AstraZeneca

| **Clinical Study Protocol** | |
|---|---|
| Drug Substance | RDEA3170 |
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# Effects of Intensive Uric Acid Lowering Therapy with RDEA3170 (Verinurad) and Febuxostat in Patients with Albuminuria

**Sponsor:** AstraZeneca AB, 151 85 Södertälje, Sweden

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# VERSION HISTORY

**Version 5.0, 20 Nov 2017**
Changes to the protocol are summarised below:

**Protocol synopsis and Section 3.1 (Inclusion criteria):**

- Increased the planned number of sites from 'up to 15' to 'up to 25', to facilitate recruitment in the study.
- The serum uric acid level as an inclusion crierion was modified from >6.0 to ≥6.0 mg/dL - to facilitate enrolment.

**Sections 4.1.4 and 4.2.1 (MRI and Reactive Hyperemia assessments):**

- Added a sentence, that not performing of Reactive Hyperemia assessment due to logistical reason will not be considered as a protocol violation.

**Minor typographical errors**

**Version 4.0, 17 Aug 2017**
Changes to the protocol are summarised below:

**Section 3.1 (Inclusion criteria):**

- Updated criterion number 4, to allow inclusion of patients who are not treated with an ACE inhibitor or an ARB, in scenarios that preclude use or safe use of an ACE inhibitor or an ARB.

**Section 3.2 (Exclusion criteria) and other related sections:**

- Updated criterion number 4, to allow enrollment of patients with a prior history of gout, should prophylaxis therapy not be needed or suitable in the opinion of the investigator.

**Section 5.1.2 (MRI procedures):**

- Minor typographical updates.

**Version 3.0, 25 May 2017**
Changes to the protocol are summarised below:

**Table 1 (Study plan) and various other sections:**

- In response to comments from FDA on 16 May 2017, a new visit has been added 1 week post randomization, focusing on safety monitoring. This new visit encompasses safety and CCI , PK sampling, collection of vitals, adverse event and concomitant medication. With the addition of the new visit, subsequent visit numbers have been updated.
- Additionally, AstraZeneca will add procedures to visits at weeks 2 and 4 making them consistent with the new visit at week 1, thereby further increasing patient monitoring for the safety of patients and simplifying the protocol to reduce risk and increase quality.

**Section 4.1 (Screening/enrolment period):**

- Wording was added to allow the screening period to be extended beyond 6 weeks in case of logistical issues.

**Table 2 (Blood volumes drawn at each visit):**

- The addition of a new visit after randomization and updating the lab assessments of other

treatment visits to be similar to the new visit, resulted in increase in the blood volume.

**Section 7.1 (Identity of investigational product(s)):**

- The text regarding drug accountability was updated to be consistent with Table 1.
- Information on the RDEA3170 formulation used in the study was added.

**Corrected typographical errors in the document.**

**Version 2.0, 05 May 2017**

Changes to the protocol are summarised below:

**Study title, protocol synopsis and various other sections of the protocol:**

- Following FDA comments received on 02 May 2017 on the intended patient population in the study, and with reference to international guidelines - the study title, synopsis and other sections in the protocol where it was stated that patients suffering from "mild to moderate CKD" has been amended to state that patients suffering from "albuminuria".

**Protocol synopsis, Sections 1.3.6 (Invasive/non-invasive procedures), 5.1.4.1 (Flow mediated dilatation) and wherever applicable:**

- Changed the language related to CCI systems technology and the terminology of "Flow Mediated Dilatation" (FMD) to "Reactive Hyperemia", and by stating in few sections of the protocol that Reactive Hyperemia is also referred to as FMD.
- Added additional conditions that exclude the assessment of Reactive Hyperemia and added a reference to the manual describing the details of the assessment.

**List of abbreviations and definition of terms:**

- Updated the list with LMP and SDTM

**Section 1.5.2 (Data monitoring committee):**

- The section is updated to clarify that it only applies to external reviews of the emerging data. An internal periodic review of the safety data will be carried out at monthly intervals by the physicians at CCI and AstraZeneca.

**Table 1 (Study plan):**

- Specified the measurement of NT-pro-BNP as a biomarker for the exploratory objective at Visits 2, 5 and 6

**Section 3.1 (Inclusion criteria):**

- The definition of "post-menopausal" was refined to ensure women not having had their menses due to an alternative medical cause would not be considered post-menopausal.

**Section 3.8 (Restrictions) 5.1.2 (MRI procedures) and 5.1.4.1 (Flow Mediated Dilatation):**

- Specified the food restriction and water intake before Reactive Hyperemia and MRI procedures, and the reporting of clinically significant findings by investigators.

**Table 2 (Blood volumes drawn at each visit):**

- Corrected typographical errors in the calculation of the volume of blood drawn.

**Section 5.1.4.1 (Flow Mediated Dilatation):**

- Included the conditions (Raynaud's or carpal tunnel syndromes, atrial fibrillation and

premature ventricular contractions) that excludes the assessment of Reactive Hyperemia.

- Mentioned about the device manual that will be shared with sites for the Reactive Hyperemia procedure.
- Added date of Last Menstrual Period as an additional information collected for the confounding factors.

**Table: 7 (Laboratory safety variable):**

- Included Blood Urea Nitrogen as an additional safety parameter.

**Section 5.4.3 (Storage and destruction of pharmacokinetic samples):**

- Corrected the Biobank details.

**Section 7.2 (Dose and treatment regimens):**

- Clarification on the bottles from which the medication is taken on visit days.

**Section 8.5.2 (Analysis of the secondary variable (s)):**

- Additional text added to clarify that for parameters assessed both at Visit 1 and prior to randomization at Visit 2 the mean of the values collected at the two visits may be used as baseline for assessments of change from baseline.

**Updated section numbers:**

The heading for Section number 3.3 was missed out in the original version of the protocol, updating which lead to changes in the numbering of subsequent sections.

**Version 1.0, 16 March 2017**

Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

# CLINICAL STUDY PROTOCOL SYNOPSIS

## Effects of Intensive Uric Acid Lowering Therapy with RDEA3170 and Febuxostat in Patients with Albuminuria

### International Co-ordinating Investigator

Not applicable.

### Study site(s) and number of patients planned

The study will be performed by CCI on behalf of AstraZeneca. The study sites will be selected by CCI from a network of associated sites. The study will aim to randomize approximately 60 patients at up to 25 investigational sites.

| Phase of development II |
|---|

### Study design

This is a randomized, double-blind, double-dummy, placebo-controlled, parallel, independent groups, repeated measures study designed to evaluate signals of potential clinical benefit of the combination of RDEA3170 and febuxostat in lowering concentrations of circulating uric acid and thus improving kidney or cardiovascular status of patients with hyperuricemia, albuminuria, and Type 2 diabetes.

Evidence shows independent associations between elevated serum uric acid levels and the risk of chronic kidney and cardiovascular disease even though the role of hyperuricemia (elevated uric acid in the blood) in the development of chronic kidney disease and cardiovascular disease is still unclear, and clinical studies have reported conflicting results. RDEA3170 (verinurad) is a novel inhibitor of the renal urate transporter URAT1in Phase 2 development for treatment of hyperuricemia and gout. Results to date have demonstrated that, in combination with the drug febuxostat, RDEA3170 safely and effectively lowers uric acid levels in patients with recurrent gout. The efficacy of the combination of RDEA3170 and febuxostat provides a unique opportunity to study whether intensive therapy to reduce uric acid levels can improve kidney or cardiovascular function.

This study aims to investigate whether the combination of RDEA3170 and febuxostat can improve kidney function in patients with albuminuria, hyperuricemia, and Type 2 diabetes mellitus, but no prior history of gout (unless initiation of prophylaxis therapy is not be needed in the opinion of the investigator). Changes in kidney and cardiovascular function will be monitored using the urinary albumin to creatinine ratio and glomerular filtration rate, as well as functional renal and cardiac magnetic resonance imaging. The study objectives and endpoints are described more fully in the following section of the synopsis. Patients will be

screened for entry into the study at Visit 1. Those patients consenting to participate, who meet all of the inclusion and none of the exclusion criteria (except laboratory test based criteria) will enter the screening phase of the study. Within one week of Visit 1 patients will collect three morning void urinary samples on separate, consecutive days. The samples will be delivered to the study site for proteinuria measurements. Those patients with acceptable urinalysis results will be scheduled to participate in Visit 2. Patients eligible to participate in the study will undergo magnetic resonance imaging prior to randomization and before or on the day of Visit 2. Visit 2 will occur no later than six weeks after Visit 1. Patients will be randomized 1:1 at Visit 2 to receive either a combination of RDEA3170 (9 mg once daily) and febuxostat (80 mg once daily) or matching placebo. Patients will be treated for 24 weeks. Markers of kidney function (urinary albumin to creatinine ratio, estimated glomerular filtration rate, serum uric acid, and other markers) will be measured at 1, 2, 4, 12, 24 weeks after randomization, and 4 weeks after the end of treatment. Other endpoints may be assessed less frequently.

Magnetic resonance imaging to examine functional changes in the heart and kidney will be performed at baseline and 24 weeks after randomization. Magnetic resonance imaging of the heart will allow assessment of left ventricular strain and end diastolic volume as sensitive markers of efficacy in pre-symptomatic heart failure frequently present in Type 2 diabetes patients. Blood oxygenation-dependent level magnetic resonance imaging will be utilized to measure kidney oxygenation in addition to the cardiac magnetic resonance imaging parameters described above, in patients undergoing cardiac magnetic resonance imaging. The CCI, via a reactive hyperemic procedure, provides a direct measurement of endothelial dysfunction via a calibrated measurement of arterial compliance over the entire transmural pressure range of the artery at baseline, 12, and 24 weeks. Reactive hyperemia (also referred to as Flow Mediated Dilatation) is defined as the transient change in vasomotor tone which occurs following a brief period of ischemia (e.g., arterial occulusion).

Urine and blood samples will be obtained and stored in a biobank and will be analyzed if there is evidence of efficacy in this study.

## Objectives

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on albuminuria | Urinary albumin to creatinine ratio after 12 weeks of treatment |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on kidney function | Estimated glomerular filtration rate<br>Cystatin C, creatinine |
| To assess the metabolic effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat | Serum uric acid<br>Serum uric acid lowering corrected for estimated glomerular filtration rate |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To assess the structural and functional effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on the heart and kidney using magnetic resonance imaging | Left ventricular cardiac strain, as assessed by magnetic resonance imaging<br>Left ventricular function and mass, as assessed by magnetic resonance imaging<br>Kidney oxygenation, as assessed by blood oxygen level dependent magnetic resonance imaging (BOLD MRI) |
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on biomarkers and parameters related to inflammation, and cardiac health | High sensitivity C-reactive protein<br>High sensitivity Troponin I |
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on cardiovascular parameters | Blood pressure (systolic and diastolic) |
| To assess plasma exposure of RDEA3170 in this patient population | RDEA3170 plasma concentration at trough (approximately 24 h post dosing). |

| **Safety Objective:** | **Outcome Measure:** |
|---|---|
| To assess the safety and tolerability of intensive uric acid lowering therapy with RDEA3170 and febuxostat | Rates of adverse events and serious adverse events<br>Changes in vital signs, physical examinations, and electrocardiograms<br>Changes in clinical laboratory parameters, including assessment of creatinine, cystatin C, and blood urea nitrogen |

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| CCI | Serum aldosterone<br>CCI<br>Hemoglobin A1c |
| CCI | CCI<br>Reactive Hyperemia (also referred to as Flow Mediated Dilatation) of the brachial artery |

## Target patient population

The study will be conducted in male and female adults (≥18 years of age) with Type 2 diabetes who provide informed consent to participate in the study and are not pregnant. Patients will have serum uric acid concentrations ≥6.0 mg/dL and should be receiving stable background standard of care treatment for albuminuria in patients with diabetes for at least 1 month prior to entry into the study. Standard of care therapy should include an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (unless contraindicated, not

tolerated, or in the opinion of the investigator not practically available or suitable). Patients should have an estimated glomerular filtration rate ≥30 mL/min/1.73m$^2$ and a urinary albumin to creatinine ratio between 30 mg/g and 3500 mg/g (inclusive).

Patients with prior exposure to RDEA3170 or treatment with medication for hyperuricemia within the six months preceding randomization will be excluded.

**Duration of treatment**

The screening period will take place from the signing of the informed consent until all baseline assessments have been performed and the patient has been found to meet all inclusion and none of the exclusion criteria no later than 6 weeks after signing the informed consent.

The treatment period will last from randomization until 24 weeks later. Patients will continue to be followed for 4 weeks after end of treatment to allow assessment of any rebound effects on serum uric acid, urinary albumin to creatinine ratio, estimated glomerular filtration rate, and other selected biomarkers.

**Investigational product, dosage and mode of administration**

| Investigational product | Dosage form and strength | Supplier |
|---|---|---|
| Febuxostat | 80 mg capsule for oral administration | AstraZeneca |
| Febuxostat matched placebo | A placebo capsule for oral administration | AstraZeneca |
| RDEA3170 | 9 mg capsules for oral administration | AstraZeneca |
| RDEA3170 matched placebo | Placebo capsules for oral administration | AstraZeneca |

**Statistical methods**

Analyses on the primary objective as well as other efficacy variables will be performed on the Full Analysis Set following the Intent To Treat principle, comprising all patients randomized.

Variables related to safety will be analyzed using the safety analysis set, comprising all patients randomized, exposed to study drug and with available post dose data.

The primary endpoint variable urinary albumin to creatinine ratio will be log-transformed for application of normal theory based statistical models. Variables related to secondary and explorative objectives (as outlined above) may also be log-transformed when viewed as necessary for the same purpose.

Primary analysis will be conducted using a mixed effects model with repeated measures with log-transformed UACR as the response variable, randomized treatment and visit as fixed factors and log-transformed UACR at baseline as covariate. The least squared mean change from baseline in the log-transformed UACR will be calculated by treatment and by visit together with its 95% confidence intervals. The least squared mean difference between the two treatments will be calculated by the same MMRM model by visit together with its 90% confidence interval.

The above least squared mean change from baseline (and the 95% confidence interval) for each treatment and each visit will be exponentiated to yield the least squared mean ratio from baseline for each treatment and each visit together with its 95% confidence interval at the original scale of UACR. The least squared mean difference between the two treatments (and its 90% confidence interval) at each visit will also be exponentiated to yield the least squared mean ratio between the two treatments at each visit and its 90% confidence interval at the original scale of UACR.

Analysis of variables related to secondary or explorative efficacy objectives will be assessed in a similar mixed model analysis with treatment and visit as fixed factors and baseline value as covariate. Log-transformation of values should be done when applicable, also for these variables.

Variables associated with primary, secondary or explorative efficacy objectives will also be presented using standard descriptive statistics by treatment and visit as well as change from baseline. Standard descriptive statistics comprise (but are not limited to) the number of observations, mean value, standard deviation, coefficient of variation (or CV, for log-normal data), median value, minimum and maximum values.

RDEA3170 trough plasma concentrations will be presented using standard descriptive statistics and graphical representation, and stratified by renal function. The relationship between change in serum uric acid and change in log urinary albumin to creatinine ratio (and secondary variables where applicable) will be explored using different types of statistical models, not only linear ones.

Safety variables will be presented using standard descriptive statistics by treatment and visit as well as change from baseline. Standard descriptive statistics for continuous safety variables comprise (but are not limited to) the number of observations, mean value, standard deviation, median value, minimum and maximum values. Standard descriptive statistics for categorical safety variables comprise (but are not limited to) the number of observations and percentages.

Adverse events will be presented according to AstraZeneca standards.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ARB | Angiotensin II Receptor Blocker |
| AST | Aspartate Aminotransferase |
| CDM | Clinical Data Management |
| CKD | Chronic Kidney Disease |
| CrCl | Creatinine Clearance |
| CRF | Case Report Form (electronic/paper) |
| CSA | Clinical Study Agreement |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CV | Cardiovascular or Coefficient of Variation, dependent upon context |
| DILI | Drug Induced Liver Injury |
| ED | Endothelial Dysfunction |
| eGFR | Estimated Glomerular Filtration Rate |
| FMD | Flow Mediated Dilatation (also referred to as Reactive Hyperemia) |
| GCP | Good Clinical Practice |
| HL | Hy's Law |
| IATA | International Airline Transportation Association |
| ICH | International Conference on Harmonization |
| IMP | Investigational Medicinal Product |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LMP | Last Menstrual Period |
| MMRM | Mixed Effects Model with Repeated Measures |
| MRI | Magnetic Resonance Imaging |
| MRI-BOLD | Blood Oxygenation Level Dependent Magnetic Resonance Imaging |
| PHL | Potential Hy's Law |

| Abbreviation or special term | Explanation |
|---|---|
| SAE | Serious Adverse Event |
| SDTM | Study Data Tabulation Model |
| SGLT2 | Sodium-glucose Cotransporter-2 |
| sUA | Serum Uric Acid |
| T2DM | Type 2 Diabetes Melitis |
| TBL | Total Bilirubin |
| UA | Uric Acid |
| UACR | Urinary Albumin to Creatinine Ratio |
| ULN | Upper Limit of Normal |
| URAT1 | Urate Transporter 1 |
| WBDC | Web Based Data Capture |
| XO | Xanthine Oxidase |

# 1. INTRODUCTION

## 1.1 Background and rationale for conducting this study

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 DNA and RNA, the bearers of genetic information. Metabolism of endogenous and ingested purines results in production of urate. In contrast to many lower species, the human body is unable to metabolize urate further, and therefore eliminates urate through excretion. Urate is excreted primarily through the kidneys, but urate is also eliminated through excretion into the intestines, where it can be degraded by the uricase activity in the intestinal microbiome to $CO_2$ and allantoin (Hyndman et al 2016).

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

The level of urate in the circulation is determined by the balance between production and elimination. At steady state production and elimination are similar (Hyndman et al 2016). Pharmacological modification of the levels of urate is possible through multiple mechanisms. Inhibition of xanthine oxidase (XO), a key enzyme in the transformation of purines into urate, lowers serum urate by increasing renal excretion. Inhibition of urate transporter 1 (URAT1), a key transporter responsible for reabsorption of urate from the primary urine in the proximal tubule, lowers serum urate by increasing excretion. Intravenous administration of drugs with uricase activity such as pegloticase, decreases serum urate by directly degrading urate.

Hyperuricemia (elevated levels of urate in the circulation) is a prerequisite for development of gout, an inflammatory arthritis caused by deposition of monosodium urate crystals in joints. Gout occurs in patients with serum urate >6.8 mg/dL, which is the solubility limit of monosodium urate. The prevalence of gout increases with higher serum urate (Choi et al 2005). Gout affects approximately 4% of the adult US population (Hamburger et al 2011). The prevalence of hyperuricemia is higher than the prevalence of gout, as not all patients with hyperuricemia develop gout.

Evidence shows independent associations between elevated serum uric acid (sUA) and the risk of hypertension, myocardial infarction, chronic kidney disease (CKD), Type 2 diabetes (T2DM), heart failure (HF), and metabolic syndrome, including obesity (Nakagawa et al 2006, Grayson et al 2011, Kodama et al 2009, Leyva et al 1998, Anker et al 2003). Gout is associated with an increased risk of all-cause death, as well as cardiovascular (CV) death (Iochimescu et al 2008, Kim et al 2008, Niizeki et al 2006, Jankowska et al 2007). The causal relationship between elevated sUA, gout, and these disease outcomes remains to be proven.

RDEA3170 (verinurad), is a novel URAT1 inhibitor in Phase II development. RDEA3170 combined with the XO inhibitor febuxostat has been shown to lower sUA in patients with recurrent gout in Phase II studies by >80% (see Investigator Brochure, Section 5.2.1.2 for

details on Study 203). The extensive lowering of sUA delivered by the combination presents a unique opportunity to explore whether intensive urate lowering therapy can improve kidney and/or cardiac health.

This Clinical Study Protocol (CSP) describes a study that will assess if intensive serum urate lowering therapy, more potent than ever explored before in the chronic out-patient setting, can improve chronic kidney or cardiac function in the study population.

## 1.2 Rationale for study design, doses and control groups

In order to maximize the scientific value of the study and minimize the risk for systemic biases a parallel group, double blind, randomized design will be utilized.

The study will recruit patients with hyperuricemia and presenting with albuminuria. Hyperuricemic patients are expected to benefit more from urate lowering, and albuminuria at baseline is required, as the primary objective of the study will be to assess changes in albuminuria. Patients with severe CKD (GFR <30mL/min/1.73m$^2$) are excluded, as they are presumed to be less likely to benefit from therapy.

Patients are also required to be diagnosed with T2DM. Patients with T2DM frequently exhibit changes in cardiac function detectable using magnetic resonance imaging (MRI) that represents an early, pre-symptomatic state of heart failure. By limiting recruitment to patients with T2DM and by performing MRI at baseline and 6 months of therapy, the study will deliver insights into whether or not intensive urate lowering therapy can positively affect not only chronic kidney disease, but also cardiac disease.

The primary endpoint in the study will be albuminuria, measured as urinary albumin to creatinine ratio (UACR), which is a standard Phase II endpoint frequently used in Phase II intervention trials in CKD. All drugs shown to provide benefit in diabetic patients with CKD when tested in long term studies (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARB], sodium-glucose coptranporter-2 [SGLT2] inhibitors) have also been shown to decrease albuminuria in shorter term studies. In studies with efficacious drugs most of the decrease in UACR is evident already after a couple of weeks, hence 3 months of treatment will be sufficient to determine if intensive urate lowering will improve UACR.

Estimated glomerular filtration rate (eGFR) will be a key secondary endpoint, as GFR is a direct measure of kidney function, and predicts longer term outcomes, such as the time to renal replacement therapy. Patients will be treated for 24 weeks in this study as changes in GFR are much slower than UACR. Short- and long-term changes in sUA concentrations will also be tracked.

MRI assessments of cardiac strain (left ventricular strain and left ventricular function and mass) at baseline and 24 weeks was included as a secondary endpoint to assess the potential for further development of intensive urate lowering as a treatment for heart failure (HF). MRI testing will also provide the opportunity for assessment of kidney oxygenation via blood

oxygenation level dependent MRI (MRI-BOLD). CV assessments will include blood pressure and heart rate.

Reactive Hyperemia will be assessed as a measure of endothelial dysfunction (ED) at baseline, 12 and 24 weeks. Reactive Hyperemia will be an exploratory endpoint providing data to support the hypothesis that intensive sUA lowering will improve arterial compliance. Improved arterial compliance relative to placebo will be an indicator that intensive sUA lowering could translate into CV benefits and thus support further development in cardiovascular disease.

Additional exploratory assessments include s-aldosterone, high-sensitivity C-reactive protein (hsCRP), CCI [redacted]. The biomarkers have been included to investigate the mechanism(s) through which intensive uric acid lowering therapy may cause a positive effect. Understanding the mechanism of action will benefit any subsequent studies in the program.

The doses of febuxostat and RDEA3170 selected for study were chosen as they represent the doses achieving maximal serum urate reduction in Phase II studies in patients with gout. Study 108 in renally impaired patients indicated that RDEA3170 exposure increased with decreasing renal function, but did not result in an increase in the incidence of adverse events (AEs) (see the Investigator Brochure Section 5.1.2.2). Hence the same dose will be used in all recruited patients irrespective of baseline renal function.

## 1.3 Benefit/risk and ethical assessment

Data from prior studies indicate hyperuricemia is linked to chronic kidney disease, heart failure, hypertension, diabetes, and cardiovascular events (Nakagawa et al 2006, Grayson et al 2011, Kodama et al 2009, Iochimescu et al 2008, Kim et al 2008).

The RDEA3170-febuxostat fixed-dose combination regimen is expected to offer a convenient and safe treatment that potently lowers uric acid levels by addressing both the production and urine excretion of urate. A dual-inhibition approach using low doses of two agents with complementary mechanisms of action is expected to synergistically improve efficacy outcomes while reducing potential safety issues that would be of concern with higher doses of each agent alone.

The following is a brief summary of the relevant potential benefits and risks associated of the RDEA3170-febuxostat combination regimen.

### 1.3.1 Combination of RDEA3170 and febuxostat

RDEA3170 has been studied in combination with febuxostat in Studies RDEA3170-105, RDEA3170-204, and RDEA3170-205. Results from 2 Phase 2a studies (RDEA3170-204 and RDEA3170-205) demonstrated that the combination of RDEA3170 and febuxostat resulted in significant reductions of urate compared with high doses of febuxostat alone. The increased efficacy provides an opportunity to lower urate more than with any other out-patient treatment regimen. The RDEA3170-febuxostat combination is therefore ideally suited to testing of the

hypothesis that hyperuricemia is a contributing factor to chronic kidney disease (specifically albuminuria in diabetic patients), cardiovascular disease and/or diabetes.

Urinary uric acid excretion profiles for patients treated with the RDEA3170-febuxostat combination were similar to time-matched baseline (predose) profiles. The uric acid excretion profiles suggest that the combination may reduce the risk for renal dysfunction that was observed in the monotherapy studies of RDEA3170 (RDEA3170-201 and RDEA3170-203).

The potential for drug-drug interactions between RDEA3170 and febuxostat was assessed in a Phase 1 study (RDEA3170-105). Results demonstrated that dosing of the RDEA3170-febuxostat combination showed no meaningful drug interactions and led to decreases in uric acid excretion when compared to baseline, even in the context of potent URAT1 inhibition.

These results highlight the potential of combination XO inhibition and URAT1 inhibition to significantly reduce urate levels, while mitigating the potential adverse effects of acute increases of uric acid through the renal tubules, including urate nephrolithiasis and urate nephropathy.

### 1.3.2 RDEA3170

RDEA3170 inhibits the URAT1 transporter. URAT1 is responsible for most of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, RDEA3170 increases uric acid excretion and thereby lowers serum urate. Increases in renal tubular uric acid concentration may lead to crystallization of uric acid and manifest clinically as acute urate nephropathy and/or nephrolithiasis. Other agents that increase urinary uric acid excretion have been associated with acute renal failure, which is thought to be related to this mechanism of action.

Increases in serum creatinine and liver enzymes have been reported with RDEA3170 in monotherapy clinical studies in patients with gout. Gout flares may occur after initiation of anti-hyperuricemic therapy, including RDEA3170. Nephrolithiasis is a potential risk due to increased uric acid excretion.

For more information on RDEA3170 clinical and nonclinical data, refer to the RDEA3170 Investigator's Brochure (IB).

### 1.3.3 Febuxostat

Febuxostat is an approved and marketed XO inhibitor for the chronic management of hyperuricemia in patients with gout. Febuxostat is approved in the United States (US) for use in doses of 40 mg and 80 mg (Uloric Prescribing Information 2013). Increases in gout flares, cardiovascular events, and hepatic effects have been observed with use of febuxostat. Adverse reactions occurring in at least 1% of febuxostat-treated patients, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. For more information, refer to the manufacturer's prescribing information on febuxostat.

### 1.3.4 Gout flares

Patients with gout may experience an acute gout flare event with initiation or an increase in dose of urate lowering therapies (Borstad et al 2004). To prevent this, the manufacturer's prescribing information for urate lowering therapies like lesinurad, allopurinol and febuxostat, as well as the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and British Society of Rheumatology treatment guidelines (Zhang et al 2006; Jordan et al 2007; Khanna et al 2012), recommend acute gout flare prophylaxis with colchicine or a nonsteroidal anti-inflammatory drug when initiating or increasing the dose of such therapies.

To protect participating patients from experiencing gout flares, patients with a history of gout will be excluded from the study (unless initiation of prophylaxis therapy is not be needed in the opinion of the investigator). 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 investigators' best medical judgment is recommended. The risks and benefits of colchicine and other therapies used to manage gout flares can be found in the package inserts of the respective products.

### 1.3.5 Renal impairment

This will be the first study of chronic dosing of RDEA3170 in combination with febuxostat in patients with mild to moderate renal impairment. A prior study exploring the PK of RDEA3170 in patients with mild, moderate or severe renal impairment has been performed (RDEA3170-108). Renal impairment was associated with a higher exposure to RDEA3170 and metabolites of RDEA3170, but was well tolerated in all renal function groups. No creatinine or hepatic enzyme elevations were reported as AEs. Consult the IB for further details.

### 1.3.6 Invasive/non-invasive procedures

Standard clinical procedures for urine and blood sampling are planned with attention to the total volume of blood taken over time.

Extensive research to evaluate whether the magnetic fields and radio waves used during an MRI scan pose a risk to the human body has not identified any risks. MRI is thus considered one of the safest medical procedures currently available.

The CCI provides a direct measurement of ED via a calibrated measurement of arterial compliance over the entire transmural pressure range of the artery. The method used is similar to an automated blood pressure measurement with regards to risks and discomfort for patients.

### 1.3.7 Summary and conclusions

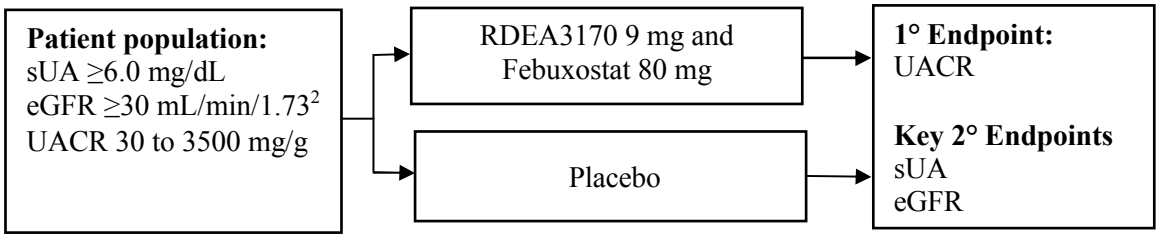
The study has been designed to minimize the risks to participating patients by excluding patients at high risk of AEs and by applying appropriate safety monitoring of recruited study patients. The doses selected have been carefully considered in light of the target patient

population. The potential benefits of developing a new treatment for chronic kidney disease, heart failure, diabetes and/or other cardiovascular diseases therefore outweigh the limited risks to the patients exposed to treatment with RDEA3170 and febuxostat in this trial.

## 1.4 Study design

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

**Figure 1 Study Flow Diagram**




Abbreviations: eGFR Estimated glomerular filtration rate; FBX Febuxostat; sUA Serum uric acid; UACR Urinary albumin to creatinine ratio; VER RDEA3170.

## 1.5 Study governance and oversight

### 1.5.1 Steering committee

Due to the limited sample size and low number of open sites a formal steering committee is not anticipated to be required for the study.

### 1.5.2 External Data Monitoring Committee

It is not planned to set up an external Data Monitoring Committee for the study. The limited sample size, short anticipated recruitment period and a treatment duration of 6 months limits the usefulness of a data monitoring committee, as the study would be completed or close to completed before a significant amount of clinical data can be collected, analyzed and acted on by an external data monitoring committee. Moreover, the treatment combination evaluated in the study has been previously assessed in Phase II studies in patients, limiting the risk of new or unexpected toxicities emerging from the study data.

### 1.5.3 Scientific advisory committee

The study design and rationale has been thoroughly discussed with external scientific leaders in the hyperuricemia, CKD, and HF fields. Hence, it is not planned to set up a formal scientific advisory committee.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on albuminuria | Urinary Albumin to Creatinine Ratio after 12 weeks of treatment |

## 2.2 Secondary objectives

| Secondary Objective: | Outcome Measure: |
|---|---|
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on kidney function | Estimated glomerular filtration rate<br>Cystatin C, creatinine |
| To assess the metabolic effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat | Serum uric acid<br>Serum uric acid lowering corrected for estimated glomerular filtration rate |
| To assess the structural and functional effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on the heart and kidney using magnetic resonance imaging | Left ventricular cardiac strain, as assessed by magnetic resonance imaging<br>Left ventricular function and mass, as assessed by magnetic resonance imaging<br>Kidney oxygenation, as assessed by blood oxygen level dependent magnetic resonance imaging (BOLD_MRI) |
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on biomarkers and parameters related to inflammation, and cardiac health | High sensitivity C-reactive protein<br>High sensitivity Troponin I |
| To assess the effects of intensive uric acid lowering therapy with RDEA3170 and febuxostat on cardiovascular parameters | Blood pressure (systolic and diastolic) |
| To assess plasma exposure of RDEA3170 in this patient population | RDEA3170 plasma concentration at trough (approximately 24 h post dosing). |

## 2.3 Safety objectives

| Safety Objective: | Outcome Measure: |
|---|---|
| To assess the safety and tolerability of intensive uric acid lowering therapy with RDEA3170 and febuxostat | Rates of adverse events and serious adverse events<br>Changes in vital signs, physical examinations, and electrocardiograms<br>Changes in clinical laboratory parameters, including assessment of creatinine, cystatin C, and blood urea nitrogen |

## 2.4 Exploratory objectives

| Exploratory Objective: | Outcome Measure: |
|---|---|
| CCI | Serum aldosterone<br>CCI<br>Hemoglobin A1c |
| CCI | CCI<br>Reactive Hyperemia (also referred to as Flow Mediated Dilatation) of the brachial artery |

# 3. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. CCI will select the study sites for this study from a network of associated sites.

## 3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Female and/or male patients aged ≥18 years
3. Serum Uric Acid ≥6.0 mg/dL
4. Patients should receive background standard of care treatment for albuminuria and T2DM and be treated according to locally recognized guidelines, as appropriate. Guideline-recommended medications should be used at recommended doses. Therapy should have been optimized and stable for ≥1 month before study entry and include an ACE inhibitor or an ARB, unless contraindicated, not tolerated, or in the opinion of the investigator not practically available or suitable.
5. eGFR ≥30 mL/min/1.73 $m^2$ (CKD-EPI formula)
6. UACR between 30 mg/g and 3500 mg/g inclusive
7. Diagnosed with T2DM
8. Negative pregnancy test (urine or serum) for female patients of childbearing potential (defined as any female who has experienced menarche and who is not permanently sterile or postmenopausal)
9. Female subjects must be post-menopausal (defined as 12 consecutive months with no menses without an alternative medical cause), surgically sterile, or be willing to

use two acceptable methods of contraception from signing the informed consent until 3 months after the last dose of study medication. One of the two methods of contraception must be a male condom with spermicide. Acceptable second methods of contraception are a vasectomized partner, tubal occlusion, intrauterine device (with copper-banded coils), intrauterine system with levonorgestrel (eg, Mirena), and medroxyprogesterone injections (eg, Depo-Provera). Patients agreeing to total sexual abstinence can also be included, assuming it is their usual lifestyle.

## 3.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, CCI staff, and staff at the study site)
2. Participation in another clinical study with an investigational product during the last 12 weeks
3. Treated with any drug for hyperuricemia in the 6 months preceding randomization. Drugs for hyperuricemia include all XO inhibitors (allopurinol, febuxostat and topiroxostat) and URAT1 inhibitors (lesinurad, RDEA3170, probenecid, and benzbromarone).
4. Prior history of gout, as patients with a history of gout should receive prophylaxis therapy with NSAID or colchicine before starting uric acid lowering therapy to avoid gout flares, and such therapy will not be provided in this study. However, patients with a prior history of gout may be included should initiation of prophylaxis therapy not be needed or is not suitable for the patient in the opinion of the investigator.
5. Uncontrolled hypertension presenting with systolic blood pressure >180 mm Hg
6. Diagnosed with HF and New York Heart Association Functional Classification (NYHA) Class IV (refer to Appendix E)
7. Known hypersensitivity to or previous anaphylactic reaction to febuxostat or RDEA3170
8. Dose of losartan, fenofibrate, guaifenesin, or SGLT-2 inhibitors changed within 2 weeks of randomization or further dose titration expected after randomization.
9. Patients diagnosed with tumor lysis syndrome or Lesch-Nyhan syndrome
10. Patients who are severely physically or mentally incapacitated and who in the opinion of investigator are unable to perform the patients' tasks associated with the protocol
11. Patients who are pregnant, lactating, or planning to become pregnant
12. Presence of any condition which, in the opinion of the investigator, places the patient at undue risk or potentially jeopardizes the quality of the data to be generated

13. Patients unsuitable or unable to undergo MRI assessment for the following reasons:
    - Body mass index (BMI) >40
    - Claustrophobia
    - Metallic implant such as cochlear implant, non-removeable insulin pump, pacemaker, or implantable defibrillator
14. Bilateral upper or lower arm pathology:
    - Presence of fistula / AV Shunt
    - Other structural or vascular abnormality

Procedures for withdrawal of incorrectly enrolled patients - refer to Section 3.4.

## 3.3 Patient enrolment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Assign potential patient a unique enrolment number. Patients being enrolled at study Visit 1 will be assigned an enrollment code, starting with an "E" followed by 7 digits, where the leading 4 digits identifies study site and the final 3 digits are allocated in numerical order within site, starting with 001 for the first enrolled subject, 002 for the second enrolled subject, and so on.
3. Determine patient eligibility. Consult Section 3.1 and 3.2.
4. Assign eligible patient unique randomization code

If a patient withdraws or is deemed not eligible for participation in the study (screen failure), then his/her enrolment/randomization code cannot be reused. Patients may be screened multiple times, but can be randomized only once. Before re-screening patients must sign the latest version of the informed consent form, and will thereafter be assigned a new enrolment number. Re-screened patients will undergo all procedures as if screened for the first time.

Randomization codes will be computer generated by AstraZeneca R&D using AZRand (AZ Global Randomization system). Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

## 3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who

are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the CCI study physician or the medical monitor immediately, and a discussion should occur between the two regarding whether to continue or discontinue the patient from treatment. The CCI study physician or the medical monitor must ensure all decisions are appropriately documented.

## 3.5 Methods for assigning treatment groups

A randomization scheme will be produced by AstraZeneca R & D using the global randomization system (AZRand). The randomization will be done using consecutive randomization codes (patient numbers). Patients will be randomized 1:1 at study Visit 2 to receive either the RDEA3170 and febuxostat combination or matching placebo.

## 3.6 Methods for ensuring blinding

The study will be double blind and utilize a double dummy approach for blinding. Placebo tablets will be matched to the active tablets in appearance.

## 3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomised patient, will be available to the Investigator(s) or pharmacists at the study site long with the personnel analyzing the pharmacokinetic (PK) samples.

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 Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 3.8 Restrictions

Patients who are blood donors should not donate blood during the study and for 12 weeks following their last dose.

Patients should not interrupt, stop or start any concomitant medications that may affect UACR; eg, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and antihypertensives, during the treatment period, unless medically required. Any change in the aforementiond medications must be properly documented in the WBDC.

Female patients of childbearing potential and their partners must adhere to the required use of contraceptives described in Section 3.1 if sexually active.

**Reactive Hyperemia:**

Patients will be instructed to:

- refrain from using caffeine 6 hours and all OTC medications, supplements/vitamins and nicotine 12 hours prior to the Reactive Hyperemia procedure.
- either preferably not eat anything for 6-8 hours prior to the test or eat a light snack the morning of the test that does not include coffee, caffeine or chocolate.
- not to exercise within 24 hours of the Reactive Hyperemia procedure.
- not to use the following substances during 7 days prior to the Reactive Hyperemia procedure: vaso-active agents such as decongestants (eg, pseudoephedrine); Recreational drugs such as marijuana, cocaine, and amphetamines; sildenafil (Viagra), vardenefil (Levitra), or tadalafil (Cialis).

**MRI procedures:**

Patients will be instructed to:

- refrain from using caffeine and nicotine 6 hours prior to MRI procedures.
- not to have a large meal just prior to the MRI procedure.
- to drink at least 250 ml water within one hour before the scan.

## 3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Investigator decision, due to an AE
- Investigator decision, due to severe non-compliance with the study protocol
- Risk to patients as judged by the investigator and/or AstraZeneca
- Patients potentially lost to follow-up
- Pregnancy confirmed by a positive pregnancy test, or otherwise verified
- Study treatment will be temporarily stopped if a patient's creatinine levels are elevated to greater than 1.5 times the pre-treatment value and retest of the creatinine and cystatin-C will be performed as soon as possible (refer to Appendix D)
- In patients who report symptoms that may indicate acute urate nephropathy including flank pain, nausea, or vomiting, treatment may need to be temporarily

stopped or permanently discontinued. Appendix D contains guidelines on management of such patients.

**Patients should be encouraged to continue in the study even if she/he has discontinued from the investigational product.**

### 3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments - Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s) and undergo the assessments and procedures scheduled for the final follow-up visit. AEs will be followed up (Section 6); and all study drugs should be returned by the patient.

If a patient is withdrawn from study, refer to Section 3.10.

## 3.10 Criteria for withdrawal

### 3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Screen failure'(the potential patient who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is valid only for not randomized patients). 'Failure to meet randomization criteria' should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomized group (it is applicable only for randomized studies and should be used for patient withdrawal post-screening).

### 3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

Should a patient withdraw consent, they will always be asked about the reason(s) and the presence of any AEs.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn patients will not be replaced.

## 3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,

- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the Case Report Form (CRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

The study plan for the screening, treatment, and follow-up periods is outlined in Table 1 and elaborated in Sections 4.1 through 4.3.

**Table 1 Study Plan**

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

**Table 1 Study Plan**

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

[a] Patient to deliver 3 morning urine samples to site within 1 week
[b] Visit 7 has to be before or on last day of treatment
[c] Women of Childbearing Potential only
[d] NT-pro-BNP will be assessed at Visit 2, Visit 6 and Visit 7
[e] MRI and Reactive Hyperemia must be performed before randomization, but not before Visit 1.
[f] Post-treatment MRI and Reactive Hyperemia to be performed earlier than at 24 weeks if patient is withdrawing and has been treated with study drug for at least 2 months. The MRI and Reactive Hyperemia may be performed up to 2 weeks before the End of Treatment Visit (Visit 7), but not later than the last day of treatment
[g] Trough levels; ie, prior to dosing on the day of the Visit

## 4.1 Screening/enrolment period

Procedures will be performed according to the Study Plan (Table 1).

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

All patients will be required to provide consent to supply a sample of their blood and urine for entry into this study. This consent is included in the main patient informed consent form.

Patients will be screened for entry into the study at Visits 1 and 2 which will be separated by a maximum of 6 weeks, allowing for laboratory determinations of criterion values for eGFR, sUA, and UACR. Visit 2 (randomization) will occur no later than six weeks after Visit 1. The screening period can only be extended beyond 6 weeks if it is impossible to perform Visit 2 within 6 weeks of Visit 1 due to logistical reasons, and following written approval by the sponsor. Agreed extensions of the screening period due to logistical necessity will not consitute a protocol violation.

### 4.1.1 Screening blood sampling

As criterion values for eGFR and sUA are necessary for enrolment into the study, 20 mL of blood will be drawn at Screening Visit 1 for the determination of these values as well as for that of cystatin-C and general clinical laboratory assessments (Table 2). Samples will be collected, aliquoted, labelled, stored, and shipped as detailed in the Laboratory Manual.

### 4.1.2 Screening urine sampling

Criterion values of UACR will be assessed from 3 morning void urine samples collected at home on separate days into containers supplied to the prospective participant at Screening Visit 1. These samples should be provided within one week of time after the screening Visit 1. Prospective participants will collect urine into the provided containers and refrigerate the sample. After collecting three samples, the subject should deliver them to the site within 5 days of first urine sample collection. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

### 4.1.3 Electrocardiograms

Electrocardiography (ECG) methods for both screening and treatment periods are described in Section 5.2.3.

### 4.1.4 MRI and Reactive Hyperemia assessments

No earlier than at Visit 1 but before randomization, and after patient eligibility has been established, patients will undergo MRI and Reactive Hyperemia assessments as described in Sections 5.1.3 and 5.1.4.1. It should not be considered a protocol violation if Reactive Hyperemia assessments can not be performed in time for a scheduled assessment due to logistical reasons.

### 4.1.5 Collection of demographic data

Demographic variables including age, gender, race, and ethnicity, and characteristics such as height and weight will be collected for each subject.

### 4.1.6 Medical and Surgical History and Concomitant Medications

Subject medical and surgical history and concomitant medication use will be recorded. For the restricted and prohibited concomitant medications please refer to Section 7.7.

## 4.2 Treatment period

### 4.2.1 MRI and Reactive Hyperemia assessments

During the 24-week treatment period, patients will undergo MRI procedures (Section 5.1.2) at the end of treatment visit (24 weeks) to provide assessments of cardiac and renal function.

Assessments of Reactive Hyperemia (refer to section 5.1.4.1) will be performed at Visit 6 (12 weeks), and at the end of treatment visit (24 weeks) to provide a measure of endothelial function. It should not be considered a protocol violation if Reactive Hyperemia assessments can not be performed in time for a scheduled assessment due to logistical reasons.

### 4.2.2 Blood Collections

Blood draws will be performed at Visits 2 through 8 as shown in Table 2 to gather data for efficacy, safety, pharmacokinetics (PK), and potential biomarker analyses. Specifics for the data derivations for efficacy are given in Section 5.1, for safety in Section 5.2, for PK in Section 5.4, and for biomarker analysis in Section 5.7. Samples will be collected, aliquoted, labelled, stored, and shipped as detailed in the Laboratory Manual.

**Table 2 Blood volumes drawn at each visit**

| | Visit | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Sample Type** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| Efficacy | 10 mL | 10 mL | 10 mL | 10 mL | 10 mL | 10 mL | 10 mL | 10 mL |
| Safety | 13 mL | 13 mL | 13 mL | 13 mL | 13 mL | 13 mL | 13 mL | 13 mL |
| PK | | | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | |
| CCI | | | | | | | | |
| Total | 23 mL | 35 mL | 38 mL | 38 mL | 38 mL | 38 mL | 38 mL | 35 mL |

### 4.2.3 Urine collection

At Visits 2 through 7, patients will be given 3 containers for first morning void urine collection on the 2 days preceding and on the day of the next visit (Visits 3 through 8). Patients will store urine samples refrigerated until the third one is collected, following which the 3 samples will be taken to the investigative site. The patient will deliver the samples to the study site at the scheduled visit and the study site will label, store, and ship the samples for analysis as detailed in the Laboratory Manual. A separate urine sample will be collected at the

site. Urine samples will be processed to yield both efficacy (Section 5.1) and safety (Section 5.2) assessments.

### 4.2.4 Monitoring of patient compliance, safety, and tolerability

Evaluation of compliance with medication administration, concomitant medications, and AE occurence will be performed as noted in Table 1.

## 4.3 Follow-up period

Patients will return 4 weeks after Visit 7 and the cessation of active treatment for a follow-up visit. Assessments specified in Table 1 will be performed as noted in Section 4.2

# 5. STUDY ASSESSMENTS

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

## 5.1 Efficacy assessments

### 5.1.1 Clinical laboratory variables

Efficacy assessments include vital signs and laboratory analyses of plasma and serum elements, urine components. Laboratory assessments are shown in Table 3. The schedule for blood sampling is shown in Table 2.

**Table 3 Laboratory efficacy variables**

| Urinalysis | Clinical chemistry (serum or plasma) |
|---|---|
| U-Albumin (mg/dL) [a] | S-Uric Acid (mg/dL) [b] |
| U-Creatinine (g/dL) [a] | S-Creatinine (mg/dL) [b] |
| | S/P-Cystatin C (mg/L) [b] |
| | S-high sensitivity C-reactive protein (mg/L) [b] |
| | S-high sensitivity Troponin I (ng/mL) [b] |

[a] For derivation of UACR (primary outcome variable)
[b] Secondary outcome variables

Urine samples will be gathered as 3 daily morning void samples of urine at 7 separate post-screening time points in containers supplied by the study site (Section 4.2.3).

A central laboratory will be utilized for efficacy and safety analyses as specified in the laboratory manual. Urine and blood reserved for future exploratory analyses will be deposited in the AstraZeneca Biobank.

#### 5.1.1.1 Primary outcome - UACR

The ratio of urinary albumin to urinary creatinine (milligrams of albumin per grams of creatinine) will be assessed. The mean ratio will be reported for each time-point based on three samples.

First morning void urine samples will be used for assessment of UACR. Patients will receive a urine sample collection kit allowing them to collect the first morning void urine on three days. Collected samples will be stored in a refrigerator until they can be brought to the study site for further processing in accordance with the laboratory manual. Ideally the urine samples should be collected 2 days before, the day before and on the day of a study visit to minimize storage and transportation of collected samples.

If a patient has forgotten to collect one or more of the samples before a visit, then the samples should be collected on the up to three consecutive days following the visit instead (with exception for the Visit 2 urine samples, which must be collected before treatment is started).

In the absence of results from three analyzed samples the UACR for a time-point will be calculated based on the available results.

Urine samples collected for assessment of UACR must not be confused with urinalysis samples collected at study site during visits for assessment of safety parameters and pregnancy testing.

#### 5.1.1.2 Secondary outcomes

Secondary outcome measures of renal function include:

- eGFR calculated using the CKD-EPI formula as previously published (Levey et al 2009). Details of the method are presented in Appendix F.
- Serum cystatin-C
- Serum creatinine

Secondary outcome measures for general metabolic effects include:

- sUA - as simple measurement and also corrected for eGFR

Secondary outcome measures for inflammation and cardiac status include:

- Serum high-sensitivity C-reactive protein
- Serum high-sensitivity Troponin

### 5.1.2 MRI procedures

MRI to examine functional changes in the heart and kidney will performed at baseline and 24-weeks post-treatment. The MRI scan performed while patients are treated with study drug must be performed between 2 and 12 hours after the administration of verinurad and febuxostat. After successful screening patients will undergo magnetic resonance imaging prior to randomization and before or on the day of Visit 2.

In order to protect patients and equipment during the MRI examination all personal and medical metallic and magnetic items (including credit cards etc.) have to be left outside the MRI room. Although no risks are described in the literature for pregnant women to undergo an MRI scan, as an extra precaution these patients will be excluded.

MRI scan protocols will be set up during the MRI site initiation routine as per the local standard procedures at each MRI site.

The patients will undergo MRI scanning after Visit 1, but not later than before randomization at Visit 2 (baseline) to assess cardiac and kidney function (MRI-BOLD) as well as morphology (parameters listed in Table 4). In addition an MRI will be performed up to 2 weeks before the End of Treatment Visit (Visit 7), but not later than on the last day of treatment.

Total scan time is estimated to be 45 minutes. Images from all sites will be analyzed centrally at the Antaros Medical core-lab in Uppsala, Sweden using a dedicated software package.

A radiology assessment of the MRI will be performed by qualified medical personnel at the MRI site. The assessment will be reported to the Principal investigator at the referring site, who will review and file the assessment in the subject´s source documents. If clinically significant findings are noted the Principal Investigator will inform the CCI Study Physician.

CCI will then inform both the Sponsor and Antaros of the finding. The participants will be invited for follow up if there are clinically significant incidental findings and findings will be evaluated as potential AEs (refer to Section 6.2.7).

**Table 4 MRI variables**

| Variables | Unit |
|---|---|
| LV global longitudinal strain | % |
| LV global radial strain | % |
| LV global circumferential strain | % |
| LV global diastolic longitudinal strain rate | $s^{-1}$ |
| LV global systolic longitudinal strain rate | $s^{-1}$ |
| LV global diastolic radial strain rate | $s^{-1}$ |
| LV global systolic radial strain rate | $s^{-1}$ |

**Table 4 MRI variables**

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

Abbreviations: LV Left ventricle; LVEF Left ventricular ejection fraction

### 5.1.3 Clinical assessments

Cardiovascular function will be monitored for both efficacy and safety objectives:

- Blood pressure (systolic and diastolic)
- Heart rate

Specific methods for clinical assessment of cardiac function are presented in Section 5.2.4.

### 5.1.4 Exploratory outcomes

#### 5.1.4.1 Reactive Hyperemia

An assessment of Reactive Hyperemia will be performed at baseline and at 12 and 24 week post-randomization as an exploratory endpoint to assess endothelial dysfunction. The baseline Reactive Hyperemia assessment will be performed after patients have been deemed eligible for randomization but must be performed before any administration of study drug. The 24-week Reactive Hyperemia assessment will be performed no earlier than 2 weeks before the last treatment visit and must be performed no later than on the last day of treatment. The Reactive Hyperemia assessments performed while patients are treated with study drug must be performed between 2 and 12 hours after the administration of the study drugs, and at approximately (+/- 2h) the same time of the day as during the baseline assessment of Reactive Hyperemia.

Patient information will be captured (in a dedicated eCRF form) to facilitate correct assessment of confounding factors. Table 5 outlines the information captured. Patients will be excluded from performing assessment of Reactive Hyperemia at all time-points if they have upper or lower arm pathology, including fistula, AV-shunt and structural or vascular abnormality, Raynaud's syndrome or carpal tunnel syndrome, affecting both arms, or if they present with arrhythmias with a potential to interact with the assessment, such as atrial

fibrillation or frequent premature ventricular contractions. With single arm pathology assessment of Reactive Hyperemia will be performed on the contralateral arm if possible. Patients will be asked to refrain from using caffeine 6 hours and all OTC medications, supplements/vitamins and nicotine 12 hours prior to the Reactive Hyperemia procedure. Patients will be instructed to either preferably not eat anything for 6-8 hours prior to the test or eat a light snack the morning of the test that does not include coffee, caffeine or chocolate. Patients will also be asked not to exercise within 24 hours of the Reactive Hyperemia procedure. Moreover, patients will be asked not to use the following substances during 7 days prior to the Reactive Hyperemia procedure: vaso-active agents such as decongestants (eg, pseudoephedrine); Recreational drugs such as marijuana, cocaine, and amphetamines; sildenafil (Viagra), vardenefil (Levitra), or tadalafil (Cialis).

The Reactive Hyperemia procedure will involve the application of the CCI system, a device similar to a traditional automatic blood-pressure measurement cuff, but with refined sensors and data capturing. The details of the procedure will be provided to sites in the device manual. The data captured will be analyzed by CCI, MD using a proprietary software. The output parameters will include pulse, systolic and diastolic blood pressure and score for endothelial dysfunction.

**Table 5 Patient information to capture at each visit for analysis of confounding factors**

| Item to capture | Comment |
|---|---|
| Use of long acting nitrates | Yes / no (details on the con med CRF pages) |
| Known autoimmune disease | Yes / no (details on the Med Hist CRF pages) |
| Last Menstual Period (LMP) | Date of LMP before procedure |
| Infection with fever (> 38°C) within 1 week prior to Reactive Hyperemia assessment | Yes / No (details on the AE / Med Hist CRF pages) |
| Food intake | Date and time of last meal before procedure |
| Nicotine intake | Date and time of last nicotine intake before procedure |
| Caffeine intake | Date and time of last caffeine intake before procedure |
| Use of vaso-active agents such as decongestants (eg, pseudoephedrine) within 7 days of assessment | Yes / no (details on con med CRF pages) |
| Use of recreational drugs such as marijuana, cocaine, and amphetamines within 7 days of assessment | Yes / no |
| Use of Sildenafil (Viagra), vardenefil (Levitra), or tardalafil (Cialis) within 7 days of assessment | Yes / no (details on con med CRF pages) |
| Exercise within 24h of assessment | Yes / no |

#### 5.1.4.2 Exploratory biomarkers

Additional exploratory assessments to be analyzed as relevant to the expanding database include those shown in Table 6.

**Table 6 Exploratory Variables**

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

## 5.2 Safety assessments

### 5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (Section 4).

The clinical chemistry, hematology and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes will be detailed in the laboratory manual.

The following laboratory variables will be measured:

**Table 7 Laboratory safety variables**

| Hematology/hemostasis (whole blood) | Clinical chemistry (serum or plasma) |
|---|---|
| B-Hemoglobin (Hb) | S/P-Creatinine |
| B-Leukocyte count | S/P-Bilirubin, total |
| B-Leukocyte differential count (absolute count) | S/P-Alkaline phosphatise (ALP) |
| B-Platelet count | S/P-Aspartate transaminase (AST) |
| | S/P-Alanine transaminase (ALT) |
| **Urinalysis** (dipstick) | S/P-Albumin |
| U-Hb/Erythrocytes/Blood | S/P-Potassium |
| U-Glucose | S/P-Calcium, total |
| | S/P-Sodium |
| | S/P-Creatine kinase (CK) |
| | S/P-Blood Urea Nitrogen |

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, refer to Section 6.2.7.

**NB.** In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy's Law', for further instructions.

### 5.2.2 Physical examination

Physical examinations will be performed and include an abdominal exam and an assessment of the following: general appearance, and the respiratory, cardiovascular, and musculo-skeletal systems.

### 5.2.3 ECG

#### 5.2.3.1 Resting 12-lead ECG

A 12-lead ECG will be performed after the patient has been lying down for 5 minutes at the times indicated in the Study Plan. The overall assessment of the ECG (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be recorded in the CRF. Any clinically significant findings should be reported as AEs or in the Medical History, as appropriate.

### 5.2.4 Vital signs

#### 5.2.4.1 Pulse and blood pressure

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed using non-invasive equipment by an adequately trained health care professional.

Measurements with a calibrated sphygmomanometer are preferred. If not available, another device calibrated carefully in proportion to a mercury sphygmomanometer is preferred. Use of aneroid manometers should be avoided. Appropriate cuff size must be used to ensure accurate measurement.

Three (3) readings separated by 2 minutes should be averaged, and the average result will be recorded in the eCRF. If the first two readings of SBP differ by more than 5 mmHg, additional readings should be obtained.

Blood pressure should be checked in both arms at the first visit. Subsequent blood pressure measurements should be recorded in the arm with the higher pressure.

Blood pressure should be measured in either supine or sitting position. No shift from one position to another should be made during the study. Supine or sitting posture should be adopted for at least 5 minutes before measurement. The patient should be relaxed and with the arm outstretched and supported.

Blood pressure should be measured under standardized conditions, as nearly as possible at the same time each visit, on the same arm, by the same personnel, and with the same apparatus.

## 5.3 Other assessments (Not applicable)

## 5.4 Pharmacokinetics

### 5.4.1 Collection of samples

Blood samples (3 mL) for determination of RDEA3170 in EDTA plasma will be taken at the times presented in the study plan (Table 1). Samples will be taken prior to administration of the daily dose on the day of the Visit, and the time of administration of the last dose (ie the day before the visit) will be documented.

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

### 5.4.2 Determination of drug concentration

Samples for determination of RDEA3170 concentration in plasma will be analyzed by CCI on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Analysis of any placebo samples are conducted only when there is cause to suspect administration of another study treatment. In such cases, a plasma sample, around the expected $t_{max}$ will be analyzed to confirm the presence or not of another study treatment.

### 5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (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 back-up PK samples may be used for future exploratory 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; refer to details in the Laboratory Manual).

## 5.5 Pharmacodynamics

No further pharmacodynamic samples, apart from those already described above, will be taken during the study.

## 5.6 Genetics

Genetic samples will not be taken during the study.

## 5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

Urine and blood samples will be collected, aliquoted and analyzed or stored in a biobank. Some of the planned biomarker analyses may be performed only if the study provides evidence of efficacy, and may be performed in a staggered fashion to minimize resource spend.

### 5.7.1 CCI

[redacted]

### 5.7.2 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or

publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

### 5.7.3 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled 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), refer to Appendix B 'IATA 6.2 Guidance Document'.

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

### 5.7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca and/or its representatives keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca designated BioBank during the entire life cycle.

### 5.7.5 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 of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) 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
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

## 6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

## 6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 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.
- 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, refer to Appendix A to the Clinical Study Protocol.

### 6.2.1 Time period for collection of adverse events

All Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period.

### 6.2.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment (Visit 8) in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. 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.

### 6.2.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity or intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Select the appropriate as required: AE caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of AE.

The following intensity rating scale 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)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

### 6.2.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 investigational product?'

For SAEs causal relationship will also be assessed for other medication 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 A to the Clinical Study Protocol.

### 6.2.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit?,' or revealed by observation will be collected and recorded in the CRF. 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.

### 6.2.6 Gout flare

If a subject experiences an acute gout flare event, study medication should continue uninterrupted.

Acute treatment options include:

- Colchicine, as per the local approved dosing regimen for the treatment of acute gout flare events (eg, in the US, refer to Colcrys® package insert).

- Nonsteroidal anti-inflammatory drugs may be added, as per the manufacturer's prescribing information, for up to 7 days with concomitant gastroprotection with a proton pump inhibitor if indicated.
- Intra-articular steroid injection of methylprednisolone acetate, 5 mg to 40 mg or equivalent.
- Oral steroids for up to 7 days, not to exceed total weekly dose of 84 mg of methylprednisolone; or 105 mg of either prednisone or prednisolone. Maximal daily dose should not exceed 24 mg of methylprednisolone, or 30 mg of either prednisone or prednisolone.

Patients experiencing a gout flare will be treated with colchicine, steroids and/or non-steroidal anti-inflammatory drugs as appropriate and according to the investigators' best medical judgement.

### 6.2.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated examinations and tests should therefore be reported as AEs only if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, 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.

### 6.2.8 Hy's Law

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

## 6.3 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate CCI representatives within one day; ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CCI representative works with the Investigator 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform CCI representatives of any follow-up information on a previously reported SAE within one calendar day; ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The CCI representative will advise the Investigator/study site staff how to proceed.

## 6.4 Overdose

In this trial any dose of more than 2 (9 mg) capsules of RDEA3170 or 1 (80 mg) tablet of febuxostat should be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is reported only on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate CCI representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated CCI representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply (Section 6.3). For other overdoses, reporting must occur within 30 days.

## 6.5 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to CCI except for:

- If the pregnancy is discovered before the study patient has received any study drug
- Pregnancies in the partner of male patients

### 6.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, both RDEA3170 and febuxostat should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a

contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate CCI representatives within 1 day; ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CCI representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (refer to Section 6.3) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

## 6.6 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg tablet dissolved in water when it should be taken as a solid tablet

- Drug not stored as instructed eg kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from randomization - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate CCI representative within 1 day; ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CCI representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (Section 6.3) and within 30 days for all other medication errors.

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity of investigational product(s)

Patients will be randomized 1:1 at Visit 2 to receive either a combination of RDEA3170 (9 mg once daily) and febuxostat (80 mg once daily) or matching placebo (Table 8). The RDEA3170 capsules will be packaged in 40 mL bottles and the febuxostat capsules will be packaged in 75 mL bottles, each containing 35 capsules. At Visit 2 one bottle of each study drug will be dispensed. All bottles will have the randomization code printed on the label, and the lowest randomization code available shall be selected and allocated to the patient at Visit 2. At Visit 5 two bottles will be dispensed, and at Visit 6 three bottles will be dispensed. At visits where drug is being returned and new drug is being dispensed, all bottles should be returned for drug accountability. In order to facilitate drug accountability the patient's E-code as well as the visit number must be filled in on the label before dispensing.

**Table 8 Investigational product, dosage and mode of administration**

| Investigational product | Dosage form and strength | Supplier |
|---|---|---|
| Febuxostat | 80 mg capsule for oral administration | AstraZeneca |
| Febuxostat matched placebo | Placebo capsule for oral administration | AstraZeneca |
| RDEA3170 | 9 mg capsule for oral administration | AstraZeneca |
| RDEA3170 matched placebo | Placebo capsule for oral administration | AstraZeneca |

The febuxostat active formulation is an overencapsulated commercial Uloric® tablet 80 mg to preserve the blinding of the study. The febuxostat capsules are different in shape, size and color from the RDEA3170 capsules.

The RDEA3170 capsules used release RDEA3170 over 8 hours, hence the formulation is referred to as ER8 (Extended Release over 8 hours). The properties of the ER8 formulation were studied in study RDEA3170-111 and are detailed in the IB.

The manufacturing, labelling, packaging and release of the study drugs will be conducted following Good Manufacturing Practices.

## 7.2 Dose and treatment regimens

Patients will be treated with either the RDEA3170 and febuxostat combination or placebo. One capsule of each type will be taken once daily in the morning with water. Patients will be instructed to stay adequately hydrated and pause dosing in the event of dehydration. On visit days study drug should be taken at site from the bottles scheduled to be returned during the visit. At the randomization visit study drug will be taken from the bottle handed out at the visit.

## 7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be in English.

Patients participating in the study will be provided with an identification card where the Investigator's details including telephone number are included and will be instructed to keep this identification card with them at all times.

## 7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

## 7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

Patients will be required to bring study drug containers to each clinic visit, regardless of whether the study medication container is empty.

If a patient is persistently noncompliant with the sponsor-supplied double blind study drugs (<80% or >120% of the allocated medication for the period since the last visit) it may be appropriate to withdraw the subject from the study.

All patients should be reinstructed about the dosing requirement during study visits. The authorized study personnel conducting the re-education must document the process in the patient source records.

## 7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to and returned from the patient.

Study site staff will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed, in accordance with instructions by CCI . Destruction must not take place unless the responsible person at CCI has approved it.

## 7.7 Concomitant and other treatments

| **Restricted Medication/Class of drug:** | **Usage:** |
|---|---|
| Treatments known to lower albuminuria, e.g. ACE-inhibitors, ARBs, mineralocorticoid receptor antagonists, or sodium-glucose linked transporter-2 inhibitors. | Proteinuria lowering therapies must not be started, and doses not changed, before the end of the treatment period of the study. Patients on stable doses at study entry should continue on the same doses. |

| **Prohibited Medication/Class of drug:** | |
|---|---|
| Any investigational drugs.<br><br>Azathioprine, mercaptopurine, or other medication prohibited by the febuxostat package insert.<br><br>Strong or moderate CYP3A inhibitors or inducers, strong or moderate P-gp inhibitors, strong or moderate OAT1 or OATP1B3 inhibitors, or digoxin must be avoided if possible due to a potential pharmacokinetic interaction with RDEA3170 (see Investigators Brochure for details) | |

| **Rescue/Supportive Medication/Class of drug:** | **Usage:** |
|---|---|
| Consult Section 6.2.6 on treatments to be used to treat gout flares. | |

### 7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

## 7.8 Post study access to study treatment

Study drug will not be provided after the study.

# 8. STATISTICAL ANALYSES

## 8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol violators identified.
- Analyses will be performed by CCI or its representatives.
- Refer to the Statistical Analysis Plan for details.

## 8.2 Sample size estimate

The standard deviation for change in log-UACR is assumed to be 0.8, based on the AVOID study with aliskiren in 599 patients with albuminuria and T2DM (Parving et al 2008), as well as a study with tenapanor in a patient population similar to that planned for this study (Ardelyx 2015).

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

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

## 8.3 Definitions of analysis sets

### 8.3.1 Efficacy analysis set

Analyses on the primary objective as well as other efficacy variables will be performed on the Full Analysis Set (FAS) following the ITT principle, comprising all patients randomized.

### 8.3.2 Safety analysis set

Variables related to safety will be analyzed using the safety analysis set, comprising all patients randomized, exposed to study drug and with available post dose data.

### 8.3.3 PK analysis set

The PK analysis set will include all patients who received febuxostat and RDEA3170 treatment and who have at least 1 post-dose plasma concentration measurement of RDEA 3170 at a scheduled time point, without protocol deviations or violations that would have an impact on the absorption, distribution, metabolism or excretion of RDEA3170.

### 8.3.4 Per-protocal analysis set

The Per Protocol Set is defined as all subjects in the FAS without any major protocol deviations. The set of major protocol deviations will be finalized prior to database lock. This dataset is a candidate for any sensitivity analyses of the efficacy endpoints (to be outlined in the statistical analysis plan[SAP]).

## 8.4 Outcome measures for analyses

The primary variable UACR will be log-transformed for application of normal theory based statistical models. Variables related to secondary and explorative objectives may also be log-transformed when viewed as necessary for the same purpose.

## 8.5 Methods for statistical analyses

### 8.5.1 Analysis of the primary variable (s)

Primary analysis will be conducted using a mixed effects model with repeated measures (MMRM) with log-transformed UACR as the response variable, randomized treatment and visit as fixed factors and log-transformed UACR at baseline as covariate. The least squared mean change from baseline in the log-transformed UACR will be calculated by treatment and by visit together with its 95% confidence intervals. The least squared mean difference between the two treatments will be calculated by the same MMRM model by visit together with its 90% confidence interval.

The above least squared mean change from baseline (and the 95% confidence interval) for each treatment and each visit will be exponentiated to yield the least squared mean ratio from baseline for each treatment and each visit together with its 95% confidence interval at the original scale of UACR. The least squared mean difference between the two treatments (and its 90% confidence interval) at each visit will also be exponentiated to yield the least squared

mean ratio between the two treatments at each visit and its 90% confidence interval at the original scale of UACR.

### 8.5.2 Analysis of the secondary variable(s)

Analysis of variables related to secondary or explorative efficacy objectives will be assessed in a similar mixed model analysis with treatment and visit as fixed factors and baseline value as covariate. Log-transformation of values should be done when applicable, also for these variables.

Variables associated with primary, secondary or explorative efficacy objectives will also be presented using standard descriptive statistics by treatment and visit as well as change from baseline. Standard descriptive statistics comprise of (but are not limited to) Number of observations, mean value, standard deviation, coefficient of variation (or CV, for log-normal data), median value, minimum and maximum values.

RDEA3170 trough plasma concentrations will be presented using standard descriptive statistics and graphical representation, and stratified by renal function. The relationship between change in serum uric acid and change in log urinary albumin to creatinine ratio (and secondary variables where applicable) will be explored using different types of statistical models, not only linear ones.

Safety variables will be presented standard descriptive statistics by treatment and visit as well as change from baseline. Standard descriptive statistics for continuous safety variables comprise (but are not limited to) number of observations, mean value, standard deviation, median value, minimum and maximum values. Standard descriptive statistics for categorical safety variables comprise (but are not limited to) number of observations and percentages.

Adverse events will be presented according to AZ standards.

For parameters measured at multiple time-points prior to randomization, such as creatinine and cystatin C, the baseline will be defined as the mean of the reported measurement for all timepoints prior to randomization.

### 8.5.3 Subgroup analysis (If applicable)

Will be defined in the SAP.

### 8.5.4 Sensitivity analysis (If applicable)

Will be defined in the SAP.

### 8.5.5 Exploratory analysis (If applicable))

Will be defined in the SAP.

# 9. STUDY AND DATA MANAGEMENT

## 9.1 Training of study site staff

Before the first patient is entered into the study, a CCI representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the system utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.2 Monitoring of the study

During the study, an CCI representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The CCI representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

### 9.2.1 Source data

Source data are maintained at the respective sites throughout the course of the trial. Following completion of the study, records are archived and stored at an off-site facility per site SOP.

### 9.2.2 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA,or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between CCI and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### 9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

## 9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with RDEA3170.

## 9.4 Data management

Data management will be performed by the CCI Clinical Data Management (CDM) department, according to the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary Enhanced. All coding will be performed by CCI CDM staff and approved by AstraZeneca.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data.

The data will be validated as defined in the Data Management Plan and the Data Validation Specifications. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

**Serious adverse event reconciliation**

SAE reconciliation reports are produced from the Patient Safety database to allow reconciliation with the clinical database.

**Data associated with human biological samples**

Data associated with biological samples will be transferred from laboratory (ies) internal or external to CCI .

**Management of external data**

Data external to the clinical database will include, but are not limited to: safety lab results, PK data, and/or PD data. CCI CDM will develop and maintain Data Transfer Agreements for all external data with the appropriate external data vendors. External data will be reconciled with the clinical database to ensure quality; queries will be generated as needed to clarify any discrepancies found between the external data and the clinical database. Final external datasets will be incorporated into SDTM (Study Data Tabulation Model) datasets.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 10.2 Patient data protection

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

## 10.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to CCI before enrolment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the IRB annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB s and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

## 10.4 Informed consent

The Principal Investigator(s) at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## 10.5 Changes to the clinical study protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator, and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

CCI will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to an IRB refer to Section 10.3.

If a change to a Clinical Study Protocol requires a change to a site's Informed Consent Form, AstraZeneca and the site's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

## 10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CSP, GCP, guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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# Appendix A Additional Safety Information

## Further guidance on the definition of an SAE

### 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 (eg, hepatitis that resolved without hepatic failure).

### Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 one 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 judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization

Development of drug dependency or drug abuse

### A guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- 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?
- De-challenge 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 another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- 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.

# Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

**Labelling and shipment of biohazard samples**

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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, eg, Ebola, Lassa fever virus:

- 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, eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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 650

**Exempt** - 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.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and 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.

# Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## 1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

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

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

## 2. Definitions

### Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

### Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## 3. 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 ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (refer to Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

## 4. Follow-up

### 4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator 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 Clinical Study Protocol.

### 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The CCI Study Physician contacts the Investigator, 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 Investigator will:

- Monitor the patient until liver biochemistry parameters 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 CCI Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the CCI Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

**5. Review and Assessment of Potential Hy's Law Cases**

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the CCI Study Physician contacts the Investigator 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 Global Clinical Lead or equivalent 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 Investigator 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 explain the ALT or AST and TBL elevations other than the IMP:

- 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

**References**

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# Appendix D 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.

## 1. 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 (eg, reduced urinary output, generally feeling unwell, fatigue, nausea, vomiting, metallic taste, or loss of appetite) or nephrolithiasis (eg, 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 the CRF.

## 2. Renal function

Renal function will be assessed during the course of the study at prespecified times by measuring serum creatinine and calculating the estimated CrCl. All results will be documented in source documents and the CRF. 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 $\geq 3.0 \times$ 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 prespecified and unscheduled visits throughout the study and analyzed relative to the baseline serum creatinine (ie, Day -1; refer to Section 8.5 for the definition of baseline). 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:

*(A) Serum creatinine elevations ≥1.5 to <2.0 × baseline*

For a serum creatinine elevation ≥1.5 to <2.0 × 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 ≤1.2 × 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 × 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 ≤1.2 × 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 × 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 75) for a flow chart diagram.

*(B) Serum creatinine elevations ≥2.0 to <3.0 × baseline or an absolute value ≥3.0 mg/dL*

If a serum creatinine elevation is ≥2.0 to <3.0 × baseline serum creatinine value or an absolute serum creatinine value of ≥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 ≤1.2 × 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 × baseline serum creatinine value, additional retests of serum creatinine should be performed weekly until resolution to ≤1.2 × baseline. Once the serum creatinine elevation is resolved to ≤1.2 × 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 × 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 76) for a flow chart diagram.

*(C) Serum creatinine elevations ≥3.0 ×baseline or an absolute value ≥4.0 mg/dL*

If a serum creatinine elevation is ≥3.0 × baseline serum creatinine value or an absolute serum creatinine value of ≥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 ≤1.2 × 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 77) for a flow chart diagram.

*(D) Patient's Last Study Visit and Post-Follow-Up Assessments*

If at the patient's last study visit the serum creatinine value is ≥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 ≥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 77) for a flow chart diagram.

*(E) Other Considerations*

Patients who have a serum creatinine value of ≥1.5 × baseline should be encouraged to remain adequately hydrated.

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

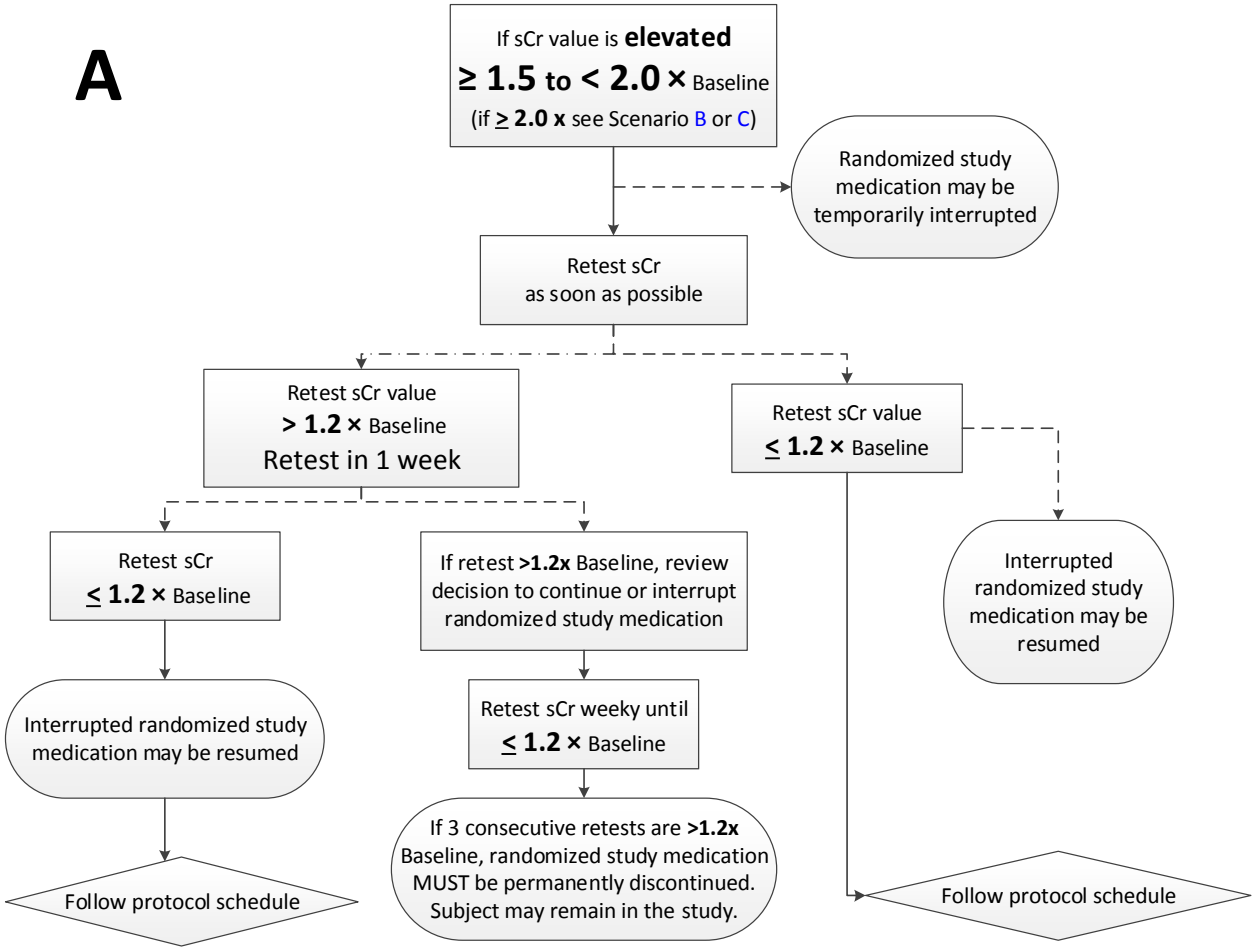


**Figure 1 (continued): Flow chart for serum creatinine elevation monitoring**

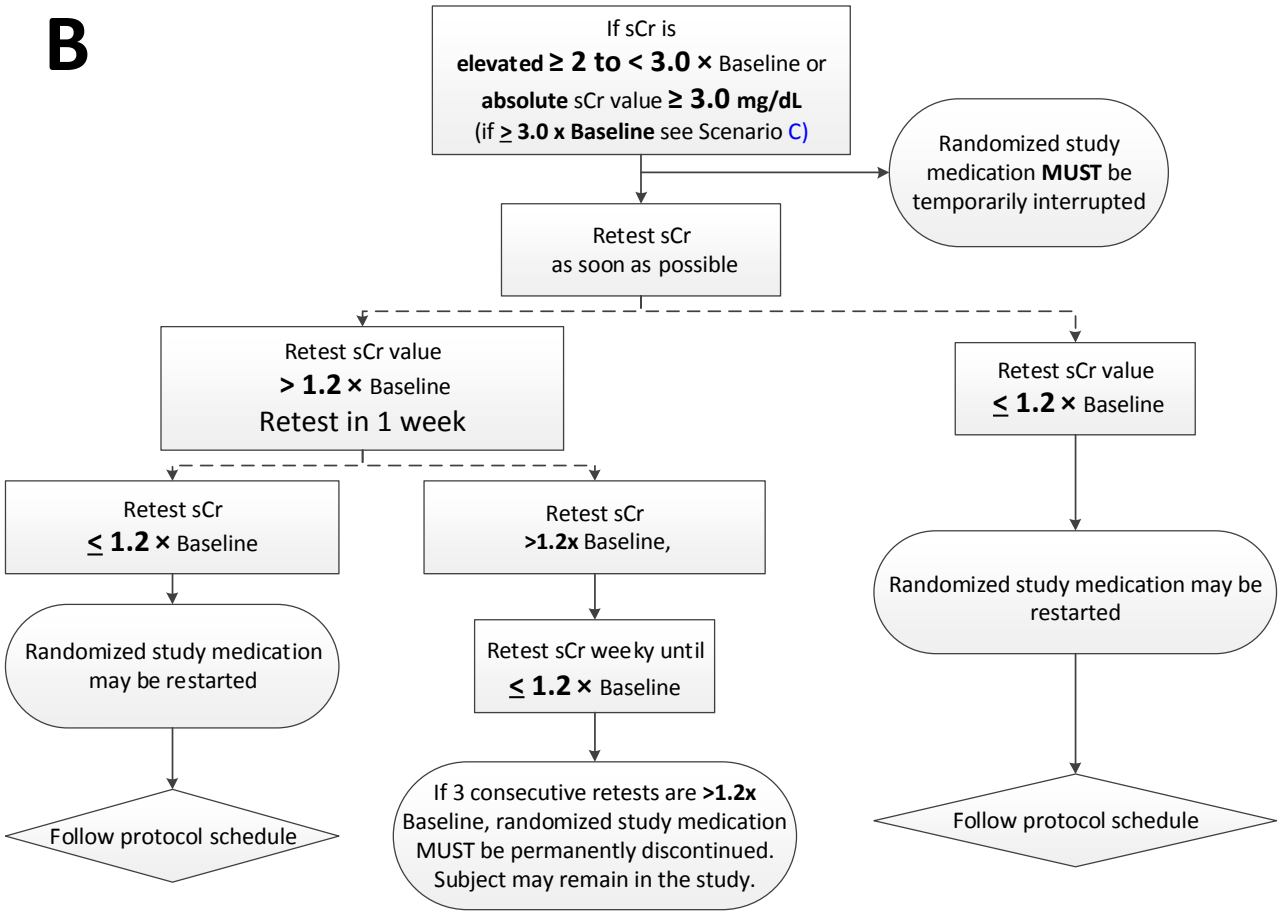
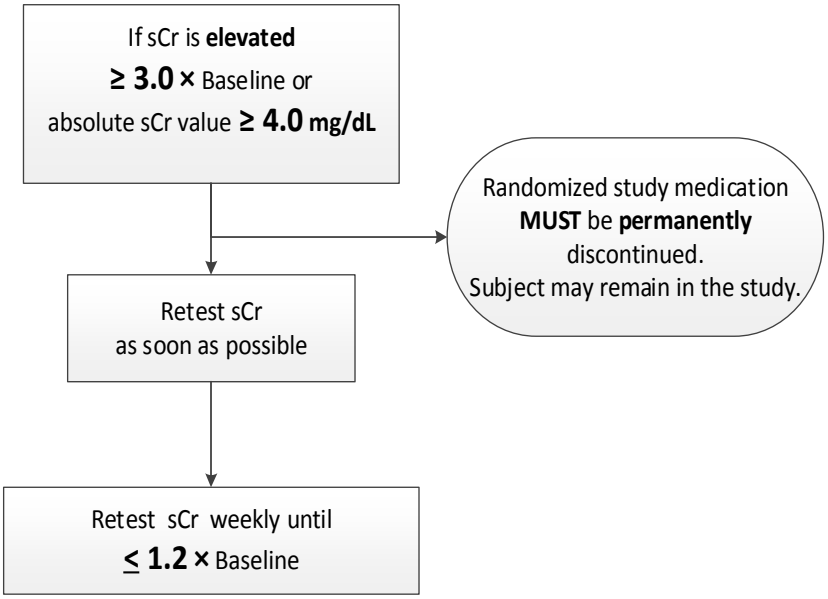
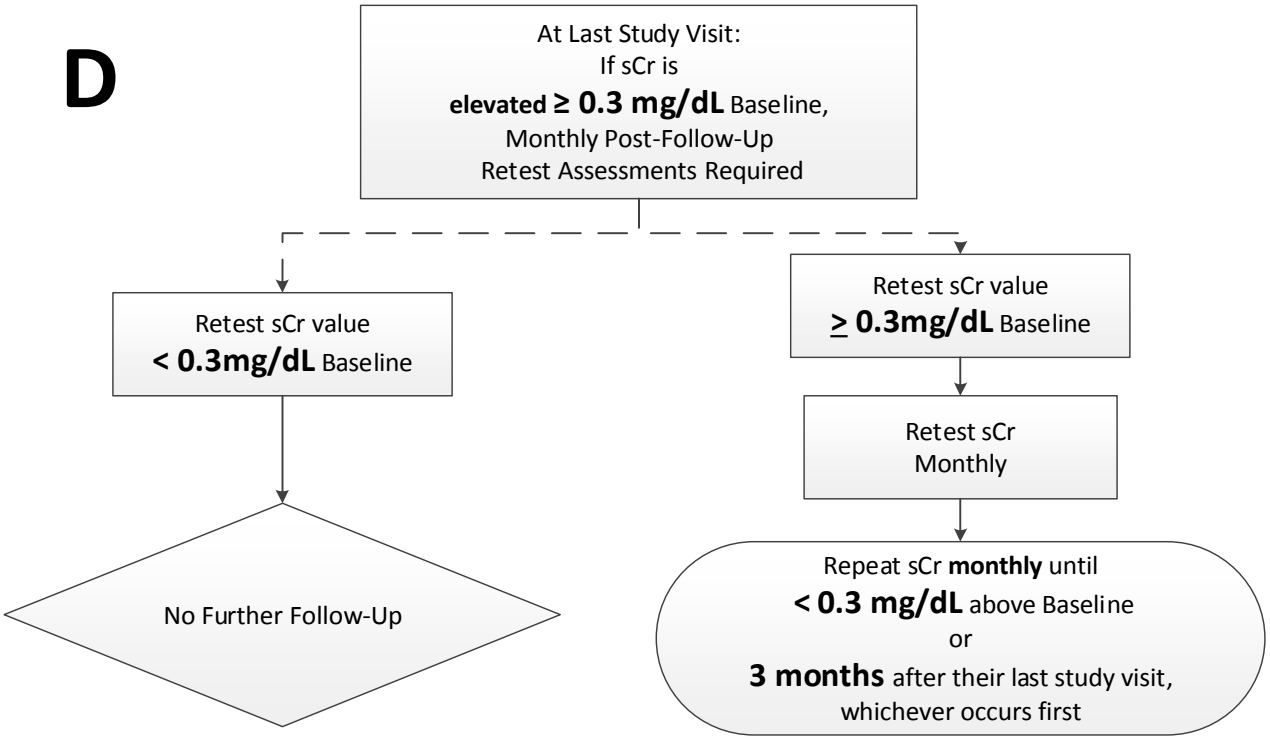


**Figure 1 (continued): Flow chart for serum creatinine elevation monitoring**

**C**




**D**



***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 ≥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**

**Ricci et al 2011**
Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. Nat Rev Nephrol 2011;7(4):201-8.

# Appendix E New York Heart Association (NYHA) Functional Classification

| Class | Patient symptoms |
|---|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath). |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath). |
| III | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| IV | Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. |

# Appendix F The CKD-EPI Equation for Estimating GFR on the Natural Scale

| Race and Sex | Serum Creatinine µmol/L (mg/dL) | Equation |
|---|---|---|
| Black | | |
| Female | ≤62 (≤0.7) | $GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$ |
| | >62 (>0.7) | $GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$ |
| Male | ≤80 (≤0.9) | $GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$ |
| | >80 (>0.9) | $GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$ |
| White or other | | |
| Female | ≤62 (≤0.7) | $GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$ |
| | >62 (>0.7) | $GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$ |
| Male | ≤80 (≤0.9) | $GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$ |
| | >80 (>0.9) | $GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$ |

- CKD-EPI Chronic Kidney Disease Epidemiology Collaboration; GFR glomerular filtration rate; Scr Serum creatinine.
- In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

The CKD-EPI equation, expressed as a single equation, is:

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] or 1.159 [if black]

**Where;**

- Scr is serum creatinine
- $\kappa$ is 0.7 for females and 0.9 for males
- $\alpha$ is -0.329 for females and -0.411 for males
- min indicates the minimum of Scr/$\kappa$or 1, and
- max indicates the maximum of Scr/$\kappa$ or 1.

Table, text adapted from Levey et al 2009

# SIGNATURE PAGE

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