Statistical Analysis Plan

Sponsor: BeiGene, Ltd.

Protocol Number: BGB-Sitravatinib-101

A Phase 1, Open-label, Single-dose, Randomized Crossover Study to Evaluate the Relative Bioavailability of Two Different Capsule Formulations of Sitravatinib in Healthy Subjects

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the methodology that will be followed in the analysis of the data that were collected for the BeiGene, Ltd., BGB-Sitravatinib-101 study.

This SAP is based on assessments and methods described in the study Protocol Amendment Version 1 dated 12 July 2020. The SAP contains a complete and detailed specification of the statistical analyses that will be performed.

All analyses described in this document will be conducted in accordance with Resolutum Global's standard operating procedures (SOPs).

1.1 Rationale

Sitravatinib (MGCD516) is an orally available, potent small-molecule inhibitor of a closely related spectrum of tyrosine kinases. This subset of tyrosine kinases is involved in several processes implicated in human cancer, including regulation of tumor growth and cell survival pathways, tumor invasion and metastatic progression, as well as tumor angiogenesis. Antitumor activity of sitravatinib has been observed in several human tumor xenograft models exhibiting genetic alterations in receptor tyrosine kinase targets, providing the rationale for evaluating sitravatinib monotherapy in tumors driven by these pathways in the clinical setting. Additionally, based on its tyrosine kinase target profile, sitravatinib may modulate effects on the tumor microenvironment to overcome resistance to checkpoint inhibitors by effects on relevant immune cell populations. These effects are predicted to complement and augment the activity observed with checkpoint inhibitor therapy (CIT).

In clinical studies, sitravatinib has been administered as a single agent in the ongoing first-in-human Study 516-001 and in Study 516-006 (Mirati Therapeutics, Inc.).

Study 516-001 is an ongoing multicenter, Phase 1/1b clinical study characterizing the safety, pharmacokinetics (PK), metabolism, the pharmacodynamic, and clinical activity of sitravatinib in patients with advanced solid tumors. The primary objective of the Phase 1 study was the determination of the maximum tolerated dose (MTD), while Phase 1b objectives included assessment of safety and clinical activity in patients with certain tumor types (e.g., renal cell carcinoma) or with tumors characterized by certain genetic alterations. The MTD was identified as 150 mg once daily (QD), and based on long-term tolerability observed in patients enrolled into Study 516-001 treated with 120 or 150 mg QD, the Sponsor selected 120 mg QD as the current recommended Phase 2 dose, using the sitravatinib free base capsule formulation.

Study 516-006 is an open-label, two part, phase 1 study assessing relative bioavailability and pharmacokinetics (PK) of a single oral dose of sitravatinib administered as free base capsules (reference formulation) and malate salt capsules (test formulation, developed by Mirati) in healthy male subjects. The primary objective is to investigate the relative bioavailability and PK of sitravatinib free base and malate salt capsule formulations following oral administration in healthy subjects. The results showed that PK exposure of 100 mg sitravatinib malate salt capsule (roller compaction) was comparable with 120mg free base capsule.

In order to introduce BeiGene malate salt capsule formulation (roller compaction) into the development of sitravatinib in China, this study will be conducted to compare the systemic exposure of sitravatinib between the malate salt capsule (roller compaction, manufactured by BeiGene) and the free base formulation. The primary objective of the study is to evaluate the relative bioavailability and PK of the different formulations.

The sitravatinib doses in this study are based on the results from study 516-006. To ensure comparable exposures, the free base reference dose will be 120 mg and the malate salt capsule dose will be 100 mg. The exposure ratio information will be used to guide the dose for the selected malate salt capsule formulation needed to achieve exposure comparable to the recommended Phase 2 dose (RP2D) of the free base product.

Doses of 100 or 120 mg sitravatinib proposed in this study are considered safe and appropriate for the evaluation of sitravatinib PK profiles in healthy subjects.

2. Summary of the Protocol

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to investigate the relative bioavailability and PK of sitravatinib free base and malate salt capsule formulations following oral administration in healthy subjects.

2.1.2 Secondary Objectives

The secondary objective of the study is to assess the safety and tolerability of single-dose free base and malate salt capsule formulations of sitravatinib in healthy subjects.

2.2 Study Endpoints

2.2.1 Primary Endpoints

The following PK endpoints will be evaluated during this study:

- AUC from time zero to infinity (AUC_{0-inf})
- AUC from time zero to the last quantifiable concentration (AUC_{0-t})
- Maximum observed concentration (C_{max})
- Time of the maximum observed concentration (T_{max})
- Half-life ($t_{1/2}$)
- Apparent total plasma clearance (CL/F)
- Apparent volume of distribution (V_z/F)
- Dose-normalized AUC_{0-inf}, AUC_{0-t} and C_{max}.

Other PK parameters may also be reported as appropriate.

2.2.2 Secondary Endpoints

The safety outcome measures for this study are as follows:

- Incidence and severity of AEs
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead electrocardiogram parameters
- Vital sign measurements
- Physical examinations.

2.3 Study Design

This will be a phase 1, open-label study using a two-period crossover design to compare the bioavailability and PK of the free base formulation at 120 mg and the malate salt capsule formulation (roller compaction, manufactured by BeiGene) at 100 mg after a single oral administration to healthy male subjects.

Subjects will be randomized into one of two sequences and will participate in two dosing periods (Table 1). The minimum washout period between dose administrations will be 14 days. Up to 26 subjects (include ≥16 Asian subjects) will be enrolled to guarantee that at least 24 subjects complete the study.

Table 1 Dosing Sequences

Dosing sequence	Period 1	Washout (minimum)	Period 2
1 N=13	120 mg sitravatinib free base capsule	14 days	100 mg sitravatinib malate salt capsule
2 N=13	100 mg sitravatinib malate salt capsule	14 days	120 mg sitravatinib free base capsule

N: number of subjects

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. In Periods 1 and 2, subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and will stay in the CRU until discharge on Day 4. In each period, subjects will attend a nonresidential visit on Day 8 for PK (168 hours post-dose) sampling. Subjects will receive a Follow-up phone call on Days 13 to 15 of Period 2. A Schedule of Assessments is presented in Table 2.

The total duration of study participation for each subject (from Screening through Follow-up phone call) is anticipated to be up to approximately 8 weeks.

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of randomization number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

2.4 Sample Size Determination

Up to 26 subjects (13 per dosing sequence) will be enrolled to guarantee that at least 24 subjects complete the study. The number of subjects is justified in powering the study to delineate comparability of the sitravatinib mean exposure between the two dose formulations. Assuming an intrasubject coefficient of variation (CV%) of 40% (which was the maximum CV% observed on C_{max} in previous study), and a malate salt capsule to free base ratio of 100 ± 5%, 24 subjects in a two-way crossover design will provide a probability of 92% for the ratio of geometric means (malate salt to free base) to be within the 80% to 125% limits if the true ratio is between 95% and 105%. The conclusions in the clinical study report will be drawn based on the estimated ratios of geometric means only and the 90% confidence intervals (CIs) will be presented for informational purposes.

2.5 Schedule of Assessments

Table 2 presents the schedule of study events for Treatment Periods 1 and 2.

Table 2 Schedule of Assessments

Study procedures	Screening (within 28 days prior to first dose)	Periods 1 and 2			Follow-up telephone call (Period 2, Days 13 to 15)
		Day -1	Days 1 to 4	Day 8 (168 hours postdose)/ Early termination	
Assessment/Administrative procedures:					
Informed consent	X				
Inclusion/exclusion criteria	X				
Medical history, demographic data	X				
Urinary drug screen (including cotinine)	X	X			
Alcohol test		X			
Serology	X				
TSH testing	X				
Height and body weight	X[a]	X			
COVID-19 swab collection & analysis	X				
Study residency:					
Check-in		X			
Check-out			Day 4 (72 hours postdose)		
Nonresidential visit	X			X	
Study drug administration:			Day 1 (0 hour)		
Pharmacokinetics:					

Study procedures	Screening (within 28 days prior to first dose)	Periods 1 and 2			Follow-up telephone call (Period 2, Days 13 to 15)
		Day -1	Days 1 to 4	Day 8 (168 hours postdose)/ Early termination	
Blood sampling[b]			Predose (-0.5), 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours postdose	X	
Safety and tolerability:					
Adverse event recording	X	X	Ongoing	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X
Clinical laboratory evaluations[c]	X	X	Day 4	X (Period 2 only or early termination, if applicable)	
Vital signs (supine)[d]	X	X	Predose, 4, 24, 48, and 72 hours postdose	X	
Single 12-lead ECG[e]	X	X	Predose, 4, and 72 hours postdose	X	
Physical examination	X	X[f]	Day 4[g]	X[g]	

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic; QTcF = QT interval corrected for heart rate using Fridericia's method; TSH = thyroid-stimulating hormone.

Note: The minimum washout period between dose administrations will be 14 days.

a. Height measured at Screening only.

b. PK blood sampling: predose (within 30 minutes prior to dosing) and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 168 hours post-dose, a total of 12 samples in each study period. The allowed time window will be ±2 minutes for the post-dose timepoints ≤ 12 hr, ±10 minutes for 24 to 72 hr post-dose, and ±2 hr for 168 hr post-dose.

c. Blood and urine samples will be collected (hematology, chemistry, and urinalysis) for clinical laboratory evaluations. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in the case of dropouts or rechecks, subjects may be permitted not to have fasted for 8 hours before the serum chemistry sample is taken.

d. Blood pressure and pulse rate, respirations, and oral body temperature. Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements. The assessment will be performed after ECG, with the allowed time window of within 3 hr before dose administration for predose time point, ±20 minutes for the 4 hr post-dose, and ±30 minutes for 24 hr, 48 hr and 72 hr post-dose.

e. Electrocardiograms are to be performed as close to PK sampling time as possible and followed by vital assessment. The allowed time window will be within 3 hr before dose administration for Predose, and ±20 minutes for the 4 hr postdose, and ±30 minutes for the 72 hr postdose. Assessments will include an evaluation of heart rate, QT, and QTc intervals. RR interval should be recorded during each ECG assessment in order to calculate QTcF. ECGs are to be

performed prior to collection of vital signs and PK sample collection blood draws. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply: QTcF >500 msec OR QTcF change from the baseline (predose) is >60 msec.

f. Full physical examination at Check-in for Period 1; symptom-directed physical examination at Check-in for Period 2.

g. Symptom-directed physical examination.

3. Analysis Sets

The analysis sets of interest are:

- Safety Analysis Set
- PK Concentrations Analysis Set
- PK Parameters Analysis Set
- Relative Bioavailability Analysis Set.

Each of the analysis sets, as well as the criteria for exclusion from each set will be described in the following sections.

Screen failure data will not be included in any output.

3.1 Safety Analysis Set

The Safety Analysis Set is defined as the set of subjects who received at least one dose of sitravatinib.

The following are reasons for exclusion from the Safety Analysis Set:

- Subject did not provide informed consent.
- Subject did not receive at least one dose of sitravatinib.

The Safety Analysis Set will be used as the analysis set for all baseline characteristics, disposition, and safety outputs.

3.2 Pharmacokinetic (PK) Concentrations Analysis Set

The PK Concentrations Analysis Set is defined as all subjects who received at least one dose of sitravatinib and have at least one quantifiable concentration of sitravatinib.

The following are reasons for exclusion from the PK Concentrations Analysis Set:

- Subject did not receive at least one dose of sitravatinib.
- Subject does not have at least one quantifiable concentration of sitravatinib.

At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

The PK Concentrations Analysis Set will be used as the analysis set for the PK concentration outputs.

3.3 Pharmacokinetic (PK) Parameters Analysis Set

The PK Parameters Analysis Set is defined as all subjects who received at least one dose of sitravatinib and have at least one PK parameter of sitravatinib.

The following are reasons for exclusion from the PK Parameters Analysis Set:

- Subject did not receive at least one dose of sitravatinib.
- Subject does not have at least one sitravatinib PK parameter.
- Subject experienced an event that may affect their PK profile (e.g., has an AE of vomiting that occurs at or before 2 times median T_{max}).

At the discretion of the pharmacokineticist, PK parameter results may also be excluded from the analysis if it is not sufficient to characterize the PK profile (e.g. percentage of AUC extrapolation >20%.).

The PK Parameters Analysis Set will be used as the analysis set for the PK parameter outputs.

3.4 Relative Bioavailability Analysis Set

The Relative Bioavailability Analysis Set is defined as the subset of subjects in the PK Parameters Analysis Set who have at least one primary PK parameter (AUC_{0-t}, AUC_{0-inf} and C_{max} of sitravatinib) in both periods.

The following are reasons for exclusion from the Relative Bioavailability Analysis Set:

- Subject is not included in the PK Parameters Analysis Set.
- Subject does not have at least one of the primary sitravatinib PK parameters AUC_{0-t}, AUC_{0-inf} or C_{max} for both periods.

The Relative Bioavailability Analysis Set will be used as the analysis set for the bioavailability analysis.

3.5 Analysis of Subgroups

No subgroup analyses are planned for this study.

4. Study Measures

This section describes the measures that were collected and/or derived during the study at the time points specified in the Schedule of Assessments (Section 2.5).

4.1 Safety Measures

The safety endpoints described in this section will be analysed according to the analysis methods described in Section 6.8.

4.1.1 Exposure to Study Drug

Study drug administration information, including the date and time of the administration and the actual dose administered will be reported on the 'Dose Administration' CRF page.

4.1.2 Adverse Events

An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the study treatment or procedure, that occurs during the course of the study.

Adverse events data will be collected and recorded on the 'Adverse Event' CRF page from the time that informed consent was given, for the duration of the trial.

Missing and partial AE dates will be handled according to the rules specified in Sections 5.1.4 and 5.6.2.1.

4.1.2.1 Adverse Event Definitions

Treatment emergent adverse events (TEAEs) are defined as AEs that commenced on or after the first study drug administration. If only partial information is available, the rules specified in Section 5.6.2.1 will be applied to determine treatment emergence. TEAEs will be assigned to the last treatment that was administered prior to the start or worsening of the event. If an AE cannot be assigned based on the available information, the AE will be assigned to both treatment groups.

Treatment-related AEs are defined as AEs where the relationship to study drug is reported as 'Related' or is missing. An AE will be classified as not related to study drug if the relationship to study drug was recorded as 'Not Related'.

Serious AEs (SAEs) are defined as AEs where the events are reported as serious.

Severe AEs are defined as AEs where the event severity rating is reported as 'Severe', 'Life-threatening' or 'Death' or missing.

Adverse events leading to the withdrawal of study drug are defined as AEs where the action taken with study drug is reported as 'Dose Withdrawn'.

Adverse events leading to study withdrawal will be defined as AEs where the reason for study withdrawal (on the 'Study Completion' CRF page) was recorded as being an AE.

4.1.2.2 Coding of Adverse Event Terms

Adverse event terms (Investigator terms) will be coded to a lowest level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 23.0, depending on the latest version available during the study. Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via a single HLT, HLGT route.

4.1.3 Laboratory Evaluations

Laboratory evaluations will be performed in accordance with the Schedule of Study Events (Section 2.5). Blood and urine samples will be collected, analysed by a local laboratory and the results will be reported on the CRF.

In the event that the results for a specific laboratory test are not required by the study protocol (for example, only one subject has data for a specific test that was performed in error) or for urine microscopy tests that were only required in the presence of abnormal urinalysis results, the results will not be included in the summary tables, but the data will be listed.

The test panels and parameters presented in the Table 3 will be collected and analysed.

Parameter names will be based on the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Controlled Terminology terms. The mapping of the reported parameter names to the standardised names will be presented in the SDTM specifications. Parameters will be presented in the order specified in Table 3.

In the event that the results for a parameter were reported in different units, the results (including the actual measurement and the normal range limits) will be converted to the Système International (S.I.) unit for the specific parameter and the standardised results/units will be reported. The specific conversion rules will be documented in the SDTM specifications.

If a result for a parameter that is normally considered continuous is reported as a range (i.e., the result for basophils is reported as '<0.01' for a single time point), the result may be converted to a numeric value that is smaller than the reported result to contribute to the derivations and the summary statistics. Any conversion rules that are applied will be highlighted in the footnotes of the affected tables and listings. The original reported result value will however be included in the listing.

If a re-test was performed at any visit, the results from the repeat test will be used in all analyses for the specific visit. The repeat test result will be flagged in the data listing.

Where applicable, parameter names in the outputs will comprise of the test name and the standardised unit of measure (if applicable), for example, 'Albumin (g/L)'. If a specific test is qualitative or unitless, the parameter name will be the test name only.

For all parameters where a normal range limit value was reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as '(Lower, Upper)'. In the event that only one of the limit values exist, 'N/A' will be used to replace the 'missing' limit value (for example, '(N/A, Upper)'), unless a direction has been specified, in which case the normal range will be displayed as '(< or > Limit)'.

Table 3 Laboratory Assessments

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bilirubin total (fractionate [direct and indirect bilirubin] only if total bilirubin is > upper limit of normal) Blood urea nitrogen Calcium Chloride CO_2/bicarbonate Creatinine Gamma-glutamyl transferase Glucose Phosphorus Potassium Sodium Total protein	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[a]:	**Drug screen:**	**Hormone panel:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Cotinine test Alcohol test[b]	Thyroid-stimulating hormone[a]
SARS-CoV-2 test[a]:		
COVID-19 Swab Collection & Analysis		

[a] Only analyzed at Screening.
[b] Only analyzed at Check-in (both dosing periods). Alcohol testing not included at Screening.

Quantitative parameter results will be classified as 'Normal' (within the normal range) or 'Abnormal' (outside the normal range) according to the subjects' individual normal ranges that were provided by the analysing laboratory. Abnormal results will further be classified as being 'Low' or 'High' depending on whether the result is below or above the normal range limits. The clinical significance of any abnormal results will be determined by the Investigator and reported on the CRF.

Qualitative parameter results (excluding serology, SARS-CoV-2 test, urine drug test and alcohol breath test) will be classified as 'Normal' or 'Abnormal' based on the absence (results reported as 'Negative', 'None', 'Null', etc.) or presence (results reported as 'Positive', 'Trace', '+', etc. or where the

result is outside of the normal range) in the findings for the specific parameter. All other test results will be presented as reported.

Baseline and change from baseline values will be derived for each parameter (as appropriate) in accordance with the methods defined in Section 5.1.2.

4.1.4 Electrocardiogram (ECG) Evaluations

Electrocardiogram (ECG) evaluations will be performed in accordance with the Schedule of Study Events (Section 2.5).

The following parameters will be assessed, and measurements and findings will be reported on the 12-Lead ECG CRF page:

- Overall Assessment ('Normal', 'Abnormal Not Clinically Significant [NCS]' or 'Abnormal Clinically Significant [CS]').
- Heart Rate (bpm).
- RR Interval (msec).
- PR Interval (msec).
- QRS Duration (msec).
- QT Interval (msec).
- QTcB Interval (msec).
- QTcF Interval (msec).

Baseline and change from baseline values will be derived for each parameter (as appropriate) in accordance with the methods defined in Section 5.1.2.

Based on the criteria presented in Appendix 1, abnormal ECG measurements ('Low' or 'High') will be identified and reported at each visit and/or scheduled time point.

4.1.5 Vital Signs Evaluations

Vital signs evaluations will be performed in accordance with the Schedule of Study Events (Section 2.5).

The following parameters will be assessed, and measurements and findings will be reported on the Vital Signs CRF page:

- Height (cm).
- Weight (kg).
- Body Mass Index (kg/m^2).
- Supine systolic blood pressure (SBP) (mmHg).
- Supine diastolic blood pressure (DBP) (mmHg).
- Supine pulse rate (bpm).
- Respiratory rate (breaths/min)
- Temperature (°C)

Baseline and change from baseline values will be derived for each parameter (as appropriate) in accordance with the methods defined in Section 5.1.2.

Based on the criteria presented in Appendix 2, abnormal vital signs measurements ('Low' or 'High') will be identified at each visit and/or scheduled time point and clinical significance (as assessed by the Investigator) will be reported.

4.1.6 Physical Examination

Full and symptoms-directed physical examinations will be performed in accordance with the Schedule of Study Events (Section 2.5).

The following body systems will be assessed ('Normal' or 'Abnormal') and findings and clinical significance (as assessed by the Investigator) will be reported on the Physical Examination eCRF page:

- Head, eyes, ears, nose, and throat.
- Cardiovascular system
- Dermatological system
- Musculoskeletal system
- Respiratory system
- Gastrointestinal system
- Neurological system
- Other abnormalities.

4.1.7 Fasting Status and Water Restrictions

The dates and time of the meals before and after the study drug administrations will be collected on the 'Overnight Fasting Status' and 'Post-Dose Fasting Status' CRF pages. Water intake will be restricted before and after the study drug administration and the timing of the restriction period will be reported on the 'Water Restriction' CRF pages.

4.2 Pharmacokinetic Concentrations

Plasma PK samples will be collected during Treatment Period 1 and Period 2 at the time points specified in the Schedule of Study Events (Section 2.5). The actual sample collection dates and times will be reported on the 'PK Blood Collection' CRF pages.

The actual elapsed time (hours) from the reference study drug administration in each period will be calculated as the difference between the date/time of the sample collection at the nominal time point and the date/time of the study drug administration for the specific period.

The time deviation at each time point (hours), defined as the difference between the nominal (planned) and actual collection times will be calculated as the difference between the nominal collection time point value (i.e., 2 hours post-dose will be 2 hours) and the elapsed time based on the actual collection date and time.

Deviations from the collection time points will be used to identify out of window samples that may be excluded from the PK analysis if deemed to have a major impact on the overall analysis.

Plasma concentrations of sitravatinib will be determined using a validated analytical procedure. Specifics about the analytical method will be provided in the bioanalysis report. Concentrations data will be provided electronically by the analysing laboratory.

The Lower Limit of Quantitation (LLOQ) for sitravatinib is 0.05 ng/mL.

Concentrations below the LLOQ (BLQ) observed prior to the maximum observed concentration (C_{max}) for the specific period will be set to zero for all calculations and analyses. BLQ concentrations observed after C_{max} will be treated as missing.

4.3 Pharmacokinetic Parameters

The PK parameters described in this section will be derived based on the plasma sitravatinib concentration-time profiles as observed after the study drug administrations on Day 1 of each treatment period. The parameters will be calculated separately for each treatment period based on concentrations collected during the specific period.

BLQ concentrations observed prior to the maximum observed concentration (C_{max}) for the specific period will be set to zero and BLQ concentrations observed after C_{max} will be treated as missing in all

parameter calculations. Derivations will be based on the actual elapsed time (hours) since the study drug administration in the specific period.

The pharmacokinetic concentrations will be processed using standard noncompartmental analytical procedures to derive the required parameters. The software used for the analysis will be Phoenix™ WinNonlin® v8.2 (Pharsight Corporation, USA).

The PK parameters described in Table 4 will be derived for each period provided that the required concentrations data are available. Supporting PK parameters (used to derive or assess the validity of $t_{1/2}$ and associated parameters) which include R^2, number of points for estimation of kel and $\%AUC_{ext}$ will only be listed and not included in the summary tables.

Table 4 Plasma PK Parameters

PK Parameter (Unit)	Method
C_{max} (ng/mL)	Maximum observed plasma concentration.
t_{max} (h)	Time to reach maximum plasma concentration.
AUC_{0-t} (h*ng/mL)	Area under the plasma concentration-time curve from the time of the dose administration to the time of the last measurable concentration calculated by the linear up log down trapezoidal method.
$t_{1/2}$ (h)	Elimination half-life associated with the terminal slope (kel) of the semilogarithmic drug concentration-time curve, calculated as 0.693/kel.
AUC_{0-inf} (h*ng/mL)	Area under the plasma concentration-time curve from the time of the dose administration to time infinity calculated by the linear up log down trapezoidal method.
CL/F (L/h)	The apparent total clearance.
V_z/F (L)	The apparent total volume of distribution.
R^2 (*)	R-squared.
No. of Points (*)	No. points for determination of kel.
kel (1/h) (*)	Apparent terminal elimination rate constant.
$\%AUC_{ext}$ (%) (*)	Percentage of the area under the plasma concentration-time curve extrapolated from the time of the last measurable concentration to time infinity as a percentage of AUC_{0-t}
DN C_{max} (ng/mL)/mg	Dose-normalized C_{max} will be calculated by dividing C_{max} by the administered dose.
DN AUC_{0-t} (h*ng/mL)/mg	Dose-normalized AUC_{0-t} will be calculated by dividing AUC_{0-t} by the administered dose.
DN AUC_{0-inf} (h*ng/mL)/mg	Dose-normalized AUC_{0-inf} will be calculated by dividing AUC_{inf} by the administered dose.
F_{rel} (%)	Relative bioavailability (F_{rel}) (%) will be calculated based on the AUC_{0-inf} results using the following formula: F_{rel} (%) = 100 * ([AUC_{MSC} * 120 {the FCB dose}] / [AUC_{FBC} * 100 {the MSC dose}]).

(*) Derived to determine $t_{1/2}$, results will only be listed.

Results for $t_{1/2}$, AUC_{0-inf}, CL/F and V_z/F will only be included in the summary statistics if the following criteria are met:

- A minimum of 3 measurable concentrations-time points is available during log-linear portion of the terminal elimination phase (excluding C_{max}), i.e., No. of Points is ≥ 3.
- $R^2 > 0.80$.
- $\%AUC_{ext} < 20\%$.

4.4 Baseline Characteristics and Other Measures

4.4.1 Subject Disposition

Subject disposition data will be collected on the 'Study Completion' CRF page when a subject completed or discontinued from the study.

The following data will also be presented in the disposition listing:

- Date/time of informed consent ('Informed Consent' CRF page).
- Date/time of the first and second study drug administrations ('Dose Administration' CRF page).
- Date/time of Follow-Up phone call ('Follow Up Phone Call' CRF page).

The analysis sets defined in Section 3 will be summarised and presented as part of the subject disposition data.

4.4.2 Protocol Deviations and Eligibility

Protocol deviations will be reported on the 'Protocol Deviations' CRF page.

Important protocol deviations are defined as violations that might affect the safety or pharmacokinetics of a subject, and lead to the exclusion of subjects from the analysis sets defined in Section 3. Non-important protocol deviations are protocol deviation that, in the Investigator's judgment, do not adversely affect the risk/benefit ratio of the study, the rights, safety, or welfare of the subjects or others, or the integrity of the study.

Eligibility will be reported on the 'Eligibility Criteria' CRF page.

The eligibility of all subjects for entry into the study will be assessed at Screening and Day -1 of each treatment period. A subject should have met all the inclusion, and none of the exclusion criteria before entry into the study.

4.4.3 Demography

Demographic information provides data regarding the subjects and is necessary for the determination of whether the individuals in the study a representative sample of the target population are.

The following demography data will be collected on the 'Demographics' CRF page at Screening.

- Year of birth and Age (Years)
- Gender ('Male', 'Female')
- Ethnicity ('Hispanic or Latino', 'Not Hispanic or Latino')
- Race:
    - 'American Indian or Alaskan Native'
    - 'Native Hawaiian or Other Pacific Islander'
    - 'White'
    - 'Black or African American'
    - 'Asian'
        - 'Asian Indian'
        - 'Chinese'
        - 'Filipino'
        - 'Japanese'
        - 'Korean'
        - 'Vietnamese'
        - 'Other Asian'
    - 'Other'

4.4.4 Baseline Subject Characteristics

Baseline subject characteristics include characteristics that subjects presented with prior to the first administration of study drug.

The following subject characteristics will be collected on the 'Body Measurements' CRF page at Screening:

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)

4.4.5 Medical History

Medical history is information about conditions that a subject might have suffered from prior to the first administration of study drug, or conditions that were ongoing at the time of the first administration of study drug.

Medical history data will be collected at Screening on the 'Medical History & Allergies' CRF page.

4.4.5.1 Coding of Medical History Terms

Medical history terms (Investigator terms) will be coded to a LLT, PT, HLT, HLGT and SOC according to the MedDRA dictionary, Version 23.0, depending on the latest version available during the study. Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via a single HLT, HLGT route.

Medical history will be reported on a per-subject basis. This means that even if a subject suffered the same clinical event repeatedly (i.e., events mapped to the same PT) the event will be counted only once.

4.4.6 Prior and Concomitant Medications

Prior and concomitant medications data will be collected throughout the study on the 'Prior Medications' and 'Concomitant Medications' CRF pages.

Missing and partial concomitant medications dates will be handled according to the rules specified in Sections 5.1.4 and 5.6.2.2.

4.4.6.1 Medication Definitions

Prior medications are defined as any medication where the use was stopped prior to the first administration of study drug. Medications that were stopped on the same date as the first study drug administration are considered to be prior medications unless there is clear evidence that the medication was used after the first study drug administration (for example, a medication start/stop time is available, or the medication was administered to treat a treatment-emergent AE).

Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of study drug.

4.4.6.2 Coding of Medication Terms

Prior and concomitant medication terms will not be coded.

4.4.7 Assignment to Treatment

Subjects will be randomised to a treatment sequence prior to the first study drug administration and the randomisation number will be reported on the 'Pre-Dose Randomisation' CRF page.

5. Statistical Methodology

5.1 General Statistical Methods

5.1.1 Software

All analysis data sets and outputs will be produced by the Biostatistics Department of Resolutum Global using the SAS® system Version 9.4 (SAS Institute, Cary, North Carolina, USA) or higher.

The pharmacokinetic concentrations will be processed using standard noncompartmental analytical procedures to derive the required parameters. The software used for the analysis will be Phoenix™ WinNonlin® v 8.2 (Pharsight Corporation, USA).

5.1.2 Definitions

The following definitions will be used:

- Date of the First Study Drug Administration: The date of the first study drug administration is defined as the earliest date on which study drug was administered as reported on the Dose Administration CRF page.
- Date of the Last Study Drug Administration: The date of the last study drug administration is defined as the latest known date on which study drug was administered as reported on the Dose Administration CRF page.

  The date of the last study drug administration will be derived based on the available information for all subjects who did not complete the study.
- Overall Baseline: The baseline value is defined as the last available valid, non-missing observation prior to the first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values. Results including, but not limited to, 'Not done', 'Not applicable', 'Unknown' will not be included in the baseline derivations.
- Period Baseline: The baseline value for the specific treatment period is defined as the last available valid, non-missing observation prior to the study drug administration in that period. Repeat and unscheduled assessments will be included in the derivation of the baseline values. Results including, but not limited to, 'Not done', 'Not applicable', 'Unknown' will not be included in the baseline derivations.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit and the baseline value (for that specific period for changes from the period baseline values).

  The change from baseline value at each post-baseline visit will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Post-Baseline Visit – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit result and the baseline value for the parameter are both available and will be treated as missing otherwise. In the data listings, the change values will be set to 'N/A' (not applicable) for pre-baseline assessments.
- Overall Study Day: The overall study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

For events occurring on or after Day 1, study day will be calculated as:

Study Day = (Date of Event - Date of First Study Drug Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined otherwise.

- Period Study Day: The study day of an event is defined as the relative day of the event starting with the date of the study drug administration in the specific period (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the study drug administration will be calculated as:

  Study Day = (Date of Event - Date of Study Drug Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of Study Drug Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined otherwise. Study days for events that started prior to the first study drug administration will be calculated relative to the Period 1 study drug administration and study days for events that started after the end of Period 2 will be calculated relative to the Period 2 study drug administration.

5.1.3 Default Descriptive Statistics and Data Presentation Rules

Unless otherwise stated, summary statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum, will be presented for all continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. Derived values will be presented to 4 significant digits.

For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Unless specifically stated otherwise, denominator for all percentage calculations will be the number of subjects in the specific treatment sequence/group and analysis population. All percentages will be presented to one decimal place.

For PK concentration and parameters data, descriptive statistics will include the number of non-missing values (n), the arithmetic mean, standard deviation (SD), median, minimum, maximum, coefficient of variation (CV), geometric mean, geometric SD and geometric CV values, as appropriate. For the PK concentration summaries, the number of concentrations below the limit of quantification will also be presented.

The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal, and the SD values will be displayed to two more decimals than the source data for the specific variable. The geometric mean values will be presented to one more decimal place than the arithmetic mean and the CV and geometric CV values will be converted to percentages and presented to one decimal place.

If required, results will be rounded using the SAS® function ROUND. Values will be rounded after all calculations have been performed.

5.1.4 Date and Time Display Conventions

The following display conventions will be applied in all outputs where dates and/or times are displayed:

- Date only: YYYY-MM-DD
- Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will not be presented, for example if only the year is known, '2016'. Times will be reported in military time.

5.1.5 General Display Conventions

All data collected during the study (data originating from the CRFs or electronic transfers), except for screen failure data, will be presented in the data listings. Event-based listings will be sorted by treatment sequence, subject number, study period and event start and end dates. Assessment-based listings will be sorted by treatment sequence, subject number, study period, parameter name (alphabetically unless specifically stated otherwise), visit and time point (if applicable).

Fields that are missing because they are not applicable for the subject/time point (for example change from baseline results at the baseline visit) will be presented as "N/A", unless otherwise specified. Missing data points will be presented as blank fields in the data listings.

All summary tables presenting baseline characteristics, disposition or concomitant medication results will be presented by treatment sequence. All other summary tables will be presented by treatment group. Assessment-based tables will be sorted alphabetically by parameter (unless specifically stated otherwise) and chronologically by visits/time point within parameter. Only values collected at scheduled study visits/time points will be presented in summary tables. Event-based tables will be ordered as specified in Section 6.

The All Subjects group will be presented on all tables where indicated in the mock shells. Subjects will only be counted once in the All Subjects group; for event-based tables all relevant events will included, whereas for assessment-based tables only visits/time points that are not linked to as specific treatment period will be included (for example, Screening, Day 8/Early Termination and Follow-Up [see Table 6])

Tables 5, 6, and 7 presents the treatment group, visit and time point labels that will be used in the tables, listings, and figures (TLFs).

Table 5 Study Treatments

Actual Treatment	Treatment Label
Sequence 1: 120 mg Sitravatinib Free Base Capsule - 100 mg Sitravatinib Malate Salt Capsule	120 mg Sitravatinib FBC (Period 1) - 100 mg Sitravatinib MSC (Period 2)
Sequence 2: 100 mg Sitravatinib Malate Salt Capsule - 120 mg Sitravatinib Free Base Capsule	100 mg Sitravatinib MSC (Period 1) - 120 mg Sitravatin b FBC (Period 2)
100 mg Sitravatinib Malate Salt Capsule	100 mg Sitravatinib MSC
120 mg Sitravatinib Free Base Capsule	120 mg Sitravatinib FBC
All Subjects	All Subjects

Table 6 Study Visits

Period	Actual Visit	Listing Label	Table Label
Not Applicable	Screening (Day -28 to -2)	Screening	Screening
Period 1	Period 1 - Day -1	Period 1 Day -1	Day -1
	Period 1 - Day 1	Period 1 Day 1	Day 1
			Baseline
	Period 1 - Day 2	Period 1 Day 2	Day 2
	Period 1 - Day 3	Period 1 Day 3	Day 3
	Period 1 - Day 4	Period 1 Day 4	Day 4
	Period 1 - Day 8/Early Termination	Period 1 Day 8 [or Early Termination]	Day 8/Early Termination
Period 2	Period 2 - Day -1	Period 2 Day -1	Day -1
	Period 2 - Day 1	Period 2 Day 1	Day 1
			Baseline
	Period 2 - Day 2	Period 2 Day 2	Day 2
	Period 2 - Day 3	Period 2 Day 3	Day 3
	Period 2 - Day 4	Period 2 Day 4	Day 4
	Period 2 - Day 8/Early Termination	Period 2 Day 8 [or Early Termination]	Day 8/Early Termination
	Follow-up Phone Call	Follow-Up Phone Call	Follow-Up

Table 7 Scheduled Time Points

Scheduled Time Point	Scheduled Time Point Label
Pre-dose (- 30 Minutes)	Pre-Dose
30 Minutes Post-Dose	0.5 Hours Post-Dose
1 Hour Post-Dose	1 Hour Post-Dose
2 Hours Post-Dose	2 Hours Post-Dose
4 Hours Post-Dose	4 Hours Post-Dose
6 Hours Post-Dose	6 Hours Post-Dose
8 Hours Post-Dose	8 Hours Post-Dose
12 Hours Post-Dose	12 Hours Post-Dose
24 Hours Post-Dose (Day 2)	24 Hours Post-Dose
48 Hours Post-Dose (Day 3)	48 Hours Post-Dose
72 Hours Post-Dose (Day 4)	72 Hours Post-Dose
168 Hours Post-Dose (Day 8)	168 Hours Post-Dose

5.2 Hypotheses and Decision Rules

Not applicable.

5.3 Multiple Comparisons and Adjustments for Multiplicity

Not applicable.

5.4 Covariates

Not applicable.

5.5 Multi-Centre Data

Not applicable.

5.6 Handling of Missing Data

5.6.1 Efficacy Endpoints

Not applicable.

5.6.2 Safety Endpoints

5.6.2.1 Adverse Events

Missing start dates/times will be imputed to one minute after the first study drug administration.

Partial start dates will be imputed to the last day of the month/year considering that the start date should not be after the stop date/time. Missing start times will be imputed to '23:59'. If the imputation results in the start date/time being after the stop date/time, the start date/time will be set to the stop/date time.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study drug. In the even that no clear determination can be made, the event will be deemed to have started at the same time as the study drug, i.e., the event will be analysed as being treatment emergent.

Stop dates/times will not be imputed if the AE is ongoing.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, 'Severe' will be imputed. If causality data are missing, 'Related' will be imputed.

5.6.2.2 Prior and Concomitant Medications

Missing concomitant medication dates will be handled in a similar fashion as described for Adverse Events in Section 5.6.2.1.

5.7 Windowing Conventions

Not applicable.

5.8 Interim Analyses

No interim analyses are planned for this study.

5.9 Clinical Data Interchange Standards Consortium (CDISC) Specifications

The study data will be converted into CDISC-compliant datasets based on the Study Data Tabulation Model Implementation Guide (SDTMIG) Version 3.2 and the Analysis Data Model Implementation Guide (ADaMIG) Version 1.0.

The SDTM data package will be based on raw data (clinical database and external data) and will include SAS® datasets and transport files (.XPT format) for each required SDTM domain, as well as the SDTM Case Report Tabulation Data Definition Specifications (CRT-DD) (define.xml Version 2.0) that describes the origin of the data and all of the derivations and imputations that were applied, and includes an SDTM-annotated CRF and the Study Data Reviewer's Guide (SDRG).

The ADaM datasets will be based on the SDTM datasets and will be used for the analysis. The ADaM data package will include SAS® datasets and transport files (.XPT format) for each analysis dataset, as well as the ADaM CRT-DD (define.xml Version 2.0) and the Analysis Data Reviewer's Guide (ADRG).

The SDTM and ADaM data packages will be validated using Pinnacle 21 Community (531 Plymouth Road, Suite 508, Plymouth Meeting, PA 19462) and the validation reports will be included with the respective data packages.

All data conversions will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) with program code prepared specifically for the study.

The output SAS® programs will generate rich-text-formatted (RTF) output with the ".RTF" extension using the SAS® Output Delivery System (ODS). Each output display will show the name of the SAS® program which was used to produce it.

5.10 Additional Analyses to Assess the Impact of COVID-19

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

COVID-19 has been recognized as a public health emergency that may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

Additional sensitivity analyses may be performed to address the impact that COVID-19 may have had on this study and the details of any such analyses will be incorporated into the Clinical Study Report.

6. Statistical Analyses

6.1 Subject Disposition and Analysis Sets

Summary tables will be based on the Safety Analysis Set.

The number and percentage of enrolled subjects, subjects completing or withdrawing from the study as well as the primary reason for withdrawal will be presented by treatment sequence and for all subjects overall in the subject disposition table. The denominator for the reason for withdrawal percentage calculations will be the number of subjects that withdrew from the study.

All subject disposition information collected on the 'Study Completion' CRF page will be listed together with the date/time that the subject provided informed consent, the dates/times of the first and second study drug administrations, and the date/time of the Follow-Up phone call.

The number of subjects included in of each of the analysis sets defined in Section 3 will be summarised by treatment sequence and for all subjects overall using frequencies and percentages.

In addition, the inclusion/exclusion of each subject into/from each of the defined analysis set, as well as the reasons for exclusion (where applicable) will be listed.

The randomisation information including the assigned treatment sequence will be listed.

6.2 Protocol Deviations and Eligibility

Summary tables will be based on the Safety Analysis Set.

The number and percentage of subjects with at least one important protocol deviation, as well as the number and percentage of subjects with a deviation in each of the deviation categories will be presented by treatment sequence and for all subjects overall in the protocol deviation table. Subject will be counted once per category, but all deviation will be counted.

Important protocol deviation information collected on the 'Protocol Deviations' CRF will be listed.

All eligibility data collected on the 'Eligibility Criteria' CRF page will be listed.

6.3 Demography

Summary tables will be based on the Safety Analysis Set.

Demography data (as described in Section 4.4.3) will be summarised and presented by treatment sequence and for all subjects overall in the demography table. The homogeneity between treatment groups will be assessed based on the descriptive statistics only.

All collected and derived demography data will be listed.

6.4 Baseline Subject Characteristics

Summary tables will be based on the Safety Analysis Set.

Baseline subject characteristics data (as described in Section 4.4.4) will be summarised and presented by treatment sequence and for all subjects overall in the demography table.

The vital signs parameters will be listed as part of the vital signs listing.

6.5 Medical History

Summary tables will be based on the Safety Analysis Set.

Medical history conditions will be summarised by SOC and by PT within SOC. Within each category, the number of subjects who experienced a condition (frequency and percentage) and the actual number of events (frequency only) will be presented by treatment sequence and for all subjects overall. Subjects who experienced the same condition on more than one occasion (based on the specific category) will only be counted once in each relevant category (SOC and PT), but all

conditions will be included in the event frequencies. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table. In addition to the coded terms, the number of subjects with at least one medical history condition and the total number of events will be presented.

All information that was collected on the 'Medical History & Allergies' CRF as well as the coded MedDRA terms, and the start and end study days (relative to the first study drug administration) will be included in the listing. Partial dates will not be imputed.

6.6 Prior and Concomitant Medication

Summary tables will be based on the Safety Analysis Set.

Concomitant mediations will be summarised by reported verbatim medication name. Within each medication name, the number of subjects who used the medication (frequency and percentage) will be presented. Subjects who used the same medication on multiple occasions will only be counted once. Medication names will be sorted alphabetically. In addition to the summaries by the verbatim terms, the number of subjects who used at least one concomitant medication during the study will be presented.

All information that was collected on the 'Prior Medications' and 'Concomitant Medications' CRF page will be included in the listings. Furthermore, the relative medication start and end days (relative to the first study drug administration) will be presented where complete medication start and end dates are available.

Prior medications (history of medication use) will be listed as part of the baseline characteristics. Concomitant medications will be listed separately.

6.7 Efficacy Analyses

Not applicable for this study.

6.8 Safety Analyses

Statistical methods for the safety analyses will be descriptive in nature and no formal statistical comparisons will be made. Endpoints will be summarised by treatment group and period based on the methods described in Section 5.1.

Safety endpoints will be analysed based on the Safety Analysis Set.

6.8.1 Exposure to Study Drug

All collected study drug administration data will be listed.

6.8.2 Adverse Events

All tables will present the number of subjects who experienced an AE (count and percentage) and the actual number of AEs (count only) within each specific category by treatment group and for all subjects overall. Subjects who experienced multiple AEs will only be counted once in each relevant category (high-level summary, SOC, PT, severity rating or relationship to study drug category), but all events will be included in the event counts. Percentages will be based on the number of subjects in the Safety Analysis Set. Tables will only include treatment-emergent events.

The overall summary of TEAEs table will present the total number of subjects who experienced a TEAE and the total number of TEAEs in each of the following categories:

- At least one TEAE.
- At least one serious TEAE.
- At least one severe TEAE.
- At least one treatment-related TEAE.
- At least one TEAE leading to the withdrawal of study drug.

- At least one TEAE leading to study withdrawal.

The summary of TEAEs table will include the number of subjects who experienced at least one TEAE and the corresponding number of events, and furthermore summarise the TEAE data by SOC and preferred term within SOCs. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table.

The summary of SAEs table will include the number of subjects who experienced at least one SAE and the corresponding number of SAEs, and furthermore summarise the SAE data by SOC and preferred term within SOCs. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table.

The summary of treatment-related TEAEs table will include the number of subjects who experienced at least one treatment-related TEAE and the corresponding number of events, and furthermore summarise the TEAE data by SOC and preferred term within SOCs. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table.

The summary of TEAEs leading to study drug withdrawal table will include the number of subjects who experienced at least one TEAE that lead to the withdrawal of study drug and the corresponding number of events, and furthermore summarise the TEAE data by SOC and preferred term within SOCs. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table.

The summary of TEAEs leading to study withdrawal table will include the number of subjects who experienced at least one TEAE that lead to study withdrawal and the corresponding number of events, and furthermore summarise the TEAE data by SOC and preferred term within SOCs. System organ class terms will be sorted alphabetically, and preferred terms will be sorted alphabetically within SOCs in the table.

The summary of TEAEs by severity table will include the number of subjects who experienced at least one TEAE, the number of subjects who experienced at least one TEAE within each severity rating ('Mild', 'Moderate', 'Severe', 'Life-threatening', 'Fatal') and the corresponding number of events for each rating. In addition, the TEAE data will be summarised by SOC, preferred term within SOC, and severity rating within preferred term. System organ class terms will be sorted alphabetically, preferred terms will be sorted alphabetically within SOCs and severity ratings will be sorted in increasing order of severity within preferred terms in the table.

The summary of TEAEs by relationship to study drug (causality) table will include the number of subjects who experienced at least one TEAE, the number of subjects who experienced at least one TEAE within each relationship category ('Related', 'Not Related') and the corresponding number of events for each category. In addition, the TEAE data will be summarised by SOC, preferred term within SOC, and relationship category within preferred term. System organ class terms will be sorted alphabetically, preferred terms will be sorted alphabetically within SOCs and relationship category will be sorted from the least to the most likely relationship to study drug within preferred terms in the table.

The listing of AEs will include all AE data in the clinical database. The listing will present all the information (fields) collected on the 'Adverse Event' CRF page, as well as the SOC and preferred terms obtained from the MedDRA dictionary. In addition, the AE period start and end days (relative to the study drug administration of the treatment group that the AE was assigned to) and a flag indicating whether the AE was treatment emergent will be presented. Non-TEAEs will be listed under the first treatment that a subject received. If the AE was ongoing at the end of the study, 'Ongoing' will be presented under the 'Stop Date/Stop Time/Study Day' heading. Partial dates/times will be presented as described in Section 5.1.4. The subsets of SAEs, treatment-related AEs, AEs leading to the withdrawal of study drug or withdrawal from the study will be listed separately and will include all the information presented in the main AE listing.

6.8.3 Laboratory Parameters

The laboratory parameters described in Section 4.1.3 will be summarised and listed.

The summary of hematology and biochemistry results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit. Refer to Section 4.1.3 for the handling of character results.

The summary of urinalysis result classification table will present summaries for the baseline and each scheduled post-baseline visit for each of the defined categories ('Normal' and 'Abnormal') within each urinalysis parameter.

The listings of hematology and biochemistry data will include all laboratory data (collected at scheduled and unscheduled visits) in the clinical database. The listings will present all the information (fields) that is available in the laboratory data set. In addition, the observation that was used as the baseline records (values) for each parameter will be flagged, the change from baseline value and the derived result classification (based on the normal ranges where applicable) at each post-baseline visit will be presented. A separate listing that includes only the subset of subjects that had at least one abnormal result will also be created for each test panel. All the subjects' results for every parameter where at least one abnormal classification was observed will be included.

The listing of urinalysis data will include all laboratory data (collected at scheduled and unscheduled visits) in the clinical database. The listings will present all the information (fields) that is available in the laboratory data set. In addition, the observation that was used as the baseline record (value) for each parameter will be flagged and the result classification (derived or based on the normal range where applicable) will be presented. A separate listing that includes only the subset of subjects that had at least one abnormal result will also be created. All the subjects' results for every parameter where at least one abnormal classification was observed will be included.

The listings of alcohol breath test results, urine drug screen and cotinine test, thyroid-stimulating hormone, SARS-CoV-2 test, serology and urine microscopy data will include all available results (collected at scheduled and unscheduled visits) in the clinical database. The listing will present all the information (fields) that is available in the laboratory data set.

6.8.4 Electrocardiogram (ECG) Parameters

The ECG parameters described in Section 4.1.4 will be summarised and listed.

The summary of ECG measurements tables will present summary statistics of the results at the baseline and each scheduled post-baseline visit/time point for each parameter. In addition, summaries will be presented for the change from baseline values (period baselines) at each scheduled post-baseline visit/time point.

The summary of ECG overall assessments tables will present table will present summaries for the baseline and each scheduled post-baseline visit/time point for each of the defined categories ('Normal', 'Abnormal NCS' and 'Abnormal CS').

The listings of ECG results will include all data (collected at scheduled and unscheduled visits) in the clinical database. Results will be listed per visit and scheduled time point, including the results, normal range values and the normal range indicator for each parameter. The observations that were used as the baseline records for each parameter will be flagged and the change from baseline values at each post-baseline visit/time point will be presented. The listing will also include the normal ranges for each parameter (where defined) and a normal range indicator.

6.8.5 Vital Signs

The vital signs parameters described in Section 4.1.5 will be summarised and listed.

The summary of vital signs results tables will present summary statistics for results at the baseline and each scheduled post-baseline visit/time point for each parameter. In addition, summaries will be

presented for the change from baseline values (period baselines) at each scheduled post-baseline visit/time point.

The listings of vital signs results will include all data (collected at scheduled and unscheduled visits) in the clinical database. The observations that were used as the baseline records for each parameter will be flagged and the change from baseline values at each post-baseline visit/time point will be presented. The listing will also include the normal ranges for each parameter (where defined), a normal range indicator and the clinical significance flags (if applicable) as reported by the Investigator.

6.8.6 Physical Examination

The physical examination assessment data described in Section 4.1.6 will be listed.

6.8.7 Fasting Status and Water Restrictions

The collected fasting status and water restriction information data described in Section 4.1.7 will be listed.

6.9 Pharmacokinetic Analyses

6.9.1 Plasma Concentrations

The analysis of the PK concentration data will be based on the PK Concentrations Analysis Set.

The plasma sitravatinib concentrations data will be summarised by treatment group and nominal collection time points using the statistics described in Section 5.1.3. BLQ concentrations that occurred prior to C_{max} will be set to 0, and treated as missing otherwise, for the calculation of summary statistics. Zero values will be treated as missing for the calculation of the geometric statistics. Missing values will be omitted from the calculation of descriptive statistics.

Figures of the individual plasma concentrations vs. actual time profiles (both treatment groups for each subject on the same plot) will be presented on a linear and a log-linear scale. All concentration for both treatment groups will also be presented in the same spaghetti plot presented on a linear and a log-linear scale. BLQ concentrations that occurred prior to C_{max} will be set to 0 and treated as missing otherwise in the linear plots. BLQ concentrations will be set to missing in the log-linear plots.

Mean concentration profiles vs. nominal time curves will be presented on a linear and log-linear scale. Both treatment groups will be presented on the same plot. Standard deviation bars will also be presented.

All plasma concentration data will be listed, and the listing will include the calculated elapsed time since the study drug administration in the specific period and the time deviations between the actual and planned sample collection times.

6.9.2 Pharmacokinetic Parameters

The calculated plasma PK parameters described in Section 4.3 will be summarised by treatment group using the statistics described in Section 5.1.3. The summary tables will be based on the PK Parameters Analysis Set.

Relative bioavailability will be summarised separately based on the Relative Bioavailability Analysis Set.

The analysis of the relative bioavailability between the two different formulations of sitravatinib (sitravatinib MSC as test and sitravatinib FBC as reference) will be based on the dose-dependent parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max}. The $\log_e$-transformed parameters will be analyzed separately using a mixed effect model (data permitting) with the treatment group (formulation), sequence and period as fixed effects and subject nested within sequence as a random effect. The geometric means (exponentiated least squares means) and the associated 90% confidence intervals for each treatment group and the geometric mean ratio (exponentiated difference between sitravatinib MSC least-squares mean as test and sitravatinib FBC least-squares mean as reference) and the associated 90% confidence interval will be presented. The geometric mean ratios and the associated confidence

intervals will be expressed as percentages. Bioequivalence will be concluded if the 90% confidence intervals of the geometric mean ratios of all three parameters lies entirely within the bioequivalence interval of 80% to 125%. Refer to Appendix 3 for the SAS® code that will be used for the analysis. The analysis will be based on the Relative Bioavailability Analysis Set.

The analysis will also be repeated based on the dose-normalized $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} results.

The parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} will also be presented graphically by means of box-and-whiskers plots. The results for the two treatment groups will be presented on the same plot. The dose-normalized $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} results will also be plotted separately. The plots will be based on the Relative Bioavailability Analysis Set.

All parameter results will be listed based on the PK Parameters Analysis Set, and any results that may have been excluded from the summary tables will be flagged. The SAS® outputs generated by the respective models will be presented in listings.

7. Changes to the Planned Analyses

7.1 Changes to the Analyses Described in the Study Protocol and Protocol Amendments

No changes were made to the analyses described in the study protocol.

7.2 Changes from the Statistical Analysis Plan Version x.x to Version x.x

Not applicable.

8. Attachments and Appendices

Appendix 1 ECG Normal Ranges

ECG Parameter (Unit)	Normal Range
Heat Rate (bpm)	40-100 bpm
PR Interval (msec)	120-200 msec
QRS Duration (msec)	< 110 msec
QTcB Interval (msec)	< 450 msec (Male) or < 470 msec (Female)
QTcF Interval (msec)	< 450 msec (Male) or < 470 msec (Female)

Appendix 2 Vital Signs Normal Ranges

Vital Signs Parameter (Unit)	Normal Range
Systolic Blood Pressure (mmHg)	90-140 mmHg
Diastolic Blood Pressure (mmHg)	40-90 mmHg
Pulse Rate (bpm)	40-100 bpm
Respiratory Rate (breaths/min)	10-20 breaths/min
Temperature (°C)	35.5-37.5 °C

Appendix 3 Comparative Bioavailability SAS® Code

The following SAS® code will be used for the comparative bioavailability analysis:

```
ODS Output lsmeans=lsmeans;
ODS Output diffs=diffs;

Proc Mixed data = pk;

   Class sequence aperiod subjid trt;

   Model log_aval = sequence aperiod trt;

   Random subjid (sequence);

   LSmeans trt/pdiff cl alpha=0.1;

Run;
```

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