# Clinical Study Protocol

# A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

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| **PAREXEL Study No.:** | CCI [redacted] |
| **Sponsor Study Code:** | D5495C00005 |
| **IND No./Eudra CT No:** | 2019-001446-18 |
| **Study Type:** | Randomised, single-dose, crossover study |
| **Reference Product:** | Verinurad (RDEA3170), ER8 capsules<br>12 mg: 1 x 12 mg dose |
| **Test Product:** | Verinurad (RDEA3170), A-capsule<br>12 mg: 2 x 6 mg dose<br>Verinurad (RDEA3170), B-capsule<br>12 mg: 2 x 6 mg dose |
| **Therapeutic Indication:** | Chronic kidney disease |
| **Pharmacological Class:** | URAT1 inhibitor |
| **Development Phase:** | Phase 1 |
| | |
| **Sponsor:** | AstraZeneca AB<br>151 85 Södertälje<br>Sweden |
| **Study Centre:** | PAREXEL Early Phase Clinical Unit Berlin<br>On the premises of DRK Kliniken Berlin Westend, Haus 31<br>Spandauer Damm 130<br>14050 Berlin<br>Germany |
| **Date of Protocol:** | Final 1.0, 06 May 2019 |
| **Date of Protocol Amendment #1** | Final 1.0, 24 June 2019 |

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki (Version 1996) and with other applicable regulatory requirements.

# PROTOCOL SYNOPSIS

**Title of the Study**
A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

**Principal Investigator**
PPD

**Study Centre**
This study will be conducted at a single study centre.

PAREXEL Early Phase Clinical Unit Berlin
On the premises of DRK Kliniken Berlin Westend, Haus 31
Spandauer Damm 130
14050 Berlin
Germany

**Study Rationale**
This study is intended to assess the relative bioavailability between the (extended-release) ER8 capsule formulation (used in study D5495C00002) given under fasted conditions and 2 new capsule formulations of verinurad (A-capsule and B-capsule) given under fed or fasted conditions. All three capsules target an 8-h release profile (extended-release).
The highest dose (12 mg) currently tested in patients will be tested in this study. The study is designed to provide information to optimize the verinurad part of a fixed dose combination capsule to be used in future development.

**Number of Subjects Planned**
Twenty-five (25) subjects will be randomised to ensure at least 20 evaluable subjects at the end of the last treatment period.

**Study Period**
Estimated date of first subject enrolled: June 2019 (signing of informed consent)
Estimated date of last subject completed: September 2019 (last subject, last visit)

**Study Objectives**
***Primary Objective:***

- To evaluate the relative bioavailability between the A-capsule and B-capsule formulations under both fed and fasted conditions with the ER8 capsule formulation under fasted conditions and with each other under the same food conditions.

***Secondary Objectives:***

- To evaluate the relative bioavailability between fed and fasted conditions for the A-capsule and B-capsule formulations as well as between the A-capsule and B-capsule formulations.

- To examine the pharmacokinetic (PK) profiles of verinurad when administered as the 3 different capsule formulations under fasted conditions.
- To assess the safety and tolerability of single doses of verinurad in healthy volunteers.

**Study Design**

This study will be a randomised, open-label, single-dose, 5-period, 5-treatment, crossover study in healthy male and female subjects, performed at a single study centre.
The study will comprise of:

- A screening period of maximum 28 days;
- Five treatment periods during which subjects will be resident from the morning of the day before dosing with verinurad (Day -1) until at least 72 hours after dosing; discharged on the morning of Day 4 of each treatment period; and
- A Follow-up Visit within 7 to 14 days after the last administration of verinurad.
- There will be a minimum washout period of 5 days between each dose administration.

A total of 25 healthy male and female subjects will be randomised into this study. Each subject will receive 5 single-dose treatments of 12 mg verinurad with 240 mL water, following an overnight fast of at least 10 hours or following a high-fat, high-calorie breakfast (after the overnight fast):

- Treatment 1: 1 x 12 mg verinurad ER8 capsule formulation, fasted.
- Treatment 2: 2 x 6 mg verinurad A-capsule formulation, fasted.
- Treatment 3: 2 x 6 mg verinurad A-capsule formulation, fed.
- Treatment 4: 2 x 6 mg verinurad B-capsule formulation, fasted.
- Treatment 5: 2 x 6 mg verinurad B-capsule formulation, fed.

For both the fasted and fed dosing, no fluids will be allowed apart from water which can be given until 1 hour prior and 1 hour after administration of verinurad, water to be given with the verinurad administration and the beverages provided with the high-fat, high-calorie breakfast in dosing periods with administration under fed conditions. All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day (including Day -1) throughout the duration of the study.
All subjects will follow an overnight fast of at least 10 hours before the dosing procedures on Day 1: for the fed dosing, a high-fat, high-calorie standard breakfast will be provided 30 minutes before the administration of verinurad, to be consumed in full at least 5 minutes before dosing; for the fasted dosing, no breakfast will be served, and subjects will remain fasted. A meal can be given 4 hours after administration of verinurad for both dosing conditions.

**Expected Duration of the Study**

The duration of the study is expected to be approximately 9 weeks for each individual subject (including the 28-day screening period).

**Targeted Study Population**

This study will be conducted in healthy male and female subjects, 18 to 50 years of age (inclusive) with a body mass index (BMI) between 18 and 30 kg/$m^2$ (inclusive).

**Investigational Medicinal Product**

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|---|---|
| Supplier: | AstraZeneca |
| Formulation: | Verinurad ER8 capsule formulation<br>Verinurad A-capsule formulation<br>Verinurad B-capsule formulation |
| Strength/concentration: | 12 mg: ER8 capsule formulation<br>6 mg: A-capsule formulation<br>6 mg B-capsule formulation |
| Dose: | 12 mg |
| Route of administration: | Oral |
| Regimen: | Treatment 1: 1 x 12 mg verinurad ER8 capsule formulation, fasted.<br>Treatment 2: 2 x 6 mg verinurad A-capsule formulation, fasted.<br>Treatment 3: 2 x 6 mg verinurad A-capsule formulation, fed.<br>Treatment 4: 2 x 6 mg verinurad B-capsule formulation, fasted.<br>Treatment 5: 2 x 6 mg verinurad B-capsule formulation, fed. |

**Outcome Endpoints**

***Pharmacokinetic Endpoints:***

Serial venous blood samples will be obtained for the determination of verinurad in plasma. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

- Primary PK parameters: area under plasma concentration-time curve from zero to infinity (AUC), AUC from time 0 to the last quantifiable concentration (AUC0-t), and maximum observed plasma concentration (Cmax).
- Secondary PK parameters: AUC from time 0 to 24 hours post dose (AUC0-24), time to reach maximum observed plasma concentration (tmax), associated half-life (t½λz), apparent total body clearance of drug from plasma after extravascular administration (CL/F), mean residence time of the unchanged drug in the systemic circulation from zero to infinity (MRT), time of last quantifiable plasma concentration (tlast), volume of distribution at steady state (intravenous dosing) (Vss/F), and apparent volume of distribution during the terminal phase after extravascular administration (Vz/F).

Additional PK parameters may be determined where appropriate.

***Safety and Tolerability Endpoints:***

Safety and tolerability variables will include

- Adverse events (AEs)
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate)
- 12-lead electrocardiograms (ECGs)

- Physical examination
- Laboratory assessments (haematology, clinical chemistry and urinalysis).

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

**Statistical Methods**

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

Pharmacokinetic parameters will be summarized for each treatment using descriptive statistics. The descriptive statistics may include: n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic standard deviation (SD), median, minimum and maximum. The ratios of Cmax, AUC0-t and AUC will be calculated for the Test treatments to those of Reference treatment as well as the fed versus fasted conditions of the test products in each individual comparison. For tmax, only n, median, minimum and maximum will be presented.

Analyses will be performed using a linear fixed-effects analysis of variance model using the natural logarithm of AUC, AUC0-t and Cmax as the response variables, sequence, period and treatment as fixed-effects, subject nested within sequence as a random effect). Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUC, AUC0-t, and Cmax will be calculated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented. Additionally, the 90% CI for the difference in tmax will be calculated and presented.

The following comparisons of relative bioavailability (AUC, AUC0-t and Cmax) of verinurad will be performed:

- Treatment 2 versus 1 i.e., “A capsule, fasted” versus “ER8 capsule, fasted”
- Treatment 4 versus 1 i.e., “B capsule, fasted” versus “ER8 capsule, fasted”
- Treatment 3 versus 1 i.e., “A capsule, fed” versus “ER8 capsule, fasted”
- Treatment 5 versus 1 i.e., “B capsule, fed” versus “ER8 capsule, fasted”
- Treatment 4 versus 2 i.e., “B capsule, fasted” versus “A capsule, fasted”
- Treatment 5 versus 3 i.e., “B capsule, fed” versus “A capsule, fed”
- Treatment 3 versus 2 i.e., “A capsule, fed” versus “A capsule, fasted”
- Treatment 5 versus 4 i.e., “B capsule, fed” versus “B capsule, fasted”

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

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

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs, will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarized for the observed values at each scheduled assessment, together with the

corresponding changes (and/or percentage change) from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory and in Système International units in the Clinical Study Report.
Out-of-range values for safety laboratory, vital signs and ECG will be flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (e.g., AZ, program or laboratory ranges).

***Determination of Sample Size***

CCI [redacted]

Twenty-five (25) subjects will be equally randomised to 5 treatment sequences: 12345, 23451, 51234, 34512 and 45123 in order to ensure at least 20 evaluable subjects at the end of the last treatment period.

# PROTOCOL AMENDMENTS

## Protocol Amendment No. 1 Dated 24 June 2019

The following changes were made to the original Clinical Study Protocol, Final 1.0, dated 06 May 2019 to include changes requested by the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and a few additional minor corrections to the text were made.

1. The Schedule of Assessments (Table 5-2) were updated to include body weight, height and BMI calculation indicated at the Screening Visit.

2. Exclusion criteria #5 (Section 7.1.2) was updated to match the previous study (D5495C00006) with lesser restriction on exclusion heartrate criteria and the lower limit to the diastolic blood pressure was added.

3. Exclusion criteria #9 (Section 7.1.2) was updated with more detail on the excessive alcohol consumption criteria for exclusion.

4. Exclusion criteria #16 (Section 7.1.2) was updated with more detail on the excessive caffeine consumption criteria for exclusion.

5. Section 8, Study Stopping Rules were updated with more confirmatory wording (e.g., “may” changed to “must”).

6. The details of the Food and Drug Administration approved breakfast (Section 9.6.1) were corrected and updated according to the site specifications.

7. Standalone urea was removed from the Serum Clinical Chemistry panel (Section 10.3.5.2). Considering a conversation factor of 1.0, the urea concentration indicated in mmol/L is identical to the blood urea nitrogen (BUN) concentration indicated in mmol/L. Therefore, urea measurement was removed from the panel and only BUN was kept.

8. Details were clarified on reporting appropriate clinically significant changes from baseline to safety parameters as adverse events during the study (Section 13.2.6).

# 1. TABLE OF CONTENTS

## 1.1. List of Tables



## 1.2. List of Figures

# 2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 13.1.1) |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under plasma concentration-time curve from zero to infinity |
| AUC0-t | Area under the plasma concentration-curve from time zero to time of last quantifiable concentration |
| AUC0-24 | Area under the plasma concentration-time curve from time zero to 24 hours after dosing |
| %AUCextr | Percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve from the time of the last quantifiable concentration to infinity |
| AV | Atrioventricular |
| CCI | CCI |
| BLQ | Below the limit of quantification |
| BMI | Body mass index |
| BP | Blood pressure |
| bpm | Beats per minute |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| Clast | Drug concentration at last observed time point |
| CL/F | Apparent total body clearance of drug from plasma after extravascular administration |
| CCI | [redacted] |
| Cmax | Maximum observed plasma concentration |
| CRO | Contract research organization |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CV | Coefficient of variation |
| DMP | Data management plan |
| DVS | Data validation specification |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| gCV% | Geometric coefficient of variation |

| Abbreviation or special term | Explanation |
|---|---|
| GGT | Gamma glutamyl transpeptidase (transferase) |
| gmean | Geometric mean |
| GMP | Good Manufacturing Practice |
| gSD | Geometric standard deviation |
| Hb | Haemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HCT | Haematocrit |
| HIV | Human immunodeficiency virus |
| HL | Hy's Law |
| IATA | International Airline Transportation Association |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| IMP | Investigational medicinal product |
| IUD | Intrauterine device |
| λz | Terminal elimination rate constant |
| λzN | Number of data points included in the log-linear regression analysis |
| LLOQ | Lower limit of quantification |
| max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minimum |
| MRT | Mean residence time |
| ms | milliseconds |
| N | Number of subjects |
| NA | Not applicable |
| NC | Not calculable |
| ND | Not determined |
| NQ | Non-quantifiable |
| NR | No result |
| NS | No sample |
| OAE | Other significant adverse events |
| OTC | Over-the-counter |
| PD | Pharmacodynamics |
| PDF | Portable Document Format |

| Abbreviation or special term | Explanation |
|---|---|
| PDS | Protocol deviation specification (document) |
| PHL | Potential Hy's Law |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PR(PQ) | ECG interval measured from the onset of the P wave to the onset of the QRS complex |
| QP | Qualified Person |
| QRS | ECG interval measured from the onset of the QRS complex to the J point |
| QT | ECG interval measured from the onset of the QRS complex to the end of the T wave |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| R&D | Research and Development |
| RBC | Red blood cell |
| RR | The time between corresponding points on 2 consecutive R waves on ECG |
| Rsq_adj | Regression coefficient adjusted for λzN, Goodness-of-fit statistic for calculation of λz |
| SAE | Serious adverse event (see definition in Section 13.1.2). |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SOC | System Organ Class |
| SOP | Standard operating procedure |
| SRC | Safety Review Committee |
| sUA | Serum uric acid |
| SUSAR | Suspected unexpected serious adverse reaction |
| t½λz | Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve |
| TCA | Tricyclic anti-depressant |
| TCS | Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire |
| tlast | Time of last quantifiable plasma concentration |
| t lower | Start of exponential fit |
| tmax | Time to reach maximum observed plasma concentration |
| t upper | End of exponential fit |
| UA | Uric acid |
| UK | United Kingdom |
| ULN | Upper limit of normal |

| Abbreviation or special term | Explanation |
|---|---|
| ULT | Urate-lowering therapy |
| USA | United States of America |
| uUA | Urinary uric acid |
| Vss/F | Apparent volume of distribution at steady state |
| Vz/F | Apparent volume of distribution during the terminal phase after extravascular administration |
| WBC | White blood cell |
| XO | Xanthine oxidase |
| XOI | Xanthine oxidase inhibitor |

# 3. ETHICAL AND REGULATORY REQUIREMENTS

## 3.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (version 1996) and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 3.2. Subject Data Protection

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

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

The anonymity of participating subjects must be maintained. Subjects will be specified in outputs and other documents containing subject data by their subject number, not by name. Documents that identify the subject (e.g., signed ICF) will be maintained in confidence by the PI.

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

## 3.3. Ethics and Regulatory Review

The study will be submitted to the national Regulatory Agency, Federal Institute for Drugs and Medical Devices (BfArM), for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Independent Ethics Committee (IEC) for ethical review and approval by the PI in accordance with local procedures.

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

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

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

## 3.4. Insurance

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

## 3.5. Informed Consent

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

The nature of the informed consent will comply with the Declaration of Helsinki (version 1996), the current requirements of GCP (CPMP/ICH/135/95) and local regulation whichever offers the greater subject protection.

## 3.6. Changes to the Protocol and Informed Consent Form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

If a protocol amendment requires a change to the ICF the IEC should approve the revised ICF before the revised form is used.

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

# 4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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| Sponsor: | AstraZeneca AB<br>151 85 Södertälje<br>Sweden |
| Sponsor's Lead Physician: | PPD<br>AstraZeneca R&D GothenBurg<br>Pepparedsleden 1<br>431 83 Mölndal<br>Sweden<br>PPD |
| Sponsor's Biostatistician: | PPD<br>AstraZeneca,<br>Gaithersburg, MD 20878<br>United States of America<br>PPD |
| Principal Investigator: | PPD<br>PAREXEL Early Phase Clinical Unit Berlin<br>On the premises of DRK Kliniken Berlin Westend, Haus 31<br>Spandauer Damm 130<br>14050 Berlin<br>Germany<br>PPD |
| Deputy PI: | PPD<br>PAREXEL Early Phase Clinical Unit Berlin<br>On the premises of DRK Kliniken Berlin Westend, Haus 31<br>Spandauer Damm 130<br>14050 Berlin<br>Germany<br>PPD |

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| Contract Research Organization (CRO): | PAREXEL Early Phase Clinical Unit Berlin<br>On the premises of Klinikum Westend, Haus 31<br>Spandauer Damm 130<br>14050 Berlin<br>Germany<br>PPD |
| Clinical Laboratory: | Synlab Clinical Trial GmbH<br>Turmstr. 21 (House M)<br>10559 Berlin<br>Germany<br>**Contact:**<br>PPD |
| Pharmacy: | PPD<br>Salzufer 13/14, 10587 Berlin,<br>Germany<br>**Contact:**<br>PPD<br>PPD |
| Analytical Laboratory:<br>(pharmacokinetic [PK] sample analysis) | Covance Bioanalytical Services, LLC<br>8211 SciCor Drive, Suite B<br>Indianapolis, IN 46214<br>United States of America<br>Contact:<br>PPD<br>Bioanalytical Chemistry<br>Covance Laboratories, Inc.<br>3301 Kinsman Blvd.<br>Madison, Wisconsin 53704<br>United States of America |

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|---|---|
| Pharmacokineticist | Covance Clinical Development Services (CDS)<br>Clinical Pharmacology Services<br>Springfield House, Hyde Street, LS2 9LH, Leeds,<br>UK<br>**Contact:**<br>PPD |
| PAREXEL Laboratory Contact | PAREXEL International GmbH,<br>Spandauer Damm 130, 14050 Berlin, Germany<br>**Contact:**<br>PPD |
| Adverse Event Reporting: | AstraZeneca Patient Safety Data Entry Site<br>Tata Consultancy Services<br>PPD |

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

# 5. INTRODUCTION

## 5.1. Background Information

Purines are essential building blocks in all living organisms as adenosine triphosphate, 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 the 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 urate can be degraded by the uricase activity in the intestinal microbiome to carbon dioxide ($CO_2$) and allantoin [1].

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

The level of urate in the circulation is determined by the balance between production and elimination. At steady state, production and elimination are similar [1].

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 decreasing production. Inhibition of URAT1, a key transporter responsible for reabsorption of urate from the primary urine in the proximal tubule, lowers serum urate by increasing renal excretion. Intravenous administration of drugs with uricase activity such as rasburicase, decreases serum urate by directly degrading urate.

Hyperuricaemia (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 can occur 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 [2]. Gout affects approximately 4% of the adult United States (US) population [3]. The prevalence of hyperuricaemia is higher than the prevalence of gout, as not all subjects with hyperuricaemia develop gout.

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

Evidence shows independent associations between elevated sUA and the risk of hypertension, myocardial infarction, heart failure, Chronic Kidney Disease (CKD), type 2 diabetes, and metabolic syndrome, including obesity [7, 8, 9, 10, 11]. Gout is associated with an increased risk of all-cause death, as well as CV death [12, 13, 14]. The causal relationship between elevated sUA and the aforementioned diseases and outcomes remains to be proven, however.

Combination therapy with verinurad, a URAT1 inhibitor, and a xanthine oxidase inhibitor (XOI) such as allopurinol targets both excretion and production of UA, providing a dual mechanism approach that would effectively lower sUA and thereby potentially enable more patients to achieve and maintain target treatment goals to control their disease [15, 16, 17] and establish a potential causal relation between sUA lowering therapy and chronic kidney and cardiovascular disease.

Potent URAT1 inhibition monotherapy has previously been associated with serum creatinine elevations. Although the mechanism is yet to be proven, these URAT1 effects with monotherapy have been linked to increased concentrations of uric acid in the primary urine, which have the potential to induce uric acid crystallization in tubuli and collecting ducts.

Based on these findings, verinurad will be exclusively developed as combination therapy, together with an XOI. This combination aims to provide a dual mechanism for lowering sUA and to reduce the risk of potential crystallization of UA in the renal tubules. However, when necessary for the development, verinurad mono-therapy may be used in specific clinical studies applying appropriate safety monitoring and risk mitigation.

The Investigator's Brochure (IB) describes results from pre-clinical studies, clinical pharmacology studies, and clinical monotherapy and combination therapy with febuxostat or allopurinol.

## 5.2. Investigational Medicinal Product Information

### 5.2.1. Description of Verinurad

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

### 5.2.2. Pre-clinical Findings

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

Verinurad was not genotoxic or carcinogenic based on results from the *in vitro* and *in vivo* batteries of genotoxicity tests and carcinogenicity studies in mice and rats. Verinurad is not considered a reproductive hazard based on the results of reproductive toxicology studies and the lack of effects on reproductive organs in the 6- and 9-month studies in rats and dogs, respectively. Verinurad is judged to not present a photosafety concern. The 2 identified disproportionate human metabolites M1 and M8 have been assessed and qualified in Ames test, in a rabbit embryo-foetal development study and in a 3-month general oral dose toxicity study in the cynomolgus monkey.

Further information on pre-clinical findings is available in the IB [18].

### 5.2.3. Clinical Studies

Verinurad has been studied in healthy volunteers, subjects with gout, asymptomatic hyperuricemia and renally impaired patients. As of 1 October 2018, a total of 831 subjects have received verinurad in 10 Phase 1 and 7 Phase 2 clinical studies (293 healthy subjects, 63 subjects with renal impairment, and 507 subjects with gout or asymptomatic hyperuricaemia). Verinurad alone has been given at multiple doses ranging from 2.5 mg to 15 mg (given as the MR4 tablet). Studies of verinurad in combination with an XOI have investigated verinurad doses ranging from 2.5 mg to 20 mg (MR4 tablet) where 20 mg of the MR4 tablet is comparable to 12 mg ER8 capsule.

#### 5.2.3.1. Safety Profile

**Healthy Subjects**

Safety was assessed in a pooled analysis of the completed Phase 1 studies in healthy subjects (101, 103, 104, 105, 106, 110, 111, and 112). Collectively, these studies enrolled 293 male subjects treated at the following verinurad dose ranges: 53 received < 5 mg; 131 received 5 mg to < 10 mg; 131 received 10 mg to 15 mg, and 30 received > 15 mg. Overall, 94.5% completed the planned treatment.

***Adverse Events***

The incidence of AEs was similar among the pooled verinurad groups and pooled placebo groups. Most AEs were RCTC toxicity Grade 1, and only 2 AEs were >Grade 2. The 2 higher severity AEs were Grade 3 blood creatinine increased and Grade 3 tooth infection, both in subjects dosed with verinurad in the 5 to < 10 mg range. There were no serious adverse events (SAEs). Overall, 86 subjects (29.4%) experienced AEs. The most common AE was headache, which occurred in 12 subjects (4.1%). There was no apparent relationship between the incidence of these AEs and verinurad dose. Three subjects withdrew from the study due to AEs: 2 subjects in Study 103 who had received verinurad 5 mg (dehydration and influenza,

respectively) and 1 subject in Study 104 who had received verinurad 15 mg and experienced urticaria.

***Laboratory Evaluations***

In the pooled Phase 1 safety dataset, sCr elevations ≥ 1.25 × baseline and ≥ 1.5 × baseline were reported for 13.7% and 1.7% of subjects, respectively. A change from baseline ≥0.3 mg/dL was reported for 6.8% of all subjects. There was no apparent relationship between sCr elevation and dose of verinurad.

In the pooled dataset, 18.4% of all subjects treated with verinurad experienced ALT elevations ≥ 1.5 × baseline, 5.1% experienced elevations ≥ 2.0 × baseline, and 2.0% experienced elevations ≥ 3.0 × baseline. There was no clear relationship with dose. Aspartate aminotransferase elevations ≥ 1.5 × baseline were reported for 6.1% of all subjects, while < 1.5% experienced AST elevations ≥ 2.0 or ≥ 3.0 × baseline.

***Vital signs, Physical findings, and Other Observations***

There were no clinically relevant or apparent dose-related post-treatment changes in vital signs. Although transient changes in blood pressure, heart rate, and body temperature were noted at isolated timepoints for some subjects, none of these findings were judged to be clinically significant by the Investigator.

***Potential Effects on Electrocardiograms, Including Rate-corrected QT (QTc) Intervals***

In most of the Phase 1 studies in healthy subjects (Studies 103, 104, 105, 106, 110, 111, and 112) there were no apparent treatment or dose-related trends in the 12-lead ECG parameters and no clinically important findings in the morphology of the 12-lead ECG for individual subjects. However, in Study 101, prolongations in corrected QTcB (Bazett's QTc correction) of > 60 msec occurred in 2 subjects in the 1 mg fasted dose group; yet, no subjects had prolonged QTcB intervals >450 msec. Three subjects in the 1 mg fasted dose group and 1 subject in the 5 mg fasted dose group had prolonged QTcF (Fridericia's QTc correction) intervals (> 450 to 480 msec) although no subjects had a QTcF interval > 480 msec. All episodes of QTcF >450 msec occurred at heart rates < 50 bpm.

Further information on clinical safety findings in healthy subjects is available in the IB [18].

**Subjects with Gout or Asymptomatic Hyperuricemia**

Information on clinical safety findings in subjects with gout or asymptomatic hyperuricemia is available in the IB [18].

#### 5.2.3.2. Pharmacokinetics

Following administration of verinurad as an extended-release capsule formulation (ER8), maximum plasma concentration (Cmax) occurs 4 hours after dosing. Food did not affect verinurad exposure except for a 2-hour increase in tmax. The degree of protein binding of verinurad in human plasma was 97%. Glucuronidation is the major metabolic pathway of verinurad with oxidation as the minor pathway. The major metabolites observed in humans after oral verinurad dosing are the acyl glucuronides M1 and M8 which are renally cleared. The amount of verinurad in urine is small (< 2% of given dose). The terminal half-life (t½) of verinurad was 13 hours in those with normal renal function and 21 hours in those with moderate renal impairment. The exposure (area under the concentration-time curve [AUC] and maximum observed concentration [Cmax]) of verinurad increased in a dose-proportional manner and the accumulation was minimal after once daily dosing. Subjects with moderate renal impairment have a < 1.6-fold higher verinurad exposure compared to those with normal renal function. Japanese subjects have about a 1.5-fold higher exposure than Western subjects.

Further information on PK findings is available in the Investigator's Brochure [18].

## 5.3. Study Rationale and Justification of Study Design

### 5.3.1. Study Rationale

This study is intended to assess the relative bioavailability between the ER8 capsule formulation (used in study D5495C00002) given under fasted conditions and 2 new capsule formulation of verinurad (A-capsule and B-capsule) given under fed or fasted conditions. All three capsules target an 8-h release profile (extended-release).

The highest dose (12 mg) currently tested in patients will be tested in this study. The study is designed to provide information to optimize the verinurad part of a fixed dose combination capsule to be used in future development.

### 5.3.2. Overall Study Design

This study will be a randomised, open-label, single-dose, 5-period, 5-treatment, crossover study in healthy male and female subjects, performed at a single study centre.

The study will comprise:

- A screening period of maximum 28 days;
- Five treatment periods during which subjects will be resident from the morning of the day before dosing with verinurad (Day -1) until at least 72 hours after dosing; discharged on the morning of Day 4 of each Treatment Period; and
- A Follow-up Visit within 7 to 14 days after the last administration of verinurad.
- There will be a minimum washout period of 5 days between each dose administration.

A total of 25 healthy male and female subjects will be randomised into this study. Each subject will receive five single-dose treatments of 12 mg verinurad with 240 mL water, following an overnight fast of at least 10 hours:

- Treatment 1: 1 x 12 mg verinurad ER8 capsule formulation, fasted.
- Treatment 2: 2 x 6 mg verinurad A-capsule formulation, fasted.
- Treatment 3: 2 x 6 mg verinurad A-capsule formulation, fed.
- Treatment 4: 2 x 6 mg verinurad B-capsule formulation, fasted.
- Treatment 5: 2 x 6 mg verinurad B-capsule formulation, fed.

For both the fasted and fed dosing, no fluids will be allowed apart from water which can be given until 1 hour prior and 1 hour after administration of verinurad, water to be given with the verinurad administration and beverages provided with the high-fat, high-calorie breakfast (see Section 9.6.1) in dosing periods with the administration under fed conditions. All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day (including Day -1) throughout the duration of the study.

Subjects will follow an overnight fast of at least 10 hours before the dosing procedures: for the fed dosing, a high-fat, high-calorie standard breakfast will be served 30 minutes before the planned administration of verinurad to be consumed in full at least 5 minutes before dosing; for the fasted dosing, no breakfast will be served. A meal can be given 4 hours after administration of verinurad for both dosing states.

#### 5.3.2.1. End of Study

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

#### 5.3.2.2. Expected Duration of the Study

Each subject will be involved in the study for approximately 9 weeks (including the screening period).

**Table 5-1 Expected Duration of Each Study Part**

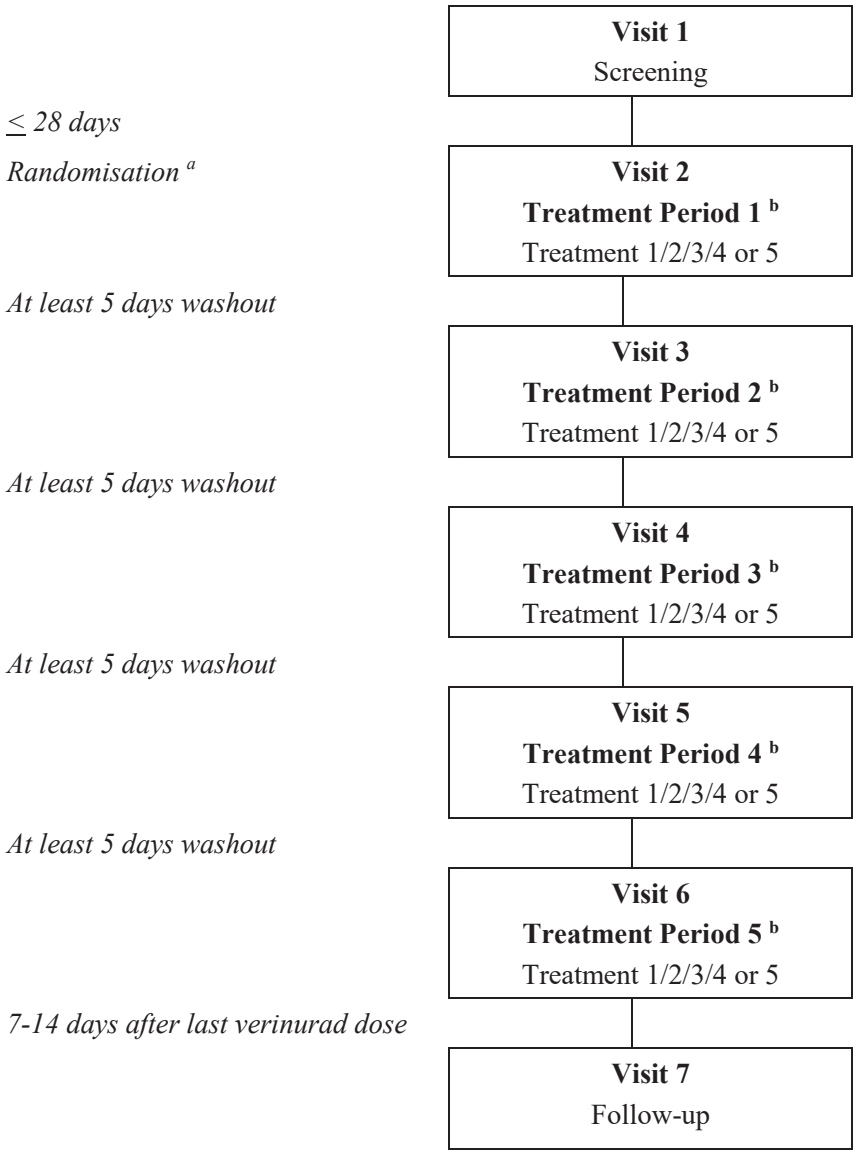
| | |
|---|---|
| **Screening** | 28 days before dose |
| **Treatment Periods** | 5 treatment periods during which subjects will be resident at the Clinical Unit from the day before dosing (Day -1) until at least 72 hours after dosing; discharged on Day 4 of each treatment period |
| **Washout Period** | At least 5 days between each dose administration |
| **Follow-up** | 7 to 14 days after dose |
| **Total Duration** | Up to 63 days (9 weeks) |

### 5.3.3. Study Flow Chart and Schedule of Assessments

The flow of events is illustrated in Figure 5-1 for all treatments, depending on the subject's assigned randomization (refer to Section 9.9.2).

The Schedule of Assessments displaying assessments/tasks and time points are presented in Table 5-2.

**Figure 5-1 Study Flow Chart**




Treatment 1: 1 x 12 mg verinurad ER8 capsule formulation, fasted.;
Treatment 2: 2 x 6 mg verinurad A capsule formulation, fasted.
Treatment 3: 2 x 6 mg verinurad A capsule formulation, fed.
Treatment 4: 2 x 6 mg verinurad B capsule formulation, fasted.
Treatment 5: 2 x 6 mg verinurad B capsule formulation, fed

[a] Randomization on Day -1 of Treatment Period 1.

[b] Residential period. Admission to Clinical Unit on Day -1, discharge from Clinical Unit on Day 4

**Table 5-2 Schedule of Assessments**

| | Screening | Treatment Periods 1, 2, 3, 4 and 5 | | Follow-up Visit | Corresponding Section in Protocol |
|---|---|---|---|---|---|
| **Visit** | **1** | **2, 3, 4, 5 and 6** | | **7** | |
| **Study Day** | **Day -28 to -2** | **Day -1** | **Day 1 to 4** | **7 to 14 days post-final dose** | |
| Inclusion/exclusion criteria [1] | X | X | | | Section 7.1 |
| Demographic data | X | | | | Section 12.7 |
| Medical history | X | | | | Section 12.8 |
| Urinary drug/alcohol screen | X | X | | | Section 10.3.5.6 |
| Serology | X | | | | Section 10.3.5.5 |
| Informed consent | X | | | | Section 3.5 |
| Randomization | | X [2] | | | |
| **Study Residency:**<br>Check-in | | X<br>(in the morning) | | | Section 5.3.2 |
| Check-out | | | Day 4 (after 72 h post-dose assessments) | | Section 5.3.2 |
| Non-residential visit | X | | | X | Section 5.3.2 |
| **Verinurad Administration:** | | | Day 1 (0 h) | | Section 5.3.2 and Section 9.6 |
| **Safety and Tolerability:**<br>Adverse event questioning [3] | X | X | Spontaneous plus<br>Day 1: pre-dose, 3 and 12 h post-dose<br>Day 2: 24 h post-dose<br>Day 3: 48 h post dose<br>Day 4: 72 h post-dose | X | Section 10.3.1 |

| | Screening | Treatment Periods 1, 2, 3, 4 and 5 | | Follow-up Visit | Corresponding Section in Protocol |
|---|---|---|---|---|---|
| **Visit** | **1** | **2, 3, 4, 5 and 6** | | **7** | |
| **Study Day** | **Day -28 to -2** | **Day -1** | **Day 1 to 4** | **7 to 14 days post-final dose** | |
| Prior and concomitant medications questioning | X | X | X | X | Section 9.7 |
| Blood pressure and pulse rate (supine) | X | X | Day 1: Pre-dose<br>Day 4: 72 h post-dose | X | Section 10.3.2 |
| Safety 12-lead Electrocardiograms | X | | | X | Section 10.3.3 |
| Clinical laboratory evaluations [4] | X | X | | X | Section 10.3.5.1, Section 10.3.5.2 and Section 10.3.5.3 |
| Physical examination [5] | X | X(brief) | Day 4: 72 h post-dose (brief) | X (brief) | Section 10.3.5.4 |
| Body weight and height, BMI | X | | | | |
| Pregnancy test [6] | X | X | | X | |
| **Pharmacokinetics** | | | | | |
| Pharmacokinetic sampling for verinurad | | | Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h post-dose<br>Day 2: 24 and 36 h post-dose<br>Day 3: 48 h post-dose<br>Day 4: 72 h post-dose | | Section 10.2 |

BMI = Body mass index.

[1] To be reconfirmed on Day -1 of each treatment period.

[2] Randomization to take place with admission to the unit on Day -1 of Treatment Period 1.

[3] Adverse Events will be collected from the start of randomization throughout the treatment periods up to and including the Follow-up Visit. Serious adverse events will be recorded from the time of informed consent.

[4] Blood (clinical chemistry and haematology) and urine (urinalysis) sample collection. Fasting samples: collected in the morning of admission following an overnight fast at home with no breakfast before admission. Admission to take place in the morning to ensure fasted samples.

*Footnotes continues on next page*

[5] A complete physical examination should include general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.
A brief physical examination should include general appearance, skin, abdomen, cardiovascular system and respiratory; and any organ systems pertinent to the patient's signs, symptoms or AEs.
Full physical examination at screening and brief assessment at: admission to the first treatment period, 72 hours post each dose and at the Follow-up Visit.
[6] Serum pregnancy test at screening, urine pregnancy test at admission to each treatment period and the Follow-up Visit.

### 5.3.4. Total Blood Volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarized in Table 5-3.

**Table 5-3 Total Blood Volume**

| | Volume per Sample | Number of Samples | Total |
|---|---|---|---|
| **Clinical Laboratory:** | | | |
| Haematology | 2.7 mL | 7 | 18.9 mL |
| Clinical chemistry [a] | 7.5 mL | 7 | 52.5 mL |
| **Pharmacokinetics:** | | | |
| Verinurad sampling | 2 mL | 80 | 160 mL |
| Total | | | 231.4 mL |

[a] When applicable, serology, serum pregnancy (females only) and follicle stimulating hormone analyses will be performed on the sample collected for clinical chemistry analyses.

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

### 5.3.5. Order of Assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point.

The sequence at a particular time point is:

1 Electrocardiograms (ECGs)
2 Vital signs (systolic and diastolic BP and pulse rate)
3 Pharmacokinetic blood sampling (will be drawn at the specified time point)

## 5.4. Dose Rationale

The highest dose (12 mg) currently tested in patients will be tested in this study.

## 5.5. Risk-benefit Assessment

There are no direct benefits for the subjects participating in this study. However, study-related health assessments are provided without costs for the subjects. The major risks for subjects who participate in the study will come from verinurad administration.

In the current study, verinurad will be administered as a standalone therapy as a single dose in this 5-period-5-treatment crossover study.

The main safety concern noted with verinurad monotherapy in healthy subjects is creatinine elevations > 1.5 x baseline which occurred in CCI % of healthy subjects. A change from baseline of ≥ 0.3 mg/dL was reported for CCI of all subjects. There was no apparent relationship between sCr elevation and dose of verinurad. The creatinine elevations were primarily transient, and often resolved despite continued dosing with verinurad. Further information is provided in the Investigator's Brochure (IB) [18].

Providing add-on therapy with an XOI to participating subjects to minimize creatinine elevations was judged to be inappropriate in this study as the risk of significant and enduring creatinine elevations is estimated to be lower than the risk of developing toxicities to an XOI, some of which can be severe. Instead, the risk of creatinine elevations will be minimized by ensuring participating subjects are properly hydrated, and by excluding patients from study inclusion as appropriate.

Overall, the study has been designed to minimize the risks to participating subjects by excluding subjects at high-risk of AEs and by applying appropriate safety monitoring of recruited study subjects. The dose selected has been carefully considered in light of the target subject population. The potential benefits of developing a new treatment for chronic kidney disease with hyperuricemia, therefore, outweigh the limited risks to the subjects exposed to treatment with verinurad in this study.

# 6. STUDY OBJECTIVES

## 6.1. Primary Objective

**Table 6-1 Primary Objective and Outcome Measures**

| Primary Objective | Outcome Measures |
|---|---|
| • To evaluate the relative bioavailability between the A-capsule and B-capsule formulations under both fed and fasted conditions with the ER8 capsule formulation under fasted conditions and with each other under the same food conditions. | • Primary pharmacokinetic parameters: AUC, AUC0-t, and Cmax |

## 6.2. Secondary Objectives

**Table 6-2 Secondary Objectives and Outcome Measures**

| Secondary Objectives | Outcome Measures |
|---|---|
| • To evaluate the relative bioavailability between fed and fasted conditions for the A-capsule and B-capsule formulations as well as between the A-capsule and B-capsule formulations. | • Primary pharmacokinetic parameters: AUC, AUC0-t, and Cmax |
| • To examine the PK profiles of verinurad when administered as the 3 different capsule formulations under fasted conditions. | • Primary pharmacokinetic parameters: AUC, AUC0-t, and Cmax<br>• Secondary pharmacokinetic parameters: AUC0-24, tmax, t½λz, CL/F, MRT, tlast, Vss/F, and Vz/F |
| • To assess the safety and tolerability of single doses of verinurad in healthy volunteers | • Adverse events, vital signs (systolic and diastolic BP, pulse rate), resting 12-lead ECGs, physical examination, and laboratory assessments (haematology, clinical chemistry and urinalysis) |

Refer to Section 12.9.1 for PK parameters and Section 10.3 for safety variables.

# 7. SELECTION OF STUDY POPULATION AND RESTRICTIONS

## 7.1. Selection of Study Population

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

Subjects who fail to meet all the inclusion criteria, or who do meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

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

### 7.1.1. Inclusion Criteria

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

1 Provision of signed and dated, written informed consent prior to any study specific procedures.
2 Healthy male and female subjects aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venepuncture.
3 Have a body mass index (BMI) between 18 and 30 kg/$m^2$ (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive).
4 Females must have a negative pregnancy test at screening and on admission to the unit and must be:

(1) not pregnant or currently lactating or breastfeeding.
(2) of non-childbearing potential (as defined in Section 7.2.1.1.1), confirmed at screening by fulfilling one of the following criteria:

(i) postmenopausal defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range (FSH levels > 40 IU/mL).
(ii) documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

(3) OR if of childbearing potential (as defined in Section 7.2.1.1.2) must be willing to use an acceptable method of contraception (as described in Section 7.2.1.1.2) to avoid pregnancy for the entire study period.

### 7.1.2. Exclusion Criteria

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

1 History of gout or any clinically significant disease or disorder which, in the opinion of the PI, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study.
2 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of verinurad.
3 History or presence of gastrointestinal (GI), hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
4 Any clinically important abnormalities in clinical chemistry, haematology or urinalysis results as judged by the Investigator at screening and first admission, including:

   (1) Alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN),
   (2) Aspartate aminotransferase (AST) > 1.5 x ULN,
   (3) Bilirubin (total) > 1.5 x ULN,
   (4) Gamma glutamyl transpeptidase (GGT) > 1.5 x ULN.
   (5) If any of these tests are out-of-range, the tests can be repeated once.

5 Any clinically significant abnormal findings in vital signs at the Screening Visit and/or admission to the Clinical Unit, including, but not limited to, any of the following:

   (1) Heart rate (resting, supine) < 50 beats per minute (bpm) or > 85 bpm,
   (2) Systolic BP < 90 mmHg or > 140 mmHg and/or diastolic BP < 50 mmHg or > 90 mmHg sustained for > 10 min while resting in a supine position.

6 Any clinically significant abnormalities on 12-lead ECG at the Screening Visit, including, but not limited to any of the following:

   (1) QTcF > 450 ms or < 340 ms or family history of long QT syndrome,
   (2) Any significant arrhythmia,
   (3) Conduction abnormalities:
   (4) Clinically significant PR (PQ) interval prolongation (> 240 ms); intermittent second or third degree atrioventricular (AV) block, or AV dissociation,
   (5) Complete bundle branch block and/or QRS duration > 120 ms.

7 Any positive result at the Screening Visit for serum hepatitis B surface antigen or antiHBc antibody, hepatitis C antibody, and human immunodeficiency virus (HIV) antibody.
8 Suspicion or known Gilbert's and/or Lesch-Nyhan syndrome.

9 Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the PI. Excessive intake of alcohol defined as the regular consumption of more than 24 g of alcohol per day for men or 12 g of alcohol per day for women.

10 Has received another new chemical entity (defined as a compound which has not been approved for marketing in the US) within 30 days or at least 5 half-lives (whichever is longer) of the first administration of verinurad in this study.
*Note: subjects consented and screened, but not randomised in this study or a previous Phase I study, are not excluded.*

11 Subjects who have previously received verinurad.

12 Plasma donation within 1 month of screening or any blood donation/loss of more than 500 mL during the 3 months prior to the Screening Visit.

13 Subjects who are pregnant, lactating or planning to become pregnant.

14 History of severe allergy/hypersensitivity or ongoing clinically relevant allergy/hypersensitivity, as judged by the PI or history of hypersensitivity to drugs with a similar chemical structure or class to verinurad.

15 Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the 3 months prior to screening.

16 Excessive intake of caffeine-containing drinks or food (e.g., coffee, tea, chocolate) as judged by the PI. Excessive intake of caffeine defined as regular consumption of more than 600 mg of caffeine per day (e.g., > 5 cups of coffee) or would likely be unable to refrain from the use of caffeine-containing beverages during confinement at the investigational site.

17 Positive screen for drugs of abuse or cotinine (nicotine) at the Screening Visit or positive screen for alcohol, drugs of abuse and cotinine on each admission to the study centre.

18 Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of verinurad.

19 Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of verinurad or longer if the medication has a long half-life.
The use of hormonal contraception therapy and hormonal replacement therapy for females are permitted.

20 Any AstraZeneca, PAREXEL or study site employee or their close relatives

21 Subjects who cannot communicate reliably with the PI and/or is not able to read, speak and understand the German language.

22 Judgment by the PI that the subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

23 Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.
24 Subjects with any special dietary restrictions such as subjects that are lactose intolerant or are vegetarians/vegans.

## 7.2. Restrictions During the Study

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

1 Prior to Day 1 in each treatment period, all subjects will fast for 10 hours overnight before the morning dose procedures. No fluids will be allowed apart from water which can be given until 1 hour before verinurad administration and then from 1 hour after verinurad administration, beverages provided with the high-fat breakfast in periods with dosing under fed conditions and water given during administration. Verinurad will be administered with 240 mL of water on Day 1 of each treatment period under either fasted or fed conditions. All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day (including Day -1) during the entire study.
During fed dosing, subjects will be provided with a Food and Drug Administration (FDA) high-fat, high-calorie breakfast 30 minutes before the scheduled dosing time (following the overnight fast as above), subjects should consume the breakfast within 25 minutes and finish the breakfast approximately 5 min before the scheduled dosing. During the fasted dosing, subjects will remain fasted for dosing. For both dosing states, no food will be allowed for at least 4 hours after dosing.
2 Subjects should not engage in any strenuous activity from 72 hours prior to check-in (Day -1 of Treatment Period 1) until after their Follow-up Visit.
3 Subjects should abstain from alcohol for the duration of the study from the first check-in (Day -1 of Treatment Period 1) until after their last PK sampling visit. Subjects should also abstain from alcohol for 72 hours before the Screening Visit and their Follow-up Visit.
4 Subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to first check-in (Day -1 of Treatment Period 1) until the Follow-up Visit.
5 Subjects should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (e.g., tonic water) from 7 days prior to check-in (Day -1 of Treatment Period 1) until after their Follow-up Visit.
6 During admission periods, subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the Clinical Unit.
7 During the subjects' outpatient periods, subjects should abstain from consuming, high-energy drinks (e.g., red bull), and food containing poppy seeds and any Over-the-Counter (OTC) medication or herbal preparations until after their Follow-up Visit has been completed.

8 Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the study follow-up.

For medication restrictions, refer to Section 9.7.

## 7.2.1. Reproductive Restrictions

### 7.2.1.1. Female Subjects

A female subject who participates in the clinical trial must either:

- Be of non-childbearing potential (surgically sterilized or postmenopausal as described in Section 7.2.1.1.1, OR
- Of child-bearing potential and must be using highly effective methods of birth control as described in Section 7.2.1.1.2.

#### 7.2.1.1.1. Women of Non-Child Bearing Potential

Women of non-childbearing potential are defined as female subjects who are permanently surgically sterilized or postmenopausal.

Acceptable methods of sterilization include:

- Surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks before Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Hysterectomy at least six weeks before Screening.
- Bilateral salpingectomy.

Females are considered postmenopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range (e.g., age appropriate, history of vasomotor symptoms) or for women < 60 years the FSH levels is > 40 mIU/mL.)

#### 7.2.1.1.2. Women of Child Bearing Potential

Women of child bearing potential who are sexually active must agree to use, with their partner, an approved method of highly effective contraception from the time of verinurad administration until 3 months after the study Follow-up Visit.

- A barrier method must be used in combination with one of the following methods, considered to be highly effective (failure rate < 1% per year when used consistently and correctly):
    - hormonal contraception, i.e., combined oral contraceptives, injectable[1] or implantable[1] hormonal contraceptives,

- hormonal or non-hormonal intrauterine device[1] (IUD, loop), established IUD[1] or intrauterine system (Note: The IUD must have a failure rate < 1%),
- Surgical sterilization[1] (i.e., bilateral tubal ligation for females; vasectomy for male partners [must have been vasectomized before the female subject entered the clinical trial and he is the sole sexual partner of the female subject during the clinical trial,])
- observe abstinence (acceptable only if it is the subject's usual lifestyle).

- Barrier methods of contraception include:
  - Condom (**without** spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants),
  - Occlusive cap (diaphragm or cervical/vault caps) **with** spermicidal gel/film/cream/suppository,
- [1] These methods are considered to have low user dependency.

*Note: Double-barrier is not considered a highly effective method.*

Female subjects must agree not to attempt to become pregnant, must not donate ova and must not breastfeed starting at screening and throughout the clinical study and for 90 days (3 months) after the Follow-up Visit.

Women should be informed of the potential risks associated with becoming pregnant while enrolled.

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

**True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception).*

**Pregnancy Testing**

Women of child-bearing potential can be included only after a negative highly sensitive serum pregnancy test. Additionally, urine pregnancy testing will be done as per the Schedule of Assessments (Table 5-2).

#### 7.2.1.2. Male Subjects

**Restrictions for male subjects**

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

Male subjects participating in this study are not required to apply contraception. However, it is recommended that male subjects should not donate sperm until at least 3 months after the Follow-up Visit. In addition, as a precaution, all male subjects should avoid fathering a child AND exposing a foetus to verinurad by either true abstinence or use together, with their female partner/spouse, of a highly effective method of contraception (see definition above), starting from the time of verinurad administration until at least 3 months after thee Follow-up Visit.

**Pregnancy**

Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

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

## 7.3. Replacement of Subjects

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

Twenty-five (25) subjects will initially be randomised into the study in 5 treatment sequences (5 subjects per treatment sequence) to ensure at least 20 evaluable subjects (4 subjects per treatment sequence) at the end of the study. Subjects will only be replaced if the subject number for evaluable subjects fall below 20 subjects or are less than 4 evaluable subjects per treatment sequence. However, looking at previous studies and previous verinurad experience, at the current study design and dose level, it is highly unlikely to fall below these numbers, and replacements are unlikely to take place.

# 8. STUDY STOPPING RULES

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

Subjects must be discontinued from verinurad in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to the Clinical Study Protocol (CSP).
- Any significant and clinically relevant changes in the safety parameters (e.g., ECG, BP, pulse rate, laboratory assessments and AEs) making the continuation of verinurad administration unjustified.
- Study specific withdrawal criteria: If a subject reports symptoms, which are considered unacceptable by the subject or the Investigator, he/she will be withdrawn from the study. In particular:
  - Any other severe or SAE that is judged as possibly related to verinurad by the Investigator.
  - Any case of Potential Hy's Law according to Appendix 16.3.
  - Study treatment will be stopped if a subject has elevated creatinine levels greater than 1.5 times the pre-treatment value and retest of the creatinine will be performed as soon as possible (see Appendix 16.4).
  - In subjects who report symptoms that indicate acute UA nephropathy including flank pain, nausea, or vomiting, treatment will be permanently discontinued. Appendix 16.4 contains guidelines on management of such subjects.
  - See Appendix 16.4 for details on the handling of renal-related or urolithiasis treatment-emergent AEs, and the handling of serum creatinine elevation, which includes criteria for stopping treatment.
  - Pregnancy.
- The appropriate AE form in the case report form is to be completed.

## 8.2. Premature Termination of the Study and Stopping Criteria

The study will be put on temporary hold (defined as treatment stopped for enrolled subjects; and stop enrolment of subjects into the study) pending further safety data analysis if any of the following criteria occur in subjects receiving verinurad:

- A "serious" adverse reaction (i.e., an SAE considered at least possibly related to verinurad administration as per guideline EMEA/CHMP/SWP/28367/07 Rev. 1) in 1 subject;

- "Severe" non-serious adverse reactions (i.e., severe non-serious AEs considered as, at least, possibly related to the IMP administration) in 2 subjects in the same treatment sequence, independent of within or not within the same System Organ Class (SOC).

The study must be terminated prematurely if:

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

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

# 9. TREATMENTS

## 9.1. Identity of the Investigational Medicinal Product

Details on the identity of the investigational medicinal product (IMP) are presented in Table 9-1.

**Table 9-1 Identity of the Investigational Medicinal Product**

| | |
|---|---|
| Supplier: | AstraZeneca |
| Formulation: | Verinurad ER8 capsule formulation<br>Verinurad A-capsule formulation<br>Verinurad B-capsule formulation |
| Strength/concentration: | 12 mg: ER8 capsule formulation<br>6 mg: A-capsule formulation<br>6 mg B-capsule formulation |
| Dose: | 12 mg |
| Route of administration: | Oral |
| Regimen: | Treatment 1: 1 x 12 mg verinurad ER8 capsule formulation, fasted.<br>Treatment 2: 2 x 6 mg verinurad A-capsule formulation, fasted.<br>Treatment 3: 2 x 6 mg verinurad A-capsule formulation, fed.<br>Treatment 4: 2 x 6 mg verinurad B-capsule formulation, fasted.<br>Treatment 5: 2 x 6 mg verinurad B-capsule formulation, fed. |
| Special handling requirements: | None. |

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

## 9.2. Supply of Investigational Medicinal Product

The IMP will be supplied by AstraZeneca and provided in bulk labelled with a study specific label and re-packaged into subject specific containers by PAREXEL, as applicable.

A technical agreement between the PI and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMPs at the Clinical Unit.

A release document signed by a legally authorized Qualified Person (QP) at the Clinical Unit will be placed in the appropriate section of the Trial Master File to document labelling and dispensing of the study drug to the subject.

## 9.3. Storage and Handling Procedures

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

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

## 9.4. Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines.

The labels will fulfil Good Manufacturing Practices (GMP) Annex 13 requirements and medical device directive for labelling.

## 9.5. Drug Accountability, Dispensing and Destruction

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

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

All unused supplies of verinurad will either be destroyed by PAREXEL or returned at the end of the study in accordance with instruction by the Sponsor.

## 9.6. Dose and Treatment Regimens

Subjects will receive single doses of different formulations of verinurad under fasted or fed conditions during the 5 treatment periods.

For both the fasted and fed dosing, no fluids will be allowed apart from water which can be given until 1 hour prior and 1 hour after administration of verinurad, water to be given with the verinurad administration and the beverages provided with the high-fat, high-calorie breakfast in dosing periods with administration under fed conditions. All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day (including Day -1) throughout the duration of the study.

All subjects will follow an overnight fast of at least 10 hours before the dosing procedures on Day 1: for the fed dosing, a high-fat, high-calorie standard breakfast will be provided 30 minutes before the administration of verinurad, to be consumed in full at least 5 minutes before dosing; for the fasted dosing, no breakfast will be served, and subjects will remain fasted. A meal can be given 4 hours after administration of verinurad for both dosing states.

Following the restrictions above, each subject will receive a single-dose of different formulations of verinurad on each treatment period (5 occasions), respectively:

| | | | |
|---|---|---|---|
| Treatment 1 | Reference product | ER8 capsule, fasted | 1 x 12 mg |
| Treatment 2 | Test product | A-capsule, fasted | 2 x 6 mg |

| | | | |
|---|---|---|---|
| Treatment 3 | Test product | A-capsule, fed | 2 x 6 mg |
| Treatment 4 | Test product | B-capsule, fasted | 2 x 6 mg |
| Treatment 5 | Test product | B-capsule, fed | 2 x 6 mg |

Other restrictions are described in Section 7.2.

### 9.6.1. FDA Breakfast Menu

The breakfast [19] will constitute the following:

- 2 eggs fried in butter,
- 2 strips of bacon,
- 2 slices of toast with butter,
- 120 g of fried potatoes,
- 240 mL of whole milk.

## 9.7. Concomitant and Post-study Treatments

Apart from paracetamol/acetaminophen (if applicable) and hormone replacement therapy (if applicable) and systemic contraceptives no concomitant medication or therapy will be allowed.

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

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

When any medication is required, it should be prescribed by the PI. Following consultation with the AstraZeneca Lead Physician, the PI should determine whether or not the subject should continue in the study. Administration of concomitant medications that may influence the measurement of the PK and/or PD endpoints may be documented as a protocol deviation after consultation of the PI with the AstraZeneca Lead Physician.

## 9.8. Treatment Compliance

Dosing will take place at the PAREXEL Early Phase Clinical Unit.

The administration of all IMPs will be recorded in CCI

Compliance will be assured by direct supervision and witnessing of study drug administration. After IMP administration, a check of the subject's mouth and hands will be performed.

## 9.9. Randomization

### 9.9.1. Subject Enrolment and Randomization

The PI will ensure:

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

Randomization to be done on Day -1 of Treatment Period 1.

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization (codes to be used without leading zero[s]).

When using unique enrolment number, the specific format must be followed (i.e., reduced enrolment number "01001" in CCI and on labels, full enrolment number "E0001001" for outputs).

If a subject withdraws his/her participation in the study, then his/her enrolment/randomization code cannot be re-used. If a replacement is mandated, replacement subjects will receive a new randomization number and will be allocated to CCI

### 9.9.2. Procedures for Randomization

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

Subjects will be randomised to treatment sequences in a ratio of 1:1:1:1:1 so that all subjects will receive all formulations of verinurad. The reference capsules (Treatment 1) will be given under fasted conditions, while the new formulations (Treatments 2, 3, 4 and 5) will be given under both fasted or fed conditions as per study design (see Section 5.3.2).

The randomization will be completed using consecutive randomization codes.

The number of subject identifiers generated for the study will account for the number of randomised subjects per the sample size calculation (N = 20 [see Section 12.4]) as well as providing sufficient randomization numbers for replacements. For this study, a total of

25 subject identifiers will be randomly assigned to the 5 treatment sequences: 12345, 23451, 51234, 34512 and 45123.

### 9.9.3. Procedures for Handling Incorrectly Randomised Subjects

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

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

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

## 9.10. Blinding

This is an open-label study.

# 10. MEASUREMENTS AND METHODS OF ASSESSMENTS

## 10.1. Appropriateness of Measurements

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

For timing of assessments refer to Table 5-2.

## 10.2. Pharmacokinetics

### 10.2.1. Sample Collection and Handling

Blood samples for the determination of plasma concentrations of verinurad will be collected for each treatment period as specified in the Schedule of Assessments (Table 5-2).

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

### 10.2.2. Pharmacokinetic Drug Assays

Blood samples for determination of verinurad concentrations in plasma will be analysed by Covance Bioanalytical Services on behalf of AstraZeneca, using a validated assay. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

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

## 10.3. Safety and Eligibility Measurements

Safety and tolerability variables will include:

- Adverse events
- Vital signs (systolic and diastolic BP, pulse rate)
- ECG
- Physical examination
- Laboratory assessments (haematology, clinical chemistry and urinalysis).

Viral serology and drugs of abuse, alcohol and cotinine will be assessed for eligibility. Follicle Stimulation Hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

### 10.3.1. Adverse Events

Refer to Section 13.2.3.

### 10.3.2. Vital Signs

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

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse rate (beats per minute [bpm])

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

### 10.3.3. Electrocardiograms

**Resting 12-lead Electrocardiogram**

At the time points specified in the Schedule of Assessments (Table 5-2), a 10-second 12-lead safety ECG will be obtained after 10 minutes supine rest) using the sites own ECG machines.

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

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

All ECG readings will be digitally stored as source documents.

### 10.3.4. Physical Examination

**Full**

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

**Brief (Abbreviated)**

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory.

## 10.3.5. Laboratory Assessments

### 10.3.5.1. Haematology

| Haematology | |
|---|---|
| White blood cell count | Neutrophils absolute count |
| Red blood cell count | Lymphocytes absolute count |
| Haemoglobin | Monocytes absolute count |
| Haematocrit | Eosinophils absolute count |
| Mean corpuscular volume | Basophils absolute count |
| Mean corpuscular haemoglobin | Platelets |
| Mean corpuscular haemoglobin concentration | Reticulocytes absolute count |

### 10.3.5.2. Serum Clinical Chemistry

| Serum Clinical Chemistry | |
|---|---|
| Sodium | Alkaline phosphatase |
| Potassium | ALT |
| BUN | AST |
| Creatinine | GGT |
| Albumin | Total Bilirubin |
| Calcium | Unconjugated bilirubin |
| Phosphate | Serum uric acid |
| Glucose(fasting) | |
| C-reactive protein | |
| FSH | |

### 10.3.5.3. Urinalysis

| Urinalysis [1] | |
|---|---|
| Glucose | |
| Protein | |
| Blood | |

[1] Upon a positive urine test from leucocytes, blood, nitrite or protein, the Investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses will be included in the database. If the flow cytometry examination shows a different result than the urine sticks, the urine will be investigated by fully automated digital imaging where leukocytes, erythrocytes, casts in urine will be analysed.

### 10.3.5.4. Pregnancy Testing

| Pregnancy test (females only) | |
|---|---|
| Human-beta chorionic gonadotrophin (Blood) | Urine assessment |

#### 10.3.5.5. Viral Serology

| Viral Serology | |
|---|---|
| Human immunodeficiency virus (HIV) I and II | Hepatitis C Virus antibody |
| Hepatitis B surface antigen (HBsAg) | anti-HBc antibody |

#### 10.3.5.6. Drugs of Abuse, Alcohol and Cotinine

| Drugs of Abuse and Alcohol | |
|---|---|
| Amphetamine / Ecstasy | Benzodiazepines |
| Ethanol | Methadone Metabolites |
| Cannabinoids | Barbiturates |
| Cocaine | Phencyclidine |
| Opiates | Urine Creatinine |
| Cotinine | |
| Tricyclic anti-depressants | |

### 10.3.6. Concomitant Medication

Refer to Section 9.7.

## 10.4. Procedures for Handling of Biological Samples

### 10.4.1. Storage and Destruction of Biological Samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalized, unless samples are retained for additional or future analyses.

#### 10.4.1.1. Pharmacokinetic Samples

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

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

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

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

### 10.4.2. Labelling and Shipment of Biohazard Samples

Samples will be 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) (for International Airline Transportation Association [IATA] guidance, see Appendix 16.2 of this CSP).

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

### 10.4.3. Chain of Custody of Biological Samples

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

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

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

### 10.4.4. Withdrawal of Informed Consent for Donated Biological Samples

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

As collection of donated biological samples is an integral part of the study then the subject is withdrawn from further study participation.

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

# 11. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

## 11.1. Quality Control and Source Data Verification

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

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

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

## 11.2. Audit/Inspections

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

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

## 11.3. Study Monitoring

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

## 11.4. Data Collection

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

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

### 11.4.1. Case Report Forms and Source Documents

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

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

### 11.4.2. Access to Source Documents

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

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

## 11.5. Data Management

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

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

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

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

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the PI for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms. This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

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

# 12. STATISTICAL METHODS

## 12.1. Overview

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

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate statistical analysis plan (SAP) will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

## 12.2. General Statistical Methodology

CCI [redacted]

CCI [redacted]

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.4 or later.

### 12.2.1. Missing Data

Missing dates and times in the AE data will be handled as described in Section 12.10.1. Concentrations that are non-quantifiable (NQ) in the PK data will be handled as described in Section 12.9.2.

There will be no imputations of other missing data. All randomised and dosed subjects will be included into the safety analyses as far as the data permit.

## 12.3. Study Populations

### 12.3.1. Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of verinurad (any formulation) and for whom any safety post-dose data are available.

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

### 12.3.2. Pharmacokinetic Analysis Set

The PK analysis set will consist of all subjects in the safety analysis set for whom at least 1 of the primary PK parameters can be calculated, and who have no major protocol deviations thought to impact on the analysis of the PK data. All the eligible PK data will be presented for each treatment using descriptive statistics. For the formal relative bioavailability evaluations, only subjects who provide eligible PK data for both Test and Reference treatments can be included for each comparison.

Pharmacokinetic data for a subject during any treatment period may be excluded from the corresponding descriptive and formal statistics as a result of the following:

- an AE of vomiting occurring at or before median tmax for that treatment,

- a pre-dose concentration of verinurad > 5% of Cmax for that treatment.

If either of these occur for any subject during all treatment periods then the subject will be excluded from the PK analysis set.

Individual PK concentration data may be excluded from the PK analysis and/or statistical analyses and corresponding figures. The exclusion of any subjects from the PK analysis set, of any individual concentration-time points from the calculation of the PK parameters or from the statistical analyses and corresponding figures and of any individual PK parameters from the statistical analyses and corresponding figures will be documented by the PK Scientist including the reasons for exclusion.

All available reportable concentration data and PK parameter data will be listed. Concentration or parameter data for subjects excluded from the statistical summaries or formal statistics will be presented in the corresponding individual concentration versus time or PK parameter figures but not in the corresponding summary figures.

## 12.4. Determination of Sample Size

CCI [redacted]

[redacted]

## 12.5. Protocol Deviations

Per Protocol set will be based on protocol deviations and it is defined as all subjects included in the safety analysis set with no major protocol deviations.

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations.
- Dosing deviations (e.g., incorrect treatment received, subject was not fasted as per the protocol requirements prior to and after dosing).
- Time window deviations for safety and/or PK assessments.
- Subjects receiving prohibited concomitant medications.

- Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log.

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

Pharmacokinetic samples where the actual time of collection deviates by more than 10% from the protocol scheduled collection time will be included in the PK analysis to determine the PK parameters but will be excluded from the summary statistics and corresponding plots.

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

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

## 12.6. Subject Disposition

A randomization listing will be presented and include the following: each subject's randomization number, the subject's full enrolment number, the treatment sequence to which the subject has been randomised and the country where the study centre is located.

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: number of subjects randomised and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomised (subjects entered into the study that received a randomization number, prior to dosing).

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

## 12.7. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarized separately by treatment sequence

and overall for all randomised subjects. The denominator for percentages will be the number of randomised subjects.

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

## 12.8. Prior and Concomitant Medication and Drug Administration

### 12.8.1. Prior and Concomitant Medication

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

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

### 12.8.2. Drug Administration

Drug administration dates and times will be listed for each subject and treatment period. Details of high-fast, high-calorie breakfast will be listed.

## 12.9. Pharmacokinetic Analysis

### 12.9.1. Pharmacokinetic Parameters

Where possible, the following PK parameters will be determined for verinurad using plasma concentrations.

**Primary PK parameters**

| | |
|---|---|
| AUC | Area under plasma concentration-time curve from time zero to infinity |
| AUC0-t | Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration |
| Cmax | Maximum observed plasma concentration |

**Secondary PK parameters**

| | |
|---|---|
| AUC0-24 | Area under the plasma concentration-time curve from time zero to 24 hours |
| tmax | Time to reach maximum observed plasma concentration |

| | |
|---|---|
| t½λz | Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve |
| CL/F | Apparent total body clearance of drug from plasma after extravascular administration (parent drug only) |
| MRT | Mean residence time of the unchanged drug in the systemic circulation from zero to infinity |
| tlast | Time to reach last quantifiable plasma concentration |
| Vss/F | Apparent volume of distribution during the terminal phase after extravascular administration (parent drug only) |
| Vz/F | Apparent volume of distribution during the terminal phase after extravascular administration |

The following diagnostic parameters for plasma PK analysis will be listed, but not summarized:

| | |
|---|---|
| t lower | Start of exponential fit |
| t upper | End of exponential fit |
| λzN | Number of data points included in the log-linear regression analysis |
| Rsq_adj | Regression coefficient adjusted for the λzN, Goodness-of-fit statistic for calculation of λz |
| %AUCextr | Percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve from the time of the last quantifiable concentration to infinity |
| λz | Terminal elimination rate constant |

Additional PK parameters may be determined where appropriate.

### 12.9.2. Derivation of Pharmacokinetic Parameters

The PK analyses of the plasma concentration data for verinurad will be performed by Covance Clinical Pharmacokinetic Alliance on behalf of AstraZeneca R&D.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher. All descriptive and inferential statistical computations will be performed using SAS® Version 9.4, or higher.

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

Plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any NQ plasma concentrations will

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

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

Cmax, tmax and tlast will be taken directly from the plasma concentration-time profile.

Terminal elimination half-life, calculated as (ln2)/λz, will be estimated by log-linear least squares regression of the terminal part of the concentration-time curve. For the determination of λz, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations (t lower). The last point (t upper) will be the time of the last quantifiable plasma concentration. A minimum of 3 data points will be used in calculating λz, and the duration of time over which λz is recommended to be at least 3 times the subsequently estimated terminal half-life. Where an elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life, it will be flagged and commented upon in the study report by agreement with the Sponsor.

The Rsq_adj value will be calculated to show the goodness-of-fit of the log-linear regression taking into consideration the number of points used in the estimation. To achieve a good precision in the estimation, the Rsq_adj value should be high, a value of ≥ 0.8 being indicative of good correlation. Any λz with a Rsq_adj of < 0.8 will be flagged in the data listings along with any parameters derived from λz (e.g., t½λz, AUC, CL/F, Vz/F and %AUCextr) and agreement reached with the Sponsor regarding any exclusion of data from the summaries.

AUC values, including AUC and AUC0-t, will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up, log down method). AUC is estimated by AUC0-t + Clast/λz where Clast is the observed last quantifiable drug concentration. The AUC values where the percentage extrapolation is greater than 20% and any parameters dependent on AUC will be flagged in the data listings and agreement reached with the Sponsor on whether exclusions from the summary or formal statistics are required.

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

Apparent clearance (CL/F) will be determined from the ratio of dose/AUC. Apparent volume of distribution based on the terminal phase (Vz/F) will be determined from the ratio of dose/λz*AUC. Vss/F will be determined by multiplying CL/F by MRT.

### 12.9.3. Presentation of Pharmacokinetic Data

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations will be summarized for the PK analysis set for each time point by treatment using the following descriptive statistics: n, n below LLOQ, geometric mean (gmean), geometric coefficient of variation [CV] (gCV%), arithmetic mean, arithmetic SD, gmean ± geometric SD (gSD) (gmean + gSD and gmean - gSD), median, minimum (min) and maximum (max).

The gmean is calculated as the exponential(μ) where μ is the arithmetic mean calculated using log-transformed data.

The gCV% is calculated as 100*sqrt[exp($s^2$)-1] where s is the SD of the log-transformed data.

The gmean ± gSD (gmean - gSD and gmean + gSD) are calculated as exp[μ ± s].

Pharmacokinetic concentration data will be presented in the listings to the same number of significant figures as the data received from the bioanalytical laboratory (usually to 3 significant figures) and against the same units as received. Pharmacokinetic concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures and n and n < LLOQ which will be presented as integers.

Individual concentrations with time deviations of greater than ± 10% from the protocol scheduled time will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

Plasma concentrations that are NQ, Not Reportable or missing will be handled as follows:

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant tables, figures and listings. Individual plasma concentrations that are Not Reportable will be reported as no result (NR) and those that are missing will be reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.

- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than half of the values are NQ, the gmean, gmean + gSD, gmean-gSD and gCV% will be set to not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time-point. The gmean, minimum, median and maximum will be reported as NQ and the gCV% and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time-point together with the total number of collected values (n).

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

All reportable plasma PK parameters will be listed for each subject and treatment. A separate listing will be provided for the diagnostic PK parameters.

Plasma PK parameters will be summarized for the PK analysis set by treatment using the following descriptive statistics:

- Cmax, AUC, AUC(0-t), and AUC(0-24): present n, gmean, gmean + gSD, gmean-gSD, arithmetic mean, arithmetic SD, gCV(%), median, min and max.
- t½λz, CL/F, Vz/F, Vss/F and MRT: present n, gmean, gmean + gSD, gmean-gSD, arithmetic mean, arithmetic SD, gCV(%), median, min and max.
- tmax and tlast present n, median, min and max.
- Diagnostic parameters (e.g., λz, t upper, t lower, λzN, Rsq_adj and %AUCextr): listed only and not summarized.

Three values are required as a minimum for PK parameters to be summarized. Two values are presented as a min and max with the other summary statistics as NC.

If one or more values for a given parameter is zero (or imputed with zero), then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to NA (not applicable).

Pharmacokinetic parameter listings will be presented according to the following rules:

- Cmax – present to the same number of significant figures as received from the bioanalytical laboratory.

- tmax, tlast, t lower and t upper – present as received in the data, usually to 2 decimal places.
- AUC, AUC(0-t), AUC(0-24), t½λz, CL/F, Vz/F, Vss/F, MRT, Cmax, λz, %AUCextr, Rsq_adj will be presented to 3 significant figures.
- λzN – will be presented as an integer (no decimals).

The descriptive statistics for PK parameter data will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures apart from the following:

- tmax and tlast: –present as received in the data, usually to 2 decimal places.

Pharmacokinetic data (concentrations and parameters) from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics as appropriate.

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

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

Geometric mean plasma concentration (±gSD) versus nominal sampling time will be plotted in linear and semi-logarithmic (no SD presented) scale with separate plots for all treatments on the same figure and with the fasted and fed treatments on the same figure for each study formulation.

All gmean plots or combined plots showing all subjects by treatment will be based on the PK analysis set. Individual plots by subject will be based on the safety analysis set.

For consistency, the plasma concentration values used in the gmean data graphs will be those given in the descriptive statistics summary table for each time-point.

For gmean concentration-time plots, NQ values will be handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted will be zero for linear plots and missing for semi-logarithmic plots. Any gmean ± gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing.

### 12.9.4. Statistical Analysis of Pharmacokinetic Data

For each individual relative bioavailability comparison the ratios of Cmax, AUC0-t and AUC will be calculated for Test:Reference using log transformed data.

The following comparisons of relative bioavailability (AUC, AUC0-t and Cmax) of verinurad will be performed:

- Treatment 2 versus 1 i.e., “A capsule, fasted” versus “ER8 capsule, fasted”
- Treatment 4 versus 1 i.e., “B capsule, fasted” versus “ER8 capsule, fasted”
- Treatment 3 versus 1 i.e., “A capsule, fed” versus “ER8 capsule, fasted”
- Treatment 5 versus 1 i.e., “B capsule, fed” versus “ER8 capsule, fasted”
- Treatment 4 versus 2 i.e., “B capsule, fasted” versus “A capsule, fasted”
- Treatment 5 versus 3 i.e., “B capsule, fed” versus “A capsule, fed”
- Treatment 3 versus 2 i.e., “A capsule, fed” versus “A capsule, fasted”
- Treatment 5 versus 4 i.e., “B capsule, fed” versus “B capsule, fasted”

Analyses will be performed using a linear fixed-effects analysis of variance model using the natural logarithm of AUC, $AUC_{0-t}$ and Cmax as the response variables, sequence, period and treatment as fixed effects, volunteer nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUC, $AUC_{0-t}$ and Cmax will be estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented.

## 12.10. Analysis of Safety Data

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

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

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

Clinical laboratory data will be reported in the units provided by the clinical laboratory for the Safety Review Committee meeting, and in Système International units in the CSR.

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

### 12.10.1. Adverse Events

All AEs will be coded using MedDRA vocabulary and will be listed for each subject. A treatment-emergent adverse event is defined as an AE with onset (start date/time) after the first dose of verinurad in Treatment Period 1.

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

- Screening: all SAEs with start date/time prior to dosing in Treatment Period 1.
- Treatment Period 1: AEs with start date/time at the time of or after dosing in Treatment Period 1 until the time of dosing in Treatment Period 2.
- Treatment Period 2: AEs with start date/time at the time of or after dosing in Treatment Period 2 until the time of dosing in Treatment period 3.
- Treatment Period 3: AEs with start date/time at the time of or after dosing in Treatment Period 3 until the time of dosing in Treatment Period 4.
- Treatment Period 4: AEs with start date/time at the time of or after dosing in Treatment Period 4 until the time of dosing in Treatment Period 5.
- Treatment Period 5: AEs with start date/time at the time of or after dosing in Treatment Period 5 until the Follow-up Visit.

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

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

date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;

- If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later.
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

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

The following information will be included in the listings: verbatim term, SOC, PT and start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

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

Finally, an overview of all AEs will be presented, separately for the number and percentage of subjects and the number of events. This will include categories for any AE, AEs with the outcome of death, SAEs and discontinuations of IMP/withdrawals from the study.

### 12.10.2. Vital Signs

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

### 12.10.3. Resting 12-lead Electrocardiogram

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

### 12.10.4. Physical Examination

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

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

The results of the physical examination will be listed by body system for each subject.

### 12.10.5. Laboratory Assessments

Haematology and clinical chemistry values will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations including absolute value and changes from baseline will be presented by treatment and time point for the safety analysis set. The baseline for the measurements will be the Day -1 assessment performed prior to dosing in each treatment period. Shift tables, by treatment, will also be presented.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (e.g., AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable).
- Pregnancy testing (including FSH).
- The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

# 13. ADVERSE EVENTS

## 13.1. Definitions

### 13.1.1. Definition of Adverse Events

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

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

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

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

### 13.1.2. Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., 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 or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix 16.1 of this CSP.

### 13.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered Other significant adverse events (OAEs) and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

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

## 13.2. Recording of Adverse Events

### 13.2.1. Time Period for Collection of Adverse Events

Adverse Events will be collected from the start of randomization throughout the treatment periods up to and including the Follow-up Visit.

SAEs will be recorded from the time of informed consent.

### 13.2.2. Follow-up of Unresolved Adverse Events

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

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

### 13.2.3. Variables

The following variables will be collected for each AE:

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

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

The following intensity ratings will be used:

9 Mild (awareness of sign or symptom, but easily tolerated)
10 Moderate (discomfort sufficient to cause interference with normal activities)
11 Severe (incapacitating, with inability to perform normal activities)

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 13.1.2.

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

### 13.2.4. Causality Collection

The PI will assess causal relationship between IMP 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 IMP?"

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

A guide to the interpretation of the causality question is found in Appendix 16.1 of this CSP.

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

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"* or revealed by observation will be collected and recorded in the CCI

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.

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

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

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore be reported as AEs if they constitute a clinically significant deterioration from baseline.

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

Wherever possible the reporting PI should use the clinical, rather than the laboratory term (e.g., anaemia versus low Hb 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.

### 13.2.7. Hy's Law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN will need to be reported as SAEs. Please refer to Appendix 16.3 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

## 13.3. Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative will work with the PI to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

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

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

The reference document for definition of expectedness/listedness is the IB [18] for the AstraZeneca drug.

# 14. LEGAL AND ADMINISTRATIVE ASPECTS

## 14.1. Archiving of Study Documents

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

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

## 14.2. Publication of Study Results

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 14.3. Clinical Study Report

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

# 15. REFERENCE LIST

1 Hyndman D, Liu S, Miner JN. Urate handling in the human body. Curr Rheumatol Rep 2016;18(6):34.
2 Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann. Intern Med 2005;143(7):499-516.
3 Hamburger M, Baraf HS, Adamson TC 3rd, Basile J, Bass L, Cole B, *et al*. 2011. Recommendations for the diagnosis and management of gout and hyperuricemia. Postgrad Med 2011;123(6 Suppl 1):3-36.
4 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia: risks and consequences in the Normative Aging Study. Am J Med 1987;82(3):421-6.
5 Yamanaka H, Japanese Society of Gout. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleos Nucleot Nucl 2011;30(12):1018-29.
6 Chinese Rheumatology Association. Primary gout diagnosis and treatment guideline. Chin J Rheumatol 2011;15(6):410-3.
7 Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, *et al*. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006;290(3):F625-31.
8 Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2011;63(1):102-10.
9 Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, *et al*. Association between serum uric acid and development of type 2 diabetes. Diabetes Care 2009;32(9):1737-42.
10 Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, *et al*. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998;19(12):1814-22.
11 Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, *et al*. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107(15):1991-7.
12 Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum 2008;58(2):623-30.
13 Kim SY, De Vera MA, Choi HK. Gout and mortality. Clin Exp Rheumatol 2008;26(5)(suppl 51):S115-S119.
14 Jankowska EA, Ponikowska B, Majda J, Zymlinski R, Trzaska M, Reczuch K, *et al*. Hyperuricaemia predicts poor outcome in patients with mild to moderate chronic heart failure. Int J Cardiol 2007;115(2):151-5.
15 Richette P, Doherty M, Pascual E, *et al*. 2016 updated EULAR evidence-based recommendations for the management of gout Ann Rheum Dis. 2017;76:29-42

16 Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, *et al*. EULAR evidence-based recommendations for gout, Part II: management: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65(10):1312-24.

17 Jordan KM, Cameron JS, Snaith M, Zhang, W, Doherty M, Secki J, *et al*. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2007;46(8):1372-4.

18 Verinurad Investigator's Brochure, Edition 2, dated 26 October 2018.

19 FDA Guidance for Industry 'Food-Effect Bioavailability and Fed Bioequivalence Studies'. December 2002. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM126833.pdf

20 FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

# 16. APPENDICES

## 16.1. Additional Safety Information

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

***Life-threatening***

'Life-threatening' means that the subject 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 subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g., 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 subject 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 subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

**A Guide to Interpreting the Causality Question**

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

- Time Course / Exposure to suspect drug:

Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile:

Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR, could the AE be anticipated from its pharmacological properties?

- Dechallenge experience:

Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause:

The AE cannot be reasonably explained by other etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience:

Did the AE reoccur if the suspected drug was reintroduced after having been stopped?

*Note: AstraZeneca would not normally recommend or support a rechallenge.*

- Laboratory tests:

A specific laboratory investigation (if performed) has confirmed the relationship?

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

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

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

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

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

## 16.2. International Airline Transportation Association 6.2 Guidance Document

**Labelling and Shipment of Biohazard Samples**

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

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

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

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

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

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

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

# 16.3. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## 16.3.1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. 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 subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law 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 IMP.

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

## 16.3.2. Definitions

***Potential Hy's Law***

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x ULN **together with** total bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

***Hy's Law***

- Aspartate aminotransferase or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

### 16.3.3. 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 subject/patient who meets any of the following identification criteria in isolation or in combination:

- Alanine aminotransferase ≥ 3 x ULN
- Aspartate aminotransferase ≥ 3 x ULN
- Total bilirubin ≥ 2 x ULN

**If Central Laboratories are Being Used:**

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

The Investigator will also remain vigilant for any local laboratory reports where the PHL 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 without delay.
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.
- Determine whether the subject/patient meets PHL criteria (see definition above) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

**If Local Laboratories are Being Used:**

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 subject meets PHL criteria (see definition above) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

### 16.3.4. Follow-Up

#### 16.3.4.1. Potential Hy's Law Criteria not Met

If the subject does not meet PHL criteria the Investigator will:

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

#### 16.3.4.2. Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. When central laboratories are used, this includes deciding which the tests available in the HL lab kit should be used.
  - Complete the 3 Liver CRF Modules as information becomes available.

### 16.3.5. 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.

As soon as possible after the biochemistry abnormality was initially detected, the 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, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

Where 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 an 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: update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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:

- Send updated 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 15 calendar days 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:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to the agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

### 16.3.6. Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. If required, additional

assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

**Hy's Law lab kit for central laboratories (18 December 2018)**

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>IgM and IgG anti-HBc<br>HBsAg<br>HBV DNA<br>anti-HCV<br>HCV RNA*<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM & IgG anti-CMV<br>IgM & IgG anti-HSV<br>IgM & IgG anti-EBV |
| Alcoholic hepatitis | Carbohydrate deficient transferrin (CD-transferrin)** |
| Autoimmune hepatitis | Antinuclear antibody (ANA)<br>Anti-Liver/Kidney Microsomal Ab (Anti-LKM)<br>Anti-Smooth Muscle Ab (ASMA) |
| Metabolic diseases | alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly.

## 16.3.7. References

Aithal *et al* 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

## 16.4. Actions Required in Cases of a Renal-related or Urolithiasis 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.

### 16.4.1. Signs and Symptoms Suggestive of Urolithiasis

After initiation of study medication, if a subject experiences signs or symptoms suggestive of nephrolithiasis (e.g., flank pain or haematuria), he/she should be evaluated by a physician and serum creatinine, blood urea nitrogen (BUN), and urinalysis should be measured via central laboratory testing (preferred) and/or local laboratory testing, as appropriate, to determine renal function. Imaging (intravenous urogram, renal ultrasound, or magnetic resonance imaging) is recommended to confirm or exclude any urinary tract calculus. Abnormal results should be treated as medically appropriate by the treating physician. All symptoms, testing, and results will be documented in source documents and CCI

If a subject develops a urinary tract calculus (as confirmed and documented by imaging or passage of a stone) at any time during the study, the subject will discontinue randomised study medication and be encouraged to remain in the study for continued safety assessments. If the urinary tract calculus is passed, it should be collected and submitted to pathology for analysis of chemical composition.

### 16.4.2. Deterioration of Renal Function

The Investigator should assess subjects exhibiting elevated serum creatinine carefully to determine the most likely cause for the deterioration of renal function. Following a thorough assessment, the subject should be managed according to local medical practice. Potentially-treatable causes such as volume depletion, hypotension etc., should be corrected before following the recommendations given below.

**Serum Creatinine Increase to ≥ 1.5-fold from Baseline**

- Assess the subject to identify and manage any potential contributing factor. Correct any dehydration and ensure the subject is well hydrated prior any future evaluation.
- Contact the Sponsor's lead physician for advice and to discuss discontinuation of study medication.
- Assess creatinine daily if the elevation is detected while the subject is admitted to the Clinical Unit, and otherwise weekly.
- Subsequent management will depend on the repeat measurement(s):

If serum creatinine < 1.5-fold of baseline value for 2 successive measurements, the subject may restart/continue with study treatment on the original study visit schedule.

If repeat serum creatinine is ≥ 1.5-fold of baseline, the subject should be evaluated every week until normalization. The randomised treatment should be permanently discontinued.

# 17. SIGNATURES

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

**Protocol Title:** A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 1996) and the guidelines on GCP applicable to this clinical study.

**Sponsor Signatory/Responsible Medical Expert**

| **Signature** | **Date of signature** |
|---|---|

***PPD***

AstraZeneca R&D Gothenburg

## 17.2. Declaration of Sponsor or Responsible Medical Expert (Biostatistician)

**Protocol Title:** A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 1996) and the guidelines on GCP applicable to this clinical study.

**Sponsor Signatory/Responsible Medical Expert**

| **Signature** | **Date of signature** |
|---|---|

PPD

AstraZeneca, Gaithersburg, MD

## 17.3. Declaration of the Principal Investigator

**Protocol Title:** A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 1996) and the guidelines on GCP applicable to this clinical study.

**Principal Investigator**

| **Signature** | **Date of signature** |
|---|---|
| PPD | |

PAREXEL Early Phase Clinical Unit Berlin

## 17.4. Declaration of the Deputy Principal Investigator

Protocol Title: A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 3 Different Extended-release Formulations of Verinurad in Healthy Subjects

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

**Deputy Principal Investigator**

| **Signature** | **Date of signature** |
|---|---|

***PPD***

PAREXEL Early Phase Clinical Unit Berlin