendix C) Appendix 4 Guidelines for Interaction between Surufatinib and Concomitant Medication (formerly Appendix D) Appendix 5 Guideline to Interpreting the Causality Question (formerly Appendix E) Appendix 6 Prohibited Concomitant Medications That Have a Known Risk of QT Prolongation and/or Torsades DES Pointes (TDP) (formerly Appendix F) Appendix 7 Clinical Evaluation of Possible Drug-Induced Liver Injury (DILI) (formerly Appendix G) Appendix 8 Conversion of Urinalysis Results Table (formerly Appendix H)	Added level 1 section for appendices. Revised appendix numbering	Align with sponsor's clinical study protocol template

Protocol Amendment 10 (Version 6.0, 28 Feb 2020)

Amendment Rationale

The primary objective of this amendment is to include a section to highlight the benefit and risk assessment of surufatinib, allow the inclusion of Synovial Sarcoma patients, and to update the Investigator Brochure version referenced, along with supporting data.

Section Number	Description of Changes
2.3 Benefit and Risk Assessment (new section)	Section added as it was not included in previous version.
5.1 Inclusion Criteria	Addition of Synovial Sarcoma subtype in the STS arm (Arm D), along with applicable language throughout protocol.
4.2 Sample Size	Addition of 10 patients to Arm D
3 Study Objectives and Endpoints	Reorganized such that all endpoint subcategories (ie, safety endpoint, efficacy endpoint, pharmacokinetic endpoint) are grouped together under secondary endpoints. This is to comply with endpoint categories defined in clinical trial registries.
6.1.7 Important Safety Risks Table 5	Table and risk language updated to align with current version of surufatinib Investigator Brochure (v9).
6.1.4	Clarified that room temperature for drug storage is between 10°C to 30°C protected from light and moisture.
9 Statistical Analysis	Added that final analysis for each cohort will occur once the last patient had been followed for sufficient time for the analysis of primary endpoint.
Appendix H new section	Inclusion of a urinalysis conversion table for reference
Throughout the document	Editorial revisions were made for clarity and consistency.

Protocol Amendment 9 (Version 5.1, 27 Sep 2019)

Amendment Rationale

The reason for this amendment is to update language in Table 9 of this protocol for clarity and consistency.

Section Number	Section Title	Description of Changes
6.2.2	Table 9 Dose Modification for Proteinuria	Clarifying language added to footnote a for 24-hour urine collection, as well as updated language to align with dose modification guidelines for grade 2 and 3 proteinuria.

Protocol Amendment 8 (Version 5.0, 4 Sep 2019)

Amendment Rationale

The reasons for this amendment primarily concern: the addition of a sarcoma cohort and subtypes eligible for enrollment as well as the addition of the progression free survival rate at 4 months as a primary endpoint during the dose expansion phase of the study, in the sarcoma cohort; and, to update the schedule of events to reflect overall survival follow up and to change tumor assessment timelines.

Section Number	Section Title	Description of Changes
2.0	Study Rationale	Background information and rationale for sarcoma added
3.2.2	Primary Endpoints	PFS rate at 4 months in the sarcoma cohort added
3.2.3	Secondary Objectives	Added PK of patients with sarcoma as secondary objective
3.2.4	Secondary Endpoints	Clarified secondary endpoints for anti-tumor efficacy would include: ORR, DCR, DoR, and percentage change in tumor size.
3.2.5	Exploratory Objectives	Added to evaluate the anticancer activity of surufatinib in patients with advanced BTC and sarcoma
3.2.6	Exploratory Endpoints	Added OS as an exploratory endpoint.
3.2	Dose Expansion Phase	Removed duplicative language.
4.4	Safety Review Committee	Added language clarifying the role of the Safety Review Committee during dose expansion.
4.8	End of Treatment (Individual Patient)	Added additional guidance to clarify the end of study treatment for individual patients.
9.6	Sample Size	Updated number of patients to be enrolled
4.5	Patient Discontinuation	Added language clarifying that patients who discontinue protocol therapy for reasons other than progression should continue to under protocol defined tumor assessments per Appendix A until disease progression, start of new therapy, or withdrawal of consent.
4.6	Overall Survival Follow-up	Added language for OS follow up.
5.0	Patient Selection	Removed duplicative language
5.1	Inclusion Criteria	Item #4, added sarcoma cohort and subtypes eligible for enrollment.
7.3.3	Study Completion/Early Termination Visit	Added clarifying language regarding follow up for OS visit.
8.1.2	Adverse Events of Special Interest	Added specific language to address how AEs of special interest should be defined and characterized.

9.0	Statistical Analysis	Statistical analysis section revised to match primary and secondary objectives of study during dose escalation and dose expansion. Updated sample size requirements for the study and added specific requirements for Arm D (STS cohort). Updated primary and secondary efficacy endpoints. Added OS as an exploratory endpoint.
10.0	Ethics	Updated the language pertaining to the ethical considerations in the study according to the new guidelines in ICH E6 (R2).
Appendix A	Study flowchart	Updated to reflect OS follow up and to change tumor assessment timelines.

Protocol Amendment 7 (Version 4.0, 25 Jan 2019)

Amendment Rationale

The reasons for this amendment primarily concern: an increase in the number of patients to be enrolled in Arm A (advanced biliary tract cancer [BTC]) from 15 to 30 in the dose expansion phase; the addition of a third group of patients (Arm C, n=15 patients with advanced extrapancreatic neuroendocrine tumors [epNETs]) to the dose expansion phase and to report the change in the international nonproprietary name (INN) from sulfatinib to surufatinib (see Summary of Changes below).

Section Number	Section Title	Description of Changes
Not applicable	Title page and throughout the protocol	Changed the INN from **sulfatinib** to **surufatinib**. This information was published by the World Health Organization (WHO) on 31 October 2018 [1].
Synopsis, Section 1.3	Clinical Experience	Updated clinical experience per IB edition 8.0.
Synopsis. Section 1.4	Study Rationale	Added text describing mechanism of action of surufatinib. Fifteen (15) additional patients, for a total of 30 patients, with advanced BTC to be enrolled in Arm A (BTC) of the Expansion Phase, based on encouraging preliminary results from the present trial.
Synopsis, Section 3.1.1	Dose Escalation Phase	Added that the MTD/RP2D was declared as 300 mg QD during Cohort 7 of the dose escalation phase on 30 November 2018.
Synopsis, Section 1.4, Section 4.1, and Section 4.2	Study Rationale Inclusion Criteria Exclusion Criteria	Added a third arm (Arm C; patients with advanced extrapancreatic neuroendocrine tumors [epNETs]) to the dose expansion phase. Added the inclusion and exclusion criteria for patients in Arm C. Removed the upper age limit on inclusion criteria.
Synopsis and Section 2	Study Objectives and Endpoints	Consolidated the primary and secondary objectives and endpoints of the dose escalation and dose expansion phases under a single heading.
Synopsis and Section 3.2	Sample Size	Updated the total sample size in the dose escalation and dose expansion phases.
Section 5.1.3	Packaging and Drug Labeling	Specified that the investigational drug is packaged in white HDPE bottle with 50 capsules per bottle **(old formulation, PD-012-023**) or 30 capsules per bottle **(new formulation, PD-012-042).** Deleted expiry date from specifications for investigational drug label.
Section 5.3.1	Concomitant Therapies	Added permitted concomitant medication (somatostatin analogues) for patients with functioning advanced pNETs (Arm B) or functioning advanced epNET (Arm C) and time frame for discontinuation of SSAs by patients with functioning pNETs or epNETs. Specified INR range for patients taking Coumadin or warfarin-like drugs.
Section 6.2.1 and Study Flowchart	Tumor Assessment	Clarified scans required at baseline

Section Number	Section Title	Description of Changes
Section 6.2.2 and Study Flowchart	Exploratory Assessment of Circulating Tumor Markers	Added Section 6.2.2 to specify the circulating tumor markers to be assessed, updated Study Flowchart to show the schedule of assessments of circulating tumor markers.
Section 7.1.2	Dose Limiting Toxicities	Specified timeframe and procedures for reporting of DLTs.
Section 8	Statistical Methods	Organized Section 8 to align it with the corresponding section of 2015-013-00US1.
Section 8.1	General Methodology and Study Endpoints	Specified the primary efficacy endpoint for patients with advanced epNETs; specified that tumor markers are exploratory endpoints.
Section 8.4	Tumor Assessment	Specified the analysis population for primary efficacy endpoints and defined the Response Evaluable Population. Specified the primary efficacy endpoint for patients with advanced epNETs Described the exploratory analysis of tumor marker data
8.5	Determination of Sample Size	Specified that a cohort of at least 15 patients with advanced epNET will be added to the study (as Arm C of the dose expansion phase). Specified the definition of an evaluable patient.
14	References	Added citations supporting discussion of surufatinib mechanism of action in Section 1.4.
Appendix A	Study Flowchart	Added column for C1D16, pre-dose PK sample, and provided a copy of the PK sampling schedule sampling times. Added copy of Table 12 (PK Sampling Times) at the end of the study flowchart.
		Corrected spelling and/or grammatical errors in the document as needed.

Protocol Amendment 6 (Version 3.0, 30 May 2018):

Summary of Changes: Protocol Amendment 6 (Version 3.030 May 2018)
Specified initial dose of study drug in dose expansion phase as 300 mg QD. Per SRC review of data for patients treated with 300 mg QD, specified option of escalation to 400 mg QD for patients in dose expansion phase with decrease in tumor size but not enough to achieve CR or PR and no SAE or any AE ≥Grade 3 after 3 cycles on 300 mg QD.
Added 6 more patients in 400 mg cohort in the dose escalation phase
Specified the study population, the target number of patients to be enrolled in the dose escalation and expansion phases, and the number of sites needed to enroll the patients in a timely fashion
Specified planned enrollment of approximately 65-70 patients.
Specified the study population, the target number of patients to be enrolled in the dose escalation and expansion phases, and the number of sites needed to enroll the patients in a timely fashion
Updated the number of investigational sites.
Stipulated that the term “tumor assessment” would be used throughout the protocol; that tumors would be assessed according to RECIST V. 1.1 at Screening, Cycle 2 Day 1 (C2D1), and every 8 (±1) weeks thereafter.
Specified dose adjustment for impaired liver function.
Specified tumor markers to be assessed: CEA and CA 19-9 for patients with BTC (Arm A) and chromogranin-A for patients with pNET (Arm B).
Changed PK sampling times on C1D1, C1D15 and C2D1 post-dose 12 hours (± 60 minutes)” to post-dose 6 hours (± 60 minutes)”
Added chemistry panel and urinalysis to study flowchart C1D8 and C1D22 for safety monitoring.
Added study visit windows: Day 8 (D8), D15, D22 of Cycle 1 and D1, D15 of Cycle2 (±1d); Cycle 3 and onwards: D1 (±3 day) and then every 4 weeks.
Added the dose modification guideline to Section 5.2.2. Specified dose modification guideline for proteinuria and for Grade 3 liver function impairment.

Protocol Amendment 5 (Version 2.0, 8 December 2017): Summary of Changes: Protocol Amendment 5 (Version 2.0, 8 December 2017)
Specified study population, target number of patients to be enrolled in the dose expansion phase and the number of sites needed
Specified the number of patients to be enrolled in the two arms (BTC and pNET) of the dose expansion phase, increased the number of study sites, and increased the total planned enrollment
Specified the criteria for end of treatment (treatment completion and early discontinuation)
Clearly described the objectives of the dose escalation phase and the dose expansion phase
Defined the efficacy endpoints of the dose expansion phase
Provided the rationale for the study drug dose to be used in the dose expansion phase
Reinstated “4 weeks” as the washout period for any previous anticancer therapies prior to study drug
Added relevant new clinical data on the safety and efficacy of surufatinib
Provided the rationale for the sample size determination and describe the statistical analyses for patients in the dose expansion phase
Added to the Section 1.2.1 Nonclinical Pharmacology: CSF-1R is another target of surufatinib from preclinical data

Protocol Amendment 4 (Version 1.4, 16 Dec 2016):

Summary of Changes: Protocol Amendment 4 (Version 1.4, 16 December 2016)
Excluded patients over 75 years of age from the study population
Exempted from the DLT definition: Grade 3 hypertension which could be well managed and downgraded within 3 days
Changed exclusion criterion for anticancer medication taken prior to study drug from 4 weeks to 4 weeks or 5 half-lives, whichever is shorter

Protocol Amendment 3 (Version 1.3, 31 Oct 2016):

Summary of Changes: Protocol Amendment 3 (Version 1.3, 31 Oct 2016)
Introduced new formulation of surufatinib PD-012-042 (replacing formulation No. PD-012-023) for dose escalation and remainder of trial. Starting dose of 300 mg with formulation PD-012-042 is acceptable if safety profile of formulation PD-012-023 was acceptable (in dose escalation phase). Provided details of quality of drug substance (API) and drug product (capsule) of formulation PD-012-042.
Clarified that concomitant use of gastroduodenal mucosal protective agents, such as sucralfate, are allowed in cycle 1 of dose escalation phase.
Added close monitoring of concomitant administration of surufatinib with CYP3A substrates due to risk of drug-drug interaction
Updated the long-term storage stability data for PK plasma samples: -20°C for 317 days and at -80°C for 716 days.

Protocol Amendment 2 (Version 1.2, 17 June 2015):

Summary of Changes: Protocol Amendment 2 (Version 1.2, 17 June 2015)
Added MTD and RP2D to primary objectives
Added glomerular filtration rate (GFR) to exclusion criterion 5. Add creatinine clearance per Cockcroft-Gault per serum creatinine level.
Definition of DLT: exclude nausea/vomiting, diarrhea, constipation or electrolyte imbalance if downgraded to less than grade 3 within 3 days; deleted "tendency of" before "bleeding". Added to DLT definition: any life-threatening complication or abnormality not covered in the NCI CTCAE v4.03.
Defined MTD as the maximum dose at which no more than 1 of 6 patients in a single dose group experiences DLT in Cycle 1 (Days 1-28)
Revised the dose administration time from before breakfast to after breakfast per the results of food effect study CCI [redacted]
Added more details on cardiac monitoring (schedule of ultrasonic cardiogram or MUGA and 12-lead electrocardiogram assessments).
Added "changes in ECG/echocardiogram results" into safety analysis.

Protocol Amendment 1 (Version 1.1, 15 March 2015):

Summary of Changes: Protocol Amendment 1 (Version 1.1, 15 March 2015)
Specified planned enrollment of 21-36 patients, doses in dose escalation phase (50,100, 200, 300, and 400 mg/day) and revised duration of study to 18 months. Specified that this is a dose escalation trial with a dose expansion phase to confirm the MTD or the RP2D. The MTD or RP2D will be confirmed in the dose expansion phase.
Defined inclusion criteria. Added QTc interval prolongation to exclusion criteria.
Added to definition of DLT (any Grade 4 non-hematologic toxicity; Grade 4 thrombocytopenia or ≥Grade 3 thrombocytopenia associated with tendency of bleeding); dose interruption for > 14 days due to toxicity
Modified flowchart to show initial steps
Added to the list of excluded therapies (acid-reducing agents)
Specified ECG time points. Specified PK sample collection time points.

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LIST OF ABBREVIATIONS

Abbreviations	Definition
AE	Adverse event
ALT	Alanine amino transaminase
ANC	Absolute neutrophil count
AST	Aspartate aminotransaminase
BRCP	Breast cancer receptor protein
BTC	Biliary tract cancer
CA 19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CgA	Chromogranin A
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CSF1R	Colony stimulating factor 1 receptor
CT	Computed tomography
CTC	Common toxicity criteria
CTC AE	Common terminology criteria for adverse events
DCR	Disease control rate
DILI	Drug-induced liver inquiry
DLT	Dose-limiting toxicity
DoR	Duration of response
DVT	Deep vein thrombosis
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EC	Ethics Committee
epNET	Extrapancreatic neuroendocrine tumor
FGFR1	Fibroblast growth factor receptor 1

Abbreviations	**Definition**
G1	Grade 1 (refers to BTC, pNETs, and epNETs)
G2	Grade 2 (refers to BTC, pNETs, and epNETs)
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HR	Hazard ratio
HUVEC(s)	Human umbilical vein epithelial cells
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INN	International nonproprietary name
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
KDR	Kinase domain insert receptor
K_{inact}/K_I	Rate constant describing the efficiency of covalent bond formation resulting from the potency (K_I) of the first reversible binding event and the maximum potential rate (K_{inact}) of inactivation [2]).
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
MRT	Median residence time
MTD	Maximum tolerated dose
NET	Neuroendocrine Tumors
NCI	National Cancer Institute
NSCLC	Non - Small Cell Lung Cancer
NSE	Neuron-specific enolase
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PE	Pulmonary embolism

Abbreviations	Definition
PECAM-1	platelet and endothelial cell adhesion molecule
PFS	Progression-free survival
P-gp	p-glycoprotein
PK	Pharmacokinetics
PKAS	Pharmacokinetics analysis set
pNET	Pancreatic neuroendocrine tumor
PR	Partial response
PR	Partial response
PRES	posterior reversible encephalopathy syndrome
PT	Preferred term (MedDRA)
PVNS	Pigmented villonodular synovitis
RAS	a small GTPase involved in signal transduction
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
QD	Once daily
QTc	QT interval
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
SOC	System organ class (MedDRA)
SRC	Safety review committee
SSA(s)	Somatostatin analogue(s)
STS	Soft tissue sarcoma
Surufatinib	International nonproprietary name assigned to sulfatinib by the World Health Organization [1]
$t_{1/2}$	Half-life
TAM(s)	Tumor-associated macrophage(s)
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum concentration
TTR	Time to response
TSH	Thyroid stimulating hormone
UPS	Undifferentiated pleomorphic sarcoma
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide

Abbreviations	Definition
WHO	World Health Organization

1 SYNOPSIS

Title	A Multi-Center, Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Surufatinib (HMPL-012), Previously Named Sulfatinib in Advanced Solid Tumors
Short Title	Not Applicable
Acronym	Not Applicable
Phase	1/1b
Rationale	There is an unmet medical need for new, safe and effective therapy for patients with advanced biliary tract cancer (BTC), advanced pancreatic neuroendocrine tumor (pNET), advanced extrapancreatic neuroendocrine tumor (epNET), and advanced soft tissue sarcoma (STS). Surufatinib, discovered by Hutchison MediPharma International, primarily inhibits vascular endothelial growth factor receptor, fibroblast growth factor receptor, and colony stimulating factor 1 receptor, sparing many other kinases. Preclinical safety evaluation results supported a good safety profile for surufatinib. Surufatinib has demonstrated statistically significant and clinically meaningful efficacy in clinical studies on patients with advanced cancer in China. This is a dose escalation and dose expansion study, to be conducted in a United States patient population to confirm the safety and efficacy results of clinical studies performed in China.
Target Population	Patients at least 18 years old with locally advanced or metastatic solid tumors for whom approved therapy either does not exist or has proven to be ineffective or intolerable. In the dose expansion phase, patients with histologically or cytologically documented, locally advanced or metastatic BTC that has progressed on standard first line chemotherapy (Arm A), low-to-intermediate grade (G1 or G2), well-differentiated, unresectable or metastatic pNET that has progressed on everolimus, sunitinib, or both (Arm B), low-to-intermediate grade (G1 or G2), well-differentiated, unresectable or metastatic epNET that has progressed on everolimus (Arm C), and advanced STS (Arm D) that has progressed on at least one line of standard therapy (if available), or refused standard frontline cytotoxic chemotherapy will be evaluated for enrollment.
Intervention	Surufatinib (HMPL-012), oral once daily (QD) to be taken with 200 mL water within 1 hour after breakfast.
Description of Sites	Approximately 8 to 15 sites in the United States and Europe.

Objectives and Endpoints	
Dose Escalation	
Primary Objectives To evaluate the safety and tolerability of surufatinib in patients with advanced solid tumors of any type and to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D).	**Primary Endpoints** The incidence of dose-limiting toxicities (DLTs) in each cohort
Secondary Objectives • To evaluate the pharmacokinetic (PK) characteristics of multiple-dose surufatinib and to investigate the metabolite profile of surufatinib in the plasma of patients with solid tumors.	**Secondary Endpoints** • Pharmacokinetic parameters, which include: – Maximum plasma concentration (C_{max}) – Time to reach maximum concentration (T_{max}) – Terminal half-life ($t_{1/2}$)

• To evaluate the anticancer activity of surufatinib in patients with solid tumors according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.	– Area under the concentration-time curve in a selected time interval (AUC_{0-t}) – Area under the concentration-time curve in the time interval from 0 to infinity (AUC_{0-t}) – Apparent clearance (CL/F) – Apparent volume of distribution (V_z/F) – Mean residence time (MRT) – Accumulation index based on AUC • The objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR) • Progression-Free Survival (PFS) • Percentage change in tumor size from baseline according to RECIST Version 1.1
Dose Expansion	
Primary Objectives To evaluate the anticancer activity of surufatinib at the RP2D from the dose escalation phase, in patients with advanced BTC, patients with advanced pNETs, patients with locally advanced, unresectable, metastatic epNETs, and patients with STS treated at a dose of 300 mg QD.	**Primary Endpoints** • PFS rate at 16 weeks in the BTC cohort (Arm A); • PFS rate at 11 months in the pNET cohort (Arm B); • PFS rate at 11 months in the epNET cohort (Arm C); • PFS rate at 4 months in the STS cohort (Arm D).
Secondary Objectives • To evaluate the PK profile of multiple dose surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS. • To evaluate the safety of surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS. • To evaluate the anticancer activity of surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS.	**Secondary Endpoints** • Pharmacokinetic parameters, which include C_{max}, T_{max}, first-order rate constant K_{el}, AUC, $t_{1/2}$, CL/F, V_z/F, and dose proportionality between AUC and dose and C_{max} and dose • Safety, as assessed by: – The frequency and severity of adverse events – Physical examination findings – Vital signs – Laboratory test results (ie, hematology, chemistry panel, and urinalysis) – 12-lead electrocardiogram – Echocardiogram • Efficacy treatment outcomes, which consist of: – ORR – DCR – TTR – DoR – Percentage change in tumor size from baseline according to RECIST Version 1.1

Brief Summary: The purpose of this study is to evaluate the safety and tolerability of surufatinib and to confirm the safety and efficacy results of clinical studies performed in China in a Western patient population. Accordingly, this is an open-label trial of surufatinib, which consists of 2 phases: a dose escalation phase in patients with advanced solid tumors of any type, and a dose expansion phase in patients with advanced BTC (Arm A), advanced pNETs (Arm B), advanced epNETs (Arm C), or STSs (Arm D).Study details are outlined below.	
Condition/Disease	Dose escalation phase will enroll patients with advanced solid tumors of any type. Dose expansion phase will enroll patients with advanced BTC (Arm A), advanced pNETs (Arm B), advanced epNETs (Arm C), and STSs (Arm D).
Study Duration	Study duration for patients in the dose escalation is up to approximately 1 year and 2 months, including: • Screening period of up to 28 days • Treatment period until disease progression, death, end of study, or early discontinuation as specified in the protocol, or up to 1 year • Dose Completion visit at 30 (±7) days after the last dose of study drug Study duration for patients in the dose expansion consists of: • Screening period of up to 28 days • Treatment period until disease progression, death, end of study, or early discontinuation as specified in the protocol • Dose Completion visit at 30 (±7) days after the last dose of study drug
Treatment Duration	Treatment duration is: • Up to 1 year for patients in the dose escalation phase • Approximately 16 weeks for Arm A • Approximately 11 months for Arms B and C • Approximately 4 months for Arm D
Health Measurement/ Observation	The dose escalation phase will evaluate the safety and tolerability of surufatinib in patients with advanced solid tumors of any type and determine the MTD and/or RP2D by evaluating the incidence of DLT. The expansion phase evaluates the anticancer activity of surufatinib at the RP2D determined in the dose escalation phase as determined from the PFS.
Visit Frequency	All enrolled patients undergo screening, which may be up to 28 days prior to the first dose of study drug. Each treatment cycle is 28 days. Patients are assessed at day 1, day 8 (±1), day 15 (±1), and day 22 (±1) in cycle 1, day 1 and day 15 (±1) in cycle 2, and then day 1 (±3) of cycle 3 and all subsequent treatment cycles. Tumor assessments are conducted according to RECIST Version 1.1 criteria at screening, cycle 2 day 1 and every 8 (±1) weeks thereafter. After receiving the last dose of study drug, patients undergo a Treatment Completion visit at 30 (±7 days) after receiving the last dose of surufatinib. The safety of all enrolled patients will be closely monitored from the time of the initial dose of investigational treatment until 30 days after the last treatment dose.

Number of Participants	In the dose escalation phase, approximately 35 patients will be enrolled. In the dose expansion phase, approximately 115 patients will be enrolled into the 4 open-label treatment arms: at least 30 patients with advanced BTC that have progressed on standard first-line chemotherapy will be assigned to Arm A, at least 15 patients with advanced pNET that have progressed on either everolimus, sunitinib, or both will be assigned to Arm B, and at least 15 patients with advanced epNETs that have progressed on everolimus will be assigned to Arm C, and at least 55 patients with STS will be assigned to Arm D.
Intervention Groups and Duration	In the dose escalation phase, patients are observed for toxicity at each dose level. The DLT assessment window is the 28 days in the first cycle (Day 1 to Day 28). Patients who complete the DLT observation window and are deemed, in the Investigator's judgment, to have benefited from surufatinib treatment could be permitted, at the Investigator's discretion, to continue with surufatinib treatment until disease progression, death, intolerable toxicity, pregnancy, or loss of benefit from the study drug. Patients with acceptable toxicity and ongoing clinical benefit were to be permitted to receive surufatinib for up to 1 year. In the dose expansion phase, patients receive treatment until disease progression, death, end of study, or early discontinuation as specified in the protocol. Patients in both the dose escalation and dose expansion portions undergo a Treatment Completion visit at 30 days (±7) after receiving the last dose of surufatinib.
Data Monitoring/Other Committee	Safety monitoring and evaluation for dose escalation will be carried out by the Safety Review Committee (SRC) upon completion of the DLT observation period of each cohort in dose escalation. The SRC is chaired by the Sponsor's Clinical Program Leader of the surufatinib program, and members will include the principal investigators (PIs), the Sponsor's PK scientist, medical monitor, safety scientist, and the contract research organization's medical monitor. For the dose expansion phase of the trial, a separate, specific SRC will be established to ensure the safety of all patients treated with study drug in the STS cohort (STS-SCR). Review of available safety laboratories, adverse events, and any other pertinent data available will be reviewed after the first 4 patients in each sarcoma cohort have completed at least 1 cycle of treatment.

2 BACKGROUND

2.1 Physical, Chemical and Pharmaceutical Properties of Surufatinib

- International nonproprietary name (INN): Surufatinib, previously named Sulfatinib [1].
- Lab Code：HMPL-012
- Chemical name：N-(2-(dimethylamino)ethyl)-1-(3-(4-(2-methyl-1H-indol-5-yloxy)pyrimidin-2-ylamino)phenyl)methanesulfonamide
- Molecular formula：C24H28N6O3S
- Molecular weight：480.58 g/mol
- Surufatinib is a study drug formulated as odorless, white or off-white powder in capsules, with strength of 50 mg or 200 mg per capsule.
- The active ingredient is insoluble in water, and slightly soluble in methyl alcohol or ethyl alcohol.
- The melting point of the active ingredient is 162to170°C.

2.2 Summary of Nonclinical Studies

2.2.1 Nonclinical Pharmacology

Surufatinib is an anti-angiogenesis agent. It selectively targets tyrosine kinases involved in vascular formation, mainly on the vascular endothelial growth factor receptor family (VEGFR1, 2, and 3), fibroblast growth factor receptor 1 (FGFR1) and colony stimulating factor 1 receptor (CSF1R). In the [32p-ATP] incorporation assay, the IC50s of surufatinib on VEGFR1, 2, 3 (also known as Flt1, KDR, and Flt4) were found to be 2 nM, 24 nM, and 1 nM, respectively. The IC50s of the kinase activity of FGFR1, 2, 3 were determined as 15 nM, 236 nM and 181 nM, respectively. The IC50 for CSF1R (FMS) was 4 nM.

Consistent with its biochemical activity on inhibiting KDR kinase, surufatinib demonstrated strong activity in inhibiting VEGF stimulated phosphorylation of KDR in the HEK293-KDR engineered cell line, with an IC50 of 2 nM. In addition, the activation of KDR downstream signaling cascade pathways, including the PI3K/AKT pathway, RAS/RAF/MEK/ERK pathway, and p38 were also inhibited dose-dependently. Furthermore, in functional assays using HUVECs (human umbilical vein endothelial cells), surufatinib demonstrated inhibition of VEGF-dependent cell proliferation with an IC50 of 16 nM and HUVEC tube formation with an inhibition of 75% at 0.3 M. In the rat aortic ring model, surufatinib inhibited vessel outgrowths of rat aortic rings in a dose-dependent manner with an IC50 of 192 nM.

Surufatinib was evaluated for cytotoxicity in 11 human tumor cell lines and 3 normal human cell lines. Surufatinib showed a weak effect on cell survival with IC50≥5 μM, which was about 300-fold less potent than the IC50 of surufatinib in a VEGF- dependent anti-proliferation assay in HUVEC (16 nM), consistent with its good kinase selectivity.

The inhibitory effect of surufatinib on the phosphorylation of KDR, angiogenesis and tumor growth were evaluated in vivo. The results indicated that upon stimulation with VEGF (i.v., 0.5 g/mouse), KDR phosphorylation (p-KDR) in the mouse lung tissue was significantly induced. Surufatinib orally dosed at 20 and 40 mg/kg completely inhibited VEGF-stimulated KDR phosphorylation for 4 hours and at 80 mg/kg for 8 hours, suggesting

a dose dependent inhibition. In this experiment, the drug exposure was determined. For instance, at 4 hr after oral administration of 20 mg/kg of surufatinib, the drug concentration in plasma reached 181 ng/mL (AUC for 20 mg/kg was 2720 ng·h/mL). These data provided pharmacokinetic (PK)/PD correlation and the effective concentration for complete p-KDR inhibition (EC100=181 ng/mL) useful to guide clinical dose selection.

Surufatinib was further evaluated for anti-tumor activity and demonstrated high potency on inhibiting tumor growth in multiple human tumor xenografts, such as gastric cancer BGC-823, non-small cell lung cancer (NSCLC) NCI-H460, human renal cell carcinoma Caki-1 and colon cancer HT-29. Surufatinib was orally dosed at 20, 40, and 80 mg/kg twice daily and there appeared to be good dose response in these studies. Among the four models, gastric cancer BGC-823 showed the highest sensitivity to surufatinib. The tumor growth inhibition (TGI) achieved 68%, 90% and 103% at 20, 40 and 80 mg/kg, respectively.

The anti-angiogenesis effect of surufatinib in the anti-tumor efficacy studies was investigated by detecting the changes of endothelial cell marker CD31 (PECAM-1) in tumor tissue by immunohistochemistry (IHC) technology. Surufatinib significantly decreased the vascular vessel density (CD31) significantly in both NCI-H460 and Caki-1 xenografts. A clear dose-dependent inhibition of surufatinib on angiogenesis in Caki-1 xenograft tumor tissue was observed. The level of CD31 inhibition appeared to correlate with the tumor growth inhibition.

The plasma and tumor concentrations of surufatinib were analyzed in BGC-823 tumor bearing mice at the end of the efficacy study after last dosing. AUC increased with the increase of dose from 20 to 80 mg/kg. The minimum efficacious dose was 20 mg/kg twice daily ($TGI \geq 58\%$, $P<0.05$) in BGC-823 model (TGI=68%), and the corresponding minimum efficacious exposure, $AUC_{0\text{-}24h}$, in plasma was 4712 ng·h/mL. Surufatinib given orally at 80 mg/kg twice daily resulted in tumor regression with an $AUC_{0\text{-}24h}$ of 16444 ng·h/mL. PK/PD analysis indicated that at this dose complete p-KDR inhibition was maintained for more than 16 hours/day.

2.2.2 Nonclinical Pharmacokinetics

After a single intravenous dose of 10mg/kg surufatinib in rats, the plasma elimination half-life of surufatinib was measured as 2.8 hours, and plasma clearance and apparent volume of distribution were 3.53 L/h/kg and 13.1 L/kg, respectively. Following dosing via oral gavage at low, medium and high dose levels, the mean value of time to reach maximum concentration was 3.0~4.2 hours. The oral bioavailability was observed to be dose dependent. At the dose level of 10 mg/kg, the bioavailability was just 9.9%. When the dose was increased to 40 mg/ml or above, the bioavailability exceeded 50%. The low bioavailability observed at the low dose level might be associated with the efflux by P-glycoprotein in intestinal epithelial cells.

After a single intravenous dose of 5 mg/kg in dogs, the plasma elimination half-life was 3.3 hours, and plasma clearance and apparent volume of distribution were 3.94 L/h/kg and 18.5 L/kg, respectively. Following a single oral dose of 5, 10 and 20 mg/kg, the mean value of time to reach maximum concentration was 3.5~4.5 hours. In the dose range of 5~20 mg/kg, surufatinib exposure (C_{max} and $AUC_{0\text{-}t}$) increased dose-proportionally. Feeding had no obvious effect on the extent and speed of surufatinib absorption. At the oral dose level of 10 mg/kg, the absolute bioavailability was 30.5%.

After administration via oral gavage in rats, surufatinib was distributed widely in various tissues mainly including lung, liver, spleen, adrenal gland, kidney, pancreas and stomach wall. The lowest drug concentration was observed in brain, indicating poor brain blood penetration. At 24 hours post-dose, concentrations in most tissues reduced to 10% or lower than the peak concentrations.

The results of [14C]-surufatinib excretion study revealed that surufatinib was mostly excreted via faeces (approximately 80% of the dose, including 40% for bile excretion), and a small amount was excreted via urine (approximately 10% of the dose).

In-vitro liver microsomal metabolic stability assays in various species showed high liver extraction of surufatinib. The clearance of surufatinib in liver microsomes was higher in male rats than in female rats. No significant gender difference was observed in other species. In an in-vitro liver microsomes incubation study, phase 1 enzymes mediating the metabolism of surufatinib included CYP3A4/5 (dehydrogenation, N-demethylation), CYP2C8 (dehydrogenation, N-demethylation), CYP2E1 (mono-oxidization), and FMO.

Surufatinib showed weak reversible inhibition against CYP2D6 and CYP3A4/5 with the IC50 of 13 μM and 14 μM, respectively. Time-dependent inhibition study of CYP3A4/5 indicated the potential with a kinact [2] of 0.73 min-1 and KI [2] of 163 μM. The results of CYP1A2 and CYP3A4 induction assay in primary human hepatocytes revealed that surufatinib did not significantly induce CYP1A2 at a concentration of 10 μM or CYP3A4 at a concentration of 2 μM. In an in-vitro permeability and efflux transportation assay using Caco-2 cells, it was found that surufatinib might be a substrate of P-gp.

The protein binding rates of surufatinib were found to be 93~96% in plasma of various species, indicating a moderate to high extent of protein binding in plasma.

2.2.3 Nonclinical Toxicology

2.2.3.1 Safety Pharmacology

The effect of surufatinib on hERG tail currents was evaluated in CHO cells using a patch clamp technique. The effect on the cardiovascular system was evaluated in anesthetized Beagle dogs and no adverse effects were found at the doses evaluated. No adverse effect was observed on behaviors in mice and respiratory system in anesthetized dogs.

2.2.3.2 General Toxicology

In single dose toxicity studies in rat and dog, no deaths were found up to the highest dose tested at 2000 mg/kg, suggesting good tolerability following single oral dosing. Repeated dose toxicity studies were carried out for surufatinib in rat (1-month, 3-months and 6-months) and dog (1-, 3-, and 9-months), respectively. The NOAEL (No-observed-adverse-effect-level) of surufatinib in 28-day repeated dose toxicity was 20 and 6 mg/kg in rats and dogs, respectively. The toxicokinetic results indicated that the exposures of surufatinib in rats at the NOAEL dose were higher than the exposures at the efficacious dose in mice (40 mg/kg/day). According to the results of toxicity studies, the digestive system (GI, liver), lymphatic system (thymus, spleen, and lymph nodes), kidney, hemapoietic system, reproductive system, endocrine system and skeletal muscle were considered to be the target organs. The toxic responses were found to be completely or nearly completely recovered after a 28-day recovery phase.

The key findings included kidney changes at high doses (60 mg/kg or higher) in rats in the 28-day study. At lower doses, with extended duration of treatment, changes in lymphatic system were found in the rats. In addition, injury to teeth was a consistent finding possibly related to the target inhibition. In the dog, findings in the GI tract were noted in all 3 repeated dose studies. Changes in the lymphatic system were also present in the 9-month study. Taken together, it is worthwhile to note that at high doses surufatinib might cause kidney and GI toxicities. In addition, with extended dosing at lower/tolerated doses, the lymphatic system might be affected. Therefore, during initial dose escalation phase in humans, attention should be paid to kidney and GI side effects. Adverse effects related to lymphatic system should also be monitored for long term use of surufatinib. Most adverse events (AEs) may be reduced or resolved by discontinuation of surufatinib treatment.

2.2.3.3 Reproductive and Development Toxicology

In fertility and early embryonic development to implantation study, the NOAEL of surufatinib was 15 mg/kg for parental male rats, and 10 mg/kg for parental female rats. The NOAEL for fertility and early embryonic development in male and female rats was found to be 45 mg/kg and 10 mg/kg, respectively. In the embryo-fetal development study, the NOAEL for maternal effects and the embryo-fetotoxic dose was found to be 5 and 3 mg/kg in rats, respectively. In rabbits, the NOAEL of surufatinib for maternal effects and embryo-fetotoxic effects was found to be 48mg/kg and 24 mg/kg, respectively.

2.2.3.4 Genetic toxicology

No potential genetic toxicity was found in the bacterial reverse mutation test, the chromosome aberration test in Chinese Hamster Lung Cell, or the micronucleus test in mice.

2.3 Clinical Experience

As of 11 February 2020, the safety database includes 717 patients (714 in monotherapy and 3 in combination therapy) and 60 healthy patients who received surufatinib as monotherapy or combination therapy in completed or ongoing studies.

Of 714 patients who received at least 1 dose of monotherapy of surufatinib, 693 (97.1%) reported treatment-emergent adverse events (TEAEs) and 675 (94.5%) reported treatment-related TEAEs. Treatment-related TEAEs reported in ≥20% of patients included proteinuria, hypertension, diarrhea, blood bilirubin increased, blood thyroid stimulating hormone increased, aspartate aminotransferase (AST) increased, and hypertriglyceridemia. A total of 476 (66.7%) 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 ≥1%) were gastrointestinal hemorrhage, intestinal obstruction, hepatic function abnormal, proteinuria, pneumonia, acute kidney injury, jaundice cholestatic, abdominal pain, and anemia. The reported fatal SAEs that were considered related to study drug (9 patients) included hypovolemic shock, diarrhea, gastrointestinal hemorrhage, disseminated intravascular coagulation and hepatic encephalopathy, liver injury, cerebral hemorrhage, and death. A total of 113 (15.8%) patients reported TEAEs leading to drug discontinuation. The TEAEs leading to drug discontinuation reported in ≥1% of patients included proteinuria (2.0%) and hepatic function abnormal (1.1%).

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). The SANET-ep study met its primary endpoint at the planned interim analysis, with significantly improved progression-free survival (PFS) in surufatinib treated patients compared with placebo-treated patients (median PFS of 9.2 months in surufatinib treated patients versus 3.8 months in placebo-treated patients; hazard ratio [HR] 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-treated patients versus 3.7 months in placebo-treated patients; HR 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 overall response rate (ORR), disease control rate (DCR), duration of response (DoR), and time to response (TTR).

Please refer to the surufatinib Investigator's Brochure (IB) for additional details regarding clinical safety and efficacy in ongoing and completed studies of surufatinib.

3 STUDY RATIONALE

During the pathogenesis of cancer, tumors can secrete a variety of factors to stimulate the formation of tumor vasculatures in order to increase their supply of nutrients and oxygen. Such tumor vasculatures are often formed by rapid endothelial cell proliferation and packed coarsely, leading to increased permeability and tumor cell leakage into the circulation [3]. Vascular endothelial cell growth factor (VEGF) and fibroblast cell growth factor (FGF) play key roles in tumor angiogenesis and have become two molecular targets of intense research for anti-angiogenesis therapies [4-5].

Highly selective antibodies against VEGF or its receptor VEGFR have demonstrated significant clinical benefit and have been widely used for the treatment of certain cancers [6]. Small molecule drugs, including sunitinib and sorafenib, targeting the VEGF receptor (VEGFR) tyrosine kinase signaling pathway have also contributed significantly in treating cancer [7,8]. However, most of the early generation small molecule VEGFR tyrosine kinase inhibitors (TKIs) inhibit many kinases (multi-kinase inhibitors) in addition to VEGFR, resulting in "off-target" toxicities [9]. Improving kinase selectivity has become a key focus for newer generation TKIs.

Surufatinib, discovered by Hutchison MediPharma International, primarily inhibits VEGFR, fibroblast growth factor receptor (FGFR), and CSF-1R, sparing many other kinases. Preclinical safety evaluation results supported a good safety profile for surufatinib.

3.1 Mechanism of Action

The primary action of surufatinib is anti-angiogenic, by inhibition of VEGFR 1, 2, and 3. As stated above, angiogenesis is a validated target in a variety of solid malignancies, through inhibition VEGF or VEGFR, and either by a monoclonal antibody or small molecule tyrosine kinase inhibitor. Surufatinib also inhibits fibroblast growth factor receptor (FGFR) and colony stimulating factor-1 receptor (CSF-1R).

Fibroblast growth factor receptor (FGFR) signaling plays important roles in tumor cell proliferation, angiogenesis, migration, and survival [10]. Inhibition of FGF and/or its receptor are therefore attractive targets in cancer therapy. A recent finding is that approximately 10-16% of patients with intrahepatic cholangiocarcinoma, a type of BTC, have FGFR genetic aberrations; the most common of these are gene fusions of FGFR-2 [11]. This raises the possibility that the FGFR is a potential target in the treatment of a subset of patients with BTC. There is an intensive ongoing research effort to address this question. It is possible that surufatinib could have an anti-tumor effect through FGFR in patients with gene fusions or other genetic aberrations of FGFR-2.

CSF-1 is produced by tumor cells and/or other cells in the tumor microenvironment to stimulate tumor associated macrophages (TAMs), which result in local suppression of the immune response to malignant tumor cells [12]. Drugs that inhibit CSF-1 or CSF-1R are currently under investigation. The aim is to block the local immunosuppressive effect of TAMs that protects tumor cells. Inhibition of CSF-1 signaling can change TAMs from an immunosuppressive to a pro-inflammatory state with tumoricidal activity [12]. Surufatinib may exert such an action on TAMs through inhibition of CSF-1R.

The results of completed and ongoing clinical studies of surufatinib in China are reviewed in Section 2.3. The most encouraging preliminary results are in patients with BTC, pNET, and epNET, and this is the rationale for including patients with these malignancies in the

expansion phase of this study. Soft tissue sarcomas (STSs) have also been chosen as an expansion cohort based upon anti-tumor activity of multitargeted kinase inhibitors for the indication. Information about these malignancies and how surufatinib, if approved, would fit into current practice guidelines, is discussed below.

3.2 Unmet Medical Need

There is an unmet medical need for new, safe and effective therapy for patients with advanced BTC, advanced pNET, advanced epNET, and advanced STS.

Biliary Tract Cancers (BTCs) include the following malignancies: gallbladder carcinoma, intrahepatic and extrahepatic cholangiocarcinoma, and cancer of the Ampulla of Vater. According to current NCCN practice guidelines [13], standard first-line therapy for locally advanced or metastatic BTC is cytotoxic chemotherapy with gemcitabine and cisplatin; for patients with microsatellite-instability high (MSI-H) tumors, immunotherapy with pembrolizumab is also indicated [13]. However, there is no established second-line therapy, so patients who have failed first-line therapy have an unmet medical need, and will be investigated in the expansion phase of the current study.

Neuroendocrine Tumors (NETs): Neuroendocrine cells are widely distributed throughout the body, and neuroendocrine tumors arise from almost any part of the gastrointestinal tract, lungs, and other sites [14]. These tumors are broadly divided into well differentiated, relatively slow-growing tumors, and poorly differentiated, aggressively growing tumors termed neuroendocrine carcinomas.

Table 1 Distribution of Neuroendocrine Tumors by Primary Site

Primary site	Number	Percent
Lung	20,948	24.6
Rectum	14,938	17.5
Small intestine	10,519	12.4
Pancreas	7,612	8.9
Stomach	3,967	4.7
Appendix	3,341	3.6
Colon	2,989	3.5
Cecum	2,206	2.6
Liver	509	0.6
Thymus	237	0.3
Other/ unknown	17,865	21.0
Total	85,131	100

Source: Sackstein P, et al. Seminars Oncol. 2018 Aug; 45(4):249-258 [14]

Well-differentiated tumors that arise from the digestive system or lungs have traditionally been called carcinoid tumors, but now are called gastrointestinal NETs or extrapancreatic (EP)-NETs. Those that arise from the pancreas were traditionally called pancreatic islet cell tumors, but are now called pancreatic NETs, or pNETs. Collectively, the well differentiated tumors are called Gastroenteropancreatic (GEP) NETs. In considering the distribution of GEP-NETs by site of origin according to the Surveillance, Epidemiology, and End Results (SEER) database (Table 1), it is evident that pNETs comprise approximately 8.9% of all NETs [13].

Functioning NETs: GEP-NETs can also be defined by their functional status. Functioning epNETs are characterized by the presence of clinical symptoms (carcinoid syndrome) due to excess secretion of a variety of substances by the tumor (polypeptides, biogenic amines, and prostaglandins). The most common symptoms of carcinoid syndrome are flushing and diarrhea. Carcinoid syndrome is treated with somatostatin analogues (SSAs), octreotide and lanreotide, both of which are effective in relieving symptoms [16-19].

Functioning (hormone-secreting) pancreatic NETs are classified according to the predominant hormone they secrete and the resulting clinical syndrome (eg, insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma).

Treatment of NETs: The names, routes of administration, and indications of FDA-approved drugs for the treatment of patients with well-differentiated, low to intermediate grade NETs are summarized in Table 2. The somatostatin analogues (SSAs) octreotide [17] and octreotide LAR [18] are approved for the symptomatic treatment of patients with functioning metastatic carcinoid tumors (diarrhea, flushing) and functioning VIPomas (profuse watery diarrhea). The SSA lanreotide depot [19] is approved for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP-NETs to improve PFS.

When there is disease progression (during treatment with SSAs, where applicable) in patients with pNETs, the oral kinase inhibitors everolimus [20] and sunitinib [21] are indicated to improve PFS. Everolimus is also approved for the treatment of patients with progressing, well-differentiated, non-functioning, epNETs (carcinoid tumors) of GI tract or lung origin, to improve PFS [20], but is not approved for functioning carcinoid tumors.

Patients with a clinically high disease burden are treated with cytotoxic chemotherapy [22]. A recently approved option for patients with somatostatin receptor-positive gastroenteropancreatic (GEP-NETs) is Peptide Receptor Radioligand therapy (PRRT) with Lutathera® (^{177}Lu-Dotatate) [23]. Current limitations of ^{177}Lu-Dotatate include the complexity of its administration, lack of widespread availability, and uncertainty of its efficacy relative to more established therapies.

Table 2 FDA-Approved Drugs for the Treatment of Neuroendocrine Tumors (NETs)

Drug Name Brand (INN)	Route of administration	Drug Type and FDA-Approved Indication
Sandostatin® Injection (octreotide)	s.c. injection	Sandostatin Injection is a somatostatin analogue for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease. (Symptomatic) treatment of profuse watery diarrhea associated with VIPomas. Sandostatin studies were not designed to show an effect on the size, rate of growth, or development of metastases.
Sandostatin LAR Injection® (octreotide LAR)	i.m. injection	Sandostatin LAR is a somatostatin analogue indicated for treatment in patients who have responded to and tolerated Sandostatin Injection for severe diarrhea/flushing episodes associated with metastatic carcinoid tumors; and profuse watery diarrhea associated with VIPomas. The effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

Table 2 FDA-Approved Drugs for the Treatment of Neuroendocrine Tumors (NETs)

Drug Name Brand (INN)	Route of administration	Drug Type and FDA-Approved Indication
Somatuline Depot Injection® (depot lanreotide)	deep s.c. injection	Somatuline is a somatostatin analogue indicated for the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
Afinitor® (everolimus)	oral	Afinitor is a kinase inhibitor indicated for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin (pNET) and adults with progressive, well-differentiated, non-functional neuro-endocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.
Sutent® (sunitinib)	oral	Sutent is a kinase inhibitor indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.
Lutathera (^{177}Lu-dotatate) injection®	i.v. injection (radioactive)	Lutathera is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroentero-pancreatic (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

In the current study, patients with NETs must have unresectable or metastatic, well-differentiated, low-to-intermediate-grade (G1-G2) disease that has progressed over the 12 months prior to enrollment. Patients with pNETS must have failed prior therapy with either everolimus or sunitinib, and those with epNETs must have failed therapy with everolimus. Patients may receive SSAs for symptomatic control of functioning tumors if they have been on a stable dose of the SSA for at least 2 months prior to enrollment. SSA therapy during the study is not permitted in patients with non-functioning NETs. Patients who have received SSA therapy in the absence of symptoms, with the intention of prolonging PFS, should also have received targeted therapy (everolimus or sunitinib) in order to be eligible for enrollment. Since disease progression is a requirement for enrollment, both the SSA and the targeted therapy must have been discontinued at least 4 weeks before the first dose of study drug.

Preliminary data from the ongoing Phase 2 study of surufatinib in the treatment of patients with advanced BTC CCI , and the completed Phase 1b/2 study CCI in patients with advanced NETs (both pNETs and epNETs) in China are promising. These data support the inclusion of patients with advanced BTC, advanced pNETs, and advanced epNETs in the expansion phase of the current study.

Soft tissue sarcomas (STSs) are malignant tumors that arise in mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). International incidence rates range from 1.8 to 5 cases per 100,000 individuals per year [24]. In the year 2019, there was an estimated 12,750 new cases and 5,270 deaths from soft tissue sarcoma in the United States (US) [25]. Soft tissue sarcomas are heterogeneous, with more than 100 different subtypes identified by the World Health Organization and are classified according to tissue of origin [26].

For patients with incurable disease not amenable to locoregional therapies, first line systemic treatment consists of cytotoxic chemotherapy. Doxorubicin has been considered the standard systemic therapy in the management of metastatic sarcomas for several years [27], [28]. Gemcitabine and docetaxel were found to have similar outcomes as doxorubicin alone [29]. Other drugs that may have clinical activity as single agents are ifosfamide, and paclitaxel (depending on histology) [30],[31],[32],[33].

Since 2012, three drugs have been approved for the treatment of soft tissue sarcomas after failure of a first-line chemotherapy: pazopanib for all soft tissue sarcomas except adipocytic subtypes, eribulin for liposarcoma, and trabectedin for leiomyosarcoma and liposarcoma [34],[35],[36],[37]. Despite new agents, treatment for advanced STS remain paliative only, and remains an unmet medical need.

Pazopanib is a multitargeted, oral, small molecule inhibitor of several tyrosine kinases including vascular endothelial growth factor receptors-1, -2, and -3; platelet-derived growth factor receptor alpha and beta; and fibroblast growth factor receptor-1, and -3. The phase 3 randomized, double-blind PALETTE study (NCT00753688) from the European Organization for Research and Treatment of Cancer compared pazopanib to placebo in 369 patients with different subtypes, excluding adipocytic sarcomas and gastrointestinal stromal tumors, after progression on a first-line anthracycline-based regimen [38]. The median PFS was 4.6 months for patients who received pazopanib versus 1.6 months for patients who received placebo. Overall survival (OS) difference was not statistically significant at 12.5 months for patients who received pazopanib versus 10.7 months for patients who received placebo (HR, 0.86; 95% confidence interval [CI], 0.67–1.1). Overall response rate was 6% for patients who received pazopanib versus 0% for patients who received placebo. The most common grade 3/4 toxicities associated with pazopanib were fatigue, hypertension, diarrhea, anorexia, and transient liver function tests abnormalities. Based on the above data, pazopanib was approved by the U.S. Food and Drug Administration (FDA) in 2012 for the treatment of patients with soft tissue sarcomas, excluding adipocytic subtypes, who have received previous chemotherapy.

Given the limited efficacy of currently available treatment options for patients with unresectable or metastatic soft tissue sarcomas, testing of new agents is warranted.

This is a dose escalation and dose expansion study, which is conducted in a US patient population to confirm the safety and efficacy results of clinical studies performed in China. During the dose expansion portion of the study, 4 expansion cohorts have been added, Arm A (BTC cohort), Arm B (pNET cohort), Arm C (epNET cohort), and Arm D (STS). Preliminary data from the cohort of patients with advanced BTC in the Expansion Cohort of the present study have shown encouraging results. In order to characterize further the safety and efficacy of surufatinib in this patient population, an additional 15 patients will be enrolled into Arm A (BTC) of the expansion phase, for a total enrollment of at least 30 patients. Arm B (pNET) and Arm C (epNET) will enroll no less than 15 patients each. If needed, Arm B and Arm C could also enroll additional patients to characterize further the safety and efficacy of surufatinib in these patient populations. Arm D (STS) will enroll approximately 55 patients.

3.3 Benefit and Risk Assessment

Based on the available non-clinical and clinical data, identified risks of surufatinib include hepatic disorders, proteinuria, hypertension, myelosuppression, haemorrhage, and acute kidney injury. Potential risks include infection, intestinal obstruction, myocardial

ischaemia, cardiac failure, thromboembolism, pancreatitis, GI perforation, and posterior reversible encephalopathy syndrome. These are further described in the surufatinib IB.

Appropriate exclusion criteria, monitoring, and dose modification guidance are included in the protocol to ensure the safety of patients enrolled in the clinical trial. Patients are excluded if they have signs, symptoms, or history that may put them at risk in the context of the identified and potential risks of surufatinib including abnormal serum total bilirubin or ALT/AST or other signs of hepatic damage; urine protein ≥2+; uncontrolled hypertension; abnormal neutrophil count, platelet count, or haemoglobin level; signs of risk of haemorrhage; creatinine clearance <60 mL/min; conditions that could possibly result in gastrointestinal tract hemorrhage or perforation; clinically significant cardiovascular disease; history of thromboembolic events; and posterior reversible encephalopathy syndrome (PRES). Patients with other disease, metabolic disorder, physical examination abnormality, abnormal laboratory result, or any other condition that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the patient at high risk are also excluded.

Section 7.2.3 provides detailed guidance on dose modifications for important identified risks including hypertension, proteinuria, liver function and haemorrhage, and general dosing guidance to protect subjects are included in Section 7.2.2. Thus, the identified and potential risks of treatment with surufatinib are appropriately mitigated by measures in the protocol.

There remains an unmet need for patients with advanced BTC, NETs, and STS. Evidence to date suggests that surufatinib may potentially be efficacious in the treatment of various cancers, including those to be included in the proposed trial. Based on the preclinical toxicology data, the safety profile from clinical trials, the proposed safety management actions, the limited life expectancy of patients with advanced malignancies, the lack of effective alternative treatments and the scientific design of clinical trial protocol, and the overall benefit/risk assessment support the administration of surufatinib to patients with advanced cancer as an investigational treatment in this clinical trial.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Dose Escalation Phase

4.1.1 Primary Objective

The primary objective of the dose escalation phase is to evaluate the safety and tolerability of surufatinib in patients with advanced solid tumors of any type and to determine the MTD and/or RP2D.

4.1.2 Primary Endpoint

The incidence of DLTs in each cohort.

DLT is defined as:

- Any Grade 4 non-hematologic toxicity;
- Any Grade 3 non-hematologic toxicity related to study drug except for nausea/vomiting, diarrhea, constipation, hypertension and electrolyte imbalances downgraded within 3 days with appropriate supportive treatment;
- Grade 4 neutropenia lasting >3 days;
- Grade 3 febrile neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding;
- Dose interruption for >14 days due to toxicity;
- Any life-threatening complication or abnormality not covered in the NCI CTCAE v. 4.03.
  - In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.
  - The MTD is the highest dose at which no more than 1 of 6 patients developed DLT. If 2 or more of 6 patients developed DLT at a particular dose level, then that dose has exceeded the MTD.
  - In general, the safety and tolerability of surufatinib will be evaluated based on the AE data. Other safety parameters include physical examination, vital signs, laboratory test results (ie, hematology, chemistry panel, thyroid function, and urinalysis), 12-lead electrocardiogram, and echocardiogram.

4.1.3 Secondary Objectives

- To evaluate the PK characteristics of multiple-dose surufatinib and to investigate the metabolite profile of surufatinib in the plasma of patients with solid tumors

- To evaluate the anticancer activity of surufatinib in patients with solid tumors according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

4.1.4 Secondary Endpoints

The secondary endpoints of the study include the primary PK parameters and the treatment outcomes (per RECIST Version 1.1) as described below.

- Pharmacokinetic parameters, which include:
  - Maximum plasma concentration (C_{max})
  - Time to reach maximum concentration (T_{max})
  - Terminal half-life ($t_{1/2}$)
  - Area under the concentration-time curve in a selected time interval (AUC_{0-t})
  - Area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0-\infty}$)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V_z/F)
  - Mean residence time (MRT)
  - Accumulation index based on AUC
- ORR
- DCR
- DoR
- PFS
- Percentage change in tumor size from baseline according to RECIST Version 1.1

4.2 Dose Expansion Phase

4.2.1 Primary Objective

To evaluate the anticancer activity of surufatinib at the recommended phase 2 dose (RP2D) from the dose escalation phase, in patients with advanced BTC, patients with advanced pNETs, patients with locally advanced, unresectable, metastatic epNETs, and patients with STS treated at a dose of 300 mg QD .

NOTE: The MTD/RP2D of 300 mg QD was declared at the time Amendment 7 was written. The RP2D in this trial is the same as the RP2D used in clinical trials in China.

4.2.2 Primary Endpoints

The primary efficacy endpoints are:

- PFS rate at 16 weeks in the BTC cohort (Arm A);
- PFS rate at 11 months in the pNET cohort (Arm B);
- PFS rate at 11 months in the epNET cohort (Arm C);
- PFS rate at 4 months in the STS cohort (Arm D).

4.2.3 Secondary Objectives

- To evaluate the PK profile of multiple dose surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS.

- To evaluate the safety of surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS.
- To evaluate the anticancer activity of surufatinib in patients with advanced BTC, patients with advanced pNET, patients with advanced epNET, and patients with advanced STS.

4.2.4 Secondary Endpoints

- Pharmacokinetic parameters, which include but are not limited to, C_{max}, T_{max}, first-order rate constant K_{el}, AUC, $t_{1/2}$, CL/F, V_z/F, accumulation ratio, and dose proportionality between AUC and dose and C_{max} and dose
- Safety, as assessed by:
  - The frequency and severity of adverse events
  - Physical examination findings
  - Vital signs
  - Laboratory test results (ie, hematology, chemistry panel, and urinalysis)
  - 12-lead electrocardiogram
  - Echocardiogram
- Efficacy treatment outcomes, which consist of:
  - ORR
  - DCR
  - TTR
  - DoR
  - Percentage change in tumor size from baseline (per RECIST Version 1.1)

4.2.5 Exploratory Objectives

- To assess selected tumor markers based on type of malignancy
- To evaluate the OS in patients with advanced BTC and advanced STS

4.2.6 Exploratory Endpoints

- Tumor markers may include, but are not be limited to, serum CEA and CA 19-9 (patients with BTC) serum chromogranin A (CgA) and neuron-specific enolase (NSE) for patients with pNET and epNET; and VEGF for the BTC, pNET, and epNET disease cohorts. Assessment of tumor markers will be performed within 28 days prior to the start of treatment with study drug (C1D1) and at each tumor assessment visit.
- Overall survival limited to patients enrolled to the BTC and STS cohorts only.

5 INVESTIGATIONAL PLAN

5.1 Description of the Study

This is an open-label trial of surufatinib taken orally once daily (QD), and it consists of two phases: a dose escalation phase in patients with advanced solid tumors of any type, and a dose expansion phase in patients with advanced BTC (Arm A), advanced pNETs (Arm B), advanced epNETs (Arm C), or STSs (Arm D). The two phases will be conducted as described below.

5.1.1 Dose Escalation Phase

A 3+3 design will be used for this phase of the study. As of Amendment 7, a total of 35 evaluable patients have been enrolled in the dose escalation phase and the MTD/RP2D has been declared at 300 mg QD.

The trial was to evaluate 5 dose levels of surufatinib 50 mg, 100 mg, 200 mg, 300 mg and 400 mg on a QD dosing schedule.

A minimum of 3 patients were to be enrolled and observed for toxicity at each dose level. If the 3 patients initially enrolled in a dose cohort completed the DLT assessment window (Cycle 1, Days 1-28) without experiencing a DLT, another 3 patients were to be enrolled at the next higher dose level. If 1 of the initial 3 patients enrolled at any dose level experienced a DLT during the DLT assessment window, additional patients were to be enrolled at that dose level for a minimum of 6 evaluable patients for the DLT evaluation. If 1 DLT was observed in 1 of the 6 evaluable patients at this dose level, dose escalation was to proceed to the next pre-defined dose level. If 2 or more DLTs were observed in the 6 evaluable patients at a given dose level, the dose escalation was to be halted. If this dose level was ≥50% higher than the previous dose level, an intermediate dose level was to be evaluated for toxicity in the same manner as described above. If the dose level was <50% higher than the previous dose level, additional patients were to be enrolled at the previous dose level, if necessary, to form a dose cohort of minimum 6 evaluable patients. The MTD is the highest dose reached with no more than 1 DLT among 6 evaluable patients.

Pharmacokinetic samples will be collected as specified in Table 12.

Safety monitoring and evaluation for dose escalation will be carried out by the Safety Review Committee (SRC) upon completion of the DLT observation period of each cohort. Dose escalation decisions are based on safety and PK data from this ongoing trial, as well as consideration of safety and PK data at comparable drug exposures from patients in previously conducted clinical trials in China.

If a patient meets any DLT non-evaluable criteria during the DLT assessment period, the patient will be replaced.

Patients who complete the DLT observation window (Cycle 1, Day 1-28) and are deemed, in the investigator's judgment, to have benefited from surufatinib treatment could be permitted, at the investigator's discretion, to continue with surufatinib treatment until disease progression, death, intolerable toxicity, pregnancy, or loss of benefit from the study drug. Patients with acceptable toxicity and ongoing clinical benefit were to be permitted to receive surufatinib for up to 1 year at the investigator's discretion and with the sponsor's agreement. Intra-patient dose escalation to a higher dose that has been cleared (ie, no DLT

in 3 patients or 1 or less DLT in at least 6 patients) was to be allowed if the sponsor and investigator both agreed.

Please see the flowchart for dose escalation in Table 3 and Section 7.2 for dose modification instructions.

Table 3 Flowchart of Dose Escalation

Cohort	Dose	Patients	DLTs/patients	Dose Escalation Decision
1	50 mg QD	3-6		
			0/3	Escalate to 100 mg QD
			1/3	Enroll 3 additional patients
			1/3+0/3	Escalate to 100 mg QD
			1/3+1/3 or 2/3 or 3/3	Stop dose escalation
2 (or 3, 4, etc.)	100 mg QD or higher	3-6 per cohort	Follow the same rules as above	

An improved surufatinib formulation in 50 mg and 200 mg capsules (formulation No. PD-012-042) was introduced while the dose escalation phase of the study was ongoing. The improved surufatinib capsules have replaced the older surufatinib capsules (formulation No. PD-012-023), and will be used for the rest of the trial. Improved formulation (PD-012-042) showed improved consistency of production capability compared to the prior formulation (PD-012-023), including content uniformity with comparable quality attributes. The dose escalation of the new surufatinib capsules will follow the same rules as described above.

After considering the safety, tolerability, and PK data in the 300 mg QD (n=9) and initial 400 mg QD (n=7) cohorts, the SRC members agreed to enroll another 6 patients in the 400 mg QD cohort of the dose escalation phase. A total of 13 patients were enrolled in 400 mg QD dose escalation cohorts: Cohort 6 (n=4), Cohort 6+ (n=3), and Cohort 7 (n=6). However, the MTD and RP2D were declared at 300 mg QD on 30 November 2018, when 2 of 6 DLT-evaluable patients reported DLTs in Cohort 7 (400 mg QD) of the dose escalation phase (see subheading d. below for additional information).

5.1.1.1 Dose-Limiting Toxicity Assessment Window

The DLT assessment window is the 28 days in the first cycle (Days 1-28). Any patient considered to be non-evaluable for DLT as defined below was to be replaced by an additional patient at that same dose level.

5.1.1.2 Definition of DLT Evaluable Patients

A patient will be DLT evaluable if the patient:

- Has not received any preventive treatment during the DLT period; AND
- Has completed the first 28-day treatment cycle with complete safety evaluations and has received at least 75% of the assigned surufatinib dose;

  OR

- Has a confirmed DLT during the first 28-day treatment cycle.

5.1.1.3 Definition of a Dose-Limiting Toxicity (DLT)

All AEs, including DLTs, are to be graded according to the NCI CTCAE, v. 4.03. A DLT is defined as one of the following toxicities occurring during the DLT assessment window (Cycle 1, Days 1-28) and determined by the investigator to have a reasonable possibility of being related to surufatinib.

- Any Grade 4 non-hematological toxicity;
- Any Grade 3 non-hematological toxicity except for nausea/vomiting, diarrhea, constipation, electrolyte imbalances, or transient hypertension downgraded within 3 days with appropriate supportive treatment;
- Grade 4 neutropenia lasting >7 days;
- Grade 3 febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour;
- Grade 4 thrombocytopenia or ≥Grade 3 thrombocytopenia associated with tendency to bleed;
- Dose interruption or delay for >14 days due to toxicity;
- Any life-threatening complication or abnormality not covered in the NCI CTCAE v. 4.03.

In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

5.1.1.4 Definition of Maximum Tolerated Dose (MTD)

The MTD is defined as the maximum dose at which no more than 1 out of 6 patients in a single dose group experiences a DLT in Cycle 1 (Days 1-28).

5.1.2 Dose Expansion Phase

The expansion phase will evaluate the anti-cancer activity of surufatinib, and confirm the safety and tolerability of surufatinib at the RP2D determined at the end of the dose escalation phase.

Under amendment 7 of this protocol, the MTD was declared when 2 of the 6 DLT evaluable patients in Cohort 7 (400 mg QD dose) of the dose escalation phase reported DLTs. There was an ad hoc meeting of the SRC on 30 November 2018. The SRC agreed with the declaration of 300 mg QD as the MTD of surufatinib in this trial and agreed that 300 mg QD is the RP2D going forward. The minutes of this ad hoc SRC meeting were distributed to all investigative sites on the same day. It was also agreed that patients who were already receiving 400 mg QD could remain on this dose, provided that 1) there was no major toxicity and 2) the affected patients gave informed consent not to reduce the dose to 300 mg after discussion with the investigator. However, no patients could have their dose escalated to 400 mg going forward, including all patients in the dose expansion phase.

The safety of all enrolled patients will be closely monitored from the time of the initial dose of investigational treatment until 30 days after the last treatment 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 AEs will be graded in accordance with the NCI CTCAE v. 4.03. Tumor assessments will be conducted according to RECIST Version 1.1 criteria at screening, Cycle 2 Day 1 and every 8 (±1) weeks thereafter. Confirmation of

CR and PR is required at no less than 4-week intervals between the date of initial response/progression and the confirmation assessment date.

5.2 Sample Size

Approximately 95 to 150 patients will be enrolled in this two-phase study: 35 patients in the dose escalation phase and approximately 115 additional patients in the dose expansion phase. The actual enrollment number may vary, depending on the number of dose levels evaluated and the number of DLTs observed in each cohort, as well as the potential need to further characterize individual cohorts in the dose expansion phase.

As of Amendment 7, an additional 15 patients will be enrolled into Arm A (BTC) of the Expansion phase, for a total enrollment of at least 30 advanced BTC patients. The reason for increasing enrollment into Arm A (advanced BTC) is that preliminary data from the ongoing patients in this cohort have shown encouraging results. The additional patients will allow further characterization of the safety and efficacy of surufatinib in this patient population. Arm B (pNET) and Arm C (epNET) will enroll at least 15 patients each. If needed, Arm B and Arm C could enroll additional patients in order to characterize further the safety and efficacy of surufatinib in these patient populations.

As of Amendment 8, approximately 45 additional patients with STS will be enrolled to Arm D.

As of Amendment 10, an additional 10 patients will be added to the arm D (STS) for a total enrollment of 55 patients.

5.3 Investigational Site

The study plans to enroll patients at approximately 8 to 15 sites.

5.4 Safety Review Committee

Safety monitoring and evaluation for dose escalation will be carried out by the Safety Review Committee (SRC) upon completion of the DLT observation period of each cohort in dose escalation. The SRC is chaired by the Sponsor's Clinical Program Leader of the surufatinib program, and members will include the principal investigators (PIs), the Sponsor's PK scientist, medical monitor, safety scientist, and the contract research organization's (CRO's) medical monitor. Dose escalation decisions are based on safety and PK data from this ongoing trial, as well as consideration of safety and PK data at comparable drug exposures from patients in previously conducted clinical trials in China.

For the dose expansion phase of the trial, a separate, specific SRC will be established to ensure the safety of all patients treated with study drug in the STS cohort (STS-SCR). Review of available safety laboratories, adverse events, and any other pertinent data available will be reviewed after the first 4 patients in each sarcoma cohort have completed at least 1 cycle of treatment. The recommendations of the STS-SRC will be based on the members' clinical assessment of the cumulative safety data provided for review. The SRC will not be charged with the application of formal statistical stopping rules for safety.

5.5 Patient Discontinuation

All study participants have the right to withdraw from the study at any time.

The investigator has the right to discontinue a patient from the study 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 non-compliance (eg, missed doses, visits) or 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 Appendix 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 CRF. Patients discontinuing surufatinib for reasons other than progression of the underlying malignancy are to continue tumor assessments per Appendix 1, until documentation of disease progression, start of new anti-tumor therapy, or withdrawal of informed consent.

5.6 Overall Survival Follow Up

Overall survival is defined as the time from the date of the first dose of study drug until the date of patient death (any cause). Investigators and/or delegated site staff should follow patients enrolled to the BTC and STS expansion cohorts, who have signed informed consent under sponsor Amendment 8 (or later), until death or until the patient is lost to follow up. Follow up for OS will begin after the end of treatment (EOT) visit has been completed. Patients should be followed every 8 weeks (± 2 weeks) via telephone or in a manner that follows local site SOPs. Site staff should attempt to contact a patient 3 times and consult with authorized family members for the status of the patient (when applicable) before considering a patient lost to follow up. Data to be collected should include the date the patient was last known to be alive, the date of death, and the cause of death.

Treatment completion of patients will occur if any of the following 3 criteria is met:

1. Disease progression (according to RECIST Version 1.1), unless there is reasonable evidence of clinical benefit to justify continuation on the study drug. The continuation decision should be made by the investigators in consultation with the sponsor. The disease progression date is the date when radiological disease progression is first reported according to RECIST Version 1.1 criteria;
2. Death;
3. End of this study.

Early discontinuation of study drug will occur if any of the following criteria is met:

1. Patient withdrawal of informed consent;
2. Intolerable toxicity;
3. Poor patient compliance;
4. Use of other antitumor treatment during the study;
5. Pregnancy occurred during the study treatment period;
6. Patient is lost to follow-up;
7. Treatment discontinuation is in the best interest of the patient based on the assessment of the investigator and sponsor.

5.7 Study Discontinuation

Hutchison MediPharma has the right to stop the study at any time. The reasons for stopping the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

5.8 End of Treatment (Individual Patient)

5.8.1 End of Study

A subject is considered to have completed the study once he or she has completed the last visit or the last scheduled procedure as outlined in the Schedule of Events (Table 12).

5.8.2 Study Completion Date

The study will be considered completed once the following has occurred:

- The last subject has completed the last visit or last scheduled procedure.

6 PATIENT SELECTION

Patients with locally advanced or metastatic solid tumors for whom approved therapy either does not exist or has proven to be ineffective or intolerable are eligible to participate in the dose escalation phase of this study. Patients will undergo a screening period of up to 4-weeks, during which they will be assessed for compliance with the inclusion and exclusion criteria as outlined below.

6.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet all of the following criteria:

1. Fully understand the study and voluntarily sign the ICF;
2. At least 18 years old;
3. Dose escalation phase: Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type, that has progressed on available standard systemic therapy, and for which no effective therapy or standard of care exists;
4. Dose expansion phase: Histologically or cytologically documented, locally advanced or metastatic BTC that has progressed on standard first line chemotherapy (Arm A), low-to-intermediate grade (G1 or G2), well-differentiated, unresectable or metastatic pNET that has progressed on everolimus, sunitinib, or both (Arm B), low-to-intermediate grade (G1 or G2), well-differentiated, unresectable or metastatic epNET that has progressed on everolimus (Arm C), and advanced STS (of the subtypes listed below) that has progressed on at least one line of standard therapy (if available) or refused standard frontline cytotoxic chemotherapy will be evaluated for enrollment;

   NET expansion patients must also meet the following criteria:

   a. Gastroenteropancreatic NETs (GEP-NETs) or NETs of origins other than the lung or thymus (including unknown origins), with a mitotic rate of ≤ 20/10 high powered field (HPF) and/or a Ki-67 proliferative index of ≤ 20%; if the mitotic rate and Ki-67 index indicated different grades, the higher grade is used to assign classification; or
   b. NETs of the lung or thymus with a mitotic rate of ≤10/10 HPF;

   STS subtype eligible to be enrolled:

      i. Leiomyosarcoma (LMS)
      ii. Undifferentiated pleomorphic sarcoma (UPS)
      iii. Epitheloid sarcoma
      iv. Angiosarcoma
      v. Pigmented villonodular synovitis (PVNS)
      vi. Synovial sarcoma (SS)

5. Patients taking a somatostatin analogue (SSA) to control symptoms of functioning pNET or epNET will be permitted to enroll in the study provided that they have been on a stable SSA regimen for at least 2 months before enrollment and will continue on this regimen during the study;
6. Patients taking SSAs in the absence of secretory symptoms must also have been treated with everolimus (pNET or epNET) or sunitinib (pNET) in order to be eligible for this study. Since disease progression is a requirement for enrollment

in the dose expansion phase, in such cases both the targeted therapy (everolimus and sunitinib) and the SSA must be discontinued at least 4 weeks before the first dose of study drug.
7. Patients must have measurable disease (according to RECIST Version 1.1);
8. Patients must have radiological documentation of progression of disease in the last 12 months prior to the initiation of study drug;
9. ECOG performance status of 0 or 1;
10. Expected survival of more than 12 weeks;
11. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and partner) 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 hormonal contraception (combined estrogen/progestogen, or progestogen-only), associated with inhibition of ovulation together with another additional barrier method (e.g., diaphragm, always containing a spermicide), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), or sexual abstinence. Oral contraception should always be combined with an additional contraceptive method (i.e., barrier method) because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical trial if they have a partner of childbearing potential. Male patients must always use a condom. A woman 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).

6.2 Exclusion Criteria

Patients will be excluded from the study, if any of the following criteria is met:

1. Patients with high-grade (G3) neuroendocrine tumor, even if it is well differentiated;
2. Absolute neutrophil count (ANC) of $< 1.5 \times 10^9$/L, or platelet count of $<100 \times 10^9$/L, or hemoglobin <9 g/dL;
3. Serum total bilirubin >1.5 times the upper limit of normal (× ULN);
4. ALT or AST >1.5 × ULN without hepatic metastases or ALT or AST >3 × ULN with hepatic metastases;
5. Serum potassium, calcium, or magnesium levels out of normal laboratory range, and clinically significant in the investigator's judgment;
6. Creatinine clearance <60 mL/min on the basis of either 24-hour urine collection or the glomerular filtration rate estimated by Cockcroft-Gault equation:

$$[(140 - \text{age}) \times (\text{weight in kg}) \times 0.85 \text{ if female}] \div$$

$$[72 \times (\text{serum creatinine in mg/dL})]$$

7. Urine protein ≥2+; patients discovered to have ≥1+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤1 g of protein in 24-hour urine;
8. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg;
9. International Normalized Ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the patient is currently receiving or intending to receive anti-coagulants for therapeutic purposes;
10. Risk of or active hemorrhage; history of: active gastric/duodenal ulcer or ulcerative colitis; active hemorrhage of an unresected gastrointestinal tumor; history of gastrointestinal perforation or fistulas; or any other condition that could possibly result in gastrointestinal tract hemorrhage or perforation within 6 months prior to first dose of study drug;
11. History of severe hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to first dose of study drug;
12. History of thromboembolic event (including deep vein thrombosis [DVT], pulmonary embolism [PE], stroke and/or transient ischemic attack [TIA]) within 6 months prior to the first dose of study drug;
13. Patients with squamous non-small cell lung cancer (NSCLC);
14. 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, New York Heart Association Class III/IV congestive heart failure, ventricular arrhythmias requiring treatment or left ventricular ejection fraction (LVEF) <50%;
15. Mean corrected QT interval by Fridericia's formula (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in a first-degree relative;
16. Concomitant use of any medication known to cause QT prolongation or torsades de pointes (See the table in Appendix 6; see full list at http://www.qtdrugs.org/);
17. Systemic anti-neoplastic therapies within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;
18. Administration of SSAs in the absence of secretory symptoms must be discontinued at least 4 weeks before the first dose of study drug;
19. Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug;
20. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the first dose of study drug;
21. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks before the first dose of study drug (3 weeks for St John's Wort).
22. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug;
23. Surgery or invasive procedure (ie, procedure that include a biopsy), or unhealed surgical incision, within 60 days prior to the first dose of study drug;
24. Toxicity from a previous anti-tumor treatment that does not return to Grade 0 or 1 (except for alopecia);
25. Known human immunodeficiency virus (HIV) infection;

26. Known clinically significant history of liver disease, including active viral or other hepatitis, current alcohol abuse, or cirrhosis. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load;
27. Evidence of ongoing or active infection requiring intravenous antibiotics;
28. Women who are pregnant or lactating;
29. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; patients requiring steroids within 4 weeks prior to start of study treatment will be excluded;
30. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product;
31. Received investigational treatment in another clinical study within 4 weeks prior to the initiation of investigational treatment;
32. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition that investigators suspect may prohibit use of the investigational product (ie, hypersensitivity to excipients of the study drug), affect interpretation of study results, or put the patient at high risk.

7 STUDY TREAMENT

7.1 Investigational Product

7.1.1 Investigational Product Supply

Surufatinib will be supplied by Hutchison MediPharma Limited.

7.1.2 Drug Formulation and Specification

Hutchison MediPharma Limited authorizes Shanghai STA Pharmaceutical Product Co., Ltd. (ie originally WuXi AppTec (Shanghai) Co., Ltd) to manufacture and package surufatinib capsules. The technical guidance and quality assurance will be conducted by Hutchison MediPharma Limited. The drug information is provided in Table 4.

Table 4 Drug Formulation and Strength

Formulation	Strength	Route of Administration	Manufacturer
Capsule	50 mg	Oral	Shanghai STA Pharmaceutical Product Co., Ltd.
Capsule	200 mg	Oral	Shanghai STA Pharmaceutical Co., Ltd.

7.1.3 Packaging and Drug Labeling

The investigational drug is packaged in white HDPE bottle with 50 capsules per bottle (old formulation, PD-012-023) or 30 capsules per bottle (new formulation, PD-012-042).

The following information will appear on the label affixed to either the bottle or carton; additional information may be added as required:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Route of administration
- Blank spaces to write the patient's identification number
- Finishing lot #

7.1.4 Drug Storage

Study drugs should be sealed and stored in a secure, limited access area between 10°C to 30°C, protected from light and moisture. Surufatinib capsule should not be used beyond expiration date provided by the manufacturer.

The temperature log should be recorded and filed in the study binder.

7.1.5 Drug Accountability

All study drug required for this study will be provided by Hutchison MediPharma. The recipient will acknowledge receipt of the 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.

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

7.1.6 Dose and Administration

If baseline (pre-dose) PK blood samples need to be collected on the days of PK sample collection, patients must take the investigational product after sampling.

It is recommended that surufatinib be taken with 200 mL water within 1 hour after breakfast. The administration time should be accurately recorded on the day of PK sampling.

For patients treated with surufatinib under new formulation, the minimum number of capsules will be administrated in combination of two strengths (50 mg and 200 mg), eg for 300 mg QD dose, one 200 mg capsule and two 50 mg capsules will be administrated; for 400 mg QD dose, two 200 mg capsules will be administrated, etc. For patients enrolled in the European Union, only 50 mg capsules will be available.

On the day of PK sampling, patients should avoid high-fat, high-calorie meals for the entire day. No caffeine containing foods or drinks, no grapefruit or grapefruit juice, tobacco and tobacco containing products, or alcohol or recreational drugs will be allowed during the PK assessment period (Cycle 1).

If patients miss a dose in the morning, a replacement dose can be taken before 10 pm on the same day. Otherwise, the patient 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 in the CRF.

7.1.7 Important Safety Risks

The important Identified Risks reported for patients who have received surufatinib may be found in the current version of the surufatinib IB.

7.1.8 Important Potential Risks

The important potential risks of surufatinib include the following: infection, intestinal obstruction, gastrointestinal perforation, myocardial ischaemia, cardiac failure, venous thromboembolism, arterial thromboembolism, and pancreatitis. One patient in the 2015-012-00US1 trial experienced grade 3 PRES, which was deemed related to study drug and was considered resolved. For more information, please see surufatinib IB.

7.2 Dose Modification

7.2.1 General Dose Adjustment Note

The severity of AEs will be graded according to the NCI CTCAE v. 4.03. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the CRF.

- 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 one 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 anaemia (non-haemolytic) 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 drug. 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.

7.2.2 Dose Modification Guidance

The dose modification sequence by starting dose is shown in Table 5. A patient is normally allowed to have dose reductions no more than twice, e.g. dose reductions from 300 mg QD to 250 mg QD and then 200 mg QD or from 400 mg QD to 300 mg QD and then 200 mg QD is allowed. 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.

Table 5 Dose Modification Sequence by Starting Dose

Daily Starting Dose	300 mg	400 mg**
-1 Dose	250 mg	300 mg
-2 Dose	200 mg	200 mg
-3 Dose*	200 mg on reduced schedule*	200 mg on reduced schedule*
	Off study drug	Off study drug

*Dosing schedule 200 mg QD, 3 weeks on/1 week off, every 28-day cycle.
**No new patients will be enrolled at the 400 mg QD dose.

Dose reduction guidelines for hematologic and non-hematologic toxicities other than hypertension, proteinuria, liver function impairment and hemorrhage are shown in Table 6. In principle, treatment should be held until 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 Grade 3 non-haematologic toxicity that does not resolve to ≤Grade 1 within 3 weeks should permanently discontinue the study drug.

Table 6 Dose Modification for Hematologic and Non-Hematologic Toxicities

NCI CTCAE v4.03 Toxicity Grading	Action
Grade 1 or 2	None
Grade 3 or 4	
Expected manageable/reversible with dose reduction	Hold[a]
Toxicity remains Grade 3 >7 days	Discontinue treatment
Toxicity lasts ≤7 days and resolves to ≤Grade 1	Reduce 1 dose level
Reoccurrence of Grade 3 toxicity	Reduce 1 dose level or discontinue treatment[a]
Reoccurrence of Grade 4 toxicity	Discontinue treatment
Not expected manageable/irreversible with dose reduction	Discontinue treatment

[a] Treatment should be withheld until toxicity recovers to ≤Grade 1. For patients who cannot recover within 21 days, the study drug should be discontinued permanently.

7.2.3 Dose Modification for Important Identified Risks

Dose modifications for important identified risks are provided in Table 7 (hypertension), Table 8 (proteinuria), Table 9 (liver function impairment), and Table 10 (hemorrhage).

Table 7 Dose Modification for Hypertension

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: prehypertension (systolic BP120-139 mmHg or diastolic BP 80-89 mmHg)	None.	None.
Grade 2: Stage 1 hypertension (systolic BP140-159 mmHg or diastolic BP 90-99 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 anti-hypertensive treatment guidelines for dose administration and modification and consult cardiologist if necessary.
Grade 3: Stage 2 hypertension (Systolic pressure ≥ 160mmHg or diastolic pressure ≥ 100mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	If BP >160/100mmHg lasts for >3 days after initiation of anti-hypertensive treatment or modification of current anti-hypertensive treatment, surufatinib treatment should be held. If hypertension resolves to Grade 1 or baseline level within 21 days, sulfatinib treatment could be re-started 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.

Table 7 Dose Modification for Hypertension

Grade and Definition	Dose Modification	Suggested Actions
Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Discontinue surufatinib treatment.	Emergent medical intervention.

Table 8 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 as planned schedule.
Grade 2: 2+or 3+ proteinuria; urinary protein 1.0 - 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 - 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 resolves 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.

[a] If urine dipstick reveals proteinuria 2+, 24-hour urine collection should be performed for determination of total protein within one 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 instant of proteinuria (i.e. urine dipstick). If surufatinib dose has been reduced to 200mg 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 1-week drug holiday and repeat for each treatment cycle, (i.e. 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 9 Dose Modification for Liver Function Impairment

Grade and Definitions	Dose Adjustment	Suggested Actions
Grade 1: ALT >1-3 × ULN or AST >1-3 × ULN	None.	Follow up per planned schedule. Check total bilirubin.[a]
Grade 2: ALT >3-5 × ULN or AST >3-5 × ULN	Maintain the original dose, provide supportive care of complications of liver impairment, observation for 1 week, If the ALT and AST is	Check total bilirubin.[a] Provide supportive care and increase the frequency of liver function monitor to 1-2 times a week.

Table 9 Dose Modification for Liver Function Impairment

Grade and Definitions	Dose Adjustment	Suggested Actions
	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.	
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.[a] 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.[a] Urgent medical intervention indicated.

[a] 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 7 for important additional information.

Table 10 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.

7.3 Concomitant and Excluded Therapies

7.3.1 Concomitant Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the termination visit.

- Patients who use hormonal therapy with GnRH agonists for prostate cancer, 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 anti-coagulation at study entry:

  - Patients who are receiving warfarin or Coumadin-like products should have their INR monitored and maintained at the lower end of the therapeutic range (ie, close to 2.0 if the therapeutic range is 2.0 – 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 drug. If a patient suffers a venous thromboembolic event whilst still receiving study drug, it may still be possible for him or her to remain on study drug under adequate monitoring and dose modification.
- Patients who have functioning pNETs or epNETs and have been on a stable dose of a somatostatin analogue (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 in the dose expansion phase.
- 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 CRF.

7.3.2 Excluded Therapies

Any therapy intended for the treatment of cancer (with the exceptions as noted above), 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.

Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin are not allowed during DLT observation period in the dose escalation phase.

Concomitant use with acid-reducing agents (eg, proton pump inhibitors, histamine receptor antagonists, antacids) in Cycle 1 of the dose escalation phase should be avoid as those agents may interfere with reliable identification of the MTD and/or RP2D. However, use of gastroduodenal mucosal protective agents, such as sucralfate, is allowed.

Concomitant use of SSAs by patients with non-functioning pNETs or NETs is not permitted, and must have been discontinued at least 4 weeks before administration of the first dose of study drug.

Concomitant use of medications that are known to cause QTcF prolongation, and/ or Torsades des Pointes. See Appendix 6 for a table of current medications in this category, and also consult the current list at http://www.qtdrugs.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 only after meeting the following criteria:

- Radiation related toxicities resolves to ≤ Grade 2;
- No disease progression observed.

7.3.3 Drug-Drug Interactions

The in-vitro metabolism study in liver microsomes studies indicated that phase 1 metabolic enzymes for surufatinib included CYP3A4/5 (dehydrogenation, N-demethylation), CYP2C8 (dehydrogenation, N-demethylation), CYP2E1 (mono-oxidization) and FMO. Surufatinib showed weak and reversible inhibition against CYP2D6 and CYP3A4/5 with the IC50 of 13 μM and 14 μM, respectively. Time-dependent inhibition study of CYP3A4/5 indicated the potential with a kinact of 0.73 min-1 and KI of 163 μM. Induction tests of CYP1A2 and CYP3A4 in primary human hepatocytes indicated that surufatinib had no obvious induction to CYP1A2 and CYP3A4 at 10 μM and 2 μM, respectively. Caco-2 in-vitro permeability and efflux transportation tests indicated that surufatinib was a substrate of the P-gp efflux transporter.

Although the overall risk of a drug interaction between surufatinib and other drugs is not significant, the use of surufatinib should be with caution when combined with certain drugs. Patients receiving a CYP3A4 strong inhibitor or inducer within 2 weeks (3 weeks for hyperforin perforatum) prior to receiving the study drug treatment should be excluded from the study. CYP3A4 strong inhibitors or inducers should be avoided throughout the study. The list of CYP3A4 substrates, strong inhibitors or inducers is provided in Appendix 4. If investigators consider necessary, CYP3A4 substrates, strong inhibitors or inducers can be used with close monitoring of potential drug- drug interaction.

8 STUDY ASSESSMENTS AND METHODS

8.1 Safety Assessments

8.1.1 Vital Signs Assessment

Vital signs will include measurements of body temperature, heart rate, respiratory rate, 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 anti-hypertensive medications, with either a baseline history of hypertension or new onset of hypertension during the study, blood pressure should be monitored daily by the patient at home. Affected patients will be provided with home blood pressure monitoring equipment, educated on how to measure blood pressure, take their own blood pressure daily at 3 hours (±2 hours) after the daily doses of anti-hypertensive medication. The patient will keep a record of home blood pressure readings in a Blood Pressure Diary, and bring this to each study visit.

8.1.2 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.

At subsequent visits, a limited physical examination will be performed to assess changes from baseline abnormalities, any new abnormalities, and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as adverse events 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.

8.1.3 Laboratory Test Evaluations

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

Hematology: complete blood count [CBC], including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count), INR, PT and aPTT.

Serum chemistry: blood urea nitrogen [BUN], creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactic dehydrogenase [LDH], amylase, total cholesterol, triglycerides, total protein, albumin, and uric acid.

Serum pregnancy test at screening and within 30 days after treatment completion for all women of childbearing potential, including those who have had a tubal ligation. In

addition, urine pregnancy tests will be performed on Day 1 of Cycle 2, and continue on Day 1 at each 28-day cycle thereafter.

Urinalysis (pH, glucose, protein, and blood); if there is ≥2+ protein on urinalysis, then a 24-hour urine protein should be done within in one week. For urinalysis results conversions, please refer to Appendix H

Thyroid function: TSH, free T3, free T4 ；

Stool blood test (as per the institutions standard practice);

Plasma surufatinib concentrations (for PK evaluations) will be assessed using a validated assay.

8.1.4 Cardiac Monitoring

Left ventricular ejection fraction (LVEF) assessed via echocardiogram or MUGA at Screening-Baseline and every 12 (± 1) weeks thereafter and at the end of study treatment. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible.

The 12-lead ECGs should be performed at screening, pre-dose and at 2 hours ± 15minutes post surufatinib dose on Days 1 and 15 in Cycle 1, on Day 1 of each cycle from Cycle 2 and onward and at the end of study treatment. The QTcF interval will be closely monitored (See Appendix 1).

Test results will be reviewed by the investigator to determine patient eligibility at screening. Additional test and other cardiac monitoring will be provided as clinically indicated during the study.

8.2 Efficacy Assessments

8.2.1 Tumor Assessment

All measurable lesions should be assessed and documented at screening and re-assessed at each subsequent tumor evaluation (see Appendix 1). Response assessments will be performed by the investigator using physical examination and image-based evaluation.

Screening assessments include CT scans with oral or IV contrast (unless contraindicated) of the chest, abdomen, and pelvis. MRI scans are allowed if CT contrast is contraindicated. Bone scans and CT scan of neck should also be performed if clinically indicated. The same radiographic procedure used to define measurable or non-measurable lesions at baseline must be used throughout the study for each patient. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Disease status will be assessed using RECIST Version 1.1 (see Appendix 3). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST Version 1.1 may be used. Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response/progression and the confirmation assessment date.

8.2.2 Assessment of Tumor Markers

Tumor markers assessment will be performed at each tumor assessment visit. Tumor markers may include, but are not be limited to, serum CEA and CA 19-9 (patients with BTC) serum chromogranin A (CgA) and neuron-specific enolase (NSE) for patients with pNET and epNET; and VEGF for all 3 disease cohorts. Assessment of tumor markers will be performed within 28 days prior to the start of treatment with study drug (C1D1) and at each tumor assessment visit.

8.3 Study Visits and Assessments

8.3.1 Screening and Pretreatment Assessment

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or procedures. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site. 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.

Please see the Study Flowchart provided in Appendix 1 for the schedule of screening and pre-treatment assessments. Screening and pre-treatment tests will be performed within 28 days to the first dose day of study drug, unless otherwise specified. 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, urinalysis, and stool blood test results); such tests do not need to be repeated for screening.

8.3.2 Assessments during Treatment Phase

All visits must occur within ± 3 days (± 1 day during the DLT observation window) from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified.

Please see the Study Flowchart provided in Appendix 1 for the schedule of treatment period assessments.

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.

If during the DLT assessment window, 2 or more patients in a single cohort experience the same study drug-related Grade 3 toxicity that does not otherwise qualify as a DLT, the patients subsequently enrolled to this dose level and to the subsequent dose level will undergo increased monitoring during Cycle 1, as clinically indicated.

8.3.3 Study Completion/Early Termination Visit

Patients who complete the study or discontinue study drug will be asked to return to the clinic at 30 ± 7 days after the last surufatinib administration for a follow-up visit. Ongoing adverse events thought to be related to surufatinib will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study drug or participation is not the cause of the adverse event.

Subjects enrolled to the BTC and STS expansion cohorts, who have signed informed consent under sponsor Amendment 8 (or later), will enter into OS follow up at the completion of their Study Completion/Early Termination Visit.

Please see the Study Flowchart provided in Appendix 1 for assessments to be performed at the study completion or early termination visit.

8.4 Assay Methods

8.4.1 Bioanalysis Assay Methods

Concentrations of the surufatinib in plasma will be measured using a pre-validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) by a qualified central laboratory.

All plasma samples from patients having received surufatinib will be analyzed.

8.4.2 Pharmacokinetic Samples Handling and Shipment

Blood samples will be taken for pharmacokinetic evaluation by cannula or direct venipuncture at nominated time points. See Table 11 for the sampling time points. The exact time and dates of blood sampling are to be recorded in the CRFs.

Blood sample (2.5 mL) for surufatinib pharmacokinetics will be collected into Sodium Heparinate vacutainers. The tubes will be immediately inverted gently at least 5 times to mix the blood and then placed in ice bath prior to centrifugation. The tubes will be centrifuged at approximately 1000g and 4°C for 10 min and then the plasma will be transferred into 2 clean prelabelled tubes immediately. About 0.5mL plasma will be placed in each tube (Tube A and Tube B). After tightly capping the tubes, the samples should be stored at -20°C or -80°C immediately. The whole process of plasma collection should be completed within 2 hours of the blood sampling. According to plasma stability results, surufatinib can be stored at -20°C for 317 days and at -80°C for 716 days. It is recommended that the plasma samples are stored at -80°C for the long-term storage.

Each sample will be identified by date of collection, study number, patient number and initials, and sample time point identifier (ie, 30 minutes, 1 hour, 4 hour etc.). Tube B samples must be labeled as “duplicate”.

All plasma samples will be shipped on dry ice to the central laboratory within 30 days of sample collection. The dry ice should be sufficient to keep the samples frozen during the whole shipment period. The samples of Tube B are shipped out after the prior batch of Tube A has been received safely by the central lab. Tube A samples will be used for bioanalysis. Tube B samples will be stored in -80°C freezer for future use. The laboratory should be notified at least 1 day prior to the arrival of the sample and be provided shipping details and tracking numbers for the shipment.

Prior to shipment, a PK sample requisition form (containing the details of each sample / label identification included in the shipment) will be prepared. All sample correspondence must contain the Study Number, Study Drug, and Site references (including emergency contact details and responsible shipment coordinator). All of the sample details on this log must correspond with the details included on the individual sample labels, as each sample label will be checked against the list by Centre Laboratories’ sample coordination personnel. The log should be reviewed by the preparer and a second individual for accuracy and signed/dated by both individuals. (An example sample transfer sheet is used to document the general information regarding the shipment). To avoid sample mix-ups

or misidentification, the samples in the shipment will be sorted by patient number and sample time using segmented cartons.

Table 11 Pharmacokinetic Sampling Time Points

Visit Cycle and Day	Time Point
Cycle 1, Day 1	Pre-dose ≤10 minutes Post-dose 1 hour (± 15 minutes) Post-dose 2 hours (± 15 minutes) Post-dose 4 hours (± 30 minutes) Post-dose 6 hours (± 60 minutes) Post-dose 8 hours (± 60 minutes)
Cycle 1, Day 2	Pre-dose ≤10 minutes
Cycle 1, Day 15	Pre-dose ≤10 minutes Post-dose 1 hour (± 15 minutes) Post-dose 2 hours (± 15 minutes) Post-dose 4 hours (± 30 minutes) Post-dose 6 hours (± 60 minutes) Post-dose 8 hours (± 60 minutes)
Cycle1, Day 16	Pre-dose ≤10 minutes

9 SAFETY MONITORING

9.1 Definitions

9.1.1 Adverse Events and Serious Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution.

An SAE is defined as any life-threatening AE resulting in death, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or any other important medical event requiring intervention, in-patient hospitalization or prolongation of existing hospitalization

A SAE is any AE that is any of the following:

- Fatal (ie, the AE actually causes or leads to death)
- Life threatening (ie, the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a female patient or female partner of a male patient exposed to the investigational product(s)
- Considered a significant medical event by the investigator (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

9.1.2 Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) 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. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

9.2 Reporting of Dose-Limiting Toxicity

Investigators are required to report DLT events to the Sponsor within 48 hours of first awareness. The communication must include an email that describes the event and indicates which DLT criterion was met (see Section 5.1.1.3, Definition of a Dose-Limiting Toxicity). The Sponsor's medical monitor must confirm that the event meets the DLT definition and communicate this back to the investigator by email. A notification of each DLT event will be distributed by email to all investigators shortly after confirmation. DLT events are again reviewed together with other safety data and PK data, at the dose escalation SRC meeting upon completion of the DLT window of each dose cohort.

9.3 Adverse Events Reporting Period

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study medications, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study drug or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study drug.

9.4 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive 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?"

9.5 Assessment of Severity

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.

For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of seriousness, severity, and causality.

- Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
- 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 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 (ADL)

*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.

NOTE: The NCI CTCAE v 4.03 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 v 4.03, then the investigator should name the AE and report the severity based on the general guideline shown in the paragraph above.

9.6 Causality of Adverse Events

The investigator will assess a causal relationship between the IP and each AE, and 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 investigational product?'

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 as 'yes'.

A guideline to the interpretation of the causality question is found in Appendix 5 to the Clinical Study Protocol.

9.7 Documenting Adverse Events

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

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid colloquialisms and abbreviations.

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

Only one medical concept should be recorded in the event field on the CRF.

9.8 Diagnosis vs Symptom and Signs

If known, a diagnosis should be recorded on the CRF 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 CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.9 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 CRF.

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 CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

9.10 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 CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an AE/SAE CRF.

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 CRF.

9.11 Abnormal Laboratory Values

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

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

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 CRF. 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 CRF, unless their severity, seriousness, or etiology changes.

9.12 Death

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, should be recorded on an AE/SAE CRF 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 AE and death being the outcome of the event on the AE/SAE CRF. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, record "Unknown Death" on the AE/SAE CRF.

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

9.13 Previously Existing Medical Condition

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History CRF.

A preexisting 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 CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

9.14 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 preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

9.15 Pregnancy

A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor or its designee. The investigator should counsel the patient; 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 medication 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 CRF, and expeditiously reported to sponsor 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 investigational product should be recorded and reported as an SAE.

9.16 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 Adverse Event CRF and reported to the sponsor

or its designee within 1 working day after learning of the event as an SAE. See Appendix 7 for important additional information.

9.17 Worsening of Solid Tumor

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

9.18 Expedited Reporting Requirements for Serious Adverse Events

9.18.1 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 investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on the SAE report Form within 24 hours.

9.19 Adverse Event Follow-Up Duration

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study drug 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 CRF and in the patient's medical record to facilitate source data verification (SDV). 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 Adverse Event CRF.

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.

9.20 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 drug.

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 felt to be related to prior study drug. 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 in a subsequently conceived offspring of a patient that participated in this study.

10 STATISTICAL ANALYSIS

All statistical analysis will be performed under the direction of Hutchison MediPharma personnel. Any data analysis carried out independently by the investigator should be submitted to Hutchison MediPharma prior to publication or presentation.

The final analysis will be based on patient data collected through study discontinuation or study termination. There is no planned formal interim analysis. However, the accrued data may be analyzed for internal decision-making purposes, for example to provide information for a potential Phase 3 study design.

Final analysis for each cohort will occur once the last patient had been followed for sufficient time for the analysis of primary endpoint. For instance, for Arm A, final analysis will occur when the last patient had been on treatment for at least 16 weeks or discontinued early following discontinuation criteria. Timing of final analyses for cohorts may be combined if they occur close together. Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock.

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. Information regarding compliance with efficacy testing and availability of data will be documented. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves) will be used when such methods are appropriate and informative. The baseline value used in each analysis will be the last (most recent) pre-treatment value. Time to event variables will be summarized descriptively using Kaplan-Meier medians and quartiles. Analyses will be based upon the observed data unless methods for handling missing data are specified. Analyses will be performed using SAS® (Version 9.1 or higher).

10.1 Determination of Sample Size

The total number of patients enrolled will depend on the number of dose escalations and the need to further characterize individual cohorts in the expansion phase.

The planned enrollment for this study is approximately 95 to 150 patients, including 35 patients in the dose escalation phase, and approximately 115 patients for the dose expansion phase. Dose expansion phase will enroll patients in specific disease cohorts, 30 patients in the BTC Arm, at least 15 patients each in the pNET and epNET arms, and 55 patients in the STS arm (10 patients with LMS, 10 patients with UPS, 10 patients with epithelioid sarcoma, 10 patients with angiosarcoma, 10 patients with SS, and 5 patients with PVNS).

Sample size for Arm A: BTC cohort in dose expansion phase:

The PFS rate at 16 weeks was selected as the primary endpoint for the expansion phase of the study in patients with BTC. The PFS rate at 16 weeks is defined as the percent of patients without evidence of disease progression or death after 16 weeks on study among the PFS-evaluable patients.

For a BTC cohort with at least 30 evaluable patients, the treatment effect may be considered positive if there are at least 9 evaluable patients without evidence of progression or death after 16 weeks on study. This event will occur with probabilities 90.6% (true positive

rate) if the true PFS rate at 16 weeks is 40%, and 2.8% (false positive rate) if the true PFS rate at 16 weeks is 15%.

In addition, for a cohort with 30 evaluable patients, if 9 (30.0%) patients, or 10 (33.3%) patients without progression or death at 16 weeks are observed, then the lower limit of the 80% two-sided CIs for PFS rate at 16 weeks would be 19.0% and 21.8%, respectively.

Sample size for Arm B: pNET cohort in dose expansion phase:

For a pNET cohort with at least 15 evaluable patients, the treatment effect may be considered positive if there are at least 6 evaluable patients without evidence of disease progression or death after 11 months on study. This event will occur with probabilities 84.9% (true positive rate) if the true PFS rate at 11 months is 50%, and 4.9% (false positive rate) if the true PFS rate at 11 months is 19%.

In addition, for a cohort with 15 evaluable patients, if the 6 (40%) patients or 7 (47%) patients without progression or death at 11 months are observed, the lower limit of the 80% two-sided CIs for PFS rate at 11 months would be 22.6% and 28.2%, respectively.

Sample size for Arm C: epNET cohort in dose expansion phase:

For a pNET cohort with at least 15 evaluable patients, the treatment effect may be considered positive if there are at least 6 evaluable patients without evidence of disease progression or death after 11 months on study. This event will occur with probabilities 84.9% (true positive rate) if the true PFS rate at 11 months is 50%, and 4.9% (false positive rate) if the true PFS rate at 11 months is 19%.

In addition, for a cohort with 15 evaluable patients, if the 6 (40%) patients or 7 (47%) patients without progression or death at 11 months are observed, the lower limit of the 80% two-sided CIs for PFS rate at 11 months would be 22.6% and 28.2%, respectively.

Sample size for Arm D: STS cohort in dose expansion phase:

Arm D will consist of 6 cohorts of STS subtypes. The LMS, UPS, epitheloid sarcoma, angiosarcoma, and SS cohorts will enroll at least 10 evaluable patients each. The treatment effect may be considered positive if there are at least 3 evaluable patients in each cohort without evidence of disease progression or death after 4 months on study. This event will occur with probabilities of 83.3% (true positive rate) if the true PFS rate at 4 months is 40%, and 7% (false positive rate) if the true PFS rate at 4 months is 10%.

For the PVNS cohort, it is planned to enroll 5 evaluable patients. This sample size is based on feasibility.

10.2 Analysis Populations

The following analysis populations have been defined for the study:

- Note: the **DLT Evaluable Set** (dose escalation phase) is defined in Section 5.1.1.
- **Safety Analysis Set (SAS) – (All Treated Population):** This population includes all patients who have received at least one dose of surufatinib. Safety data will be evaluated based on this population's outcome. Patients in the SAS will be analyzed by their actual dose initially received. If patients have dose reduction during the study, all data will be summarized/analyzed based on the initial dose of

study drug received. Efficacy endpoints PFS and OS (OS applies to BTC and STS cohorts only) will be analyzed based on this population.

- **Pharmacokinetic Analysis Set (PKAS)**: This population will include all patients who received at least one dose of surufatinib and have at least one PK sample obtained and analyzed.
- **Efficacy Analysis Set (EAS)**: This population includes all patients who have received at least 1 dose of surufatinib and have had at least 1 post- baseline tumor assessment. All efficacy endpoints will be analyzed will based on this analysis set, except for PFS and OS, which will be analyzed based on SAS.

10.3 Statistics and Analysis Method

There is no formal hypothesis testing in this study. In general, the study data will be summarized descriptively by dose group and disease cohort (ie, BTC arm, pNET arm, epNET arm, and STS arm), unless otherwise specified. In general, all summaries will be presented by assigned dose level in the dose escalation phase and by disease cohort (BTC, pNET, epNET, and STS) in the dose expansion phase. Where applicable, certain summaries may be provided by STS subtypes: LMS, UPS, epithelioid sarcoma, angiosarcoma, SS, and PVNS.

A patient listing of all treated patients will be generated to describe site, patient number, screening date, first dosing date, duration of study treatment, analysis set in which the patient included and disposition. In the patient disposition listing, reason for study drug discontinuation will be included. A table will be created to summarize these categories in terms of number and percent for each of the analysis set defined above.

Patient demographics and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be listed and summarized. All summaries will be presented by dose level in the dose escalation phase and by disease cohort in the dose expansion phase.

Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment will be listed.

Study drug administration data will be listed by dose level and by disease cohort, and any dose modifications will be flagged. Descriptive information will be provided regarding number of cycles, total duration of study drug exposure, actual duration of study drug taken, cumulative dose of study drug, dose intensity and relative dose intensity and the number and timing of prescribed dose reductions and interruptions.

The study endpoints are described in Section 4. The planned analyses are described in detail in Sections 10.4 to 10.6.

10.4 Safety Analysis

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in ECG/echocardiograms results and changes in vital signs. All patients who receive at least one dose of surufatinib will be included in the safety analysis (ie, the Safety Analysis Set - All Treated Population).

All AE data will be listed by individual patient and cohort. All AEs will be graded using the NCI CTCAE (v.4.03) severity grading system. All adverse events will be coded with

MedDRA. The frequency of AEs will be summarized by MedDRA System Organ Class (SOC), Preferred Term (PT), and NCI CTCAE grade.

Incidence rates of DLTs by SOC and PT will be summarized for DLT set defined as all treated patients who are evaluable for DLT assessment (see Section 5.1.1.2).

Changes in laboratory data will be summarized by grade using the NCI CTCAE, v.4.03. Selected vital signs and selected laboratory data may be plotted over time for each patient.

10.5 Pharmacokinetic Analysis

All patients whose plasma samples are collected for analysis of the plasma surufatinib concentration and derivation of PK parameters will be included in the Pharmacokinetic Analysis Set (PKAS).

A non-compartmental model analysis will be performed for plasma concentration data by central lab using WinNonlin (enterprise version). The following statistic data will also be reported: mean value, standard deviation, median value, minimum value, maximum value, geometric mean value, and geometric mean coefficient of variation.

The individual and mean pharmacokinetic parameters determined following analysis of the surufatinib concentration versus time data, will include, but not be limited to total plasma exposure ($AUC_{0-\infty}$), Cmax, CL/F, and Vz/F. The t1/2 will also be estimated. Mean, standard deviation (SD) and coefficient of variation (CV) will be presented. The actual times of plasma sample collection will be used in the determination of the pharmacokinetic parameters.

The methods for calculating pharmacokinetic parameters of surufatinib:

- Cmax: the maximum observed plasma concentration over the sampling period, taken directly from the data.
- Tmax: time at which Cmax occurred, taken directly from the data.
- K_{el}: the first-order rate constant associated with the negative slope of the terminal portion of the log-linear concentration-time curve. A minimum of three points will be used.
- Area under the plasma concentration versus time curve (AUC) to be determined by the linear trapezoidal rule, where AUC_{last} is the AUC from time zero until the last concentration point and $AUC_{0-\infty}$ is the AUC_{last} + last concentration point divided by K_{el}.
- Half-life (t1/2) to be determined according to $t1/2 = 0.693/K_{el}$ where possible.
- CL/F: systemic clearance to be determined according to $Dose/AUC_{\infty}$
- V_z/F: apparent volume of distribution, determined according to $CL/F/K_{el}$
- Dose Proportionality: to be evaluated by investigating the linearity of the relationship between AUC and dose, and Cmax and dose.
- Accumulation ratio: AUC_{Day15}/AUC_{Day1} or AUC_{Day29}/AUC_{Day1}

Where the concentration data are missing, or listed as less than Lower Limit of Quantification, they will be regarded as zero (0) if occurring before C_{max}. After C_{max}, zero points will not be included in calculations.

Individual and mean surufatinib concentrations will be plotted by dose level.

10.6 Tumor Assessment

Efficacy data will be summarized by dose group in the dose escalation phase and by disease cohort in the dose expansion phase. For the dose expansion phase, all summaries of efficacy data will be presented separately for the BTC, pNET, epNET, and STS arms.

The following efficacy endpoints will be analyzed:

10.6.1 Primary Efficacy Endpoints

- Patients with BTC: PFS rate at 16 weeks (according to RECIST Version 1.1);
- Patients with p-NET: PFS rate at 11 months (according to RECIST Version 1.1)
- Patients with epNET: PFS rate at 11 months (according to RECIST Version 1.1)
- Patients with STS: PFS rate at 4 months (according to RECIST Version 1.1).

PFS is defined as the time from the start date of study drug until the date of objective disease progression or death (by any cause in the absence of progression).

PFS will be described in tabular and graphical format using Kaplan-Meier method, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 80% and 95% CIs at several time points (including at least 16 weeks for BTC group and 11 months for pNET group). Censoring reasons will also be summarized.

10.6.2 Secondary Efficacy Endpoints

- ORR, defined as the proportion of patients with a best overall response of complete response (CR) and partial response (PR) per RECIST Version 1.1. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.
- DCR, defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST Version 1.1.
- TTR, defined as the time between the start date of study drug until first documented response (CR or PR) according to RECIST Version 1.1.
- DoR, 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).
- Percent changes of tumor size from baseline of target lesion will be calculated at each visit, and the maximum percent per patient will be selected. Waterfall plots will be used to depict the tumor shrinkage in target lesion. These plots will display the best percentage change in target lesion size.

ORR and DCR will be estimated and 95% exact CIs based on the Clopper-Pearson method will be presented. The time to event endpoints, TTR and DoR will be described in tabular and graphical format using Kaplan-Meier method, including estimated median (in months) with 95% CI, 25th and 75th percentiles.

10.6.3 Exploratory Endpoints

- The values and changes from baseline in tumor markers will be summarized by tumor type (BTC, pNET, epNET, or STS) using descriptive statistics. Other exploratory analyses may be performed as appropriate.
- Overall survival is defined as the time interval between the start date of study drug and the date of death (any cause). The final known date of survival will be used as the censoring date for patients who have not been reported to have died by the time of analysis cut-off date. OS will be analyzed for only the BTC and STS cohorts based on the All Treated Population. OS will be described in tabular and graphical format using Kaplan-Meier method, including estimated median (in months) with 95% CI, 25th and 75th percentiles.

11 ETHICS

11.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, consensus and the ethical principles derived from international guidelines, including the following: Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and Applicable ICH GCP Guidelines that have their origin in the Declaration of Helsinki.

11.2 Ethics Review

The Independent Ethics Committee (IEC)/Institutional Review Board (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 site.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. All SAEs and other significant safety findings should be reported to the sponsor, the IEC/IRB, and applicable regulatory authorities as required. 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 subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC 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 IRB/IEC, 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

11.3 Patient Informed Consent

- Investigators or designees must obtain the signed ICF from patients prior to conducting any study-related procedures.
- The investigator or his/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 IRB/IEC 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 authorized 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 electronic case report form (eCRF).
- If the risk/benefit 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).

11.4 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. Electronic case report forms and other documents submitted to the sponsor should not contain the patient's name.

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- Patients are identified only by the 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 participant must be informed that his/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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.5 Disclosure

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

11.6 Data Quality Assurance

- To ensure the safety of participants 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 participant data relating to the study will be recorded on printed or eCRF 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 CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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 non-compliance 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, CROs).

11.7 Biological Specimens and Data

For participants who provide informed consent agreeing to participate in future biomedical research, any unused samples for study-related research, as well as unused PK samples, may be stored for no longer than 15 years, or other period as per local requirements, after the final date of the database lock. After this storage period, any residual samples will be destroyed. The sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality.

The unused samples may be utilized for future biomedical research as permitted by local regulations. Permission will be required from subjects for prior to any new analysis to be conducted on the biological specimens that are not related to the current study .

The results of these future biomedical research analyses will not be shared with patients and will not be presented in the clinical study report.

If there are specific site or country requirements involving the pharmacogenomic analyses that the sponsor is unable to comply with, samples will not be collected at those sites.

All samples will be single/double coded as defined by ICH guideline E15.

12 OVERSIGHT

12.1 Independent Monitoring

No independent data monitoring is planned for this study. The sponsor will review study safety data on an annual basis, or more frequently, if safety concerns arise.

12.2 Quality Control and Assurance

In accordance with ICH E6(R2), the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data are generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The sponsor will ensure that all aspects of the trial are operationally feasible and will avoid unnecessary complexity, procedures, and data collection. The sponsor is responsible for ensuring that the protocols, CRFs, and all other operational documents are clear, concise, and consistent.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

The sponsor and investigator ensures that any individual or party who performs trial-related duties or functions on behalf of the sponsor/investigator is qualified to perform the trial-related duties or functions.

The planned quality assurance and quality control procedures for the study are described in this section.

12.2.1 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 CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to GCP, and the progress of enrollment, and to ensure that study drug 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 field 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 CRFs will be performed according to the study-specific monitoring plan.

12.2.2 Audits

Authorized representatives of the sponsor, a regulatory/competent authority, and/or an IRB/IEC 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, IRB/EC 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.

12.2.3 Records

12.2.3.1 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. Data from ECG will be collected at the study sites, and the data will be transmitted to a designated CRO for centralized analysis, as well as for further processing and data reconciliation. Imaging data will be collected at the study sites, and a designated CRO will perform further processing, data reconciliation, and holding.

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.

12.2.3.2 Source Data 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).

12.2.3.3 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.

12.3 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 subject/ within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the ECs/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 subject and should assure appropriate subject therapy and/or follow-up.

13 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 multi-center studies only in their entirety and not as individual site data. In this case, a principal investigator will be designated by mutual agreement.

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

14 FINANCING AND INSURANCE

Financing and insurance information are addressed in a separate agreement.

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