STATISTICAL ANALYSIS PLAN AMENDMENT

Protocol D5495C00001

Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

PAREXEL Study Number CCI

Version: 1.0
Date 16 July 2018

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

PPD

13 Aug 2018

Date (dd mmm yyyy)

Associate Manager, EP Biostatistics
PAREXEL International Corporation

SIGNATURE PAGE - AstraZeneca

Declaration

The undersigned agree to the statistical analyses and methods described in this Statistical Analysis Plan.

PPD

17 JUL 2018
Date (dd mmm yyyy)

Global Project Statistician
AstraZeneca AB

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Abbreviations and Definitions

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
AUC	Area under plasma concentration-time curve from zero to infinity
AUClast	Area under plasma concentration time curve from time zero to the time of last measurable concentration
AUCτ	Area under plasma concentration time curve over a dosing interval (24 hours)
CCI	[redacted]
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence Interval
CCI	[redacted]
CS	Clinically significant
Cmax	Maximum observed plasma concentration
CO2	Carbon dioxide
CrCL	Creatinine Clearance
CV	Coefficient of Variation
DDI	Drug-Drug Interaction
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FAS	Full Safety Analysis Set
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GGT	Gamma glutamyl transpeptidase (transferase)
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen

HCG	Human beta chorionic gonadotrophin
HCT	Hematocrit
HIV	Human immunodeficiency virus
IV	Intravenous
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ms	milliseconds
n	Number of subjects
NC	Not Calculated
NCS	Not Clinically Significant
ND	Not determined
NR	No result
NQ	Non-quantifiable
PD	Pharmacodynamics
PDS	Protocol deviation specification (document)
PK	Pharmacokinetics
QTcB	QT Interval Corrected by Bazett's Formula
QTcF	QT Interval Corrected by Fridericia's Formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
sUA	Serum uric acid
TEAE	Treatment-Emergent Adverse Event

t1/2	Apparent terminal half-life
tlast	Time of last measurable concentration
tmax	Time to reach maximum observed plasma concentration
UA	Uric acid
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1. Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is based on the final protocol D5495C00001 Version 1.0 dated 05 September 2017 and incorporates protocol amendment #1 dated 02 October 2017 and protocol amendment #2 dated 02 May 2018. The SAP provides details on the planned statistical methodology for analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures. It describes the safety, pharmacodynamic (PD) variables, and the pharmacokinetic (PK) variables; as well as the anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP covers the planned analysis of all data collected electronically in CCI and provided by external vendors.

2. Study Objectives and Hypotheses

2.1 Primary Objectives

To assess the effects of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA.

2.2 Secondary Objectives

- To assess the effects of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin on sUA levels.
- To assess the PK of RDEA3170 and its main metabolites (M1 and M8), febuxostat and dapagliflozin in this patient population.
- To assess the renal and general safety and tolerability of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin.

2.3 Exploratory Objectives

- CCI

- CCI

2.4 Primary Outcome Measures

Peak UA excretion during the first 8 hours (maximum amount excreted in an interval out of the first 8 hours) on Day 7 of treatment (Day 1 is the first day of treatment).

2.5 Secondary Outcome Measures

- Serum uric acid levels after 7 days of treatment.
- RDEA3170, M1, M8, febuxostat and dapagliflozin plasma concentrations and PK parameters.
- Changes in clinical laboratory parameters, including assessment of serum and urinary levels of creatinine and cystatin-C, BUN, serum and urinary electrolytes, urinary pH. Changes in vital signs. Rates of AEs and SAEs.

2.6 Exploratory Outcome Measures

- CCI

3. Study Design

This is a randomized, placebo controlled, double-blind, 2-way crossover study to assess the effect of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA, in asymptomatic hyperuricemic patients. Twenty-four asymptomatic hyperuricemic patients aged 18 to 65 years (inclusive) will be enrolled into this study at 2 study centers. Each patient will receive the 2 treatments listed below for 7 consecutive days (1 treatment per treatment period).

- **Treatment A:** 9 mg RDEA3170 + 80 mg febuxostat + 10 mg dapagliflozin
- **Treatment B:** 9 mg RDEA3170 + 80 mg febuxostat + placebo

The study consists of a screening period of maximum 28 days. As well as:

- Two treatment periods during which patients will be resident in the Clinical Unit from Day -2 to Day 1 and from Day 6 to Day 8; and
- A Follow-up Visit within 14 to 28 days after the first administration of IMP in Treatment Period 2.

Before any study specific assessments are performed, potential patients must provide informed consent. Patients that provided informed consent will attend the Screening Visits within 28 days before receiving the first dose of IMP. Patients that are meet all of the inclusion criteria and none of the exclusion criteria, will return to the Clinical Unit on Day -2 of Treatment Period 1 and will be randomized (1:1) to 1 of 2 treatment sequences (AB or BA) before the start of urine collection on Day -1 of Treatment Period 1.

For each treatment period, baseline measurements will be performed. Patients receive the IMP for 7 consecutive days (Day 1 to Day 7). Patients will be residential in the Clinical Unit from Day -2 to Day 1. On Day 1, after all dosing and all assessments have been performed, patients will receive instruction to administer the IMP at home once daily in the morning from Day 2 to Day 6 and the IMP will be dispensed for home dosing. Patients will return to the Clinical Unit on Day 6 and will be residential in the Clinical Unit from Day 6 to Day 8.

Treatment Period 1 and Treatment Period 2 will be separated by a washout period of 7 to 21 days. Patients will return to the Clinical Unit for a Follow-up Visit, 14 to 28 days after Day 1 of Treatment Period 2.

The end of study is defined as the last patient's last visit to the Clinical Unit.

3.1 Study Population

The study population will consist of 20 to 24 male and female patients.

All enrolled patients must meet all of the inclusion criteria and none of the exclusion criteria outlined in the study protocol. Any patient who fails to meet the inclusion

criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

3.2 Statistical Basis for Sample Size

Detailed information regarding the formal calculation of sample size can be found in the study protocol section 11.4.

3.3 Randomization

Upon completion of the randomization requirements specifications form, the randomization will be produced by PAREXEL according to the AstraZeneca randomization system (AZRand). For this study, a total of 24 patient identifiers will be randomly assigned to the treatment sequence(s): AB, BA, with 12 patients assigned per sequence. An additional set of replacement random numbers will be generated within AZRand on a like for like treatment sequence basis.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization (codes to be used without leading zero[s]). When using unique enrolment number, the specific format must be followed (i.e., reduced enrolment number, e.g., CCI ” [for Baltimore] and CCI ” [for Los Angeles] for outputs). The site number for Baltimore is CCI and the site number for Los Angeles is CCI .

If a patient withdraws his/her participation in the study, then his/her enrolment/randomization code cannot be reused. If a replacement is mandated, replacement patients will receive a new randomization number and will be allocated to the same treatment sequence as the replaced patient.

3.4 Blinding

This study is double-blind with regard to treatment (dapagliflozin or placebo) in each treatment period.

Dapagliflozin and placebo will be matched for formulation, appearance and amount. Patients randomized to placebo received the same number of tablets as patients on active drug.

3.5 Dose Administration

Patients will receive 9 mg RDEA3170 plus 80 mg febuxostat once daily in combination with either placebo or dapagliflozin 10 mg once daily for 7 consecutive days.

Clinical Unit Dosing

Patients will be residential in the Unit from Day -2 to Day 1, and from Day 6 to Day 8.

On Days -2, -1, 1, 6 and 7, patients will receive standardized meals, and will be encouraged to consume the entire meal.

On Day -1, Day 1 and Day 7 of each treatment period, patients will be fasted for 10 hours before dosing (for Day -1, clock time of planned dose administration for dosing days) until 4 hours after dosing, and will receive standardized meals thereafter. On Day 1 and Day 7, patients will receive the IMPs in the morning with 240 mL water, after an overnight fast of at least 10 hours. A standard meal will be given 4 hours after dosing.

Home Dosing

Patients will self-administer the IMPs at home on a daily basis, from Day 2 to Day 6.

3.6 Treatment compliance

Dosing will take place at the PAREXEL Early Phase Clinical Unit and at the patient's homes. The administration of all IMPs will be recorded in CCI .

Compliance will be assured by direct supervision and witnessing of study drug administration when administration is performed at the Clinical Unit. After IMP administration, a check of the patient's mouth and hands will be performed.
Compliance will be assured during at home dosing by drug accountability.

3.7 Interim Analysis

Not applicable

4. Study Analysis Variables

4.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Medical/surgical history
- Urine drug, blood alcohol
- Age calculated as (date of informed consent – date of birth)/365.25
- Gender
- Ethnic origin
- Race
- Height (cm)
- Body weight (kg)
- Body mass index (BMI) (kg/m^2)
- eGFR

4.2 Safety Variables

4.2.1 Adverse Events

The Adverse events will be collected from the start of randomization throughout the treatment period up to and including the Follow-up Visit.

Serious adverse events will be recorded from the time of informed consent.

4.3 Potential Events of Diabetic Ketoacidosis

All potential events of DKA will be recorded in CCI and submitted to an independent DKA Adjudication Committee. The DKA Committee T2DM will assess available information on each potential DKA event and will classify the event in accordance with the definitions in the DKA Adjudication Charter T2DM.

4.3.1 Clinical Laboratory Tests

Laboratory safety tests for hematology and chemistry will be performed at Screening, Period 1 (Day-2, Day 7), Period 2 (Day -2, Day 7), and at Follow-up.

The following safety laboratory parameters will be measured:

Hematology

- White blood cell (WBC) count
- Red blood cell (RBC) count
- Hemoglobin (Hb)
- Hematocrit (HCT) [(c)]
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Neutrophils absolute count
- Lymphocytes absolute count
- Monocytes absolute count
- Eosinophils absolute count
- Basophils absolute count
- Platelets
- Reticulocytes absolute count
- Hemoglobin A1c (HbA1c) (Screening Visit only)

Clinical Chemistry

- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma glutamyl transpeptidase (GGT)
- Potassium
- Blood Urea Nitrogen (BUN)
- Creatinine[(c)]
- Albumin
- Calcium
- Phosphate
- Uric acid[(c)]
- Total Bilirubin
- Unconjugated bilirubin
- Cystatin-C[(c)]
- Sodium
- Estimated Creatinine Clearance (CrCl)
- eGFR[(a)]
- Glucose (Fasting)[(b)(c)]

Notes:
(a) eGFR collected at screening visit only (Visit 1)
(b) Plasma glucose after at least 4 hours fasting (Day -1 of each period)

Urinalysis by dipstick

- Glucose
- Protein
- Blood
- Microscopy (if dipstick is positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)

Urinalysis for urine collection interval[(c)]

- Uric Acid
- Creatinine
- Glucose
- Sodium
- pH
- Cystatin-C

Pregnancy Test (females only)

- Human beta chorionic gonadotrophin (HCG)
- Follical-stimulating hormone (FSH) – Screening visit.

Vital Serology

- Human immunodeficiency virus (HIV) I and II
- Hepatitis C Virus antibody
- Hepatitis B surface antigen (HBsAg)

Drugs of Abuse

- Amphetamine/Ectasy
- Benzodiazepines
- Ethanol
- Cannabinoids
- Cocaine
- Opiates
- Tricyclic anti-depressants (TCA)
- Methadone Metabolites
- Barbiturates
- Phencyclidine

Note: Laboratory results indicated (c) will be listed, summarized, and analyzed as part of the PD panel, as described in section 8 below.

4.3.2 Vital Signs

Vital signs will be collected at Screening, Period 1 (Day -2, Day 7), Period 2 (Day -2, Day 7), and at Follow-up.

The following variables will be collected after the patient has rested in the supine position for at least 5 minutes:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse rate (bpm)

4.3.3 Electrocardiograms

Standard 12-lead ECGs will be collected at Screening, Day-2 of each period, and at Follow-up.

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

4.3.4 Physical Examination

Complete physical examinations will be performed at Screening and Follow-up.

A brief physical examination will be performed at Day -1 and Day 7 of each period.

Subject body weight will be assessed at Screening, Day -1 and Day 7 of each period and at Follow-up.

4.3.5 Prior and Concomitant Medications

Prior medications are those that started and stopped before the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started before dosing and continued after). Prior medication started within 3 months before the first dose of IMP will be recorded also in the concomitant medication module of CCI .

4.4 Pharmacokinetics

Plasma pharmacokinetic samples will be collected at Pre-dose and 15 minutes, 30 minutes, 1 hour, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose.

The PK analyses of the plasma concentration data for RDEA3170, febuxostat, dapagliflozin, M1, and M8 will be performed by Covance, on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca R&D.

Where possible, the following plasma PK parameters will be calculated for RDEA3170, febuxostat, dapagliflozin, M1, and M8 using plasma concentrations.

AUCτ	Area under plasma concentration time curve over a dosing interval (24 hours)
AUClast	Area under plasma concentration time curve from time zero to the time of last measurable concentration
Cmax	Maximum observed plasma concentration
tmax	Time to reach maximum observed plasma concentration
tlast	Time of last measurable concentration

4.4.1 Pharmacokinetic Parameter Calculation Methods

Pharmacokinetic parameters will be derived using non-compartmental methods with CCI

Pharmacokinetic analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used.

Plasma concentrations which are NQ before the first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any NQ plasma concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

Cmax and tmax will be obtained directly from the individual concentration-time profiles.

AUCτ and AUClast will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUCτ and AUClast will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following Cmax.

4.5 Pharmacodynamic Data

The following PD data will be collected:

Time Urine Sample Collections

The times of urine sample collection will occur at Day -1 and 7 of each period.
Day -1 baseline collection of urine consists of hourly collections from -24 to -12 hours (inclusive, counted from the time of dosing on Day 1 where 0 hours is time of dosing) at the following sampling intervals: -24 to -23 hours, -23 to -22 hours, -22 to -21 hours, -21 to -20 hours, -20 to -19 hours, -19 to -18 hours, -18 to -17 hours, -17 to -16 hours, -16 to -15 hours, -15 to -14 hours, -14 to -13 hours, -13 to -12 hours, followed by a single 12-hour collection from -12 to 0 hours.

Directly following the dose of study treatment on Day 7, hourly collection of urine is performed every hour from 0 to 12 hours (inclusive), at the following post-dose sampling intervals (0 to 1 hour, 1 to 2 hours, 2 to 3 hours, 3 to 4 hours, 4 to 5 hours, 5 to 6 hours, 6 to 7 hour, 7 to 8 hours, 8 to 9 hours 9 to 10 hours, 10 to 11 hours, 11 to 12 hours). These sampling intervals will be followed by a single pooled collection from 12 to 24 hours.

Time matched PD Urine Samples for Each Period

Day -1	**Day 7**
-24 to -23 hours	0 to 1 hour
-23 to -22 hours	1 to 2 hours
-22 to -21 hours	2 to 3 hours
-21 to -20 hours	3 to 4 hours
-20 to -19 hours	4 to 5 hours
-19 to -18 hours	5 to 6 hours
-18 to -17 hours	6 to 7 hours
-17 to -16 hours	7 to 8 hours
-16 to -15 hours	8 to 9 hours
-15 to -14 hours	9 to 10 hours
-14 to -13 hours	10 to 11 hours
-13 to -12 hours	11 to 12 hours
-12 to 0 hours*	12 to 24 hours**

*single 12-hour collection
**Single Pooled Collection

Blood Samples for Serum Uric Acid

A single sUA assessment (matched by time of day, e.g. always in the morning, and after a 10 hour overnight fast) will be taken at screening, Day -1 of each period and at the follow-up visit. The screening sUA can be repeated once during the screening period.

In each period day 7 blood samples for serum UA will match the PK sample times: pre-dose and 15 minutes, 30 minutes, 1 hour, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose. This will allow for 26 possible blood samples for PD serum UA.

4.6 Efficacy Variables

Not applicable

4.7 Analysis Populations

4.7.1 Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of IMP and for whom any safety post-dose data are available

4.7.2 Pharmacokinetic Analysis Set

The PK analysis set will consist of all patients in the safety analysis set for whom at least 1 of the primary PK parameters can be calculated for at least 1 analyte (RDEA3170, M1, M8, Febuxostat or dapagliflozin), and who have no major protocol deviations thought to impact on analysis of the PK data.

Patients may be excluded from the PK analysis set as a result of the following:

- Data from patients who experienced vomiting during the PK samples collection day may be excluded from summary statistics and statistical analysis if vomiting occurred at or before the median tmax for each respective analyte.

A patient may be excluded from the analysis only for the specific treatment period in which the AE occurred.

4.7.3 Pharmacodynamic Analysis Set

Analysis of the primary variable, maximum uric acid excretion in urine per hour, as well as the secondary variable serum UA at 7 days will be done using the full Safety Analysis Set as defined in section 4.7.1 above. Any sensitivity analysis will be

considered using the Per Protocol (PP) Set. The PP Set will be defined as all patients in the randomized set without major protocol deviations (to be defined before database lock).

4.7.4 Randomized Set

The Randomized Set will consist of all patients randomized into the study.

5. STATISTICAL REPORTING

For the purposes of this SAP IMP will include any of the study drugs: RDEA3170, febuxostat, dapagliflozin, or placebo.

5.1 General Considerations for Data Presentations

Data for all enrolled subjects will be presented in the data listings.

A subject who is enrolled but does not receive IMP will be included in those data listings for which they have data but will be excluded from all data summaries. Data summaries will only include those subjects that receive IMP.

For those listings or data summaries where baseline and change from baseline measurements will be presented, unless stated otherwise the last observed measurement prior to the first dose of IMP in a given treatment period will be considered the baseline measurement for all post-dose assessments in that treatment period.

All pre- and post-dose assessments, including unscheduled assessments and repeats, will be included in the data listings. For unscheduled (repeat) assessments collected pre-dose, the last assessment taken for a time point will be used in the data summaries (summary tables, figures, and statistical analysis); for all post-dose time points, the original assessment for any given time point will be used in the data summaries (summary tables, figures, and statistical analysis).

Data summaries of continuous variables will be summarized using descriptive statistics including: number of observations (n), mean (arithmetic and/or geometric), median, standard deviation (SD), minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. In summaries for safety the denominator for all percent's will be the number of subjects in a given treatment.

Data that are reported as missing will be excluded from all descriptive and non-descriptive data analysis. There will be no imputation of data. Observations that might be considered spurious (extreme relative to the majority of the data) will not be

altered or removed from any presentation of the data, including the calculation of summary statistics (means, medians, etc.), unless approved by the sponsor.

For data listings, all raw data will be reported/displayed exactly as provided. For summaries of quantitative safety data, the minimum and maximum value will be reported exactly as the raw data are reported; measures of central tendency (means, medians) will be reported to one more decimal place than the raw data; measures of variance (SD) will be reported to two more decimal places than the raw data. Methods for summarizing PK data are described in Section 7 of this SAP.

Listings will include all subjects and will be sorted by subject identifier (enrolment number) and time point (where applicable). All listings will include the site number identifier, the subject identifier, and the subject's treatment sequence. All derived data used in a data summary or statistical analysis will be listed. In all data presentations treatment will be defined by the 2 categories:

- **Treatment A:** 9 mg RDEA3170 + 80 mg febuxostat + 10 mg dapagliflozin
- **Treatment B:** 9 mg RDEA3170 + 80 mg febuxostat + placebo

SOFTWARE

All statistical analyses will be performed using [redacted] Institute Inc., Cary, North Carolina, United States of America [USA]) Version 9.2 or higher. The PK analysis will be performed using [redacted] (Certara, L.P., 9666 Olive Blvd, Suite 425, St. Louis MO 63132).

6. Subject and Treatment Information

6.1 Randomization Scheme and Codes

A listing of randomization codes will be provided including the subject identifier, the randomization number, as well as the treatment associated with each period that defines each subject's treatment sequence.

6.2 Discontinued Subjects

All subjects who discontinued early from the study will be listed including the date of study exit, duration of treatment, and the reason for early discontinuation.

6.3 Subject Disposition

The number of subjects randomized and the frequency and percentage of subjects who received treatment, subjects who did not receive treatment, subjects who completed at least one treatment period, subjects who discontinued any treatment period, subjects who completed the study, and subjects who withdrew from the study early will be summarized overall. The number and percent of subjects in the safety population, PD population, and PK population will be summarized by treatment sequence and overall.

6.4 Protocol Deviations

All reported protocol deviations will be listed. Protocol deviations that are used to identify the Per Protocol population will be determined and finalized prior to DB lock.

6.5 Subject and Data Exclusions

Listings will be provided showing any subjects or data excluded from the safety population, the PD population, and the PK population.

6.6 Demographic Data

Demographic information will be listed. Descriptive statistics will be obtained for the continuous variables: height, age, BMI, and baseline body weight. Frequencies and percentage of subjects will be tabulated by treatment sequence and overall for the categorical variables ethnicity, race, and gender.

6.7 Informed Consent Response

Each subject's informed consent response will be listed including date and time of informed consent, whether a subject complies with all inclusion/exclusion criteria, and the actual date/time of eligibility.

6.8 Medical History

Medical history data will be listed for each subject including a description of the condition or abnormality, system organ class, and preferred term. Medical history will be coded using Medical Dictionary Regulatory Activities (MedDRA Version 20.1). Only those body systems where a condition or abnormality has been reported will be listed. Included will be the date and time recoded.

6.9 Pregnancy Test Results

Pregnancy test results from serum and urine pregnancy tests will be listed for all female subjects.

6.10 Medication on Entry and During the Study

Medication on entry and during the study will be listed for each subject.
Included will be the medication name, WHO Drug name, and ATC classification.

Datasets	Coding Dictionary	Version
Previous and Concomitant Medications	WHODDE +HD	WHODDE+HD 201709

6.11 Dose Administration

The in-clinic dose administration of each subject will be listed including the date and time of dose administration, drug name, and the nominal dose planned per protocol.

A separate listing will be provided showing the home dosing of each subject.

All drug accountability data collected will be listed for each subject.

6.12 Meal Administration

Controlled meals and fluid intake will be listed for each subject.

7. Pharmacokinetic Concentrations and Parameters

Table presentations of the PK concentrations and PK parameter data will be conducted using the PK analysis set.

All tables, listings and figures for RDEA3170, febuxostat, dapagliflozin, M1, and M8 will be presented in the units as provided in the source file received from the bioanalytical laboratory.

The following descriptive statistics will be presented in PK parameter summary tables: n (number of non-missing observations), arithmetic mean, SD, median, minimum, maximum, geometric mean, geometric CV% (CV%), geometric +GSD, geometric –GSD.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

CV%=SQRT[exp(s²)-1] x 100 and 's' is the standard deviation of the log-transformed values.

The standard deviation of the geometric mean (GSD) will be displayed as:
exp(lgmean +/- s), where 'lgmean' is the mean of the data on the log scale.
For tmax and tlast, only n, median, minimum and maximum will be presented.

All PK tables, listings, and figures will be presented by analyte and treatment defined by the following two categories of drug administration:

- Treatment A: 9 mg RDEA3170 + 80 mg febuxostat + 10 mg dapagliflozin
- Treatment B: 9 mg RDEA3170 + 80 mg febuxostat

For presentations in data listings, concentration data will be presented using the same number of significant figures as the data received from the bioanalytical laboratory.

For PK parameters, the listings will be presented according to the following rules:

- Cmax – will be presented to the same number of significant figures as received from the bioanalytical laboratory.
- tmax and tlast – will be presented as received in the data, usually to 2 decimal places.
- AUCτ and AUClast - will be presented to 3 significant figures.

Descriptive statistics and statistical analyses will be calculated using un-rounded results. For tmax and tlast, only median, minimum, maximum, and n will be calculated.

Below is a summary of the rounding rules to be applied to the PK tables.

Concentration Tables	**Rounding**
Individual concentrations	*n* s.f. as supplied in source
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean/GSD	4 s.f.
CV%	4 s.f.
PK Parameter Tables	
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied in source
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean/GSD	4 s.f.
CV%	4 s.f.
CI and other percentages	2 d.p.
p-values	4 d.p.

Exceptions for PK Tables	
$t_{max,}$ tlast individual values and all descriptive statistics (median, minimum, and maximum)	Presented as received in the data, usually 2 d.p.

s.f = signficant figures, d.p. = decimal place

7.1 Handling Of Values Below The Limit Of Quantification (BLQ)

Individual plasma concentrations below the LLOQ of the bioanalytical assay will be listed as NQ (not quantifiable) with the LLOQ defined in the Tables, Figures and Listings (TFLs), as applicable. For calculation of descriptive statistics, plasma concentrations that are NQ or if there are missing values (e.g., no result [NR]) will be handled as follows:

Where results are reported as 'NR', these will be set to missing in calculations of descriptive statistics.

- At a time point where less than or equal to 50% of the values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half (but not all) of the values are NQ, the mean, SD, geometric mean, geometric +GeoSD, geometric –GeoSD and CV% will be set to Not Calculated (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. Not calculated "NC" will be written in the field for SD, geometric +GeoSD, geometric –GeoSD and CV% and NQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of NQ values (n below LLOQ) will be reported for each time point.

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarized. Two values are presented as a minimum and maximum with the other summary statistics as NC.

7.2 PK Plasma Concentrations

Pharmacokinetic concentration data for RDEA3170, febuxostat, dapagliflozin, M1, and M8 concentrations will be listed for each subject by treatment and time point. Actual sampling times relative to dosing, nominal scheduled times, and the difference between the actual and nominal sample time will also be listed.

Plasma concentrations for RDEA3170, febuxostat, dapagliflozin, M1, and M8 will be summarized by treatment and nominal time.

7.3 PK Parameters

All derived plasma PK parameters for RDEA3170, febuxostat, dapagliflozin, M1, and M8 will be listed by subject and treatment, and summarized by treatment.

7.4 Graphical Presentation of PK Data

PK plasma concentrations will be presented graphically by analyte, treatment and time point. Graphical presentations of the plasma concentrations will include geometric mean profiles of the plasma concentration vs. time data for each of RDEA3170, febuxostat, dapagliflozin, RDEA3170 M1metabolite, and M8. For each of the above analytes individual subject profiles on linear and semi-logarithmic scale will be provided as well as combined subject profiles on linear and semi-logarithmic scale.

For each of the mean plasma concentrations profiles, error bars will be displayed as exp(lgmean +/- sd_lg), where 'lgmean' is the mean of the data on the log scale, and 'sd_lg' is the SD of the data on the log scale. Error bars will be excluded from mean figures on the log scale.

For the mean figures and individual subject profiles, all treatments will be overlaid on the same plot, and seprate plot for each analyte.

Nominal sampling times will be used in the PK concentrations summary tables and mean plasma concentration figures. Actual times from dosing will be used in the individual subject concentration -time profiles.

For mean plots, NQ values will be handled as described for the summary tabulations; for individual plots, plasma concentrations which are NQ before the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing. All plots will be based on the PK analysis set, with the exception of individual plots by patient which will be based on the safety analysis set.

7.5 Statistical Analysis of Pharmacokinetic Drug-Drug Interaction

To assess the potential drug-drug interaction of RDEA3170 and febuxostat given with and without dapagliflozin, the natural log-transformed PK parameters AUCτ, AUClast and Cmax of RDEA3170, febuxostat, M1, and M8 will be separately analyzed using a linear mixed effects ANOVA model, with fixed effects terms for sequence, period, and treatment. In this analysis, subjects nested within sequence will be assumed to be a random effect. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). The point estimate and 90% CI for the difference between treatments (RDEA3170 + febuxostat + dapagliflozin versus RDEA3170 + febuxostat) will be constructed. The point estimate and adjusted 90% CIs will be exponentially back transformed to

provide point and CI estimates for the treatment ratio (RDEA3170 + febuxostat + dapagliflozin versus RDEA3170 + febuxostat). Additionally, for each treatment, back transformed geometric means together with 95% CIs for AUCτ, AUClast and Cmax, for RDEA3170, M1, M8, and febuxostat will be estimated and presented.

To make the treatment comparison the following SAS code maybe used as reference:

```
PROC MIXED data = data ;
CLASS subject treatment period sequence;
MODEL log(var) = treatment period sequence ;
RANDOM  subject(sequence) ;
LSMEAN treatment /  CL ALPHA=0.05 ;
ESTIMATE 'A vs. B' treatment 1 -1  / ALPHA=0.1 CL;
RUN;
```

For all ANOVA PK models described above the geometric mean ratios, their 90% CI, along with the ratios of individual patient values will be plotted to visualize the treatment comparisons.

7.6 Multiplicity

Since there is only one primary hypothesis on pharmacokinetics there is no need for a multiplicity adjustment.

8. Pharmacodynamic Results

8.1 Primary PD Variables

PD urine collection times will be provided including the derived sampling time deviations. From the uric acid concentrations the urinary excretion of uric acid will be derived as follows:

- Amount Excreted = urine acid concentration * weight of produced urine * 1.000

The primary outcome variable, the 'Peak uric acid excretion during the first 8 hours', will be identified as the maximum amount excreted in an interval out of the first 8 hours of collection on Day 7 of treatment. Subject listings will be provided of the raw uric acid concentrations and the derived values for the urinary excretion of uric acid. Among the Day -1 and Day 7 timepoints tabulated below, the peak (maximum) uric acid excretion will be flagged in the data listing.

The maximum change from baseline in the amount excreted in urine for each period will be derived as the difference between the peak amount excreted during Day 7

versus peak amount excreted during Day -1. For each day, only the first 8 hours of sampling will be considered when selecting the peak excretion.

PD Urine Samples

Day -1	**Day 7**	
-24 to -23 hours	**0 to 1 hour**	**First 8 hours of assessment**
-23 to -22 hours	**1 to 2 hours**	
-22 to -21 hours	**2 to 3 hours**	
-21 to -20 hours	**3 to 4 hours**	
-20 to -19 hours	**4 to 5 hours**	
-19 to -18 hours	**5 to 6 hours**	
-18 to -17 hours	**6 to 7 hours**	
-17 to -16 hours	**7 to 8 hours**	
-16 to -15 hours	8 to 9 hours	
-15 to -14 hours	9 to 10 hours	
-14 to -13 hours	10 to 11 hours	
-13 to -12 hours	11 to 12 hours	
-12 to 0 hours*	12 to 24 hours**	

*single 12-hour collection, **Single Pooled Collection

For each subject the derived values for the maximum change from baseline in the amount excreted in urine for each period will be listed.

Descriptive summary tables will be provided for the raw uric acid concentrations, the derived values for the urinary excretion of uric acid, the peak uric acid excretions, as well as the change from baseline of the peak uric acid excretions.

Subject profiles will be used to visualize the derived values for the urinary excretion of uric acid for each treatment over time. Side-by-side box plots will be used to visualize the distribution of the peak uric acid excretions at Day -1 and Day 7 for each treatment.

For the data analysis, only subjects with urine data collected every hour as per the schedule of events will be included.

8.2 Secondary Pharmacodynamic Variables

Subject listings will be provided for the raw serum uric acid concentrations. The serum uric acid results will be analyzed for each period as the Day 7 predose assessment compared to the Day -1 assessment using change from baseline (Day 7 predose versus Day -1). Change from baseline values will be listed for each subject.

Descriptive summary tables will be provided for the raw serum uric acid concentrations as well as the derived change from baseline serum uric acid values looking at Day 7 predose versus Day -1.

Subject profiles will be used to visualize the raw serum uric acid concentrations for each treatment over time.

Other secondary PD outcome variables of interest include change from baseline (Day 7 versus Day -1) for the following clinical laboratory parameters:

- Estimated glomerular filtration rate
- serum levels of creatinine
- urinary levels of creatinine
- cystatin-C
- Blood urea nitrogen
- Serum electrolytes
- Urinary electrolytes
- Urinary pH

All secondary PD variables will be listed for each subject as observed values and changes from baseline. Descriptive summary tables by treatment and day for the observed and change from baseline values will be provided for each secondary PD variable.

8.3 **Statistical Analysis of Pharmacodynamic Variables**

Due to the explorative nature of this study, no adjustment for multiple testing of primary variable and secondary variables will be done.

8.3.1 **Analysis of Primary PD Variable**

The primary PD variable of interest is the peak uric acid excretion in subject urine per hour observed over the first 8 hours. Analysis of the primary variable will be done on log-transformed values. Using the peak uric acid excretion the analysis will consider the maximum change from baseline difference from placebo at day 7 of treatment. The maximum change from baseline is the change from baseline (Day 7 versus Day -1) in the peak uric acid excretion where the baseline is the peak urine excretion observed over the first 8 hours of Day -1. A linear mixed effects analysis of variance (ANOVA) model will be used, with fixed effects terms for sequence, period, and treatment. In this analysis, subjects nested within sequence will be assumed to be a random effect. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). A geometric mean ratio for the change from baseline response will be calculated by taking the anti-logarithm of the difference between treatment means. A 95% CI for each treatment ratio will be obtained by taking the anti-logarithm of the 95% CI endpoints

for each mean difference. Results will be presented as geometric mean ratios for the change from baseline difference from placebo including 95% Cis for the mean ratios, based on Student's t-distribution.

8.3.2 **Analysis of Secondary PD Variables**

The PD variable of secondary interest is the serum uric acid (sUA) levels on Day 7. Analysis of serum UA will be conducted in an equivalent way as urine UA, using log-transformed values and change from baseline (Day -1) to observed serum UA at Day 7. A linear mixed effect model of the change from baseline will be used with fixed effects terms for sequence, period, and treatment. In this analysis, subjects nested within sequence will be assumed to be a random effect. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). Results will be presented in the same way as the results for urine UA: using the geometric mean ratios for the change from baseline difference from placebo including 95% Cis for the mean ratios.

Statistical analysis of the other secondary PD variables will be conducted in an equivalent way as described for serum and urine UA.

8.3.3 **Analysis of Exploratory PD Variables**

8.3.4 **Visualizing the Pharmacodynamic Results**

For all ANOVA PD models described above the geometric mean ratios, their 95% CI, and data permitting the ratio of individual patient values will be plotted to visualize the treatment comparisons.

8.3.5 Analysis of Urinary PD Variables Over a 24 hour Interval

Using the amount excreted in urinary uric acid, derived as:

- Amount Excreted = urine uric acid concentration * weight of produced urine * 1.000

For each 24 hour profile (Day -1 and Day 7), the amount excreted for each individual time point will be summed over each 24 hour period. For each subject this will provide a total value for each period for each day defined as: the 'Total Amount of Uric Acid Excreted in Urine over a 24 hour period (mg/day)'.

Similar calculations will be applied to the other quantitative urinalysis PD parameters: Sodium, Creatinine, Cystatin-C, and pH.

For each of these secondary urine PD parameters, the amount excreted will be listed and the total amount excreted in urine over a 24 hour period will be listed. These total values derived over a 24 hour period will be summarize by treatment and day.

9. Safety Analysis

The analysis of the safety variables will be conducted using the safety analysis set.

9.1 Adverse Events

All verbatim AE terms reported will be coded according to MedDRA, version 20.1.
A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) after the first dose of IMP in Treatment period 1.

Adverse events will be assigned to a treatment based on the start date/time of the AE in relation to dosing in that period; for tabulation purposes the AE will then be assigned to the treatment received in the respective treatment period as follows:

- Screening: all AEs with start date/time before dosing in Treatment period 1.
- Treatment period 1: AEs with start date/time at the time of or after dosing in Treatment period 1 until the time of dosing in Treatment period 2 will be assigned to the treatment received in period 1.
- Treatment period 2: AEs with start date/time at the time of or after dosing in Treatment period 2 until the Follow-up Visit, will be assigned to the treatment received in period 2.

Adverse events with missing start dates/times will be handled as follows:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended

before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing;

- If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;
- If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing, then the date will be imputed as 01Jan or with the date of screening if this is later.

Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

All AE data as captured in CCI will be listed for each subject (Listing 16.2.7.1). All serious AEs (SAEs) will be listed (Listing 16.2.7.2). A listing of all AEs leading to treatment discontinuation will be presented, if applicable (Listing 16.2.7.3).
The following information will be included in the listings: verbatim term, SOC, Preferred Term and lowest level term, start date/time, end date/time, time from most recent dose, causality, action taken, whether the AE was classified as serious and the outcome.

Unless specified otherwise, all adverse event summaries will include the TEAEs only and adverse event summary counts of AEs will be the number of subjects reporting adverse events and not the number of events reported. The number and percentage of subjects with adverse events will be tabulated by body system and preferred term by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of that body system. If the same AE (preferred term) is reported several times for the same subject within a treatment period, it will only appear once for that specified treatment in the summary tables.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related.

As defined in the protocol, within the source data all AEs will be assigned a severity grade of: Mild, Moderate, Severe. For subjects with multiple adverse events of the same preferred term and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity.

A general summary of all treatment-emergent adverse events will show the number and percentage of subjects, as well as the number of events, according to the following categories:

- All treatment emergent adverse events
- Treatment emergent adverse events 'Related to IMP'
- Mild treatment emergent adverse events
- Moderate treatment emergent adverse events
- Severe treatment emergent adverse events
- Treatment emergent adverse events leading to death
- Serious treatment emergent adverse events
- Treatment emergent adverse events leading to early termination

Other summary tables for adverse events will include:

- Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment
- Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, Severity, and Treatment.
- Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Not Related to the IMP' by System Organ Class, Preferred Term, Severity, and Treatment.
- Number and Percentage of Subjects with Treatment Emergent Adverse Events by Preferred Term and Treatment

For tabulations of AEs by treatment; for those subjects assigned to the 'AB' treatment sequence, any AE occurring during the first period and before the Period 2 dose, will be assigned to the 'A' treatment (9 mg RDEA3170 + 80 mg febuxostat + 10 mg dapagliflozin). Any AE occurring after the period 2 dose, will be assigned to the 'B' treatment (9 mg RDEA3170 + 80 mg febuxostat + placebo).

For those subjects assigned to the 'BA' sequence, any AE occurring during the first period and before the period 2 dose, will be assigned to the 'B' treatment (9 mg RDEA3170 + 80 mg febuxostat + placebo). Any AE occurring after the period 2 dose, will be assigned to the 'A' treatment (9 mg RDEA3170 + 80 mg febuxostat + 10 mg dapagliflozin).

If a subject has multiple AEs with the same preferred term but occurring after each dose administration, then one AE will be counted for each treatment. Adverse events that emerge in one treatment period and carry over into the next period will be attributed to only the period in which the AE emerged.

9.2 Diabetic Ketoacidosis (DKA)

All DKA events will be listed for each subject.

9.3 Clinical Safety Laboratory Tests (Hematology, Chemistry, Urinalysis)

9.3.1 Hematology and Chemistry

A by-subject listing of all observed chemistry and hematology laboratory data will be provided. Laboratory results outside the normal range will be flagged. The abnormal values will be flagged with 'L' (low) for values below the lower limit of the laboratory's normal range or 'H' (high) for values above the upper limit of the laboratory's normal range. Abnormal values will be graded as not clinically significant (NCS) or clinically significant (CS). Clinically significant laboratory results will be included in the AE listings.

Change from baseline will be derived and listed for each subject.

The observed values and change from baseline values of all safety laboratory assessments for clinical chemistry and hematology will be summarized using descriptive statistics showing the number of observations (n), mean, median, SD, minimum, and maximum value. Table summaries will be presented by and time point.

Baseline values for all clinical chemistry and hematology parameters will be categorized as being below the normal range (Low), within the normal range (Normal), and above the normal range (High). Shift from baseline tables will present the frequency and percentage of subjects who have observations that are Normal, Low, or High. Shift tables will be presented by time point.

A moving baseline will be used for shift tables and calculation of change from baseline: baseline in each period will be the last laboratory assessment prior to the first dose day 1 of each period.

Only laboratory parameters noted in Section 4.2.2 of this SAP will be tabulated.

Clinical laboratory data will be reported in the units provided by the clinical laboratory and in Système International units in the CSR.

9.3.2 Urinalysis

Urinalysis test results noted in Section 4.2.2 of this SAP will be listed for each subject. All positive findings in the microscopic examination will be listed.

Observations outside the normal range will be flagged. The abnormal quantitative

values will be flagged with 'L' for values below the lower limit of the laboratory's normal range, 'H' for values above the upper limit of the laboratory's normal range, or 'Ab' for abnormal qualitative test results. All original and unscheduled assessments will be listed. Clinically significant laboratory results that are considered by the investigator to be AEs will be included in the AE listings.

9.4 Vital Signs

The observed data for blood pressure (systolic and diastolic), heart rate (pulse), will be listed by subject, treatment, and time point (Listings 16.2.9.1). Change from baseline for blood pressure (systolic and diastolic), heart rate (pulse), will be derived and listed by subject, treatment, and time point (Listing 16.2.9.2).

The baseline for vital signs measurements will be the pre-dose assessment on Day 1 in each treatment period.

For systolic, diastolic blood pressure, and heart rate, the observed and change from baseline data will be summarized by treatment and time point. Summaries will include tables of descriptive statistics showing the number of observations (n), mean, SD, median, minimum, and maximum value.

9.5 12-Lead Safety ECG

Raw quantitative results for: PR interval, QRS interval, RR interval, QT interval, QTcB (corrected QT according to Bazett), QTcF (corrected QT according to Fridericia), and heart rate will be listed for each subject.

The overall qualitative ECG assessment for each subject will be listed by subject, and time point.

9.6 Physical Examination

All abnormal physical examination findings (pre and post-dose assessments) will be listed. Weight collected at pre and post dose time points will be listed.

10. Reporting Output

The tables, listings, figures and any non-descriptive statistical analysis will be produced using [redacted]). The REPORT procedure will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

Tables, listings, and figures will be produced in the order that they appear in the textual sections of the plan.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 8pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins: top, left, right, and bottom: 1 inch). A separate RTF document will be created for each table, figure and listing individually.

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