# STATISTICAL ANALYSIS PLAN

**Study: UP0152**

**Product: Minzasolmin**

# AN OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE RELATIVE BIOAVAILABILITY OF A NEW TABLET FORMULATION OF MINZASOLMIN AND THE POTENTIAL EFFECT OF FOOD ON THE PHARMACOKINETICS OF MINZASOLMIN IN HEALTHY PARTICIPANTS

A randomized, open-label Phase 1 study to assess the relative bioavailability of a new formulation of Minzasolmin in healthy participants.

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**Confidentiality Statement**

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# VERSION HISTORY

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1 | 23 SEP 2024 | Not Applicable | Original version |

# LIST OF ABBREVIATIONS

## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ASPS | All Study Participants Set |
| BP | blood pressure |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| BW | body weight |
| CDE | Center for Drug Evaluation |
| CI | Confidence Interval |
| CSR | clinical study report |
| CRF | clinical report form |
| CTR | Clinical Trials Registry (CTR) |
| CV | coefficient of variation |
| D | dose |
| DBP | diastolic blood pressure |
| DEM | Data Evaluation Meeting |
| ECG | electrocardiogram |
| FSH | follicle-stimulating hormone |
| geometric cv | geometric coefficient of variation |
| hCG | human chorionic gonadotropin |
| HLT | high level term |
| ICF | informed consent form |
| ICH | The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IQR | interquartile range |
| IPD | Important protocol deviations |
| LLOQ | Lower limit of quantification |

## List of Abbreviations

| | |
|---|---|
| ln | natural logarithm |
| LSMEAN | least square mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| msec | milliseconds |
| NC | not calculable |
| NE | not estimable |
| PK | Pharmacokinetic |
| PKS | Pharmacokinetic Set |
| PT | preferred term |
| QD | once daily |
| REML | restricted maximum likelihood |
| RS | Randomized Set |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SBP | systolic blood pressure |
| SD | Single Dose |
| sd | standard deviation |
| SFU | Safety Follow-Up |
| SMC | Safety Monitoring Committee |
| SMQ | Standardized MedDRA Query |
| SOC | system organ class |
| SS | Safety Set |
| TEAE | Treatment-Emergent Adverse Event |
| TFLs | tables, figures and listings |
| TOST | two 1-sided ratios of means tests |
| WHO-DRL | World Health Organization Drug Reference List |
| WHODD | World Health Organization Drug Dictionary |
| WO | Washout Period |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide all necessary information to perform the statistical analyses and defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) of study UP0152, according to the protocol and using UCB Standard TFL Shells.

The SAP is based on the following study documents:

- Protocol Amendment 2 UP0152, 8 Aug 2024
- Clinical report form (CRF), 09 Aug 2024

## 1.1 Objectives and Endpoints

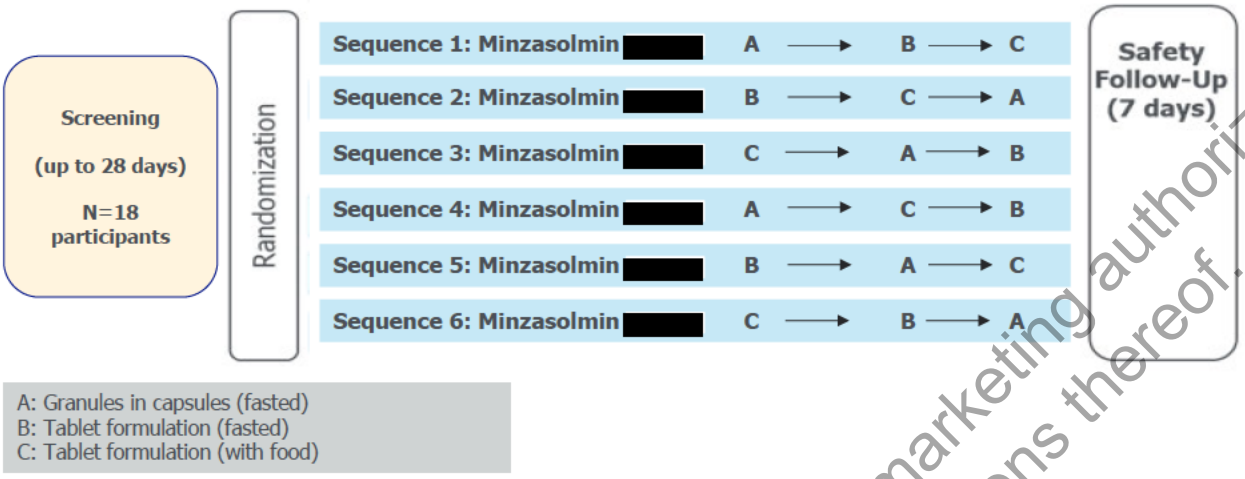
### Table 1 Objectives and endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To estimate the relative bioavailability of a new minzasolmin tablet formulation versus reference 'granules in capsule' formulation in healthy participants and to evaluate the effect of food with the new tablet formulation on the PK of minzasolmin. | Primary PK Endpoint(s)<br>• $AUC_{0-t}$, AUC, and $C_{max}$ in fasting (for both granules in capsule and tablet formulations) and fed (tablet formulation only) conditions for minzasolmin |
| **Secondary** | |
| • To evaluate the safety and tolerability of single-dose administration of minzasolmin in healthy participants using different formulations in fed condition (tablet formulation) and fasting condition (tablet and 'granules in capsule' formulations). | Secondary Safety Endpoint(s)<br>• Occurrence of TEAEs<br>• Occurrence of treatment-emergent SAEs<br>• Occurrence of TEAEs leading to withdrawal from study |
| **Other** | |
| • To further evaluate the PK of minzasolmin and its [redacted] metabolites after single-dose administration with reference 'granules in capsule' formulation or the new tablet formulation in fasting (tablet and 'granules in capsule' formulations) or fed condition (tablet formulation). | Other PK Endpoints<br>• For minzasolmin:<br>– $t_{max}$, $t_{½}$, CL/F, and Vz/F (if possible but not limited)<br>• For [redacted] metabolites:<br>– $AUC_{0-t}$, AUC, $C_{max}$, and $t_{max}$, in fasting and fed conditions<br>– metabolite/parent $C_{max}$ and AUC ratio, as appropriate |

AUC=area under the plasma concentration-time curve from time zero to infinity; $AUC_{0-t}$=area under the plasma concentration-time curve from time zero to t ; CL/F=apparent total body clearance; $C_{max}$=maximum observed plasma concentration; PK=pharmacokinetic(s); SAE=serious adverse event; $t_{½}$=apparent terminal elimination half-life; TEAE=treatment-emergent adverse event; $t_{max}$=time of occurrence of $C_{max}$; Vz/F=apparent volume of distribution

## 1.2 Study design

### Figure 1: Overall study schematic




ETV=Early Termination Visit; SFU=Safety Follow-Up
Note: Participants who have been confirmed eligible will be randomized to receive single doses of minzasolmin [redacted] with a 4-day Washout Period between doses.
Note: Study participants will have SFU procedures performed within 5 to 9 days after their final dose. Participants who prematurely withdraw from the study will return to the study clinic center for the ETV as soon as possible after the time of withdrawal and will have all SFU procedures performed.

### Table 2 Relative bioavailability of minzasolmin under fasting and fed condition (3-treatment, 6-sequence, 3-period crossover design)

| Sequence | Period 1 | Washout | Period 2 | Washout | Period 3 | Washout | Discharge | SFU |
|---|---|---|---|---|---|---|---|---|
| Day | D1 | D2-5 | D6 | D7-10 | D11 | D12-15 | D15 | D18 (±2 days) |
| 1 (ABC) | A | | B | | C | | | |
| 2 (BCA) | B | | C | | A | | | |
| 3 (CAB) | C | | A | | B | | | |
| 4 (ACB) | A | | C | | B | | | |
| 5 (BAC) | B | | A | | C | | | |
| 6 (CBA) | C | | B | | A | | | |

D=day; SFU=Safety Follow-Up
Note: A: Granules in capsule (fasting); B: Tablet formulation (fasting); C: Tablet formulation (fed).

This is a Phase 1, 3-treatment, 6-sequence, 3-period crossover, open-label study in healthy male and female participants designed to evaluate the relative bioavailability under fasting condition of a new tablet formulation when compared with the current granules in capsule formulation

used in clinical studies (Treatment B and A, respectively). The study is also designed to evaluate effect of high fat meal on the PK of minzasolmin following administration of a single dose of the new tablet formulation in fed condition (Treatment C). The safety and tolerability of single-dose administration of minzasolmin will also be investigated.

Within each sequence, study participants will receive a single dose of minzasolmin ([redacted] capsules or tablets as shown in the 3 treatment conditions below) on 3 separate occasions (Day 1, Day 6, and Day 11 [Period 1, Period 2, and Period 3]):

- Treatment A: under fasting conditions [redacted] granules in capsules (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period
- Treatment B: under fasting conditions [redacted] tablet (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period
- Treatment C: under fed condition [redacted] tablet (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period

The order of the 3 treatment conditions received will differ between each sequence.

# 2 STATISTICAL HYPOTHESES

**Primary Comparison:**

Non-inferiority of the primary PK parameters of a new tablet formulation versus the reference 'granules in capsule' formulation in fasting state (relative bioavailability)

**Secondary Comparison:**

Non-inferiority of the primary PK parameters of a new tablet formulation in fed state vs the same formulation in fasting state (food effect).

**Other comparisons:**

Non-superiority of the primary PK parameters of a new tablet formulation vs 'granules in capsule' formulation in fasting state (relative bioavailability).

Non-superiority of the primary PK parameters of a new tablet formulation in fed state versus the same formulation in fasting state (food effect).

# 3 SAMPLE SIZE DETERMINATION

The plan is to randomize 18 participants into the study; dropouts are assumed to be minimal and will not be replaced.

Conditional power was estimated for the key comparisons of interest based on the Primary PK Objective.

**Primary comparison:**

- To assess noninferiority of the $AUC_{0-t}$ of a new tablet formulation versus the reference 'granules in capsule' formulation in fasting state (relative bioavailability)

**Secondary comparison:**

- To assess noninferiority of the $AUC_{0-t}$ of a new tablet formulation in fed state versus the same formulation in fasting state (food effect)

**Other comparisons:**

- To assess nonsuperiority of the $C_{max}$ of a new tablet formulation versus the reference 'granules in capsule' formulation in fasting state (relative bioavailability)
- To assess nonsuperiority of the $C_{max}$ of a new tablet formulation in fed state versus the same formulation in fasting state (food effect)

The assessments were based on a one-sided noninferiority t-test, calculated exact via noncentral t-distribution for a 2-treatment 2-period crossover design for continuous response data on the log scale with significance level of 0.05 (5%), assuming:

- A ratio of geometric means (ρ) between the new tablet formulation and the reference formulation under the alternative hypothesis (H1) of 1.0 for $AUC_{0-t}$ or 0.95 for $C_{max}$
- A lower margin of 0.8 for noninferiority and 1.25 for nonsuperiority
- A geometric intra-participant CV based on estimates of the residual variance obtained from linear mixed effect models (ANOVA) applied to the log-transformed $AUC_{0-t}$ and $C_{max}$ data from UP0073, a minzasolmin Phase 1 study with similar participant demographics (males and females aged 18 to 55 years) which used a crossover design

**Relative bioavailability comparisons:**

For the assessment of noninferiority of the $AUC_{0-t}$ or the assessment of nonsuperiority of the $C_{max}$, for the new tablet formulation versus the reference 'granules in capsule' formulation, the estimates of variability were based on the UP0073 2-by-2 ANOVA models comparing the (nonencapsulated) fumaric acid tablet to the 'granules in capsule' formulation under condition of normal gastric pH (ie, relevant treatment periods from UP0073 Part A).

This assumes homogenous variance for the 2 different formulations under fasting condition.

**Food effect comparisons:**

For the assessment of noninferiority of the $AUC_{0-t}$ or the assessment of nonsuperiority of the $C_{max}$, for the new tablet formulation under fed state versus the fasting state, the estimates of variability were based on the UP0073 2-by-2 ANOVA models comparing the encapsulated fumaric acid tablet to the (nonencapsulated) fumaric acid tablet formulations under condition of normal gastric pH (ie, relevant treatment periods from UP0073 Part A).

This assumes homogenous variance for the encapsulated and the nonencapsulated forms of the fumaric acid tablet, homogenous variance for the nonencapsulated tablet with or without fumaric acid, and homogenous variance for the fed and fasting states of the new tablet.

Analyses were performed using the function power.noninf from the R package PowerTOST (https://CRAN.R-project.org/package=PowerTOST).

For the primary treatment comparison of interest, 12 completers would provide over 96% power to assess noninferiority of the $AUC_{0-t}$ conditional on the GMR being 1.0. For a GMR of 0.95 (equivalent to the GMR observed in UP0073 for the fumaric acid tablet versus the 'granules in capsule' formulation), power would be 85% for 12 completers, 92% power for 15 completers and 96% for 18 completers.

For the secondary treatment comparison of interest, 12 completers would provide over 99% power to assess noninferiority of the $AUC_{0-t}$ conditional on the GMR being 0.95, equivalent to the GMR observed in UP0073 for the encapsulated fumaric acid tablet versus (nonencapsulated) fumaric acid tablet.

Details of the conditional power estimations can be found in the "UP0152 sample size documentation form" located in the sample size folder of the electronic trial master file.

# 4 POPULATIONS FOR ANALYSIS

Analysis Sets will be generated using the definitions in Table 3

**Table 3 Definition of analysis sets**

| Population | Definition/Criteria | Randomized vs. Actual Treatment |
|---|---|---|
| ASPS | All Study Participants Set includes all study participants who signed the ICF. | ASPS will be analyzed as randomized. Non-randomized participants will be defined as "Screen Failures" |
| RS | Randomized Set includes all study participants who are randomized. | RS will be analyzed as randomized |
| SS | The Safety Set includes all study participants who are randomized and receive full or partial study medication. Study participants will be classified according to the treatment that the participants actually received. Participants who have data documenting they did not administer investigational intervention, even if received, are excluded from the SS. | SS will be analyzed according to the treatment actually received. |
| PKS | The Pharmacokinetic Set includes all participants of the SS, who received at least 1 total dose of study medication and have at least 1 observable PK measurement without important protocol deviations that would affect the PK.<br>If a study participant in the PKS is missing individual time points or individual time points are otherwise non-evaluable, the study participant will be included in the PKS, but those individual time points will be identified as missing in listings. | PKS will be analyzed according to the treatment actually received. |

| Population | Definition/Criteria | Randomized vs. Actual Treatment |
|---|---|---|
| | All study participants in the PKS will be included in the listings and derivation of PK parameters. Note: some participants may have missing PK parameters if there are insufficient concentrations to derive them. | |

ASPS=All Study Participants Set; ICF=Informed Consent Form; PK=pharmacokinetic(s); PKS=Pharmacokinetic Set; RS=Randomized Set; SS=Safety Set

# 5 STATISTICAL ANALYSIS

## 5.1 General Considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS Version 9.4. The PK noncompartmental analysis will be performed using Phoenix WinNonlin® Version 8.0 or higher (Certara L.P., Princeton, NJ, USA) for PK parameters estimation.

A complete set of listings containing both all documented data and all calculated data will be generated by parts and treatment sequence, unless otherwise specified. Missing data will not be imputed, unless otherwise specified. Outlier detection and statistical analysis of outliers will not be performed.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical endpoints, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of study participants, mean, standard deviation (sd), median, interquartile range (IQR), minimum, and maximum. The descriptive statistics for plasma concentrations and PK parameters will be described in Appendix 2 (Section 6.2.1).

Unless otherwise noted, the denominator for percentages should be based on the number of participants included in the respective analysis set. For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the relevant analysis set and include a potential "Missing" category (corresponding to participants with missing data at the time of the variable being summarized) as the last row in the list of categories being summarized.

Percentages for frequency tables will be presented to 1 decimal place. If the percentage is 100%, do not present a decimal. If the percentage is 0, do not present the percentage. Typically, the % sign should be presented in the column header, but not with each individual value.

Decimal places for descriptive statistics will always apply the following rules, unless otherwise stated:

- "n" will be an integer
- Mean, sd, median, and IQR will use one additional decimal place compared to the original data
- Coefficient of variation (CV) [%] will be presented with one decimal place

- Minimum and maximum will have the same number of decimal places as the original value.

Derived variables in general will display the mean, sd, median, and IQR to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics. If participants have more than one observation for a given time point, the observation closest to the intended time point will be used. If both observations are equidistant from the intended time point, then the later value will be used.

Refer to Appendix 2 (Section 6.2.1 and Section 6.2.2) for standard reporting procedures of PK concentrations and parameters in listings, tables, and figures.

### 5.1.1 General study level definitions

#### 5.1.1.1 Analysis Time Points

##### 5.1.1.1.1 Study Day

Study day will be derived with the date of first planned treatment of the study. There is no study day 0. Study day 1 is date of the first treatment of the study.

- Study Day 1 is the date of treatment.
- For days prior to first treatment:

  Study day = Current date – Date of first treatment.
- For days after the first treatment:

  Study day = Current date - Date of first treatment +1.

##### 5.1.1.1.2 Relative day

Relative day will be derived with the date of treatment in each Period (treatment and washout) as reference for that specific Period.

- Relative Day 1 is the date of treatment.
- For days prior to first treatment:

  Relative day = Current date – Date of first treatment.
- For days after the day of treatment in Period:

  Relative day = Current date - Date of treatment within the same Dosing Period +1.
- For days after the day of last treatment:

  Relative day = Current date - Date of last treatment +1.

There is no Relative day 0. Relative day will not be calculated for partial dates. Relative day for partial days will be displayed as '--' to distinguish it from missing values which are displayed as blanks.

##### 5.1.1.1.3 End date of the Treatment Period

Treatment periods are specified in Section 5.1.1.1.4.

#### 5.1.1.1.4 Study Periods

The maximum study duration will be 48 days, including the Treatment Period and the Safety Follow-Up (SFU) Period. There are 3 study periods in this study:

- Screening Period: Eligibility will be assessed during the Screening Period (up to 28 days). Treatment must be started as soon as possible for participants who have fulfilled the eligibility criteria.
- Treatment Period: Participants who have been confirmed eligible will be randomized to receive open-label single doses of minzasolmin [redacted] on Days 1, 6, and 11 with a 4-day Washout Period between doses.
- Safety Follow-Up Period: Study participants will have SFU procedures performed within 5 to 9 days after final dose. Participants who prematurely withdraw from the study will return to the clinic center for the Early Termination Visit (ETV) as soon as possible after the time of withdrawal and will have all SFU procedures performed.

**Table 4 Study Periods and Durations**

| Period | Study Day | Duration | Relative Day |
|---|---|---|---|
| Screening Period | Study Day -28 to -2 | Day -28 to Day -2 | Relative Day -28 to -2 |
| Treatment Period 1 | Study Day -1 to 1 | Day -1 to Day 1 | Relative Day -1 to 1 |
| Washout Period 1 | Study Day +2 to +5 | Day 2 to Day 5 | Relative Day +2 to +5 |
| Treatment Period 2 | Study Day 6 | Day 6 | Relative Day 1 |
| Washout Period 2 | Study Day 7 to Day 10 | Day 7 to Day 10 | Relative Day +2 to +5 |
| Treatment Period 3 | Study Day 11 | Day 11 | Relative Day 1 |
| Washout Period 3 | Study Day 12 to Day 15 | Day 12 to Day 15 | Relative Day +2 to +5 |
| Safety Follow-Up | Study Day 16 to 20 | Day 16 to 20 | Relative Day +6 to +10 |

#### 5.1.1.1.5 Mapping of assessments performed at Early Termination Visit

Safety assessments made at an early termination visit that correspond to a scheduled visit will be summarized at the scheduled visit to corresponding to the early termination visit if the assessment was scheduled to occur at that visit. Such assessments at the early termination visit will also be considered for safety follow up/ termination visit.

#### 5.1.1.1.6 Definition of Baseline values

Unless otherwise stated, a Baseline value refers to the last non-missing value collected prior to the first treatment. Scheduled or unscheduled measurements can be used as the Baseline value. If a Baseline measurement is repeated and is obtained prior to the first treatment, then the last available measurement will be used as the Baseline value. If an unscheduled measurement occurs after the planned Baseline measurement time point but before the first treatment, then the unscheduled measurement will be used.

**Table 5 Definition of Baseline**

| Procedure | Baseline Day |
|---|---|
| Vital sign | Predose on Day 1 or if missing then the Baseline data will be missing. |
| Single 12-lead ECG | |
| Laboratory assessments (hematology, clinical chemistry, and urinalysis) | Baseline is defined as the value on Day -1. If this value is missing, the most recent value obtained prior to Day 1 will be used as Baseline. |

ECG= electrocardiogram

#### 5.1.1.2 Protocol Deviations

Protocol deviations are specified in Appendix 1 (Section 6.1.2).

All protocol deviations will be reviewed at the Data Cleaning Meetings (DCM) and decisions made on whether they should be considered important or not.

Important protocol deviations (IPDs) are deviations from the protocol which could potentially have a meaningful impact on study conduct or on either the primary or key secondary outcome(s) for an individual study participant. The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

Important protocol deviations will be categorized as follows:

1. Inclusion/exclusion criteria deviations
2. Incorrect treatment or dose administered
3. Procedural non-compliance
4. Prohibited concomitant medication use
5. Withdrawal criteria deviation

All IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. At least one Data Evaluation Meeting (DEM) will be performed prior to the final database lock after all data have been verified/coded/entered into the database to discuss exclusion of study participants from analysis populations.

Participants may be excluded from the safety set if they do not pass the inclusion/exclusion criteria. However, should a participant be mistakenly dosed despite failing the inclusion/exclusion criteria, then their safety data would need to be reported as part of the safety analysis. Participants may be excluded from other analysis sets, but this will be determined on a case-by-case basis. If the deviation is deemed to have the potential to bias the analyses for the duration of the study then the whole participant may be removed in a sensitivity analysis on the key endpoints. The removal of the participant and the rationale will be clearly documented within the relevant TFLs.

Important protocol deviations will be identified and classified by the deviation types in the IPD document. A listing of all IPDs identified at the DCMs will be presented for all participants based on the safety set and will include the deviation type and description.

The IPDs will be tabulated using the SS and will present the deviation type and description by treatment group.

#### 5.1.1.3 Treatment assignment and treatment groups

It is expected that participants will receive treatment as randomized; hence safety analyses will be based on the SS-as randomized. However, if it is determined that participants received treatment other than what they were randomized to, then for PK and safety analyses purposes participants will be allocated to the actual treatment they received (SS-as treated).

#### 5.1.1.4 Definition of Analysis by Variables

Analysis of study parameters and corresponding to be tabulated by variables are defined in below Table 6 and Table 7

**Table 6 Definition of Analysis by Variables**

| Term | Variables |
|---|---|
| Sequence | Sequence 1 (ABC) |
| | Sequence 2 (BCA) |
| | Sequence 3 (CAB) |
| | Sequence 4 (ACB) |
| | Sequence 5 (BAC) |
| | Sequence 6 (CBA) |
| Formulation and feeding conditions | A: Granules in capsule [redacted] (fasted condition) |
| | B: Tablet formulation [redacted] (fasted condition) |
| | C: Tablet formulation [redacted] (fed condition) |

Note: A: Granules in capsule (fasting); B: Tablet formulation (fasting); C: Tablet formulation (fed).

**Table 7 Analysis to be performed by variables**

| Analysis | Variable |
|---|---|
| Disposition | Sequence |
| Medical History | |
| Concomitant Medications | |
| Important Protocol Deviations | |
| PK Concentration | Formulation and feeding condition |
| Adverse Events | Formulation and feeding condition |
| Laboratory Values | Time Point and Sequence |

| Analysis | Variable |
|---|---|
| Vital Signs | |
| ECG | |

#### 5.1.1.5 Center pooling strategy

This is a single center study.

#### 5.1.1.6 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) at time of database lock. Medications will be coded using the current version of World Health Organization Drug Reference List (WHO-DRL) at time of database lock. Medical procedures will not be coded.

#### 5.1.1.7 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at same time point. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of study medication the latest value (which may be scheduled or unscheduled) will be used in the calculation of the descriptive statistics.
- For repeated measurements obtained for the designated Baseline value, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of study medication.
- Unscheduled measurements and repeated measurements after the first one at a given time point will not be used in the descriptive statistics at time points after first dose of study medication.
- Unscheduled measurements performed for the Early EOS/WD visit will be assigned to the EOS Visit and analyzed accordingly as an EOS Visit.

## 5.2 Participant Dispositions

Participant screening and primary reason for screen failure will be summarized using the ASPS. The summaries will include the following:

- Number of participants screened
- Number and proportion of participants rescreened
- Number and proportion of participants with screen failures (Not counting successfully rescreened participants)
- Number and proportion of screen failures by primary reason for screen failure (Based on the later screening visit)

By-participant listings of rescreened participants will be presented using the ASPS.

Participant disposition will be summarized using the ASPS. Each summary will include the following:

- Date of first screening visit
- Date of last visit for last participant
- Number of participants screened
- Number of participants in each analysis set, by treatment sequence (according to randomized treatment).

Disposition of analysis sets will be tabulated using the ASPS. Each table will present the total number of participants in the ASPS, as well as the number and percentage of participants in each analysis set by treatment sequence.

Study completion/discontinuation and primary reason for discontinuation will be summarized using the RS. Each table will present the following, by treatment sequence:

- Number and percentage of participants that started the study
- Number and percentage of participants completing the study
- Number and percentage of participants discontinuing the study
- Number and percentage of participants discontinuing the study by primary reason for discontinuation.

Participants that started the study are defined as participants that were randomized. Participants completing the study are those participants completing the SFU visit AND who did not discontinue dosing or withdraw from the study for any reason before the SFU.

Study discontinuation due to AEs will be tabulated using the RS. Table will present the number and percentage of participants who discontinued the study due to AE by treatment sequence.

By-participant listings of participant who did not meet study eligibility criteria will be presented by treatment sequence, using the ASPS. The listing will include inclusion criteria that were not met and the exclusion criteria that were met.

By-participant listings of participant disposition will be provided using the ASPS by treatment sequence. The listings will include:

- Study termination/completion status
- Date of informed consent
- Date of randomization
- Date and time of first study treatment (first start date and time)
- Date and time of last study treatment (last stop date and time)
- Date of last contact
- Date of premature study termination for successfully screened participants dropping out of the study.

- Date of screen failure for screen failure participants (based on the last screening visit in case of rescreen)
- Primary reason for premature study termination
- Primary reason for screen failure (Based on the last screening visit in case of rescreen)

By-participant listings of participant inclusion in each analysis set will be presented by sequence, using the ASPS.

By-participant listings of study discontinuation will be presented by sequence, using the RS.

## 5.3 Pharmacokinetics

Unless otherwise stated, PK analysis will be performed on the PKS.

### 5.3.1 Analysis of Concentration Measures

The plasma concentration-time profiles will be summarized by formulation and feeding condition, using descriptive statistics (number of available observations, arithmetic mean, sd, geometric mean, geometric coefficient of variation (geometric cv), median, IQR, minimum, and maximum).

Individual concentration-time profiles will be displayed graphically on a linear-linear scale and semilogarithmic scale. Individual concentration-time profiles for a given formulation and feeding condition will be presented on the same plot.

Overall geometric mean plasma concentrations-time curves and corresponding 95% CIs will be displayed by formulation and feeding condition.

Individual concentrations will be listed by formulation and feeding condition.

Standard reporting procedures of individual values and descriptive statistics for plasma concentration data in listings, tables, and figures are described in Appendix 2 (Section 6.2.1).

### 5.3.2 Pharmacokinetic Parameters

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin® (Version 8 or higher), as applicable using Guideline on performing NCA analysis (2017) : $C_{max}$, $t_{max}$, $AUC_{0-t}$, AUC, AUC%Extrap, $t_{½}$, Lambda z ($\lambda_z$), CL/F (Minzasolmin only), Vz/F (Minzasolmin only), $MRC_{max}$, and MRAUC from the plasma concentration-time data.

**Table 8 Non-compartmental PK parameters for Minzasolmin in plasma**

| PK Parameter | Definition |
|---|---|
| AUC | The AUC from time zero to infinity (mass * time * volume$^{-1}$). |
| $AUC_{0-t}$ | The AUC from time zero to the last measurable drug concentration sampling time ($t_{last}$) (mass * time * volume$^{-1}$). |
| $C_{max}$ | The maximum (peak) observed drug concentration following a single dose administration (mass * volume$^{-1}$). |
| $t_{max}$ | The time to reach maximum (peak) drug concentration following a single dose administration (time). |
| $t_{½}$ | The elimination half-life associated with the terminal slope ($\lambda_z$) of a semilogarithmic concentration-time curve (time). |
| CL/F[a] | The total apparent body clearance of drug (volume/time). |
| Vz/F[a] | The apparent volume of distribution during terminal phase (associated with $\lambda_z$) (volume). |
| Lambda_z ($\lambda_z$) | Terminal elimination rate constant (1/time). |
| AUC%Extrap[b] | Area under the <matrix> concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC. |
| Rsq_adj[c] | Square of the correlation coefficient (adjusted for the number of data points included) associated with λz. |
| $MRC_{max}$[d] | $C_{max}$ metabolite to parent ratio. |
| MRAUC[d] | AUC from time zero to infinity metabolite to parent ratio. |

[a] For Minzasolmin only
[b] AUC%Extrap is listed if AUC is presented
[c] Rsq_adj is listed only
[d] Metabolites only

PK parameters of Minzasolmin will be listed and summarized using descriptive statistics similarly to the plasma concentrations. Additionally, the PK parameters will be presented via boxplot by formulation and feeding condition. GeoMean ratio and 90%CI of primary PK parameters obtained from mixed model will be presented via forest plot.

Standard reporting procedures of individual values and descriptive statistics for PK parameters in listings, tables, and figures are described in Appendix 2 (Section 6.2.2 ).

## 5.4 PK Endpoints Analysis

### 5.4.1 Definition of endpoint(s)

PK endpoints are based on the definitions in Table 8.

The primary endpoints for PK objectives in both parts are:

- $AUC_{0-t}$
- AUC
- $C_{max}$

The other PK endpoints are defined as follows:

- For minzasolmin:
  - $t_{max}$, $t_{½}$, CL/F, and Vz/F (if possible but not limited)
- For [redacted] metabolites:
  - $C_{max}$, $t_{max}$, $AUC_{0-t}$, and AUC in fasting and fed conditions
  - metabolite/parent $C_{max}$ and AUC ratio, as appropriate.
  -

#### 5.4.1.1 Analyses required for the Primary Objective (on Primary PK endpoints)

The primary comparisons of interest are:

- New tablet vs 'granules in capsule' under fasted condition (B vs A)
- New tablet formulation under fasted condition vs under fed condition (B vs C)

To estimate these comparisons, the primary analysis model will be applied to the 2 sets of data separately: namely, all data under fasted condition (B vs A comparison) and all data for the new tablet formulation (B vs C comparison).

The PK parameters $C_{max}$, $AUC_{0-t}$, and AUC will be estimated using analysis of variance (ANOVA), adapted to crossover designs. The model will include a random intercept term for participant within sequence and fixed effect categorial terms for sequence, period, and Treatment condition? (3 formulation x feeding conditions).

The dependent variables will be logarithmically transformed by natural logarithms (ln) prior to statistical testing, following the usual recommendations.

The linear mixed model is given as following:

$$\ln(Y) = Q + S_i + P + T + \varepsilon, \text{ where} \quad \textbf{(1)}$$

- *ln(Y)* is the log transformed PK parameter value,
- $Q$ is the fixed effect term for the sequence,
- $P$ is the fixed effect term for the period,
- $T$ is the fixed effect term for the treatment condition,
- $S_i$ is the random effect term of the participant nested to the sequence,
- $\varepsilon$ is the random error.

The PROC MIXED procedure in the Statistical Analysis Software (SAS) will be used for this analysis. For estimation based on a linear mixed model, covariance matrix applied to the within-subject error will be estimated by restricted maximum likelihood (REML). The Kenward-Roger approximation will be used to estimate the degree of freedom. Variance component structure will be used for the variance-covariance matrix for this linear mixed model.

For each PK parameter the least square mean (LSMEAN) and corresponding 95% confidence interval (CI) for each Treatment condition, the difference in LSMEANs between Treatment conditions, and corresponding 90% CI will be calculated. These values will then be back-transformed to give the estimate of the geometric mean ratio (GMR) for each Treatment condition comparison alongside with their corresponding 90% CI.

The estimates of the geometric mean ratios with their corresponding 90% CI will be displayed in a summary plot. Additionally, the within-participant CVs will be calculated based on the within-participant estimate of variance obtained from each ANOVA model. Please check Table 12 at Appendix 3 for model specifications.

#### 5.4.1.2 Sensitivity analysis required for Primary Objective (on Primary PK endpoints)

The comparisons of interest described in Section 5.4.1.1 will be assessed for each PK parameters by applying a mixed model procedure to all trial data. Please check Table 1Table 12 at appendix 3 for sensitivity analysis model specifications.

#### 5.4.1.3 Analyses required for Other Objective (on Other PK endpoints)

The other PK parameters of Minzasolmin and metabolites will be summarized by formulation and feeding condition using descriptive statistics as described in Section 5.3.1.

- For Minzasolmin: $t_{max}$, $t_{½}$, CL/F, and Vz/F (if possible but not limited). For $t_{max}$, only the median, IQR, minimum, and maximum will be reported.
- For [redacted] metabolites: $C_{max}$, $t_{max}$, $AUC_{0-t}$, AUC, and each metabolite/parent $C_{max}$ and AUC ratio (corrected for the molecular weight of the entities), as appropriate.

$$MR\_C_{max} = \frac{Cmax(metabolite)}{Cmax(parent)} * \frac{Molecular\ weight\ (parent)}{Molecular\ weight\ (metabolite)}$$

$$MR\_AUC = \frac{AUC(metabolite)}{AUC(parent)} * \frac{Molecular\ weight\ (parent)}{Molecular\ weight\ (metabolite)}$$

where,

Molecular weight (parent) = 425.59 g/mol

Molecular weight [redacted]

Molecular weight [redacted]

## 5.5 Safety Analyses

Unless stated otherwise, all safety analyses will be performed on the SS.

### 5.5.1 Extent of Exposure

Administration of treatments will be listed by sequence. Exposure data will be listed only.

### 5.5.2 Adverse Events

An Adverse Event is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study medication, whether considered related to the study medication.

Adverse events with start date/time prior to first treatment are defined as pre-treatment. These events will not be included in any tabulated summaries but will be listed.

Treatment emergent AEs (TEAE) are all AEs starting on or after the date/time of first treatment and up to including 4 days after last treatment, or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment.

AEs with a start date after 4 days of last treatment are defined as post-treatment. These events will not be included in any tabulated summaries but will be listed.

In case of missing or partially missing AE dates, the following rules will apply. Start and stop dates of AEs will be displayed as reported in the participant data listings (ie, no imputed values will be displayed in data listings).

The following rules will be applied for partial start dates and time:

- If only the month and year are specified and the month and year of the first treatment is not the same as the month and year of the start date, then use the 1st of the month, or the date of Screening if this is later (if the imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing, it will be imputed as 00:00 h
- If only the month and year are specified and the month and year of the first treatment is the same as the month and year of the start date, then use the date of the first treatment. If the imputed start date that is after the specified end date, then use the 1st of the month, or the date of Screening if this is later (if the imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of treatment then time will be imputed as the start time of the treatment (ie, event will be regarded as treatment emergent)
- If only the year is specified, and the year of the first treatment is not the same as the year of the start date, then January 01 will be used. If time is missing, it will be imputed as 00:00 h
- If only the year is specified, and the year of the first treatment is the same as the year of the start date, then the date of the first treatment will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of Screening if this is later will be used (if the imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first treatment then time will be imputed as the start time of the treatment (ie, event will be regarded as treatment emergent)
- If the start date is completely unknown, then use the date of first treatment. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month

- If only the year is specified, then use December 31 of the known year
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing date and/or times will be imputed as described in Table 9 for the calculation of duration of each AE. AE duration is computed and reported in day and time format.

**Table 9 Calculation Rules for Duration of AEs**

| Data Availability | Onset Date/Time | Outcome Date/Time | Calculation Rules |
|---|---|---|---|
| Complete data | D1/T1 | D2/T2 | Duration = (D2-D1)*24+(T2-T1) |
| End time missing | D1/T1 | D2/-- | End time is substituted by time 23:59h (=23.98 in decimal format). Duration=<(D2-D1)*24+(23.98-T1) |
| Start time missing | D1/-- | D2/T2 | Onset time is substituted by 00:00h. Duration=<(D2-D1)*24+T2 |
| Start and end time missing | D1/-- | D2/-- | Duration=<[(D2-D1)+1]*24 |
| Start day and time missing | --/-- | D2/T2 | Duration=<(D2-D0)*24+(T2-T0) For a participant in the SS, D0 and T0 are the date and time of the first administration of study medication and for screen failures, D0 is the date of the Screening Visit date and T0=00:00h. |
| End day and time missing | D1/T1 | --/-- | If the stop date is missing, duration will not be calculated. |
| Start and end date missing | --/-- | --/-- | If the stop date is missing, duration will not be calculated. |

The duration of each AE will be calculated as follows and will be presented in dd:hh:mm format where dd represent days, hh: hours, and mm: minutes:

Duration of AE = End date/time of AE – Start date/time of AE **(2)**

Adverse events will be assigned to Treatment Periods, based on the onset date/time of the AE. Assignment to Treatment Periods will be done after missing dates have been imputed as described above. AE will be assigned to a treatment based on the treatment received in the Treatment Periods as given in Table 10.

**Table 10 AE Treatment Period Assignment**

| Study | Period | Start | End |
|---|---|---|---|
| UP0152 | Treatment Period 1 | Start date is on or after administration of treatment in Treatment Period 1 | Prior to administration of treatment in Treatment Period 2 |
| | Treatment Period 2 | Start date is on or after administration of treatment in Treatment Period 2 | Prior to administration of treatment in Treatment Period 3 |
| | Treatment Period 3 | Start date is on or after administration of treatment in Treatment Period 3 | |

The following summaries will be provided by formulation and feeding condition groups:

- Incidence of TEAEs – Overview
- Incidence of TEAEs
- Incidence of Serious TEAEs
- Incidence of TEAEs leading to study discontinuation
- Incidence of TEAEs leading to permanent treatment discontinuation
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by relationship to study medication

AEs will be presented as "number of participant (percentage of participant) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual participant, while "number of participant" will count each participant only once.

AEs will be presented by system organ class (SOC), high level term (HLT) and preferred term (PT) in a frequency table, giving the number of events, the number of participants, and the percentage of participants who experienced the event. Participants with multiple AEs are only counted once within each PT, each HLT and within each SOC.

Summaries by maximum severity will count each participant at most once within each MedDRA level based on the maximum severity/event intensity within that MedDRA level.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

All summaries will be sorted alphabetically by SOC. Within SOC, it will be sorted by decreasing frequency of PT.

A by-participant listing will be presented for by formulation and feeding condition for all AEs for the SS. This will include reported term, SOC, PT, the onset date/time and outcome date/time

of the event (including relative days), stop date and time (or ongoing, if applicable; relative days), the AE duration, severity, relationship, action taken, and outcome. In addition, the listing will flag TEAEs, Serious TEAEs, and AE of special interest. A glossary of AE terms including reported term, SOC and PT will also be presented.

### 5.5.3 Additional Safety Assessments

#### 5.5.3.1 Clinical laboratory evaluations

The protocol-required laboratory parameters collected within UP0152 are given in Table 11. All non-protocol-required laboratory parameters will not be presented in any tabulated summaries but will be listed.

**Table 11 Protocol-required Laboratory Assessments**

| Laboratory Assessment | Parameters |
|---|---|
| Hematology | Platelet count |
| | Red blood cell count |
| | Hemoglobin |
| | Hematocrit |
| | Red blood cell indices – Mean corpuscular volume, Mean corpuscular hemoglobin, % reticulocytes. |
| | *White blood cell counts with differentials – Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils |
| Clinical Chemistry | Blood urea nitrogen |
| | Potassium |
| | Aspartate Aminotransferase/Serum Glutamic-Oxaloacetic Transaminase |
| | Total and direct bilirubin |
| | Creatinine |
| | Sodium |
| | Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase |
| | Total Protein |
| | Glucose (fasted) |
| | Calcium |
| | Alkaline Phosphatase |
| Routine Urea (Urinalysis) | Specific gravity |
| | pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick |
| | Microscopic examination (if blood or protein is abnormal) |

| Laboratory Assessment | Parameters |
|---|---|
| | Renal biomarker analysis (Cystatin C) |
| Other screening tests | Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) |
| | Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, methadone, and benzodiazepines) |
| | Serum and urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) |
| | Serology (HIV antibody, HBsAg and hepatitis C virus antibody) |

*White blood cell count parameters will be presented by absolute values only.

#### 5.5.3.1.1 Laboratory values over time

Laboratory variables and changes from Baseline will be summarized using descriptive statistics by time point and sequence. A by-participant listing will be provided for the SS.

Measurements that are below the limit of quantification (BLQ) or above the limit of quantification (ALQ) will be presented as BLQ or ALQ in the listings. For the purpose of calculating change from Baseline or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLoQ) and ALQ values will be imputed to the upper quantification limit.

### 5.5.3.2 Vital Signs

Supine vital signs measured within UP0152 include:

- Pulse rate
- Systolic blood pressure
- Diastolic blood pressure
- Respiratory rate
- Body temperature

Vital signs will be measured in triplicate. The mean values will be calculated and recorded on the CRF.

Reference ranges for each vital sign will be recorded on the CRF. Clinically significant abnormalities will be flagged in the listings.

#### 5.5.3.2.1 Vital Sign Values Over Time

The vital sign variables and changes from Baseline will be summarized using descriptive statistics by time point and sequence. A listing will be provided for the SS.

### 5.5.3.3 Electrocardiograms

The following ECG parameters will be obtained:

- Heart rate (beats/min),
- PR-interval (msec [milliseconds]),
- QRS-duration (msec),
- QT-interval (msec),
- QTcF (QT corrected for heart rate using Fridericia's formula) (msec),
- Investigator's conclusion on ECG profile.

#### 5.5.3.3.1 Electrocardiogram Values Over Time

The electrocardiogram results and changes from Baseline will be summarized using descriptive statistics by time point and sequence. A by-participant listing will be provided for the SS.

The following cut-points in QTcF based on the mean of the triplicate data will be summarized categorically (number and percentage of participants).

For observed data:

- <450 msec
- ≥450 to <480 msec
- ≥480 to <500 msec
- ≥500 msec

For change from Baseline in QTcF:

- <30 msec
- ≥30 to <60 msec
- ≥60 msec

#### 5.5.3.4 Physical examination

A by-participant listing will be provided for physical examinations for the SS.

## 5.6 Subgroup analyses

Not Applicable.

## 5.7 Interim Analyses

No Interim Analysis is planned in this study.

## 5.8 Safety Monitoring Committee (SMC)

No Safety Monitoring Committee is planned in this study.

# 6 SUPPORTING DOCUMENTATION

## 6.1 Appendix 1 Non-key analysis specifications

### 6.1.1 Baseline characteristics and demographics

The body mass index (BMI) value collected in the eCRF will not be used for this summary. The BMI will be
recalculated using the following formula and reported to 1 decimal place:

$$BMI(kg/m^2) = \frac{body\ weight\ at\ screening\ (kg)}{[height\ at\ screening\ (m)]^2} \quad \textbf{(3)}$$

### 6.1.2 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol that potentially could have a meaningful impact on study conduct, safety, or PK outcomes for an individual study participant. Furthermore, study participants will be excluded from the Safety Set only when there is documented evidence that they received no treatment. The criteria for identifying IPDs and the classification of IPDs will be defined within the Protocol Deviation Assessment Plan. IPDs will be reviewed as part of the Data Cleaning Meeting and Data Evaluation Meeting (DEM). Any important deviation will be identified and documented before unblinding to confirm exclusion from analysis sets.

Protocol deviations will be classified as follows:

- AE SAE
- Disallowed medications
- Inclusion/Exclusion criteria
- Informed Consent
- Study treatment
- Other
- Procedures/tests
- Procedures/tests/lab
- Visit schedule
- Withdrawal criteria
- Time window deviation

The IPDs will be tabulated using the SS by study parts and sequence, and will present the deviation type.

### 6.1.3 Medical history

Medical history and ongoing medical conditions will be listed and summarized for the RS by study parts, treatment sequence, and for all participants by MedDRA SOC and PT. The reported term will be included in the listing. The summary will include the number and percentage of

study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Participants' column.

### 6.1.4 Meals and dietary restrictions

Study participants completion of High-fat High-calory breakfast at fed condition treatment period and compliance of fluid and meal restrictions during fasted condition treatment period will be listed.

### 6.1.5 Prior/concomitant medications

Medications with a start date prior to the first treatment will be considered as prior medications. Medications with a start date prior to, at or after the first treatment will be considered as concomitant medications if the duration overlaps at least 1 day with the any treatment period. Medications with a missing start date whose stop date is either unknown or after the date of the first treatment will be considered as concomitant.

Concomitant medications will be listed and summarized for the RS by study parts and treatment sequence, and will include WHODD (World Health Organization Drug Dictionary) Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Prior medications and concomitant medications will be summarized separately within the same table, ie, paged by prior and concomitant medications. Prior medications which continued into the study period are also classified as concomitant and are included in both summaries.

In the case of missing dates, the classification of medications as prior or concomitant will be performed after imputation of dates as described below. Imputations of missing dates will be performed prior to calculation of relative days.

The following rules are applied to impute partial start dates for medications:

- If only the month and year are specified and the month and year of first treatment is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first treatment is the same as the month and year of the start date, then use the date/time of first treatment.
- If only the year is specified, and the year of first treatment is not the same as the year of the start date, then use January 1 of the year of the start date.
- If only the year is specified, and the year of first treatment is the same as the year of the start date, then use the date/time of first treatment.
- If the start date is completely unknown, then use the date/time of first IMP dose.

The following rules will be applied for partial stop dates and will be imputed for the calculation of duration of each medication:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

Medications permitted to be continued during the study are limited to those listed in Section 6.5.1 of the protocol. No rescue medications are permitted.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Participants' column.

### 6.1.6 Data derivation rules

Not applicable.

### 6.1.7 AEs of Special Interest

AE of special interest are:

- Possible Hy's Law: Potential Hy's Law is defined as ≥3xULN, ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded).
- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis).

A listing will be produced of Potential Hy's Law for the SS by formulation and feeding condition.

A listing will be produced for Hypersensitivity reactions for the SS by formulation and feeding condition group using the following search strategy: Standardized MedDRA Queries (SMQ)='Hypersensitivity' (Broad) AND SMQ=Anaphylactic reaction (Broad).

### 6.1.8 Potentially Clinically Significant Criteria for Safety Endpoints

Not applicable.

### 6.1.9 Compliance

For all study participants, study medication will be administered at the study unit.

Drug accountability must be recorded on the Drug Accountability form.

As dosing is performed in-house by the investigator or member of staff, no specific assessment or compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR.

## 6.2 Appendix 2: Standard Reporting Procedures

### 6.2.1 PK Concentrations

When reporting individual data in listings the following rules will apply:

- Missing data will be reported as NV (no value).
- Concentrations below the limit of quantification will be reported as BLQ.
- Concentrations will be listed to the same number of significant figures supplied by the bioanalytical laboratory.

When reporting individual data in figures the following rules will apply:

- BLQ values prior to $C_{max}$ will be set to 0 for purposes of plotting the figure (to capture lag-time).

- Actual sampling times will be used.

When summarizing the data in tables the following rules will apply:

- To calculate descriptive statistics, BLQ values will be set to half the LLOQ (lower limit of quantification) value and missing values will be excluded.
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum will be reported for this time point. Other descriptive statistics will be reported as missing ("-"). The minimum will be reported as "BLQ".
- When the summary statistic includes one or more replaced BLQ values then a footnote will be included to say, "contains one or more BLQ value replaced by half the LLOQ value".
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these will be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").
- If no participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- Descriptive statistics for plasma concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant digits, ie, 35.12 will be 35.1, 0.0004649 will be 0.000465 - for the arithmetic mean, sd, median, IQR, geometric mean, geometric cv, the 95% CI for the geometric mean, minimum and maximum.
- The 95% CI should be left blank if the sd (or equivalently, the geometric cv) is 0
- The geometric cv will be calculated using the following formula where sd is the standard deviation from the log-transformed data:

$$Geometric\ cv\ (\%) = \sqrt{(\exp(SD^2) - 1)}\ \text{x}\ 100 \qquad \textbf{(4)}$$

- Geometric cv will be reported as a percentage to 1 decimal place

When summarizing the data in figures the following rules will apply:

- The data plotted in the figure will match the data presented in the summary table, with the exception of missing values prior to $C_{max}$ which should be set to 0 in the figure (to capture lag-time).
- Geometric mean should be plotted (as opposed to arithmetic mean) due to the log-normal distribution of concentrations. Variability should be plotted as de-transformed sd computed on ln-transformed data.
- Nominal sampling times will be used.
- Both linear and semi-logarithmic scales will be presented.

### 6.2.2 PK Parameters

When reporting individual data in listings the following rules will apply:

- Individual PK parameters will be reported to 3 significant figures.
- If a parameter cannot be calculated, it will be reported as NE (not estimable ie, if input data is missing which prevents calculation) or NC (not calculable ie, if the data were available but the calculation was considered unreliable).

When summarizing the data in tables the following rules will apply:

- The derived PK parameters will be considered as source data and this data without rounding will be used for calculation of summary statistics of PK parameters.
- Descriptive statistics will be reported to 4 significant figures for the mean (arithmetic and geometric), median, sd, and IQR to 3 significant figures to the others including the 90% CI for the geometric mean.
- Geometric cv will be reported as a percentage to 1 decimal place.
- If at least two thirds of the participants have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as NE (ie, not estimable).
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-")
- For $t_{max}$ only the median, minimum, and maximum will be reported.

## 6.3 Appendix 3:

### Table 12 Analysis Models

| Model Name | Formulation & Feeding condition (Trt arms in the model) | ANOVA | Estimation |
|---|---|---|---|
| Model 1.1 | B; A | • Random effect for participant within sequence<br>• Fixed effect categorical terms for<br>o Formulation & Feeding Cond. (2 levels)<br>o Sequence (6 levels)<br>o Period (3 levels) | 90% CI for GMR estimate B vs. A |
| Model 1.2 | B; C | | 90% CI for GMR estimate C vs. B |
| Model 2.0 (Sensitivity Analysis) | A; B; C | • Random effect for participant within sequence<br>• Fixed effect categorical terms for<br>o Formulation & Feeding Cond. (3 levels)<br>o Sequence (6 levels)<br>o Period (3 levels) | 90% CI for GMR estimate B vs. A<br>90% CI for GMR estimate C vs. B |

## 6.4 Appendix 4: Changes to Protocol-Planned Analyses

Not applicable.

## 6.5 Clinical Trials Registry (CTR)

The following tables outlined in previous SAP sections fulfil the criteria for transparency reporting for clinicaltrials.gov and EudraCT:

- DS_T_03 Disposition and Discontinuation Reasons [ASPS].
- DM_T_01 Demographics (all age categories are mandatory) [SS].
- AE_T_01 Incidence of TEAEs – Overview (mandatory, including both All Deaths and TEAE leading to Deaths)] [SS].
- AE_T_06 Incidence of Non-Serious TEAEs Above Reporting Threshold of X% of Participants [SS].
- For small studies in populations where these events are not expected then the study team may utilize the lines from AE_T_01. The zeros in the relevant lines are sufficient for the CTR reporting. However, if an event is observed then the relevant table must be produced by CTR reporting.
- DS_T_04 Discontinuation due to AEs [SS]
- AE_T_04b Incidence of serious TEAEs by Relationship [SS]
- AE_T_04b Incidence of fatal TEAEs by Relationship [SS]

# 7 REFERENCES

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