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Statistical Analysis Plan	
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Effects of Intensive Uric Acid Lowering Therapy with RDEA3170 (Verinurad) and Febuxostat in Patients with Albuminuria

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemistry
BMI	Body Mass Index
CK	Creatinine Kinase
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
CysC	Cystatin C
DBP	Diastolic Blood Pressure
ED	Endothelial Dysfunction
eDISH	Evaluation of drug induced serious hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
Hb	Hemoglobin
HL	Hy's Law
hs-CRP	High-Sensitivity C-Reactive Protein
hs-TropI	High-Sensitivity Troponin I
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
LS	Least Squares
LOCF	Last Observation Carried Forward
MAR	Missing at Random

Abbreviation or special term	Explanation
Max	Maximum
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-Model Repeated Measures
Min	Minimum
MRI	Magnetic Resonance Imaging
PP	Per-protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCr	Serum creatinine
SD	Standard Deviation
SOC	System organ class
sUA	Serum Uric Acid
T2DM	Type 2 Diabetes Mellitus
TBL	Total Bilirubin
TEAE	Treatment-emergent adverse event
UACR	Urinary Albumin to Creatinine Ratio
ULN	Upper Limit of Normal
UALT	Uric Acid Lowering Therapy
WHO DDE	WHO Drug Dictionary Enhanced

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of efficacy and safety of the combination of RDEA3170 and febuxostat over 24 weeks in adult patients with hyperuricemia, albuminuria and Type 2 Diabetes (T2DM) without prior medical history of gout. The version 1 SAP was developed based on Clinical Protocol Version 3.0 amended on May 25th, 2017. This version 2 SAP is developed to include additional exploratory endpoints that will be analyzed based on the outcome of the primary study objective, and to include additional clarifications related to definitions and statistical analysis methods.

2. STUDY DETAILS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objective of this study is to assess the effects of intensive uric acid lowering therapy (UALT) with RDEA3170 and febuxostat on albuminuria.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the effects of intensive UALT with RDEA3170 and febuxostat on kidney function
- To assess the metabolic effects of intensive UALT with RDEA3170 and febuxostat
- To assess the structural and functional effects of intensive UALT with RDEA3170 and febuxostat on the heart and kidney using magnetic resonance imaging
- To assess the effects of intensive UALT with RDEA3170 and febuxostat on biomarkers and parameters related to inflammation, and cardiac health
- To assess the effects of intensive UALT with RDEA3170 and febuxostat on cardiovascular parameters
- To assess plasma exposure of RDEA3170

2.1.3 Safety Objective

The safety objective of this study is to assess the safety and tolerability of intensive UALT with RDEA3170 and febuxostat.

2.1.4 Exploratory Objective

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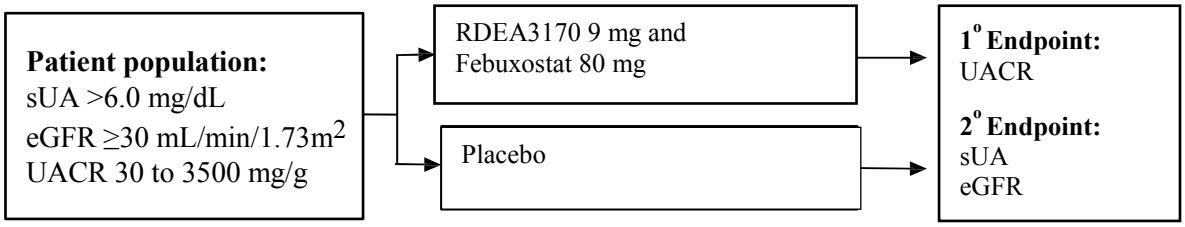
2.2 Study Design

This is a randomized, double-blind, double-dummy, multi-site, placebo-controlled, parallel, independent groups, repeated measures study designed to evaluate signals indicative of clinical outcomes by the combination of RDEA3170 and febuxostat in lowering concentrations of circulating uric acid and thus improving kidney or cardiovascular status of patients with hyperuricemia, albuminuria and T2DM. Patients meeting clinical entry criteria will be randomly assigned to active or placebo treatment for a 24-week period and evaluated at multiple time points for changes in physiological parameters indicative of functional renal and cardiovascular status. Study design is illustrated in Figure 1.

Figure 1. Study Flow Diagram



Abbreviations: eGFR - Estimated glomerular filtration rate; sUA - Serum uric acid; UACR - Urinary albumin to creatinine ratio

Patients will be screened for entry into the study at Visit 1. Those patients consenting to participate, who meet all the inclusion and none of the exclusion criteria (except laboratory test based criteria) will enter the screening phase of the study. Within one week of Visit 1 patients will collect three morning void urinary samples on three separate consecutive days. The samples will be delivered to the study site for proteinuria measurements. Those patients with acceptable urinalysis results will be scheduled to participate in Visit 2. Patients eligible to participate in the study will undergo magnetic resonance imaging prior to randomization and before or on the day of Visit 2. Visit 2 will occur no later than six weeks after Visit 1. Patients will be randomized 1:1 at Visit 2 to receive either a combination of RDEA3170 (9 mg once

daily) and febuxostat (80 mg once daily) or matching placebo. The length of treatment period for patients will be 24 weeks.

Markers of renal function (urinary albumin to creatinine ratio, estimated glomerular filtration rate, serum uric acid, and other markers) will be measured at 2, 4, 12, 24 weeks after randomization, and 4 weeks after the end of treatment. Other endpoints may be assessed less frequently.

Magnetic resonance imaging to examine functional changes in the heart and kidney will be performed at baseline and 24 weeks after randomization. Magnetic resonance imaging of the heart will allow assessment of left ventricular strain and end diastolic volume as sensitive markers of efficacy in pre-symptomatic heart failure frequently present in Type 2 diabetes patients. Blood oxygenation-dependent level magnetic resonance imaging will be utilized to measure kidney oxygenation in addition to the cardiac magnetic resonance imaging parameters described above, in patients undergoing cardiac magnetic resonance imaging.

The CCI, via a reactive hyperemic procedure, provides a direct measurement of endothelial dysfunction via a calibrated measurement of arterial compliance over the entire transmural pressure range of the artery at baseline, 12, and 24 weeks. Reactive hyperemia (also referred to as Flow Mediated Dilatation) is defined as the transient change in vasomotor tone which occurs following a brief period of ischemia (e.g., arterial occlusion). Urine and blood samples will be obtained and stored in a biobank and will be analyzed if there is evidence of efficacy in this study.

2.3 Schedule of Events

The following table provides an overview of the clinical schedule of assessments and events for the screening, treatment and follow-up period in Table 1. Study Plan and elaborated in the Clinical Protocol Sections 4.1 through 4.3.

Table 1. Study Plan

Study Period	Screening period	Treatment period						Follow up period	
Visit	**Enrollment**	**Randomization**	**Treatment**				**End of treatment**	**Follow up**	
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7[b]**	**8**	**CSP Section**
Week	**-6 to-1**	**0**	**1**	**2**	**4**	**12**	**24**	**EoT + 4w**	
Day	**-42 to -7**	**1**	**8**	**15**	**29**	**85**	**169**	**190**	
Window				**±3d**	**±3d**	**±5d**	**-14 to 0 d**	**±7d**	
Written informed consent	X								3.3, 10.4
Demographics	X								4.1
Physical examination, height, and weight	X					X	X		4.1
Pregnancy test	X[c]								4.1
Medical/surgical history	X								4.1
Inclusion / exclusion criteria	X	X							3.1, 3.2
12-lead ECG		X				X	X		5.2.3
Vital signs	X	X	X	X	X	X	X	X	5.2.4
Randomization to study treatment		X							3.5
Treatment dispensed		X			X	X			7.1
Treatment returned and compliance checked					X	X	X		7.5, 7.6
Concomitant medication	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X	X	X	X	X	X	X	X	6
UACR, eGFR, sUA and Serum cystatin-C	X	X	X	X	X	X	X	X	4.2.2, 5.1.1

Table 1. Study Plan (Continued)

Study Period	Screening period	Treatment period						Follow up period	
Visit	**Enrollment**	**Randomization**	**Treatment**				**End of treatment**	**Follow up**	
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7[b]**	**8**	**CSP Section**
Week	**-6 to-1**	**0**	**1**	**2**	**4**	**12**	**24**	**EoT + 4w**	
Day	**-42 to -7**	**1**	**8**	**15**	**29**	**85**	**169**	**190**	
Window			**±3d**	**±3d**	**±3d**	**±5d**	**-14 to 0 d**	**±7d**	
Samples for CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
Blood samples for hematology and additional clinical chemistry	X	X	X	X	X	X	X	X	4.2.2, 5.2.1
Urinalysis	X	X	X	X	X	X	X	X	5.2.1
MRI		X[e]					X[f]		5.1.2
Reactive hyperemia		X[e]				X	X[f]		5.1.4.1
Blood sampling for limited PK			X[g]	X[g]	X[g]	X[g]	X[g]		4.2.2, 5.4.1

a. Patient to deliver 3 morning urine samples to site within 1 week
b. Visit 6 has to be before or on last day of treatment
c. Women of Childbearing Potential only
d. NT-pro-BNP will be assessed at Visit 2, Visit 5 and Visit 6
e. MRI and Reactive hyperemia must be performed before randomization, but not before Visit 1.
f. Post-treatment MRI and Reactive hyperemia to be performed earlier than at 24 weeks if patient is withdrawing and has been treated with study drug for at least 2 months. The MRI and Reactive hyperemia may be performed up to 2 weeks before the End of Treatment Visit (Visit 6), but not later than the last day of treatment.
g. Trough levels; i.e., prior to dosing on the day of the Visit

2.4 Sample Size Consideration

Based on the results of a prior study, the standard deviation (SD) for change in natural logarithmic log-transformed Urinary Albumin to Creatinine Ratio (UACR), ln(UACR), is assumed to be 0.8, based on the AVOID study with aliskiren in 599 patients with albuminuria and T2DM (Parving et al 2008), as well as a study with tenapanor in a patient population similar to that planned for this study (Ardelyx 2015).

A placebo-corrected reduction in UACR of 30%, corresponding to a ratio of 0.7 (-0.357 on natural logarithmic log-scale) was considered a clinically meaningful target for further investigation of RDEA3170 and febuxostat in this patient population.

Twenty-seven (27) patients per arm with available UACR data at baseline and 12 weeks should ensure with 90% probability that the observed placebo-controlled reduction does not differ from the true, unknown reduction with more than this clinically meaningful effect under the assumed SD above. To ensure the availability of 27 evaluable patients per arm, 30 patients per arm will be randomly assigned in a 1:1 fashion.

3. ANALYSIS SETS

The following analysis sets will be used in study summaries and analyses.

3.1.1 Full Analysis Set

All efficacy analyses will be performed on the Full Analysis Set (FAS) following the Intent-To-Treat (ITT) principle. The FAS will consist of all randomized subjects. Summary tables of baseline and demographic data will be calculated based on FAS.

3.1.2 Per-protocol Analysis Set

The per-protocol (PP) analysis set is defined as all subjects in the FAS that are compliant with treatment and have appropriate exposure to study medication for the 12-week treatment period and without any major protocol deviations that may impact primary efficacy analysis. The set of major protocol deviations and the range of treatment compliance percentage required will be finalized prior to database lock. If a subject withdrew from the study prematurely without Week 12 data to assess the primary and/or key secondary endpoints, he or she may be excluded from the PP analysis set. A memo-to-file will be prepared to document the selection of PP analysis set prior to study database lock. The PP analysis set will be used for supportive analyses of the efficacy endpoints. Summary tables of baseline and demographic data will also be calculated based on the PP analysis set.

3.1.3 Pharmacokinetics Analysis Set

The PK analysis set will include all subjects who received febuxostat and RDEA3170 treatment and have at least 1 post-dose plasma concentration measurement of RDEA3170 at a scheduled time point, without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism or excretion of RDEA3170. The PK analysis set will be used to summarize the PK data. Subjects' inclusion/exclusion to the PK analysis set will be documented in the memo-to-file.

3.1.4 Safety Analysis Set

The Safety analysis set will consist of all randomized subjects exposed to study drug and with available post dose safety data. Summary tables of baseline and demographic data will also be presented based on the Safety analysis set if it is different from full analysis set. As the safety evaluation will be based on the as-treated principle, errors in study medication dispense and administration will be evaluated to determine if any adjustments to safety data analysis are needed upon treatment unblinding. The rationale and method will be discussed in the clinical study report (CSR), if any.

If the Safety analysis set contains same subjects as the FAS and there is no dosing error that distinguishes the two populations, statistical analyses and summary tables will be provided for either the FAS or Safety analysis set.

4. PRIMARY AND SECONDARY VARIABLES

4.1 General Consideration

Detailed descriptions of most of the study variables are provided in the clinical study protocol (CSP) and will not be repeated for those variables in the SAP.

4.2 Primary Variable

- Change from baseline in UACR and ln(UACR)

4.3 Secondary Variables

- Change from baseline in sUA levels and ln(sUA)
- Change from baseline in eGFR (calculated using CKD-EPI equation) and ln(eGFR)

CKD-EPI equation is defined as:

$$eGFR = 141 \times \min(sCr/k, 1)^{\alpha} \times \max(sCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

- sCr is serum creatinine (mg/dL)
- k is 0.7 for females and 0.9 for males
- α is -0.329 for females and -0.411 for males
- min indicates the minimum of sCr/k or 1, and
- max indicates the maximum of sCr/k or 1.

- Change from baseline in serum cystatin C (CysC), ln(CysC), serum creatinine (sCr), and ln(sCr)
- Change from baseline in serum high-sensitivity C-reactive protein (hs-CRP), ln(hs-CRP), serum high-sensitivity Troponin I (hs-TropI), and ln(hs-TropI)
- Systolic blood pressure (SBP), diastolic blood pressure (DBP)
- RDEA3170 at trough plasma concentrations
- MRI variables listed in Table 2

Table 2. MRI variables

Variables	Unit
LV global longitudinal strain	%
LV global radial strain	%
LV global circumferential strain	%
LV global diastolic longitudinal strain rate	s^{-1}
LV global systolic longitudinal strain rate	s^{-1}
LV global diastolic radial strain rate	s^{-1}
LV global systolic radial strain rate	s^{-1}
LV global diastolic circumferential strain rate	s^{-1}
LV global systolic circumferential strain rate	s^{-1}
LV end-diastolic volume	mL
LV end-systolic volume	mL
LV stroke volume	mL
LV mass	g
LV mass/end-diastolic volume	g/mL
LVEF	%
Kidney cortex T2*	ms
Kidney medulla T2*	ms

Abbreviations: LV Left ventricle; LVEF Left ventricular ejection fraction
Kidney cortex T2* and Kidney medulla T2* will be analyzed as % change from baseline.

4.4 Exploratory Variables

- CCI .
- Reactive hyperemia parameters: pulse, systolic and diastolic blood pressure and the score for endothelial dysfunction.

Table 3. Exploratory Variables

Urinalysis	Clinical chemistry
Protein	aldosterone
Albumin	Hemoglobin A1c
Creatinine	N-terminal pro b-type natriuretic peptide
CCI	CCI
Uric Acid	CCI
Urinary protein to creatinine ratio	CCI
CCI	

* indicates the biomarkers that will be analyzed and reported in an addendum to the CSR.

4.5 Safety Variables

The incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), changes in vital signs, physical exams, ECG, and the changes in clinical laboratory variables listed in Table 4.

Table 4. Laboratory Safety Variables

Hematology/hemostasis	Clinical chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)

	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Glucose	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase (CK)
	S/P-Blood Urea Nitrogen

5. STUDY SUBJECTS

5.1.1 Subject Disposition, Demographic and Baseline Characteristics

The number and percentage of enrolled subjects that are randomized, randomized and treated with study medication, randomized but not treated with study medication will be summarized by treatment group and overall. Number and percentage of subjects who completed or discontinued from the study (including the reason for discontinuation) will be summarized by treatment group.

Demographic and baseline characteristics will be summarized using descriptive statistics for FAS, PP, and Safety analysis sets. The summary include age, gender, race, ethnicity, height, weight, body mass index (BMI), HbA1C.

5.1.2 Medical History and Surgical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment. Medical history will also be listed.

5.1.3 Randomized Study Medication Compliance

Randomized study medication compliance within the whole 24-week study period will be calculated and summarized using descriptive statistics and by categories (<80%, 80%-120%, >120%) for each treatment group using Safety analysis set. Treatment compliance data will also be listed.

Randomized study medication compliance will be calculated as (total number of tablets taken/ (2*total days on randomized study medication)) * 100%, where total days on randomized study medication will be calculated as (last randomized study medication dose date – first randomized study medication dose date + 1).

Additional treatment compliance for the 12-week treatment period will be computed for the selection of PP analysis set.

5.1.4 Concomitant Medications

The WHO DRUG Dictionary Enhanced (WHO DDE) will be used to categorize the verbatim descriptions of medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

A prior concomitant medication is defined as any medications that start before the first randomized study dose date and continue beyond that date; while a new concomitant medication is defined as any medications the start after the first randomized study dose date, including those started in the follow-up period (Visit 8).

The number and percentage of subjects receiving concomitant medications will be summarized by treatment group and by ATC classification level 4 and trade name for the Safety analysis set.

Any non-study medications that stop before the first randomized study dose date are deemed the pre-treatment medications which will be provided in listing and may be summarized if needed.

5.1.5 Protocol Deviations

Major protocol deviations will be identified prior to study database lock, and will be summarized by treatment group and listed by subjects for FAS. Subjects with major protocol deviations that may impact the primary efficacy endpoint will be excluded from the PP analysis set. Refer to Section 3.1.2 for PP analysis set definition and memo-to-file.

6. STATISTICAL ANALYSIS METHODS

6.1 General Principles

6.1.1 Statistical Notation and Presentation

The continuous variables will be summarized by number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For categorical variables, frequency and percentage in each category will be provided.

Min and max values will be rounded to the precision of the original value. Means, least squares (LS) means, and medians will be rounded to one decimal place greater than the precision of the original value. SDs, standard errors (SEs), and 95% and 90% confidence intervals (CIs) will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values will be presented with four decimal places and values less than 0.0001 will be presented as <0.0001.

All inferential statistical testing will be two-sided and conducted at the 0.10 significance level for between treatment comparisons and 0.05 significant level for the change from baseline assessment. No multiplicity adjustment is planned for this study.

6.1.2 Handling of Multiple Observations

A subject may have multiple scheduled or unscheduled visits that are associated with a protocol defined visit (nominal visit). Each unscheduled visit is assigned a nominal scheduled visit number (e.g., unscheduled visit number 5.1 is associated with protocol scheduled visit 5) in the clinical database. The assessment at the scheduled visit will be used for data summary and analysis. If no scheduled visit assessment exists but at least one unscheduled visit assessment is available within that visit window (e.g., unscheduled visit number 5.1 and 5.2 exist but not the scheduled visit 5), then the latest unscheduled visit within the visit window will be used for data summary and analysis.

All values, scheduled or unscheduled, will be presented in data listings.

6.1.3 Handling of Missing or Partial Dates

In cases of incomplete dates for adverse events (AEs) or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. For example, the imputation rule is to conservatively capture AEs with missing start dates as TEAEs:

- If "day" is the only missing field, impute the "day" as the first randomized dose date if their "month" are the same; otherwise, the first day of the non-missing month.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the first randomized dose date if their "year" are the same; otherwise, January 1 of the non-missing year.
- If "day", "month", and "year" are all missing, to be conservative, the event will be assumed to occur on the same day as the first randomized dose date.

Non-study medications with missing or partial dates will be imputed similarly.

Date imputation will only be used for computational purposes; e.g., treatment-emergent status or identifying concomitant medications. Actual data values as they appear in the clinical database will be shown in the data listings.

6.1.4 Handling of Missing Data

Missing data will be handled by mixed-model repeated measures (MMRM) method based on observed-case data under the assumption of missing at random (MAR). Additional sensitivity analysis to assess the impact of missing data on the estimated treatment effect, e.g. multiple

imputation (MI), last observation carried forward (LOCF) method, or applying the PP analysis set, will be performed. Refer to Section 6.2.1.2 for methodology.

6.1.5 Study Baseline

Baseline is defined as the last non-missing observation obtained prior to administration of the first randomized study medication. For parameters measured at multiple time-points prior to randomization, such as UACR and other urinalysis laboratory tests that were collected from three separate days in the week prior to receiving the first randomized dose, baseline is defined as the mean of the reported measurements from all days prior to randomization. For secondary endpoints CysC and sCr where the data were collected at multiple visits at Screening, Visit 2 (Day 1), or any Unscheduled visits prior to randomization, baseline is defined as the mean of the reported measurements from all visits prior to randomization.

6.2 Analysis Methods

6.2.1 Primary Efficacy Analysis

The primary efficacy endpoint, UACR will be collected per applicable visit. The mean ratio will be reported for each time-point based on the three samples. Patients will receive a urine sample collection kit allowing them to collect the first morning void urine on three days. Ideally the urine samples should be collected 2 days before, the day before and on the day of a study visit to minimize storage and transportation of collected samples. If a patient has forgotten to collect one or more of the samples before a visit, then the samples should be collected on the up to three consecutive days following the visit instead (with exception for the Visit 2 urine samples, which must be collected before treatment is started). In the absence of results from three analyzed samples the UACR for a time-point will be calculated based on the available results.

The analysis of the primary efficacy endpoint UACR will be based on the FAS. UACR and the ratio of UACR from baseline will be summarized using descriptive statistics by treatment and visit. Change from baseline in ln(UACR) will be analyzed using MMRM model with treatment group, visit, interaction of treatment group and visit as fixed effects, ln(UACR) at baseline as a covariate, and subjects as random effects. The least squared (LS) mean change from baseline in ln(UACR) and the 95% CI of the LS mean change will be derived from the model by treatment and by visit. The LS mean difference between the two treatments and the 90% CI of the LS mean difference will be derived from the same MMRM model by visit.

The above LS mean change from baseline and the 95% CI for each treatment at each visit will be exponentiated to yield the geometric LS estimated mean ratio versus baseline and the geometric 95% CI at the original scale of UACR. The LS mean difference between the two treatments and its 90% CI at each visit will also be exponentiated to yield the geometric LS estimated mean ratio between the two treatments at each visit and its geometric 90% CI at the

original scale of UACR. Percent change from baseline will be derived from the LS estimated mean ratio by (exp(LS mean ratio)-1)×100%.

In addition, the primary endpoint will be presented graphically. The first graph will present the LS estimated mean ratio from baseline in UACR with 95% CI over time (visits) by treatment. The second graph will present LS estimated mean ratio (active vs. placebo) with 90% CI over time (visits). The third graph will present the descriptive mean change from baseline with SE in UACR over time (visits) by treatment, with data from the follow-up visit.

6.2.1.1 Supportive Analyses to the Primary Efficacy Analyses

The same MMRM model for the primary endpoint will also be performed for the PP analysis set.

6.2.1.2 Sensitivity Analyses to the Primary Efficacy Analyses

Additional sensitivity analyses will be explored to exam the impact of missing data on the conclusion of the primary endpoint analysis.

The MI method will be based on regression model for monotonic missing pattern under the assumption of MAR, and will be performed for the FAS including data up to Week 24. The intermittent missing data will be imputed for 100 sets using MI Markov chain Monte Carlo (MCMC) procedure. ANCOVA model with treatment as a factor and baseline ln(UACR) as a covariate will be applied to the multiple-imputed change from baseline in ln(UACR) at Week 12 and Week 24. The results of ANCOVA model on the multiple imputed datasets will be combined and summarized.

In addition, the missing UACR at Week 12 and Week 24 will be imputed using LOCF on FAS. The same ANCOVA model will be applied to the imputed change from baseline in ln(UACR) at Week 12 and Week 24.

6.2.2 Secondary Efficacy Analysis

The analysis of the secondary efficacy endpoints will be based on the FAS. The following secondary efficacy endpoints and the change from baseline values will be summarized using descriptive statistics by treatment and visit. Change from baseline in these secondary efficacy endpoints will also be assessed in a similar MMRM model as the one applied to the primary efficacy analysis. Natural log-transformation will be applied to these endpoints to ensure data normality for statistical modeling assumption. eGFR will be analyzed with MMRM model at both logarithm and original scales. All secondary efficacy endpoints will be plotted similarly as the primary efficacy endpoint.

- sUA
- eGFR

- Serum CysC
- sCr
- Serum hs-CRP
- Serum hs-TropI

MRI variables and change from baseline of these endpoints will be summarized by treatment and visit with descriptive statistics on FAS. Additional sensitivity analyses excluding measurements collected after the last treatment date or measurements that could be impacted by a protocol deviation will be conducted. Kidney Cortex T2* and Kidney Medulla T2* will be analyzed using percent change from baseline.

6.2.3 Pharmacokinetics Analysis

The analysis of PK data will be based on the PK analysis set. Plasma concentrations of RDEA3170 will be summarized using descriptive statistics (e.g., n, arithmetic mean, SD, geometric mean, coefficient of variation (CV), minimum, median, maximum) by visit and by baseline renal function (eGFR ≥90, ≥60 to <90, and ≥30 to <60 ml/min/1.73 m^2). The plasma trough concentration will be plotted.

6.2.4 Exploratory Analysis

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6.2.5 Subgroup Analysis

The primary efficacy endpoint will be analyzed with descriptive and inferential statistical models by subgroups of race, sex, age-group category (<65 vs. ≥65 yr), BMI category (<30, ≥30 kg/m^2), and baseline renal function (eGFR ≥90, ≥60 to <90, and ≥30 to <60 ml/min/1.73 m^2). The treatment-by-subgroup interaction will be evaluated using ANCOVA model with observed data at Week 12 and Week 24 on FAS.

6.3 Safety Analysis

The analysis of the safety variables will be based on the Safety analysis set. Safety parameters in the study include TEAEs, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs, ECGs, and physical examinations. Safety variables will be summarized descriptively if continuous variables or by frequency and percentage if categorical variables.

6.3.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 20.0). AEs with onset date/time on or after receiving the first dose of randomized study medication, or pre-existing AEs that increase severity on or after receiving the first dose of randomized study medication will be considered as TEAE. AEs with onset during the follow-up period (Visit 8) will also be considered as TEAE. AEs with onset on or after the date of informed consent but before the date of first dose of blinded study medication will be considered pre-treatment AEs. Pre-treatment AE will be listed separately, but not be summarized.

TEAE will be summarized by treatment group and by:

- SOC and PT
- PT in descending order
- SOC, PT and maximum severity

TEAE leading to study discontinuation, TEAE related to study medication, and SAE will be summarized by treatment group, SOC, and PT.

6.3.2 Extent of Exposure

The duration of study medication administration will be calculated as the date of the last randomized dose in the double-blind treatment period minus the date of first randomized dose, plus 1 day. Extent of exposure will be summarized with descriptive statistics by treatment group.

6.3.3 Gout Flare

The incidence of gout flares be summarized by treatment group.

6.3.4 Hy's Law

Hy's Law (HL): cases where a patient shows elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) evaluation ≥ 3x upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2xULN, where no other reason, other than investigational medicinal product (IMP), can be found to explain the combination of increase.

eDISH (evaluation of drug induced serious hepatotoxicity) plot will be generated with the peak TBL values vs peak ALT values to visualize the Hy's Law cases.

6.3.5 Laboratory Safety Variables

Laboratory safety values (serum chemistry, hematology, and urinalysis) and change from baseline will be summarized with descriptive statistics by visit and by treatment group.

Laboratory data will also be summarized using shift tables by treatment group. These tables compare the baseline value (low, normal, high) vs post-baseline value (low, normal, high). Additionally, percentages of abnormal laboratory tests will be summarized and listed by visit and by treatment group.

Number of subjects with sCr elevation will be summarized as ≥1.5 to < 2.0 × baseline, ≥2.0 to <3.0×baseline or absolute value ≥3.0 mg/dL, ≥3.0 × baseline or absolute value ≥ 4.0 mg/dL by treatment group.

6.3.6 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate,) values and changes from baseline will be summarized by visit and treatment group using descriptive statistics.

6.3.7 ECG

The overall assessment of the ECG (i.e., normal, abnormal but not clinically significant, abnormal and clinically significant) will be summarized using shift table by treatment group. All data will be provided in listing as well.

6.3.8 Physical Examinations

Clinically significant post-baseline physical exam findings will be reported as AEs. Physical examination data will be listed by subject.

7. REFERENCES

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