STATISTICAL ANALYSIS PLAN

2015-012-00US01

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.2 (Dated 04NOV2022) for Protocol 2015-012-00US1 V7.0.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	25Feb2016	PPD	Not Applicable – First Version
0.2	17Mar2016	PPD	Updated per sponsor's comments. Details can be found in the track change version. Additionally, following updates performed based on email communication: 1. ECG part added 2. Baseline definition added ECG time-point consideration 3. Subject disposition table modified to include completion status of DLT observation window. 4. Note added to explain EoT visit tumor assessment will contribute to all efficacy endpoints
0.3	26Apr2016	PPD	According to sponsor's comments, updated RECIST related details regarding tumor response confirmation are added to the SAP. One additional update regarding 2 or more missing consecutive visits' impact on PFS. Added Lab parameters grading according to CTC-AE guideline.
0.4	30Sep2016	PPD	Update comments. Update TLF according to new CRF. Add descriptions in SAP for each TLF. Previously, some TLFs don't have corresponding description in SAP. Revise layout
0.5	24Nov2016	PPD	Update comments

			"Shift Table of Laboratory Grade from Baseline" is replaced by "Shift in Toxicity Grading from Baseline to Worst CTCAE Grade" Add figures for QTcF and QTcB Merge lesion listings Merge some laboratory listings Remove or merge some tables to control the number of TLFs
0.6	15Feb2017	PPD	Update comments Update table "TEAEs by Severity" to have severity presented under each SOC/PT Combine table for "overall response" and "ORR and DCR" Remove table for DoOR and PFS Update derivation for exposure in Section 14.1 to more general description as new formulation, 200mg, is used.
0.7	31JUL2017	PPD	Update while preparing dry run outputs 1. Drop ATC 2nd level as ATC coding is not used for the study. 2. Add baseline flags for data listings 3. Move(add) definition for response evaluable set to section 6 for clear understanding 4. Update section for ECG (external data) 5. Update/modify table shells, especially ECG and laboratory parameters.
0.8	13May2019	PPD	1. Updated study title. 2. Updated study primary objective and secondary objective. 3. Updated study design. 4. Updated definition of DLT evaluable patients. 5. Updated analysis population and protocol deviation.

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			6. Updated the total sample size in the dose escalation phase and dose expansion phases. 7. Updated the number of investigational centers. 8. Updated efficacy objectives and endpoints.
0.9	28MAY2019	PPD	Updated comments from Hutchison
1.0	28JUN2019	PPD	Updated comments from Hutchison
1.1	01JUN2020	PPD	1. Updated study title. 2. Updated primary and secondary objectives and endpoints description based on protocol version 6.0 (Amendment 10). 3. Updated the number of patients to be enrolled. 4. Added sarcoma analysis description. 5. Updated description for exploratory endpoints.
2.0	01JUL2020	PPD	1. Updated comments from Hutchison. 2. Updated Appendix 2 AESI list.
2.1	24AUG2020	PPD	1. Updated the definition of DLT evaluable patient per sponsor's note to file on 17Aug2020. 2. Added the definition of treatment-emergent adverse event (TEAE).
2.2	04NOV2022	PPD	1. Updated the Appendix 2 AESI list. 2. Updated the protocol version as 7.0 (Amendment 11) 3. Updated the MedDRA and WHO-DDE version 4. Updated descriptions based on the wording changes in protocol version 7.0 (Amendment 11) 5. Added additional analysis items for ECG in section 4.4 6. Updated section 16.1.2 for BOR and add unconfirmed CR and PR for BOR

TABLE OF CONTENTS

1. List of Abbreviations

Terms and Abbreviations	Definition
ACS	Abnormal, clinically significant
AE	Adverse event
ALT	Alanine aminotransaminase
ANCS	Abnormal, not clinically significant
aPTT	Activated partial thromboplastin time
AST	Aspartate amino transaminase
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
BTC	Biliary tract cancers
CA 19-9	Carbohydrate antigen 19-9
CCr	Creatinine clearance
CEA	Carcinoembryonic antigen
CgA	Chromogranin A
CI	Confidence interval
CR	Complete response
CRF	Case report form
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
DBL	Database Lock
DBP	Diastolic blood pressure
DCR	Disease control rate
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DoR	Duration of Response
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

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Terms and Abbreviations	Definition
ENR	All patients enrolled set
epNETs	Extrapancreatic neuroendocrine tumors
ICF	Informed consent form
INR	International nonproprietary ratio
LEVF	Left ventricular ejection fraction
LMS	Leiomyosarcoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NSE	Neuron-specific enolase
ORR	Overall response rate
OS	Overall survival
PD	Progression of disease
PFS	Progression-free survival
PK	pharmacokinetic
pNET	Pancreatic neuroendocrine tumors
PR	Partial response
RP2D	Recommended phase II dose
PT	Preferred term (MedDRA)
PVNS	Pigmented villonodular synovitis
QTc	QT interval corrected
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SBP	Systolic blood pressure
SCr	Serum creatinine

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Terms and Abbreviations	Definition
SD	Stable disease
SMQ	Standardized MedDRA queries
SOC	System organ class (MedDRA)
SRC	Safety review committee
STS	Soft tissue sarcoma
Surufatinib	International non-proprietary name assigned to sulfatinib by the World Health Organization
TSH	Thyroid stimulating hormone
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TTR	Time to response
UPS	Undifferentiated pleomorphic sarcoma
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 2015-012-00US1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 7.0 (amendment 11) dated 19Mar2021.
The pharmacokinetics analysis plan will not be included in this document.

3. STUDY OBJECTIVES

3.1. DOSE ESCALATION PHASE

3.1.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of surufatinib in patients with advanced solid tumors of any type, and to determine the maximum tolerable dose (MTD) and/or recommended phase II dose (RP2D).
Primary Endpoint: The incidence of Dose Limiting Toxicities (DLTs) in each cohort. DLT is defined in Section 6.3.

3.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the pharmacokinetic (PK) characteristics of multiple-dose surufatinib and to investigate the metabolite profile of surufatinib in the plasma of patients with solid tumors.
- To evaluate the anticancer activity of surufatinib in patients with advanced solid tumors of any type according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Secondary Endpoints

- PK parameters: refer to pharmacokinetics analysis plan for details. PK parameters are listed below:.
    - Maximum plasma concentration (C_{max})
    - Time to reach maximum concentration (T_{max})
    - Terminal half-life ($t_{1/2}$)
    - Area under the concentration-time curve in a selected time interval (AUC_{0-t})
    - Area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0-\infty}$)
    - Apparent clearance (CL/F)
    - Apparent volume of distribution (V_z/F)
    - Mean residence time (MRT)
    - Accumulation index based on AUC

- The objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and percentage change in tumor size from baseline according to RECIST Version 1.1.

3.2. Dose Expansion Phase

3.2.1. Primary Objective

The primary objective is to evaluate the anticancer activity of surufatinib at the recommended Phase 2 dose (RP2D) from the dose escalation phase, in patients with advanced biliary tract cancer (BTC), patients with advanced Pancreatic Neuroendocrine Tumors (pNETs), patients with locally advanced, unresectable, metastatic Extrapancreatic Neuroendocrine Tumors (epNETs), and patients with soft tissue sarcoma (STS) treated at a dose of 300 mg QD (ie, the MTD/RP2D was declared in Protocol Amendment 7). The RP2D in this trial is the same as the RP2D used in clinical trials in China.

Primary Endpoints

- Patients with BTC (Arm A): progression-free survival (PFS) at 16 weeks (according to RECIST V.1.1.)
- Patients with pNET (Arm B): PFS at 11months (according to RECIST V.1.1.)
- Patients with epNET (Arm C): PFS at 11months (according to RECIST V.1.1.)
- Patients with STS (Arm D): PFS at 4 months (according to RECIST V.1.1.)

3.2.2. Secondary Objectives

The secondary objectives are:

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

Secondary Endpoints:

- Pharmacokinetic parameters, which include but are not limited to, C_{max}, T_{max}, first-order rate constant K_{el}, AUC, $t_{1/2}$, CL/F, V_z/F, accumulation ratio, and dose proportionality between AUC and dose and C_{max} and dose.
- Safety, as assessed by:
  - The frequency and severity of adverse events
  - Physical examination findings
  - Vital signs

- Laboratory test results (ie, hematology, chemistry panel, and urinalysis)
- 12-lead electrocardiogram
- Echocardiogram

- ORR, DCR, time to response (TTR), DoR, and percentage change in tumor size from baseline defined according to RECIST V 1.1.

3.2.3. Exploratory Objective

The exploratory objectives are:

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

Exploratory Endpoint

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

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is an open-label, multi-center clinical trial of surufatinib taken orally once daily (QD), and it consists of 2 phases: a dose escalation phase in patients with advanced solid tumors of any type, and a dose expansion phase in patients with advanced BTC (Arm A), advanced pNETs (Arm B), advanced epNETs (Arm C), or STSs (Arm D) for whom standard therapy either does not exist or has proven to be ineffective or intolerable.
Approximately 95-150 patients will be enrolled in this 2-phase study: 35 patients in the dose escalation phase and approximately 115 patients in the dose expansion phase. The two phases will be conducted as described below.

4.1.1. Dose Escalation Phase

In this phase, a 3+3 design will be used. Enrollment of 35-40 patients was planned. As of Protocol Amendment 7, a total of 35 evaluable patients have been enrolled in the dose escalation phase. The trial was to evaluate 5 surufatinib dose levels at 50,100, 200, 300 and 400 mg on a QD dosing schedule.

The study conduct was to follow a 3+3 design, with the dose limiting toxicity (DLT) assessment window being Cycle 1, from Day 1 to Day 28. Detailed description of a 3+3 design can be found in protocol section 5.1.1.

In addition to the five dose levels, in the occasion where 2 or more DLTs were observed in the 6 evaluable patients at a given dose level, the dose escalation was to be halted. If this dose level is greater than or equal to 50% higher than the previous dose level, an intermediate dose level was to be evaluated for toxicity in the same manner as a 3+3 dose level. If the dose level was less than 50% higher than the previous dose level, additional patients were to be enrolled at the previous dose level, if necessary, to form a dose cohort of minimum 6 evaluable patients. The MTD is the highest dose reached with no more than 1 DLT among 6 evaluable patients.

Any patient who was considered non-evaluable for DLT as defined in protocol section 5.1.1 'Dose escalation phase' was to be replaced by an additional patient at that same dose level.

Safety monitoring and evaluation for dose escalation will be carried out by a Safety Review Committee (SRC) upon completion of the DLT observation period of each dose level.

Patients who have completed the DLT observation window (Cycle 1, day 1-28) and were deemed to be benefiting from surufatinib treatment could have been permitted, at the investigator's discretion, to continue with surufatinib treatment until disease progression, death, intolerable toxicity, pregnancy, or loss of benefit from the study drug. Intra-patient dose escalation to a higher dose that had been cleared was allowed if the sponsor and investigator both agreed.

The MTD/RP2D of surufatinib has been declared at 300 mg QD (Protocol Amendment 7).

4.1.2. Dose Expansion Phase

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

Approximately 115 additional patients will be enrolled into the 4 open-label treatment arms during this phase: at least 30 patients with advanced BTC that have progressed on standard first-line chemotherapy will be assigned to Arm A, at least 15 patients with advanced pNET that have progressed on either everolimus, sunitinib, or both will be assigned to Arm B, and at least 15 patients with advanced epNETs that have progressed on everolimus will be

assigned to Arm C, and at least 55 patients with STS will be assigned to Arm D.

The safety of all enrolled patients will be closely monitored from the time of the initial dose of investigational treatment until 30 days after the last treatment dose. Any SAEs that occur after the ICF is signed, but before the first dose of study drug is taken, should also be reported. All AEs will be graded in accordance with the NCI CTCAE v. 4.03.

Patients will receive surufatinib continuously by 28-day treatment cycles until disease progression (according to RECIST Version 1.1), death, intolerable toxicity, or at investigator's discretion that the patient can no longer benefit from the study treatment. Tumor assessments will be conducted according to RECIST v. 1.1 criteria at screening, Cycle 2 Day 1 and every 8 (±1) weeks thereafter. Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response/progression and the confirmation assessment date.

4.2. SAMPLE SIZE

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

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

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

As per Protocol Amendment 8, 45 patients with STS (10 patients with Leiomyosarcoma (LMS), 10 patients with Undifferentiated pleomorphic sarcoma (UPS), 10 patients with epithelioid sarcoma, 10 patients with angiosarcoma, 10 patients with synovial sarcoma, and 5 patients with Pigmented villonodular synovitis (PVNS)) are planned to be

enrolled.

As per Protocol Amendment 10, an additional 10 patients will be added to the arm D (STS) for a total enrolment of 55 patients.
Additional details on sample size can be found in Protocol Section 10.1.

4.3. SCHEDULE OF EVENTS

Schedule of events can be found in Protocol Appendix 1 - Study Flowcharts.

4.4. CHANGES TO ANALYSIS FROM PROTOCOL

Additional Analysis for ECG will be included the evaluation of change from baseline in QTcF (ΔQTcF) intervals and the relationship between QT/QTc and RR intervals at baseline will be evaluated graphically. Refer to the section 17.3.3 and 17.3.4 for the details.

5. PLANNED ANALYSES

The following formal analyses are planned for the study:

5.1. SAFETY REVIEW COMMITTEE (SRC)

Safety monitoring and evaluation for dose escalation will be carried out by a Safety Review Committee (SRC) upon completion of the DLT observation period of each cohort.
The SRC is chaired by the Sponsor's Clinical Program Leader of the surufatinib program, and members will include the principal investigators (PIs), the Sponsor's PK scientist, medical monitor, and safety scientist, and the CRO's medical monitor. Dose escalation decisions are based on safety and PK data from this ongoing trial, as well as consideration of safety and PK data at comparable drug exposures from patients in previously conducted clinical trials in China.
For the dose expansion phase of the trial, a separate, specific SRC will be established to ensure the safety of all patients treated with study drug in the STS cohort (STS-SCR). Review of available safety laboratories, adverse events, and any other pertinent data available will be reviewed after the first 4 patients in each sarcoma cohort have completed at least 1 cycle of treatment. The recommendations of the STS-SRC will be based on the members'

clinical assessment of the cumulative safety data provided for review. The SRC will not be charged with the application of formal statistical stopping rules for safety.

5.2. Interim Analysis

An informal interim analysis was performed using data cut-off date of 30JUN2020. This SAP covers the analyses for efficacy and safety based on the data cut-off for the interim analysis. The interim analysis was performed using cleaned eCRF data collected until data cut-off date. In addition, SAEs were be summarized based on all patients recruited into study on or before data cut-off date. All SAE data to be included in the interim analysis was to be cleaned.
Considering the goal of this interim analysis was to support regulatory submission, the efficacy analysis for this interim analysis was limited to pNET and epNET cohorts while the safety was cover all patients enrolled on the trial as of the planned cut-off date.

In addition, the overall survival analysis for BTC and STS cohorts were not included in this interim analysis. The tumor assessment after the end of treatment was not applied to this interim analysis as well. The tumor assessment data after the end of treatment was cut-off for this interim analysis.

5.3. Snap Shot Analysis

A snap shot analysis was performed using data at cut-off date of 14Jun2019.
All summaries of safety and efficacy data were presented by assigned dose level in escalation phase, and disease type which pooled the patients who enrolled in the dose expansion phase and patients of the same tumor type (BTC, pNET, epNET) at the RP2D dose level in the dose escalation phase.

5.4. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics by following sponsor's authorization of this SAP and final Database Lock (DBL) for this study.

6. Analysis Sets and Protocol Deviations

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the

DBL for the final analysis of the study.

All summaries will be presented by assigned dose level in escalation phase, and by disease type which will pool the patients who enrolled in the dose expansion phase and patients of the same tumor type (BTC, pNET, epNET, STS) at the RP2D dose level in the dose escalation phase.

All patients will be presented according to their initial assigned dose level regardless of any dose adjustment during study conduct.

6.1. ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled set (ENR) will include all patients who signed informed consent form (ICF) for this study.

6.2. SAFETY ANALYSIS SET (SAS) – (ALL TREATED POPULATION)

This analysis set includes all patients who have received at least one dose of surufatinib. Safety data will be evaluated based on this analysis set outcome. Patients in the SAS will be analyzed by their actual dose initially received. If patients have dose reduction during the study, all data will be summarized/ analyzed based on the initial dose of study medication received.

All safety analyses except for DLT summaries will be based on the SAS. Efficacy endpoints PFS and OS (OS applies to BTC and STS cohorts only) will be analyzed based on this analysis set.

6.3. DOSING LIMITING TOXICITY (DLT) EVALUABLE SET

The DLT set comprises all SAS patients who are evaluable for DLT assessment. DLT evaluable patients can be identified via answers to the question "DLT evaluable patients" on CRF "DLT Assessment" page.

DLT set (and summaries of DLTs) only applies to dose escalation phase patients.

A DLT evaluable patient has to meet the following criteria, which will not be confirmed via programming:

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

6.4. EFFICACY ANALYSIS SET (EAS)

This analysis set includes all patients who have received at least one dose of surufatinib and have had at least one

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post-baseline tumor assessment.
All efficacy endpoints will be analyzed based on this analysis set except for analysis of PFS and OS, which will be analyzed based on the SAS. The OS analysis will be performed for the BTC and STS cohorts only.

6.5. PROTOCOL DEVIATION

Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment will be listed for SAS.
The study team will discuss, identify and classify the important eligibility criteria or post-entry deviations from operational team monitor reports before final data base lock.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE, REFERENCE END DATE AND STUDY DAY

Reference start date is defined as the date of the first administration of study medication. Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study medication.
Reference end date will be defined as the day of the last administration of study medication within the patient's last treatment cycle.
Study day (Day 1 is the day of the first administration of study medication) will appear in each listing where an assessment date or event date appears.
If the date of the event is on or after the reference start date then:

Study day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date then:

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, Study day, and any corresponding durations will be presented based on the imputations specified in Section 8.2.
In addition to the overall reference start and end date, the start and end of treatment within each cycle will be identified based on the data collected on the eCRF form and will be used when assigning events or assessments to a particular treatment cycle.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In case where the last non-missing measurement and the reference start date coincide, that measurement will be considered as baseline, but AEs and medications commencing on the reference start date will be considered post-baseline, that is, treatment-emergent or concomitant ("worst case" approach).

7.3. END OF TREATMENT

End of treatment reasons and treatment discontinuation date are captured on CRF page "End of Treatment". Patients who complete or prematurely discontinue the study medication need to return to the study site for a follow-up within 30±7 days after the last dose of surufatinib. Measurements obtained during this visit will be considered as the 'End of Treatment' assessment.

7.3.1. End of Study

A patient is considered to have completed the study once he or she has completed the last visit, or the last scheduled procedure as outlined in the Schedule of Events in Protocol Appendix 1.

7.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. Unscheduled measurements will contribute to worst-case summaries.
In the case of a retest (visit-specific unscheduled visit number assigned), the latest non-missing measurement among all scheduled and unscheduled measurements for that visit will be used for by-visit summaries.
Early termination data of patients prematurely discontinued from study medication will be presented together with the end of treatment assessment for study medication completers.
By-parient listings will include scheduled, unscheduled, retest, and early discontinuation data.

7.5. VISIT WINDOWS CONVENTIONS

Unless otherwise indicated, in the treatment period, during Cycle 1 and Cycle 2, the visit window will be ±1 day. From Cycle 3 onward, the visit window will be ±3 days. In the follow-up visit, the visit window is ±7 days. All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit

denoted on the Case Report Form (CRF).

7.6. Statistical Tests

There is no formal statistical hypothesis testing in this study. The confidence intervals will be 95%, unless otherwise specified in the description of the analyses.

7.7. Common Calculations

For quantitative measurements, change from Baseline will be calculated as:

- Change from baseline = Test Value at Visit X – Baseline Value
- Percentage change from baseline = [(Test Value at Visit X – Baseline Value) / Baseline Value] * 100

The time from Date of Event A to Date of Event B (years) is calculated as:

- (Date of Event B - Date of Event A + 1)/365.25.

The time from Date of Event A to Date of Event B (months) is calculated as:

- (Date of Event B - Date of Event A + 1)/30.4375.

7.8. Software Version

All analyses will be conducted using SAS® Version 9.4 or higher.

8. Statistical Considerations

8.1. Multicenter Studies

This study will be conducted by multiple investigators at approximately 8-15 sites. No adjustment in aspect of site effect will be performed. Data from all centers will be pooled prior to analysis.

8.2. Missing data

Generally, the missing efficacy and safety data will not be imputed except for the critical missing and incomplete dates which will be handled as described in this section.

For partially missing dates, the Age (Years), Duration of malignancy (years) and Duration of metastasis (years) will be based on imputed values. For all calculation elements, if the date part is missing while year and month present, 15th of the month will be used for imputation. If both date and month part are missing while year presents, July 1st will be used for imputation.
When no imaging/measurement was done at all at a particular time point, the patient is not evaluable at that time-point. If only a subset of lesion measurements were made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.
For ORR and DCR calculation, patients with missing responses will be considered non-responders, thus contribute only to the denominator.

Initial Diagnosis Date
If year and month are known but the day is unknown, day will be imputed as 15. If only year is known, month and day will be imputed to July 1st. If the diagnosis date is completely missing or the year part is unknown, the diagnosis date will not be imputed. The imputed date will be compared to reference start date. If it is later than the reference start date, the incomplete date will be imputed as the reference start date.

Adverse Events Date
For adverse event, incomplete start dates and/or stop dates will be imputed. Start date will be imputed first when the start date and stop date are both incomplete for a patient. If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date, assuming year is available.

Missing or incomplete start date
In case the start date of an AE is completely missing, or year part is unknown, the start date of AE will not be imputed.
In case the start date of AE is in the same year as reference start date (when only year is recorded), or the start date is in the same month and year (if only the day is missing) as the reference start date, then the start date of the AE will be imputed by the minimum of the reference start date and the AE resolution date. In all other cases the available year and month are not equal to the corresponding year and month of the reference start date or the available year is not equal to the corresponding year of the reference start date, the missing start day will be imputed by the 1st day of the month and the missing start month will be replaced by January.
In the case only the month is missing while year and day are recorded, then both day and month will be considered as missing. If the year part of start date of an AE occurs in the same year as reference start date, then the start date of

the AE will be imputed by the minimum of the reference start date and the AE resolution date. If an AE is observed on different year of the reference start date, January 1st will be used to complete the start date of the AE..

Missing or incomplete end date

Incomplete end dates will be imputed to the last possible date. In the case the year and month are known, AE end date will be imputed as the last day of the month. In the case if only the year is known, AE end date will be imputed as the December 31st of the year. If the imputed AE end date is after the death date, then the date of the death will be imputed as the AE end date. If the end date is completely missing or the year part is unknown, the end date will not be imputed. If the imputed end date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using start date.

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

Medications/Procedures Date

There will be no imputation for complete missing start date or end date of medications/procedures.

Impute incomplete start date as earliest possible date, i.e. first day of month if day unknown or 1st January if day and month are unknown.

Impute end date as latest possible date, i.e. last day of month if day unknown or 31st December if day and month are unknown, if not resulting in a date later than the date of patient's death. In the latter case the date of the death will be used to impute the incomplete stop date.

Above rules will be applied for prior/ concomitant medications/ procedures and prior oncology therapies.

Duration will not be calculated in case either the start date or end date is completely missing, but it will be calculated based on the imputed start/ end date if either the start date or end date is incomplete.

Last Tumor Assessment Date

If year and month are known but the day is unknown, day will be imputed as the first day of the month. If only year is known or a date is complete missing, the date will not be imputed. If the date of death is complete, the imputed date will be compared with the death date, the earlier date will be used for the date of last tumor assessment.

Subsequent Anti-tumor Therapy Date

When an incomplete subsequent anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of subsequent anti-tumor therapy relative to the reference end date and the date of disease progression (if happened). Generally, records of subsequent therapy should all start after EOT/ PD.

	Condition	Reference end date (D1)	Date of earliest disease progression (D2)	Imputed start date for anti-tumor therapy
Known part or clinical evidence to show precedence relationship	1	Before	Before	Minimum (D1, D2) -1
	2	After	After	Maximum (D1, D2) +1
	3	Before	After	D2+1
	4	After	Before	D2-1
	5	No or not applicable	Before	D2-1
	6	No or not applicable	After or others	D2+1
	7	Before	No or not applicable	D1-1
	8	After or others	No or not applicable	D1+1

For example, condition 3, if the known part of the anti-tumor therapy indication that the anti-tumor therapy starts before reference end date but after date of disease progression, then incomplete start date of anti-tumor therapy will be imputed as one day posterior to date of disease progression.

If the imputed start date is later than date of death, then the imputed start date will be further imputed to date of death.

Death Date

If year and month of death date are known but the day is unknown, day will be imputed as 15. If only year is known, month and day will be imputed to July 1st. There are two exceptions of the below two scenarios:

- If the imputed death date is prior to the last known alive date, then the death date will be imputed to the next day of last known alive date.
- If the imputed death date is after end of study date with the year and month are the same as end of study date, then the death date will be imputed to the date of end of study.

9. OUTPUT PRESENTATIONS

Appendix 1 details the conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

Continuous variables will be summarized using descriptive statistics, i.e., number of patients(n), mean, median, standard deviation (SD), and ranges (minimum, maximum).

Qualitative variables will be summarized by count(s) and percentages (%). Unless otherwise stated, the calculation of percentages will be based on the total number of included in the relevant analysis set.

10. DISPOSITION AND WITHDRAWALS

All patients who signed ICF will be involved in the analysis of disposition and withdrawals being described in this section for this study.

The number of patients who signed ICF for the study, screen failed patients along with the reason for screen failure, patients who passed screening but withdraw before the first dose of study treatment will also be summarized.

The number of patients included/excluded from each analysis set as well as the reason(s) for exclusion (as described in Section 6) will also be summarized by dose level in escalation phase and by disease cohort in dose expansion phase. A corresponding by-patient listing will also be provided.

The number and percentage of patients who completed, discontinued from study medication and reasons for study medication discontinuation will be presented for each dose level, by disease cohort, and overall for the SAS.

Reasons for discontinuation of study medication will be presented as recorded on the CRF page "End of Treatment".

The number and percentage of patients who completed, discontinued from study and reasons for study discontinuation will be presented for each dose level, disease cohort, and overall for the SAS. Reasons for study discontinuation will be presented as recorded on the CRF page "End of Study".

A patient listing will be generated to include site, patient number, informed consent information (date), screening date, first and last study medication dosing date, duration of study medication, study medication discontinuation information (date and reason), and end of study information (date, status, and reason for discontinuation if applicable) will be provided. Besides, the violation of inclusion/exclusion criteria will also be listed for ENR analysis set.

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

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by dose cohort in dose escalation phase and by disease cohort in dose expansion phase for the SAS. Data listing will also be provided.

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

- Age (years) - Calculated relative to date of ICF
- Age group
  - <65 years
  - ≥65 years
- Gender

- Male
- Female
  - With Child Bearing Potential
  - Without Child Bearing Potential
  - Undifferentiated
- Unknown

- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islanders
  - White
  - Other

- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
  - Unknown

- Baseline Weight (kg)
- Baseline Height (m)
- Baseline BMI (kg/m^2)
- Baseline ECOG performance status (refer Section 17.6.1)
  - 0
  - 1
  - >1

- Baseline Sum of Diameters of Target Lesions (mm)

Other baseline characteristics related to the oncology history will be described in Section 12.

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11.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Age (Years) = (Date of Informed Consent Signed – Date of Birth + 1)/365.25

12. MEDICAL HISTORY AND ONCOLOGY HISTORY

Pre-existing medical conditions are recorded on the "Medical History" CRF page.
Medical history (excluding oncology history) will be summarized by system organ class (SOC) and preferred term (PT) for the SAS set. Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.0 (MedDRA 23.0) or higher will be used for coding. Number and percentage will be presented in frequency tables by dose cohort in dose escalation phase and disease cohort in dose expansion phase, and ordered by primary SOC and PT in descending order of the frequency in total within each category. For SOCs or PTs with the same frequency in total, categories will be sorted alphabetically.
Oncology history information will be captured on CRF page "Oncology History" and the following oncology history information will be summarized:

- Type of malignancy
- Duration of malignancy (years) – Calculated relative to date of ICF
- Time since the initial diagnosis to first administration of study medication (years) – Calculated relative to date of first administration of study medication
- Stage of the disease at the time of initial diagnosis
    - Stage I
    - Stage II
    - Stage III
    - Stage IV
- Metastasis Status (Yes, No)
- Duration of Metastasis (Years) – Calculated relative to date of ICF
- Prior oncology treatments
    - Oncology Chemotherapy and Medication
    - Oncology Radiation Therapy
    - Oncology Surgery and Procedures

Medical history and oncology history will be listed for the SAS.

12.1. DERIVATIONS

- Duration of malignancy (years) = (Date of Informed Consent Signed – Date of first confirmed malignancy + 1)/365.25.
- Time since the initial diagnosis to first administration of study medication (years) = (Date of first administration of study medication – Initial primary diagnosis date for solid tumor + 1)/365.25.
- Duration of metastasis (years) = (Date of Informed Consent Signed – Date of metastasis observed + 1)/365.25.

13. MEDICATIONS AND PROCEDURES

Prior medications are medications which ended prior to the first dosing date of study medication. Concomitant medications/procedures are medications/procedures which started no later than 30+7 days following the last dose administration, and ended on or after the date of first dose of medication or were ongoing at the end of the study. Relevant information is collected on CRF page "Prior and Concomitant Medications", "Concomitant Procedures". Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE), version Mar2020 or latest version. Anatomical Therapeutic Chemical (ATC) level 2 classification and Preferred term (PT) will be used for coding.

Concomitant medications will be summarized by ATC level 2 and PT for each dose cohort in dose escalation phase and each disease cohort in dose expansion phase for the SAS. PT will be sorted in descending frequency of the total number of patients with at least one medication in the corresponding category, PTs will be presented alphabetically for PTs of the same total frequency.

Concomitant procedures will be coded by MedDRA 23.0 or higher and will be presented by PT by dose cohort in dose escalation phase and by disease cohort in dose expansion phase. PT will be sorted in descending frequency of the total number of patients with at least one procedure in the corresponding category, PTs will be presented alphabetically for PTs of the same total frequency.

Prior and concomitant medications will be presented in listings with flag to differentiate whether the medication was prior medication or concomitant medication. Similar for prior and concomitant procedures information.

14. ONCOLOGY THERAPIES

Prior oncology therapies include oncology chemotherapy and medication, oncology radiotherapy, and oncology surgery and procedures. Oncology chemo therapy and medication will be captured on "Oncology Chemotherapy and

Oncology Medication" CRF page, oncology radiotherapy will be captured on "Oncology Radiotherapy" CRF page, and oncology surgery and procedures will be captured on "Oncology Surgery and Procedure" CRF page.
Prior oncology chemotherapies and medications will be coded using WHO-DDE, version Mar2020 or latest version, and will be presented by ATC level 2 classsification and PTs for each dose cohort in dose escalation phase and each disease cohort in dose expansion phase for the SAS. PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, PTs will be presented alphabetically for PTs of the same total frequency. In addition, number and percentage of patients who received prior oncology chemotherapies and medications, number of regimens, best response, treatment failure information and appearance of adverse reaction with severity above grade 3 will be summarized for prior oncology chemotherapies and medications.
The number and percentage of patients who received prior oncology radiotherapy, purpose, best response, and appearance of adverse reaction with severity above grade 3 will be summarized for prior oncology radiotherapy.
Prior oncology surgery and procedure will be coded using MedDRA 23.0 or higher, and will be summarized by SOC and PT for each disease cohort in dose expansion phase and dose escalation phase for the SAS. SOC and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, SOCs/PTs will be presented alphabetically for SOCs/PTs of the same total frequency.
Since on-study oncology therapies are not allowed, oncology therapies will be classified and reported as prior. Any concurrent oncology therapy will be considered and reported as protocol deviation.
. All the oncology therapies as well as general therapies will be listed by disease cohort in dose expansion phase and dose escalation phase.
Oncology chemotherapy and oncology medication, oncology radiotherapy, and oncology surgery and procedure will be listed for SAS. Oncology surgery and procedure will be listed for SAS and will be presented separately from concomitant procedures.
New anti-tumor therapy is defined as any anti-tumor therapy started after first dose of study medication. New anti-tumor therapy will be flagged in the listing of oncology medication/radiotherapy/surgery.

15. STUDY MEDICATION EXPOSURE

The extent of exposure to study medication will be presented by dose cohort and disease cohort for cycle 1 (DLT window) and overall respectively for the SAS.
Study medication exposure calculation will be based on study medication administration information, which is collected on the CRF pages "Study Drug Administration". In the case of missing data on the eCRF or if derivations are required, the "Study Drug Administration" or "Study Drug Dispensation and Return" form will be used in order

to determine the first and the last date of study medication.

Descriptive information will be provided regarding number of cycles exposure to study drug, total duration of study medication exposure, actual duration of study medication taken, cumulative dose of study medication, dose intensity and relative dose intensity as both continuous variable and categorical variable (<80%, >=80% and <=120%, >120%). The number and percentage of patients with any prescribe dose increased, reductions and interruptions will be presented, the timing of prescribe dose increased, reductions and interruptions and reasons for dose increased, reductions and interruptions will be summarized as well.

Additionally, the relative dose intensity calculated for DLT observation window (28 days since first dose regardless of the actual date of C2D1 visit) will facilitate the determination of DLT set and will be presented together in a listing with overall study medication exposure.

Study medication administration in each cycle will be taken from CRF page "Study Drug Administration" at each visit.

Study drug administration data will be listed by dose cohort in dose escalation phase and by disease cohort in dose expansion phase. And any dose modifications will be flagged.

Another listing of study medication accountability with relevant information will be provided.

15.1 DERIVATIONS

- Total duration of study medication (Days) in cycle 1= Stop date of administration in cycle 1 – Start date of administration +1
- Total duration of study medication (Days) for overall = Stop date of administration in last cycle – Start date of administration +1
- Actual duration of study medication (Days) in cycle1 = sum of days with the administration of study medication during cycle 1, Dose interruption will be excluded from actual duration of exposure
- Actual duration of study medication (Days) for overall = sum of days with the administration of study medication, Dose interruption will be excluded from actual duration of exposure

- Cumulative dose of study medication (mg) in cycle 1 = Sum [Actual Daily Dose (mg/day) * (Start Date of Administration – Stop Date of Administration + 1) of each record in cycle 1 in "Study Drug Administration" form. For patients who did not receive any dose of study medication, the cumulative dose will be set to zero
- Cumulative dose of study medication (mg) for overall = Sum [Actual Daily Dose (mg/day) * (Start Date of Administration – Stop Date of Administration + 1) of each record in "Study Drug Administration" form. For patients who did not receive any dose of study medication, the cumulative dose will be set to zero

- Dose intensity (%) = Cumulative dose of study medication/ Total duration of study medication for each period (cycle 1 or overall)

- Relative dose intensity (%) = 100%*Dose intensity/planned dose intensity, in this study, planned dose

intensity in each dose level is just the planned dose with unit of mg/day.

16. EFFICACY OUTCOMES

Efficacy data will be summarized by dose cohort in dose escalation phase and by disease cohort in dose expansion phase. PFS and OS will be analyzed for the SAS. The other efficacy variables (BOR, ORR, DCR, TTR, and DOR) will be analyzed for EAS.

Treatment efficacy will be evaluated by using tumor responses which will be assessed and documented at Screening, Day 1 of Cycle 2 and every 8 (+/-1 week) weeks on Day 1 of every other cycles afterwards (i.e. Cycle 4, 6… etc), until the occurrence of progressive disease (PD) according to the standard of Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response/progression and the confirmation assessment date. When the patient interrupts study medication due to AEs or other reasons, the evaluation should be conducted as scheduled. For suspected cases of PD before the start of the next scheduled assessment, additional tumor assessments will be done.

Tumor responses data are captured on CRF page "Tumor Measurement - Target Lesions", "Tumor Assessment - Non-Target lesions", "Tumor Assessment - New Lesions" and "Assessment of Disease". The confirmed best overall response (BOR, refer Section 16.1.2) will be summarized for EAS and will be presented together with summaries for objective response rate (ORR) and disease control rate (DCR).

The baseline sum of diameters will be presented with other baseline characteristics.

Tumor assessments for target lesion, non-target lesion, and new lesion will be presented in a listing. In addition, a listing of overall response including lesion responses, sum of diameters, and the corresponding change from baseline in tumor diameter will be provided.

Tumor assessment performed at the treatment completion visit (details can be found in SAP Section 7.3) is an eligible data point for the derivation of all efficacy endpoints, following the derivation rules described in Section 16.1.

16.1. EFFICACY VARIABLE(S) & DERIVATION(S)

16.1.1. Progression-Free Survival

Progression-free survival (PFS) is defined as the time (in months) from the start date of study medication (Day 1) until the date of objective disease progression as defined by RECIST Version 1.1 or death (by any cause in the absence of progression), whichever occurred earlier.

The PFS time will always be derived based on scan/assessment dates and not based on visit dates. RECIST

assessments/scans contributing towards a particular visit, which consists of assessment for "Non-Target lesions", "Target lesions", and "New lesions", may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the radiological component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

If a patient has not experienced progressive disease (PD) or died before the end of study for any reason, progression-free survival will be censored at the date of the last evaluable tumor assessment on or prior to the PD, which is not necessarily confirmed.

Three additional rules apply to PFS only:

- If a patient misses two or more consecutive tumor assessment visits, and showed PD or death afterwards, PFS will be censored at the date of last tumor assessment prior to the consecutive missed visits. Two consecutive missed/non-evaluable tumor assessment visit window is calculated as 2*(8 weeks+1week window time), which is 126 days.
- If a patient reports no baseline tumor assessments or has no evaluable tumor assessment visits after the first dose of study medication, PFS will be censored at the start date of study medication unless they die within two consecutive tumor assessments since the first dose of study medication, i.e., PFS=1 day.
- Of note that tumor assessments after the first new anti-cancer treatment (same day inclusive) will be considered inadequate. If a patient starts new anti-tumor therapy initiated prior to documented disease progression or death on study, PFS will be censored at the date of the last tumor assessment prior to or on the date of new anti-tumor therapy.

See Table 1 for the detailed information of event/censoring rules for PFS:

Table 1: PFS Events/censoring rules

Description	Event/Censor	Date of Event/Censor
Documented progression before start use of new anti-tumor therapy and no two consecutive missed tumor assessment visits	Event	Date of documented disease progression
Death without progression and without use of new anti-tumor therapy and without missing two consecutive tumor assessment visits	Event	Date of death
Death or progression after two or more consecutive missed tumor assessments	Censor	Date of last evaluable tumor assessment prior to the consecutive missed tumor

		assessment visits
No evaluable baseline or post-baseline tumor assessment and no new lesion found and no death within two scheduled tumor assessment visits post-baseline	Censor	Date of first dosing of study medication
New anti-tumor therapy started prior to documented disease progression or death on study	Censor	Date of last evaluable tumor assessment before start use of new anti-tumor therapy
No progression and no death before end of study or data cut-off	Censor	Date of last evaluable tumor assessment

Note: Symptomatic deterioration will not be regarded as a progression event.

The PFS will be programmatically derived as follows:

1. If a patient had disease progression or death, then

PFS (month) = ([date of earliest evidence of disease progression or death (including death from any cause) – start date of study medication] + 1)/ 30.4375; Otherwise,

2. If the patient was known to have developed one of above censoring criteria, then the PFS is censored and

PFS (month) = ([date of censoring – start date of study medication] + 1)/ 30.4375.

3. Special scenario such as two or more consecutive missing tumor assessment visits or new anti-cancer treatment will be handled according to the rules provided in Table 1.

16.1.2. Best Overall Response

Best overall response (BOR) will be calculated based on the overall visit responses obtained up until RECIST progression is documented, irrespective of whether patients discontinued study medication. In the absence of RECIST progression, BOR is determined by using visit responses up until the last evaluable overall visit response. Note, CR or PR response(s) after receiving subsequent anti-cancer therapy will not be included.

A patient's overall best objective response will be determined:

- CR: At least one visit response of CR confirmed by subsequent imaging at least 25 days (4 weeks – 3 days window) later with no evidence of progression between confirmation visits. It is required that there is no other overall response, except CR and NE, between the first CR and the subsequent confirming CR which meet the confirmed CR criteria, i.e. CR-NE-CR is the confirmed CR.
- PR: At least one visit response of PR confirmed by subsequent imaging at least 25 days (4 weeks – 3 days window) later with no evidence of progression between confirmation visits. It is required that there is no other overall response, except CR or PR or NE, between the first PR and the subsequent confirming CR or

PR which meet the confirmed CR or PR criteria, i.e PR-NE-PR is the confirmed PR. If the first PR followed by SD and no matter the requirement of SD is satisfied or not, i.e. PR-SD-PR, the subsequent PR will not be qualified as confirmed PR.

- SD needs to sustain for at least 8 weeks: Stable disease recorded at least 53 days after start of treatment (8 weeks from start of treatment, and also allowing a 3-day visit window). For example, an overall visit response of SD on day 28 will not be considered as SD.
- PD: Progression, or death in the absence of CR/PR or SD.
- NE: No evidence of CR/PR or SD or PD or death.
- Unconfirmed CR: If the BOR is not qualified as confirmed CR or PR but with at least one visit response of CR prior to subsequent new anti-tumor therapy or PD, then it will be considered as unconfirmed CR.
- Unconfirmed PR: If the BOR is not qualified as confirmed CR or PR but with at least one visit response of PR prior to subsequent new anti-tumor therapy or PD, then it will be considered as unconfirmed PR.

In addition, following special scenarios shall be considered for the determination of BOR:

- If a patient receives new anti-tumor therapy(s), for that patient, tumor assessments after the first new anti-tumor therapy (same day inclusive) will be considered inadequate, thus not counted towards the determination of BOR.

The table below illustrates the derivation of BOR (with confirmed response) and BOR (regardless of confirmation). Category of confirmed response is dependent on response at the subsequent time-point, and whether the minimum duration criterion for SD has been satisfied.

Overall Response at First Time-point	Overall Response at Subsequent Time-point	SD Sustaining Duration Met at First Time-point	BOR Based on the Two Visits	BOR Regardless of Confirmation (for Unconfirmed CR or PR)
CR	CR	Yes/No	CR	CR
CR	PR	Yes/No	SD/PD	CR (Unconfirmed)
CR	SD	Yes/No	SD/PD	CR (Unconfirmed)
CR	PD	Yes/No	SD/PD	CR (Unconfirmed)

CR	NE	Yes/No	SD/NE	CR (Unconfirmed)
PR	CR	Yes/No	PR/PR	PR
PR	PR	Yes/No	PR	PR
PR	SD	Yes/No	SD/SD	PR (Unconfirmed)
PR	PD	Yes/No	SD/PD	PR (Unconfirmed)
PR	NE	Yes/No	SD/NE	PR (Unconfirmed)
NE	NE	Yes/No	NE	NE

CR = Complete Response; NE = Not Evaluable; ORR = Objective Response Rate; PD = Progressive Disease; PR= Partial Response; SD = Stable Disease.

For patients who progress and subsequently have a response, then the best objective response is only derived from assessments up to and including the time of the progression (i.e., it will not include the response after the patient has progressed).

Tumor response data for dosed patients that had non-measurable disease at baseline (i.e. did not meet study inclusion criteria 7) will be flagged and reviewed according to procedures described in Appendix 3 of the protocol.

16.1.3. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a best overall complete response (CR) or partial response (PR) per RECIST V.1.1. To be assigned a status of PR or CR, changes in tumor measurement must be confirmed by repeat assessment performed no less than 4 weeks after the criteria for response are first met. ORR (regardless of confirmation) will also be computed separately, including in the numerator subjects who have CR, unconfirmed CR, PR or unconfirmed PR. The denominator for the calculation of ORR and ORR regardless of confirmation will include all patients in EAS.

16.1.4. Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients whose best overall response from baseline is either CR, PR, or SD per RECIST v.1.1. The denominator for the calculation of DCR will include all patients in EAS subset of response evaluable patients. Response evaluable patients refer to patients with a baseline RECIST assessment.

16.1.5. Time to Response

Time to response (TTR) is defined as the time between the start date of study medication until first documented response (CR or PR, which is subsequently confirmed) according to RECIST v.1.1. Time to response is only applicable to patients whose BOR is either CR or PR. TTR (months) will be calculated as (First CR/PR date – start date of study medication + 1) / 30.4375.

16.1.6. Duration of Objective Response

Duration of objective response (DoR) is defined as the time from the first time that the objective response reaches CR or PR, whichever comes first, until the occurrence of PD or death (if the death of the patient occurs before recording the PD). If the response is not confirmed, it will not be included. If a patient does not progress (or does not progress before receiving new anti-cancer treatment) following a response, then their duration of response will use the PFS censoring time.

For those patients with confirmed response, the date of response will be the date of first documented response, not the date of confirmatory tumor assessment for that response. The DoR (months) will be calculated as (PD/Death date - First CR/PR date + 1) / 30.4375 when a patient is deemed to experience a PFS event after first CR/PR, or calculated as (PFS censoring date - First CR/PR date +1)/30.4375 when a patient is deemed to be censored.

16.1.7. Percentage Change in Tumor Size

Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target lesions compared to baseline. Best (minimum) percentage change from baseline (PCFB) in tumor size will be summarized by dose cohort and disease cohort using descriptive statistics and a waterfall plot will be presented also. The sum of diameters will be taken from the field "Sum of Diameters of Target Lesions" in "Assessment of Disease (According to RECIST 1.1) (RS)" form of eCRF or be calculated from the field "Measured Diameter" in "Tumor Results: Target Lesion (TARGET)" form of eCRF.

16.2. Primary Analysis of Efficacy Variable(s)

For each dose level in dose escalation phase and each disease cohort in dose expansion phase, PFS will be described in tabular and graphical format using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles, minimum, maximum. The 95% CI for the median survival time will be derived using the log-log transformation based on Brookmeyer and Crowley method.

Besides, Kaplan-Meier estimated probabilities with corresponding 80% and 95% CIs at several time points

[redacted]

(including 4 Months/ 16 Weeks and 11 months) will also be provided and the 80% and 95% CIs will be derived using the log-log transformation based on Greenwood's formula.

Censoring reasons will also be summarized by categories that will be determined using the treatment completion page, the study evaluation completion page and survival page.
The other endpoints including TTR and DoR will be analyzed in the same way where appropriate. In case the number of responses in each treatment group is very small, DoR and TTR may be listed only.
ORR and DCR will be estimated and 95% exact confidence intervals (CIs) based on the Clopper-Pearson method will be presented.

The time to event/censoring and the censoring status for PFS will be listed for the SAS, and for DOR and BOR will be listed for the EAS.

16.3. Exploratory Efficacy

16.3.1. Tumor Markers

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

The values and change from baseline in tumor markers will be summarized by disease cohort (BTC, pNET, or epNET, or STS) using descriptive statistics. The individual tumor marker test results will be listed by dose cohorts in each phase and by patients. Other exploratory analyses may be performed as appropriate.

16.3.2. Overall Survival

Overall survival (OS) (in months) is defined as the time interval between the start date of study drug and the date of patient death (any cause). The final known date alive will be used as the censoring date for patients who have not been reported to have died by the time of analysis cut-off date. OS will be analyzed for only the BTC and STS cohorts based on the SAS.

Patients who fail to provide any follow-up information will be censored on the date of enrolment. OS (months) will be calculated as (Date of death – start date of study medication + 1) / 30.4375.

[redacted]

Median, 25th and 75th Quartiles, minimum and maximum will be provided for OS. Kaplan-Meier estimated probabilities with corresponding 80% and 95% CIs at several time points (including 16 weeks, 6 months, 8 months and 11 months for BTC and STS cohort) will be provided. Kaplan-Meier curves will be constructed to provide a visual presentation of the OS change with time.

16.4. Sensitivity Analysis of Efficacy Variable(s)

No sensitivity or supportive analyses will be performed on efficacy variables.

17. Safety Outcomes

All outputs for safety outcomes except DLT summary will be based on the SAS. Safety data will be summarized by dose cohort in escalation phase and disease cohort in dose expansion phase.

17.1. Adverse Events

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational medicinal product or other protocol-imposed intervention, regardless of attribution. Relevant information is recorded on CRF page "Adverse Event/Serious Adverse Event".
If a persistent AE becomes more severe, it should be recorded again with the updated severity. All recurrent AEs (AEs that occurs and resolves between patient evaluation time points and subsequently recurs) should be recorded on "Adverse Event/Serious Adverse Event" CRF.
A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study.
After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected.
After initiation of study medications, all AEs and SAEs regardless of attribution will be collected until 37 days (30 days + 7 days window) following the last administration of study medication or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment.
Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened in severity on or after the first administration date of study medication and no later than 30 (+7) days after the last administration date of study

medication or initiation of new anti-tumor therapy (whichever occurs first).

An exception is that study medication related SAEs collected later than 37 days after the last dosing date will be treated as TEAEs.

If the start date coincides with the reference start date, a query "Prior/ post 1st dose" will be used to identify TEAEs (only when 'Post 1st dose' will be considered as TEAE, if 'Prior' then not TEAE). When there is no definite answer to the query, the AE will be considered as a TEAE. See section 8.2 for handling of partial dates for AEs. In the case where it is not possible to classify an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

If a subject reports a TEAE more than once in the SOC/PT, the TEAE with highest severity will be used in the corresponding summaries.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided for all AEs as specified in the templates.

For all SOC/PT summaries, AEs will be presented in alphabetic order except the uncoded SOC/PT. Uncoded SOC/PT will be presented as "Uncoded" and be presented at the end of relevant AE summaries.

A Listing of all AEs with relevant information being reported during study with flag to distinguish TEAE and Non-TEAE will be provided.

17.1.1. All TEAEs

In the analysis of AEs, the MedDRA adverse event dictionary Version 23.0 or higher will be used to map verbatim terms to SOC and PT.

An overall summary of TEAEs including severity, relationship, action taken, and outcome will be provided.

Incidence of TEAEs will be presented by SOC and then PT and also broken down further by maximum severity (Section 17.1.1.1) and relationship to study medication (Section 17.1.1.2) for each dose level, and each disease cohort. Number (n) and percentage (%) will be presented with the % calculated relative to the total number of patients in the SAS. In the case that a patient report multiple TEAEs, the TEAE with worst severity and strongest relationship (related to study medication) will be used in the corresponding summaries.

17.1.1.1 Severity

The severity of all TEAEs will be graded according to 5 grades (Grade 1 to Grade 5) in accordance with the National Cancer Institute Common Terminology criteria for adverse events (NCI-CTCAE) V4.03 as defined in the Study Protocol Section 7.1.5.

TEAEs missing severity will be classified as Grade 3.

TEAEs of each severity grade will be summarized usingincidence (frequencies and percentages) by SOC and PT will be summarized by dose level in the dose escalation phase and by disease cohort in the dose expansion phase. If

[redacted]

a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

17.1.1.2 Relationship to Study Medication

As indicated by the Investigator, causal relationship between AEs and study medication will be classified as "reasonably possible" or not. TEAEs with missing relationship to study medication will be regarded related. Related and Not Related TEAEs will be summarized by dose level in dose escalation phase, and by disease cohort in dose expansion phase using incidence (frequencies and percentages) by SOC and PT. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst relationship (ie, related) to study medication will be used in the corresponding relationship summaries.

17.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified as those records with a response of "Drug Withdrawn" to the item "Action taken with the study drug" on the "Adverse Event/Serious Adverse Event (AE/SAE)" form of the CRF.

For TEAEs leading to drug discontinuation, summaries of incidence (frequencies and percentages) by SOC and PT will be prepared. Summaries for TEAEs leading to discontinuation of study medication by SOC and PT will be further broken down by maximum severity and relationship to study medication.

17.1.3. TEAEs Leading to Study Medication Adjustment

TEAEs leading to study medication adjustment will be identified as those records with a response of "Drug interrupted" or "Dose reduced" or 'Dose increased' to the item "Action taken with the study drug" on the AE/SAE form of the CRF.

For TEAEs leading to study medication adjustment, summaries of incidence (frequencies and percentages) by SOC and PT will be prepared. Summaries for TEAEs leading to study medication adjustment by SOC and PT will be further broken down by maximum severity and strongest relationship to study medication.

17.1.4. Serious TEAEs

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

Detailed definition of SAEs can be found in Protocol Section 9.1.1.

On the CRF, SAEs are those events with a response of "Yes" for the item "Does the Adverse Event meet seriousness criteria?". Summaries of incidence (frequencies and percentages) of serious TEAEs by SOC and PT will be

prepared. In addition, summaries for serious TEAEs by SOC and PT will be further broken down by maximum severity and strongest relationship to study medication.
SAEs will be flagged and included in a listing of AEs.

17.1.5. TEAEs Of Special Interest (TEAESI)

The preferred terms for TEAESI are included in Appendix 2. Summaries of incidence (frequencies and percentages) of TEAESIs by Standardized MedDRA Queries (SMQ) and PT based on the Appendix 2 will be prepared. The broad search will be used for SMQ terms. Time to TEAESI onset is defined as time interval from date of first administration of study medication to the earliest onset date among TEAEs within the same SMQ. Time to TEAESI onset will be summarized by SMQ for each dose cohort and disease cohort.
AESIs will be flagged and included in a listing of AEs.

17.1.6. Dose Limiting Toxicity (DLT)

A detailed definition of DLT can be found in Protocol Section 4.1.2. On the CRF, DLT will be identified among all AEs using question "Is it DLT?", and details will be captured on CRF page "DLT Assessment". Incidence of DLTs by SOC and PT will be summarized for DLT set. Time between date of first dose of study medication and DLT event onset will be presented for DLT evaluable set.
All relevant information of DLT assessment will be listed for DLT evaluable set by dose cohort and by patient.

17.1.7. Deaths

If any patients die during the study conduct, as recorded on the "Death" CRF form, the count and cause of death and on treatment death (event occurs on or after first study medication dose and prior to 37 days [30 days + 7 days window] after the last dose) will be summarized by dose level in dose escalation phase, and by disease cohort in dose expansion phase.
Individual information of subject ID, death date and primary reason for death will be presented in the listing. On-treatment death will be flagged.

17.2. LABORATORY EVALUATIONS

Laboratory samples will be analyzed at the study site's local laboratory. Laboratory assessments will include the following:

- Hematology, which is recorded on CRF page "LAB – Hematology"
- Coagulation, INR and aPTT, which is captured on CRF page "LAB - Coagulation".

- Serum chemistry, which is recorded on CRF page "LAB - Blood Chemistry"
- Serum pregnancy test at screening for all women of childbearing potential, which is captured on CRF page "Pregnancy Test"
- Urinalysis, which is recorded on CRF page "LAB – Urinalysis" and "LAB- 24hrs Urine Protein"
- Thyroid function: TSH, free T3, free T4, which is captured on CRF page "LAB - Thyroid Function Tests"
- Stool occult blood test, which is recorded on CRF page "LAB - Fecal Occult Blood Test"

Test normal ranges of all quantitative tests above (ie, all tests excluding stool occult blood test and serum pregnancy test) are also recorded on corresponding normal range CRF pages.

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 normal range (LLN), or "> X", i.e. above the upper limit of normal range (ULN), 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.

The following summaries will be provided for laboratory data:

- For quantitative results, actual value of each scheduled visit, change from baseline for each post-baseline scheduled measurement.
- For quantitative measurements and categorical measurements, Incidence of abnormal values assessed by investigator. Shift from baseline according to markedly abnormal criteria based on investigators' assessment.
- Shift from baseline to worst grade in CTCAE grade according to Common Toxicity (CTC) grading system for parameters of hematology and serum biochemistry whose CTCAE scale is available.
- Listing of all laboratory data by patient, abnormal values identified according to normal range (low, normal and high), and markedly abnormal criteria by investigators' assessment will be flagged.

17.2.1. Laboratory Specific Derivations

Creatinine clearance (CCr) will be calculated by using the serum creatinine (SCr) values according to the the following formulas:

- Male: $CCr = [(140 - age) \times weight\ (kg)] / [0.818 \times SCr\ (umol/L)]$
- Female: $CCr = [(140 - age) \times weight\ (kg)] / [0.818 \times SCr\ (umol/L)] \times 0.85$

The units for creatinine clearance will be converted to SI unit: umol/L.

17.2.2. Laboratory Reference Ranges and Markedly Abnormal Criteria

All laboratory assessments except serum pregnancy test and stool occult blood test will be analyzed as following.

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and

categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be evaluated as normal/abnormal, not clinically significant (NCS)/ abnormal, clinically significant (CS) by investigator. For laboratory assessments collected with both quantitative and qualitative results, if most assessments are quantitative, quantitative assessments will be summarized, and vice versa if most assessments are qualitative, and all the assessments will be listed.

17.2.3. CTCAE Grading for Laboratory Data

Quantitative laboratory measurements will be graded according to NCI CTCAE V4.03 wherever applicable. All grading will be based on lab values (being direct or some derived, corrected values) ONLY, regardless of its interventional or symptomatic consequences.

Some modifications to the grading system will be applied:

- Grade 5 refers to fatal outcomes, which cannot be determined solely by lab values, therefore will not appear in the grading system. In addition to the usual defined categories.
- A further category denoted Grade 0 will include all other laboratory values except missing values.
- Missing results shall be graded as missing.

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.

Shifts in toxicity grade from baseline to the worst toxicity grade will be provided for the SAS.

17.2.4. Liver Function Abnormality

Liver function abnormality is defined in Protocol Section 7.1.7 and the below events will be identified via programming and summarized by categories and dose cohort for SAS. Separate listings for patients with drug-induced liver injury (DILI) will also be provided.

- ALT/AST > 3 x ULN and ≤ 5 x ULN
- ALT/AST > 5 x ULN
- Total Bilirubin > 2 x ULN
- ALT/AST > 3 x ULN AND concurrent Total bilirubin > 2 x ULN

17.3. ECG EVALUATIONS

The 12- Lead Electrocardiogram (ECG) will be performed at screening, and on Days 1 and 15 in Cycle 1. when ECG data will be collected at pre-dose and at 2 hours +-15 minutes post-dose (around C_{max} after single dose and at steady state in order to evaluate concentration-QT relationship for surufatinib). The ECG values at C1D1 pre-dose will be used as 'baseline' value in the analysis. ECG will also be conducted on Day 1 of each cycle from Cycle 2 and onward, as well as the treatment completion visit.

For each time-point, following measurements with change from baseline values will be presented for the SAS:

- Heart rate (bpm)
- RR (ms)
- PR (ms)
- QRS (ms)
- QT (ms)
- QT correction by Bazett (ms)
- QT correction by Fridericia (ms)
- Overall ECG interpretation
    - Abnormal, clinically significant (CS)
    - Abnormal, not clinically significant (NCS)
    - Normal
    - Incomplete analysis
    - Uninterpretable
    - Not applicable

17.3.1. ECG Specific Derivations

There will be no specific derivations for ECG.

17.3.2. ECG Markedly Abnormal Criteria

The number and percentage of patients with notable ECG values at baseline and post-baseline will be summarized. These summaries will be done for worst post-baseline value for each category. The criteria for notable ECG values are provided in Table 2 below.

Table 2 Notable ECG Values

Test	Notable ECG Values
CCI	[redacted]

QTcF/QTcB (absolute)	interval >450 to 480 msec interval >480 to 500 msec interval >500 msec
Heart rate (absolute)	<50 bpm >100 bpm
PR (absolute)	interval >200 msec
QRS (absolute)	interval >120 msec

•

17.3.3. Analysis of QTc Change from Baseline (ΔQTc)

The change from baseline in QTcF (ΔQTcF) intervals will be evaluated as follows:

- ΔQTcF at each time point will be listed for each patient and treatment. For each time point of measurement, ΔQTcF will be summarized using descriptive statistics (mean, SD, median, min, max).
- The incidence of patients with ΔQTcF increase >30 to 60 msec and >60 msec will be summarized.
- The incidence of patients with ΔQTcF increase >30 to 60 msec and >60 msec by time-point in Cycle 1 will also be summarized.
- Patients with ΔQTcF increase >60 msec will be listed.
- Mean ΔQTcF versus time profile for each dose group will be plotted on the same graph.

17.3.4. Analysis of the Relationship Between QT/QTc and RR at Baseline

The relationship between QT/QTc and RR intervals at baseline will be evaluated graphically as follows:

- The logarithm of baseline QT values will be plotted against the logarithm of corresponding RR intervals.
- A linear regression model will be fitted to the data with logarithm of baseline QTc interval values as the dependent variable and logarithm of RR as the predictor.
- The slope of the regression line and its standard error, along with 2-sided 95% confidence intervals for the slope, will be estimated from this model.
- The analysis will be repeated for QTcB and QTcF and plotted on the same graph for QT.

17.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Weight (kg)
- Baseline BMI (kg/m^2)
- Baseline Height (cm)

Vital sign values and change from baseline (applicable to post-baseline measurements) will be summarized by each scheduled time-point.

All vital signs results including change from baseline for quantitative parameters will be listed. A flag of oral temperature derived from axillary temperature will be provided.

Selected vital signs (SBP, DBP and heart rate) change from baseline will be plotted over time for each patient.

17.4.1. Vital Signs Specific Derivations

There will be no specific derivations for vital signs.

17.4.2. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Table 3 Vital Sign Markedly Abnormal Criteria.

Variable	Unit	Baseline Category	High
SBP	mmHg	≤ 140 mmHg	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 mmHg
DBP	mmHg	≤ 90 mmHg	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 mmHg

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Variable	Unit	Baseline Category	High
Heart rate	Bpm	< 100 / ≥ 100 bpm	Absolute change from baseline of: > 0 - ≤ 20 / > 20 - ≤ 40 / > 40 bpm
Weight	Kg	None	Percentage change from baseline of < 5% / ≥ 5 - <10% / ≥ 10 - < 20% / ≥ 20%

17.5. Physical Examination

A complete physical examination at screening should include the evaluation of head, eye, ear, nose, and throat; and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.
At subsequent visits, a limited physical examination will be performed to assess changes from baseline abnormalities, any new abnormalities, and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.
All physical examination results will be listed.

17.6. Other Safety Assessments

17.6.1. ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be summarized descriptively by visit and a shift table will be also summarized from the "ECOG Performance Status" CRF page. In addition, the summary descriptive table by visit will include specific ECOG grades and binary grouping grades (0-1, 2-5). The shift table will be summarized from baseline to worst post-baseline.
Details about ECOG performance status scores can be found in Protocol Appendix B.
A listing of ECOG Performance Status will be provided.

17.6.2. Echocardiogram

Echocardiography, including left ventricular ejection fraction (LVEF) assessment contains both quantitative results (%) and overall evaluation [Normal; Abnormal, Not Clinically Significant (ANCS); Abnormal, Clinically Significant (ACS)].
Actual value of echocardiography measured at each scheduled visit, change from baseline to each post-baseline

scheduled measurement will be presented by visit. Overall evaluation will be summarized separately.

All echocardiography results including change from baseline for LVEF and relevant information will be listed.

18. REFERENCES

Protocol 2015-012-00US1 Version 7.0 (Amendment 11), Dated 19Mar2021

Case Report Forms Version 11 Dated 30Aug2021

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the Quintiles' general guidelines and template for outputs conventions.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM:SS.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

All summaries will be presented by assigned dose level in dose escalation phase.

Treatment Group	For Tables, Listings and Graphs
50 mg/day dose level	50 mg
100 mg/day dose level	100 mg
200 mg/day dose level	200 mg
300 mg/day dose level	300 mg
400 mg/day dose level	400 mg
Additional intermediate dose level	XXX mg (XXX=Actual dose level)
Screen failures (in listings only)	SF
Untreated eligible patients (in listings only)	NOTTRT

PRESENTATION OF DISEASE COHORT

All summaries will be presented by disease cohort in dose expansion phase.

Disease Cohort	For Tables, Listings and Graphs
Arm A: Biliary tract cancer	BTC
Arm B: Pancreatic neuroendocrine tumor	pNET
Arm C: Extrapancreatic neuroendocrine tumor	epNET
Arm D: Soft tissue sarcoma	STS

PRESENTING ORDER

All listings will be ordered by the following (unless otherwise indicated in the template):

- SitePatient ID,
- Treatment group, in the order as above table,
- date (where applicable)

All tables containing coded terms (CM, MH, AE, etc), coded records will be sorted in descending order of incidence.

APPENDIX 2. ADVERSE EVENTS OF SPECIAL INTEREST

AESI SMQ	PT Term	PT Code
Acute renal failure	Acute kidney injury	10069339
	Acute phosphate nephropathy	10069688
	Anuria	10002847
	Azotaemia	10003885
	Continuous haemodiafiltration	10066338
	Dialysis	10061105
	Foetal renal impairment	10078987
	Haemodialysis	10018875
	Haemofiltration	10053090

	Neonatal anuria	10049778
	Nephropathy toxic	10029155
	Oliguria	10030302
	Peritoneal dialysis	10034660
	Prerenal failure	10072370
	Renal failure	10038435
	Renal failure neonatal	10038447
	Renal impairment	10062237
	Renal impairment neonatal	10049776
	Subacute kidney injury	10081980
Haemorrhages	Abdominal wall haematoma	10067383
	Abdominal wall haemorrhage	10067788
	Abnormal withdrawal bleeding	10069195
	Achenbach syndrome	10079562
	Acute haemorrhagic leukoencephalitis	10058994
	Acute haemorrhagic ulcerative colitis	10075634
	Administration site bruise	10075094
	Administration site haematoma	10075100
	Administration site haemorrhage	10075101
	Adrenal haematoma	10059194
	Adrenal haemorrhage	10001361
	Anal fissure haemorrhage	10079765
	Anal haemorrhage	10049555
	Anal ulcer haemorrhage	10063896
	Anastomotic haemorrhage	10056346
	Anastomotic ulcer haemorrhage	10002244
	Aneurysm ruptured	10048380
	Angina bullosa haemorrhagica	10064223
	Anorectal varices haemorrhage	10068925
	Anticoagulant-related nephropathy	10083346
	Aortic aneurysm rupture	10002886
	Aortic dissection rupture	10068119
	Aortic intramural haematoma	10067975
	Aortic perforation	10075729
	Aortic rupture	10060874
	Aponeurosis contusion	10075330
	Application site bruise	10050114
	Application site haematoma	10068317
	Application site haemorrhage	10072694
	Application site purpura	10050182
	Arterial haemorrhage	10060964
	Arterial intramural haematoma	10074971
	Arterial perforation	10075732
	Arterial rupture	10003173
	Arteriovenous fistula site haematoma	10055150
	Arteriovenous fistula site haemorrhage	10055123
	Arteriovenous graft site haematoma	10055152

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	Arteriovenous graft site haemorrhage	10055126
	Astringent therapy	10067372
	Atrial rupture	10048761
	Auricular haematoma	10003797
	Basal ganglia haematoma	10077031
	Basal ganglia haemorrhage	10067057
	Basilar artery perforation	10075736
	Bladder tamponade	10062656
	Bleeding varicose vein	10005144
	Blood blister	10005372
	Blood loss anaemia	10082297
	Blood urine	10005863
	Blood urine present	10018870
	Bloody discharge	10057687
	Bloody peritoneal effluent	10067442
	Bone contusion	10066251
	Bone marrow haemorrhage	10073581
	Brain contusion	10052346
	Brain stem haematoma	10073230
	Brain stem haemorrhage	10006145
	Brain stem microhaemorrhage	10071205
	Breast haematoma	10064753
	Breast haemorrhage	10006254
	Broad ligament haematoma	10006375
	Bronchial haemorrhage	10065739
	Bronchial varices haemorrhage	10079163
	Bullous haemorrhagic dermatosis	10083809
	Bursal haematoma	10077818
	Cardiac contusion	10073356
	Carotid aneurysm rupture	10051328
	Carotid artery perforation	10075728
	Catheter site bruise	10063587
	Catheter site haematoma	10055662
	Catheter site haemorrhage	10051099
	Central nervous system haemorrhage	10072043
	Cephalhaematoma	10008014
	Cerebellar haematoma	10061038
	Cerebellar haemorrhage	10008030
	Cerebellar microhaemorrhage	10071206
	Cerebral aneurysm perforation	10075394
	Cerebral aneurysm ruptured syphilitic	10008076
	Cerebral arteriovenous malformation haemorrhagic	10008086
	Cerebral artery perforation	10075734
	Cerebral cyst haemorrhage	10082099
	Cerebral haematoma	10053942
	Cerebral haemorrhage	10008111
	Cerebral haemorrhage foetal	10050157

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	Cerebral haemorrhage neonatal	10008112
	Cerebral microhaemorrhage	10067277
	Cervix haematoma uterine	10050020
	Cervix haemorrhage uterine	10050022
	Chest wall haematoma	10076597
	Choroidal haematoma	10068642
	Choroidal haemorrhage	10008786
	Chronic gastrointestinal bleeding	10050399
	Chronic pigmented purpura	10072726
	Ciliary body haemorrhage	10057417
	Coital bleeding	10065019
	Colonic haematoma	10009996
	Conjunctival haemorrhage	10010719
	Contusion	10050584
	Corneal bleeding	10051558
	Cullen's sign	10059029
	Cystitis haemorrhagic	10011793
	Deep dissecting haematoma	10074718
	Diarrhoea haemorrhagic	10012741
	Disseminated intravascular coagulation	10013442
	Diverticulitis intestinal haemorrhagic	10013541
	Diverticulum intestinal haemorrhagic	10013560
	Duodenal ulcer haemorrhage	10013839
	Duodenitis haemorrhagic	10013865
	Dysfunctional uterine bleeding	10013908
	Ear haemorrhage	10014009
	Ecchymosis	10014080
	Encephalitis haemorrhagic	10014589
	Enterocolitis haemorrhagic	10014896
	Epidural haemorrhage	10073681
	Epistaxis	10015090
	Exsanguination	10015719
	Extra-axial haemorrhage	10078254
	Extradural haematoma	10015769
	Extradural haematoma evacuation	10082797
	Extravasation blood	10015867
	Eye contusion	10073354
	Eye haematoma	10079891
	Eye haemorrhage	10015926
	Eyelid bleeding	10053196
	Eyelid contusion	10075018
	Eyelid haematoma	10064976
	Femoral artery perforation	10075739
	Femoral vein perforation	10075745
	Foetal-maternal haemorrhage	10016871
	Fothergill sign positive	10081749
	Gastric haemorrhage	10017788

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	Gastric ulcer haemorrhage	10017826
	Gastric ulcer haemorrhage, obstructive	10017829
	Gastric varices haemorrhage	10057572
	Gastritis alcoholic haemorrhagic	10017857
	Gastritis haemorrhagic	10017866
	Gastroduodenal haemorrhage	10053768
	Gastrointestinal haemorrhage	10017955
	Gastrointestinal polyp haemorrhage	10074437
	Gastrointestinal ulcer haemorrhage	10056743
	Gastrointestinal vascular malformation haemorrhagic	10080561
	Genital contusion	10073355
	Genital haemorrhage	10061178
	Gingival bleeding	10018276
	Graft haemorrhage	10063577
	Grey Turner's sign	10075426
	Haemangioma rupture	10084040
	Haemarthrosis	10018829
	Haematemesis	10018830
	Haematochezia	10018836
	Haematocoele	10018833
	Haematoma	10018852
	Haematoma evacuation	10060733
	Haematoma infection	10051564
	Haematoma muscle	10055890
	Haematosalpinx	10050468
	Haematospermia	10018866
	Haematotympanum	10063013
	Haematuria	10018867
	Haematuria traumatic	10018871
	Haemobilia	10058947
	Haemoperitoneum	10018935
	Haemophilic arthropathy	10065057
	Haemophilic pseudotumour	10073770
	Haemoptysis	10018964
	Haemorrhage	10055798
	Haemorrhage coronary artery	10055803
	Haemorrhage foetal	10061191
	Haemorrhage in pregnancy	10018981
	Haemorrhage intracranial	10018985
	Haemorrhage neonatal	10061993
	Haemorrhage subcutaneous	10018999
	Haemorrhage subepidermal	10019001
	Haemorrhage urinary tract	10055847
	Haemorrhagic adrenal infarction	10079902
	Haemorrhagic arteriovenous malformation	10064595
	Haemorrhagic ascites	10059766
	Haemorrhagic breast cyst	10077443

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	Haemorrhagic cerebral infarction	10019005
	Haemorrhagic cyst	10059189
	Haemorrhagic diathesis	10062713
	Haemorrhagic disease of newborn	10019008
	Haemorrhagic disorder	10019009
	Haemorrhagic erosive gastritis	10067786
	Haemorrhagic hepatic cyst	10067796
	Haemorrhagic infarction	10019013
	Haemorrhagic necrotic pancreatitis	10076058
	Haemorrhagic ovarian cyst	10060781
	Haemorrhagic stroke	10019016
	Haemorrhagic thyroid cyst	10072256
	Haemorrhagic transformation stroke	10055677
	Haemorrhagic tumour necrosis	10054096
	Haemorrhagic urticaria	10059499
	Haemorrhagic vasculitis	10071252
	Haemorrhoidal haemorrhage	10054787
	Haemostasis	10067439
	Haemothorax	10019027
	Henoch-Schonlein purpura	10019617
	Hepatic haemangioma rupture	10054885
	Hepatic haematoma	10019676
	Hepatic haemorrhage	10019677
	Hereditary haemorrhagic telangiectasia	10019883
	Hyperfibrinolysis	10074737
	Hyphaema	10020923
	Iliac artery perforation	10075731
	Iliac artery rupture	10072789
	Iliac vein perforation	10075744
	Immune thrombocytopenia	10083842
	Implant site bruising	10063850
	Implant site haematoma	10063780
	Implant site haemorrhage	10053995
	Incision site haematoma	10059241
	Incision site haemorrhage	10051100
	Increased tendency to bruise	10021688
	Induced abortion haemorrhage	10052844
	Inferior vena cava perforation	10075742
	Infusion site bruising	10059203
	Infusion site haematoma	10065463
	Infusion site haemorrhage	10065464
	Injection site bruising	10022052
	Injection site haematoma	10022066
	Injection site haemorrhage	10022067
	Instillation site bruise	10073630
	Instillation site haematoma	10073609
	Instillation site haemorrhage	10073610

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	Internal haemorrhage	10075192
	Intestinal haematoma	10069829
	Intestinal haemorrhage	10059175
	Intestinal varices haemorrhage	10078058
	Intra-abdominal haematoma	10056457
	Intra-abdominal haemorrhage	10061249
	Intracerebral haematoma evacuation	10062025
	Intracranial haematoma	10059491
	Intracranial tumour haemorrhage	10022775
	Intraocular haematoma	10071934
	Intrapartum haemorrhage	10067703
	Intraventricular haemorrhage	10022840
	Intraventricular haemorrhage neonatal	10022841
	Iris haemorrhage	10057418
	Joint microhaemorrhage	10077666
	Kidney contusion	10023413
	Lacrimal haemorrhage	10069930
	Large intestinal haemorrhage	10052534
	Large intestinal ulcer haemorrhage	10061262
	Laryngeal haematoma	10070885
	Laryngeal haemorrhage	10065740
	Lip haematoma	10066304
	Lip haemorrhage	10049297
	Liver contusion	10067266
	Lower gastrointestinal haemorrhage	10050953
	Lower limb artery perforation	10075730
	Lymph node haemorrhage	10074270
	Mallory-Weiss syndrome	10026712
	Mediastinal haematoma	10049941
	Mediastinal haemorrhage	10056343
	Medical device site bruise	10075570
	Medical device site haematoma	10075577
	Medical device site haemorrhage	10075578
	Melaena	10027141
	Melaena neonatal	10049777
	Meningorrhagia	10052593
	Menometrorrhagia	10027295
	Menorrhagia	10027313
	Mesenteric haematoma	10071557
	Mesenteric haemorrhage	10060717
	Metrorrhagia	10027514
	Mouth haemorrhage	10028024
	Mucocutaneous haemorrhage	10076048
	Mucosal haemorrhage	10061298
	Muscle contusion	10070757
	Muscle haemorrhage	10028309
	Myocardial haemorrhage	10048849

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	Myocardial rupture	10028604
	Naevus haemorrhage	10062955
	Nail bed bleeding	10048891
	Nasal septum haematoma	10075027
	Neonatal gastrointestinal haemorrhage	10074159
	Nephritis haemorrhagic	10029132
	Nipple exudate bloody	10029418
	Ocular retrobulbar haemorrhage	10057571
	Oesophageal haemorrhage	10030172
	Oesophageal intramural haematoma	10077486
	Oesophageal ulcer haemorrhage	10030202
	Oesophageal varices haemorrhage	10030210
	Oesophagitis haemorrhagic	10030219
	Optic disc haemorrhage	10030919
	Optic nerve sheath haemorrhage	10030941
	Oral blood blister	10076590
	Oral contusion	10078170
	Oral mucosa haematoma	10074779
	Oral purpura	10083533
	Orbital haematoma	10083565
	Orbital haemorrhage	10031045
	Osteorrhagia	10051937
	Ovarian haematoma	10033263
	Ovarian haemorrhage	10065741
	Palpable purpura	10056872
	Pancreatic haemorrhage	10033625
	Pancreatic pseudocyst haemorrhage	10083813
	Pancreatitis haemorrhagic	10033650
	Papillary muscle haemorrhage	10059164
	Paranasal sinus haematoma	10069702
	Paranasal sinus haemorrhage	10080108
	Parathyroid haemorrhage	10059051
	Parotid gland haemorrhage	10051166
	Pelvic haematoma	10054974
	Pelvic haematoma obstetric	10034248
	Pelvic haemorrhage	10063678
	Penile contusion	10073352
	Penile haematoma	10070656
	Penile haemorrhage	10034305
	Peptic ulcer haemorrhage	10034344
	Pericardial haemorrhage	10034476
	Perineal haematoma	10034520
	Periorbital haematoma	10034544
	Periorbital haemorrhage	10071697
	Periosteal haematoma	10077341
	Peripartum haemorrhage	10072693
	Peripheral artery aneurysm rupture	10079908

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	Peripheral artery haematoma	10081077
	Peritoneal haematoma	10058095
	Periventricular haemorrhage neonatal	10076706
	Petechiae	10034754
	Pharyngeal contusion	10083176
	Pharyngeal haematoma	10068121
	Pharyngeal haemorrhage	10034827
	Pituitary apoplexy	10056447
	Pituitary haemorrhage	10049760
	Placenta praevia haemorrhage	10035121
	Polymenorrhagia	10064050
	Post abortion haemorrhage	10036246
	Post procedural contusion	10073353
	Post procedural haematoma	10063188
	Post procedural haematuria	10066225
	Post procedural haemorrhage	10051077
	Post transfusion purpura	10072265
	Postmenopausal haemorrhage	10055870
	Postpartum haemorrhage	10036417
	Post-traumatic punctate intraepidermal haemorrhage	10071639
	Premature separation of placenta	10036608
	Procedural haemorrhage	10071229
	Proctitis haemorrhagic	10036778
	Prostatic haemorrhage	10036960
	Pulmonary alveolar haemorrhage	10037313
	Pulmonary contusion	10037370
	Pulmonary haematoma	10054991
	Pulmonary haemorrhage	10037394
	Pulmonary haemorrhage neonatal	10082194
	Puncture site bruise	10082035
	Puncture site haematoma	10081957
	Puncture site haemorrhage	10051101
	Purpura	10037549
	Purpura fulminans	10037556
	Purpura neonatal	10037557
	Purpura non-thrombocytopenic	10057739
	Purpura senile	10037560
	Putamen haemorrhage	10058940
	Radiation associated haemorrhage	10072281
	Rectal haemorrhage	10038063
	Rectal ulcer haemorrhage	10038081
	Renal artery perforation	10075737
	Renal cyst haemorrhage	10059846
	Renal haematoma	10038459
	Renal haemorrhage	10038460
	Respiratory tract haemorrhage	10038727
	Respiratory tract haemorrhage neonatal	10038728

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	Retinal aneurysm rupture	10079121
	Retinal haemorrhage	10038867
	Retinopathy haemorrhagic	10051447
	Retroperitoneal haematoma	10058360
	Retroperitoneal haemorrhage	10038980
	Retroplacental haematoma	10054798
	Ruptured cerebral aneurysm	10039330
	Scleral haemorrhage	10050508
	Scrotal haematocoele	10061517
	Scrotal haematoma	10039749
	Scrotal haemorrhage	10061361
	Shock haemorrhagic	10049771
	Skin haemorrhage	10064265
	Skin neoplasm bleeding	10060712
	Skin ulcer haemorrhage	10050377
	Small intestinal haemorrhage	10052535
	Small intestinal ulcer haemorrhage	10061550
	Soft tissue haemorrhage	10051297
	Spermatic cord haemorrhage	10065742
	Spinal cord haematoma	10076051
	Spinal cord haemorrhage	10048992
	Spinal epidural haematoma	10050162
	Spinal epidural haemorrhage	10049236
	Spinal subarachnoid haemorrhage	10073564
	Spinal subdural haematoma	10050164
	Spinal subdural haemorrhage	10073563
	Spleen contusion	10073533
	Splenic artery perforation	10075738
	Splenic haematoma	10041646
	Splenic haemorrhage	10041647
	Splenic varices haemorrhage	10068662
	Splinter haemorrhages	10041663
	Spontaneous haematoma	10065304
	Spontaneous haemorrhage	10074557
	Stoma site haemorrhage	10074508
	Stomatitis haemorrhagic	10042132
	Subarachnoid haematoma	10076701
	Subarachnoid haemorrhage	10042316
	Subarachnoid haemorrhage neonatal	10042317
	Subcapsular hepatic haematoma	10083383
	Subcapsular renal haematoma	10083385
	Subcapsular splenic haematoma	10083384
	Subchorionic haematoma	10072596
	Subchorionic haemorrhage	10071010
	Subclavian artery perforation	10075740
	Subclavian vein perforation	10075743
	Subcutaneous haematoma	10042345

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	Subdural haematoma	10042361
	Subdural haematoma evacuation	10042363
	Subdural haemorrhage	10042364
	Subdural haemorrhage neonatal	10042365
	Subendocardial haemorrhage	10082459
	Subgaleal haematoma	10069510
	Subgaleal haemorrhage	10080900
	Subretinal haematoma	10071935
	Superior vena cava perforation	10075741
	Testicular haemorrhage	10051877
	Thalamus haemorrhage	10058939
	Third stage postpartum haemorrhage	10043449
	Thoracic haemorrhage	10062744
	Thrombocytopenic purpura	10043561
	Thrombotic thrombocytopenic purpura	10043648
	Thyroid haemorrhage	10064224
	Tongue haematoma	10043959
	Tongue haemorrhage	10049870
	Tonsillar haemorrhage	10057450
	Tooth pulp haemorrhage	10072228
	Tooth socket haemorrhage	10064946
	Tracheal haemorrhage	10062543
	Traumatic haematoma	10044522
	Traumatic haemorrhage	10053476
	Traumatic haemothorax	10074487
	Traumatic intracranial haematoma	10079013
	Traumatic intracranial haemorrhage	10061387
	Tumour haemorrhage	10049750
	Ulcer haemorrhage	10061577
	Umbilical cord haemorrhage	10064534
	Umbilical haematoma	10068712
	Umbilical haemorrhage	10045455
	Upper gastrointestinal haemorrhage	10046274
	Ureteric haemorrhage	10065743
	Urethral haemorrhage	10049710
	Urinary bladder haematoma	10083358
	Urinary bladder haemorrhage	10046528
	Urogenital haemorrhage	10050058
	Uterine haematoma	10063875
	Uterine haemorrhage	10046788
	Vaccination site bruising	10069484
	Vaccination site haematoma	10069472
	Vaccination site haemorrhage	10069475
	Vaginal haematoma	10046909
	Vaginal haemorrhage	10046910
	Varicose vein ruptured	10046999
	Vascular access site bruising	10077767

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	Vascular access site haematoma	10077647
	Vascular access site haemorrhage	10077643
	Vascular access site rupture	10077652
	Vascular anastomotic haemorrhage	10084092
	Vascular graft haemorrhage	10077721
	Vascular pseudoaneurysm ruptured	10053949
	Vascular purpura	10047097
	Vascular rupture	10053649
	Vein rupture	10077110
	Venous haemorrhage	10065441
	Venous perforation	10075733
	Ventricle rupture	10047279
	Vertebral artery perforation	10075735
	Vessel puncture site bruise	10063881
	Vessel puncture site haematoma	10065902
	Vessel puncture site haemorrhage	10054092
	Vitreous haematoma	10071936
	Vitreous haemorrhage	10047655
	Vulval haematoma	10047756
	Vulval haematoma evacuation	10047757
	Vulval haemorrhage	10063816
	Withdrawal bleed	10047998
	Wound haematoma	10071504
	Wound haemorrhage	10051373
Cholestasis and jaundice of hepatic origin	Bilirubin excretion disorder	10061009
	Cholaemia	10048611
	Cholestasis	10008635
	Cholestatic liver injury	10067969
	Cholestatic pruritus	10064190
	Drug-induced liver injury	10072268
	Hepatitis cholestatic	10019754
	Hyperbilirubinaemia	10020578
	Icterus index increased	10021209
	Jaundice	10023126
	Jaundice cholestatic	10023129
	Jaundice hepatocellular	10023136
	Mixed liver injury	10066758
	Ocular icterus	10058117
	Parenteral nutrition associated liver disease	10074151
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	Acquired hepatocerebral degeneration	10080860
	Acute hepatic failure	10000804
	Acute on chronic liver failure	10077305
	Acute yellow liver atrophy	10070815
	Ascites	10003445
	Asterixis	10003547
	Bacterascites	10068547
	Biliary cirrhosis	10004659

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	Biliary fibrosis	10004664
	Cardiohepatic syndrome	10082480
	Cholestatic liver injury	10067969
	Chronic hepatic failure	10057573
	Coma hepatic	10010075
	Cryptogenic cirrhosis	10063075
	Diabetic hepatopathy	10071265
	Drug-induced liver injury	10072268
	Duodenal varices	10051010
	Gallbladder varices	10072319
	Gastric variceal injection	10076237
	Gastric variceal ligation	10076238
	Gastric varices	10051012
	Gastric varices haemorrhage	10057572
	Gastrooesophageal variceal haemorrhage prophylaxis	10066597
	Hepatectomy	10061997
	Hepatic atrophy	10019637
	Hepatic calcification	10065274
	Hepatic cirrhosis	10019641
	Hepatic encephalopathy	10019660
	Hepatic encephalopathy prophylaxis	10066599
	Hepatic failure	10019663
	Hepatic fibrosis	10019668
	Hepatic hydrothorax	10067365
	Hepatic infiltration eosinophilic	10064668
	Hepatic lesion	10061998
	Hepatic necrosis	10019692
	Hepatic steato-fibrosis	10077215
	Hepatic steatosis	10019708
	Hepatitis fulminant	10019772
	Hepatobiliary disease	10062000
	Hepatocellular foamy cell syndrome	10053244
	Hepatocellular injury	10019837
	Hepatopulmonary syndrome	10052274
	Hepatorenal failure	10019845
	Hepatorenal syndrome	10019846
	Hepatotoxicity	10019851
	Immune-mediated cholangitis	10083406
	Immune-mediated hepatic disorder	10083521
	Intestinal varices	10071502
	Intestinal varices haemorrhage	10078058
	Liver dialysis	10076640
	Liver disorder	10024670
	Liver injury	10067125
	Liver operation	10062040
	Liver transplant	10024714
	Lupoid hepatic cirrhosis	10025129

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	Minimal hepatic encephalopathy	10076204
	Mixed liver injury	10066758
	Nodular regenerative hyperplasia	10051081
	Nonalcoholic fatty liver disease	10082249
	Non-alcoholic steatohepatitis	10053219
	Non-cirrhotic portal hypertension	10077259
	Oedema due to hepatic disease	10049631
	Oesophageal varices haemorrhage	10030210
	Peripancreatic varices	10073215
	Portal fibrosis	10074726
	Portal hypertension	10036200
	Portal hypertensive colopathy	10079446
	Portal hypertensive enteropathy	10068923
	Portal hypertensive gastropathy	10050897
	Portal vein cavernous transformation	10073979
	Portal vein dilatation	10073209
	Portopulmonary hypertension	10067281
	Primary biliary cholangitis	10080429
	Regenerative siderotic hepatic nodule	10080679
	Renal and liver transplant	10052279
	Retrograde portal vein flow	10067338
	Reye's syndrome	10039012
	Reynold's syndrome	10070953
	Splenic varices	10067823
	Splenic varices haemorrhage	10068662
	Steatohepatitis	10076331
	Subacute hepatic failure	10056956
	Sugiura procedure	10083010
	Varices oesophageal	10056091
	Varicose veins of abdominal wall	10072284
	White nipple sign	10078438
Hepatitis, non-infectious	Acute graft versus host disease in liver	10066263
	Allergic hepatitis	10071198
	Alloimmune hepatitis	10080576
	Autoimmune hepatitis	10003827
	Chronic graft versus host disease in liver	10072160
	Chronic hepatitis	10008909
	Graft versus host disease in liver	10064676
	Hepatitis	10019717
	Hepatitis acute	10019727
	Hepatitis cholestatic	10019754
	Hepatitis chronic active	10019755
	Hepatitis chronic persistent	10019759
	Hepatitis fulminant	10019772
	Hepatitis toxic	10019795
	Immune-mediated hepatitis	10078962
	Ischaemic hepatitis	10023025

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	Lupus hepatitis	10067737
	Non-alcoholic steatohepatitis	10053219
	Radiation hepatitis	10051015
	Steatohepatitis	10076331
Liver related investigations, signs and symptoms	Alanine aminotransferase abnormal	10001547
	Alanine aminotransferase increased	10001551
	Ammonia abnormal	10001942
	Ammonia increased	10001946
	Ascites	10003445
	Aspartate aminotransferase abnormal	10003477
	Aspartate aminotransferase increased	10003481
	AST/ALT ratio abnormal	10082832
	Bacterascites	10068547
	Bile output abnormal	10051344
	Bile output decreased	10051343
	Biliary ascites	10074150
	Bilirubin conjugated abnormal	10067718
	Bilirubin conjugated increased	10004685
	Bilirubin urine present	10077356
	Biopsy liver abnormal	10004792
	Blood bilirubin abnormal	10058477
	Blood bilirubin increased	10005364
	Blood bilirubin unconjugated increased	10005370
	Bromosulphthalein test abnormal	10006408
	Child-Pugh-Turcotte score abnormal	10077020
	Child-Pugh-Turcotte score increased	10068287
	Computerised tomogram liver abnormal	10078360
	Congestive hepatopathy	10084058
	Foetor hepaticus	10052554
	Galactose elimination capacity test abnormal	10059710
	Galactose elimination capacity test decreased	10059712
	Gamma-glutamyltransferase abnormal	10017688
	Gamma-glutamyltransferase increased	10017693
	Guanase increased	10051333
	Hepaplastin abnormal	10019621
	Hepaplastin decreased	10019622
	Hepatic artery flow decreased	10068997
	Hepatic enzyme abnormal	10062685
	Hepatic enzyme decreased	10060794
	Hepatic enzyme increased	10060795
	Hepatic function abnormal	10019670
	Hepatic hydrothorax	10067365
	Hepatic hypertrophy	10076254
	Hepatic mass	10057110
	Hepatic pain	10019705
	Hepatic sequestration	10066244
	Hepatic vascular resistance increased	10068358

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	Hepatic venous pressure gradient abnormal	10083172
	Hepatic venous pressure gradient increased	10083171
	Hepatobiliary scan abnormal	10066195
	Hepatomegaly	10019842
	Hepatosplenomegaly	10019847
	Hyperammonaemia	10020575
	Hyperbilirubinaemia	10020578
	Hypercholia	10051924
	Hypertransaminasaemia	10068237
	Kayser-Fleischer ring	10023321
	Liver function test abnormal	10024690
	Liver function test decreased	10077677
	Liver function test increased	10077692
	Liver induration	10052550
	Liver palpable	10075895
	Liver scan abnormal	10061947
	Liver tenderness	10024712
	Magnetic resonance imaging liver abnormal	10083123
	Magnetic resonance proton density fat fraction measurement	10082443
	Mitochondrial aspartate aminotransferase increased	10064712
	Molar ratio of total branched-chain amino acid to tyrosine	10066869
	Oedema due to hepatic disease	10049631
	Perihepatic discomfort	10054125
	Retrograde portal vein flow	10067338
	Total bile acids increased	10064558
	Transaminases abnormal	10062688
	Transaminases increased	10054889
	Ultrasound liver abnormal	10045428
	Urine bilirubin increased	10050792
	White nipple sign	10078438
	X-ray hepatobiliary abnormal	10056536
Hypertension	Accelerated hypertension	10000358
	Blood pressure ambulatory increased	10005732
	Blood pressure diastolic increased	10005739
	Blood pressure inadequately controlled	10051128
	Blood pressure increased	10005750
	Blood pressure management	10063926
	Blood pressure orthostatic increased	10053355
	Blood pressure systolic increased	10005760
	Catecholamine crisis	10081751
	Dialysis induced hypertension	10063067
	Diastolic hypertension	10012758
	Eclampsia	10014129
	Endocrine hypertension	10057615
	Essential hypertension	10015488
	Gestational hypertension	10070538
	HELLP syndrome	10049058

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	Hyperaldosteronism	10020571
	Hypertension	10020772
	Hypertension neonatal	10049781
	Hypertensive angiopathy	10059238
	Hypertensive cardiomegaly	10020801
	Hypertensive cardiomyopathy	10058222
	Hypertensive cerebrovascular disease	10077000
	Hypertensive crisis	10020802
	Hypertensive emergency	10058179
	Hypertensive encephalopathy	10020803
	Hypertensive end-organ damage	10079496
	Hypertensive heart disease	10020823
	Hypertensive nephropathy	10055171
	Hypertensive urgency	10058181
	Labile hypertension	10049079
	Malignant hypertension	10025600
	Malignant hypertensive heart disease	10025603
	Malignant renal hypertension	10026674
	Maternal hypertension affecting foetus	10026924
	Mean arterial pressure increased	10026985
	Metabolic syndrome	10052066
	Neurogenic hypertension	10067598
	Orthostatic hypertension	10065508
	Page kidney	10076704
	Postoperative hypertension	10050631
	Pre-eclampsia	10036485
	Prehypertension	10065918
	Procedural hypertension	10062886
	Renal hypertension	10038464
	Renal sympathetic nerve ablation	10074864
	Renovascular hypertension	10038562
	Retinopathy hypertensive	10038926
	Secondary aldosteronism	10039808
	Secondary hypertension	10039834
	Supine hypertension	10078932
	Systolic hypertension	10042957
	Withdrawal hypertension	10048007
Proteinuria	Albumin globulin ratio increased	10001567
	Albumin urine present	10001582
	Albuminuria	10001580
	Bence Jones protein urine present	10053112
	Bence Jones proteinuria	10004231
	Beta 2 microglobulin urine increased	10004501
	Globulinuria	10018352
	Microalbuminuria	10027525
	Myoglobinuria	10028629
	Orthostatic proteinuria	10031129

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	Protein urine	10037018
	Protein urine present	10053123
	Proteinuria	10037032
	Urine albumin/creatinine ratio increased	10053541
	Urine protein/creatinine ratio abnormal	10053539
	Urine protein/creatinine ratio increased	10053538
Thyroid dysfunction	Basedow's disease	10004161
	Endocrine ophthalmopathy	10060742
	Exophthalmos	10015683
	Hashitoxicosis	10067873
	Hyperthyroidism	10020850
	Immune-mediated hyperthyroidism	10083517
	Inappropriate thyroid stimulating hormone secretion	10075007
	Malignant exophthalmos	10075386
	Marine Lenhart syndrome	10068828
	Primary hyperthyroidism	10075899
	Secondary hyperthyroidism	10053260
	Thyroid dermatopathy	10069771
	Thyroid tuberculosis	10043774
	Thyrotoxic cardiomyopathy	10075043
	Thyrotoxic crisis	10043786
	Thyrotoxic myopathy	10081524
	Thyrotoxic periodic paralysis	10043788
	Toxic goitre	10075050
	Toxic nodular goitre	10044242
	Anti-thyroid antibody	10060325
	Anti-thyroid antibody positive	10060310
	Antithyroid arthritis syndrome	10073029
	Autoimmune thyroid disorder	10079165
	Autoimmune thyroiditis	10049046
	Biopsy thyroid gland abnormal	10004889
	Blood thyroid stimulating hormone abnormal	10005830
	Blood thyroid stimulating hormone decreased	10005832
	Blood thyroid stimulating hormone increased	10005833
	Butanol-extractable iodine decreased	10006818
	Butanol-extractable iodine increased	10006819
	Congenital thyroid disorder	10076602
	Euthyroid sick syndrome	10015549
	Free thyroxine index abnormal	10050747
	Free thyroxine index decreased	10050748
	Free thyroxine index increased	10050749
	Gamma radiation therapy to thyroid	10017685
	Goitre	10018498
	Hashimoto's encephalopathy	10069432
	Immune-mediated thyroiditis	10083071
	Infectious thyroiditis	10071250
	Iodine uptake abnormal	10022918

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	Iodine uptake decreased	10022920
	Iodine uptake increased	10022922
	Orbital decompression	10072141
	Photon radiation therapy to thyroid	10034957
	Polyglandular autoimmune syndrome type II	10036073
	Polyglandular autoimmune syndrome type III	10064115
	Protein bound iodine decreased	10037001
	Protein bound iodine increased	10037002
	Radioactive iodine therapy	10037784
	Radiotherapy to thyroid	10062098
	Reverse tri-iodothyronine decreased	10060307
	Reverse tri-iodothyronine increased	10060306
	Silent thyroiditis	10079012
	Thyreostatic therapy	10065359
	Thyroglobulin absent	10054025
	Thyroglobulin decreased	10054011
	Thyroglobulin increased	10054010
	Thyroglobulin present	10054024
	Thyroid disorder	10043709
	Thyroid dysfunction in pregnancy	10056525
	Thyroid electron radiation therapy	10043722
	Thyroid function test abnormal	10043730
	Thyroid gland scan abnormal	10062149
	Thyroid hemiagenesis	10077609
	Thyroid hormone replacement therapy	10068076
	Thyroid hormones increased	10063161
	Thyroid operation	10062126
	Thyroid pain	10043757
	Thyroid releasing hormone challenge test abnormal	10043764
	Thyroid stimulating immunoglobulin increased	10071389
	Thyroid therapy	10065358
	Thyroidectomy	10062127
	Thyroiditis	10043778
	Thyroiditis acute	10043780
	Thyroiditis chronic	10043781
	Thyroiditis fibrous chronic	10043782
	Thyroiditis subacute	10043784
	Thyroxin binding globulin abnormal	10051423
	Thyroxin binding globulin decreased	10051421
	Thyroxin binding globulin increased	10051420
	Thyroxine abnormal	10043814
	Thyroxine decreased	10043816
	Thyroxine free abnormal	10055158
	Thyroxine free decreased	10055162
	Thyroxine free increased	10055163
	Thyroxine increased	10043818
	Thyroxine therapy	10052702

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	Tri-iodothyronine abnormal	10044592
	Tri-iodothyronine decreased	10044594
	Tri-iodothyronine free abnormal	10053794
	Tri-iodothyronine free decreased	10053791
	Tri-iodothyronine free increased	10053790
	Tri-iodothyronine free normal	10053793
	Tri-iodothyronine increased	10044596
	Tri-iodothyronine uptake abnormal	10062215
	Tri-iodothyronine uptake decreased	10044601
	Tri-iodothyronine uptake increased	10044602
	Ultrasound thyroid abnormal	10060987
	X-ray therapy to thyroid	10048207
	Autoimmune hypothyroidism	10076644
	Congenital hypothyroidism	10010510
	Generalised resistance to thyroid hormone	10018096
	Hypothyroidic goitre	10059844
	Hypothyroidism	10021114
	Immune-mediated hypothyroidism	10083075
	Myxoedema	10028665
	Myxoedema coma	10060819
	Post procedural hypothyroidism	10065306
	Primary hypothyroidism	10036697
	Secondary hypothyroidism	10039840
	Tertiary hypothyroidism	10043289
	Thyroid atrophy	10043693
	Thyroid stimulating hormone deficiency	10078564
	Transient hypothyroxinaemia of prematurity	10075901
	Atrophic thyroiditis	10077172

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Initials: 0
PPD
AutoNav: Enabled
One IMS Way
EnvelopeId Stamping: Disabled
Plymouth Meeting, 19462
Time Zone: (UTC+08:00) Taipei
PPD

Record Tracking

Status: Original
06-Nov-2022 | 18:28
Holder: PPD
Location: DocuSign

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: 06-Nov-2022 | 18:40 Viewed: 07-Nov-2022 | 09:54 Signed: 07-Nov-2022 | 10:59
Electronic Record and Signature Disclosure: Accepted: 07-Nov-2022 | 09:54 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 am the author of this document	Sent: 07-Nov-2022 | 10:59 Viewed: 07-Nov-2022 | 17:34 Signed: 07-Nov-2022 | 17:35
Electronic Record and Signature Disclosure: Accepted: 28-Apr-2021 | 02:03 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: 07-Nov-2022 | 17:35 Viewed: 07-Nov-2022 | 19:26 Signed: 07-Nov-2022 | 19:27
Electronic Record and Signature Disclosure: Accepted: 07-Nov-2022 | 19:25 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**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	06-Nov-2022 | 18:40
Certified Delivered	Security Checked	07-Nov-2022 | 19:26
Signing Complete	Security Checked	07-Nov-2022 | 19:27
Completed	Security Checked	07-Nov-2022 | 19:27
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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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

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

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