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## Clinical Study Protocol

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### Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

<b>PAREXEL Study No.:</b>	CC1
<b>Sponsor Study Code:</b>	D5495C00001
<b>Study Type:</b>	Drug-Drug Interaction
<b>Victim Drugs:</b>	RDEA3170 and Febuxostat
<b>Perpetrator Drug:</b>	Dapagliflozin
<b>Pharmacological Class:</b>	RDEA3170: URAT1 Inhibitor Febuxostat: Xanthine Oxidase Inhibitor; Dapagliflozin: SGLT2 Inhibitor
<b>Development Phase:</b>	Phase 2
<b>Sponsor:</b>	AstraZeneca AB 151 85 Södertälje Sweden
<b>Study Centers:</b>	PAREXEL Early Phase Clinical Unit Baltimore 3001 S. Hanover St. Baltimore, MD 21225, United States of America PAREXEL Early Phase Clinical Unit-Los Angeles 1560 Chevy Chase Drive, Suite 140 Glendale, CA 91206, United States of America
<b>Original Protocol:</b>	Final 1.0, 05 September 2017
<b>Amendment No. 1</b>	Final 1.0, 02 October 2017
<b>Amendment No. 2</b>	Final 1.0, 02 May 2018
<b>Amendment No. 3</b>	Final 1.0, 10 May 2018

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

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#### Confidentiality Statement

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## PROTOCOL AMENDMENTS

### Clinical Study Protocol Amendment No. 1, Final 1.0, dated 02 October 2017

The following changes were made to the original Clinical Study Protocol, Final 1.0, dated 05 September 2017.

1. Administrative details were updated to include laboratories for exploratory samples and pharmacogenetic samples.
2. Time points were clarified for controlled meals and fluid intake, and safety procedures (vital signs, 12-lead ECGs and safety laboratory investigations) in the Schedule of Assessments (Table 1). Restrictions regarding meals and fluid intake were aligned accordingly.
3. Intervals of urine collections were clarified in the footnotes of the Schedule of Assessments (Table 1).
4. The randomization day was changed from Day -2 (Treatment Period 1) to Day -1 (Treatment Period 1)
5. The definition and confirmation of post-menopausal status were clarified. Where there is uncertainty regarding post-menopausal status, an option was added to include a post-menopausal female after discussion between the PI and the Medical Monitor.
6. It was added that male patients participating in this study are not required to apply contraception.
7. For fasting plasma glucose, a separate blood sample was added and the total blood volume to be collected during the study per patient was updated.
8. The format of unique enrolment numbers was adjusted to differentiate between the Baltimore and Los Angeles study sites.
9. ECGs in this study will be recorded using Cardiosoft in COI
10. It was included that a Statistical Analysis Plan (SAP) will be written for this study.
11. It was clarified that other study team members may perform certain procedures as designee of the PI.
12. Typographical errors were corrected.

## Clinical Study Protocol Amendment No. 2, Final 1.0, dated 02 May 2018

The changes listed below were made to the Clinical Study Protocol Amendment No. 1, Final 1.0, dated 02 October 2017, to include 8 additional patients.

During the Blind Data Review Meeting (BDRM), the unblinded data were reviewed and the following patients from site [PPD] were identified as invalid for purposes of analysis of the primary endpoint: [PPD]

[PPD] Based on these results, it was decided to include an additional 8 patients to ensure an adequate sample size (at least 20 evaluable patients) to evaluate the effects of intensive uric acid (UA) lowering with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA.

1. The protocol was updated to include 8 additional patients to ensure a minimum of 20 evaluable patients with complete data as per protocol are included in the pharmacodynamics analyses set for statistical analyses, see Section 7.1, Section 8.9.2 and Section 11.4.
2. The Sponsor's Biostatistician has been changed from [PPD] to [PPD] see Section 4 and Section 16.2.
3. Inclusion criterion no. 4 and exclusion criterion no. 19 were updated to clarify that the criteria is only applicable to assessments performed at the Screening Visit and Day -2, not at each admission to the Clinical Unit, see Section 7.5.1 and Section 7.5.2.
4. The protocol has been updated to clarify that the peak UA excretion will be the maximum UA excreted as measured in mg, in the hourly urine samples during the first 8 hours at baseline (Day -1) and on Day 7 during Treatment Period 1 and Treatment Period 2., see Section 6.1.1 and Section 11.9.1.
5. General inconsistencies and typographical errors have been corrected throughout the protocol.
6. The synopsis has been updated to reflect changes made in the protocol, see [PROTOCOL SYNOPSIS](#).

### **Clinical Study Protocol Amendment No. 3, Final 1.0, dated 10 May 2018**

Based on the emerging data, it was decided to adjust the number of additional patients from 8 to 12 to ensure an adequate sample size to evaluate the effects of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA.

1. The protocol was updated to include 12 additional patients to ensure a minimum of 20 evaluable patients with complete data as per protocol are included in the pharmacodynamics analyses set for statistical analyses, see [Section 7.1](#), [Section 8.9.2](#) and [Section 11.4](#).
2. The synopsis has been updated to reflect changes made in the protocol, see [PROTOCOL SYNOPSIS](#).

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## PROTOCOL SYNOPSIS

### Title of the Study

Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

### Principal Investigator (PI)

PPD

### Study Centers

This study will be conducted at 2 study centers.

PAREXEL Early Phase Clinical Unit-Los Angeles  
1560 Chevy Chase Drive, Suite 140  
Glendale, CA 91206  
United States of America (USA)

PAREXEL Early Phase Clinical Unit Baltimore  
Harbor Hospital  
3001 South Hanover St.  
Baltimore, MD 21225  
USA

### Study Rationale

RDEA3170 is a novel uric acid transporter 1 (URAT1) inhibitor in Phase 2 development. RDEA3170 combined with febuxostat has been proven to be a safe and effective therapy to lower serum uric acid (sUA) and manage patients with recurrent gout and hyperuricemia (in Japan) in Phase 2 studies. Inhibition of URAT1 results in increased renal excretion of uric acid (UA). In order to avoid high peak excretion rates, RDEA3170 should be used in combination with a xanthine oxidase inhibitor (XOI), such as febuxostat, as RDEA3170 may deliver the most potent UA lowering effect via renal excretion reported for any treatment.

Dapagliflozin is a stable, reversible, highly selective and orally active inhibitor of human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption in the kidney. Results from non-clinical- and clinical studies have shown that dapagliflozin can be used to promote urinary excretion of glucose as a safe and effective method of reducing blood glucose levels.

Given the recent data from the EMPA-REG trial, SGLT2 inhibitors are expected to be commonly used in the proposed target patient population for the RDEA3170 + febuxostat combination (chronic kidney disease and/or heart failure). Thus, the objective of the study is to explore whether intensive UA lowering therapy with febuxostat and RDEA3170 can be safely combined with dapagliflozin, and if the sUA lowering effects would be additive.

### Number of Patients Planned

Thirty-six patients will be randomized to ensure at least 20 evaluable patients at the end of the last treatment period.

### Study Period

Estimated date of first patient enrolled: October 2017

Estimated date of last patient completed: July 2018

### Study Objectives

#### *Primary Objective:*

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

#### *Primary Objective Outcome Measure*

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

#### *Secondary Objectives:*

- To assess the effects of intensive UA lowering therapy with RDEA3170, febuxostat and dapagliflozin on sUA levels.

- To assess the pharmacokinetics (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.

*Secondary Objectives Outcome Measures*

- Serum UA 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, blood urea nitrogen, serum and urinary electrolytes, urinary pH. Changes in vital signs. Rates of adverse events (AEs) and serious adverse events (SAEs).

COI [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**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. Thirty-six, asymptomatic hyperuricemic patients aged 18 to 65 years (inclusive) will be enrolled into this study at 2 study centers. Twenty-four patients have been enrolled and completed the study to date. Due to inadequate urine sampling, it was decided to include 12 additional patients to ensure an adequate sample size (at least 20 evaluable patients) to evaluate the effects of intensive UA lowering with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA. 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 will comprise of:

- A screening period of maximum 28 days;
- 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 Investigational Medicinal Product (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 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.

### Expected Duration of the Study

Each patient will be involved in the study for 8 to 11 weeks.

### Targeted Study Population

This study will be conducted in male and female asymptomatic hyperuricemic patients aged 18 to 65 years.

### Investigational Medicinal Products

Investigational product	Dosage form and strength	Provider
RDEA3170	9 mg capsules for oral administration	AstraZeneca
Febuxostat	80 mg tablets for oral administration	PAREXEL
Dapagliflozin	10 mg tablets for oral administration	AstraZeneca
Dapagliflozin matched placebo	Placebo	AstraZeneca

### Outcome Endpoints

#### Pharmacodynamic Endpoints:

Where possible, the following pharmacodynamic (PD) variables will be assessed.

- Uric acid excretion in urine per hour (UUA)
- Serum UA levels on Day 7 (after 7 days of treatment).

#### Pharmacokinetic Endpoints:

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

- Primary PK parameters: AUC<sub>τ</sub>, AUC<sub>last</sub>, C<sub>max</sub>
- Secondary PK parameters: t<sub>max</sub>, t<sub>last</sub>

Additional PK parameters may be determined where appropriate.

#### Safety and Tolerability Endpoints:

Safety and tolerability variables will include:

- Adverse events
- Events of diabetic ketoacidosis
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate)
- Electrocardiograms (ECGs)
- Physical examination
- Weight
- Laboratory assessments (hematology, clinical chemistry and urinalysis)

Viral serology and drugs of abuse and alcohol will be assessed for eligibility. Follicle-stimulating hormone (FSH) (post-menopausal females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

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[REDACTED]  
[REDACTED]  
[REDACTED]

- [REDACTED]

## Statistical Methods

### ***Presentation and Analysis of Pharmacodynamic Data:***

A listing of PD blood sample and urine collection times, as well as derived sampling time deviations will be provided. Serum and urine concentrations will be summarized by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation (CV), arithmetic mean, arithmetic standard deviation (SD), median, minimum and maximum.

Analysis of the primary variable, maximum UUA, as well as the secondary variable sUA at 7 days will be done.

Analysis of the primary variable and secondary variable sUA will be done on log-transformed values, looking at changes at day 7 of treatment (Day 7) from maximum baseline excretion. A mixed effects Analysis of Variance (ANOVA) model, correcting for treatment (dapagliflozin/placebo) and sequence (dapagliflozin-placebo or placebo-dapagliflozin) as fixed effects as well as patient within sequence as random effect, will be used.

No adjustment for multiplicity will be done for secondary variables, due to the explorative nature of the study.

In these analyses, an adjustment for multiple comparisons will not be considered.

For all ANOVA models described above the geometric mean ratios, their 95% confidence interval (CI), along with the ratios of individual patient values will be plotted to visualize the treatment comparisons.

### ***Presentation and Analysis of Pharmacokinetic Data:***

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized by treatment and analyte using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, geometric +SD, geometric -SD arithmetic mean, arithmetic SD, median, minimum and maximum. For tmax and tlast, only n, median, minimum and maximum will be presented.

Plasma concentrations of RDEA3170, M1, M8, febuxostat and dapagliflozin will be presented descriptively by analyte, study day/treatment and time point, using both summary tables and figures as well as individual plots of plasma concentration vs. time and day per IMP. Derived PK parameters will be presented descriptively by IMP and study day/treatment.

To assess the potential drug-drug interaction between RDEA3170 and febuxostat given with and without dapagliflozin, the natural log-transformed PK parameters Cmax, AUC $\tau$  and AUClast of RDEA3170, M1, M8 and febuxostat will be separately analyzed using a mixed effects ANOVA model, fitting a fixed effect for treatment and random effect for patient.

For all ANOVA models described above the geometric mean ratios, their 95% CI, along with the ratios of individual patient values will be plotted to visualize the treatment comparisons.

### ***Presentation and Analysis of Safety and Eligibility Data:***

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables will be based on the safety analysis set.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs, will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory and in Système International units in the CSR.

Out-of-range values for safety laboratory, vital signs and ECG will be flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (e.g., AZ, program or laboratory ranges).



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### **Determination of Sample Size**

Basis for this sample size calculation is the study RDEA3170-204. Baseline (as well as Day 7) UUA data are highly skewed and hence log-transformation is applied.

Based on the RDEA3170-204 study, we assume that the within patient SD for the between treatment difference in UUA (comparing within patient changes on log-scale from baseline to Day 7 for the respective treatments) is 0.32.

A study with 10 patients completing each sequence of treatments (dapagliflozin-placebo or placebo-dapagliflozin) will then (under the assumed SD above) estimate the true, unknown, mean ratio for dapagliflozin/placebo with a precision of 16.6% as half-width of the 95% CI.

Thus, 24 patients in total were randomized to ensure 20 ( $2 \times 10$ ) patients complete the study (12 randomized patients per sequence).

Twenty patients completing their treatment sequence, is based on previous experience of studies investigating relative bioavailability in presence of concomitant treatments, seen as a suitable sample size. As based on previous experience of studies investigating relative bioavailability in presence of concomitant treatments, 12 patients completing each treatment sequence is considered a suitable sample size.

### ***Interim Analysis of Sample Size and Power of the Statistical Test***

During the Blind Data Review Meeting (BDRM), the unblinded data were reviewed and P patients from site PPD were identified as invalid for purposes of analysis of the primary endpoint.

Based on these results, it was decided to include an additional 12 patients to ensure an adequate sample size to evaluate the effects of intensive UA lowering with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA. This will allow for 36 evaluable patients overall; of these it is expected that at least 20 patients will provide evaluable data for the primary endpoint.

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## 2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Special Term	Explanation
AE	Adverse event (see definition in Section 12.1.1)
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
AUC <sub>last</sub>	Area under plasma concentration time curve from time zero to the time of last measurable concentration
AUC <sub>τ</sub>	Area under plasma concentration time curve over a dosing interval (24 hours)
CCI	
BDRM	Blind Data Review Meeting
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
CCI	
	management system
C <sub>max</sub>	Maximum observed plasma concentration
CO <sub>2</sub>	Carbon dioxide
CrCL	Creatinine Clearance
CRF	Case report form
CRO	Contract research organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
CYP	Cytochrome P450
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DGR	Dangerous Goods Regulations

<b>Abbreviation or Special Term</b>	<b>Explanation</b>
DILI	Drug Induced Liver Injury
DKA	Diabetic ketoacidosis
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
ECG	Electrocardiogram
EDV	Early discontinuation visit
eGFR	Estimated glomerular filtration rate
FAS	Full Safety Analysis Set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCG	Human beta chorionic gonadotrophin
HCT	Hematocrit
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

<b>Abbreviation or Special Term</b>	<b>Explanation</b>
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
ms	milliseconds
n	Number of patients
NC	Not Calculated
ND	Not determined
NR	No result
NQ	Non-quantifiable
OAE	Other significant adverse events
OTC	Over-the-counter
PD	Pharmacodynamics
PDS	Protocol deviation specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
QP	Qualified Person
R&D	Research and Development
RBC	Red blood cell
RCTC	Rheumatology Common Toxicity Criteria
RNA	Ribonucleic acid
SAE	Serious adverse event (see definition in Section 12.1.2).
SAP	Statistical Analysis Plan
sCr	Serum creatinine
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SOC	System Organ Class
SOP	Standard operating procedure
sUA	Serum uric acid
SUSAR	Suspected unexpected serious adverse reaction
TCA	Tricyclic anti-depressant
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures and Listings

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<b>Abbreviation or Special Term</b>	<b>Explanation</b>
t <sub>1/2</sub>	Apparent terminal half-life
t <sub>last</sub>	Time of last measurable concentration
t <sub>max</sub>	Time to reach maximum observed plasma concentration
UA	Uric acid
UGT	Uridine 5'-disphospho-glucoronsyltransferase
ULN	Upper limit of normal
ULT	Uric acid-lowering therapy
URAT1	Uric acid transporter 1
USA	United States of America
USPI	United States Package Insert
UUA	Uric acid excretion in urine per hour
WAD	Windows Allowance Document
WBC	White blood cell
XO	Xanthine oxidase
XOI	Xanthine oxidase inhibitor

---

### **3. ETHICAL AND REGULATORY REQUIREMENTS**

#### **3.1. Ethical Conduct of the Study**

The clinical study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

#### **3.2. Patient Data Protection**

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The Principal Investigator (PI) and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be specified in outputs and other documents containing patient data by their patient number, not by name. Documents that identify the patient (e.g., signed ICF) will be maintained in confidence by the PI and members of his/her research team.

Study data will be stored in accordance with local and global data protection laws.

#### **3.3. Ethics and Regulatory Review**

The study will be submitted to the national Regulatory Authority, Food and Drug Administration (FDA), for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Institutional Review Board (IRB) for ethical review and approval by the PI in accordance with local procedures.

PAREXEL will provide the IRB and PI with safety updates/reports according to local requirements, including Suspected Unexpected Adverse Reactions (SUSARs), where relevant.

AstraZeneca will provide the Regulatory Authority with safety updates/reports according to local requirements, including SUSARs, where relevant.

The PI is also responsible for providing IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the Investigational Medicinal Product (IMP). AstraZeneca will provide this information to the PI so he/she can meet these reporting requirements.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the clinical study. Information on how participants will be compensated is contained in the ICF.

### **3.4. Insurance**

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

### **3.5. Informed Consent**

The patients shall be informed of the nature, significance, implications and risks of the clinical study, and informed consent will be freely given and evidenced in writing, dated and signed or otherwise marked, by the patient as evidence to indicate his/her free informed consent, before the start of the clinical study.

The nature of the informed consent will comply with the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation which ever offers the greater patient protection.

### **3.6. Changes to the Protocol and Informed Consent Document**

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol (CSP), then these changes will be documented in a CSP amendment and where required in a new version of the CSP.

If a CSP amendment requires a change to the ICF, the IRB should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

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Pharmacogenetic Samples:

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[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] [REDACTED]  
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AstraZeneca Patient Safety Data Entry Site

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[REDACTED]

A list and contact details of Investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating Investigators will be provided in the Clinical Study Report (CSR).

## 5. INTRODUCTION

### 5.1. Background Information

Purines are essential building blocks in all living organisms as adenosine triphosphate (ATP), the cellular carrier of energy, is a purine, and purines and pyrimidines make up deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), the bearers of genetic information. Metabolism of endogenous and ingested purines results in production of uric acid (UA). In contrast to many lower species, the human body is unable to metabolize UA further, and therefore eliminates urate through excretion. Uric acid is excreted primarily through the kidneys, but UA is also eliminated through excretion into the intestines, where UA can be degraded by the uricase activity in the intestinal microbiome to carbon dioxide (CO<sub>2</sub>) and allantoin. The level of urate in the circulation is determined by the balance between production and elimination. At steady state, production and elimination are similar [1].

Uric acid is the protonated form of urate and can also be found in the human body. At physiological pH ≈1% of the circulating urate is in the form of UA, but in urine the fraction of excreted urate present in the form of UA increases with lower urinary pH.

Uric acid has proven and emerging roles in human disease. Hyperuricemia (elevated levels of UA in the circulation) is a prerequisite for development of gout, an inflammatory arthritis caused by deposition of monosodium UA crystals in joints. Gout occurs in patients with serum UA > 6.8 mg/dL, which is the solubility limit of monosodium UA. The prevalence of gout increases with higher serum UA (sUA) [2]. Gout affects approximately 4% of the adult United States of America (USA) population [3]. The prevalence of hyperuricemia is higher than the prevalence of gout, as not all subjects with hyperuricemia develop gout.

Hyperuricemia without clinical symptoms (e.g., gouty attack [acute gouty arthritis], gouty tophus, renal disorder) is called “asymptomatic hyperuricemia” [4]. In the USA and Europe, asymptomatic hyperuricemia is not an approved indication for UA-lowering therapy (ULT). The Japanese and Chinese treatment guidelines propose that ULT should be considered for patients with asymptomatic hyperuricemia with a sUA level of ≥ 8.0 mg/dL with complications (e.g., urinary calculus, renal disease and hypertension) and ≥ 9.0 mg/dL without complications [5, 6].

Evidence shows independent associations between elevated sUA and the risk of hypertension, myocardial infarction, heart failure, chronic kidney disease, type 2 diabetes and metabolic syndrome, including obesity [7, 8, 9, 10, 11]. Gout is associated with an increased risk of all

cause death, as well as cardiovascular death [12, 13, 14, 15]. However, the causal relationship between elevated sUA and the aforementioned diseases and outcomes remains to be proven.

Pharmacological modification of the levels of UA is possible through multiple mechanisms. Inhibition of xanthine oxidase (XO), a key enzyme in the transformation of purines into UA, lowers sUA by decreasing production. The prototypical XO inhibitor (XOI) allopurinol, has been the cornerstone of the clinical management of gout and conditions associated with hyperuricemia for several decades. More recently, febuxostat, another XOI, has been approved for the treatment of patients with gout. Xanthine oxidase inhibitor therapy is recommended as a first-line pharmacologic ULT approach in gout.

Inhibition of UA transporter 1 (URAT1), a key transporter responsible for reabsorption of UA from the primary urine in the proximal tubule, lowers sUA by increasing renal excretion. Increased renal excretion of UA is mediated by uricosuric agents. Probenecid is recommended either as an alternative or as an addition to XOI, whereas Lesinurad (Zurampic<sup>®</sup>), is a URAT1 inhibitor approved by the FDA in 2015 for treatment of gout in combination with a XOI.

Combination therapy with RDEA3170, a URAT1 inhibitor, and a XOI such as febuxostat targets both excretion and production of UA, providing a dual mechanism approach that would effectively lower sUA and thereby potentially enables more patients to achieve and maintain target treatment goals to control their disease [16, 17, 18] and establish a potential causal relation between sUA lowering therapy and chronic kidney and cardiovascular disease.

Initial Phase 1 development of RDEA3170 explored multiple formulations to identify an agent with an optimized pharmacokinetic (PK) and food-effect profile. Initial studies explored RDEA3170 given as monotherapy. Although these studies demonstrated that RDEA3170 resulted in effective lowering of UA, a higher rate of serum creatinine (sCr) elevations was observed with no clear relationship to dose.

Based on an in-depth evaluation of sCr elevations in conjunction with the known mechanism of action of RDEA3170, the Sponsor concluded that the likely basis for the increased sCr levels following treatment with RDEA3170 was oversaturation of UA in the urine. Results from 3 Phase 2a studies (Studies 204, 205 and 206) and a Phase 1b study (Study 107) demonstrated an enhanced sUA-lowering effect of RDEA3170 in combination with an XOI, and an improved UA excretion profile. This dual-mechanism approach may result in a lower incidence of renal-related adverse events (AEs), thereby improving safety.

## **5.2. RDEA3170**

RDEA3170 (also known as verinurad) is a potent and specific URAT1 inhibitor. Uric acid transporter 1 is responsible for most of the reabsorption of filtered UA from the renal tubular lumen. By inhibiting URAT1 RDEA3170 increases UA excretion and thereby lowers sUA.

### **5.2.1. Pre-Clinical Findings**

A series of pre-clinical studies were performed with results supporting clinical development of RDEA3170. Overall, RDEA3170 was well tolerated in the chronic rat and dog studies at high multiples of the exposures achieved at the highest doses tested in man. No additive or new toxicity was observed in 13-week combination studies of RDEA3170 and febuxostat or allopurinol in rats.

RDEA3170 was not genotoxic based on results from the *in vitro* and *in vivo* batteries of genotoxicity tests. RDEA3170 is not considered a reproductive hazard based on the results of reproductive toxicology studies and the lack of effects on reproductive organs in the 6- and 9-month studies in rats and dogs, respectively.

Further information on pre-clinical findings is available in the Investigator's Brochure [19].

### **5.2.2. Clinical Studies**

RDEA3170 has been studied in healthy volunteers, subjects with gout, asymptomatic hyperuricaemia and renally impaired patients. In total 763 subjects have received RDEA3170 in 10 Phase 1 and 5 Phase 2 clinical studies (293 healthy subjects, 31 subjects with renal impairment, and 439 subjects with gout or asymptomatic hyperuricemia). The maximum duration of exposure was 183 days for RDEA3170 monotherapy and 21 days for RDEA3170 in combination with allopurinol or febuxostat.

#### **5.2.2.1. Safety Results**

##### **Healthy Subjects**

Safety was assessed in a pooled analysis of the completed Phase 1 studies in healthy subjects. Collectively, these studies enrolled 293 male subjects treated at the following RDEA3170 dose ranges: 53 received < 5 mg; 131 received 5 to < 10 mg; 131 received 10 to 15 mg, and 30 received > 15 mg. Overall, 94.5% completed the planned treatment.

The incidence of AEs was similar among the pooled RDEA3170 groups and pooled placebo groups. There were no serious adverse events (SAEs). Overall, 86 subjects (29.4%) experienced AEs. The most common AE was headache, which occurred in 12 subjects (4.1%). There was no apparent relationship between the incidence of these AEs and RDEA3170 dose. Three subjects withdrew from the study due to AEs: 2 subjects in Study 103 who had received RDEA3170 5 mg (dehydration and influenza, respectively) and 1 subject in Study 104 who had received RDEA3170 15 mg and experienced urticaria.

### **Subjects with Gout or Asymptomatic Hyperuricemia**

In Study 204, subjects received RDEA3170 in combination with febuxostat. No deaths, other SAEs or AEs leading to study withdrawal were reported in the study. Adverse events were reported for 21% of pooled subjects receiving RDEA3170 and febuxostat combination treatment, and in 4.9% and 15.7% of subjects receiving febuxostat 40 mg and 80 mg doses alone, respectively. No AEs of Grade 4 were reported, and a single Grade 3 AE (hypertriglyceridemia) was reported for 1 subject receiving febuxostat 80 mg alone. The only AEs reported in more than 1 subject were pain in extremity (3 subjects), and dyspepsia, musculoskeletal pain, and headache, (2 subjects each). Of note, a Grade 1 AE of hepatic enzyme increased occurred during treatment with febuxostat 40 mg alone and cases of Grade 1 hepatitis and hepatitis acute occurred with febuxostat 80 mg alone. No sCr elevations were reported as AEs.

In Study 205, male Japanese subjects received RDEA3170 in combination with febuxostat. No deaths, other SAEs, withdrawals due to AEs or other significant AEs were reported during the study. A total of 6 AEs were reported in 5 subjects: 1 subject in Cohort 1 (vomiting and influenza), 2 subjects in Cohort 2 (influenza and myalgia), 1 subject in Cohort 3 (eczema eyelids), and 1 subject in Cohort 6 (diarrhea). All AEs were Rheumatology Common Toxicity Criteria (RCTC) Grade 1 or 2 in severity, except for the myalgia (Grade 3), which was accompanied by increased creatine kinase and related to physical activity.

Further information on safety findings is available in the Investigator's Brochure [19].

#### **5.2.2.2. Clinical Efficacy**

Dose-dependent decreases in sUA levels were observed following once daily oral doses of RDEA3170 from 5 to 15 mg under fed conditions for 10 days. Maximum reduction in sUA levels occurred within 24 hours after the Day 10 dose. The observed changes in urinary excretion and renal handling of UA were consistent with changes in sUA values.

When RDEA3170 was co-administered with febuxostat or allopurinol in healthy subjects, the combination treatment resulted in enhanced sUA lowering compared with either single agent administered alone, while the 24-hour urinary UA amounts remained below baseline, indicative of a reduced risk of creatinine elevations compared with RDEA3170 monotherapy.

The sUA-lowering efficacy of RDEA3170 in combination with a XOI in patients with gout was demonstrated in 3 Phase 2a studies. In all 3 studies the efficacy was higher when RDEA3170 was administered in combination with the XOI than for the XOI alone.

Further information on clinical efficacy findings is available in the Investigator's Brochure [19].

### **5.2.2.3. Pharmacokinetics**

RDEA3170 undergoes oxidative metabolism by cytochrome P450 (CYP)3A to form an N-oxide metabolite (M4) that undergoes sequential metabolism to form an acylglucuronide (M8) by uridine 5'-disphospho-glucuronosyltransferases (UGTs). Additionally, RDEA3170 can undergo direct glucuronidation by UGTs to form the acylglucuronide (M1), which may undergo further oxidation by CYP2C8 to form M8. Most of RDEA3170 is eliminated as M1 and M8.

Plasma apparent terminal half-life ( $t_{1/2}$ ) of RDEA3170 was approximately 15 hours. The metabolites were formed quickly after absorption of RDEA3170 (median  $t_{max}$  0.5 to 0.75 hours) with  $t_{1/2}$  values of approximately 13 and 18 hours, respectively.

Further information on PK findings is available in the Investigator's Brochure [19].

## **5.3. Febuxostat**

Febuxostat is a XOI indicated for the chronic management of hyperuricemia in patients with gout. Febuxostat achieves its therapeutic effect by decreasing sUA. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations. [20]

### **5.3.1. Safety Clinical Trials Experience**

A total of 2757 subjects with hyperuricemia and gout were treated with febuxostat 40 mg or 80 mg daily in clinical studies. For febuxostat 40 mg, 559 patients were treated for  $\geq 6$  months. For febuxostat 80 mg, 1377 subjects were treated for  $\geq 6$  months, 674 patients were treated for  $\geq 1$  year and 515 patients were treated for  $\geq 2$  years. [20]



The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of febuxostat 40 mg, 1.2% of febuxostat 80 mg, and in 0.9% of allopurinol-treated subjects.

The most common AEs reported as related to the study drug at a rate of at least 1% in febuxostat treatment groups and at least 0.5% greater than placebo were liver function abnormalities, nausea, arthralgia and rash.

Further information is available in the highlights of prescribing information - ULORIC (febuxostat) [20].

### **5.3.2. Pharmacodynamics**

In healthy subjects, febuxostat resulted in a dose dependent decrease in 24-hour mean sUA concentrations, and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary UA excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean sUA concentrations was between 40% to 55% at the exposure levels of 40 mg and 80 mg daily doses. [20]

Further information is available in the highlights of prescribing information - ULORIC (febuxostat) [20].

### **5.3.3. Pharmacokinetics**

In healthy subjects, maximum plasma concentrations (C<sub>max</sub>) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. Febuxostat has an t<sub>1/2</sub> of approximately 5 to 8 hours. Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. [20]

Febuxostat is extensively metabolized by both conjugation via UGT enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via CYP enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. Febuxostat is eliminated by both hepatic and renal pathways [20]

Further information is available in the highlights of prescribing information - ULORIC (febuxostat) [20].

## **5.4. Dapagliflozin**

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [21]

### **5.4.1. Safety Clinical Trials Experience**

The AEs below reflect the data of 2338 patients to exposed to dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), dapagliflozin 5 mg (N=1145), or dapagliflozin 10 mg (N=1193) once daily.

Adverse events that were not present occurred more commonly on dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg. The following AEs occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg, female genital mycotic infections, nasopharyngitis, urinary tract infections, male genital mycotic infections, nausea, influenza, dyslipidemia, constipation, discomfort with urination and pain in extremity.

Further information is available in the highlights of prescribing information - FARXIGA (dapagliflozin) [21].

### **5.4.2. Pharmacodynamics**

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Dapagliflozin dose of 5 to 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 g of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. [21]

Further information is available in the highlights of prescribing information - FARXIGA (dapagliflozin) [21].

### **5.4.3. Pharmacokinetics**

Following oral administration of dapagliflozin, C<sub>max</sub> is usually attained within 2 hours under fasting state. The C<sub>max</sub> and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. [21]

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. [21]

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. The mean plasma  $t_{1/2}$  for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg. [21]

### 5.5. Study Rationale

RDEA3170 is a novel URAT1 inhibitor in Phase 2 development. RDEA3170 combined with febuxostat has been proven to be a safe and efficacious therapy to lower sUA and manage patients with recurrent gout and hyperuricemia (in Japan) in Phase 2 studies. Inhibition of URAT1 results in increased renal excretion of urate. To avoid high peak excretion rates, RDEA3170 should be used in combination with a XO-inhibitor, such as febuxostat, as RDEA3170 may deliver the most potent UA lowering effect via renal excretion reported for any treatment.

Dapagliflozin is a stable, reversible, highly selective and orally active inhibitor of human renal SGLT2, the major transporter responsible for renal glucose reabsorption in the kidney. The mechanism of action of dapagliflozin results in the direct and insulin-independent elimination of glucose by the kidneys. Results from non-clinical- and clinical studies have shown that dapagliflozin can be used to promote urinary excretion of glucose as a safe and effective method of reducing blood glucose levels. Currently, there are multiple oral SGLT2-inhibitors approved and indicated for the treatment of type 2 diabetes (dapagliflozin, empagliflozin and canagliflozin). In addition to providing glycemic control, body weight reduction and blood pressure lowering, SGLT2-inhibition also results in sUA lowering, potentially due to increased renal excretion of urate.

CCI

the objective of the study is to explore whether intensive UA lowering therapy with febuxostat and RDEA3170 can be safely combined with dapagliflozin, and if the sUA lowering effects would be additive.

### 5.6. Dose Rationale

The doses of RDEA3170 and febuxostat selected for this study were chosen as they represent the doses achieving maximal sUA reduction in Phase 2 studies in patients with gout. CCI

CCI [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED], the febuxostat and RDEA3170 doses and formulations used in this study have been previously administered to patients with more advanced disease than recruited in this study, without raising any safety concerns to date.

For febuxostat, the United States Package Insert (USPI) recommends a starting dose of 40 mg once daily while a starting dose of 80 mg is recommended in Europe, and for patients who do not achieve a sUA less than 6 mg/dL after 2 weeks an increase to 80 mg and 120 mg is recommended in the USA and Europe, respectively. No dose adjustment is necessary in patients with mild or moderate renal impairment (Creatinine Clearance [CrCl] 30 to 89 mL/min). As this study does not aim to achieve a predefined sUA target of < 6 mg/dL, but rather to lower sUA as much as possible, a dose of 80 mg from the start of the study is relevant to adequately reduce the sUA production and to maintain the proportional contributions of febuxostat and RDEA3170 to the overall sUA acid lowering effects. The current study will be performed at 2 Clinical Units with close monitoring of all study participants through frequent visits, an extensive safety laboratory panel, and close monitoring of safety data as it emerges.

For dapagliflozin, the USPI recommends a starting dose of 5 mg once daily while a starting dose of 10 mg is recommended in Europe. The marketed dose 10 mg have been found to be well tolerated in subjects with chronic kidney disease 3 (estimated glomerular filtration rate [eGFR] 30 to 60 mL/min/1.73 m<sup>2</sup>) [22]. From a PK and pharmacodynamic (PD) perspective, dapagliflozin 10 mg is appropriate for use in patients with renal impairment.

### 5.7. Choice of Study Population, Risk-Benefit Assessment and Risk Mitigation

There are no direct benefits for the patients participating in this study. However, study related health assessments are provided without costs for the subjects. The major risks for patients who participate in the study will come from AEs caused by RDEA3170, febuxostat and/or dapagliflozin. In addition, there may be a slight risk of infection or bruising that may occur after insertion of an intravenous (IV) cannula for frequent blood sampling. CCI [REDACTED] is an approved URAT1 inhibitor. Most common AEs identified in the prescribing information are headache, increased blood creatinine and gastroesophageal reflux disease.

Asymptomatic hyperuricemic subjects (sUA > 6.0 mg/dL) will be included in this study. It is the most suitable population to explore whether there is an additive effect on urinary excretion of urate and sUA levels, when dapagliflozin is combined with RDEA3170 and febuxostat.

Initial Phase 1 development of RDEA3170 explored multiple formulations to identify an agent with an optimized PK and food-effect profile. Initial studies explored RDEA3170 given as monotherapy. Although these studies demonstrated that RDEA3170 resulted in effective lowering of UA, a higher rate of sCr elevations was observed with no clear relationship to dose. These elevations have usually been transient and reversible, and most have resolved without interruption of RDEA3170.

Based on an in depth evaluation of sCr elevations in conjunction with the known mechanism of action of RDEA3170, the Sponsor concluded that the likely basis for the increased sCr levels following treatment with RDEA3170 was oversaturation of urate in the urine. Results from 3 Phase 2a studies (Studies 204, 205 and 206) and a Phase 1b study (Study 107) demonstrated an enhanced sUA lowering effect of RDEA3170 in combination with an XO1, and an improved UA excretion profile. This dual mechanism approach may result in a lower incidence of renal-related AEs, thereby improving safety.

During the clinical development program, subjects with gout or asymptomatic hyperuricemia were included in Study 107 (RDEA3170 in combination with allopurinol), Study 201 (RDEA3170 monotherapy), Study 203 (RDEA3170 monotherapy in Japanese subjects), Study 204 (RDEA3170 in combination with febuxostat) and Study 205 (RDEA3170 in combination with febuxostat in Japanese subjects).

Serum creatinine elevations have occurred in patients with gout treated with RDEA3170 alone. Therefore, only subjects with eGFR > 45 mL/minute/1.73 m<sup>2</sup> at screening will be included in the study. Renal safety parameter (including assessment of serum and urinary levels of creatinine and cystatin-C, blood urea nitrogen [BUN], serum and urinary electrolytes, urinary pH) are monitored during the study. Elevations in sCr will be monitored and appropriate actions taken as described in Appendix 15.4.

In patients reporting symptoms that may indicate acute urate nephropathy including flank pain, nausea, or vomiting, treatment will be immediately discontinued and renal safety parameter will be measured and appropriate actions taken as described in Appendix 15.4. Implementation of a hydration scheme is considered an appropriate risk mitigation measure.

Initiating or increasing the dose of ULT has been shown to induce gout flares in some patients with a history of gout. To protect participating patients from experiencing gout flares, patients with a history of gout will be excluded from the study. Should a patient nevertheless experience a gout flare, treatment with colchicine, steroids and/or non-steroidal anti-inflammatory drugs as appropriate, and according to the Investigator's best medical judgment is recommended.

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients.

A multiple-dose interaction study showed that RDEA3170 did not affect C<sub>max</sub> and AUC of febuxostat.

The predictable risks and disadvantages for the study subjects are acceptable, compared to the presumed future importance of the triple therapy, expected to be commonly used in the proposed target patient population (chronic kidney disease and/or heart failure).

## 6. STUDY OBJECTIVES

### 6.1. Primary Objective

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

#### 6.1.1. Primary Objective Outcome Measure:

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

### 6.2. 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.

#### 6.2.1. Secondary Objective Outcome Measures:

- Serum UA 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.

### 6.3. Exploratory Objectives

- (C) [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- (C) [Redacted]

**6.3.1. Exploratory Objectives Outcome Measures:**

- (C) [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

Refer to Section 11.9.1 for details on PD variables, Section 11.10.1 for details PK parameters, Section 9.4 for details safety variables and Section 11.12 for details on exploratory outcomes.



## 7. OVERALL DESIGN AND PLAN OF THE STUDY

### 7.1. Overall 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. Thirty-six, asymptomatic hyperuricemic patients aged 18 to 65 years (inclusive) will be enrolled into this study at 2 study centers. Twenty-four patients have been enrolled and completed the study to date. Due to inadequate urine sampling, it was decided to include 12 additional patients to ensure an adequate sample size (at least 20 evaluable patients) to evaluate the effects of intensive UA lowering with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA. 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 will comprise of:

- A screening period of maximum 28 days;
- Two treatment periods during which patients will be residential 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 (Section 7.5.1) and none of the exclusion criteria (Section 7.5.2), 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.

See [Table 1](#) for details on assessment that will be performed during the treatment periods.

### 7.1.1. End of Study

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

### 7.1.2. Interim Analyses

No interim analyses will be performed in this study.

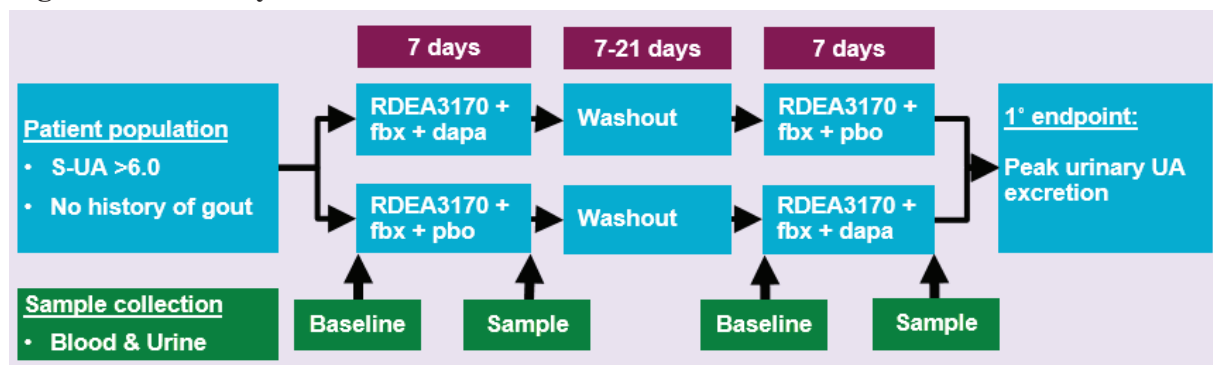
### 7.1.3. Expected Duration of the Study

Each patient will be involved in the study for 10 to 11 weeks.

## 7.2. Study Flow Chart and Schedule of Assessments

The flow of events is illustrated in [Figure 1](#) for all treatments, depending on the patient's assigned randomization (refer to [Section 8.9.2](#)).

**Figure 1 Study Flow Chart**



Dapa: Dapagliflozin; fbx: Febuxostat; pbo: placebo

The Schedule of Assessments displaying assessments/tasks and time points is presented in [Table 1](#).

**Table 1 Schedule of Assessments**

	Screening	Treatment Period 1								Washout (7 to 21 days)	Treatment Period 2					Follow-up Visit / EDV
		1	2	3	4	5	6	7	8		1	2-5	6 <sup>a</sup>	7	8	
<b>Visit</b>		1	2	3	4	5	6	7	8		1	2-5	6 <sup>a</sup>	7	8	
<b>Study Day</b>		-28	-2	-1	1	2-5	6	7	8		-1	2-5	6 <sup>a</sup>	7	8	
<b>Visit Window (days)</b>		0 to 28	±0	±0	±0	±0	±0	±0	±0		-2 <sup>a</sup>	±0	±0	±0	±0	
Written informed consent	X															
Demographics	X															
Medical/surgical history	X															
Inclusion/exclusion criteria	X	X														
Urinary drug/blood alcohol screen	X	X								X						
Complete physical examination <sup>b</sup>	X															X
Height and BMI	X															
Serology	X															
Pregnancy tests (women only)	X (Serum)	X (Urine)									X (Urine)					X (Urine)
FSH (post-menopausal women only)	X															
Randomization		X														
<b>Study Residency:</b>																
Admission to Clinical Unit		X				X					X					
Discharge from Clinical Unit					X				X						X	
Non-residential visit	X															X
<b>RDEA3170, Febuxostat, Dapagliflozin Administration</b>																
Treatment administered at Clinical Unit					X <sup>c</sup>			X <sup>d</sup>			X <sup>c</sup>			X <sup>d</sup>		
Controlled meals and fluid intake <sup>e</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment dispensed					X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>							
Treatment administered at home											X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	
Treatment returned															X	

	Screening		Treatment Period 1								Treatment Period 2							Follow-up Visit / EDV
	1		2		3		4		5		6		7		8			
	-28 0 to 28		-2 ±0	-1	1	2-5	6 ±0	7	8	-2 <sup>a</sup>	-1	1	2-5	6 <sup>a</sup> ±0	7	8	23 <sup>a</sup> 0-7	
<b>Visit</b>	1		2	3	4	5	6	7	8									
<b>Study Day</b>	-28		-1															
<b>Visit Window (days)</b>	0 to 28		±0															
<b>Safety and tolerability:</b>																		
Adverse event review (AEs and SAEs)	X		X		X		X		X		X		X		X		X	
Concomitant medication	X		X		X		X		X		X		X		X		X	
Vital signs (BP and pulse)	X		X		X		X		X		X		X		X		X	
12-lead ECG	X		X		X		X		X		X		X		X		X	
Blood samples for hematology, clinical chemistry <sup>g</sup>	X		X		X		X		X		X		X		X		X	
Urine analysis (dipstick and spot urine collection)	X		X		X		X		X		X		X		X		X	
eGFR	X		X		X		X		X		X		X		X		X	
Brief physical <sup>h</sup> examination	X		X		X		X		X		X		X		X		X	
Weight	X		X		X		X		X		X		X		X		X	
<b>Pharmacodynamics</b>																		
Timed urine sample collection including hourly samples at specific study day <sup>i,j</sup>			X <sup>i</sup>		X <sup>j</sup>		X <sup>i</sup>		X <sup>j</sup>		X <sup>i</sup>		X <sup>j</sup>		X <sup>i</sup>		X <sup>j</sup>	
Blood samples for sUA	X <sup>k</sup>		X <sup>k</sup>		X <sup>l</sup>		X <sup>k</sup>		X <sup>l</sup>		X <sup>k</sup>		X <sup>l</sup>		X <sup>k</sup>		X <sup>l</sup>	
<b>Pharmacokinetics</b>																		
Blood samples <sup>m</sup> for PK analysis					X				X				X					
<b>Exploratory</b>																		
CCI																		

AE: Adverse event; BMI: Body Mass Index; BP: Blood pressure; ECG: Electrocardiogram; EDV: Early discontinuation Visit; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; FSH: Follicle stimulating hormone; IMP: Investigational Medicinal Product; PK: Pharmacokinetic; SAE: Serious adverse event; sUA: Serum uric acid;

- a) Visit 4 admission cannot occur earlier than 5 days nor later than 19 days post Visit 3 discharge (minimum of 7 days where study drug is not administered). The relative timing of Visit 4 to Visit 5 (admission for Visit 5 should occur 5 days post Visit 4 discharge) and Visit 6 (15 to 22 days after Visit 4 discharge) must remain the same irrespective of when Visit 4 is performed.
- b) A complete physical examination should include general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.
- c) First dose on site, then once daily at home until next visit, including dosing at home the morning of admission day for next visit (Day 6).
- d) Treatment administered at Clinical Unit.
- e) On urine collection days, (Day -1 and Day 7) 400 mL water will be consumed by the patients within 15 minutes after IMP administration (for Day -1, clock time of planned dose administration for dosing days), followed by 200 mL water every 2 hours until 12 hours after IMP administration (for Day -1, clock time of planned dose administration for dosing days). On Days -2, -1, 1, 6 and 7, patients will receive standardized meals, and will be encouraged to consume the entire meal. Mealtimes and other activities will be synchronized for all patients and food and liquid intake specified and monitored. 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 patients will receive standardized meals thereafter. After discharge on Day 1 and Day 8, the food and liquid intake of the patients will be *ad libitum*. On Days -2 and 6 identical standardized lunch and dinner meals will be provided.
- f) Treatment administered at home in the morning.
- g) Fasting samples, collected before breakfast (food) and before dose (when applicable).
- h) A brief physical examination should include general appearance, skin, abdomen, cardiovascular system and respiratory; and any organ systems pertinent to the patient's signs, symptoms or AEs.
- i) 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.
- j) 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. Mealtimes and other activities should be synchronized for all patients and food and liquid intake specified and monitored.
- k) A single sUA assessment (matched by time of day, e.g. always in the morning, and after a 10 hour overnight fast). This does not apply to the screening sUA. The screening sUA can be repeated once during the screening period.
- l) Time-points for sUA to match the pharmacokinetic time-points (see the bullet m), detailing PK time-points).
- m) Time points for plasma collection for pharmacokinetics: Pre-dose and 15 minutes, 30 minutes, 1 hour, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose.

### 7.3. Order of Assessments

It is important that PD and PK sampling occurs as close as possible to scheduled time. To achieve this, other assessments scheduled at the same time may be initiated before the time point.

The sequence at a time point is:

1. Electrocardiograms (ECGs).
2. Vital signs (systolic and diastolic BP and pulse).
3. Blood samples for sUA (will be drawn at the specified time point).
4. Pharmacokinetic blood sampling (will be drawn at the specified time point).

### 7.4. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1. On urine collection days, (Day -1 and Day 7) 400 mL of water will be consumed by the patients within 15 minutes after IMP administration (for Day -1, clock time of planned dose administration for dosing days), followed by 200 mL water every 2 hours until 12 hours after IMP administration (for Day -1, clock time of planned dose administration for dosing days). On Days -2, -1, 1, 6 and 7, patients will receive standardized meals, and will be encouraged to consume the entire meal. Mealtimes and other activities will be synchronized for all patients and food and liquid intake specified and monitored. 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 until discharge. On Day -2 and Day 6 patients will receive identical standardized meals from the time they arrive at the site. See Section 8.6.
2. Patients should not engage in any strenuous activity from 72 hours before check-in until after their final Follow-up Visit.
3. Before each treatment period, patients should abstain from alcohol for 72 hours before admission to the Clinical Unit until after their last PD/PK sampling visit. Patients should also abstain from alcohol for 72 hours before their final Follow-up Visit.
4. Before each treatment period, patients should abstain from caffeine-containing foods and beverages for 24 hours before admission to the Clinical Unit until the last dose of IMP in each treatment period.

5. Patients should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (e.g., tonic water) from 7 days before admission to the Clinical Unit on Day -2 until after their Follow-up Visit.
6. During admission periods, patients will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the Clinical Unit
7. During the patients' outpatient periods, patients should abstain from consuming high-energy drinks (e.g., red bull), and food containing poppy seeds and any Over-the-Counter (OTC) medication or herbal preparations until after their final Follow-up Visit has been completed. Patients should also limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup = 12 oz soda, 6 oz coffee or 8 oz tea). Patients should consume no more than 2 units of alcohol per day and completely abstain from alcohol from 72 hours before each admission to the Clinical Unit.
8. Patients will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the Follow-up Visit.
9. Patients must not smoke for 1 hour before any vital sign or ECG assessments. Smoking is prohibited while patients are confined to the Clinical Unit.
10. For medication restrictions, please refer to Section 8.8.

#### **7.4.1. Reproductive Restrictions**

##### ***7.4.1.1. Women of Non-Childbearing Potential***

Women of non-childbearing potential are defined as female patients who are permanently surgically sterilized or post-menopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation.

Females are considered post-menopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels are in the post-menopausal range (FSH levels is > 40 mIU/mL). If there is any uncertainty, this must be discussed between the Investigator and the Medical Monitor.



#### **7.4.1.2. Women of Childbearing Potential**

Women of childbearing potential who are sexually active must agree to use, with their partner, an approved method of highly effective contraception from the time of IMP administration until 3 months after the study Follow-up Visit. The following are considered highly effective methods:

- Surgical sterilization<sup>1</sup> (i.e., bilateral tubal ligation for females; vasectomy for male partners).
- Placement of an intrauterine device<sup>1</sup> or intrauterine hormone releasing system<sup>1</sup>.
- Hormonal contraception associated with inhibition of ovulation (injectable<sup>1</sup>, implantable<sup>1</sup>, patch and oral).

<sup>1</sup> *These methods are considered to have low user dependency*

In addition, a barrier method must also be used i.e., condom (with spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants); or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Alternatively, true abstinence is acceptable when it is in line with the patient's preferred and usual lifestyle.

#### **Pregnancy Testing**

Women of childbearing potential can be included only after a negative highly sensitive serum pregnancy test. Additionally, urine pregnancy testing will be done as per the Schedule of Assessments, see [Table 1](#).

#### **7.4.1.3. Male Patients**

##### **Restrictions for Male Patients**

RDEA3170 had no effects on fertility or embryo-fetal development in rats at doses up to 300 mg/kg/day, and did not affect embryo-fetal development in rabbits at doses up to 30 mg/kg/day.

Male patients participating in this study are not required to apply contraception.

#### **Pregnancy**

Patients will be instructed that if their partner becomes pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but



confirmed after completion of the study. In the event that a patient's partner is subsequently found to be pregnant after the patient is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

## **7.5. Selection of Study Population**

The PI should keep a patient screening log of all potential patients who consented and were subjected to screening procedures.

Patients who fail 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.

This study will be conducted in male and female patients. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

### **7.5.1. Inclusion Criteria**

For inclusion in the study, patients should fulfill the following criteria:

1. Provision of signed and dated, written informed consent before any study specific procedures.
2. Male and female asymptomatic hyperuricemic patients aged 18 to 65 years at the Screening Visit with suitable veins for cannulation or repeated venipuncture.
3. Male and female patients with a sUA > 6.0 mg/dL at the Screening Visit. The screening sUA can be repeated once during the screening period.
4. Females must have a negative pregnancy test at the Screening Visit and Day -2 of each treatment period, must not be lactating and must be:
  - 4.1. of non-childbearing potential, confirmed at the Screening Visit by fulfilling one of the following criteria
    - 4.1.1. Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the post-menopausal range (FSH levels > 40 mIU/mL). If there is any uncertainty, inclusion must be discussed between the Investigator and the Medical Monitor.

- 4.1.2. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
- 4.2. OR if of childbearing potential must be willing to use an acceptable method of contraception to avoid pregnancy for the entire study period, as described in Section 7.4.1.2.
5. Have a body mass index (BMI) between 18 and 35 kg/m<sup>2</sup> inclusive and weigh at least 50 kg and no more than 150 kg inclusive.
6. Provision of signed, written and dated informed consent for optional genetic/biomarker research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this CSP.

#### 7.5.2. Exclusion Criteria

Patients will not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.
3. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP.
4. eGFR\* < 45 mL/minute/1.73 m<sup>2</sup> at Screening (blood sample obtained at Screening Visit).  
*\*According to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation, using central laboratory measurements of serum creatinine (sCr). [eGFR (mL/min/1.73 m<sup>2</sup>) = 175 x (standardized sCr)<sup>-1.154</sup> x (Age)<sup>-0.203</sup> x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL ]*
5. Diagnosed with type 2 diabetes mellitus with either hemoglobin A1c (HbA1c) > 8% or doses of oral antidiabetic drugs changed within 4 weeks before the Screening Visit.
6. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma.
7. History of gout.

8. Patient with any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient.
9. Ongoing treatment with an SGLT2-inhibitor, a URAT1-inhibitor, and/or an XOI.
10. Dose of losartan, fenofibrate or guaifenesin changed within 2 weeks of first admission to the Clinical Unit (Day -2 of Treatment Period 1) or further dose titration expected after first admission to the Clinical Unit (Day -2 of Treatment Period 1).
11. Any clinically significant abnormalities in clinical chemistry, hematology or urinalysis results, at the Screening Visit and/or first admission to the Clinical Unit as judged by the Investigator.  
*Note: Screening and Day -2 tests may be repeated, at the discretion of the Investigator, if abnormal.*
12. Any clinically significant abnormal findings in vital signs at the Screening Visit and/or first admission to the Clinical Unit, as judged by the Investigator.  
*Note: Screening and Day -2 tests may be repeated, at the discretion of the Investigator, if abnormal.*
13. Any clinically significant abnormalities on 12-lead ECG at the Screening Visit and/or first admission to the Clinical Unit, as judged by the Investigator.  
*Note: Screening and Day -2 tests may be repeated, at the discretion of the Investigator, if abnormal.*
14. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV) antibody.
15. Known or suspected history of drug abuse, as judged by the Investigator.
16. Has received another new chemical entity (defined as a compound that has not been approved for marketing) within 30 days before the Screening Visit.  
*Note: patients consented and screened, but not randomized in this study or a previous study, are not excluded.*
17. Plasma donation within 1 month of the Screening Visit or any blood donation/loss more than 400 mL during the 6 weeks before the Screening Visit.
18. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to RDEA3170, febuxostat or dapagliflozin.

19. Suspected history of alcohol or drug abuse or excessive intake of alcohol, as judged by the PI, or positive screen for drugs of abuse or alcohol at the Screening Visit or Day – 2 of each treatment period.
20. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks before the first administration of IMP.
21. Use of any prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks before the first administration of IMP or longer if the medication has a long half-life.  
*Note: The use of paracetamol/acetaminophen, hormone replacement therapy, systemic contraceptives, corticosteroid cream and prescription medication for chronic illness that has been approved by the PI will be allowed.*
22. Involvement of any AstraZeneca, PAREXEL or study site employee or their close relatives.
23. Patients who have previously received RDEA3170.
24. Judgment by the Investigator that the patient should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.
25. Vulnerable patients, e.g., kept in detention, protected adults under guardianship, trusteeship or committed to an institution by governmental or juridical order.

In addition, the following is considered a criterion for the exclusion from the optional genetic component of the study:

26. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection or previous bone marrow transplant.

### **7.5.3. Discontinuation of Investigational Medicinal Product and Withdrawal from the Study**

Patients may be discontinued from IMP in the following situations:

- Patient decision. The Patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to the CSP.

- Any significant and clinically relevant changes in the safety parameters (e.g., ECG, BP, pulse rate, laboratory assessments and AEs) making the continuation of IMP administration unjustified.
- Study specific withdrawal criteria: If a patient reports symptoms, which are considered unacceptable by the patient or the Investigator, he/she will be withdrawn from the study. In particular:
  - Any other severe or SAE that is judged as possibly related to the IMP by the Investigator.
  - Any case of Potential Hy's Law (PHL) according to Appendix 15.3.
  - Study treatment will be temporarily stopped if a patient has elevated creatinine and cystatin-C levels greater than 1.5 times the pre-treatment value and retest of the creatinine and cystatin-C will be performed as soon as possible (see Appendix 15.4).
  - In patients who report symptoms that may indicate acute UA nephropathy including flank pain, nausea, or vomiting, treatment may need to be temporarily stopped or permanently discontinued. Appendix 15.4 contains guidelines on management of such patients.
  - Pregnancy.

The appropriate AE form in the case report form (CRF) is to be completed.

#### **7.5.4. Premature Termination of the Study**

The study may be terminated prematurely if:

- The PI and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance, when there is at least 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered related to the IMP by the PI and the Sponsor.
- The Sponsor considers the applied doses of the study drug to be no longer relevant.
- The Sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the patients.

Premature termination of the study must be mutually agreed upon by the PI and the Sponsor and must be documented. However, study results will be reported according to the requirements outlined in this CSP as far as applicable.

### 7.5.5. Replacement of Patients

Patients who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless a specific sample size is to be met for statistical purposes and if the Sponsor's responsible physician and the PI agree it is safe to do so. Patients who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the Sponsor.

### 7.5.6. Total Blood Volume

The approximate total amount of blood to be collected from each patient in this study, excluding repeat samples, is summarized in Table 2.

**Table 2 Total Blood Volume**

Assessments	Sample Volume (mL)	Number of Samples	Total Blood Volume (mL)
<b>Clinical Laboratory</b>			
Hematology	2	6	12
Clinical chemistry <sup>a</sup>	5	6	30
Serology	3.5	1	3.5
Fasting plasma glucose	4	8	32
<b>Pharmacodynamics:</b>			
Serum uric acid	3.5	26	91
<b>Pharmacokinetics:</b>			
RDEA3170 + metabolites	3	22	66
Febuxostat	2	22	44
Dapagliflozin	2	22	44
<b>Exploratory:</b>			
CC			

- a) Pregnancy and follicle stimulating hormone assessments will be performed on the sample collected for clinical chemistry at the same time point.
- b) Excluding repeat laboratory investigations.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each patient must not exceed 500 mL.

## 8. TREATMENTS

### 8.1. Identity of the Investigational Medicinal Products

Details on the identity of the IMPs are presented in [Table 3](#).

**Table 3 Identity of the Investigational Medicinal Products**

Investigational product	Dosage form and strength	Provider
RDEA3170	9 mg capsules for oral administration	AstraZeneca
Febuxostat	80 mg tablet for oral administration	PAREXEL
Dapagliflozin	10 mg tablets for oral administration	AstraZeneca
Dapagliflozin matched placebo	Placebo	AstraZeneca

Details of the batch numbers will be included in the trial master file and the final CSR.

### 8.2. Supply of Investigational Medicinal Product

RDEA3170 and dapagliflozin will be supplied by AstraZeneca and provided in bulk labeled according to the master study specific labels. Commercial Febuxostat will be supplied by PAREXEL. The IMP will be re-packaged into patient specific containers by PAREXEL, as applicable.

A release document signed by the pharmacy or designee at the Clinical Unit will be placed in the appropriate section of the Trial Master File to document labeling and dispensing of the study drug to the patient.

### 8.3. Storage and Handling Procedures

Separate instructions for preparation and handling of the IMP will be provided by AstraZeneca.

All IMPs will be stored in a secure facility, details of storage conditions will be provided on the label of the IMP.

The AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records provided that the blind of the study is not compromised.

#### **8.4. Labeling**

Labels will be prepared in accordance with local regulatory guidelines.

The IMP labels will fulfill Good Manufacturing Practice (GMP) Annex 13 requirements and medical device directive for labeling. Refer to the Drug Manual for more detail on subject specific labeling.

#### **8.5. Drug Accountability, Dispensing and Destruction**

The open-label RDEA3170 and febuxostat and the blinded dapagliflozin will be dispensed at Visit 2 (Day 1 Treatment Period 1). At Visit 3 (Day 6 Treatment Period 1) all IMPs will be returned for drug accountability. The bottles of RDEA3170 and febuxostat will be kept at site and re-dispensed to the patients at Visit 4 (Day 1 Treatment Period 2). The blinded dapagliflozin 10 mg or placebo will be replaced by the other alternative labeled with the same randomization code. At Visit 5 (Day 6 Treatment Period 2) all IMPs will be returned for drug accountability.

The IMP provided for this clinical study will be used only as directed in the CSP.

In accordance with GCP, the Investigational Site will account for all supplies of RDEA3170, febuxostat, dapagliflozin and placebo. Details of receipt, storage, assembly/dispensing and return will be recorded.

All unused supplies of RDEA3170, febuxostat, dapagliflozin and placebo will either be destroyed by PAREXEL or returned at the end of the study in accordance with instruction by the Sponsor. Refer to the Drug Manual for more details.

#### **8.6. Dose and Treatment Regimens**

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. Mealtimes and other activities will be synchronized for all patients and food and liquid intake specified and monitored as described in the Schedule of Assessments (Table 1) and Section 7.4.



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.

On urine collection days, (Day -1 and Day 7) 400 mL water will be consumed by the patients within 15 minutes after IMP administration (for Day -1, clock time of planned dose administration for dosing days), followed by 200 mL water every 2 hours until 12 hours after IMP administration (for Day -1, clock time of planned dose administration for dosing days). Patients will consume 400 mL water within 15 minutes after IMP administration, followed by 200 mL water every 2 hours until 12 hours after IMP administration.

### **Home Dosing**

Patients will take the IMPs at home on Days 2 to Day 6.

During home dosing, patients will be instructed to take the IMPs with water and to stay adequately hydrated and pause dosing in the event of dehydration, such as occurs with gastroenteritis.

Other restrictions, are described in Section 7.4.

### **8.7. 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 (b) (6)

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.

### **8.8. Concomitant Medication**

#### **8.8.1. Concomitant and Post-study Treatments**

Apart from paracetamol/acetaminophen, hormone replacement therapy, systemic contraceptives, corticosteroid cream and prescription medication for chronic illness that has been approved by the PI, no concomitant medication or therapy will be allowed.

The patients should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the PI.

Medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the PI during the residential period.

When any medication is required, it should be prescribed by the PI. Following consultation with AstraZeneca Lead Physician, the PI should determine whether the patient should continue in the study. Administration of concomitant medications that may influence the measurement of the PD and/or PK endpoints may be documented as a protocol deviation after consultation of the PI with AstraZeneca Lead Physician.

### **8.8.2. Prior and Concomitant Medication**

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.

## **8.9. Randomization**

### **8.9.1. Patient Enrolment and Randomization**

The PI will ensure:

- Signed informed consent is obtained from each potential patient before any study specific procedures are performed.
- Each potential patient is assigned a unique enrolment number at screening upon signing the Informed Consent.
- The eligibility of each patient is in accordance with the inclusion and exclusion criteria.
- Each eligible patient is assigned a unique randomization code.

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., "PPD" [for Baltimore] and "PPD" [for Los Angeles] for outputs). The site number for Baltimore is PPD and the site number for Los Angeles is PPD.

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.

### **8.9.2. Procedures for Randomization**

Upon completion of the randomization requirements specifications form, the randomization will be produced by PAREXEL according to the AstraZeneca randomization system (CC).

Twenty-four patients were randomized equally (1:1 ratio) into 1 of 2 treatment sequences (AB, BA) to ensure 20 evaluable patients. An additional set of replacement random numbers were generated within AZRand on a like for like treatment sequence basis.

Due to inadequate urine sampling, it was decided to include 12 additional patients to obtain valid assessment of the primary endpoint for at least 20 evaluable patients.

An additional 12 patients will be randomized to allow for at least 7 additional completers. With 24 completers available for the interim analysis, this will provide for a total sample size of 36 evaluable patients. A separate randomization list will be created for these additional patients.

### **8.9.3. Procedures for Handling Incorrectly Randomized Patients**

Patients who fail 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.

Where a patient, who does not meet the selection criteria, is randomized in error and this is identified before dosing, the patient should be withdrawn from the study. If a patient is withdrawn before dosing, they will be replaced.

If a patient, who does not meet the selection criteria and has been dosed before the error is identified; the patient should be withdrawn and advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision made as to whether the patient should be replaced.

### **8.10. Blinding**

#### **8.11. Methods for Ensuring 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.

The randomization list should be kept in a secure location until the database lock or equivalently, clean file is declared.

The pharmacokineticist will remain blinded during the study conduct, unless otherwise required based on study findings.

The pharmacokineticist will be unblinded to perform the final PK analyses after all patients have completed the study, final bioanalytical results are available and all required study data are considered clean. This may occur before database lock.

The following personnel will have access to the randomization list:

- The AstraZeneca personnel carrying out the labeling and packaging of patient specific treatments.
- The pharmacy personnel preparing study drug at the site.
- The personnel performing the bioanalyses of the plasma/urine samples.

The randomization list should be kept in a secure location until the end of the study.

### **8.12. Methods for Unblinding the Study**

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the PI and the pharmacist.

In most of the studies using blinding, the treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The PI documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

In the event of a medical emergency when management of a patient's condition requires knowledge of the trial medication, the treatment received may be revealed by personnel authorized by the PI. If possible, such emergencies are to be discussed with AstraZeneca before disclosure of the treatment allocation. Reasons for breaking a code will be clearly explained and justified in the patient's CRF. The date on which the code was broken together with the identity of the person responsible will also be documented.

## **9. MEASUREMENTS AND METHODS OF ASSESSMENTS**

### **9.1. Appropriateness of Measurements**

Standard measures to assess PD, PK, safety and tolerability apply during the study. For the doses of RDEA3170, febuxostat and dapagliflozin planned to be given during this study, no safety issues are expected.

For timing of assessments, refer to [Table 1](#).

### **9.2. Pharmacodynamics**

#### **9.2.1. Sample Collection and Handling**

Urine samples for the determination of urinary excretion of UA will be collected for each treatment period as specified in the Schedule of Assessments ([Table 1](#)).

Blood samples for the determination of sUA levels will be collected for each treatment period as specified in the Schedule of Assessments ([Table 1](#)).

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual.

#### **9.2.2. Pharmacodynamic Assays**

Blood samples for determination of sUA in serum and urine samples for the determination of UA in urine will be analyzed by safety laboratory, using a validated assay.

### **9.3. Pharmacokinetics**

#### **9.3.1. Sample Collection and Handling**

Blood samples for the determination of plasma concentrations of RDEA3170 (and its metabolites M1 and M8), febuxostat and dapagliflozin will be collected for each treatment period as specified in the Schedule of Assessments ([Table 1](#)).

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual. Plasma samples will be analyzed for RDEA3170 (and its metabolites M1 and M8), febuxostat and dapagliflozin using a validated assay.

### **9.3.2. Pharmacokinetic Drug Assays**

Blood samples for determination of RDEA3170 (and its metabolites M1 and M8), febuxostat and dapagliflozin concentrations in plasma will be analyzed by Covance on behalf AstraZeneca Research and Development (R&D), using a validated assay.

Full details of the analytical method and analyses performed used will be described in a separate Bioanalytical Report.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

### **9.4. Safety and Eligibility Measurements**

Safety and tolerability variables will include:

- Adverse events
- Events of diabetic ketoacidosis
- Vital signs (systolic and diastolic BP, pulse rate)
- Electrocardiogram(s)
- Physical examination
- Weight
- Laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology and drugs of abuse and alcohol will be assessed for eligibility. Follicle stimulating hormone (post-menopausal females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

#### **9.4.1. Adverse Events**

Refer to Section [12.2.3](#).

#### **9.4.2. Events of Diabetic Ketoacidosis**

Patients will be monitored for signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath. Patients with these signs and symptoms will be should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL).

### **9.4.3. Vital Signs**

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)

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

### **9.4.4. Electrocardiograms**

#### **9.4.4.1. Resting 12-lead Electrocardiogram**

At the time points specified in the Schedule of Assessments ([Table 1](#)), a 10-second 12-lead ECG will be obtained after 10 minutes supine rest) using [REDACTED].

The Investigator will judge the overall interpretation as normal or abnormal and this evaluation will be reported in [REDACTED]. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented in ClinBase. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

### **9.4.5. Physical Examination**

#### **Full**

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

## Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory; and any organ systems pertinent to the patient's signs, symptoms or AEs.

### 9.4.6. Laboratory Assessments

#### 9.4.6.1. Hematology

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##### Hematology

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

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#### 9.4.6.2. Clinical Chemistry

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##### Serum Biochemistry

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Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Blood Urea Nitrogen (BUN)	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total Bilirubin
Calcium	Unconjugated bilirubin
Phosphate	Cystatin-C
Uric acid	eGFR <sup>a</sup>
Estimated Creatinine Clearance (CrCl)	

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##### Plasma Biochemistry

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Glucose (fasting) <sup>b</sup>

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- a) Screening Visit only (Visit 1)
- b) Plasma glucose after at least 4 hours fasting.



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#### **9.4.6.3. Urinalysis by Dipstick**

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##### **Urinalysis**

Glucose

Protein

Blood

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

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#### **9.4.6.4. Urinalysis for Urine Collection Interval**

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##### **Urinalysis**

Uric acid

Creatinine

Glucose

Cystatin-C

Sodium

pH

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#### **9.4.6.5. Pregnancy Testing**

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##### **Pregnancy test (females only)**

Human beta chorionic gonadotrophin (HCG)

Follicle-stimulating hormone (FSH) (Screening Visit Only)

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#### **9.4.6.6. Viral Serology**

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##### **Viral Serology**

Human immunodeficiency virus (HIV) I and II

Hepatitis C Virus antibody

Hepatitis B surface antigen (HBsAg)

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#### **9.4.6.7. Drugs of Abuse and Alcohol**

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##### **Drugs of Abuse and Alcohol**

Amphetamine/Ecstasy

Benzodiazepines

Ethanol

Methadone Metabolites

Cannabinoids

Barbiturates

Cocaine

Phencyclidine

Opiates

Tricyclic anti-depressants (TCA)

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Drugs of abuse screen will be done via a urine sample. Alcohol screen will be done via a serum sample.

#### **9.4.7. Concomitant Medication**

Refer to Section 8.7.

## **9.5. Exploratory Assessments**

### **9.5.1. Collection of Biomarker Samples**

Blood and urine samples for biomarkers, bio-banking and metabolomics will be collected for each treatment period as specified in the Schedule of Assessments (Table 1).

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual.

### **9.5.2. Collection of Pharmacogenetic Sample**

Patients will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected in accordance with the inclusion criteria and the Schedule of Assessments, see Table 1.

If for any reason the blood sample is not drawn on Day 1 of Treatment Period 1 according to the Schedule of Assessments, it may be taken at any time up until the last study visit. Although the genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. Only 1 sample should be collected per patient for genetic research during the study.

A record of the date the patient consented to the genetic research and the date and time of the blood sample collection will be recorded in CC1. Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual.

## **9.6. Procedures for Handling of Biological Samples**

### **9.6.1. Storage and Destruction of Biological Samples**

Biologic samples will be retained for a maximum of 15 years following the last patient's last visit in the study.

#### **9.6.1.1. Pharmacokinetic Samples**

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual or back-up PK samples may be used for exploratory safety, metabolite and/or biomarker research and may be stored for up to 15 years (in this case, residual back-up PK samples will be shipped to an AstraZeneca designated BioBank).

#### **9.6.1.2. Pharmacodynamic Samples**

Pharmacodynamic samples will be retained for a maximum of 15 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR.

#### **9.6.1.3. Pharmacogenetic Samples**

CCI  
[Redacted text block consisting of multiple lines of blue bars]

CCI

### **9.6.2. Labeling and Shipment of Biohazard Samples**

Samples will be labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (for International Airline Transportation Association [IATA] guidance, see Appendix 15.2 of this CSP).

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

### **9.6.3. Chain of Custody of Biological Samples**

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will ensure full traceability of collected biological samples from the patients while in storage at the Clinical Unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca bio-bank system during the entire life cycle.

### **9.6.4. Withdrawal of Informed Consent for Donated Biological Samples**

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed if not already analyzed and the action documented.

As collection of donated biological samples is an integral part of the study then the patient is withdrawn from further study participation. If the patient withdraws consent for the genetic component of the study, then they may continue in the study.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.

## **10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT**

### **10.1. Quality Control and Source Data Verification**

Source data verification will be conducted with due regard to patient confidentiality.

The Clinical Unit will allow the study monitor and Sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, while maintaining the anonymity of the patient and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the Clinical Unit.

### **10.2. Audit/Inspections**

The Clinical Unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The PI must allow the applicable persons access to all relevant facilities and data/documents. The PI must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

### **10.3. Study Monitoring**

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

### **10.4. Data Collection**

The [CCI] system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in [CCI]. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the Clinical Unit. The PI will ensure that the data collected are accurate, complete and legible. Data will be monitored within [CCI] by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within [CCI].

#### 10.4.1. Case Report Forms and Source Documents

All data obtained using paper collection methods during the clinical study will be recorded in [CCI]. All source documents from which [CCI] entries are derived should be placed in the patient's personal records.

The original [CCI] entries for each patient will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the PI for resolution.

#### 10.4.2. Access to Source Documents

During the clinical study, a study monitor will make Clinical Unit visits to review protocol compliance, compare [CCI] entries and individual patient's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. [CCI] entries will be verified against source documents. The review of medical records will be handled confidentially to ensure patient anonymity.

Checking of the [CCI] entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IRBs may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and patient confidentiality. The PI assures the Sponsor of the necessary support at all times.

#### 10.5. Data Management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

Since this is a multi-site study, for the purposes of data management processing all data obtained during the clinical study will be recorded in [CCI].

The original [CCI] entries for each subject will be checked against [CCI] and any additional paper source documents as necessary, by the study monitor. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, Sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

Corrections resulting from these validation checks will be confirmed as response to query. This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

## 11. STATISTICAL METHODS

### 11.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should become known, different analyses may be performed. A separate Statistical Analysis Plan (SAP) will be written for the study. Any deviations from the statistical methodology defined in the SAP, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. The verification and review of all statistical modeling assumptions will be documented appropriately.

### 11.2. General Statistical Methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarized for all randomized patients. Pharmacodynamic and PK data will be summarized by treatment. Safety and tolerability data will be summarized by treatment, if applicable.

Frequency counts (number of patients [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if  $n \geq 3$ .

The following rules will apply to any repeated safety assessments occurring within each treatment period:

- If the repeated measurement of a specific parameter occurs before IMP administration (Day 1), then the last obtained value before dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.



The planned sequence for measurement of multiple assessments at the same time point is described in Section 7.3.

For safety assessments performed at the Screening Visit and the Follow-up Visit, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at the Screening Visit the last available value will be used in the summary statistics;
- If the repeated assessment occurs at the Follow-up Visit, the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using CC or later.

#### **11.2.1. Missing Data**

Missing dates and times in the AE data will be handled as described in Section 11.11.1. Concentrations that are non-quantifiable (NQ) in the PK data will be handled as described in Section 11.10.2.

There will be no imputations of other missing data. All patients will be included into the safety analyses as far as the data permit.

### **11.3. Study Populations**

#### **11.3.1. 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.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP will also be presented using the safety analysis set.

#### **11.3.2. Pharmacodynamic Analysis Set**

Analysis of the primary variable, maximum UA excretion in urine per hour (UUA), as well as the secondary variable sUA at 7 days will be done using the Full Safety Analysis Set (FAS) comprising of all patients randomized. Any sensitivity analysis will be considered using the Per Protocol (PP) Set as sensitivity analysis. The PP Set will be defined as all patients in the FAS without major protocol deviations (to be defined before database lock).

### **11.3.3. Pharmacokinetic Analysis Set**

The PK analysis set for each cohort 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, 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 study may be deleted from summary statistics and statistical analysis if vomiting occurred at or before median t<sub>max</sub>

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

The exclusion of any patients or time points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any patients excluded from the PK analysis set will be listed only. Concentration data for patients excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

### **11.3.4. Randomized Set**

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

## **11.4. Determination of Sample Size**

Basis for this sample size calculation is the study RDEA3170-204. Baseline (as well as Day 7) UUA data are highly skewed and hence log-transformation is applied.

Based on the RDEA3170-204 study, we assume that the within patient SD for the between treatment difference in UUA (comparing within patient changes on log-scale from baseline to day 7 for the respective treatments) is 0.32.

A study with 10 patients completing each sequence of treatments (dapagliflozin-placebo or placebo-dapagliflozin) will then (under the assumed SD above) estimate the true, unknown, mean ratio for dapagliflozin/placebo with a precision of 16.6% as half-width of the 95% confidence interval (CI).

Thus, 24 patients in total were randomized to ensure 20 (2\*10) patients complete the study (12 randomized patients per sequence).

Twenty patients completing their treatment sequence, is based on previous experience of studies investigating relative bioavailability in presence of concomitant treatments, seen as a suitable sample size. As based on previous experience of studies investigating relative bioavailability in presence of concomitant treatments, 12 patients completing each treatment sequence is considered a suitable sample size.

### **Interim Analysis of Sample Size and Power of the Statistical Test**

During the Blind Data Review Meeting (BDRM), the unblinded data were reviewed and [REDACTED] patients from site [REDACTED] were identified as invalid for purposes of analysis of the primary endpoint.

Based on these results, it was decided to enroll an additional 12 patients to ensure an adequate sample size to evaluate the effects of intensive UA lowering with RDEA3170, febuxostat and dapagliflozin on urinary excretion of UA. This will allow for 36 evaluable patients overall; of these it is expected that at least 20 patients will provide evaluable data for the primary endpoint.

### **11.5. Protocol Deviations**

Protocol deviations are considered any deviation from the CSP relating to a patient, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, patient was not fasted as per the protocol requirements before and after dosing)
- Time window deviations for safety and/or PD and/or PK assessments
- Patients receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD), which stipulates tolerance windows for safety, PD and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting before database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by patient.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

### **11.6. Patient Disposition**

A randomization listing will be presented and include the following: each patient's randomization number, the patient's full enrolment number, the treatment sequence to which the patient has been randomized and the country where the location of the study center is located.

Patients and/or data excluded from the PD/PK analysis set will be listed including the reason for exclusion. Patient disposition will be summarized and will include the following information: number of patients randomized and dosed, number and percentage of patients completing the study and the number and percentage of patients who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all patients randomized.

Patient discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

### **11.7. Demographic and Baseline Data**

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by patient. Demographic characteristics (age, gender, race and ethnicity) and patient characteristics (height, weight and BMI) will be summarized separately for all randomized patients. The denominator for percentages will be the number of randomized patients.

Medical history data will be listed by patient including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA Preferred Term, start date and stop date (or ongoing if applicable).

A summary of the number and percentage of patients who had relevant medical histories will be presented by treatment sequence and for all patients for the medical history Preferred Term.

### **11.8. Prior and Concomitant Medication and Drug Administration**

#### **11.8.1. Prior and Concomitant Medication**

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 [REDACTED].

Prior and concomitant medication will be listed by patient and will include the following information: reported name, Preferred Term, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the Sponsor's drug dictionary.

### **11.8.2. Drug Administration**

Drug administration dates and times will be listed for each patient and treatment period.

## **11.9. Pharmacodynamic Analysis**

### **11.9.1. Pharmacodynamic Variables**

The following PD variables will be assessed.

#### **Primary Variable**

- Uric acid excretion in urine per hour

Peak UA excretion during the first 8 hours maximum UA excreted as measured in mg, in an interval out of the first 8 hours on Day 7 (after 7 days of treatment).

#### **Secondary Variable**

- Serum UA

Serum UA levels on Day 7 (after 7 days of treatment).

### **11.9.2. Presentation of Pharmacodynamic Data**

A listing of PD blood sample and urine collection times, as well as derived sampling time deviations will be provided. Serum and urine UA concentrations will be summarized by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum and maximum.

### **11.9.3. Statistical Analysis of Pharmacodynamic Data**

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

Analysis of the primary variable will be done on log-transformed values, looking at changes at day 7 of treatment (Day 7) from maximum baseline (Day -1) excretion. A mixed effects Analysis of Variance (ANOVA) model, correcting for treatment (dapagliflozin/placebo) and sequence (dapagliflozin-placebo or placebo-dapagliflozin) as fixed effects as well as patient within sequence as random effect, will be used.

Results will be presented as geometric mean ratios from baseline within treatment with 95% CIs, based on Student's t-distribution. A geometric mean ratio for change from baseline between treatments with 95% CI will also be constructed, using Student's t-distribution.

Analysis of the secondary variable sUA will be conducted in an equivalent way as UUA, using log-transformed values and change from baseline (Day -1) to Day 7. A mixed effect model correcting for the same fixed and random effects as for UUA will be employed. Results will be presented in the same way as the results for UUA. No adjustment for multiplicity will be done for secondary variables, due to the explorative nature of the study.

Effects on kidney function (secondary objective, variables: Estimated glomerular filtration rate cystatin-C, creatinine) will be assessed in the same way as UUA and sUA. Log-transformation of data will be done when needed for application of statistical models based on normal theory.

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.

Analysis of the secondary variable sUA will be conducted using a similar approach as described above for the analysis of UUA, using log-transformed values and change from baseline (Day -1) to Day 7

In these analyses, an adjustment for multiple comparisons will not be considered.

For all ANOVA models described above the geometric mean ratios, their 95% CI, along with the ratios of individual patient values will be plotted to visualize the treatment comparisons.

## 11.10. Pharmacokinetic Analysis

### 11.10.1. Pharmacokinetic Parameters

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

#### Primary PK parameters

AUC <sub>τ</sub>	Area under plasma concentration time curve over a dosing interval (24 hours)
AUC <sub>last</sub>	Area under plasma concentration time curve from time zero to the time of last measurable concentration
C <sub>max</sub>	Maximum observed plasma concentration

#### Secondary PK parameters

t <sub>max</sub>	Time to reach maximum observed plasma concentration
t <sub>last</sub>	Time of last measurable concentration

Additional PK parameters may be determined where appropriate.

### 11.10.2. Derivation of Pharmacokinetic Parameters

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

Pharmacokinetic parameters will be derived using non-compartmental methods with [REDACTED]. All descriptive and inferential statistical computations will be performed using [REDACTED].

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.

C<sub>max</sub> and t<sub>max</sub> will be obtained directly from the individual concentration-time profiles.

AUC<sub>τ</sub> and AUC<sub>last</sub> 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 AUC<sub>τ</sub> and AUC<sub>last</sub> 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 C<sub>max</sub>.

### 11.10.3. Presentation of Pharmacokinetic Data

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized by treatment and analyte using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, geometric +SD, geometric –SD arithmetic mean, arithmetic SD, median, minimum and maximum. For t<sub>max</sub> and t<sub>last</sub>, only n, median, minimum and maximum will be presented.

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

The CV% is calculated as  $100 \cdot \sqrt{(\exp(s^2) - 1)}$  where s is the SD of the log-transformed data.

The geometric ±SD (geometric +SD and geometric –SD) is calculated as  $\exp[\mu \pm s]$  For 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:

- C<sub>max</sub> – will be presented to the same number of significant figures as received from the bioanalytical laboratory.
- t<sub>max</sub> and t<sub>last</sub> – will be presented as received in the data, usually to 2 decimal places.
- AUC<sub>τ</sub> and AUC<sub>last</sub> - will be presented to 3 significant figures.

For PK concentration data, all descriptive statistics will be presented to 4 significant figures except for the minimum and maximum which will be presented to 3 significant figures.

For PK parameters data, the descriptive statistics will be presented according to the following rules:



- C<sub>max</sub>, AUC<sub>τ</sub>, AUC<sub>last</sub> – all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.
- t<sub>max</sub>, t<sub>last</sub> – all descriptive statistics will be presented as received in the data, usually to 2 decimal places.

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 there is NR, these will be set to missing.

- 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 of the values are NQ, the mean, SD, geometric mean, geometric +SD, geometric –SD 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 +SD, geometric –SD 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.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale with all treatments overlaid on the same plot and separate plots for each patient and each analyte.

Combined individual plasma concentration versus actual times will be plotted in linear and semi-logarithmic scale. Separate plots for each treatment and each analyte.

Geometric mean plasma concentration ( $\pm$ SD) versus nominal sampling time will be plotted in linear and semi-logarithmic (no SD presented) scale with all treatments overlaid on the same figure and separate figure for each analyte.

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.

#### **11.10.4. Statistical Analysis of Pharmacokinetic Data**

Pharmacokinetic variables ( $AUC_{\tau}$ ,  $AUC_{last}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{last}$ ) and plasma concentrations of RDEA3170, M1, M8, febuxostat and dapagliflozin will be analyzed using the PK set as defined above. Plasma concentrations of RDEA3170, M1, M8, febuxostat and dapagliflozin will be presented descriptively by IMP, study day/treatment and time point, using both summary tables and figures as well as individual plots of plasma concentration vs. time and day per IMP. Derived pharmacokinetic parameters will be presented descriptively by IMP and study day/treatment.

To assess the potential drug-drug interaction of RDEA3170 and febuxostat given with and without dapagliflozin, the natural log-transformed PK parameters  $AUC_{\tau}$ ,  $AUC_{last}$  and  $C_{max}$  of RDEA3170, M1, M8 and febuxostat will be separately analyzed using a mixed effects ANOVA model, fitting a fixed effect for treatment and random effect for patient. The point estimate and 90% CI for the difference between treatments (RDEA3170 + febuxostat + dapagliflozin and RDEA3170 + febuxostat) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (RDEA3170 + febuxostat + dapagliflozin and RDEA3170 + febuxostat). Additionally, for each treatment, back transformed geometric means together with 95% CIs for  $AUC_{\tau}$ ,  $AUC_{last}$  and  $C_{max}$ , for RDEA3170, M1 and M8 will be estimated and presented.

For all ANOVA models described above the geometric mean ratios, their 95% CI, along with the ratios of individual patient values will be plotted to visualize the treatment comparisons.

#### **11.11. Analysis of Safety Data**

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median,

maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables will be based on the safety analysis set.

Adverse events will be summarized by Preferred Term and SOC using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of patients who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized. Adverse events that occur before dosing will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs, will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory and in Système International units in the CSR.

Out-of-range values for safety laboratory, vital signs and ECG will be flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (e.g., AZ, program or laboratory ranges).

#### **11.11.1. Adverse Events**

All AEs will be coded using MedDRA vocabulary, and will be listed for each patient. 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.
- Treatment period 2: AEs with start date/time at the time of or after dosing in Treatment period 2 until the Follow-up Visit.

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.

Adverse events will be summarized by treatment (where treatments will be pooled across treatment periods) and overall for all patients, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and Preferred Term. Furthermore, separate listings of SAEs, AEs that led to discontinuation (DAEs) and AEs that led to death will be presented.

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 last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of patients. In addition, a separate tabulation will be presented showing the number of events by treatment and Preferred Term.

Lastly, an overview of all AEs will be presented, separately for the number and percentage of patients and the number of events. This will include categories for any AE, AEs with outcome of death and SAEs.

#### **11.11.2. Potential Events of Diabetic Ketoacidosis**

All potential events of DKA will be recorded in [REDACTED] 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.

The DKA Adjudication Committee will be kept blinded to the study drug treatment received by each patient with a potential DKA event in the clinical study. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events/cases.

#### **11.11.3. Vital Signs**

The results of the vital signs measurements will be listed by patient and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be the pre-dose assessment on Day 1 in each treatment period. Descriptive statistics will be presented by treatment and time point for both observed values and changes from baseline.

#### **11.11.4. Resting 12-lead Electrocardiogram**

12-Lead ECG results will be listed for each patient.

#### **11.11.5. Physical Examination**

The baseline/screening results of the physical examination will be documented in medical history for each patient.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

Body weight will be listed by patient and time point.

#### **11.11.6. Laboratory Assessments**

Hematology and clinical chemistry values will be listed by patient and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations including





## **12. ADVERSE EVENTS**

### **12.1. Definitions**

#### **12.1.1. Definition of Adverse Events**

An AEs is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG).

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the patient has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

#### **12.1.2. Definitions of Serious Adverse Event**

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix 15.1 of this CSP.

#### **12.1.3. Other Significant Adverse Events**

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or where relevant AEs leading to discontinuation of



IMP (DAEs) and withdrawal from the study. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered Other significant adverse events (OAEs) and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

## **12.2. Recording of Adverse Events**

### **12.2.1. Time Period for Collection of Adverse Events**

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.

### **12.2.2. Follow-up of Unresolved Adverse Events**

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the ClinBase.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **12.2.3. Variables**

The following variables will be collected for each AE:

- Adverse event diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Principle Investigator causality rating against the IMP (yes or no)
- Action taken with regard to IMP
- Adverse event caused patient's withdrawal from study (yes or no)

- Outcome

Additional variables will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities)

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

#### 12.2.4. Causality Collection

The Investigator will assess causal relationship between IMP and each AEs, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?”

For SAEs, causal relationship will also be assessed for other medication, any additional drug and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes”.

A guide to the interpretation of the causality question is found in Appendix 15.1 of this CSP.

#### 12.2.5. Adverse Events Based on Symptoms and Signs

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “*Have you had any health problems since you were last asked?*”, or revealed by observation will be collected and recorded in the DCI.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms.

However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 12.2.6. Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information.

Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

### 12.2.7. Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3$  x upper limit of normal (ULN) together with total bilirubin  $\geq 2$  x ULN may need to be reported as SAEs. Please refer to Appendix 15.3 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

## 12.3. Reporting of Serious Adverse Events

All SAEs will be reported, whether or not considered causally related to the IMP, or to the study procedure(s). All SAEs will be recorded in the CCI.

If any SAE occurs in the course of the study, then the PI or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the PI or other site personnel to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry

site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

The PI or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

## **13. LEGAL AND ADMINISTRATIVE ASPECTS**

### **13.1. Archiving of Study Documents**

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the patients. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

The Investigator's Site File will be archived by the contract research organization (CRO) for 15 years after completion of the study.

### **13.2. Publication of Study Results**

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, the PI may prepare a joint publication with AstraZeneca. The PI must undertake not to submit any part of the individual data from this CSP for publication without prior consent of AstraZeneca at a mutually agreed time.

### **13.3. Clinical Study Report**

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IRB and the national Regulatory Authority in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

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## 15. APPENDICES

### 15.1. Additional Safety Information

#### Further Guidance on the Definition of a Serious Adverse Event

##### *Life-threatening*

‘Life-threatening’ means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

##### *Hospitalization*

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

##### *Important Medical Event or Medical Intervention*

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.



- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

### **A Guide to Interpreting the Causality Question**

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the IMP.

- Time Course/Exposure to suspect drug:  
Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile:  
Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR, could the AE be anticipated from its pharmacological properties?
- Dechallenge experience:  
Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause:  
The AE cannot be reasonably explained by other etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience:  
Did the AE reoccur if the suspected drug was reintroduced after having been stopped?  
*Note: AstraZeneca would not normally recommend or support a rechallenge.*
- Laboratory tests:  
A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## 15.2. International Airline Transportation Association 6.2 Guidance Document

### Labeling and Shipment of Biohazard Samples

International Airline Transportation Association classifies bio hazardous agents into 3 categories ([http://www.iata.org/whatwedo/cargo/dangerous\\_goods/infectious\\_substances.htm](http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)). For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are for example, Ebola and Lassa Fever viruses. Category A pathogens:

- Are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D and E viruses and HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA Instruction 650.

**Exempt** refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.  
([http://www.iata.org/whatwedo/cargo/dangerous\\_goods/infectious\\_substances.htm](http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm))
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

### **15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law**

Guidance used: FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

#### **Introduction**

During the study, the PI will remain vigilant for increases in liver clinical chemistry. The PI is responsible for determining whether a patient meets PHL criteria at any point during the study.

The PI participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug Induced Liver Injury (DILI) caused by the IMP.

The PI is responsible for recording data pertaining to PHL/HL cases and for reporting AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

#### **Definitions**

Potential Hy's Law

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 3 \times$  ULN and total bilirubin (TBL)  $\geq 2 \times$  ULN at any point during the study irrespective of an increase in Alkaline phosphatase (ALP).
- The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law

- AST or ALT  $\geq 3 \times$  ULN **and** TBL  $\geq 2 \times$  ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.
- The elevations do not have to occur at the same time or within a specified time frame.

### **Identification of Potential Hy's Law Cases**

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

The PI will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see definition above) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

### **Follow-Up**

#### ***Potential Hy's Law Criteria not Met***

If the patient does not meet PHL criteria the PI will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

#### ***Potential Hy's Law Criteria Met***

If the patient does meet PHL criteria the PI will:

- Notify the AstraZeneca representative who will then inform the central study team.

The study physician contacts the PI, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data.

Subsequent to this contact the PI will:

- Monitor the patient until liver clinical chemistry variables and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- Complete the 3 Liver CRF Modules as information becomes available.

If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

### **Review and Assessment of Potential Hy's Law Cases**

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the clinical chemistry abnormality was initially detected, the study physician contacts the PI in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the PI will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would clarify the ALT or AST and TBL elevations other than IMP causality:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.



#### **15.4. Actions Required in Cases of a Renal-related or Kidney Stone Treatment-emergent Adverse Event or a Serum Creatinine Elevation**

During the course of the study, the Investigator will remain vigilant for symptoms or signs of renal-related events, kidney stone events or changes in renal function.

##### **Signs and Symptoms Suggestive of Renal Injury or Kidney Stone**

If after initiation of study medication a patient experiences signs or symptoms suggestive of acute renal injury (e.g., reduced urinary output, generally feeling unwell, fatigue, nausea, vomiting, metallic taste, or loss of appetite) or nephrolithiasis (e.g., flank pain or hematuria), the patient should be evaluated by a physician and an assessment of serum creatinine, blood urea nitrogen, and urinalysis should be performed via central laboratory testing (preferred) and/or local laboratory testing, as appropriate, for determination of renal function. Any abnormal results should be treated as medically appropriate by the treating physician. A careful review of any AEs and evaluation for potential contributing factors should occur. All symptoms, testing and results will be documented in source documents and [REDACTED]

##### **Renal Function**

Renal function will be assessed during the course of the study at pre-specified times by measuring serum creatinine and calculating the estimated CrCl. All results will be documented in source documents and [REDACTED]. Laboratory values that meet the criteria for alert (as described in the following paragraphs) will be sent to Investigators by the central laboratory. Any clinically significant serum creatinine abnormality should be reported as an AE. The Investigator will need to determine if randomized study medication is to continue or be interrupted and the decision must be documented in source documents. As described in the following paragraphs, if a serum creatinine elevation is  $\geq 3.0$  x baseline serum creatinine, if absolute serum creatinine value is  $\geq 4.0$  mg/dL, or if estimated CrCl value is  $< 25$  mL/min at any time during the study, then randomized study medication must be permanently discontinued.

##### ***Serum Creatinine***

Serum creatinine values will be measured at pre-specified and unscheduled visits throughout the study and analyzed relative to the baseline serum creatinine. Elevations in serum creatinine will be defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines on Acute Kidney Injury and the Acute Kidney Injury Network (Ricci *et al* 2011). Any serum creatinine elevations that are identified based on this definition will be flagged as alert values and sent to the Investigators for clinical assessment. If a serum creatinine value meeting the criteria

described in this section is identified, the patient should return to the study site for further evaluation to determine the etiology for the serum creatinine elevation. The treating physician should determine if any intervention is required and if any AEs should be reported. Any potential factors contributing to the serum creatinine elevation should be reported. Additional testing of serum creatinine should be performed. Investigators should consider temporarily stopping concomitant therapies that are known to increase serum creatinine or impact renal function as medically appropriate.

Any patient who has a serum creatinine elevation should be monitored as follows:

1. Serum creatinine elevations  $\geq 1.5$  to  $< 2.0$  x baseline.

For a serum creatinine elevation  $\geq 1.5$  to  $< 2.0$  x baseline serum creatinine value, the Investigator will be notified and the patient will return to the study site for further evaluation. The randomized study medication may be temporarily interrupted at the Investigator's discretion, and retest of the serum creatinine should be performed as soon as possible.

- If the retested serum creatinine value is resolved to  $\leq 1.2$  x baseline serum creatinine value, the patient should be followed per the schedule defined by the protocol and be re-evaluated at the next study visit. Any interrupted randomized study medication may be resumed after resolution of the serum creatinine elevation.
- If the retested serum creatinine value is  $> 1.2$  x baseline serum creatinine value, additional retests of serum creatinine and a decision to continue or interrupt randomized study medication should be conducted weekly until resolution to  $\leq 1.2$  x baseline value. Any interrupted randomized study medication may be resumed after resolution of the serum creatinine elevation.
- If randomized study medication was not interrupted, and 3 consecutive retests have serum creatinine values  $> 1.2$  x baseline, randomized study medication must be permanently discontinued. The patient will be encouraged to remain in the study and follow the protocol schedule.

Consult Figure 1 Panel A (page 108) for a flow chart diagram.

2. Serum creatinine elevations  $\geq 2.0$  to  $< 3.0$  x baseline or an absolute value  $\geq 3.0$  mg/dL.

If a serum creatinine elevation is  $\geq 2.0$  to  $< 3.0$  x baseline serum creatinine value or an absolute serum creatinine value of  $\geq 3.0$  mg/dL, randomized study medication must be temporarily interrupted, and retest of the serum creatinine should be performed as soon as possible.

- If the retested serum creatinine value is resolved to  $\leq 1.2$  x baseline serum creatinine value, randomized study medication may be restarted at the Investigator's discretion and monitoring of the serum creatinine should return to the protocol defined schedule.
- If the retested serum creatinine value is  $> 1.2$  x baseline serum creatinine value, additional retests of serum creatinine should be performed weekly until resolution to  $\leq 1.2$  x baseline. Once the serum creatinine elevation is resolved to  $\leq 1.2$  x baseline, randomized study medication may be resumed at the Investigator's discretion and monitoring of the serum creatinine should return to the protocol defined schedule.
- If the results of 3 consecutive retests of serum creatinine are  $> 1.2$  x baseline serum creatinine value, randomized study medication must be permanently discontinued. The patient will be encouraged to remain in the study and follow the protocol schedule.

Consult Figure 1 Panel B (page 109) for a flow chart diagram.

3. Serum creatinine elevations  $\geq 3.0$  x baseline or an absolute value  $\geq 4.0$  mg/dL

If a serum creatinine elevation is  $\geq 3.0$  x baseline serum creatinine value or an absolute serum creatinine value of  $\geq 4.0$  mg/dL, randomized study medication must be permanently discontinued. A retest of the serum creatinine should be performed as soon as possible, and repeat testing should be performed weekly until resolution to  $\leq 1.2$  x baseline value. Randomized study medication may not be restarted. The patient will be encouraged to remain in the study and follow the protocol schedule.

Consult Figure 1 Panel C (page 110) for a flow chart diagram.

4. Patient's Last Study Visit and Post-Follow-Up Assessments.

If at the patient's last study visit the serum creatinine value is  $\geq 0.3$  mg/dL above baseline serum creatinine value, the patient is required to return to the site in 1 month for post-follow-up repeat assessments.

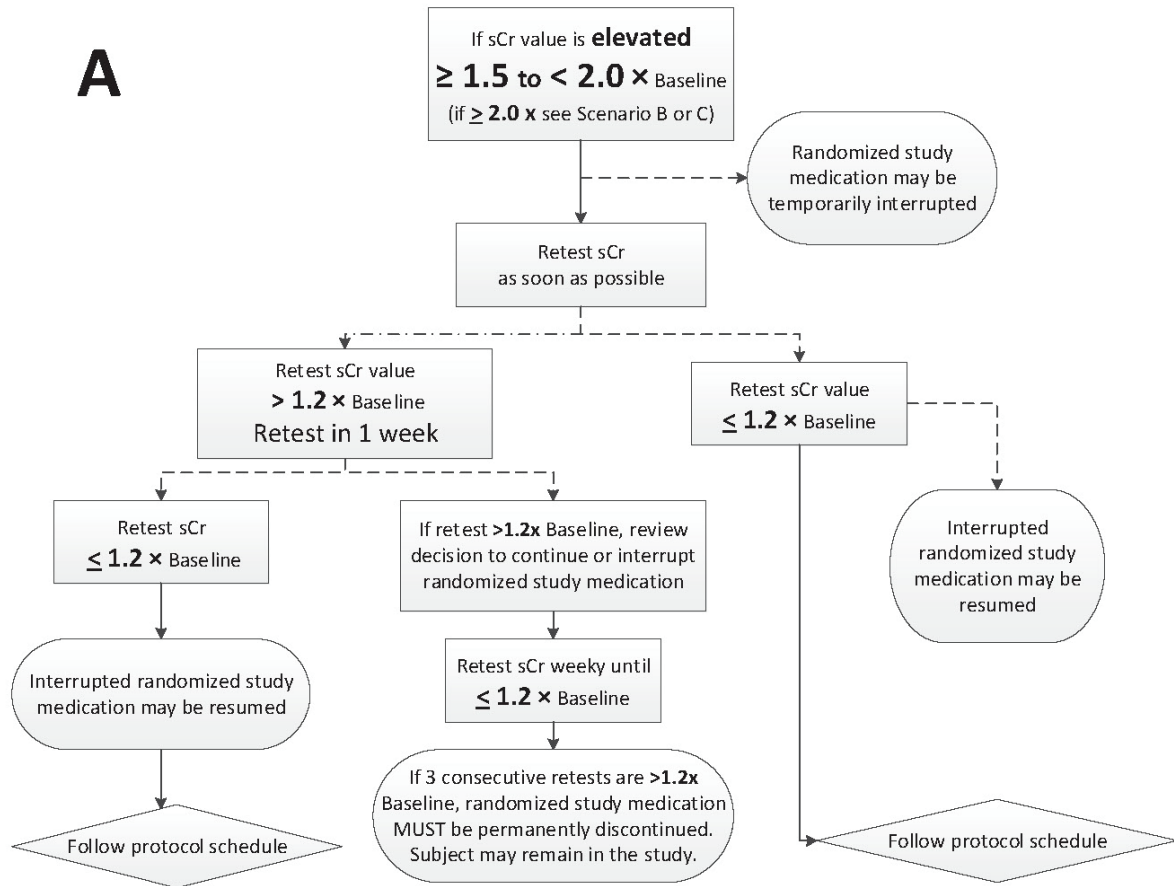
- If the retested serum creatinine value is within  $< 0.3$  mg/dL above baseline serum creatinine value, no further follow-up is required.
- If the retested serum creatinine value is  $\geq 0.3$  mg/dL above baseline serum creatinine value, repeat testing of serum creatinine should be performed monthly until the value is  $< 0.3$  mg/dL above baseline serum creatinine value or until 3 monthly assessments after their last study visit have taken place, whichever occurs first.

Consult Figure 1 Panel D (page 110) for a flow chart diagram.

## 5. Other Considerations

Patients who have a serum creatinine value of  $\geq 1.5$  x baseline should be encouraged to remain adequately hydrated.

**Figure 1: Flow chart for serum creatinine elevation monitoring**



**Figure 1 (continued): Flow chart for serum creatinine elevation monitoring**

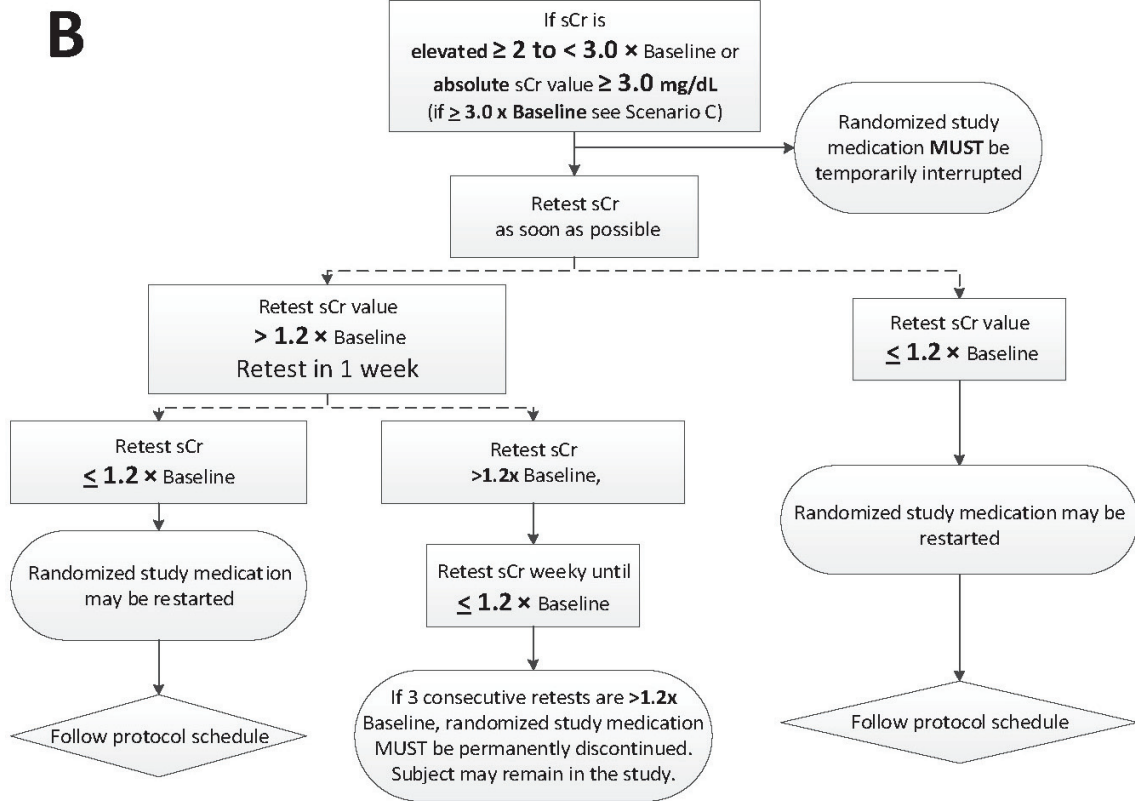
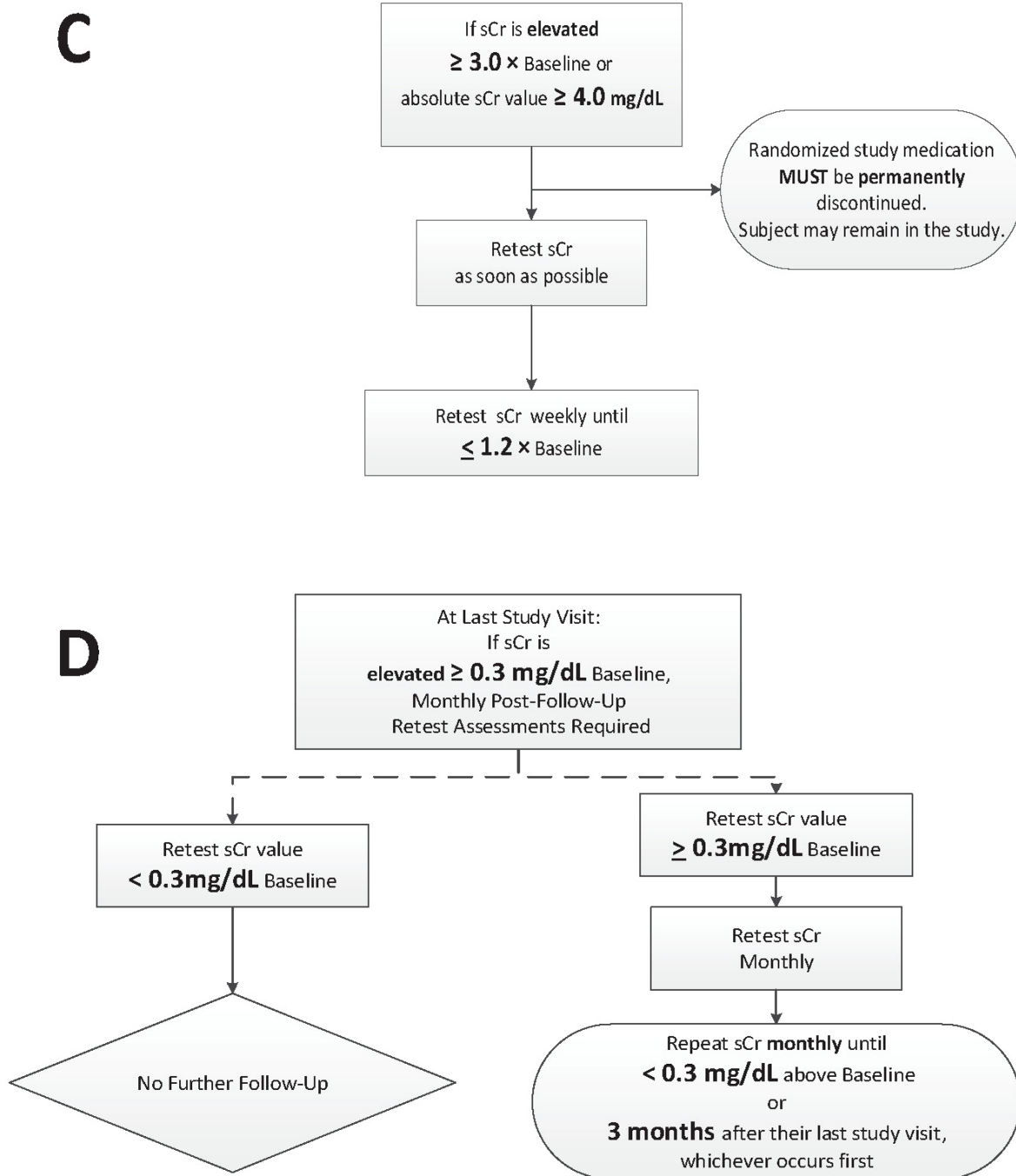


Figure 1 (continued): Flow chart for serum creatinine elevation monitoring



### ***Estimated Creatinine Clearance***

If a patient has an estimated CrCl value of  $< 25$  mL/min at any time during the study, randomized study medication must be permanently discontinued.

If a patient has a baseline estimated CrCl value of  $\geq 45$  mL/min that decreases to  $< 30$  mL/min, randomized study medication must be temporarily interrupted and a retest of CrCl should be performed as soon as possible.

- If the repeated test confirms the CrCl value of  $< 30$  mL/min, the patient will permanently discontinue randomized study medication.
- If the repeated test of CrCl shows a value of  $> 30$  mL/min, randomized study medication may be restarted with continued routine monitoring.

If a patient has a baseline estimated CrCl value of  $< 45$  mL/min that decreases to  $< 30$  mL/min, a retest of the CrCl should be performed as soon as possible.

- If the repeated test confirms the CrCl value of  $< 30$  mL/min, a decision regarding continuation of study medication should be discussed with the Sponsor's Medical Monitor.
- If the repeated test of CrCl shows a value of  $> 30$  mL/min, the patient should be followed per the schedule defined by the protocol and be re- evaluated at the next study visit.

### ***Other Changes***

If a patient develops kidney stones (as confirmed and documented by imaging or passage of kidney stone) at any time during the study, the patient will discontinue randomized study medication and be encouraged to remain in the study for continued safety assessments. If a kidney stone is passed, it should be collected and submitted to pathology for a kidney stone analysis.

### ***References***

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## 16. SIGNATURES

### 16.1. Declaration of Sponsor or Responsible Medical Expert (Physician)

**Protocol Title:** Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

This Clinical Study Protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

#### Sponsor Signatory/Responsible Medical Expert

PPD  


Signature

11 May 2018

Date of signature

PPD  




**16.2. Declaration of Sponsor or Responsible Medical Expert (Biostatistician)**

**Protocol Title:** Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

This Clinical Study Protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

**Sponsor Signatory/Responsible Medical Expert**

PPD [Redacted Signature] \_\_\_\_\_ 11 MAY 2018 \_\_\_\_\_  
Signature Date of signature

PPD [Redacted]

### 16.3. Declaration of the Principal Investigator (Baltimore)

**Protocol Title:** Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

This Clinical Study Protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

Principal/Coordinating Investigator



10 May 2018

Date of signature

#### 16.4. Declaration of the Principal Investigator (Los Angeles)

**Protocol Title:** Quantifying Uric Acid Excretion with RDEA3170, Febuxostat and Dapagliflozin

This Clinical Study Protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

**Principal/Coordinating Investigator**



10 MAY 2018

Date of signature