STATISTICAL ANALYSIS PLAN

AN OPEN-LABEL, MULTICENTER PHASE 1/2 STUDY OF SURUFATINIB IN COMBINATION WITH GEMCITABINE IN PEDIATRIC, ADOLESCENT, AND YOUNG ADULT PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

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Phase:	Phase 1/2
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Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

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REVISION HISTORY

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09 May 2023	0.5	1. Remove "No baseline tumor assessment and death" a censoring rule for PFS 2. Refine formulas in Exposure Endpoints 3. MedDRA version updated	PPD
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23 May 2023	1.0	Correcting typo in section 4.3.2 (Efficacy Endpoints)	PPD

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Plasma Concentration-Time Curve
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFB	Change From Baseline
CI	Confidence Interval
CL/F	Apparent Total Clearance from Plasma After Oral Administration
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DEAS	DLT-Evaluable Analysis Set
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICF	Informed Consent Form
ICH	International Council on Harmonization
IL-34	Interleukin 34

Abbreviation	Term
INR	International Normalized Ratio
LLoQ	Lower Limit of Quantification
MCHC	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OC	Observed Case
PE	Physical Examination
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Preferred Term
PrT	Prothrombin time
QTcF	Corrected QT Interval by Fridericia
RBC	Red Blood Cells Platelet Count
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SI	International System of Units
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
$T_{1/2}$	Half-life
T_{max}	Time to reach the maximum plasma concentration
TPR	Time Point Responses
TTR	Time To Response
ULN	Upper Limit of Normal
ULoQ	Upper Limit of Quantification
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study 2020-012-GLOB2. The SAP is based on the Protocol amendment 3, dated 24 January 2023. The SAP for pharmacokinetic will be prepared separately.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2. STUDY DETAILS

Table 1 describe the primary and secondary objectives of this study.

2.1. Study Objectives

Table 1 Objectives and Endpoints

	Objectives	Endpoints
Primary	• To determine maximum tolerated dose (MTD) and/or recommended phase 2 Dose (RP2D) of surufatinib, and to evaluate the safety and tolerability of surufatinib in combination with gemcitabine in pediatric subjects with recurrent or refractory solid tumors or lymphoma	• The incidence of Dose Limiting Toxicities (DLT) in each dose level • Safety, as assessed by: o The frequency and severity of Adverse Events (AEs) o Physical examination findings o Vital signs o Laboratory test results o 12-lead electrocardiogram (ECG)
Secondary	• To characterize the pharmacokinetics (PK) of surufatinib as a monotherapy and in combination with gemcitabine in pediatric subjects with recurrent or refractory solid tumors or lymphoma	• PK parameters for the dose escalation and PK expansion cohorts: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC), minimum plasma concentration (C_{min}), effective half-life ($T_{½}$), apparent total clearance from plasma after oral administration (CL/F), and accumulation ratio
	• To evaluate the anti-tumor activity of surufatinib in combination with gemcitabine in pediatric patients with recurrent/refractory solid tumors or lymphoma	• Efficacy will be assesses based on tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1: o Objective response rate (ORR) o Disease control rate (DCR) o Time to response (TTR) o Duration of response (DoR) o Progression-free survival (PFS)
	• Acceptability and palatability of surufatinib oral suspension	• The taste and palatability survey

2.2. Study Design

This is an open-label, multicenter, uncontrolled, Phase 1/2 study of surufatinib in combination with gemcitabine in pediatric, adolescent, and young adult subjects with recurrent or refractory solid tumors. This study design allows for dose escalation with intensive safety monitoring to ensure the safety of all subjects.

This study will utilize a rolling 6 design, with 3 dose escalation levels and 1 de-escalation level, if needed. The MTD and/or the RP2D will be designated in pediatrics.

The study duration is estimated to be approximately 36 months.

2.2.1. Dose Escalation

Dose escalation will be performed with sequential doses of surufatinib in combination with gemcitabine (Figure 1).

The first study cycle will be 35 days. During Cycle 1, surufatinib will be administered as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine on days 15 and 22. All subsequent cycles will be 21 days per cycle, where surufatinib will continue to be administered daily and gemcitabine will be administered on days 1 and 8. The starting dose of surufatinib will be 120 mg/m^2 daily. Gemcitabine (1000 mg/m^2 weekly × 2 doses) will not be escalated and will be given on days 15 and 22 of Cycle 1 and then on days 1 and 8 of all subsequent cycles. Surufatinib will be given continuously on days 1 to 35 in Cycle 1. The first 14 days of Cycle 1 serves to assess tolerability and toxicity of single agent surufatinib.

A PK expansion cohort will be conducted at the presumed RP2D/MTD and will consist of up to 6 subjects in each of the following 2 strata: subjects <12 years of age and subjects 12 to <18 years of age based on age at the time of enrollment. Surufatinib PK profiles after the first dose and at steady state will be characterized in both dose escalation cohort and PK expansion cohort. Subjects who are treated at the RP2D/MTD in dose escalation cohort will be counted in the PK expansion cohort.

To evaluate safety and tolerability for each dose escalation and determine if a DLT has been observed, safety and PK data will be reviewed by dose level.

The schedule of events can be found in Table 1 of the protocol.

2.2.2. Dose Finding

The dose finding period is the timeframe to define dose limiting toxicity (DLT) and begins with the initial dose of surufatinib and ends on the last day of Cycle 1. Should there be a delay (maximum 7 days delay) starting the subsequent cycle, dose finding will complete on the start date of the subsequent cycle.

Full details of the dose escalation and de-escalation rules can be found in Section 4.1.1 of the Protocol.

Figure 1 Study Schematic

Rolling six design with 4 dose levels
Combination Dose Finding
Patients: All recurrent/refractory solid tumors, including lymphoma

Dose Level	Cycle 1 (Cycle duration 35 days)	
	Surufatinib (mg/m^2)	Gemcitabine Days 15 and 22(mg/m^2)
-1	90	1000
1	120	1000
2	160	1000
3	200	1000

Determine RP2D of Surufatinib and Gemcitabine in combination

PK Expansion Cohort at RP2D (12 patients)

2.3. Determination of Sample Size

Up to 36 subjects are to be enrolled in this study.

2.3.1. Dose Escalation

Three dose escalation levels will be explored using the rolling 6 design which will lead to maximum 18 evaluable subjects. There is 1 additional dose level for dose de-escalation if starting dose is not tolerable. Then, up to 12 evaluable subjects will be evaluated in the PK expansion cohort. Assuming a 15% unevaluable rate with respect to the DLT evaluation for dose escalation portion or PK assessment for PK expansion cohort, it is expected to have up to 36 subjects in total.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

Data analyses will be based on the analysis sets defined below. Analysis sets, including exclusions based on major deviations, will be reviewed and approved by the Sponsor prior to the study database lock.

3.1.1. Safety Analysis Set (All Treated Population)

The Safety Analysis Set includes all subjects who receive at least 1 dose of surufatinib or gemcitabine. Safety data and efficacy will be evaluated based on this population's outcome. Subjects in the Safety Analysis Set will be analyzed by their actual dose initially received. If subjects have dose reduction during the study, all data will be summarized/analyzed based on the initial dose of subject drug received. For outputs relating to efficacy, the analysis set will be referred to as the All Treated Population.

3.1.2. DLT-Evaluable Analysis Set (DEAS)

The DLT-evaluable analysis set includes all subjects enrolled in the dose escalation phase of the study who receive at least 80% (28 of 35 doses) of the prescribed oral surufatinib dose and both doses of gemcitabine during the DLT evaluation period or who discontinued treatment due to a DLT.

3.1.3. Pharmacokinetics (PK) Analysis Set

This population will include all patients who received at least 1 dose of surufatinib and have at least one PK sample obtained and analyzed. The PK Analysis Set will not be used for any analyses described in this SAP. A PK analyses plan will be described in a separate document.

3.2. Protocol Deviation

Certain protocol deviations are major in that they may affect the ability to assess the safety and efficacy of study drug.

If a subject is enrolled, but fails to receive treatment, the reason for not receiving treatment will be noted in the CSR. Any such subjects who are not treated will be excluded from the Safety Analysis Set but will be included in the subject listings for the CSR.

All major protocol deviations will be reviewed in a data review meeting to classify protocol deviations as minor or major, and to discuss the potential impact on statistical analysis.

4. ENDPOINTS

4.1. General Principles for Derived and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

Generally, reference start date is defined as the first date when a non-zero dose of subject drug was administrated (i.e., date of first non-zero dose of any drug, whichever occurs first). Day 1 is the day of the first dose of study drug in Cycle 1.

Study day will be calculated from the reference start date, and it will be used to show start/stop day of assessments and events relative to the first administration of study drug.

If the date of the event is on or after the reference start date, Study day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date, Study day = (date of event – reference start date).

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

4.1.2. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment prior to the first administration of subject drug (i.e., date of first non-zero dose of any drug, whichever occurs first), including scheduled and unscheduled visits, unless otherwise specified. In the case where the last non-missing assessment and the first administration date coincides without time information, that measurement will be considered pre-dose. 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

All enrolled subjects enter into the treatment period. Subjects may receive up to 17 cycles of therapy as long as they continue to undergo study required assessments and meet criteria to start subsequent cycles.

Unless otherwise specified, the treatment period for analysis purposes is defined as the period from first administration date to 30 days + 7 days after last administration date of 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 assessment/event during the treatment period including both scheduled and non-scheduled visits.

Follow-up on this study is required at 30 days from the last dose of protocol therapy for late onset AEs and survival. The post-treatment follow-up will begin when the subject discontinues study treatment and all off-treatment assessments have been completed.

The severity of AEs and laboratory results depends on Common Terminology Criteria for Adverse Events (CTCAE) grade. The worst post baseline value is defined as the highest CTCAE grade during on treatment period.

The worst post-baseline abnormality is defined as Abnormal, Clinically Significant>Abnormal, Not Clinically Significant>Normal order during the on-treatment period.

4.2. Primary Endpoints

The primary endpoints are safety endpoints. Details can be found in Safety Endpoints, Section 4.5.

4.3. Secondary Endpoints

4.3.1. Pharmacokinetic Evaluations

PK evaluations details can be found in Secondary Endpoints, Section 4.6.1.

4.3.2. Efficacy Endpoints

Efficacy analysis will be assessed in the All Treated Population.

Best Overall Response (BOR)

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 or death; or (ii) withdrawal of consent.

The timing of an overall TPR will always be derived based on scan dates not response assessment dates. If there is more than one date per visit due to scans on different dates, take the earliest date if timepoint response is PD, otherwise take the latest date.

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.

The best overall response is defined as the best response (in the order of CR, PR, SD, PD and NE) among all responses recorded during the on-treatment period. SD must meet 49-day rule as follow:

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.

Objective Response Rate

ORR is defined as the proportion of subjects with a BOR of CR or PR as determined by the Investigator using RECIST version 1.1. BOR is defined as the best response recorded from the start of study drug (s) until documented RECIST version 1.1 progression.

Disease Control Rate

DCR is defined as the proportion of subjects with a BOR of CR, PR, or SD as determined by the Investigator using RECIST version 1.1. As previously stated, SD must meet 49-day rule as defined in section "Best Overall Response".

Time to Response

TTR is defined as the time (months) from start of study drug until the date of first occurrence of PR or CR for responders only.

TTR (months) = (<date of first occurrence of PR or CR > - <date of first dose of study drug> + 1)/30.4375.

Duration of Response

Duration of response is defined as the time (months) from the first occurrence of PR or CR whichever comes first, until disease progression or death. Duration of response will be summarized for responders only.

DoR (months) = (<date of first documentation of definitive PD or last tumor assessment (PFS endpoint date)> - <date of first occurrence of response> + 1)/30.4375.

Subjects will be censored using the censoring algorithm of the PFS (see Table 2).

Progression-Free Survival

Progression-free survival is defined as the time (months) from the start of subject drug (s) until the first radiographic documentation of objective progression as assessed by the investigator using RECIST Version 1.1 or death from any cause. PFS will be determined using all the assessment data up until 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. Subjects without report of PD or death from any cause at the time of analysis are censored as described in Table 2.

Table 2 Censoring Rules for PFS

No	Situation	Date of Progression or Censoring	Outcome	Censor reason
1	No baseline tumor assessment and alive	Date of first dose	Censored	No baseline assessment
2	No post-baseline tumor assessment and alive	Date of first dose	Censored	No post-baseline assessment
3	No baseline and/or post-baseline tumor assessment and death prior to the planned time of the second scheduled post-baseline assessment (i.e., Study Day 98 + a 3-day window)	Date of death	Event	
4	Progression, without missing two consecutive radiological assessment visits prior to progression	Date of progression	Event	
5	Death due to any cause, without missing two consecutive radiological assessment visits prior to death	Date of death	Event	
6	No disease progression or death	Date of last adequate tumor assessment	Censored	Progression free at time of analysis: the subject is known to be alive without any progression happened at the data cut-off date
7	Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored	

4.3.3. Taste and Palpability

Taste and palpability details can be found in Other Endpoints, Section 4.6.2.

4.4. Exposure Endpoints

No exposure endpoints are defined for this study in the protocol; however, the following exposure parameters will be derived for surufatinib and gemcitabine separately:

Total Duration of Exposure

Duration of exposure will be calculated in weeks for each treatment separately, as follows:

Total duration of exposure (weeks) = [date of last dose – date of first dose + days to the next planned dose after discontinuation (or death date if death date is earlier than the next planned dose)] / 7

If death occur within the last cycle, then death date can be used as the last dose date.

Specifically, surufatinib is dosed daily, therefore.

Duration of Exposure (weeks) = (date of last dose – date of first dose + 1) / 7

Gemcitabine is dosed on days 15 and 22 during Cycle 1 and days 1 and 8 during subsequent cycles, therefore.

Duration of Exposure (weeks) = [date of last dose – date of first dose + days to the next planned dose after Gemcitabine discontinuation (or death date if death date is earlier than the next planned dose)]/ 7

Days until the next dose will need to be computed depending on the day and cycle of administration. For example, for cycle 1 "days until the next dose" after dose administration on day 15 will be 7. Additionally, interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Number of Cycles Received

Subjects are considered to have started a cycle if, for that cycle, they have received at least one dose of any study drug.

Number of cycles is the number of cycles in which the subject took any dose of study drug.

Dose Intensity and Cumulative Dose Received

Dose intensity(mg/day) = cumulative dose (mg) / total duration of exposure (days)

Cumulative dose (mg) is defined as the sum of the total dosage that the subject actually received during an exposure period.

Relative Dose Intensity

Relative dose intensity (%) = (dose intensity (mg/day) / planned dose intensity (mg/day)) * 100

Planned dose intensity = planned total dose (mg) / total duration of exposure (days)

Planned total dose (mg) = total duration of exposure * daily dose.

Number of days with recorded dose

Number of days in which the subject took any dose of study drug.

4.5. Safety Endpoints

Safety endpoints are the primary endpoints. The Safety Analysis Set will be used to evaluate the safety variables including AEs, clinical laboratory data, vital signs, single 12-lead ECG parameters, ECHO/MUGA parameters, physical examinations, performance status (PS), and death. One of three possible scales of PE are collected per individual: Lansky, Karnofsky, or Eastern Cooperative Oncology Group (ECOG). The safety data during the treatment period will be evaluated, with treatment period as defined in section 4.1.3.

4.5.1. Dose Limiting Toxicities

DLTs are AEs where the question "Was the event due to a Dose Limiting Toxicity (DLT)?" in the CRF is selected as "yes". Determination of a DLT will be made by the Investigator and the HMPL monitor as per definition given in section 4.2 of the protocol.

4.5.2. Adverse Events (AEs)

The severity of all AEs will be graded by investigator according to National Cancer Institute (NCI) CTCAE version 5.0, and the AE, from verbatim text to Preferred Term (PT) and System Organ Class (SOC), will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be collected throughout the study, from informed consent until 30+7 days after the last dose of study drug.

Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study drug and no later than 30 + 7 days after the date of last study drug administration. After this period, treatment-related serious AEs (SAEs) will also be considered as TEAEs. AEs with an unknown/not reported onset date will also be considered as TEAEs.

Other AE variables from CRF include, but are not limited to, drug-related AEs, action taken, outcome, seriousness, AE leading to study withdrawal.

Dose Delays, Dose Interruptions, Dose Reductions, and Treatment Discontinuation Due to AE

For surufatinib, dose interruptions, dose reductions and treatment discontinuation (due to AE) information will be taken from the "Adverse Events" Case Report Form (CRF) page, question "Action Taken with Surufatinib".

For gemcitabine, dose delays, dose interruptions, dose reductions and treatment discontinuation (due to AE) will also be taken from the "Adverse Events" CRF page, question "Action Taken with Gemcitabine".

AEs of Special Interest (AESI)

AEs of special interest (AESI), serious or non-serious, will be identified based on the PT list outlined in Appendix 1. The AESIs include 4 categories:

- Hepatic disorders
- Hypertension
- Hemorrhage
- Acute renal failure

4.5.3. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 3 will be measured.

Table 3 Laboratory Assessment

Lab Category	Lab tests
Hematology	Hematocrit, hemoglobin, Red Blood Cells (RBC), platelet count, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), Mean Corpuscular Haemoglobin (MCH), white blood cell count (total), absolute neutrophil count (ANC), neutrophil %, absolute lymphocyte count, lymphocyte %, absolute monocyte count, monocyte %, absolute eosinophils count, eosinophils %, absolute basophils count, basophils %
Chemistry	Sodium, potassium, chloride, bicarbonate, calcium total, calcium corrected, calcium ionized, magnesium, phosphorus/phosphates, glucose, creatinine, total bilirubin, direct bilirubin, Alkaline Phosphatase (ALP), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Blood Urea Nitrogen (BUN), urea, total protein, albumin
Coagulation	International Normalized Ratio (INR), Prothrombin Time (PrT), and Activated Partial Thromboplastin Time (aPTT)
Thyroid Function	Serum free thyroxine (T4) and thyroid stimulating hormone (TSH).
Urinalysis	pH, glucose, protein, blood (microscopic for white blood cells and red blood cell count)
Other test	Pregnancy Test

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

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

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 (LLoQ), or "> X", i.e., above the upper limit of quantification (ULoQ), 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, Version 5.0 or higher. Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade worsening from the baseline assessment is defined as treatment emergent. Any

parameter for which CTCAE toxicity grades are not defined, 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.

- AST or ALT ≥ 3x Upper Limit of Normal (ULN) and ≤ 5x ULN
- AST or ALT ≥ 5x ULN
- Total bilirubin elevations ≥ 2x ULN
- Potential drug-induced liver injury (DILI): (AST or ALT ≥ 3x ULN) and (total bilirubin ≥ 2x ULN)
- Hy's Law criteria: (AST or ALT ≥ 3x ULN) and (total bilirubin ≥ 2x ULN) and (ALP < 2x ULN)

4.5.4. Electrocardiogram (ECG)

ECG parameters include heart rate (bpm), PR interval (msec), RR interval (msec), QT interval (msec), Corrected QT interval by Fridericia (QTcF) (msec) and QRS interval (msec) from the "Triplicate 12-lead ECG" CRF page.

ECGs will be performed in triplicate at screening or if a single read has a QTcF ≥ 480 msec, and whenever feasible. If more than one ECG is performed at a visit, the triplicate ECGs will be taken approximately 2 minutes apart. The combined values for the quantitative parameters from the ECGs will be averaged to provide a single value for each time point. The average will be used for statistical summaries, but each individual result will be presented separately in listings.

Clinically significant ECG findings will be identified from the CRF, page "Triplicate 12-lead ECG" using the "Clinical Significant" question.

4.5.5. Vital Signs

Vital signs include systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), heart rate (bpm), height (cm), weight (kg), respiratory rate (breaths/min) and body temperature (°C).

Blood pressure (BP) assessments will be performed in triplicate at screening and in triplicate at later timepoints if BP was abnormal at screening. The combined systolic/diastolic blood pressure values from the available measurements will be averaged to provide a single value for each time point. The average will be used for statistical summaries but each of the individual results will be presented separately in listings.

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

Additionally, the minimum and maximum values for each subject over the entire treatment period for each vital sign parameter will also be derived. For these minimum and maximum values, change from baseline will be derived. The potentially clinically significant findings of vital signs, based on individual readings rather than average values, will also be defined based on criteria defined in Table 4.

Table 4 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value
SBP (mmHg), DBP (mmHg), Heart rate (bpm)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40

4.5.6. Performance Status

PS will be collected for each subject at screening and during the treatment period (i.e., typically Day 1 of a Cycle). In addition to the collected PS score during a Cycle, the maximum post-baseline value for a subject will be derived; both scheduled and unscheduled assessments will be used to identify the maximum post-baseline values.

4.5.7. Echocardiogram

Echocardiograms are to be performed at Screening, and at the 30-day safety follow-up visit. Assessment parameters include left ventricular ejection fraction and overall interpretation of cardiac function. MUGAs are permitted if echocardiograms cannot be performed.

4.5.8. Physical Examination

The results on physical examination (PE) will not be tabulated but abnormal findings in PE will be reported as AEs. PE abnormalities will be presented in a listing.

4.5.9. Knee X-Ray/MRI

A by-subjects listing of knee X-Ray/MRIs data will be provided.

4.6. Other Endpoints

4.6.1. PK Endpoints

Evaluation on PK will be performed on the PK analysis set. Detailed analyses will be described in a separate analysis plan.

4.6.2. Taste and Palatability

Data for the evaluation of taste of surufatinib oral suspension will be summarized by Day 1 and Day 8 visit, on a scale of 1 (very bad) through 5 (very nice).

5. ANALYSIS METHODS

5.1. General Principles

5.1.1. General Methodology

In general, all variables will be summarized overall and by dose level.

Summaries will use descriptive statistics (continuous data), contingency tables (categorical data) and graphs as appropriate. Continuous variables will be summarized by descriptive statistics number of subjects (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).

For continuous data, unless otherwise specified, the mean will be presented to 2 more decimal places than the original values, median, Q1, and Q3 will be presented with 1 more decimal place than the original values, and standard deviation and standard error (SE) will be reported with 3 more decimal places than the original values. The minimum and maximum should report the same significant digits as the original values. 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. Individual data will be presented in subject listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e., ICH-E3, will be used for all tables and listings.

All summary tables, listings, and figures (TLF) will be presented by dose level as defined in Table 5.

Table 5 Treatment Display in TLFs

Dose Level	Treatment Description in Data Display
1	Surufatinib (120 mg/m^2) + gemcitabine
2	Surufatinib (160 mg/m^2) + gemcitabine
3	Surufatinib (200 mg/m^2) + gemcitabine
Overall	All Subjects

5.1.2. Handling Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing - no missing imputation will be performed. Safety analyses will be conducted on the OC data only. Partial dates will not be possible for death or tumor assessments.

Imputation of missing AE and concomitant medication onset and stop dates will be used to determine the prior/concomitant status of each AE and each medication. The specific imputation rules are provided below, refer to Section 5.1.2.1 for the method of imputation of missing AE onset and stop dates, Section 5.1.2.2. for the method of imputation of missing concomitant onset and stop dates. However, the listings will show the dates as reported.

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

5.1.2.1. Adverse Events 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 partial 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 subjects who are known to be dead at end of study or cut off date, then 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 subjects 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

No analysis visit windowing will be performed for this study. Any visit-based summaries, or listings where visit is provided will use the visit directly from the CRF assigned visit information.

5.1.4. Adjustment of Covariates

No adjustments for covariates will be made in this study.

5.2. Analysis Methods

5.2.1. Subject Disposition

Number of participants screened for the study will be provided for the following:

- Number of subjects who signed the informed consent
- Number of screen failures
- Primary reason for screen failure
- Number of subjects who do not receive study drug
- Number and percentage of subjects who received study drug
- Number and percentage of subjects who discontinued study drug(s)

- Subjects still on treatment
- Primary reason for study drug discontinuation
- Number of subjects going into Survival follow-up
- Number and percentage of subjects who discontinue the study
- Primary reason for study discontinuation

For enrolled subjects (non-screen failures), the number of subjects included in and excluded from each of the analysis sets will be summarized, along with reasons for exclusion from the analysis sets. A listing will also be presented.

5.2.2. Protocol Deviation

A listing of all protocol deviations will be provided.

5.2.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be presented for the Safety Analysis Set. Continuous demographic variables: age, height, weight, body surface area and body mass index will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). For all the other categorical variables, results will be presented as number and percentage of subjects. A listing will also be provided.

The following demographic and baseline characteristics will be reported for this study:

- Age (years) = (date of informed consent-date of birth+1)/365.25
- Gender
- Race
- Ethnicity
- Weight at Baseline (kg)
- Height at Baseline (cm)
- Body Surface Area (BSA) at Baseline (m^2)
- Body Mass Index (BMI) at Baseline (kg/m^2) = weight(kg)/(height(m))^2
- PS at Baseline

5.2.4. Disease History

Prior cancer diagnoses are defined as those received prior to the administration of study drug and are recorded in CRF page “Oncology History”. Safety Analysis Set will be used and results will be presented in a listing.

5.2.5. Medical History

The conditions, diseases, and therapies from the “Medical History” CRF page are those non-cancer related conditions, diseases and therapies that stopped prior to the study entry. Medical

history will be coded to SOC and PT using MedDRA central coding dictionary. The version of MedDRA to be used is 25.1.

A listing containing medical history by participants will be provided.

5.2.6. Prior Anti-cancer Medication/Radiotherapy/Procedure or Surgery (including subsequent)

Prior anti-cancer medication, radiotherapy, and procedure or surgery, as well as subsequent procedure or surgery will be summarized and listed.

5.2.6.1. Prior Anti-cancer Medication

Prior anti-cancer medications are defined as those taken by the subject prior to the administration of study drug and are recorded in CRF page "Previous cancer therapy".

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) available at the time of analysis.

The prior anti-cancer medications will be summarized by presenting the number and percentage of subjects by PT and ATC. Subjects 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 and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

In addition, the Best Overall Response (BOR) and reason for treatment discontinuation will be presented descriptively for prior anti-cancer medications.

All prior anti-cancer medications will also be presented in a subject listing.

5.2.6.2. Prior Anti-cancer Radiotherapy

Prior anti-cancer radiotherapy is defined as those taken by the subject prior to the administration of study drug and are recorded in CRF page "Radiotherapy History".

All prior anti-cancer radiotherapy, including BOR will be presented in subject listing.

5.2.6.3. Prior and Subsequent Procedure or Surgery

Prior procedures or surgeries are defined as those taken by the subject prior to the administration of study drug and are recorded in CRF page "Procedure/Surgical History". Subsequent procedure or surgery are defined as those taken by the subject after the discontinuation of the study drug and are recorded in CRF page "Related Procedures/Surgeries".

Prior and subsequent procedures and surgeries will be coded using MedDRA 25.1.

The prior procedures or surgeries will be summarized by presenting the number and percentage of subjects by SOC and PT. Subjects taking the same medication multiple times will only be counted once for that SOC and PT. Each summary will be ordered by descending order of incidence of SOC and PT within each SOC. If the frequencies tie, an alphabetic order will be applied. Similarly, the subsequent anti-cancer procedure or surgery will be summarized.

In addition, the purpose of procedure will be presented descriptively for prior procedure or surgery.

All prior and subsequent procedure or surgery will be presented in a subject listing.

5.2.7. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of subject drug(s) and are recorded in CRF page "Prior and Concomitant Medications".

Concomitant medications will be defined as medications that

1) started before the first dose of subject drug(s) and were continuing at the time of the first dose of subject drug(s), or

2) started on or after the date of the first dose of subject drug(s) up to 30 days + 7 days after the last treatment.

Concomitant medications will be coded to ATC therapeutic group and PT using the WHO-DD drug codes from the version of WHO-DD Version available at the time of analysis.

Prior and concomitant medications will be summarized and listed by drug and drug class.

5.2.8. Efficacy Analyses

All efficacy analyses will be performed on the All Treated Population.

5.2.8.1. Primary Efficacy Analyses

No primary efficacy endpoints are defined for this study.

5.2.8.2. Sensitivity Analysis for Primary Efficacy Endpoint

No sensitivity analysis for the primary efficacy endpoints is defined for this study.

5.2.8.3. Multiplicity Control

There will be no adjustments made for multiplicity.

5.2.8.4. Secondary Efficacy Analyses

Findings corresponding to efficacy analysis will be provided in listings. Tumor assessment will be presented for target lesions, non-target lesions, and new lesions. Additionally, sum of tumor diameter, and disease response will be listed as well.

5.2.9. Exposure of Study Drug

Drug exposure will be summarized and presented. Exposure of both surufatinib and gemcitabine will be summarized as follows:

- Number of cycles started as a continuous variable

  i.e., the number of cycles in which the subject took/received any dose of the study medication.

- Number of cycles started categorized as 1, 2, 3, 4, 5, and ≥ 6
- Total duration of exposure as a continuous variable
- Number of days with recorded dose
- Cumulative dose received (mg) as a continuous variable
- Dose intensity as a continuous variable
- Relative dose intensity as a continuous variable
- Relative dose intensity categorized as <50%; ⩾50 to <70%; ⩾70 to <90%; ⩾90 to <110%; ⩾ 110%
- Number and percent of subjects exposed for specific periods of time as ⩽ 1 day, 2 days to 1 week, >1 week and ⩽ 1 months, and >1 month and ⩽ 6 months

The number and percentage of subjects with any dose modification will be presented. Dose modifications will be further characterized by presenting the numbers and percentages of subjects with any dose interruption, dose delay, dose reduction, and treatment discontinuation because of AEs. Reasons for dose modifications (adverse event or 'other') for each drug will be presented in a listing.

Details of study drug administration will be included in subject listings.

5.2.10. Safety Analyses

Safety data will be summarized for the Safety Analysis Set.

5.2.10.1. Dose Limiting Toxicity (DLT)

The primary safety endpoint is the occurrence of DLTs in the DLT Evaluation Period (the first 35-day cycle). Data is recorded as in CRF page "Adverse Events".

The number and percentage of subjects with DLTs will be summarized based on the number of subjects in the DEAS by SOC and PT.

By-subject listing of DLTs will also be presented.

5.2.10.2. Adverse Events

Only those AEs that are treatment emergent will be included in summary tables as recorded in CRF page "Adverse Events".

All AEs, treatment-emergent or otherwise, will be presented in subject data listings. The number and frequency of subjects experiencing AEs will be summarized according to SOC and PT. If a subject 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 following safety summaries will be produced:

- Overview of TEAEs (summary of the following categories, but only at the subject level, not by SOC and PT)
- Summary of DLTs by SOC and PT
- Summary of TEAEs, including highest severity and relationship to each study drug (surufatinib and gemcitabine), by SOC and PT
- Summary of serious TEAEs, by SOC and PT
- Summary of TEAEs leading to dose interruption, dose reduction, or termination of study drug, by SOC and PT

The above summaries (excluding summaries by relationship to study drug) will be repeated for TEAEs related to study drug.

Toxicities for clinical labs will be characterized according to CTCAE, Version 5.0 where possible. Any occurrence of grade 3 or grade 4 during the overall treatment period will be summarized by SOC and PT.

5.2.10.3. Death

Number of deaths and primary cause of death will be summarized, and details of deaths will be presented in a data listing and are recorded in CRF page "Death Details".

5.2.10.4. Laboratory Evaluations

For hematology, clinical chemistry and coagulation laboratory data, the observed values and change from baseline will be summarized by visit and for minimum and maximum post-baseline values using descriptive statistics. Data is recorded as in CRF Laboratory pages.

Listings of all laboratory data including urinalysis, and pregnancy will be provided. Potentially clinically significant Liver Enzyme (ALT, AST, Bilirubin) will also be summarized.

5.2.10.5. Electrocardiogram

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline. A listing of all ECG data will be provided. Data is recorded as in CRF page "Triplicate 12-lead ECG".

The criteria for potentially clinically significant findings are defined in Table 5. The frequency and percentage of subjects with any potentially clinically significant findings during the induction treatment period will be presented. The supportive data will be provided in subject data listings.

Moreover, the minimum, and maximum, and their corresponding change from baseline ECG parameter values will be summarized descriptively overall treatment period.

5.2.10.6. Vital Signs

For vital sign parameters (SBP, DBP, Heart Rate (and Pulse), Respiratory Rate and Temperature) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period. Data is recorded as in CRF page "Vital Signs".

Additionally, the frequency and percentage of subjects with any potentially clinically significant findings (defined in Table 4) during the overall treatment period will be presented for SBP, DBP, and Heart Rate. A listing of all vital signs data will be provided.

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

5.2.10.7. Performance Status

Descriptive statistics will be presented for PS score for the observed values and change from baseline. Negative change scores indicate an improvement, and positive scores indicate a decline in performance. Data is recorded as in CRF page "Karnofsky / Lansky / ECOG Performance Status".

A listing of PS score for all subjects will be provided.

5.2.10.8. Echocardiogram

Descriptive statistics for Echocardiogram/MUGA parameters will be summarized by visit. A by-subjects listing of Echocardiogram/MUGA values at each time point will be listed. Data is recorded as in CRF page "ECHO or MUGA Scan".

5.2.10.9. Physical Examination

A listing of PE data for all subjects will be provided (where available). Data is recorded as in CRF page "Physical Examination".

5.3. Subgroup Analyses

No subgroup analyses will be performed for this study.

5.4. Other Analyses

5.4.1. Taste and Palatability

Data for the evaluation of taste of surufatinib oral suspension on a scale of 1 (very bad) through 5 (very nice) will be summarized by visit using frequencies and percentages. See Appendix 9 of the Protocol for details. A listing of the evaluation of taste data for all subjects will also be provided.

6. PLANNED ANALYSIS

6.1. Safety Review Committee

The Safety Review Committee (SRC) will be established under a charter to conduct safety data reviews. The SRC will be comprised of sponsor and Contract Research Organization (CRO) medical team members and the site investigators. The SRC will determine whether it is safe to continue to the next predefined dose level, stay at the currently assigned dose level, or whether the dose should be de-escalated to a lower dose level and finally to determine the MTD/RP2D.

6.2. 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 the analysis of the last cohort.

7. CHANGE FROM THE PROTOCOL

Proteinuria and Thyroid dysfunction are mentioned in Section 8.5 AESI of protocol, but they were removed as AESI in this SAP, since they are already considered fully characterized, and there are no new or additional mitigation activities. Some summaries will be dropped if there is not a sufficient amount of data to present, but rather present the data in listings. Additionally, some efficacy may not be possible to derive depending on the data available at the time of Database Lock.

REFERENCE

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982; 38:29-41.

Clopper, C.J. and Pearson, E.S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 1934;26:404-413.

APPENDIX 1 PT LIST FOR AESI

AESI should be extracted from MedDRA 25.1 by referring to the standardized queries in the table below. The Standardized MedDRA Queries (SMQ) code should only consider a 'narrow' scope, i.e., category A terms.

AESI term	Searching strategy
Hepatic disorders	20000009 Cholestasis and jaundice of hepatic origin (SMQ) 20000013 Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) 20000010 Hepatitis, non-infectious (SMQ) 20000008 Liver related investigations, signs and symptoms (SMQ)
Hypertension	20000147 Hypertension (SMQ)
Haemorrhages	20000039 Haemorrhage terms (excl laboratory terms) (SMQ)
Acute renal failure	20000003 Acute renal failure (SMQ)

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Certificate Of Completion

Envelope Id: PPD
Subject: Complete with DocuSign: 2020-012-GLOB2_SAP_V1.0.docx
Project Code (Enter 0 for non-billable projects): PPD
IQVIA ID (Login ID): PPD
Business Unit:
DSSR
Source Envelope:
Document Pages: 38
Certificate Pages: 6
AutoNav: Enabled
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Signatures: 4
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Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/26/2023 8:04:43 AM Viewed: 5/30/2023 3:43:06 AM Signed: 5/30/2023 3:44:14 AM
Electronic Record and Signature Disclosure: Accepted: 12/22/2022 10:25:03 AM ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/26/2023 8:04:42 AM Viewed: 5/26/2023 10:28:21 AM Signed: 5/26/2023 10:30:05 AM
Electronic Record and Signature Disclosure: Accepted: 1/25/2023 8:13:49 AM ID: PPD		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/26/2023 7:21:36 AM Viewed: 5/26/2023 8:27:11 AM Signed: 5/26/2023 8:28:42 AM
Electronic Record and Signature Disclosure: Accepted: 5/26/2023 8:27:11 AM ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/26/2023 7:37:33 AM Viewed: 5/29/2023 6:52:37 PM Signed: 5/29/2023 6:53:50 PM
Electronic Record and Signature Disclosure: Accepted: 5/29/2023 6:52:37 PM ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 5/26/2023 8:04:43 AM Viewed: 5/30/2023 8:09:08 AM
PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 5/26/2023 8:04:43 AM Resent: 5/30/2023 3:44:19 AM Viewed: 5/26/2023 8:15:43 AM

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/26/2023 7:21:36 AM
Envelope Updated	Security Checked	5/26/2023 7:37:33 AM
Envelope Updated	Security Checked	5/26/2023 8:04:41 AM
Envelope Updated	Security Checked	5/26/2023 8:04:41 AM
Envelope Updated	Security Checked	5/26/2023 8:04:41 AM
Envelope Updated	Security Checked	5/26/2023 8:04:41 AM
Certified Delivered	Security Checked	5/29/2023 6:52:37 PM
Signing Complete	Security Checked	5/29/2023 6:53:50 PM
Completed	Security Checked	5/30/2023 3:44:14 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

CONSENT TO ELECTRONIC DELIVERY AND EXECUTION OF DOCUMENTS

From time to time, IQVIA (“we” or “us”) may provide you certain written contracts, notices, disclosures, authorizations, acknowledgements or other documents (collectively, the "Documents") electronically. Please read this consent form carefully. It explains the terms and conditions under which such Documents are provided by us and executed by you electronically through your DocuSign, Inc. (“DocuSign”) user account. If you consent to the delivery and execution of such Documents electronically, please click the "I Agree" button.

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If you withhold consent to electronic delivery or execution, or withdraw your consent at a later date, all Documents will be sent to your mailing address following our receipt of notice of such action. The following sections explain the consequences of withholding or withdrawing your consent to electronic delivery and execution of Documents, and also the procedures you must follow in order to effectuate delivery to your mailing address.

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By electing to only receive and execute Documents sent to your mailing address, we will not be able to carry out transactions or services as efficiently. For instance, some transactions or services require your express consent. We can perform these transaction or services only if we first receive an acknowledgement that indicates you received and consent to the Document related to the proposed transaction or service.

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ii. send us an e-mail to DocuSignSupport@IQVIA.com and in the body of such request you must state your e-mail, full name, US Postal Address, telephone number, and account number. No additional information is necessary.

Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically

To confirm you can access this information electronically and that you consent to receiving and executing Documents electronically on the terms and conditions described above, please let us know by clicking the "I Agree" button.

By clicking the "I Agree" button, you confirm that

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