STATISTICAL ANALYSIS PLAN

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

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Name of Test Drug:	Surufatinib
Phase:	Phase 2
Sponsor Name:	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
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Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AESI	Adverse events of special interest
ADaM	Analysis Data Model
ALP	Alanine phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BLQ	Below the lower limit of quantification
BOR	Best Overall Response
CI	Confidence interval
CFB	Change from baseline
COVID-19	Coronavirus 2019
CTMS	Clinical trial management system
CR	Complete response
CS	Clinically significant
CSR	Clinical study report
CTMS	Clinical trial management system
CV	Coefficient of variation
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CxDy	Cycle x Day y
DBL	Database lock
DCR	Disease control rate
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DoR	Duration of response
eCRF	Electronic case report form
ECHO	Echocardiogram
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOC	End of cycle
EOT	End of treatment
HR	Hazard ratio
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
ITT	Intent-to-treat
LLQ	Lower limit of quantification
LS	Least-square
MCFB	Mean change from baseline
MedDRA	Medical Dictionary for Regulatory activities
MUGA	Multigated acquisition
NA	Not applicable
NCI	National cancer institute
NCS	Not clinically significant
NE	Not evaluable
NET	Neroendocrine tumors
ORR	Objective response rate
OS	Overall survival
P-gp	P-glycoprotein
PD	Progressive disease
PE	Physical examination
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PR	PR Interval (ECG Parameter)
PS	Performance status
PT	Preferred term
PTT	Partial thromboplastin time
QD	Once daily
QTcB	QT correction Bazett formula
QTcF	QT correction Fridericia formula
QRS	A combination of the Q wave, R wave and S wave

RBC	Red blood cells
RD	Relative dose
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Stable disease
StdDev	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SOC	System organ class
TEAE	Treatment emergent adverse event
TLFs	Tables, listings and figures
TOC	Table of contents
TPR	Time point response
TTD	Time to deterioration
TTR	Time to response
ULN	Upper limit of normal
ULQ	Upper limit of quantification
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study 2020-012-00EU1. The SAP is based on the Protocol Amendment 6, dated 01 December 2023. With this amendment, the study was terminated based upon the strategic re-evaluation of the clinical development program for surufatinib in Europe and the United States. This change was not based on any concern for patient safety or efficacy relative to surufatinib treatment. CCI [redacted]

The purpose of this statistical analysis plan (SAP) for the study is to ensure that the data listings, summary tables and figures that are to be produced, and the statistical methodologies that are used, are complete and appropriate to allow valid conclusions regarding the study objectives. The SAP adheres to the proper regulatory guidelines and most recent International Council for Harmonisation guidelines (ICH) (E3, E6, E9). All decisions regarding the final analyses, as defined in this SAP document, will be made prior to locking the database; any deviations from these guidelines will be documented in the clinical study report (CSR).

The analyses related to pharmacokinetics (PK) endpoints for cohort D will be described in a separate analysis plan.

2. STUDY DETAILS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the anti-tumour activity of surufatinib in patients with low- to intermediate-grade (Grade 1 or Grade 2), well differentiated Neroendocrine tumors (NET).

2.1.2. Secondary Objective(s)

- To characterize the PK of surufatinib in patients with NET.
- To evaluate the effect of surufatinib on cardiac repolarisation, as detected by changes in electrocardiogram (ECG) corrected QT interval (QTc), and the potential relationship with surufatinib plasma concentrations.
- To further characterize the anti-tumour activity of surufatinib in patients with NET.
- Cohort D only: To evaluate the effects of repeat dosing of surufatinib on the single-dose PK of CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) substrates in patients with NET.
- To evaluate the safety and tolerability of surufatinib in patients with NET.

Details of the study objectives and correspondent endpoints is provided in Table 1.

Table 1 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	To evaluate the anti-tumour activity of surufatinib in patients with low- to intermediate-grade (Grade 1 or Grade 2), well differentiated NET.	Disease Control Rate at 6 months
Secondary	To characterize the PK of surufatinib in patients with NET.	Observed plasma concentrations, estimated population PK, and exposure parameters of surufatinib.
	To evaluate the effect of surufatinib on cardiac repolarisation, as detected by changes in ECG QTc, and the potential relationship with surufatinib plasma concentrations.	QTc and plasma concentrations of surufatinib at specified time points.
	To further characterize the anti-tumour activity of surufatinib in patients with NET.	Additional efficacy endpoints o Overall Response Rate (ORR) o Time to Response (TTR) o Duration of Response (DoR) o Progression Free Survival (PFS)
	Cohort D only: To evaluate the effects of repeat dosing of surufatinib on the single-dose PK of	**Cohort D only:** Exposure parameters of CYP3A4, P-gp, and BCRP substrates

Tier	Objectives	Endpoints
	CYP3A4, P-gp, and BCRP) substrates in patients with NET.	
	To evaluate the safety and tolerability of surufatinib in patients with NET.	Safety assessments include: o Frequency and severity of adverse events (AEs) o Physical examination findings o Vital signs o Laboratory tests o ECG o Echocardiograms/Multigated Acquistion (MUGA)
Exploratory	None	Efficacy endpoint o Overall Survival (OS)

2.2. Study Design

2.2.1. Brief Description

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

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

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

DDI Substudy (Cohort D): Patients with NETs of any origin.
Approximately 16 additional patients with NET of any origin will be enrolled to Cohort D for the DDI substudy. The primary objective of this cohort is to investigate the potential DDI between

surufatinib and a drug cocktail containing selective probes of CYP3A4 (midazolam), P-gp (fexofenadine), and BCRP (rosuvastatin) substrates. Treatment cycles for Cohort D are outlined in Table 2. The DDI drug cocktail will be given on Day -2 during the pretreatment phase, and assessment of PK profiles of the probe substrates will be conducted at baseline on Days -2 and -1 (ie, during the 48-hour period before starting treatment with surufatinib) and after repeated dosing with surufatinib at a dose of 300 mg QD for at least 14 days (surufatinib steady state on Cycle 1 Day 15 [+1 week]). Patients enrolled to this cohort will not have to undergo Holter monitoring. For this DDI cohort, the most critical question will be answered with the completion of Cycle 1 Day 17. Therefore, once all patients in this cohort have completed the required study procedures up to Cycle 1 Day 17, a data cutoff is planned to evaluate the short-term safety and the PK profile. An interim PK report for Cohort D will be written on the basis of this data cutoff date.

Table 2 Cohort D Treatment Overview

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

2.3. Determination of Sample Size

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

Table 3A shows the range of DCR and the corresponding 95% confidence interval (CIs) for a sample size of 20 patients. Table 3B shows the range of DCR and the corresponding 95% CIs for a sample size of 35 patients.

Table 3A Estimated Disease Control Rate and 2-Sided 95% Confidence Intervals for N = 20 Patients

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

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

Table 3B Estimated Disease Control Rate and 2-Sided 95% Confidence Intervals for N = 35 Patients

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

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

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

15% dropout rate, approximately 16 patients will be enrolled to ensure a minimum of 14 completers.

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

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

3.1.1. All Enrolled Set

All enrolled set includes all patients who signed informed consent form (ICF).

3.1.2. Safety Analysis Set

This set includes all patients who have received at least 1 dose of surufatinib. Patients in this set will be analyzed according to the actual dose initially received. This will be the analysis set for all safety evaluations. PFS will also be analyzed based on this population.

3.1.3. Pharmacokinetic (PK) Analysis Set

This population includes all patients who received at least 1 dose of surufatinib and have at least 1 PK sample obtained and analyzed.

- **PK Population**: All patients who received at least 1 dose of the study drug and have at least 1 measurable plasma concentration data point for at least 1 PK analyte without protocol violations or events with potential to affect the PK concentration.
- **PK Evaluable Population**: All patients who received at least 1 dose of the study drug and have sufficient concentration data to derive at least 1 PK parameter.

The PK population is used for tabulation of surufatinib concentrations from PK plasma samples.

3.1.4. Pharmacodynamic (PD) ECG Analysis Set

This population includes all patients who received at least 1 dose of study drug and have baseline and at least 1 post-dose ECG measurement.

Patients who had reduced dosage, prolonged dose interruption of >2 days in cycle 1, any dose interruption within 7 days before cycle 1 day 15 (+1 week), or were discontinued from the study prior to the completion of ECG data collection (cycle 1 day 15 [+1 week]) will be excluded.

3.1.5. Efficacy Analysis Set

This population includes all patients who received at least 1 dose of surufatinib and had at least 1 post-baseline tumor assessment unless death occurs before first-post-baseline assessment.
All efficacy endpoints will be analyzed based on this analysis set except PFS, which will be analyzed based on the safety analysis set.

3.2. Protocol Deviations

Protocol deviations are recorded in the clinical trial management system (CTMS) as outlined in the protocol deviation and non-compliance management plan. All major and minor protocol

deviations including protocol deviations related to COVID-19 will be reviewed and confirmed during data review meeting prior to database lock.

Data analyses will be based on the analysis sets defined above.

4. ENDPOINTS

4.1. General Principles for Derived Data and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

4.1.1.1. First Dose Date

Reference start date is defined as the first date when a non-zero dose of any study drug (whichever occurs first) was administrated (first administration/dose date). Day 1 is the day of the first dose of study treatment in Cycle 1.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Reference end date is defined as the last date when a non-zero dose of any study drug was administered.

4.1.1.2. Last Dose Date

Last dose date is defined as the date of the last dose of study treatment received.

For patients on treatment at the time of analysis prior to database lock, the last dose date is the date of the most recent study visit date in the database.

4.1.1.3. Date of Last Known Alive

The date of last known alive is defined as the last alive date of contact from the end of study page on the eCRF. For patients ongoing at time of analysis, the date of last known alive is the date of the most recent study visit date in the database.

More specifically, the last known alive date will be derived for subjects not known to have died at the analysis cut-off date using the latest date (including complete and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date, and the date of adverse event becoming serious.
- Date latest known alive collected during the survival follow-up.

- Randomization date.

After sorting properly for all those available dates, if the last last known alive date is a partial date with Month and Year information, day will be imputed as 15, unless this is after the cut off date in which case the cut off date will be used as last alive date.

4.1.1.4. Date of Death

Date of death is defined as the date of death from the Death Detail page on the eCRF. Date of death is cross-checked with AEs where outcome is 'Fatal', if applicable. In rare case, if year and month of death date are known but the day is unknown, day will be imputed as 15. For example, if a patient is reported to die on Dec2017, the death date will be imputed as 15 Dec2017 (this is assuming there is no evidence patient was alive on the 15th based on date last known alive or most recent study visit date).

4.1.1.5. Study Day

The study day is determined relative to the date of the first dose of study treatment. The day of the first dose of study treatment is defined as study day 1. The day prior to the first dose of study treatment is study day -1. There is no study day 0.

For events that occur before the first dose of study treatment:

study day = date of the event – first dose date;

For events that occur on or after the first dose of study treatment:

study day = date of the event – first dose date + 1.

4.1.2. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment prior to the first administration of any study drug, including scheduled and unscheduled visits, unless otherwise specified. For quantitative measurements,

- change from baseline (CFB) will be calculated as: CFB = assessment value at visit X – baseline value;
- percentage CFB (% CFB) will be calculated as % CFB = (assessment value at each visit X – baseline value)/baseline value × 100.

4.1.3. Treatment Period

Unless otherwise specified, the treatment period is defined as the period from first administration date of treatment to [30 days + 7 days protocol defined window] after last administration date on treatment. For safety data, only the assessments/events collected during the treatment period will be evaluated.

The worst post-baseline is defined as the worst assessments/events during the treatment period including both scheduled and non-scheduled visit. The end of treatment (EOT) measurement is defined as the latest non-missing measurement taken during the treatment period.

4.2. Exposure Endpoints

Drug exposure, including number of cycles received, total duration of exposure, cumulative dose received (mg), dose intensity, and relative dose intensity of surufatinib will be calculated as per algorithms included in Table 4.

Table 4 Extent of Exposure Parameters

Parameter	Definition
Duration of Exposure (days)	Last dose date of study treatment from the last cycle – first dose date of study drug + 1.
Number of Days with Recorded Dose	Sum of days with recorded doses
Number of Cycles Treatment Received	Patients are considered to have started a cycle if they have received at least one dose of any study treatment.
Number of Cycles Treatment Received Categories	1, 2, 3, 4, 5, 6 and > 6
Cumulative Dose (mg)	Sum of doses administered in all cycles. The total dose administered in each cycle is defined as: the sum of (number of 300 mg capsules taken) where number of capsules taken = total capsules dispensed – total capsules returned.
Dose Intensity (mg/day)	Cumulative Dose (mg) / Duration of Exposure (day).
Relative Dose Intensity (%)	100 * [Dose Intensity (mg/day) / (300 × 28/28 (mg/day))]

Drug accountability data will be used to calculate the total dose administered (mg) for each cycle for surufatinib. The number of capsules taken for each dose level will be calculated as total capsules dispensed – total capsules returned in a cycle. The total dose administered (mg) in a cycle will be the sum of 50 mg capsules taken.

Dosing modifications (including both dosing interruption and dose reduction): number of patients with any dosing modification, and categorized frequency of dosing modification (0, 1, 2, 3, 4, 5, 6, >6).

Dosing interruption: number of patients with any dosing interruption and reasons for dosing interruption, and categorized frequency of dosing interruptions (0, 1, ≥2).

Dose reduction: number of patients with any dose reduction and reasons for dose reduction, and categorized frequency of dose reduction (0, 1, 2, 3).

4.3. Safety Endpoints

Safety endpoints include adverse events, serious adverse events, adverse events of special interest, laboratory results and abnormalities, physical examination findings, vital signs, ECG, Echocardiograms/MUGA and incidence of patients experiencing dose modifications (including dose reductions and dose delays) and/or dose discontinuation of study drug (and reason for discontinuation).

4.3.1. Adverse Events (AEs)

All AEs will be coded from verbatim text to preferred term (PTs) and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. AEs will be collected from the time of signature of informed consent throughout the treatment period. AEs will be graded by investigator according to NCI CTCAE v5.0.

An AE is considered a treatment emergent adverse event (TEAE):

1) If the onset date is on after the start of study treatment or if the onset date is missing; or
2) If the AE has an onset date before the start of study treatment but worsened in severity after the study drug administration until [30 days + 7 days protocol defined window] after the last dose of study treatment. After this period, treatment-related SAEs will also be considered as TEAEs.

Other AE variables include treatment-related AEs, AEs leading to study drug modifications (i.e. dose interruption, dose reduction, or study drug withdrawal), AEs leading to study discontinuation, AEs leading to death, and SAEs.

An AE is considered treatment-related in the summaries if it is assessed as related to study drug by the investigator or if the assessment of relationship to study treatment is missing.

Severity of AEs is graded from Grade 1 to Grade 5 according to the NCI CTCAE v5.0. Missing severity grade is imputed as Grade 3.

COVID-19 related AEs will be identified based on recorded verbation term and/or coded preferred terms.

For AEs which are not on-going, duration of AE (days) is defined as AE end date – AE start date +1; for on-going AEs, the end date will be listed as ‘Ongoing’ and the duration of AE (days) will be approximated as ‘≥ date of last visit – AE start date +1’.

AEs of Special Interest (AESI)

AEs of special interest (AESI) will be identified based on the searching strategy listed in Appendix 2. AESIs will be extracted from MedDRA 27.0 by referring to the standardized queries in the table. The SMQ code only consider a 'narrow' scope, i.e. category A terms.

AESIs for surufatinib include drug related hepatic disorder, hypertension, haemorrhage, and acute renal failure.

4.3.2. Laboratory

Blood and urine samples for the determination of hematology, clinical chemistry, coagulation, thyroid function, lipid panel and urinalysis laboratory variables described in Table 5 will be measured.

Table 5 Laboratory Assessment

Laboratory Category	Parameters
Hematology	Complete blood count, including Red Blood Cell Count (RBC), haemoglobin, haematocrit, white blood cell count with differential and platelet count.
Coagulation Assay	PT/INR and aPTT.
Blood Chemistry	Blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, total bilirubin, direct bilirubin, Alanine aminotransferase (ALT), Aspartate transaminase (AST), alkaline phosphatase, lactic dehydrogenase, amylase, total protein, albumin, and uric acid
Thyroid Function	Thyroid-stimulating hormone, free triiodothyronine, free thyroxine
Lipid Panel	Total cholesterol and triglycerides.
Urinalysis	pH, glucose, protein, and blood.

Change from baseline in laboratory test results to each assessment will be calculated.

The non-protocol specified tests (if any reported) and urinalysis results will not be summarized; they will only be included in listings.

Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Clinical laboratory results will be graded according to CTCAE criteria, CTCAE v5.0 criteria. Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- Alanine aminotransferase (ALT) or/and aspartate aminotransferase (AST) >5 x ULN
- AST or/and ALT > 3× upper limit of normal (ULN) and ≤ 5×ULN
- Total bilirubin > 2×ULN
- Potential Drug-Induced Liver Injury (DILI): AST and/or ALT > 3×ULN and total bilirubin > 2×ULN
- Hy's Law criteria: AST and/or ALT > 3×ULN and total bilirubin > 2×ULN and ALP < 2× ULN.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each hematology and chemistry laboratory parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

4.3.3. ECG

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR interval, QT, QTc and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 6.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each ECG parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 6 Potentially Clinically Significant Criteria for ECG

Parameter (unit)	Criterion
Heart Rate (bpm)	>100
PR Interval (msec)	>200
QRS Interval (msec)	>110
QT, QTcF, QTcB (msec)	> 450 to ≤480
	> 480 to ≤500
	> 500
	Increase from baseline > 30 to ≤60
	Increase from baseline > 60

Twelve-lead ECGs will be performed according to the time points in Table 2 for Cohorts A, B, and C and Table 3 for Cohort D of the study protocol. The QTcF will be closely monitored. In addition, a continuous 12-lead Holter monitor will be used for corrected QT interval (QTc) evaluation during cycle 1 in patients enrolled across Cohorts A, B, and C. The goal will be to enroll and assign patients to Holter monitoring until approximately 40 patients have adequate ECG measurements at baseline, cycle 1 day 1, and cycle 1 day 15. The results will be sent for central reading (see below in Continuous 12-Lead Holter Monitor for QTc Evaluation for details).

4.3.4. Vital Signs

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, heat rate, body temperature, weight, and height. Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 7.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each vital sign parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 7 Potentially Clinically Significant Criteria for Vital Signs

Variable	Criterion value
Weight (kg)	Percentage increase from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20% Percentage decrease from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20%
SBP (mmHg), DBP (mmHg), Heart rate (bpm), Respiratory rate (breaths/min)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 (except for respiratory rate)

4.3.5. ECOG Performance Status

Eastern cooperative oncology group (ECOG) performance status (PS) scores will be evaluated by the same Investigator throughout the study. Details on the ECOG assessment and grading scale are available in following Table 8.

Table 8 Eastern Cooperative Oncology Group Performance Status

Grade	Activity Level
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Death

4.3.6. Echocardiogram (ECHO)

ECHOs will be performed at Screening, every 12 weeks thereafter and at unscheduled visits. Assessment parameters include left ventricular ejection fraction (%) and overall interpretation of cardiac function. MULTIGATED ACQUISITION (MUGAs) are permitted if ECHOs cannot be performed.

4.3.7. Physical Examination

A comprehensive physical examination (PE) will be performed at Screening and end of treatment visit. It includes general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, genitourinary system, lymph nodes, musculoskeletal, neurological assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Abnormal clinically significant findings in PE are to be reported as AEs (post-baseline) or medical history (screening).

4.4. Efficacy Endpoints

4.4.1. Primary Endpoint

The primary endpoint of the study is Disease Control Rate (DCR) at 6 months. DCR is defined as the proportion of patients achieving a best overall response of confirmed CR, PR, or SD, per RECIST v1.1, as determined by the Investigator.

4.4.2. Secondary Endpoints

4.4.2.1. Objective Response Rate

ORR is defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or PR per RECIST Version 1.1. Both confirmed and unconfirmed responses will be evaluated. To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed at least 4 weeks after the criteria for response are first met.

- Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".
- Scenario #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No" hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".
  - Both ways (confirmed and unconfirmed) of assigning BOR will be implemented.

BOR will be determined using time point responses (TPRs) up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 Eisenhauer et al., 2009) or death; or (ii) withdrawal of consent; whichever is earlier.

The timing of an overall TPR will always be derived based on scan dates not response assessment dates. For a scheduled tumor scan assessment, it is expected that there may be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the overall response assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the same target lesions, the last assessment will be used. A patient's BOR will be determined based on Table 9.

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or Not Evaluable (NE)) will be summarized.

Table 9 Best Overall Response When Confirmation of CR and PR are Required, also Includes Unconfirmed CR and PR

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response* for ORR	Best Overall Response for ORR UNCONFIRMED
CR	CR	CR	CR
CR	PR	SD, PD, or PR[1]	Unconfirmed CR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	Unconfirmed CR
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	Unconfirmed CR
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD	Unconfirmed PR
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	Unconfirmed PR
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	Unconfirmed PR
NE	NE	NE	NE

CR=complete response; NE=inevaluable; PD=progressive disease; PR=partial response, SD=stable disease.

1. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
2. * A best overall response of SD can only be made after the subject is on study for a minimum of 49 days (counted from Cycle 1 Day 1). If the subject is on study for less than 49 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

4.4.2.2. Time to Response

Time to response is defined as the time (months) from start of study treatment until the date of first documented objective response, either CR or PR (whichever status is recorded first),

according to RECIST v1.1. It will be calculated for patients whose BOR is either CR or PR (ie, responders).

TTR is calculated as (date of first occurrence of CR or PR – date of start of study treatment + 1)/30.4375.

Date of CR/PR will use the latest tumor assessment date at the CR/PR visit.
Time to response will be based on tumor assessments up to PD, death or initiation of a further anti-tumor therapy, whichever occurs earlier.

Both the unconfirmed TTR based on the patients with unconfirmed CR/PR and the patients with confirmed TTR based on the confirmed CR/PR will be derived. For the confirmed TTR, the first date to observe the CR/PR will be as the response date for confirmed responder.

4.4.2.3. Duration of Response

DoR is defined as the time (months) 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 PD). Only those patients with confirmed responses of CR or PR will be included in calculating DOR. Censoring will follow the rules outlined for PFS in Table 10. DoR is calculated as (date of death or PD [or last assessment if censored] – date of first occurrence of confirmed CR or PR + 1)/30.4375. Duration of response based on unconfirmed responses will also be summarized.

4.4.2.4. Progression Free Survival

PFS is defined as the time (months) from the start of study drug until the first objective disease progression as defined by RECIST v1.1, or death, whichever comes first. More specifically, PFS will be determined using all the assessment data up to the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 or death; or (ii) withdrawal of consent; whichever is earlier. Patients without report of PD or death from any cause at the time of analysis are censored as described in Table 10 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. If PD is documented between scheduled visits, the actual date of documented progression will be used as an uncensored value in the analysis of PFS. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

1. Date of progression is determined based on the earliest of the dates of the component that triggered the progression.
2. When censoring a patient for PFS, the patient is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 10 Censoring Rules for PFS

Rule	Situation	Date of Progression or Censoring	Outcome
1	PD documented between scheduled radiological assessment visits	Date of first documented disease progression	Event
2	Death between scheduled radiological assessment visits Death before first documented PD Death after one missing radiological assessment visit	Date of death	Event
3	Documented PD directly following a missing radiological assessment visit, if having not had disease progression observed previously	Date of first documented disease progression	Event
4	No baseline nor post-baseline radiological assessments available	Date of first dose	Censored
5	No death nor PD by the time of data cut-off for final analysis	Date of last adequate radiological assessment	Censored
6	Drops out before end of study	Date of last adequate radiological assessment	Censored
7	New anti-tumor therapy started prior to PD	Date of last adequate radiological assessment prior to or on date of initiation of new therapy visit	Censored
8	Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored

Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, e.g. outcome is progression and the date is the date of the assessment of progression

Note: Two consecutive scheduled tumor assessments is equal to 126 days (=2* (8 weeks *7+ 7 days)) since previous evaluable RECIST 1.1 or baseline assessment if there is no post baseline tumor assessment.

4.4.2.5. Overall Survival

OS is defined as the time (months) from start of study treatment until the date of death due to any cause.

That is, OS is calculated as (date of death or last known alive – date of start of study treatment + 1)/30.4375.

Patients with no event during the study will be censored at the date last known to be alive.

Moreover, the last known alive date will be derived for patients not known to have died at the analysis cut-off date using the latest date (including complete date and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date.

4.5. Other Endpoints

4.5.1. Pharmacokinetic Endpoint

The PK endpoint to be covered in this SAP includes surufatinib plasma concentrations in individual patients from Cohorts A, B and C primarily. In each cycle, PK samples will be collected as per Table 3 of the study protocol. Plasma concentrations of surufatinib for individual patients in Cohort D, transferred after the cut-off date of 18-May-2023 (see Section 6.2), will be listed but not summarized.

4.5.1.1. Handling of Missing Plasma Concentration Data

Missing concentration data for all patients who are administered scheduled study treatments is considered as non-informative missing and is not imputed. No concentration estimates are provided for missing sample values.

4.5.1.2. Handling of Below the Lower Limit of Quantification (BLQ) Data

For PK concentration summary, the following rules apply:

- For predose samples on C1D1, PK concentrations below the BLQ are set to zero;
- For samples at all other timepoints, BLQ values will be set to 0.5*lower limit of quantitation (LLOQ; 1.00 ng/mL).

4.5.1.3. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Time (actual time)

For all sampling times, the actual sampling times relative to dosing are calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in hours and rounded off to two decimal digits are used, except for pre-dose samples occurring prior to dosing, which are reported as zero (0.00), regardless of the time difference. Scheduled sampling times are listed but will not be summarized. If the actual time of sampling is missing, it will be reported as NR (not recorded) in the listing, the nominal time is used for summary statistics.

5. ANALYSIS METHOD

5.1. General Principles

5.1.1. General Methodology

In general, all efficacy, safety and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics: sample size (n), mean, standard deviation, minimum, 25% percentile (Q1), median, 75% percentile (Q3), and maximum. Categorical variables will be summarized in frequency tables (frequencies and percentages).

Time to event variables will be analyzed using Kaplan-Meier method and summarized with median, 25% and 75% percentiles with their corresponding 95% confidence intervals (CIs) which are calculated using log-log transformation based on the method by Brookmeyer and Crowley (1982). Individual data will be presented in patient listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

For continuous data, unless otherwise specified, the mean, median, Q1, and Q3 will be presented with 1 more significant digits than the original values, and standard deviation and standard error (SE) will be reported with 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal point; if the count is 0, no percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%." Any rounding will be done after all calculations are made.

5.1.2. Handling Missing Data

Missing data is assumed to be missing at random. Category 'Missing' is displayed for qualitative assessments, where applicable.

There is no imputation of missing data for the analysis purpose, unless otherwise stated.

However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. The specific imputation rules are provided below for the method of imputation of missing AE onset and stop date and for the method of imputation of missing concomitant onset and stop dates. However, the imputed dates will not be shown in listings.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, patients with missing data will be excluded only from analyses for which data are not available.

5.1.2.1. Adverse Events and Start/End Date

AEs with onset/end dates that are partially/completely missing will be imputed as follows.

(i) AE start date:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date;
- If the AE onset date is partially missing, then
  - If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;
  - If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
  - If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
  - If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year

(ii) AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for patients known to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last known alive date for patients alive at the end of study or cut off date, the date of last known alive date will be use for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as “ongoing”.

5.1.2.2. Concomitant Medication/Procedure/Surgery Start/End Date

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing
- January 1st will be used to impute the start date if both the day and month are missing
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing
- December 31st of the year will be used to impute the end date if both the day and month are missing
- If the date is completely missing, assign 'continuing' status to the end date

If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the concomitant medication/procedure/surgery end date.

5.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle - defined as Day 1 - to the dates that the scheduled visits occur. 2. During Cycle 1, the visit window will be ±1 day (unless otherwise noted). From Cycle 2 onward, the visit window will be ±3 days (unless otherwise noted). To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 11. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patients listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the treatment completion visit, the last assessment in the window will be included in the summary.

For a patient who prematurely discontinues the study, the premature visit will be slotted accordingly. The window for end of treatment visit will be "last dose date of last cycle to last dose date of last cycle + 37 days".

Table 11 Visit Window Detail

	Cycle 1				Cycle 2 and onwards		End of treatment
Visit	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**CXD1**	**CXD15**	
Scheduled Day [a]	1	8	15	22	21	1	
ECOG	Day 1		12 to 18		Day -3 to 8	9 to EOC -3	Last dose date of last cycle to last dose date of last cycle + 37
Vital Sign	Day 1	2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Hematology		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Clinical Chemistry		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Blood amylase and lipase		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Coagulation		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Thyroid function		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	
Urinalysis		2 to 11	12 to 18	19 to EOC -3	Day -3 to 8	9 to EOC -3	

EOC = End of Cycle

5.1.4. Adjustment for Covariates

Not Applicable.

5.2. Analysis Methods

5.2.1. Patient Disposition

The following summaries will be presented by cohort and overall to reflect the patient disposition:

- Number of patients who signed the informed consent
- Number and percentage of screen failures
- Reason for screen failure
- Number and percentage of patients who do not receive study treatment
- Number and percentage of patients who received study treatment
- Number and percentage of patients still on treatment at the time of analysis data cutoff
- Reason for treatment discontinuation
- Number and percentage of patients who discontinue the study
- Reason for study discontinuation

For patients screened but not enrolled and for the reasons for not being enrolled the denominator used to calculate the percentage will be the number of screened patients. For all other calculations the denominator will be the number of patients enrolled.

A separate table will be presented to show the patients included in each analysis set and proper reasons for exclusion from an analysis set.

5.2.2. Protocol Deviation

Protocol deviations will be summarized descriptively as number and percentage of patients with at least 1 major protocol deviation and patients with at least 1 major protocol deviation related to COVID-19 for each cohort and overall in the Safety population. A patient may have multiple major and/or minor deviations and will be counted once per major and/or minor deviation.
A listing of protocol deviations, including COVID-19-related protocol deviations will be provided.

5.2.3. Demographic and Other Baseline Characteristics

The following parameters will be summarized descriptively for each cohort and overall for the Safety analysis set.

- Age at Screening (years)
- Sex (Female, Male); If female, Child Bearing Potential status.
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native

Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, and Other).

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline BMI (kg/m^2): calculated as Weight at Baseline (kg)/ [Height at Baseline (m)]^2
- Baseline ECOG Performance Status: 0, 1

Age (years) at screening is calculated by site personnel from the ICF date and recorded on eCRF.

Demographic data and baseline characteristics, informed consent data, and inclusion/exclusion criteria will be listed by patient.

5.2.4. Disease Characteristics

History of cancer of the safety analysis will be summarized descriptively for each cohort for the following:

- Time (months) since first diagnosis of cancer (calculated as date of first dose of treatment – date of first diagnosis of cancer + 1)/30.4375
- Stage of cancer at first diagnosis (stage I, stage II, stage III, stage IV)
- Grading of cancer at first diagnosis (Grade I, Grade II, Grade III)
- Time (months) since date of diagnosis of locally advanced or metastatic disease (calculated as date of first dose of treatment – date of diagnosis of locally advanced or metastatic disease + 1)/30.4375
- NET functional status
- Anatomical location of primary tumor

5.2.5. Medical History

Conditions/diseases from medical history can either be ongoing prior to study entry or have stopped prior to study entry. Medical history will be coded to SOC and PT using MedDRA version 27.0.

The number and percentage of patients with any past medical/surgical history within each SOC and PT will be provided by cohort and overall using the safety analysis set.

A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT).

Each summary will be ordered by descending order of incidence of SOC according to overall column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

5.2.6. Prior Anti-Cancer Therapy

Prior anti-cancer therapy, including mediation, radiotherapy, and procedure or surgery, will be summarized descriptively by cohort and overall for the safety analysis set.

5.2.6.1. Prior Anti-Cancer Medication

Prior anti-cancer medications are defined as those taken by the patient prior to the administration of study drug.

Prior anti-cancer medications will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e., ATC Level 2) and PT using the World Health Organization Drug Dictionary (WHO-DD) version March 2024.

The prior anti-cancer medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to overall column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

All prior anti-cancer medications will be presented in patient listing.

5.2.6.2. Prior Anti-Cancer Radiotherapy

Prior anti-cancer radiotherapy is defined as those taken by the patient prior to the administration of study drug.

The number and percentage of patients with at least one prior anti-cancer radiotherapy will be summarized.

All prior anti-cancer radiotherapy will be presented in patient listing.

5.2.6.3. Prior Anti-Cancer Procedure or Surgery

Prior anti-cancer procedure or surgery are defined as those taken by the patient prior to the administration of study drug.

Prior anti-cancer procedure or surgery will be coded to SOC and PT using MedDRA (Medical Dictionary for Regulatory Activities) version 27.0.

The prior anti-cancer procedure or surgery will be summarized by presenting the number and percentage of patients by PT and SOC. Patients taking the same medication multiple times will only be counted once for that PT or SOC.

Each summary will be ordered by descending order of incidence of SOC to overall column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All anti-cancer procedure or surgery will be presented in a patient listing.

5.2.7. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e. ATC Level 2) and PT using the WHO-DD version March 2024.

Medications taken and stopped prior to the first dose of study treatment are denoted "Prior". Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 37 days after the last dose are denoted "Concomitant".

Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.
The prior medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.
Similarly, the concomitant medications will be summarized.
All prior and concomitant medications will be presented in patient listing.

5.2.8. Concomitant Procedure

Medical or surgical procedures that started after first dose date but no later than 37 days after the last dose are denoted "Concomitant".
Concomitant medical or surgical procedures will be classified using the MedDRA version 27.0.

The concomitant medical or surgical procedures will be summarized by presenting the number and percentage of patients by PT and SOC. Patients having the same medical or surgical procedure multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC according to overall column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All concomitant medical or surgical procedures will be presented in patient listing.

5.2.9. Exposure of Study Treatment

The following summary for dose exposure will be summarized for each cohort:

- Duration of exposure for surufatinib.
- Number of days with recorded dose (actual duration of exposure)
- Number of surufatinib treatment cycles received.

- Number and percentage of patients with 1, 2, 3, 4, 5, 6 , >6 cycles received
- Cumulative dose for surufatinib.
- Dose intensity of surufatinib.
- Relative dose intensity of surufatinib.

The following summary for dose adjustment will be summarized for each cohort:

- Number and percentage of patients with any dose modification (including both drug interruption and dose reduction).
- Frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, > 6.
- Drug interrupted (number and percentage of patients experienced drug interruption and reasons for drug interruption; frequency of drug interruptions).
- Drug withdrawn (number and percentage of patients experienced drug withdrawn and reasons for drug withdrawn).
- Dose reduced (Number of patients with any dose reduction and reasons for dose reduction; and frequency of dose reduction: 0, 1, ≥ 2), also the dose reduction category will be summarized (from 300mg QD to 250mg QD, from 250mg QD to 200mg QD, from 200mg QD to 200mg on reduced schedule).

Study treatment accountability, study treatment administration and extent of exposure will be listed by patient and visit.

5.2.10. Safety Analyses

Safety data during the treatment period will be evaluated and reported by cohort. The treatment period is defined as the duration from the date of the first study drug administration until [30 days + 7 days protocol defined window] after last dose.

5.2.10.1. Adverse Events

An overall summary of the number and percentage of patients along with the number of adverse events for each dose level/cohort will be provided for the following categories of AEs:

Group	Summary Scope
All TEAEs	– CTCAE Grade ≥3 AEs – Treatment-related AEs – AEs Leading to Dose Reduction – AEs Leading to Dose Interruption – AEs Leading to Treatment Discontinuation – Tteatment-related AEs Leading to Dose Reduction – Treatment-related AEs Leading to Dose Interruption – Treatment-related AEs Leading to Treatment Discontinuation – AEs Leading to Death
Serious TEAEs	– CTCAE Grade ≥3 SAEs – Treatment-related SAEs – SAEs Leading to Dose Reduction – SAEs Leading to Dose Interruption – SAEs Leading to Treatment Discontinuation – Treatment-related SAEs Leading to Dose Reduction – Treatment-related SAEs Leading to Dose Interruption – Treatment-related SAEs Leading to Treatment Discontinuation – SAEs Leading to Death
Treatment-Emergent AESIs	– CTCAE Grade ≥3 AESIs – Treatment-related AESIs – AESIs Leading to Dose Reduction – AESIs Leading to Dose Interruption – AESIs Leading to Treatment Discontinuation – Treatment-related AESIs Leading to Dose Reduction – Treatment-related AESIs Leading to Dose Interruption – Treatment-related AESIs Leading to Treatment Discontinuation – AESIs Leading to Death
COVID-19-related TEAEs	CTCAE Grade ≥ 3 SAEs CTCAE Grade ≥ 3

The number and percent of patients experiencing a TEAE within each of the categories and sub-categories listed in Table above will be also summarized by SOC, PT, and highest CTCAE grade for each cohort. If a patient reports a TEAE more than once within that SOC/PT, the AE with the highest severity will be used in the corresponding severity summaries.

The summary will be sorted in descending order of frequency of SOC according to the sum of column. Within SOC, sort by descending frequency of PT according to the sum of column.

All AEs, including AEs that started prior to the study drug, will be presented in patient listings. In addition, separate listings of all SAEs, AESIs, AEs leading to death, AEs leading to dose reduction, AEs leading to dose interruption, and AEs leading to study drug discontinuation will be provided.

5.2.10.2. Death

Number of deaths, primary cause of death and whether autopsy was performed will be summarized descriptively for each cohort. Deaths occurring during the treatment period will also be tabulated.

Date of death will be provided in patient list in which the on-treatment death will be flagged.

5.2.10.3. Laboratory Evaluations

Summary tables for hematology, blood chemistry, coagulation, thyroid function, lipid panel and urinalysis (pH only) laboratory variables include descriptive statistics for result values and change from baseline for all continuous variables by visit and cohort.

Toxicities for clinical labs will be characterized according to CTCAE and the frequency and percentage of patients with each CTCAE grade for each visit during the treatment period will be summarized. Any occurrence of toxicity grade 3 or grade 4 during the overall treatment period will be summarized. Shift in toxicity grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values. For some specific parameters with CTCAE grading in both high and low direction (e.g., calcium, glucose, magnesium, potassium, sodium), CTCAE in high and low directions will be presented separately, i.e. hyper for higher values of concern and hypo for lower values of concern.

Qualitative assessments of urinalysis parameters are summarized for all patients using the number of patients with results of negative, trace, or positive.

Summary of clinical significance (Abnormal not clinically significant [NCS] and Abnormal Clinically significant [CS]) is also provided by visit and treatment group. Shift from baseline to the worst post-baseline investigators' assessment (i.e. normal, NCS, and CS for quantitative measurements and categorical measurements).

All laboratory results (including hematology, blood chemistry, blood chemistry – thyroid function, urinalysis, coagulation, pregnancy test data) in SI units are presented in data listings. Tests are listed in alphabetical order within their respective panels (hematology, blood chemistry, urinalysis, and coagulation).

A summary table and listing will also be provided for treatment-emergent liver injury by each cohort based on the pre-specified thresholds below:

1. Potential Drug-Induced Liver Injury (DILI): AST and/or ALT > 3x ULN and total bilirubin > 2x ULN
2. Hy's Law criteria: AST and/or ALT > 3x ULN and total bilirubin > 2x ULN and ALP < 2x ULN

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

5.2.10.4. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline.

The criteria for potentially clinically significant findings are defined in table 6. The frequency and percentage of patients with any potentially clinically significant findings during the induction treatment period will be presented. The supportive data will be provided in patient data listings.

The minimum, and maximum, and their corresponding change from baseline ECG parameter values will be summarized descriptively overall treatment period for each cohort.

Single 12-lead ECG interpretations by investigator data are listed by patient and visit.

5.2.10.5. Vital Signs

For vital sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature and Respiratory Rate) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (Table 7 Section 3.5.4) during the overall treatment period will be presented. A listing of all vital sign data will be provided.

The minimum, maximum, and their corresponding change from baseline vital sign values will be summarized descriptively overall treatment period for each cohort.

A listing of vital sign data will be provided.

5.2.10.6. Performance Status

The frequency and percentage of patients for each ECOG score level will be summarized by each visit and by maximum post-baseline score during the treatment period. Shift in grade from baseline to the maximum post-baseline score will be summarized.

A listing of ECOG score for all patients will be provided.

5.2.10.7. Echocardiogram

Descriptive statistics for Echocardiogram/MUGA will be summarized by visit. A by-patient listing of Echocardiogram/MUGA values at each time point will be generated.

ECHO/MUGA data is listed by patient and visit.

5.2.10.8. Physical Examination

A listing of physical examination data for all patients will be provided.

5.2.11. Efficacy Analyses

5.2.11.1. Primary Efficacy Analyses

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

Tumor evaluation data will be presented in listings.

5.2.11.2. Sensitivity Analysis for Primary Efficacy Endpoint

Not Applicable.

5.2.11.3. Multiplicity Control

Not applicable.

5.2.11.4. Secondary Efficacy Analyses

The estimate for ORR and the corresponding 95% CIs based on the Clopper-Pearson method will be provided for each cohort. Both confirmed and unconfirmed ORR will be presented.

For time to event endpoints (TTR, DoR, and PFS), the median, 25th and 75th percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI. Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using log-log transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. The Kaplan-Meier plots will be produced. The duration of follow-up for PFS will be calculated descriptively using the Kaplan-Meier method, while using different censoring rule which reverses censoring

indicator instead, i.e. patients who have event will be censored at the date of event. Patients who are censored will assigned as “event”.

5.2.11.5. Exploratory Efficacy Analyses

The estimate for OS and the corresponding 95% CIs based on the Clopper-Pearson method will be provided for each cohort.

The median, 25th and 75th percentile of OS will be estimated using Kaplan-Meier method with their corresponding 95% CI. Additionally, estimates will be provided for the survival probability along with their 95% CIs which are calculated using log-log transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. The Kaplan-Meier plots will be produced.

5.3. Other Analyses

Planned PK analyses for Cohort D will be presented in a separate analysis plan. The following sections describe the summary results and listings to be generated as part of this SAP.

5.3.1. Listing and Presentation of Individual PK Data

PK data will be presented by cohort, patient, cycle and day (for instance, C1D1, C1D21, C2D1, etc.), and time point.

1. Concentration data are presented to the same decimal place and in original units as reported by the bioanalytical lab, e.g., ng/mL;

2. Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time;

3. Concentration data of surufatinib for individual patients in Cohort D, transferred after the cut-off date of 18-May-2023, will be listed.

5.3.2. Summary of PK Concentration Data

The observed concentrations are summarized descriptively at each scheduled timepoint and dose level. Summaries are presented by cohort (A, B and C only), cycle and day (for instance, C1D1, C1D21, C2D1, etc.) and time point using descriptive statistics.

If the time deviation is greater than ± 20% from nominal time, the PK concentration value is excluded from the summary descriptives.

PK plasma concentration data at each scheduled timepoint and dose level is presented using the following descriptive statistics.

- n
- arithmetic mean and standard deviation (SD)

- geometic mean and geometric (CV)%
- coefficient of variation (CV)%
- median
- minimum and maximum
- number and percent of patient with BLQ

The conventions presented in Table 12 below are used for the presentation of the descriptive statistics of plasma concentrations.

Table 12 PK Concentration Data Reporting Precision

Variable	Summarized with:
Minimum, Maximum	3 significant digits
Mean (arithmetic), Median	3 significant digits
StdDev	3 significant digits
CV%	1 decimal point

5.3.3. Pharmacodynamic (Electrocardiogram) Analysiss

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

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

5.3.4. Corrected QT Intervals

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

The QT interval data will be corrected for heart rate using 2 correction methods (Fridericia – QTcF and Bazett – QTcB). For each QTc correction method, the relationship between QTc and RR interval at baseline will be evaluated graphically by plotting the logarithm of baseline QTc values against the logarithm of corresponding RR intervals. Fridericia will be used as the

primary correction method for statistical analysis. If the correlation between QTc and RR intervals remains significant using the Fridericia correction method, an alternative correction method may be considered for statistical analysis in addition to QTcF.

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

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

- QTc prolongation:
  - Absolute values >450 to ≤480 msec
  - Absolute values >480 to ≤500 msec
  - Absolute values >500 msec

- QTc change from baseline:
  - Increase from baseline >30 to ≤60 msec
  - Increase from baseline >60 msec

5.3.5. Heart Rate, QRS, and PR Intervals

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

6. PLANNED ANALYSIS

6.1. Independent Data Monitoring Committee

Not Applicable.

6.2. Planned Interim Analysis

For Cohort D only, once the last patient enrolled to this cohort has completed the required study procedures up to Cycle 1 Day 17, an interim analysis is planned to evaluate the short-term safety and the PK profile. CCI [redacted]

6.3. Final Analysis

The timing of analysis for each cohort may be different depending on completion of each cohort, and the final analysis of the study will be conducted at the time of analysis of the last cohort. All study data collected up through the time of the final analysis will be summarized.

7. CHANGE FROM THE PROTOCOL

Overal survival has been added as an exploratory endpoint.

Proteinuria and thyroid dysfunction have been removed from the AESI section 3.5.1 of this SAP since they are already considered fully characterized and there are no new or additional mitigation activities.
This is a change from the planned analysis specified in section 8.4 of the study protocol.

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HMP_2020_012_00EU1_7015642_Statistical_Analysis_Plan_v1.0_10October2024_to_Sign

Final Audit Report 2024-10-10

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