
# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Protocol Number:** | FYU-981-J086-301 |
| **Study Protocol Title:** | A Randomized, Multicenter, Double-Blind, Superiority Study of Dotinurad (4 mg) and Febuxostat (40 mg) for the Treatment of Subjects With Gout |
| **Date:** | 25th Aug 2023 |
| **Version:** | Version 2.0 |

# REVISION HISTORY

Revision to Version 2.0

| Changes | Rationale | Section |
|---|---|---|
| Added wording on the definition of Per Protocol Analysis set | For clarification purposes. | Section 4.2.1 |
| Updated subgroup classification of HUA. | For clarification purposes. | Section 4.2.4, Section 4.3.4, Section 4.4.1, Section 4.6.2 |
| Updated the sponsor's grading of laboratory values. | To clarify the grading rule for the analysis of TEMAV. | Appendix 1 |
| Editorial comments are made to correct typos. | For clarification purposes. | Throughout the document |

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# 1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ATC | anatomical therapeutic class |
| BMI | body mass index |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CRF | case report form |
| CSR | clinical study report |
| CV | coefficient of variation |
| DMC | data monitoring committee |
| DSMB | data safety monitoring board |
| FAS | full analysis set |
| LOCF | last observation carried forward |
| LS | least squares |
| MAR | missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-effects Models for Repeated Measures |
| NI | noninferiority |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| QTcF | QT interval corrected for heart rate by Fridericia's formula |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | Standard deviation |
| SE | standard error |
| SI | Système International |
| TEAE | treatment-emergent adverse event |
| TLG | tables, listings, and graphs |
| WHO | World Health Organization |

# 2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol FYU-981-J086-301. The planned analyses will be included in the clinical study report, regulatory submissions and/or future manuscripts. Additional exploratory or post-hoc analyses not identified in this SAP may be performed to facilitate interpretation of study results and documented in the clinical study report.

This SAP is to be reviewed and approved prior to study database lock. If any updates are made upon blinded review of study data or for any other reasons in the course of the study, such modifications and rationale are likewise to be documented and approved prior to unblinding of study database.

## 2.1 Study Objectives

### 2.1.1 Primary Objective

To confirm the superiority of dotinurad 4 mg to febuxostat 40 mg on the proportion of subjects achieving a serum uric acid (SUA) level ≤6.0 mg/dL at Week 24 in Chinese subjects with gout.

### 2.1.2 Secondary Objectives

- To confirm the non-inferiority of dotinurad 2 mg to febuxostat 40 mg on the proportion of subjects achieving a SUA level ≤6.0 mg/dL at Week 12 in Chinese subjects with gout
- To compare the proportion of subjects achieving a SUA level ≤6.0 mg/dL at each time point between treatment groups
- To compare the percent reduction in SUA level from baseline at each time point between treatment groups
- To compare the change in SUA level from baseline at each time point between treatment groups
- To compare the SUA level at each time point between treatment groups
- To evaluate the safety and tolerability of dotinurad

## 2.2 Overall Study Design and Plan

FYU-981-J086-301 is a 24-week treatment, multicenter, randomized, double-blind, superiority, parallel-group study designed to confirm if the efficacy of dotinurad (4 mg/day) was superior to febuxostat (40 mg/day) in Chinese subjects 18 years or older in gout.

The study consists of the Screening Phase (4 to 28 days), Treatment I Phase (4 weeks), and Treatment II Phase (20 weeks).

Approximately 450 subjects will be randomized to treatment groups in a ratio of 1:1 and received dotinurad 1 mg/day for the first 4 weeks, 2 mg/day for 8 weeks, and 4 mg/day for 12 weeks; or febuxostat 20 mg/day for the first 4 weeks, and 40 mg/day for 20 weeks. In addition, the randomization will be stratified by SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) and body mass index (BMI) category (<25; ≥25 kg/m$^2$).

The study design was shown in Figure 1.

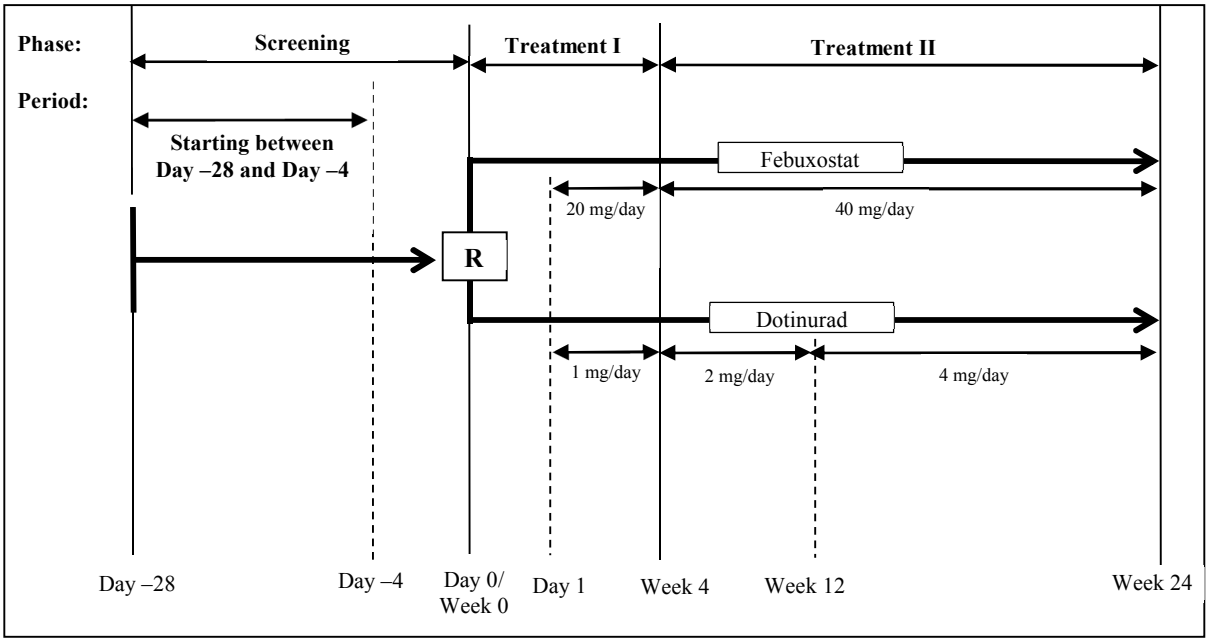


**Figure 1 Study Design**

R: Randomization

# 3 DETERMINATION OF SAMPLE SIZE

For the responder rate, assuming a rate of 45% for febuxostat 40 mg and 60% for dotinurad 4 mg, a sample size of 225 subjects in each group provides approximately 90% power to detect a between-group difference in the proportion of responders based on a two-group Chi-square test with a 0.05 two-sided significance level. The primary efficacy analysis is based on the FAS. Hence, 450 is the target number of subjects as the FAS.

# 4 STATISTICAL METHODS

All final statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

## 4.1 Study Endpoints

### 4.1.1 Primary Endpoint

Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 24 (LOCF)

### 4.1.2 Secondary Endpoints

- Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 12 (LOCF)
- Proportion of subjects with ≤6.0 mg/dL in SUA level at each time point
- Mean percent reduction from baseline in SUA level at each time point
- Mean change from baseline in SUA level at each time point
- Mean SUA level at each time point

## 4.2 Study Subjects

### 4.2.1 Definitions of Analysis Sets

Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement (ie, SUA level).

Per Protocol (PP) Analysis Set is the subset of subjects in the Full Analysis Set, who had no major protocol deviation(s) that may include but not limited to: lower study drug compliance less than 80%, administration of prohibited drug. The criteria for exclusion in this analysis set will be made and documented on a case-by-case basis from the viewpoint of reasonable clinical judgment prior to treatment unblinding.

The number (percentage) of randomized subjects in each analysis set will be summarized by treatment groups. The summaries for FAS will be based on subjects “as randomized”. The summary for Safety Analysis Set will be based on subjects “as treated”. Subject data listing for adoption of each analysis set will be listed.

### 4.2.2 Subject Disposition

The number of subjects screened, the number and percentage of screen failures, and their primary reason for screen failure will be summarized. Screen failure data will be listed.

The number and percentage of randomized subjects will be summarized by sites for each treatment group.

The number of subjects who received study drug and completed the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by

their primary reason for study termination. Other reasons for study drug and study termination will also be summarized. These tabulations will be produced for all randomized subjects by treatment group. Subject-disposition data will be listed.

### 4.2.3 Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to major/minor and standard classifications including but not limited to the following:

- Violations of inclusion/exclusion criteria
- Noncompliance with or incorrect implementation of protocol procedures
- Noncompliance of randomized study drug and dosage
- Use of prohibited concomitant medication

Major protocol deviations will be listed.

### 4.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics in the Safety Analysis Set, FAS, and PP Analysis Set will be summarized for each treatment group using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables).

Continuous variables include age, height, weight, BMI; categorical variables include sex, age category (<45; 45 to <55; 55 to <65; ≥65 years old), BMI category (<25; ≥25 kg/$m^2$), race, and ethnicity. In addition, the randomization strata will also be summarized by treatment group.

#### MEDICAL HISTORY

Characteristics of gout/hyperuricemia and the prior medications for gout/hyperuricemia for the Safety Analysis Set, FAS, and PP Analysis Set will be summarized for each treatment group using descriptive statistics.

Continuous variables include:

- SUA level (mg/dL) and eGFR (mL/min/1.73 $m^2$) measured at the screening
- Time (year) since diagnosis of gout
- Time (year) since diagnosis of asymptomatic hyperuricemia, if subjects are applicable

Categorical variables include:

- Previous urinary calculi (presence, absence)

- Asymptomatic hyperuricemia (presence, absence)
- Family history (presence, absence)
- Previous gouty arthritis (presence, absence)
- Previous gouty tophi (presence, absence)
- All medications used in the past for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others)
- The last medication for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others)
- Duration of last medication for gout/hyperuricemia (less than 1yr, over 1yr to less than 10 yrs, over 10yrs, none)
- SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL)
- eGFR category (≥30 to <60; 60 to <90; ≥90 mL/min/1.73 $m^2$)
- Classification of hyperuricemia (overproduction type, underexcretion type, combined type, other type).

All medical histories including all current medical conditions as documented by the Medical History eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percent of subjects with medical history will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

The number and percent of subjects with current medical conditions will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

A subject data listing of medical history will be provided.

### 4.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD).

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. In addition, prior and concomitant nonpharmacological procedures will be defined similarly to prior and concomitant medications.

The number (percentage) of subjects who take prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class (ATC), and World Health Organization Drug Dictionary-preferred term (PT).

The number (percentage) of subjects with prior/ concomitant nonpharmacological procedures will be summarized on the Safety Analysis Set by treatment group.

If the Safety Analysis Set and FAS differ, then the summaries will be repeated on the FAS.

All medications and nonpharmacological procedures will be presented in subject data listings.

### 4.2.6 Treatment Compliance

Compliance for each study drug during the entire study duration will be calculated on the basis of number of tablets dispensed, lost and returned, separately for each type of tablet, for Safety Analysis Set.

$$\text{Compliance} = \frac{\text{Total number of tablets dispensed} - \text{total number of tablets returned or lost}}{\text{Number of tablets expected to be taken by the subject during the study}} \times 100\ (\%)$$

Treatment compliance will be summarized using descriptive summary statistics and number (percentage) of subjects using the categories <80%, ≥ 80% to ≤100%, >100% to ≤ 120%, and > 120% for each treatment group.

## 4.3 Data Analysis General Considerations

### 4.3.1 Pooling of Centers

This study is a multicenter study. Due to expected small number of subjects from some centers, subjects from all centers will be pooled for all primary analyses.

### 4.3.2 Adjustments for Covariates

Randomization stratification factors, BMI category (<25; ≥25 kg/m$^2$) and SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) based on CRF data, will be used in stratified analysis for the primary and secondary efficacy analysis. These factors will be adjusted as covariates in statistical model.

### 4.3.3 Multiple Comparisons/Multiplicity

Treatment group comparison for the primary efficacy endpoint will be conducted at $\alpha = 0.05$ (2-sided). No multiplicity adjustments will be performed for other efficacy analyses including sensitivity analysis based on non-responder imputation and supplemental analysis based on PPS.

### 4.3.4 Examination of Subgroups

Various subgroup analyses are planned and pre-specified as described in each analysis section in this SAP. No hypothesis testing will be performed in the subgroup analyses.

The subgroups include: BMI category (<25; ≥25 kg/m$^2$), SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL), and classification of hyperuricemia (overproduction type, underexcretion type, combined type, other type).

BMI and SUA category are those assessed at the baseline. Classification of hyperuricemia group is defined as entered on the study CRF.

### 4.3.5 Handling of Missing Data, Dropouts, and Outliers

Specific methods for handling missing values in analyzing the primary and secondary endpoints are detailed in each section. In general, missing values due to subject discontinuation, missed or unusable assessments will not be imputed unless otherwise specified.

### 4.3.6 Other Considerations

Not applicable.

## 4.4 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses. The unit of SUA will be based on mg/dL for all efficacy analyses.

### 4.4.1 Primary Efficacy Analyses

The analysis for the difference in the proportion of subjects with ≤ 6.0 mg/dL in SUA level (i.e., responder rate) at Week 24 (LOCF) (see section 7) between dotinurad 4 mg and febuxostat 40 mg will be conducted based on a Cochran–Mantel–Haenszel (CMH) test stratified by baseline SUA level and baseline BMI. The difference in responder rate between dotinurad 4 mg and febuxostat 40 mg and the stratified 95% confidence interval based on Mantel-Haenszel method adjusting for the baseline SUA level and baseline BMI will be estimated. Also, the number (percentage) of responder and the asymptotic 95% confidence interval will be presented by treatment group. The same primary efficacy analysis mentioned above will be repeated supplementally based on the PP Analysis Set.

For the primary efficacy endpoint, non-responder imputation method on FAS will also be implemented as a sensitivity analysis, which will handle the missing data of SUA at Week 24 as non-responder (see section 7).

The following subgroup will be investigated for the responder rate at Week 24 (LOCF):

- SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL)

- BMI category (<25; ≥25 kg/m$^2$)
- Classification of hyperuricemia (overproduction type, underexcretion type, combined type, other type)

For the subgroup analyses, the number (percentage) of responder and the 95% confidence interval will be presented by treatment group. Furthermore, the difference in responder rate and unstratified 95% confidence interval will also be presented.

### 4.4.2 Secondary Efficacy Analyses

For all the secondary efficacy analyses, no multiplicity adjustment will be made.

- Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 12 (LOCF)

The difference in responder rate at Week 12 (LOCF) between dotinurad 2 mg and febuxostat 40 mg and the stratified 95% confidence interval will be estimated based on Mantel–Haenszel method adjusting for the baseline SUA level and baseline BMI. The prespecified non-inferiority margin will be –10% in this analysis, which will be for the reference purpose only. The number (percentage) of responder and the asymptotic 95% confidence interval at Week 12 (LOCF) (see section 7) will be presented by treatment group.

The same analysis mentioned above will be repeated supplementally based on the PP Analysis Set.

- Proportion of subjects with ≤6.0 mg/dL in SUA level at each time point

The number (percentage) of responder at each visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24) will be presented by treatment group.

Responder rate for each treatment group at each visit (Week 4, Week 8, Week 12, Week 12 (LOCF), Week 16, Week 20, Week 24, Week 24 (LOCF)) will be presented by bar chart.

- Mean percent reduction from baseline in SUA level at each time point

The mean percent reduction from baseline in SUA level at each visit (Week 4, Week 8, Week 12, Week 12 (LOCF), Week 16, Week 20, Week 24, Week 24 (LOCF)) will be summarized by treatment group using descriptive summary statistics. In addition, box-plot will be used for graphical presentation.

The following subgroup analysis will be repeated:

- SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL)
- BMI category (<25; ≥25 kg/m$^2$)
- Classification of hyperuricemia (overproduction type, underexcretion type, combined type, other type)

In addition, the mean percent reduction and difference in least squares (LS) means between dotinurad and febuxostat, and corresponding 95% confidence interval will be estimated based

on the mixed-effects models for repeated measures (MMRM). The model will be adjusted for the baseline SUA value, baseline SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) and baseline BMI category (<25; ≥25 kg/$m^2$), treatment, time (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24) and the interaction of treatment by time. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The unstructured covariance matrix (UN) will be used in the analysis. In the case of nonconvergence of UN, the toeplitz covariance matrix (TOEP) will be used. In the case of nonconvergence with TOEP, the autoregressive covariance matrix [AR (1)] will be used in the model. The use of MMRM will be based on the assumption of missing at random (MAR), which means no imputation for missing values will be conducted.

- Mean SUA level and mean change from baseline in SUA level at each time point

The mean actual value and the mean change from baseline in SUA level at each time point (Baseline, Week 4, Week 8, Week 12, Week 12 (LOCF), Week 16, Week 20, Week 24, Week 24 (LOCF)) will be summarized by treatment group using descriptive summary statistics and presented by box-plot.

### 4.4.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

## 4.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

### 4.5.1 Pharmacokinetic Analyses

Not applicable

### 4.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

## 4.6 Safety Analyses

All safety analyses will be performed based on observed data using the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics or frequency count only. No hypothesis testing will be performed for safety analyses. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

### 4.6.1 Extent of Exposure

The extent of exposure (duration of exposure) to study drug will be summarized using descriptive statistics by treatment group. Duration of exposure of study drug will be defined as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug, inclusive.

### 4.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 24.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during time from the first dose of study drug to 28 days after the subject's last dose, having been absent at pretreatment or

- Reemerges during treatment, having been present at pretreatment but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

An overview table of TEAE, including number of subjects with TEAEs, treatment-related TEAEs, severe TEAEs, SAEs (deaths and other SAEs), TEAEs leading to study drug adjustment (withdrawal, reduced, interrupted) will be provided by treatment group.

In addition, the following summaries will be produced for the TEAEs by treatment group:

- Incidence of TEAEs by PT in descending order
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and severity
- Incidence of treatment-related TEAEs by SOC, PT, and severity
- Incidence of TEAEs leading to study drug withdrawal by SOC and PT
- Incidence of serious TEAEs by SOC and PT
- Incidence of non-serious TEAEs by SOC and PT
- Incidence of TEAE by PT and time of onset (every 4 weeks)
- Incidence of treatment-related TEAE by PT and time of onset (every 4 weeks)

If a subject experiences more than one TEAE within a preferred term, the subject will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a subject experiences more than one TEAE within a SOC, the subject will be counted only once in the calculation of incidence of TEAE within that SOC. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence with the

highest severity will be used in the calculation of the incidence of TEAE within that preferred term (SOC) by severity. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence considered most closely related to study drug will be used in the calculation of the incidence of TEAE with that preferred term (SOC) by relationship (given by investigator).

In addition, the following TEAEs of interest will be summarized by PT and treatment group.

- Urinary calculi defined by MedDRA HLGT "Urolithiases"
- Liver injury defined by MedDRA SMQ "Hepatic disorders"
- Acute renal failure defined by MedDRA SMQ "Acute renal failure"

TEAEs for the following subgroups will be summarized by SOC, PT and treatment group:

- SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL)
- BMI category (<25; ≥25 kg/$m^2$)
- Classification of hyperuricemia (overproduction type, underexcretion type, combined type, other type)

A subject data listing of all AEs, all AEs leading to death, all SAEs and all AEs leading to discontinuation from study drug will be provided.

### 4.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol Section 9.5.1.4.4, the actual value and the change from baseline to each postbaseline visit will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). A TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized by treatment group.

The number (percentage) of subjects who met the following criteria for the hepatic test at the same time will be summarized by treatment group. If a subject met the criteria more than once for available laboratory data, the subject will be counted only once in the calculation of the incidence.

- Elevated AST or ALT lab value that is greater than or equal to 3× ULN
- Elevated total bilirubin lab value that is greater than or equal to 2× ULN
- Alkaline phosphatase lab value that is less than 2× ULN

A subject data listing of laboratory values will be provided.

### 4.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse and temperature) and weight, and changes from baseline will be presented by visit and treatment group. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

The number (percentage) of subjects with at least 1 postbaseline clinically notable values in vital signs and weight will be summarized by treatment group. Clinically notable values will be defined in the Table 1. A subject data listing of vital signs and weight will be provided.

**Table 1 Vital Sign Criteria**

| Variable | **Criterion value[a]** | **Change relative to baseline[a]** | **Clinically notable range** |
|---|---|---|---|
| Pulse | > 120 bpm | Increase of ≥ 15 bpm | H |
| | < 50 bpm | Decrease of ≥ 15 bpm | L |
| Systolic BP | > 180 mmHg | Increase of ≥ 20 mmHg | H |
| | < 90 mmHg | Decrease of ≥ 20 mmHg | L |
| Diastolic BP | > 105 mmHg | Increase of ≥ 15 mmHg | H |
| | < 50 mmHg | Decrease of ≥ 15 mmHg | L |
| Weight | -- | Increase of ≥ 7% | H |
| | -- | Decrease of ≥ 7% | L |

BP = blood pressure, H = high, L = low.

[a] Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

### 4.6.5 Electrocardiograms

Descriptive statistics for ECG parameters (QTcF, QT, PR, QRS, RR and heart rate) and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit and treatment group.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

A subject data listing of ECG results will be provided.

### 4.6.6 Other Safety Analyses

No analyses are planned for pregnancy tests, and abdominal ultrasound and plain abdominal radiography.

A subject data listing of urinary calculi on abdominal ultrasound/abdominal radiography will be provided.

## 4.7 Other Analyses

Not applicable.

## 4.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriate titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

# 5 INTERIM ANALYSES

Not applicable.

# 6 CHANGES IN THE PLANNED ANALYSES

Major changes of planned analysis from SAP version 1.0 are listed in the revision history.

# 7 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

Baseline Assessment

Unless otherwise specified, the baseline measurement is the last observed measurement among all available measurements, including from unscheduled assessments, prior to the first dose of randomized study drug for a given assessment.

Change from Baseline, Percent Change from Baseline

Change from baseline will be defined as: Post-baseline value - Baseline value

% change from baseline will be defined as: (Change from baseline / Baseline value) * 100

For efficacy analysis, % reduction from baseline will be calculated as: {(Baseline value – post-baseline value) / Baseline value} *100.

Visit Window

The protocol specified visits/weeks and corresponding time windows used for visit-wise analyses are presented in Table 2 in terms of days relative to the date of first dose (i.e., Day 1).

**Table 2 Windowing Rules**

| Week | Target Visit Date (Study day) | Visit Window (Study day) |
|---|---|---|
| Baseline [a] | 1 | – |
| Week 4 | 28 | 2 – 42 |
| Week 8 | 56 | 43 – 70 |
| Week 12 | 84 | 71 – 98 |
| Week 12 (LOCF) [b d] | – | – |
| Week 16 | 112 | 99 – 126 |
| Week 20 | 140 | 127 – 154 |
| Week 24 | 168 | 155 – 182 |

**Table 2 Windowing Rules**

| Week | Target Visit Date (Study day) | Visit Window (Study day) |
|---|---|---|
| Week 24 (LOCF) [c d] | – | – |
| End of Treatment [e] | – | – |

[a] The last non-missing values including unscheduled assessments on or prior to the date of first dose.

[b] The last non-missing values including unscheduled assessments up to Day 98 (inclusive) will be carried forward as the data for the efficacy analysis, which is known as Week 12 (LOCF).

[c] The last non-missing values including unscheduled assessments up to Day 182 (inclusive) will be carried forward as the data for the efficacy analysis, which is known as Week 24 (LOCF).

[d] For subjects who discontinued the study, the last non-missing values up to 14 days after the date of last dose will be carried forward as the data for the efficacy analysis.

[e] The last non-missing values including unscheduled assessments during the study will be used for the safety analysis only.

In case of multiple assessments within the same visit window, the assessment closest to the target visit day will be used in data analyses; in the event of two assessments being equally close to the scheduled visit day, the latest assessment in time will be used. In the event of two assessments being equally close to the scheduled visit day, the data will be considered in an individual case.

Missing data handling

- Non-responder imputation for responder analysis of SUA (as binary variable)

Missing values will be considered as non-responders. This handling will be applied to the sensitivity analysis of the primary efficacy analysis.

- Longitudinal data analysis of SUA using MMRM (as continuous variable)

SUA will be analyzed using MMRM based on the assumption of missing at random (i.e., MAR). This analysis assumes subjects with missing values behave the same as the observed data within that treatment group, i.e., the missingness is independent of unobserved data after accounting for the observed data in the model.

- AE severity and AE relationship to study drug

For the purpose of summarizing maximum severity, if the severity of an AE is missing for a subject, then, if this subject has another AE with the same preferred term that has "severe" severity, the maximum severity of the AE will be noted as "severe'; otherwise the maximum severity will be noted as missing. Similarly, for the purpose of summarizing treatment-related TEAE, if the relationship of an AE to study drug is missing, the AE will be noted to be related.

- Determination of TEMAVs for laboratory values

For determining TEMAVs of laboratory values, a missing baseline laboratory value will be assumed to be of grade 0.

Handling of below lower quantification values in laboratory tests

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

Handling of hemolysis or lipemia in laboratory specimen

If the hemolysis or lipemia occurs, those data will not be used in the analysis of laboratory test results and efficacy analysis (i.e., SUA).

# 8 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

# 9 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or later versions). In the event that certain features graphical analyses cannot be implemented by SAS, other validated statistical software can be employed.

# 10 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

# Appendix 1 Sponsor's Grading for Laboratory Values

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin | <LLN – 10.0 g/dL<br><LLN – 100 g/L<br><LLN – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L | |
| Leukocytes (total WBC) | <LLN – $3.0\times10^9$/L<br><LLN – 3000/$mm^3$ | <3.0 – $2.0\times10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – $1.0\times10^9$/L<br><2000 – 1000/$mm^3$ | <$1.0\times10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | <LLN – 800/$mm^3$<br><LLN – $0.8\times10^9$/L | <800 – 500/$mm^3$<br><0.8 – $0.5\times10^9$/L | <500 – 200/$mm^3$<br><0.5 – $0.2\times10^9$/L | <200/$mm^3$<br><$0.2\times10^9$/L |
| Neutrophils | <LLN – $1.5\times10^9$/L<br><LLN – 1500/$mm^3$ | <1.5 – $1.0\times10^9$/L<br><1500 – 1000/$mm^3$ | <1.0 – $0.5\times10^9$/L<br><1000 – 500/$mm^3$ | <$0.5\times10^9$/L<br><500/$mm^3$ |
| Platelets | <LLN – $75.0\times10^9$/L<br><LLN – 75,000/$mm^3$ | <75.0 – $50.0\times10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – $25.0\times10^9$/L<br><50,000 – 25,000/$mm^3$ | <$25.0\times10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | <LLN – 3 g/dL<br><LLN – 30 g/L | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | |
| Alkaline phosphatase | >ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal | >2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal | >5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal | >20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal |
| ALT | >ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal | >3.0 – 5.0×ULN if baseline was normal; >3.0 – 5.0×baseline if baseline was abnormal | >5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal | >20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal |
| AST | >ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal | >3.0 – 5.0×ULN if baseline was normal; >3.0 – 5.0×baseline if baseline was abnormal | >5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal | >20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal |
| Bilirubin (hyperbilirubinemia) | >ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal | >1.5 – 3.0×ULN if baseline was normal; >1.5 – 3.0×baseline if baseline was abnormal | >3.0 – 10.0×ULN if baseline was normal; >3.0 – 10.0×baseline if baseline was abnormal | >10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal |
| Calcium, serum-low (hypocalcemia) | <LLN – 8.0 mg/dL<br><LLN – 2.0 mmol/L<br>Ionized calcium <LLN - 1.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L<br>Ionized calcium <1.0 - 0.9 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L<br>Ionized calcium <0.9 - 0.8 mmol/L | <6.0 mg/dL<br><1.5 mmol/L<br>Ionized calcium <0.8 mmol/L |
| Calcium, serum-high (hypercalcemia) | >ULN – 11.5 mg/dL<br>>ULN – 2.9 mmol/L<br>Ionized calcium >ULN - 1.5 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L<br>Ionized calcium >1.5 - 1.6 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L<br>Ionized calcium >1.6 - 1.8 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L<br>Ionized calcium >1.8 mmol/L |
| Creatinine | >ULN – 1.5×ULN | >1.5 - 3.0×baseline;<br>>1.5 – 3.0×ULN | >3.0×baseline;<br>>3.0 – 6.0×ULN | >6.0×ULN |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| GGT (γ-glutamyl transpeptidase) | >ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5×baseline if baseline was abnormal | >2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0×baseline if baseline was abnormal | >5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0×baseline if baseline was abnormal | >20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal |
| Glucose, serum-low (hypoglycemia) | <LLN – 55 mg/dL<br><LLN – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L |
| Potassium, serum-high (hyperkalemia) | >ULN – 5.5 mmol/L | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L | >7.0 mmol/L |
| Potassium, serum-low (hypokalemia) | <LLN – 3.0 mmol/L | | <3.0 – 2.5 mmol/L | <2.5 mmol/L |
| Sodium, serum-high (hypernatremia) | >ULN – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L | >160 mmol/L |
| Sodium, serum-low (hyponatremia) | <LLN – 130 mmol/L | 125-129 mmol/L | 120-124 mmol/L | <120 mmol/L |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L |

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

# SIGNATURE PAGE

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