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STATISTICAL ANALYSIS PLAN

DZB-CS-202

A Phase 1b/2 study of derazantinib as monotherapy and combination therapy with paclitaxel, ramucirumab or atezolizumab in patients with HER2-negative gastric adenocarcinoma harboring *FGFR* genetic aberrations (FIDES-03)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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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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ABBREVIATIONS

AE	Adverse Event
ACS	Abnormal, clinically significant
ANCS	Abnormal, not clinically significant
ATC	Anatomic therapeutic class
BICR	Blinded Independent Central Review
BID	Twice a day (*bis in die*)
BMI	Body mass index
bpm	Beat per minute
BSA	Body surface area
CR	Complete response
COVID-19	Coronavirus Disease 2019
CTCAE	Common terminology criteria of adverse events
CTMS	Clinical trial management system
CxDx	Cycle (cycle number), Day (day number), e.g.C4D1 = Cycle 4, Day 1
DCR	Disease control rate
DL	Dose level
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ENR	All patients enrolled set
FGFR	Fibroblast growth factor receptor
$FGFR^{fus/amp/mt}$	FGFR2 gene fusion, rearrangement or amplification, or FGFR1–3 mutation
$FGFR1–3^{mt}$	FGFR1–3 mutation
$FGFR2^{fus}$	FGFR2 gene fusion or rearrangement
$FGFR2^{high-amp}$	High-level FGFR2 gene amplification
GAC	Gastric adenocarcinoma
HER2	Human epidermal growth factor receptor 2
$HER2^{neg}$	HER2-negative

IDMC	Independent Data Monitoring Committee
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
ms	Millisecond
MTD	Maximum Tolerated Dose
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PFS4	Progression-free survival rate at 4 months
PK	Pharmacokinetic(s)
PP	Per-Protocol
PR	Partial response
PT	Preferred Term
QD	Once Daily
RP2D	Recommended Phase 2 dose
SAP	Statistical Analysis Plan
SD	Stable disease
SI	International Standard unit
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TNM	Primitive tumor, nodes, metastasis

[redacted]

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and PK/PD data for Protocol DZB-CS-202. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed for the final analysis.

This statistical analysis plan (SAP) is based on protocol version v5.0, dated 21 May 2021.

A separated document will be prepared for PK analyses.

The study comprises three substudies; only substudy 1 and 2 are described in this document as substudy 3 was never initiated:

- Substudy 1: A Phase 2a study comprising three cohorts:
  - Cohort 1.1 $FGFR2^{fus}$ / $FGFR2^{high-amp}$ patients to be treated with 300 mg QD derazantinib
  - Cohort 1.2 $FGFR1–3^{mut}$ patients to be treated with 300 mg QD derazantinib
  - Cohort 1.3 $FGFR^{fus/amp/mut}$ patients to be treated with 200 mg BID derazantinib
- Substudy 2: A Phase 1b/2 dose-finding study of patients to be treated with derazantinib-paclitaxel-ramucirumabı in combination

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

2.1.1. PRIMARY OBJECTIVE OF SUBSTUDY 1 COHORTS 1.1 AND 1.2

The primary objective of Substudy 1 for cohort 1.1 and cohort 1.2 is to evaluate the objective response rate (ORR) of patients with $HER2^{neg}$ $FGFR^{fus/amp/mut}$ GAC treated with derazantinib monotherapy.

2.1.2. PRIMARY OBJECTIVE OF SUBSTUDY 1 COHORT 1.3

The primary objective of Substudy 1 for cohort 1.3 is to evaluate the progression-free survival rate at 4 months (PFS4) of patients with $HER2^{neg}$ $FGFR^{fus/amp/mut}$ GAC treated with derazantinib monotherapy.

2.1.3. PRIMARY OBJECTIVE OF SUBSTUDY 2

The primary objective of Substudy 2 is to determine the recommended phase 2 dose (RP2D) of derazantinib-paclitaxel-ramucirumab in combination in patients with HER2^{neg} FGFR$^{fus/amp/mut}$ GAC.

2.2. SECONDARY OBJECTIVES

2.2.1. SECONDARY OBJECTIVES OF SUBSTUDY 1

The secondary objectives of Substudy 1 are:

- To evaluate the efficacy of derazantinib, as measured by ORR (Cohort 1.3), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- To assess the safety and tolerability of the study treatments
- To characterize the PK profile of derazantinib 200 mg BID monotherapy (and, if applicable, derazantinib metabolites)

2.2.2. SECONDARY OBJECTIVES OF SUBSTUDY 2

The secondary objectives of Substudy 2 are:

- To evaluate the efficacy of derazantinib-paclitaxel-ramucirumab in combination, as measured by ORR, DCR, DOR, PFS and OS
- To assess the safety and tolerability profile of derazantinib-paclitaxel-ramucirumab in combination
- To characterize the PK profile of derazantinib (and, if applicable, derazantinib metabolites) when administered in combination with paclitaxel-ramucirumab
- To characterize the PK profile of paclitaxel when administered in combination with derazantinib-ramucirumab.

2.3. EXPLORATORY OBJECTIVES

2.3.1. EXPLORATORY OBJECTIVES OF SUBSTUDY 1

The exploratory objectives of Substudy 1 are:

- Efficacy:

- To describe the type of FGFR$^{fus/amp/mut}$ genetic aberration in responders and non-responders
- To explore the concordance of liquid biopsy and tumor biopsy results
- To explore the molecular profile and gene expression profile of radiographic and metabolic responders versus non-responders by pre-treatment biopsy
- To explore molecular profile and gene expression profile changes indicative of radiographic response versus non-response by Cycle 1 liquid biopsy
- To describe emerging genetic markers of resistance in (non)-responders

- Pharmacokinetic:
  - To explore the exposure of derazantinib alone (and, if applicable, derazantinib metabolites)

2.3.2. EXPLORATORY OBJECTIVES OF SUBSTUDY 2

No efficacy exploratory objectives for Substudy 2.

- Pharmacokinetic:
  - To explore the exposure of derazantinib in combination with paclitaxel-ramucirumab
  - To explore the exposure of paclitaxel in combination with derazantinib-ramucirumab

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This study is an open-label, multiple-cohort, multicenter study of derazantinib – a potent and well tolerated fibroblast growth factor receptor (FGFR) inhibitor of tyrosine kinases of FGFR 1, 2, and 3 – as monotherapy and combination therapy with paclitaxel and ramucirumab in patients with human epidermal growth factor receptor 2 negative (HER2$_{neg}$) adenocarcinoma of the stomach or gastro-esophageal junction harboring *FGFR2* gene fusions or other rearrangements ('FGFR2$_{fus}$'), high-level *FGFR2* gene amplifications ('FGFR2$^{high-amp}$'; i.e., a quantitative correlate of > 10 *FGFR2* gene copy numbers called by the NGS algorithm of the central diagnostic test), or *FGFR1–3* mutations ('FGFR1–3$_{mut}$'). These gene aberrations are collectively described in this protocol as 'FGFR$_{fus/amp/mut}$'. The study comprises three substudies; only substudies 1 and 2 are described in this document:

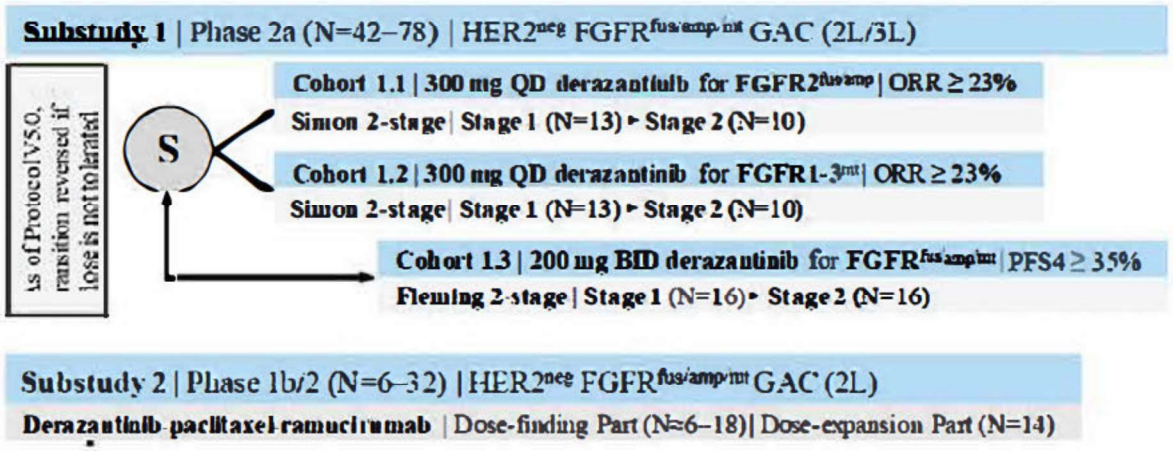
- Substudy 1: A Phase 2a study comprising three cohorts:
  - Cohort 1.1 FGFR2^{fus} / FGFR2$^{high-amp}$ patients to be treated with 300 mg QD derazantinib
  - Cohort 1.2 FGFR1–3^{mut} patients to be treated with 300 mg QD derazantinib

- Cohort 1.3 $FGFR^{fus/amp/mt}$ patients to be treated with 200 mg BID derazantinib

- Substudy 2: A Phase Ib/2 dose-finding study of patients to be treated with derazantinib-paclitaxel-ramucirumab in combination

The study enrolls patients with either metastatic or recurrent locally-advanced *HER2*-negative ($HER2_{neg}$) adenocarcinoma of the stomach or gastro-esophageal junction (gastric adenocarcinoma [GAC]) inoperable at the time of screening, and radiologically-confirmed disease progression after one (Substudy 2) or one or two (Substudy 1) standard treatment regimens. The safety cohorts of Substudy 2 comprise GAC patients considered fit to tolerate the novel combination adding derazantinib to the second-line standard-of-care treatment paclitaxel-ramucirumab.

Table A: Overview of study design



3.2. SCHEDULE OF EVENTS

Schedules of events can be found in Section 5 of the protocol (Table 1 to Table 4).

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The study has been prematurely stopped (sponsor decision). In this context, the scope of final analysis has been reduced. An exhaustive list of TLFs provided for CSR are described in the output template document.

The definition of mITT population has been updated to clarify the period of time that should be considered for the death of the patient: the death have to be considered if it occurs on or after the first dose of study treatment and until safety follow-up visit (inclusive).

3.4. FINAL ANALYSIS

All TLFs described in the output template document will be produced by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock and Sponsor Authorization of Analysis Sets.

4. ANALYSIS POPULATIONS

Agreement and authorization of patients included/excluded from each analysis population will be conducted prior the Database Lock for the Final Analysis.

4.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

Review of protocol deviations occurs at the monthly IQVIA internal review meeting. All protocol deviations will be identified and classified as major (defined as a deviation from protocol-related procedures that could affect integrity of the data or adversely affect patients) or minor during the conduct of study using CTMS.

4.2. ALL PATIENTS ENROLLED POPULATION [ENR]

The all patients enrolled (ENR) population will contain all patients who were allocated to treatment for Substudy 1 or Substudy 2.

4.3. SAFETY POPULATION

The Safety population comprises all patients who received at least one dose of study treatment (derazantinib, paclitaxel or ramucirumab). Data will be summarized according to the treatment actually received

4.4. INTENT-TO-TREAT POPULATION

The intent-to-treat (ITT) population comprises all patients enrolled and allocated to treatment for Substudy 1 or Substudy 2, regardless of the administration of the study treatment.

4.5. MODIFIED INTENT-TO-TREAT POPULATION

For single-arm non-comparison efficacy endpoint analyses in Substudies 1 and 2, a modified intent-to-treat (mITT) population will be used, comprising all patients who received at least one dose of derazantinib or derazantinib-paclitaxel-ramucirumab, in combination, and have at least one post-baseline imaging assessment in accordance with RECIST 1.1 or documented clinical progression (every effort should be made to objectively assess radiographic progression) or died from any cause on or after the first dose of study treatment and until safety follow-up visit (inclusive).

4.6. MTD POPULATION (SUBSTUDY 2 ONLY)

The MTD-determining population comprises all patients enrolled in the MTD Part who meet the following minimum criteria during the first 28-day treatment cycle (Cycle 1):

- received at least one dose of derazantinib-paclitaxel-ramucirumab in combination and has experienced a DLT
- or
- received ≥ 80% of the derazantinib-paclitaxel-ramucirumab dose, respectively, in Cycle 1 and, have been observed for ≥ 28 days following the first dose, and have been evaluated for safety.

Patients who do not meet these minimum evaluation requirements will be regarded as ineligible for the MTD-determining population. These patients will be included in the Safety and ITT populations, but will be excluded from the calculation of DLT incidence, and will be replaced by recruitment of additional patients.

If one patient experiences a DLT in any DL cohort among the first three enrolled and evaluable patients, the cohort will be expanded to six evaluable patients. The MTD is defined as the highest DL at which none or one of six participants (0% to 17%) experience a DLT (see Protocol v5.0 - Section 7.3.3 for DLT definition of treatment-related AEs). The MTD is exceeded when at least two of three to six participants (≥ 33% to 67%) experience a DLT in any DL cohort. Replacement of patients is described in Protocol v5.0 - Section 4.5.3.

5. GENERAL CONSIDERATIONS

5.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of any study treatment, (Day 1 is the day of the first dose of study treatment), and will be displayed in every listing where an assessment date or event date is displayed.

- If the date of the event is on or after the reference date then:

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

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

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in APPENDIX 2: Partial Date Conventions.

5.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, however adverse events (AEs) and medications commencing on the reference start date will be considered post-baseline.

5.3. 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 but will contribute to the best/worst case value where required (e.g. shift tables).

Listings will include scheduled, unscheduled, retest and early discontinuation data.

5.4. WINDOWING CONVENTIONS

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window (i.e., there will not be analysis by time window).

5.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

5.6. COMMON CALCULATIONS

For quantitative measurements:

- Change from baseline will be calculated as: Test Value at Visit X – Baseline Value
- Percent change from baseline will calculated as: ((Test Value at Visit X – Baseline Value) / Baseline Value) x 100

5.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

6. STATISTICAL CONSIDERATIONS

6.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

6.2. MISSING DATA

Missing/Partial dates will be handling as defined in APPENDIX 2.

Patients whose tumor imaging assessment response is unknown or not reported will be treated as non-responders.

No other missing data imputation will be done.

6.3. REPLACEMENT OF PATIENTS

Replacement of patients is described in Protocol v5.0 - Section 4.5.3.

6.4. EXAMINATION OF SUBGROUPS

No subgroup analysis will be performed.

7. OUTPUT PRESENTATIONS

APPENDIX 1 shows 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, for both interim and final analyses.

Summary statistics will be summarized by visit when appropriate and will consist of values for:

- number of patients, number of missing values, mean, standard deviation, median, lower and upper quartiles, minimum and maximum for quantitative parameters.
- number and percentage of patients for qualitative parameters. Percentages will be presented with one digit and will be computed on the analysis population.

8. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

8.1. DISPOSITION

Patient disposition and withdrawals, and reasons for exclusion from each analysis population, including inclusion and exclusion criteria will be presented for the Enrolled population.

8.2. PROTOCOL DEVIATIONS

Protocol deviations will be identified and categorized using the process outlined in the Protocol Deviation Management Plan. Protocol deviations (including a flag for protocol deviations due to COVID-19) will be provided in a by-patient listing.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT population.
No statistical testing will be carried out for demographic or other baseline characteristics.
The following demographic and other baseline characteristics will be reported for this study:

- Age (years)
- Sex
- Ethnicity
- Race
- Geographic region (Americas, Europe, Australia, Asia)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BSA (m^2)
- Child producing potential
- Surgically Sterilized status
- Menopausal status
- Use of highly effective contraception method
- ECOG at baseline

10. MEDICAL HISTORY

10.1. CANCER-RELATED MEDICAL HISTORY

Cancer-related medical history will be presented for the Safety population. Descriptive statistics on cancer-related medical history characteristics will be presented for the following:

- Prior anti-cancer therapy, surgery and radiotherapy:
  - Prior anti-cancer therapies related to study indication:
    - Number of prior regimens
    - Time since last prior anti-cancer therapy
    - Treatment setting
    - Medication received
    - Best treatment response
    - Duration of responses
    - Time to progression
    - Type of progression
    - Reason therapy ended and time since last anti-cancer related therapy calculated as date of first dose of study treatment – stop date of last anti-cancer related therapy.
  - Prior anti-cancer surgeries related to study indication:
    - Type of procedures
    - Reason for procedure
    - Time since last surgery.
  - Prior anti-cancer radiotherapy related to study indication:
    - Anatomical location
    - Total dose
    - Time since last radiotherapy.
- Cancer history at diagnosis:
  - Time since first cancer diagnosis, calculated as the date of first dose of study treatment minus date of first diagnosis.
  - Anatomical location
  - TNM Staging:
    - Primary tumor

- Regional lymph nodes
- Distant metastasis
- TNM stage classification

- Cancer history at screening:
  - Residual primary tumor present
  - Anatomical location of primary tumor
  - Tumor stage
  - Metastatic anatomical location
  - Recent histology
  - Tumor histology/cytology at screening (Lauren Classification).
  - Tumor histology/cytology at screening (WHO Classification).
  - Histopathological Grade at screening

The above parameters will also be presented in data listings by substudy and patient.

10.2. NON-CANCER RELATED MEDICAL HISTORY

Medical History information will be presented for the Safety population and coded using MedDRA v25.0 or above. Patients will be counted only once for each SOC or PT in the event that they have multiple records of the same SOC or PT in the database. All medical history data will be listed.

11. CONCOMITANT PROCEDURES

Procedures will be coded using MedDRA version 25.0 or above. All procedures will be included in a by-patient data listing.

12. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using WHO Drug Dictionary Global March 2022 or later. All prior and concomitant medications will be included in by-patient data listings.

13. STUDY TREATMENT EXPOSURE

Exposure to each study treatment in weeks will be presented for the Safety population.

The date of first study treatment administration and the date of last study treatment will be taken from the eCRF "Exposure - Derazantinib" and "Study medication administration - Atezolizumab/Paclitaxel/Ramucirumab" forms.

The number of cycles received, the duration of treatment and the total cumulative dose received will be summarized overall using continuous statistics.

The number of patients with a dose reduction/interruption will be summarized for each cycle and overall as a categorical variable, including a summary of the reduced dose level achieved and the reasons for dose reduction/interruption.

Study treatment exposure will be summarized by study treatment and by cohort/dose level and will also be included in by-patient data listings.

For derazantinib/paclitaxel/ramucirumab:
Total duration of exposure (weeks) = (date of last study treatment administration – date of first study treatment administration + 1)/7.

14. STUDY TREATMENT COMPLIANCE

Compliance to each study treatment will be presented for the Safety population.
Study treatment compliance and study treatment accountability will be included in by-patient data listings.
When used in combination with paclitaxel and ramucirumab, derazantinib should be administered first, followed by ramucirumab and then paclitaxel. Paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab infusion.

14.1. STUDY TREATMENT COMPLIANCE FOR DERAZANTINIB

Total dose received and study treatment compliance (numerical and categorical, considering cut-offs of 80% and

120%) will be summarized descriptively.

Derazantinib will be administered at:

- Substudy 1:
  - Cohort 1.1 and Cohort 1.2 - Number of capsules prescribed per day = 3
  - Cohort 1.3 - Number of capsules prescribed per day = 4
- Substudy 2:
  - DL1 - Number of capsules prescribed per day = 2
  - DL2 - Number of capsules prescribed per day = 3

Number of capsules prescribed per day could also be changed as determined per the dose reduction guidelines for toxicity considered related to derazantinib and specified in the eCRF. One capsule contains 100mg of derazantinib.

The following derivations will be performed:

$$Dose\ received\ at\ cycle\ n\ or\ last\ cycle\ (mg) = (Number\ of\ capsules\ dispensed - Number\ of\ capsules\ returned) \times 100$$

$$Overall\ dose\ received\ (mg) = \sum Dose\ received\ at\ each\ cycle$$

$$Planned\ dose\ at\ cycle\ n\ (mg) = Number\ of\ capsules\ prescribed\ per\ day \times Number\ of\ planned\ days\ at\ cycle\ n \times 100$$

The number of planned days during a dosing interval will be the number of dosing days in a cycle excluding any days that the patient was instructed to hold dosing due to an AE. All other reasons of study treatment interruption won't exclude the days of interruption of number of days calculation. Patients with discontinuation dates that fall within a cycle will have their expected days adjusted in the compliance calculation for that cycle. For example, if a patient discontinues within Week 2 of Cycle 1, the number of days in the dosing interval will be calculated based of the date of the last dose within Week 2.

$$Planned\ dose\ at\ last\ cycle\ (mg) = Number\ of\ capsules\ prescribed\ per\ day \times Duration\ of\ exposure\ at\ last\ cycle \times 100$$

$$Overall\ Planned\ dose\ (mg) = \sum Planned\ dose\ at\ each\ cycle$$

$$Compliance\ at\ cycle\ n\ (\%) = \frac{Dose\ received\ at\ cycle\ n}{Planned\ dose\ at\ cycle\ n} \times 100$$

$$Compliance\ at\ last\ cycle\ (\%) - \frac{Dose\ received\ at\ last\ cycle}{Planned\ dose\ at\ last\ cycle} \times 100$$

$$Overall\ compliance\ (\%) \quad \frac{Overall\ dose\ received}{Overall\ planned\ dose} \times 100$$

14.2. STUDY TREATMENT COMPLIANCE FOR PACLITAXEL

Total dose received and study treatment compliance (numerical and categorical, considering cut-offs of 80% and 120%) will be summarized descriptively.

Paclitaxel will be administered at 80mg/m² per cycle for Substudy 2.

The following derivations will be performed:

$$Overall\ dose\ received\ (mg) = \sum Dose\ received\ at\ each\ cycle$$

$$Planned\ dose\ at\ cycle\ n\ (mg) = \text{Planned dosing days x } 80 \times (BSA\ at\ cycle\ n\ D1)$$

The number of planned dosing days during a dosing interval will be the number of dosing days in a cycle excluding any dosing not performed due to an AE. Patients with discontinuation dates that fall within a cycle will have their expected dosing days adjusted in the compliance calculation for that cycle. For example, if a patient discontinues within Week 2 of Cycle 1, the number of days in the dosing interval will be calculated based of the date of the last dose within Week 2.

$$Overall\ Planned\ dose\ (mg) = \sum Planned\ dose\ at\ each\ cycle$$

$$Compliance\ at\ cycle\ n\ (\%) = \frac{Dose\ received\ at\ cycle\ n}{Planned\ dose\ at\ cycle\ n} \times 100$$

$$Overall\ compliance\ (\%) \quad \frac{Overall\ dose\ received}{Overall\ planned\ dose} \times 100$$

14.3. STUDY TREATMENT COMPLIANCE FOR RAMUCIRUMAB

Total dose received and study treatment compliance (numerical and categorical, considering cut-offs of 80% and 120%) will be summarized descriptively.

Ramucirumab will be administered at 8mg/kg per cycle for substudy, or as determined by the investigator following dose adjustment.

The following derivations will be performed:

$$Overall\ dose\ received\ (mg) = \sum Dose\ received\ at\ each\ cycle$$

$$Planned\ dose\ at\ cycle\ n\ (mg) = \text{Planned dosing days x planned dose per day} \times (Weight\ at\ cycle\ n\ D1)$$

The number of planned dosing days during a dosing interval will be the number of dosing days in a cycle excluding any dosing not performed due to an AE. Patients with discontinuation dates that fall within a cycle will have their expected dosing days adjusted in the compliance calculation for that cycle. For example, if a patient discontinues within Week 2 of Cycle 1, the number of days in the dosing interval will be calculated based of the date of the last dose within Week 2.

$$Overall\ Planned\ dose\ (mg) = \sum Planned\ dose\ at\ each\ cycle$$

$$Compliance\ at\ cycle\ n\ (\%) = \frac{Dose\ received\ at\ cycle\ n}{Planned\ dose\ at\ cycle\ n} \times 100$$

$$Overall\ compliance\ (\%) = \frac{Overall\ dose\ received}{Overall\ planned\ dose} \times 100$$

15. EFFICACY OUTCOMES

All efficacy analyses will be conducted using the mITT population except overall survival that will be conducted using the ITT population.

Assessments by two readers are considered for Blinded Independent Central Review (BICR). Should there be disagreement between these two readers, an adjudicator decides which reader is correct. As such, all analyses which consider BICR assessments will be based upon the first reader by default, unless the second reader is selected following adjudication.

Waterfall plots, spider plots and swimmer plots will be produced to accompany efficacy analyses.

15.1. PRIMARY EFFICACY

15.1.1. SUBSTUDY 1 COHORTS 1.1 AND 1.2

15.1.1.1. Primary Efficacy Endpoint & Derivation

The primary efficacy endpoint in substudy 1 cohorts 1.1 and 1.2 will be objective response rate (ORR), defined as the number of patients with confirmed CR or PR using RECIST 1.1 assessed by BICR divided by the total number of patients in the cohort.

Classification of best confirmed response is done according to the following hierarchy and rules, based on all reads performed up to EOT:

- Complete Response (CR): requires two consecutive CR response assessments a minimum of four weeks apart
- Partial Response (PR): requires two consecutive PR response assessments OR a PR response immediately followed by a CR response assessment (a minimum of four weeks apart)
- Stable Disease (SD): requires only one SD response assessment (provided minimum criteria for SD duration met: SD assessment at least 6 weeks after baseline)
- Progressive Disease (PD): requires only one PD response assessment

The classification as per RECIST 1.1 is summarized in Table 1.

Table 1: Best overall response when confirmation of CR and PR required.

Overall response		BEST overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

As specified in RECIST 1.1, repeated 'NE' time point assessments complicate best response determination. Should a CR/PR be followed by a NE response and then a CR/PR, then confirmed response would be achieved (as an example PR-NE-PR will be considered as a confirmed partial response).

15.1.1.2. Missing Data Methods for Primary Efficacy Variable

Primary efficacy analysis will be done on mITT population. Patients whose tumor imaging assessment response is unknown or not reported will be treated as non-responders.

15.1.1.3. Primary Analysis of Primary Efficacy Variable

All efficacy endpoints will be summarized by substudy and cohort. Point estimates and 90% exact binomial confidence intervals will be provided by cohort.

15.1.2. SUBSTUDY 1 COHORTS 1.3

15.1.2.1. Primary Efficacy Endpoint & Derivation

The primary efficacy endpoint in substudy 1 cohort 1.3 will be the proportion of patients who have progression-free

survival >4 months (i.e. > 121 days), as assessed by survival status and central radiology review as per RECIST version 1.1. See section 15.2.1.4 for PFS derivation.

15.1.2.2. Primary Analysis of Primary Efficacy Variable

Point estimate, exact 2-sided 90% confidence interval (Clopper-Pearson) and associated p-value will be provided.

15.2. SECONDARY EFFICACY

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Objective response Rate (Substudy 2)

Objective Response Rate will be considered a secondary efficacy endpoint in substudy 2 and derived in the same way as stated in Section 15.1.1.1.

15.2.1.2. Disease Control Rate

Disease control rate (DCR) will be considered as secondary efficacy endpoint for all substudies, defined as the number of patients with confirmed CR, PR or SD using RECIST 1.1 assessed by BICR divided by the total number of patients in the cohort.

Confirmed CR, PR and SD are defined in Section 15.1.1.1 and Table 1

15.2.1.3. Duration of Response

Duration of response (DOR) will be considered as a secondary efficacy endpoint for all substudies.

DOR will be calculated from the first date of documented objective tumor response (confirmed CR or PR) to the date of disease progression as assessed by BICR, or death. If a patient is discontinued or lost to follow-up with no documentation of PD, DOR is defined as the time from the date of first documented objective tumor response to the date of last tumor assessment as a censored value.

15.2.1.4. Progression-Free Survival

Progression-Free Survival (PFS) will be considered as secondary efficacy endpoint for all substudies.

PFS will be calculated as the time from enrollment until disease progression as assessed by BICR, or death from any cause, whichever comes first. Patients who either have no baseline tumor evaluation or have no post- baseline tumor

evaluation will be censored at date of enrollment (Cycle 1 Day 1). Patients without disease progression will be censored at the date of their last tumor evaluation. Patients who discontinue treatment due to reasons other than disease progression by BICR or death will be censored in the PFS analyses as the date of their last tumor evaluation prior to EOT. Patients who progress or die after missing ≥2 consecutive scheduled tumor assessments will be censored at the date of the last tumor evaluation prior to progression or death. Any deaths occurring after end of treatment are not taken into account as a PFS event. Patients who stopped treatment without PD will be censored at their last scan prior to end of treatment. For patients with missing end of treatment visit date, a +7 day window compared to the maximum of last dose date, last on treatment visit date will be applied to create a tentative end of treatment visit date and a cut-off for death occurring after this date. The rules for censoring PFS are summarized in the table below:

Table 2: Censoring scheme for PFS

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Cohort assignment (typically C1D1)	Censored
Progression documented between scheduled visits (applicable also after 1 missed scheduled tumor assessment)	Date of radiological assessment of measured lesions	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for reasons other than disease progression by BICR or death	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment (applicable also after 1 missed scheduled tumor assessment)	Date of death	Progressed
Death between adequate assessment visits (applicable also after 1 missed scheduled tumor assessment)	Date of death	Progressed

Death or progression after more than one missed tumor assessment or after end of treatment	Date of last radiological assessment of measured lesions prior to progression or death	Censored

15.2.1.5. Overall Survival

Overall Survival (OS) will be considered as secondary efficacy endpoint for all substudies.

Overall Survival will be calculated from the date of enrollment until death from any cause. Any patient without a date of death in the database at the time the survival analyses are performed will be censored at the time of their last study contact.

15.2.2. ANALYSIS OF SECONDARY EFFICACY VARIABLES

15.2.2.1. Analysis of Objective Response Rate (Substudy 2)

ORR will be analyzed in the same way as stated in Section 15.1.1.1 on mITT population.

15.2.2.2. Analysis of Disease Control Rate

Analysis of DCR will be done on mITT population.

Point estimates and 90% exact binomial confidence intervals will be provided by cohort/dose level.

15.2.2.3. Analysis of Duration of Response

Analysis of DOR will be done on mITT population.

DOR will be analyzed using Kaplan-Meier methodology. The median DOR will be presented along with the 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented.

The Kaplan-Meier survival curves will also be presented.

15.2.2.4. Analysis of Progression-Free Survival

Analysis of PFS will be done on mITT population.

PFS will be analyzed using Kaplan-Meier methodology. The median PFS will be presented along with the 2-sided

95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented.
The Kaplan-Meier survival curves will also be presented.

15.2.2.5. Analysis of Overall Survival

Analysis of OS will be done on ITT population.
OS will be analyzed using Kaplan-Meier methodology. The median PFS will be presented along with the 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented.
The Kaplan-Meier survival curves will also be presented.

15.3. EXPLORATORY EFFICACY

15.3.1.1. Investigator assessed response

In the primary analysis, tumor response will be based upon measurements evaluated by the BICR. However, an initial assessment of tumor response will be made by investigators at site. As an exploratory measure, analyses of ORR, DCR, DOR and PFS will be conducted considering investigator assessment only.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety population.
There will be no statistical comparisons between the treatment groups for safety data.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.0 or above.
Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study treatment and until safety follow-up visit (inclusive), and are reported as such in the eCRF. Pre-treatment events are reported as medical history.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case: i.e. treatment emergent.
An overall summary of number of patients within each of the categories described in the sub-section below, will be provided per cohort/dose level.

16.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study treatment.

16.1.1.1. NCI Common Terminology Criteria of Adverse Events

Adverse events will be graded according to the NCI Common Terminology Criteria of Adverse Events (NCI CTCAE) Version 5.0. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case grade will be used in the corresponding grade summaries.

16.1.1.2. Relationship to Study Treatments

Relationship is reported by the Investigator for each study treatment as "not related", "unlikely related", "possibly related", "probably related".
Relationship will be analyzed as relationship with any study treatment.
A "related" TEAE is defined as a TEAE with a relationship to any study treatment as "possibly related" or "probably related" to study treatment. TEAEs with a missing relationship to study treatment will be regarded as "probably related" to study treatment. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study treatment will be used in the corresponding relationship summaries.
"Not applicable" should be chosen for instance in case of study treatment is not received by the cohorts/patients.
Additionally, treatment-related TEAEs with NCI CTCAE grade ≥ 3 will be presented by SOC and PT.

16.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY TREATMENT

TEAEs leading to permanent discontinuation of at least one study treatment will be identified by using the modality "Drug withdrawn" in "Action taken with study medication" question in Adverse Events page of the eCRF.

For AEs leading to discontinuation of at least one study treatment, summaries of incidence rates (frequencies and

percentages) by SOC and PT will be prepared.

16.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

16.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded on the Adverse Events page of the eCRF as:

- AE Term: "Death"
- Outcome: "Death related to adverse event"
- Seriousness: Results in death
- Toxicity grade (CTCAE): Grade 5

A summary of TEAEs leading to death by SOC and PT will be prepared.

16.1.5. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESIs) are those events which are recorded as "AESI" on the Adverse Events page of the eCRF. A summary of AESIs by SOC and PT will be prepared.

16.1.6. DOSE LIMITING TOXICITY

Dose-limiting toxicities (DLTs) are applicable to substudy 1 – cohort 1.3 and substudy 2 (Dose-finding part) only. DLTs identified during the study will be listed.

16.2. SURVIVAL FOLLOW UP DATA

Data collected during the survival follow-up period will be analyzed as specified in the efficacy analysis section and will be listed.

16.3. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for hematology, blood chemistry, thyroid function tests, coagulation, Vitamin D test, serology and tuberculosis blood test and urinalysis. A list of laboratory assessments to be included in the outputs is included in APPENDIX 3.

Presentations will use SI Units.

The following summaries will be provided for laboratory data (serology and tuberculosis blood tests are presented only in a listing):

- Actual value and change from baseline by visit (for quantitative measurements)
- Shift from baseline in abnormality as per local reference ranges (for quantitative measurements and categorical measurements)
- Shift from baseline according to Common Toxicity (CTC) grading system
- Listing of laboratory assessments

16.3.1. LABORATORY REFERENCE RANGES CRITERIA

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.

16.3.2. CTCAE GRADING FOR LABORATORY DATA

Laboratory measurements will be graded using the Common Toxicity grading (CTCAE) system as defined in the following link:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

CTCAE grading that will be used is summarized in the Table 3:

Table 3: CTCAE grading for laboratory parameters

Laboratory parameters	CTCAE toxicity term	Direction
Hemoglobin	Anemia	Low
	Hemoglobin increase	High
Lymphocytes	Lymphocyte count decreased	Low
	Lymphocyte count increased	High
Neutrophils	Neutrophil count decreased	Low
Eosinophils	Eosinophilia	High
Platelets	Platelet count decreased	Low
Leukocytes	White blood cell decreased	Low
	Leukocytosis	High
Alanine Aminotransferase	Alanine aminotransferase increased	High
Aspartate Aminotransferase	Aspartate aminotransferase increased	High
Bilirubin	Blood bilirubin increased	High
Albumin	Hypoalbuminemia	Low
Alkaline phosphatase	Alkaline phosphatase increased	High
Calcium	Hypocalcemia	Low
	Hypercalcemia	High
Creatinine	Creatinine increased	High
Glucose	Hypoglycemia	Low
Magnesium	Hypomagnesemia	Low
	Hypermagnesemia	High
Potassium	Hypokalemia	Low
	Hyperkalemia	High
Sodium	Hyponatremia	Low
	Hypernatremia	High
Phosphate	Hyperphosphatemia (see definition below)	High

Laboratory parameters	CTCAE toxicity term	Direction
Lactate dehydrogenase	Blood lactate dehydrogenase increased	High
Urate	Hyperuricemia	High
Lipase	Lipase increased	High
Amylase	Serum amylase increased	High
Creatinine Clearance	Chronic kidney disease	Low
Urinary Protein	Proteinuria	High
Activated Partial Thromboplastin Time	Activated partial thromboplastin time prolonged	High
Prothrombin International normalized ratio	INR increased	High

As hyperphosphatemia is only defined by CTCAE 5.0 with regards to escalating interventional measures (without specifications triggering these interventions) and not by laboratory values exceeding the upper limits of normal leading to specific interventions. In alignment with interventions to ensure patient safety and for the purpose of this protocol, hyperphosphatemia is defined as:

Grade 1: > ULN to < 7.0 mg/dL (< 2.26 mmol/L)

Grade 2: Non-invasive intervention required (e.g., withhold drug or modify dose) or between 7.0 9.0 mg/dL (2.26 2.90 mmol/L)

Grade 3: Severe or medically significant, but not immediately life threatening or > 9.0 10.0 mg/dL (> 2.90 3.23 mmol/L)

Grade 4: Life-threatening consequences, urgent intervention indicated e.g., dialysis or > 10.0 mg/dL (> 3.23 mmol/L)

16.3.3. HY'S LAW

Subjects who have elevated ALT, AST, and total bilirubin post baseline will be summarized descriptively as follows and Hy's law cases identified.

- ALT : > 3x Upper Limit of Normal (ULN), > 5x ULN, > 10x ULN, > 20x ULN
- AST: > 3x Upper Limit of Normal (ULN), > 5x ULN, > 10x ULN, > 20x ULN
- ALT or AST: > 3x Upper Limit of Normal (ULN), > 5x ULN, > 10x ULN, > 20x ULN

- Total bilirubin >2x ULN
- ALT and AST: <= 3x ULN and Total bilirubin <= 2x ULN
- ALT or AST: > 3x ULN and Total bilirubin <= 2x ULN
- ALT or AST: <= 3x ULN and Total bilirubin > 2x ULN
- ALT or AST: > 3x ULN and Total bilirubin > 2x ULN
-

Plots of ALT or AST vs. Total bilirubin by module will also be produced with reference lines at 3×ULN for ALT. AST, and 2×ULN for total bilirubin. In each plot, peak total bilirubin x ULN will be on the vertical axis and peak ALT or AST x ULN will be on the horizontal axis.

16.4. ECG EVALUATIONS

Results from the ECG (Electrocardiogram) will be included in the reporting of this study.
The following ECG parameters will be reported for this study:

- PR Interval (ms)
- RR Interval (ms)
- QRS Interval (ms)
- QT Interval (ms)
- QTcF Interval (ms)
- Heart Rate (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, not clinically significant (ANCS)
    - Abnormal, clinically significant (ACS)

A categorical analysis of QTcF interval correction will also be presented, based on the number and percentage of patients meeting or exceeding specific thresholds for absolute QTcF interval prolongation and change from baseline in QTcF interval.
For absolute QTcF interval prolongation, the number and percentage of patients within the following thresholds will be summarized at each visit. The worst (largest) value will also be summarized.

- Interval ≤450 ms

- Interval >450 ms and ≤480 ms
- Interval >480 ms and ≤500 ms
- Interval >500 ms

The change from baseline in QTcF interval to the worst (largest) post-baseline observation and at each study visit will also be summarized, considering the following thresholds:

- Interval increased from baseline ≤30 ms
- Interval increased from baseline >30ms and ≤60 ms
- Interval increased from baseline >60 ms

For all patients, a standard, triplicate, 12-lead ECG will be performed at all study visits. Summary tables will consider the mean of the triplicate measurements at each visit as the single reported value.
For the analysis of change from baseline, the mean of the triplicate measurements will be used for baseline and post-baseline values.
For absolute QTcF interval prolongation and for change from baseline in QTcF interval, the worst (largest) value will be used.
These summary tables will be presented by timepoint. All ECG data will be provided in a by-patient listing.

The following summaries will be provided by substudy and cohort/dose level for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Absolute QTcF interval prolongation by visit (categorical analysis)
- Change from baseline in QTcF interval by visit (categorical analysis)
- Listing of ECG

16.5. VITAL SIGNS

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

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BSA (m^2)
- Temperature (^0C)

- Pulse rate (bpm)
- Respiratory Rate (breaths/min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

The following summaries will be provided by substudy and cohort/dose level for vital signs data: actual and change from baseline by visit.

All vital signs data will be reported in a by-patient listing.

16.5.1. Vital Signs Specific Derivations

BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

BSA (m^2) = 0.007184 x height $(cm)^{0.725}$ x weight $(kg)^{0.425}$ – BSA will be directly derived in eCRF.

Height and weight used for BMI and BSA will collected respectively at screening and at each visit.

16.6. Physical Examination

The following summaries will be provided for physical examination data:

- General appearance
- Skin
- Neck inclusive thyroid
- Eyes
- Nails
- Nose
- Throat
- Cardiovascular system
- Thorax/lung
- Abdomen
- Lymph nodes
- Nervous system

Physical examination will be collected as Normal, Abnormal NCS (Non-Clinically Significant) and Abnormal CS (Clinically Significant).

The number and percentage of patients with Normal. Abnormal NCS (Non-Clinically Significant) and Abnormal CS

(Clinically Significant) will be presented by substudy and cohort/dose level (Substudy 2).

All physical examination data including other systems examined will be reported in a by-patient listing.

16.7. OPHTHALMOLOGICAL EXAMINATION

All ophthalmological examination data will be reported in a by-patient listing.

16.8. ECOG

ECOG performance status will be presented using a shift table with baseline values and maximum post-baseline values.

All ECOG performance status data will be reported in a by-patient listing.

[redacted]

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the IQVIA outputs conventions.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Substudy	Cohort /Dose level	For Tables and Graphs	For Listings (include if different to tables)
Substudy 1	Cohort 1.1	Substudy 1 – Cohort 1.1 – D300 QD	Substudy 1 – Cohort 1.1 - FGFR2$^{fus/amp}$ – Derazantinib 300mg QD
Substudy 1	Cohort 1.2	Substudy 1 – Cohort 1.2 – D300 QD	Substudy 1 – Cohort 1.2 – FGFR1-3^{mt} - Derazantinib 300mg QD
Substudy 1	Cohort 1.3	Substudy 1 – Cohort 1.3 – D200 BID	Substudy 1 – Cohort 1.3 – FGFR$^{fus/amp/mt}$ - Derazantinib 200mg BID
Substudy 2	DL1	Substudy 2 – DL1 – D200QD/R8/P80	Substudy 2 – Dose level 1 – Derazantinib 200mg QD / Ramucirumab 8mg/kg / Paclitaxel 80mg/m^2
Substudy 2	DL2	Substudy 2 – DL2 – D300QD/R8/P80	Substudy 2 – Dose level 2 – Derazantinib 300mg QD / Ramucirumab 8mg/kg / Paclitaxel 80mg/m^2

[redacted]

Substudy 2 treatment groups displaying will depend to the dose-levels actually dispensed according to the dose-escalations.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name (in case long name cannot be used on the output)
Screening	Screening
Baseline	Baseline
Cycle 1 Day 8	C1D8
Cycle 1 Day 15	C1D15
Cycle 1 Day 22	C1D22
Cycle 2 Day 1	C2D1
…	…
End of treatment	EOT
Safety follow-up Day 28	SFU D29
Safety follow-up Day 90	SFU D90
Overall survival follow-up	OSFU

LISTINGS

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

- Substudy
- Cohort/Dose-level
- Center-patient ID,
- Date (where applicable),

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date. then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date. then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date. then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR ANTI-CANCER THERAPIES:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment. assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment. assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

ALGORITHM FOR CANCER DIAGNOSIS

In case of partial date cancer diagnosis:

- If only month and year are provided, the day=15 will be assumed.
- If only year is provided, month=6 and day=30 will be assumed.

APPENDIX 3. LABORATORY PARAMETERS

Laboratory parameters	SI unit
Hematology	
Hematocrit	%
Hemoglobin	g/dL
Platelet count	10^9/L
White blood cells (WBC)	10^9/L
Erythrocytes	10^12/L
Absolute neutrophils	10^9/L
Absolute lymphocytes	10^9/L
Absolute monocytes	10^9/L
Absolute eosinophils	10^9/L
Absolute basophils	10^9/L
Neutrophils	%
Lymphocytes	%
Monocytes	%
Eosinophils	%
Basophils	%
Blood chemistry	
Albumin	g/L
Amylase	IU/L
Bicarbonate	mmol/L
Blood urea nitrogen (BUN)	mmol/L
Calcium	mmol/L
Chloride	mmol/L
C-reactive protein (CRP)	mg/L
Creatinine	umol/L

[redacted]

Laboratory parameters	SI unit
Creatinine clearance	mL/min
Glucose	mmol/L
Lipase	IU/L
Magnesium	mmol/L
Phosphate	mmol/L
Potassium	mmol/L
Total protein	g/L
Sodium	mmol/L
Urate	mmol/L
Aspartate aminotransferase (AST)	IU/L
Alanine aminotransferase (ALT)	IU/L
Alkaline phosphatase (ALP)	IU/L
Total bilirubin	umol/L
Direct bilirubin	umol/L
Lactate dehydrogenase	IU/L
Thyroid function tests	
Thyrotropin	mIU/L
Tri-iodothyronine, free	pmol/L
Thyroxine, free	pmol/L
Coagulation	
Partial prothrombin time	s
Prothrombin time	s
Prothrombin International normalized ratio	-
Vitamin D test	
25-hydroxy vitamin D	nmol/L
1,25-dihydroxy vitamin D	pmol/L

[redacted]

Laboratory parameters	SI unit
Serology and tuberculosis blood test	
Human Immunodeficiency Virus (HIV 1/2 AB)	-
Hepatitis B (HBsAg)	-
HCV AB	-
HCV RNA	-
Interferon-γ release assay	-
Urinalysis	
Protein	-
Glucose	-
Occult blood	-
Ketones	-
pH	-