A Single-Centre, Randomised, Double-Blind, Placebo-Controlled, 3-Period, Cross-Over Phase I Study to Investigate the Effect on the QTcF Interval of a Single Dose of 2 Different Doses of Verinurad, Each in Combination with Allopurinol 300 mg, Compared with Placebo In Healthy Volunteers

ClinicalTrials.gov Identifier: NCT04256629

Protocol Amendment No. 2: Final 1.0, 11 May 2020

Clinical Study Protocol

A Single-Centre, Randomised, Double-Blind, Placebo-Controlled, 3-Period, Cross-Over Phase I Study to Investigate the Effect on the QTcF Interval of a Single Dose of 2 Different Doses of Verinurad, Each in Combination with Allopurinol 300 mg, Compared with Placebo In Healthy Volunteers

Parexel Study No.:	PXL244261
Sponsor Study Code:	D5495C00012
EudraCT No:	2019-003657-28
Study Type:	Randomised, double-blind, placebo-controlled, cross-over study
Test Products:	Verinurad extended-release capsule, 24 mg Verinurad immediate-release capsule, 40 mg Allopurinol, 300 mg
Reference Product:	Placebo
Therapeutic Indication:	Chronic kidney disease
Pharmacological Class:	URAT1 inhibitor
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel Early Phase Clinical Unit (Berlin) PPD 14050 Berlin Germany
Date of Protocol:	Final 1.0, 07 November 2019
Protocol Amendment No. 1:	Final 1.0, 27 January 2020
Protocol Amendment No. 2:	Final 1.0, 11 May 2020

This clinical study will be conducted according to the protocol and in compliance with the International Council for Harmonisation Tripartite guideline for Good Clinical Practice and with other applicable regulatory requirements.

PROTOCOL AMENDMENTS

Protocol Amendment No. 2, dated 11 May 2020

The protocol was amended in order to adhere to the newly issued EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic. The following sections of the protocol were changed to adapt the risk assessment in response to the current pandemic situation and describe risk mitigation measures:

- Section 5.1.1 Background to COVID-19 (section inserted)
- Section 5.3.2 Overall Study Design (text inserted)
- Section 5.3.3 Study Flow Chart and Schedule of Assessments, Table 5-2 (text and footnotes added)
- Section 5.3.4 Total Blood Volume, Table 5-4 (blood volume updated)
- Section 5.5.1 Risk Assessment for COVID-19 Pandemic (section inserted)
- Section 6.2 Secondary Objectives, Table 6-2 (text added)
- Section 7.1.2 Exclusion Criteria (criteria added)
- Section 7.2 Restrictions During the Study (restrictions added)
- Section 7.3 Replacement of Subjects (text added)
- Section 8.1 Discontinuation of Investigational Medicinal Product and Withdrawal from the Study (text added)
- Section 8.1.1 Premature Termination of the Study and Stopping Criteria (text added)
- Section 10.4 Safety Measurements (text added)
- Section 10.4.2.6 Viral Serology (text added)
- Section 10.4.2.7 SARS-CoV-2 Virology (section added)
- Section 10.4.3 Vital Signs (text added)
- Section 11.3 Study Monitoring (text added)
- Section 12.12.3 Laboratory Assessments (text added)
- Section 12.5 Protocol Deviations (text added)
- Section 13.2.8 COVID-19 (section added)
- Section 15 List of References (references added)

Further changes implemented:

- Name of Sponsor's Biostatistician changed
- Update of estimated date of 'first subject enrolled ' and 'last subject completed'.
- Minor editorial changes.

Protocol Amendment No. 1, dated 27 January 2020

- Update of estimated date of 'last subject completed' to May 2020.

Corresponding change made in protocol synopsis.

- Reduction of maximum Screening Period from 38 days to 28 days.

Corresponding changes made in protocol synopsis, Section 5.3.2, Table 5-1, Figure 5-1, and Table 5-2.

- Reduction of expected approximate study duration from 60 days to 53 days.

Corresponding changes made in protocol synopsis, Section 5.3.2.2, and Table 5-1.

- Update of stopping rules to include details for electrocardiogram.

Corresponding change made in Section 8.1.

- Clarification concerning the reporting of clinically significant adverse events.

Corresponding change made in Section 13.2.6.

- Minor editorial changes.

PROTOCOL SYNOPSIS

Title of the Study
A single-centre, randomised, double-blind, placebo-controlled, 3-period, cross-over Phase I study to investigate the effect on the QTcF interval of a single dose of 2 different doses of verinurad, each in combination with allopurinol 300 mg, compared with placebo in healthy volunteers

Principal Investigator
Thomas Körnicke, MD

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

Study Rationale
This study will be conducted to investigate the safety of verinurad, in particular its effect on electrocardiogram (ECG), with particular focus on the QT/QTc interval. A prolongation of the QT/QTc interval can be associated with increased susceptibility to cardiac arrhythmias. Therefore, adequate investigation of the safety of new non-antiarrhythmic drugs that have systemic bioavailability should include rigorous characterisation of their effects on ECG, with particular focus on the QT/QTc interval, according to the International Conference on Harmonisation (ICH) Guideline E14 and ICH E14 Question and Answers (Q&A) document.

Number of Subjects Planned
A total of 24 subjects are planned to be randomised to achieve at least 20 evaluable subjects at the end of the last treatment period.

Study Period
Estimated date of first subject enrolled: Jun 2020 (signing of informed consent)
Estimated date of last subject completed: Sep 2020

Study Objectives
Primary Objective:

- To assess the effect of a single dose of verinurad given as either a 24 mg extended-release (ER8) formulation (therapeutic exposure) or a 40 mg immediate-release (IR) formulation (supra-therapeutic exposure), both in combination with allopurinol 300 mg, on the QT interval corrected for heart rate using Fridericia's formula (QTcF) compared to placebo using a concentration-QTcF interval analysis.

Secondary Objectives:

- To investigate the effect of verinurad given either as a 24 mg ER8 formulation (therapeutic exposure) or a 40 mg IR formulation (supra-therapeutic exposure), both in combination with allopurinol 300 mg, on HR and additional digital ECG (dECG) variables (PR, QRS, QT and RR).
- To assess the pharmacokinetics (PK) of verinurad and its metabolites (M1 and M8) and allopurinol and its metabolite (oxypurinol) in healthy subjects.
- To assess the relationship between plasma concentrations of verinurad, allopurinol and the metabolites M1, M8, oxypurinol and dECG variables and HR.

- To examine the safety and tolerability of verinurad and allopurinol.

Study Design
This study will be conducted as a single-centre, randomised, placebo-controlled, double-blind, 3-period, cross-over study to assess the effect on the QTcF interval of a single oral dose of verinurad 24 mg ER8 formulation (therapeutic exposure) or verinurad 40 mg IR formulation (supra-therapeutic exposure), each in combination with allopurinol 300 mg, compared to placebo in healthy subjects.

There are 3 study treatments:

- Treatment A: Verinurad 24 mg ER8 formulation co-administered with 300 mg allopurinol
- Treatment B: Verinurad 40 mg IR formulation co-administered with 300 mg allopurinol
- Treatment C: Matched placebos for both verinurad and allopurinol

All subjects will receive a single dose of all 3 treatments (A, B, and C) in a cross-over design with wash-out periods of at least 7 days between each study dose administration. Subjects will be randomised to the treatment sequence (ABC, BCA, CAB, etc.) using William's Latin square. The treatments will be administered in a double-blind manner after an overnight fast of at least 10 hours.

The study will comprise the following periods (visits):

- Screening Period of maximum 28 days (Visit 1);
- Three treatment periods of 3 days each, during which subjects will be resident at the study centre from the morning of the day before administration of the study dose until discharge 2 days after study dose administration (Visits 2 to 4);
- Wash-out periods of at least 7 days between each study dose administration;
- Final visit within 7 to 10 days after the last study dose administration (Visit 5).

Expected Duration of the Study
Each subject will be involved in the study for approximately 53 days and have 5 study visits.

Targeted Study Population
This study will be conducted in healthy male and female subjects aged 18 to 50 years (inclusive).

Test and Reference Products
The test products are verinurad 12 mg ER8 capsules, verinurad 10 mg IR capsules and allopurinol 300 mg tablets. The reference product is placebo matching verinurad and allopurinol.

Outcome Measures

- The primary outcome measure is ΔΔQTcF (derived from concentration-QTcF modeling). Parameters for this outcome measure are QTcF and Cmax.

The secondary outcome measures are:

- Baseline-corrected and placebo-adjusted dECG parameters (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval). Parameters for this outcome measure are the dECG variables HR, RR, PR, QRS, QT and QTcF.
- As appropriate and where possible, the following PK parameters will be assessed for verinurad, M1, M8, allopurinol, and oxypurinol: AUC, AUC0-t, Cmax, tmax, tlag, t½λz, tlast, CL/F, Vz/F, Vss/F and MRT. Plasma concentration-time profile for each analyte.
- Plasma concentrations of verinurad, M1, M8, allopurinol, and oxypurinol and time-matched, baseline-corrected and placebo-adjusted dECG parameters (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval). Parameters for this outcome measure are the plasma concentration of each analyte at each time point and the time-matched dECG variables HR, RR, PR, QRS, QT and QTcF.
- Assessment of AEs, laboratory variables (haematology, clinical chemistry and urinalysis), vital sign variables (systolic and diastolic blood pressure, pulse rate, body temperature), ECG parameters, telemetry findings and physical examination findings.

Statistical Methods
Study Populations:

- The Safety Analysis Set will include all subjects who received at least 1 dose of investigational medicinal product (IMP) (verinurad, allopurinol or placebo) 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.
- The pharmacodynamic (PD) Analysis Set will consist of all subjects in the Safety Analysis Set for whom baseline and post-baseline QTcF results from smoothed dECG data are available for at least 2 treatment periods (where 1 of the treatment periods needs to be the period in which the subject received placebo), and who have no major protocol deviations thought to impact on the analysis of the dECG data.
- The PK Analysis Set will consist of all subjects in the Safety Analysis Set for whom at least 1 reportable PK parameters can be calculated and who have no major protocol deviations thought to impact on the analysis of the PK data.
- The Randomised Set will consist of all subjects randomised into the study.

Presentation and Analysis of Pharmacodynamic Data:
A linear mixed-effect concentration-QTcF model will be used as the primary analysis. Baseline-corrected and placebo-adjusted QTcF (ΔΔQTcF), using individual time-matched placebo for a given subject, will be the dependent variable and verinurad plasma concentrations will be the independent variable. Fixed effects will be: intercept in the absence of a treatment effect, slope of the assumed linear association between concentration and ΔΔQTcF and baseline QTcF. Random effects will be included on the intercept term and the slope. ΔΔQTcF at the concentration of interest will be estimated. A prolonging effect will be excluded if the upper bound of the two-sided 90% confidence

interval for model-derived ΔΔQTcF is estimated to be <10 ms at the highest clinically relevant exposure. Details of the concentration-QTcF modeling and the definition of the analysis population of the primary analysis will be provided in a separate document (C-QT analysis plan).
After the smoothing of QT and RR into target time point values, the heart rate (HR)-corrected QT will be calculated (QTcF) using the standard formula. All the statistical analyses will be performed using smoothed data. Digital ECG variables (absolute values and change from baseline for: HR, RR, PR, QRS, QT and QTcF) will be listed by subject and time point and summarised by treatment group using appropriate descriptive statistics; in addition, exploratory plots will be provided (such as time course for each dECG variable, changes from baseline for each dECG variable, by treatment group, mean with SD) and time course for ΔΔ: RR, HR, PR, QRS, QTcF for each treatment group.

Presentation and Analysis of Pharmacokinetic Data:
A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations will be summarised for the PK Analysis Set for each time point by analyte and treatment. All reportable plasma PK parameters will be listed for each subject, analyte, and treatment. A separate listing will be provided for the diagnostic PK parameters. All eligible PK data will be presented for the PK Analysis Set for each analyte (verinurad, M1, M8, allopurinol, and oxypurinol) using descriptive statistics. No inferential statistical analysis of PK parameters will be conducted.

Presentation and Analysis of Safety and Eligibility Data:
Safety data will be presented in the data listings. Continuous variables will be summarised using descriptive statistics by treatment. Changes (and/or percentage change) from baseline will be presented where applicable when baseline is defined. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment. Tabulations and listings of data for vital signs and clinical laboratory tests will be presented; 12-lead safety ECG data will be listed only.
Adverse events (AEs) will be summarised by treatment and overall for all subjects, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by System Organ Class (SOC) and Preferred Term. 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, SAEs, AEs leading to discontinuation of IMP (DAE) and AEs with outcome of death. Listings of all AEs, SAEs, DAEs and AEs that led to death will be presented.
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.
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.

Determination of Sample Size
Study sample size for a concentration-QTcF (C-QTcF)-based interval analysis is based on the recommendation from Garnett et al 2018* to have 16 to 32 subjects on drug and 8 to 16 subjects on placebo. The type-1 error rate has been shown to be controlled at around 5% when the true effect is 10 ms in small-sized studies of 6 to 12 subjects with multiple measurements per subject.

A 3-period cross-over study, using C-QTcF-based interval analysis, with 2 verinurad doses and placebo in 20 evaluable healthy volunteers is expected to exceed the recommendations proposed by Garnett et al 2018*.
Twenty-four subjects will be randomised to a 6-sequence William's design for 3 periods and 3 treatments to achieve 20 evaluable subjects based on an expected dropout of 17%.

*Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-97.

1. TABLE OF CONTENTS

1.1. List of Tables

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1.3. List of Appendices

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Special Term	Explanation
%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
AE	Adverse event (see definition in Section 13.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity
AUC(0-t)	Area under the plasma concentration-curve from time zero to time of last quantifiable concentration
AV	Atrioventricular
AZRand	AstraZeneca randomisation system
β-hCG	Beta human chorionic gonadotropin
BfArM	Federal Institute for Drugs and Medical Devices
BMI	Body mass index
bpm	Beats per minute
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug only)
ClinBase™	Parexel's electronic source data capturing and information management system
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
C-QTc	Concentration-QTc
C-QTcF	Concentration-QTcF
CPKA	Covance Clinical Pharmacokinetic Alliance
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
ΔHR	Baseline-corrected heart rate
ΔRR interval	Baseline-corrected RR interval
ΔPR interval	Baseline-corrected PR interval
ΔQRS interval	Baseline-corrected QRS interval
ΔQT interval	Baseline-corrected QT interval
ΔQTcF interval	Baseline-corrected QTcF interval
ΔΔHR	Baseline-corrected and placebo-adjusted heart rate

Abbreviation or Special Term	Explanation
ΔΔRR interval	Baseline-corrected and placebo-adjusted RR interval
ΔΔPR interval	Baseline-corrected and placebo-adjusted PR interval
ΔΔQRS interval	Baseline-corrected and placebo-adjusted QRS interval
ΔΔQT interval	Baseline-corrected and placebo-adjusted QT interval
ΔΔQTcF interval	Baseline-corrected and placebo-adjusted QTcF interval
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services
dECG	Digital electrocardiogram
DILI	Drug-Induced Liver Injury
DMP	Data management plan
DNA	Deoxyribonucleic acid
DRESS	Drug rash with eosinophilia and systemic symptoms
DVS	Data validation specification
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
eGFR	Estimated glomerular filtration rate
EClysis©	User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Centre
EMA	European Medicines Agency
ER	Extended-release
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
gCV(%)	Geometric coefficient of variation
GGT	Gamma glutamyl transpeptidase (transferase)
GI	Gastrointestinal
gmean	Geometric mean
GMP	Good Manufacturing Practice
gSD	Geometric standard deviation
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HCV	Hepatitis C virus
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus

Abbreviation or Special Term	Explanation
HL	Hy's Law
HLA	Human leukocyte antigen
HLA-B	Human leukocyte antigen B
HR	Heart rate
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalised ratio
IMP	Investigational medicinal product
IR	Immediate-release
IRB	Institutional Review Board
ISRB	Investigational Medicines Safety Review Board
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
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRT	Mean residence time of the unchanged drug in the systemic circulation from zero to infinity
ms	milliseconds
N	Number of subjects
n	Number of data values
NA	Not applicable
NC	Not calculated
NOEL	No observed effect level
NQ	Not quantifiable
NR	No result
NS	No sample
OAE	Other significant adverse events
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
PT	Preferred term
Q&A	Question and Answers
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
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
RNA	Ribonucleic acid
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
RCTC	Rheumatology Common Toxicity Criteria
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event (see definition in Section 13.1.2).
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sCR	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
sUA	Serum uric acid
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
TBL	Total bilirubin
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire

Abbreviation or Special Term	Explanation
tlag	Time delay between drug administration and the first observed concentration in plasma
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
TSH	Thyroid-stimulating hormone
UA	Uric acid
UK	United Kingdom
ULN	Upper limit of normal
US	United States
Vss/F	Apparent volume of distribution at steady state
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration (parent drug only)
WAD	Window Allowance Document
WBC	White blood cell
WHO	Word Health Organization
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 Investigator 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 (eg, signed ICF) will be maintained in confidence by the Investigator.

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 Investigator in accordance with local procedures.

Parexel will provide the IEC and Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious 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 participants will be compensated is contained in the ICF.

3.4. Insurance

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

3.5. Informed Consent

The 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 which ever 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 Investigator 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

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	PPD AstraZeneca R&D Gothenburg PPD 431 83 Mölndal Sweden Tel: PPD Mobile: PPD E-mail: PPD
Sponsor's Lead Clinical Scientist	PPD AstraZeneca R&D Gothenburg PPD 431 83 Mölndal Sweden Tel: PPD Mobile: PPD E-mail: PPD
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Deputy PI:	PPD Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany Tel.: PPD E-mail: PPD

Contract Research Organization (CRO):	Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany Tel: PPD
Clinical Laboratory:	SYNLAB Analytics & Services Germany GmbH PPD 10559 Berlin Germany **Contact:** PPD Tel: PPD Fax: PPD E-mail: PPD
Electrocardiogram (ECG) Core Laboratory:	AstraZeneca ECG Centre Cardiovascular Safety Centre of Excellence Patient Safety Centre of Excellence CMO Organization AstraZeneca Gothenburg 431 83 Mölndal Sweden **Contact:** PPD Tel: PPD E-mail: PPD
Pharmacy:	Hubertus-Apotheke PPD 10587 Berlin Germany **Contact:** PPD Tel: PPD E-mail: PPD
Parexel Laboratory Contact:	Parexel International GmbH, PPD 14050 Berlin Germany **Contact:** PPD Tel.: PPD E-Mail: PPD

Analytical Laboratory: (pharmacokinetic [PK] sample analysis)	Covance Bioanalytical Services, LLC PPD Indianapolis, IN 46214 United States of America **Contact:** PPD PPD E-mail: PPD Tel: PPD Fax: PPD
Human leukocyte antigen (HLA) sample analyses	DNA Identification Testing Division Laboratory Corporation of America Holdings PPD Burlington, NC 27215-3361 United States of America **Contact:** PPD PPD E-mail: PPD Tel : PPD
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services Fax: PPD E-mail: 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. Adenosine triphosphate, the cellular carrier of energy, is a purine; furthermore, purines, together with 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 metabolise urate further and therefore eliminates urate through excretion. Urate is excreted primarily through the kidneys, but also into the intestines, where it can be degraded by uricase activity in the intestinal microbiome to carbon dioxide and allantoin [1].

Uric acid (UA), the protonated form of urate, can also be found in the human body. At physiological pH, approximately 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 of the kidneys, 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 (eg, 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. The Japanese and Chinese treatment guidelines propose that urate-lowering therapy should be considered for patients with asymptomatic hyperuricaemia with a serum

uric acid (sUA) level of ≥8.0 mg/dL with complications (eg, urinary calculus, renal disease, and hypertension) and ≥9.0 mg/dL without complications [5, 6].

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

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 UA in the primary urine, which have the potential to induce uric acid crystallization in tubuli and collecting ducts.

Based on these findings, verinurad, a novel URAT1 inhibitor assess in this study, will be exclusively developed as combination therapy, together with a xanthine oxidase inhibitor (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 monotherapy 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 [15].

5.1.1. Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by the novel virus SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organization (WHO) to declare a pandemic situation on 11 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff and society as a whole.

Both European Medicines Agency (EMA) [16] and Food and Drug Administration (FDA) [17], as well as national health authorities in Europe, have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the

spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

5.2. Drug Information

5.2.1. Verinurad

5.2.1.1. Description of Verinurad

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

5.2.1.2. Pre-clinical Data Related to Cardiovascular Safety

Verinurad was tested for its effect on the human ether-a-go-go-related gene (hERG)-encoded potassium channel at concentrations of 10 and 300 μM. Verinurad inhibited the potassium current by less than 3% at concentrations of 10 and 300 μM.

The effects of verinurad on arterial blood pressure, heart rate (HR), lead II electrocardiogram (ECG) and body temperature were investigated in telemetered male Beagle dogs for up to 24 hours following single oral doses up to 300 mg/kg. Verinurad at 300 mg/kg resulted in a trend towards a decrease in blood pressure and increase in HR (not statistically significant). There was a statistically significant decrease in PR interval (of approximately 13 ms) at this dose level, which was considered to be related to the trend towards an increase in HR. The no observed effect level (NOEL) was considered to be 150 mg/kg. This dose level was associated with a maximum plasma concentration (Cmax) value of 172 μg/mL in male dogs on Day 1 of the 28-day repeat-dose toxicity study. Assuming a plasma protein binding of 97.8%, this equates to a free plasma concentration of 3.8 μg/mL.

5.2.1.3. Clinical Pharmacokinetics

Following administration of verinurad as an extended-release capsule formulation (ER8), Cmax occurred 4 hours after dosing. Food did not affect verinurad exposure except for a 2-hour increase in time to maximum plasma concentration (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 subjects with normal renal function and 21 hours in those with moderate renal impairment. The exposure (area under the concentration-time curve [AUC] and Cmax) of verinurad increased in a dose-proportional manner and the accumulation was minimal after once daily dosing. Subjects with an estimated glomerular filtration rate (eGFR) of 45 and 60 mL/min/1.73m^2 are predicted to have a 1.4 and 1.2-fold higher verinurad exposure, respectively, compared to those with normal renal function (eGFR of 90 mL/min/1.73m^2). Asian subjects are

predicted to have about 44% higher exposure compared to non-Asians after accounting for differences in renal function and body weight.

Further information on pharmacokinetics (PK) findings (including PK parameters of the verinurad immediate-release [IR] formulation) is available in the IB [15].

5.2.1.4. Safety Profile Derived from Clinical Studies

Verinurad has been studied in healthy subjects, patients with gout and renally-impaired patients. In total, 849 subjects have received verinurad in 11 Phase I and 7 Phase II clinical studies (data as of 01 Nov 2019).

Safety in healthy subjects was assessed in a pooled analysis of 8 Phase I (Studies 101, 103, 104, 105, 106, 110, 111, and 112) and in a single Phase I study (D5495C00006). A summary of information on clinical safety findings in healthy subjects is provided below; further details are available in the IB [15].

Adverse Events

The 8 pooled Phase I studies collectively enrolled 293 male subjects, treated at doses ranging from 5 to >15 mg; 94.5% of the subjects completed the planned treatment. Overall, 86 subjects (29.4%) experienced adverse events (AEs). The incidence of AEs was similar among the pooled verinurad groups and pooled placebo groups. 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. Most AEs were Rheumatology Common Toxicity Criteria (RCTC) toxicity Grade 1. Only 2 AEs had an RCTC toxicity >Grade 2, consisting of Grade 3 blood creatinine increased and Grade 3 tooth infection, both reported in subjects treated with verinurad doses ranging from 5 to <10 mg. There were no serious adverse events (SAEs). Three subjects withdrew from the study due to AEs: 2 subjects who had received verinurad 5 mg (dehydration and influenza, respectively) and 1 subject who had received verinurad 15 mg and experienced urticaria.

Study D5495C00006 was a double-blind safety and PK study in healthy Asian and Chinese subjects who were randomised to receive verinurad + allopurinol or placebo. No deaths or SAEs were reported in the study and no subject discontinued study treatment due to an AE. All AEs reported on study treatment were mild in intensity.

Laboratory Evaluations

In the pooled analysis of the 8 Phase I studies, serum creatinine (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. Furthermore, 18.4% of all subjects treated with verinurad experienced alanine aminotransferase (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% of subjects experienced aspartate aminotransferase (AST) elevations ≥2.0 or ≥3.0 × baseline.

In Study D5495C00006, no subjects on verinurad + allopurinol had an elevation >3.0 × upper limit of normal (ULN) for ALT or AST or >2.0 × ULN for total bilirubin. No sCr elevation ≥1.5 × baseline was observed in the study.

Vital Signs, Physical Findings, and Other Observations

In the 9 Phase I studies, there were no clinically relevant or apparent dose-related post-treatment changes in vital signs. Although transient changes in blood pressure, HR and body temperature were noted at isolated time points for some subjects, none of these findings were judged to be clinically significant by the Investigator.

Electrocardiogram Data

In 8 of the Phase I studies in healthy subjects 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 1 study (Study 101), prolongations in QT interval corrected for heart rate using Bazett's formula (QTcB) of >60 ms occurred in 2 subjects in the 1 mg fasted dose group; yet, no subjects had prolonged QTcB intervals >450 ms. Three subjects in the 1 mg fasted dose group and 1 subject in the 5 mg fasted dose group had prolonged QT intervals corrected for heart rate using Fridericia's formula (QTcF) (>450 to 480 ms) although no subjects had a QTcF interval >480 ms. All episodes of QTcF >450 ms occurred at HRs <50 beats per minute [bpm].

Subjects with Gout or Asymptomatic Hyperuricemia

Information on clinical safety findings in subjects with gout or asymptomatic hyperuricemia is available in the IB [15].

5.2.2. Allopurinol

Allopurinol is a commercially available oral XO inhibitor for conditions where urate/UA deposition has already occurred or is a predictable clinical risk. Allopurinol and its main metabolite oxipurinol lower the level of UA.

Please refer to the product information sheet of allopurinol tablets [18] for information on PK, PD and safety.

5.3. Study Rationale and Justification of Study Design

5.3.1. Study Rationale

A prolongation of the QT and/or QTc interval can be associated with increased susceptibility to cardiac arrhythmias. Therefore, according to the ICH Guideline E14 and associated Questions and Answers (Q&A) document [20], adequate investigation of the safety of new non-antiarrhythmic drugs with systemic bioavailability should include

rigorous characterisation of their effects on ECG, with particular focus on the QT and QTc interval.

Available pre-clinical (including hERG and in vivo data), clinical ECG and event data have not indicated liability for QT-prolongation for verinurad.

The present randomised, double-blind, placebo-controlled study will follow the ICH E14 guidelines (2005) [19] and answers to question 5.1 in the associated ICH E14 Q&A document (2015) [20] with respect to assessment of the potential of the combination of verinurad and allopurinol to affect the QTc interval, where concentration-QTc (C-QTc) modeling will be used as the primary analysis [20, 21]. It is considered that the supra-therapeutic dose, if it covers at least more than twice the worst-case scenario of high exposure in patients, will provoke a detectable clinically relevant QT/QTc prolongation, even if the sensitivity/quality of the ECG analytical method is not proven to be perfect in the study. It can, therefore, be acceptable not to use an active control, provided the supra-therapeutic dose fulfills such criteria. The answer to question 5.1 of the ICH E14 Q&A document states that a separate positive control would not be necessary if there are data characterising the response at a sufficiently high multiple of the clinically relevant exposure, and this criterion is fulfilled by the supra-therapeutic exposure of verinurad anticipated in this study. A cross-over design has been chosen for practical reasons since fewer volunteers will be required and because each volunteer acts as his or her own control; intra-subject variability is therefore reduced. A single-dose cross-over design is chosen based on the PK characteristics of verinurad, allopurinol, and their metabolites. The collection of PK samples and digital ECG (dECG) recordings is time matched to allow the use of pre-specified linear mixed-effects model [21].

5.3.2. Overall Study Design

This study will be a single-centre, randomised, placebo-controlled, double-blind, 3-period, cross-over Phase I study to assess the effect on the QTcF interval of a single oral dose of verinurad 24 mg ER8 formulation (therapeutic exposure) or verinurad 40 mg IR formulation (supra-therapeutic exposure), each in combination with allopurinol 300 mg, compared to placebo in healthy subjects.

There are 3 study treatments (see also Table 9-3):

- Treatment A: Verinurad 24 mg ER8 formulation co-administered with 300 mg allopurinol
- Treatment B: Verinurad 40 mg IR formulation co-administered with 300 mg allopurinol
- Treatment C: Matched placebos for both verinurad and allopurinol

All subjects will receive a single dose of all 3 treatments (A, B, and C) in a cross-over design with wash-out periods of at least 7 days between each study dose administration. Subjects will be randomised to the treatment sequence (ABC, BCA, CAB, etc.) using

William's Latin square. The treatments will be administered in a double-blind manner after an overnight fast of at least 10 hours.

There will be 5 visits to the study centre, including 3 visits that are residential. The study will comprise the following periods and visits:

- A Screening Period of maximum 28 days (Visit 1);
- Three treatment periods of 3 days each, during which subjects will be resident at the study centre from the morning of the day before administration of the study dose (check-in, Day -1) until discharge 2 days after study dose administration (check-out, Day 3; Visits 2 to 4);
- Wash-out periods of at least 7 days between each study dose administration;
- A final visit within 7 to 10 days after the last study dose administration (Follow-up Visit; Visit 5).

A total of 24 subjects are planned to be randomised to achieve at least 20 evaluable subjects.

The study design is deemed appropriate for conduct in healthy volunteers during COVID-19 pandemic.

5.3.2.1. End of Study

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

5.3.2.2. Expected Duration of the Study

Each subject will be involved in the study for approximately 53 days (see Table 5-1).

Table 5-1 Expected Duration of Each Study Part

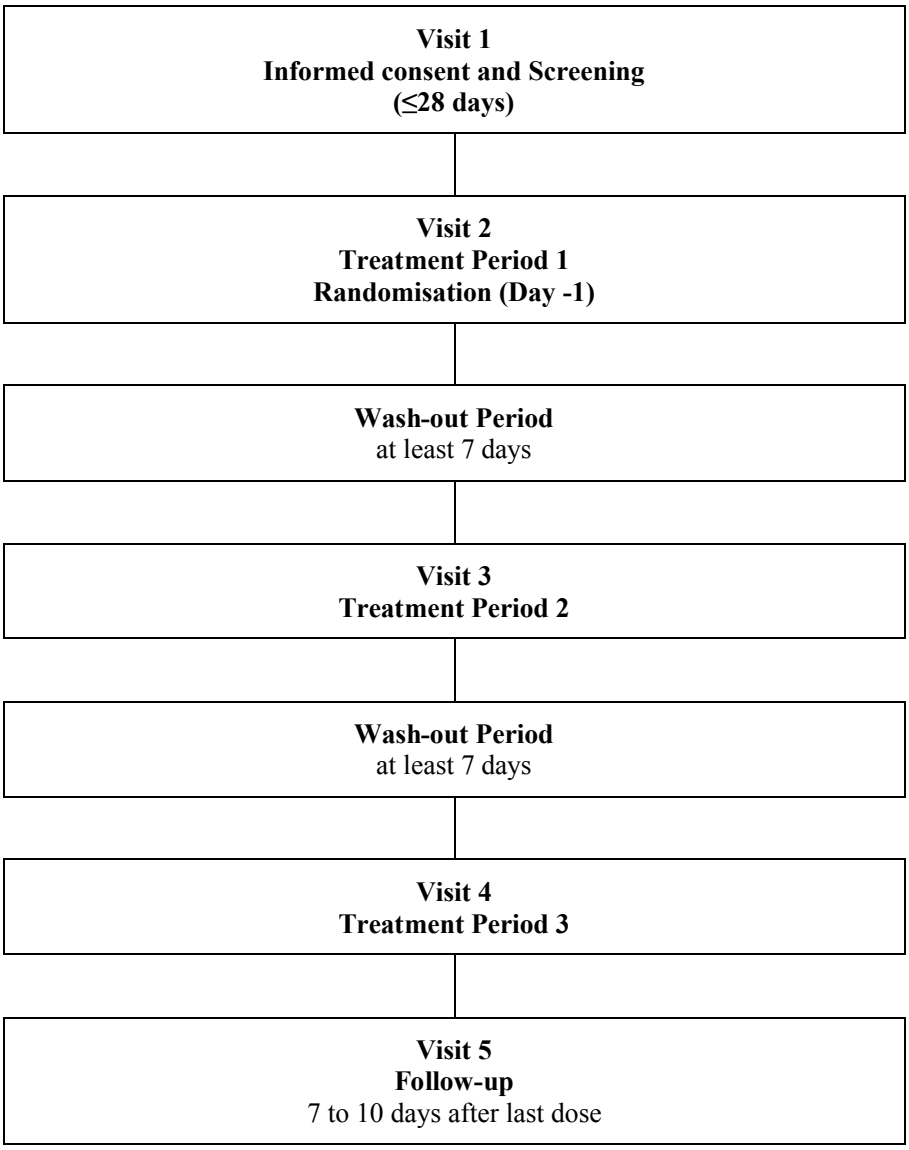
Screening	Maximum 28 days before the first study dose
Treatment Periods	3 treatment periods of 3 days each during which subjects will be resident at the study centre from the day before dosing (Day -1) until discharge on Day 3
Wash-out Period	At least 7 days between each study dose administration
Follow-up	7 to 10 days after last dose
Total Duration	Approximately 53 days

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 randomisation (refer to Section 9.9.2).

The Schedule of Assessments displaying assessments/tasks and time points is presented in Table 5-2. The time schedule for dECGs is presented in Table 5-3.

Figure 5-1 Study Flow Chart



Note: All subjects will receive all 3 treatments (A, B and C) in a cross-over design; 1 treatment per treatment period (Treatment Periods 1, 2, and 3). Treatment sequence (ABC, BCA, CAB, etc.) will be assigned randomly and the study doses administered in a double-blind manner.
The composition of Treatment A, B, and C is detailed in Table 9-3.

Table 5-2 Schedule of Assessments

Study Assessments	Visit 1 [a] Screening Day −28 to Day -2	Visits 2 to 4 [b] Treatment Days -1 to 3 (Residential)		Visit 5 Follow-up 7 to 10 Days After the Last Dose [c]	Corresponding Section in Protocol
		Day −1	Days 1 to 3		
Informed consent	X				Section 3.5
Demographics	X				Section 12.7
Medical/surgical history	X				Section 12.7
Physical examination	X	X [d]		X	Section 12.12.5
Sample for HLA-B*58:01 allele genotyping	X				Section 10.4.2.3
Inclusion/exclusion criteria	X[e]	X[e]			Section 7.1
Weight, height and BMI	X				Section 12.7
Study residency					
Check-in		X (in the morning)			Section 5.3.2
Check-out			Day 3 (after the 48 hour post-dose assessment)		Section 5.3.2
Non-residential visit	X			X	Section 5.3.2
Safety and tolerability					
AE questioning [f]	X	X	Day 1: pre-dose, 4 and 12 hours post-dose Day 2: 24 hours post-dose Day 3: 48 h post-dose	X	Section 10.4.1
Concomitant medication	X	X	X	X	Section 9.7
Blood pressure and pulse (supine)	X	X	Day 1: pre-dose, 1 and 6 hours Day 2: 24 hours post-dose Day 3: 48 h post-dose	X	Section 10.4.3
Body temperature [g]	X	X	X	X	Section 10.4.3

Study Assessments	Visit 1 [a] Screening Day −28 to Day -2	Visits 2 to 4 [b] Treatment Days -1 to 3 (Residential)		Visit 5 Follow-up 7 to 10 Days After the Last Dose [c]	Corresponding Section in Protocol
		Day −1	Days 1 to 3		
12-lead safety ECG [h]	X	X	X	X	Section 10.4.4.1
Continuous 12-lead dECG [i]			See time schedule for dECG in Table 5-3		Section 10.4.4.2
Telemetry [j]		X	X		Section 10.4.5
Safety Laboratory sampling [k]	X	X	Day 3: 48 hours post-dose	X	Sections 10.4.2.1, 10.4.2.2, and 10.4.2.4
Urine drug and alcohol screen	X	X [l]			Section 10.4.2.7
Pregnancy test [m]	X	X		X	Section 10.4.2.5
HIV status/hepatitis B and C screen, anti-HBc antibody	X				Section 10.4.2.6
COVID-19 Assessments					
Pre-visit phone call [n]	X	X		X	Section 5.5.1
SARS-CoV-2 RT-PCR		X			Section 10.4.2.6
SARS-CoV-2 antibody	X				Section 10.4.2.6
Study drug administration					
Randomisation [o]		X			
Administration of study dose			Day 1 (0 h)		Sections 5.3.2 and 9.6
Pharmacokinetics					
Blood sampling for analysis of verinurad, M1, M8, allopurinol and oxypurinol plasma concentrations			Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose Day 2: 24 and 36 hours post-dose Day 3: 48 hours post-dose		Section 10.3.1

AE: Adverse events; BMI: Body mass index; COVID-19: Coronavirus disease 2019; dECG: Digital electrocardiogram; ECG: Electrocardiogram; HBc: Hepatitis B core; HIV: Human immunodeficiency virus; HLA-B: Human leukocyte antigen B; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; sUA: Serum uric acid.

Study Assessments	Visit 1 [a] Screening Day −28 to Day -2	Visits 2 to 4 [b] Treatment Days -1 to 3 (Residential)		Visit 5 Follow-up 7 to 10 Days After the Last Dose [c]	Corresponding Section in Protocol
		Day −1	Days 1 to 3		

[a] Screening Visit may occur up to 28 days prior to Day 1 of the first treatment period and may be divided into 2 separate occasions.
[b] Each treatment visit will comprise Day -1 to Day 3 (48 hours post-dose).
[c] Follow-up visit will occur at approximately 7 to 10 days after the last dose. This visit is also applicable to subjects who prematurely discontinue from the study.
[d] A full physical examination is performed at Visits 1 and 5. A brief physical examination is performed pre-dose on Day -1 of Visits 2, 3, and 4, to reconfirm subject's eligibility.
[e] sUA must be ≤300 µmol/L at Screening Visit (Visit 1) and ≤330 µmol/L at any treatment visit (Visits 2 to 4).
[f] All AEs will be collected from the time of randomisation through Visit 5 (Follow-up Visit); SAEs will be collected from the time of obtaining informed consent through Visit 5 (Follow-up Visit).
[g] Body temperature will be measured at least once daily (in the morning) at every visit or during in-house stay.
[h] 12-lead safety ECG for safety review by the Investigator will be performed prior to the dECG recordings and at additional intervals if required.
[i] Continuous 12-lead dECG recordings with extractions (from 12-lead Telemetry Surveyor continuous files) of multiple 10-second replicates will be performed for 20 minutes pre-dose and as 5-minute recordings post-dose at time points specified in Table 5-3.
[j] Telemetry will be monitored for 4 to 6 hours at Treatment Period 1 (Visit 2), Day -1. Subjects with clinically significant abnormalities (eg, high burden of extrasystoles, etc.) will not be randomised. During Treatment Periods 1 to 3 (Visits 2 to 4) telemetry will be monitored from 30 minutes pre-dose through 24 hours post-dose.
[k] Blood (haematology and clinical chemistry) and urine (urinalysis).
[l] To be performed at admission to the study centre for each treatment period.
[m] Serum pregnancy test at Screening, urine pregnancy test at admission to the study centre for each treatment period and at the Follow-up Visit.
[n] Phone calls will be made 1 day prior to each visit to record signs and symptoms of COVID-19 or any contact with persons having confirmed SARS-CoV-2 infection. In case of signs or symptoms or contact, the visit will be cancelled and reason for cancellation will be appropriately documented.
[o] Randomisation will occur on Visit 2 (Day -1).

Table 5-3 Study Plan - Time Schedule for Digital Electrocardiogram Assessments During Residential Period (Visits 2, 3 and 4)

Study Day	ECG Number	Time Point	Time: Start of the Extraction Window, Hour:Minute	Dose	Time: Stop of the Extraction Window, Hour:Minute	dECG Continuous[a,b,c,d]	Other
1			-01:10				Apply electrodes [b]
1	1	Pre-dose	-00:40		-00:20	20 minutes	
1		Pre-dose	-00:20		-00:10		Toilet use recommended
1		IMP administration	00:00	IMP administration			
1	2	0.5 hour	00:25		00:30	5 minutes[c]	
1	3	1 hour	00:55		01:00	5 minutes[c]	
1	4	1.5 hours	01:25		01:30	5 minutes[c]	
1	5	2 hours	01:55		02:00	5 minutes[c]	
1	6	3 hours	02:55		03:00	5 minutes[c]	
1	7	4 hours	03:55		04:00	5 minutes[c]	
1	8	5 hours	04:55		05:00	5 minutes[c]	
1	9	6 hours	05:55		06:00	5 minutes[c]	
1	10	8 hours	07:55		08:00	5 minutes[c]	
1	11	12 hours	11:55		12:00	5 minutes[c]	
2	12	24 hours	23:55		24:00	5 minutes[c]	
2	13	36 hours	35:55		36:00	5 minutes[c]	
3	14	48 hours	47:55		48:00	5 minutes[c]	

dECG: Digital electrocardiogram, ECG: Electrocardiogram; IMP: Investigational medicinal product

[a] Subjects must be in the same supine body position (maximum 30 degrees flexion in the hip) at each time point and at all visits with feet out of contact with footboard.

[b] Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before the first recording.

[c] The subjects must rest in bed for at least 10 minutes prior to each dECG time point.

[d] The subject must remain awake.

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 summarised in Table 5-4.

Table 5-4 Total Blood Volume

	Volume per Sample	Number of Samples	Total
Haematology	2.7 mL	8	21.6 mL
Clinical chemistry[a]	7.5 mL	8	60.0 mL
HLA-B*58:01 allele genotyping	3.0 mL	1	3.0 mL
SARS-CoV-2 antibody ELISA	2.6 mL	1	2.6 mL
Pharmacokinetics	5.0 mL	45	225.0 mL
Total			**312.2 mL**

HLA-B: Human leukocyte antigen B; ELISA: Enzyme-linked immunosorbent assay;
FSH: Follicle-stimulating hormone; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.
[a] When applicable, serology, serum pregnancy (females only) and FSH (females only) 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 and dECG)
2 PK blood sampling (will be drawn at the specified time points)
3 Safety laboratory blood sampling
4 Vital signs
5 AE questioning

Pre-dose assessments (other than pre-dose PK assessments) may be performed up to 90 minutes prior to investigational medicinal product (IMP) administration. Tolerance windows for the assessments will be detailed in the Window Allowance Document (WAD).

5.4. Dose Rationale

A single dose of 24 mg verinurad given as the ER8 formulation to healthy subjects will give similar exposure as the highest dose tested in Phase 2b (expected therapeutic exposure) at steady state in subjects with renal impairment [15]. Subjects with impaired renal function have <2-fold higher exposure compared to those with normal renal function.

To assess the assay sensitivity, the supra-therapeutic exposure should cover at least 2× worst-case therapeutic exposure [21]. A single dose of 40 mg verinurad given as the IR formulation to healthy subjects will result in supra-therapeutic exposure (40 mg IR given to healthy subjects). The observed Cmax and AUC following 40 mg IR to healthy subjects was 760 ng/mL and 1270 ng*h/mL, respectively, which is 10-fold higher Cmax than worst-case clinical exposure.

Allopurinol dose of 300 mg was chosen because this is the dose given in combination with verinurad in Phase 2b.

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 IMP administration. In addition, there might be a slight risk of infection or bruising that might occur after insertion of an intravenous cannula for frequent blood sampling.

The main toxicity concern noted with verinurad monotherapy in healthy subjects is creatinine elevations >1.5 × baseline which occurred in 1.7% of healthy subjects. A change from baseline of ≥0.3 mg/dL was reported for 6.8% 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. This risk is mitigated by combining verinurad with an XOI, excluding subjects with high uric acid and mandating hydration. Further information is provided in the IB [15].

In previous studies, verinurad combined with allopurinol was well tolerated and associated with acceptable side effects. Most AEs were minor and not related to treatment.

Allopurinol is an approved XOI. Most common AEs identified in the prescribing information are rash and blood thyroid-stimulating hormone increased. Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as drug rash with eosinophilia and systemic symptoms [DRESS]) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The Human leukocyte antigen B (HLA-B)*58:01 allele has been shown to be associated with increased risk of developing allopurinol-related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*58:01 allele varies widely between ethnic populations: up to 20% in the Han Chinese population, 8 to 15% in the Thai population, about 12% in the Korean population and 1 to 2% in individuals of Japanese or European origin. At the Screening Visit, the subject's HLA-B*58:01 status will be tested and carriers of HLA-B*58:01 will be excluded [18].

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 verinurad and allopurinol single doses in this study.

5.5.1. Risk Assessment for COVID-19 Pandemic

Verinurad is a potent and specific URAT1 inhibitor. Allopurinol is a well-known drug to treat hyperuricemia. No impact on COVID-19 pandemic is expected in this healthy-volunteer study.

Therefore, risk of the subjects to be exposed to SARS-CoV-2 or to suffer from COVID 19 will be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the subjects may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to restart enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by subjects, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during in-house stay and outpatient visits will be implemented.
- The Investigator will not dose subjects upon identification of any signs of COVID-19 infection.
- Confirmation of COVID-19 infection by laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion. This would include serology testing at screening and virus testing prior to any admission.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for subject to adhere to local requirements for reduction of the public exposure while ambulatory.
  - All subjects are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, subjects are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, subjects will be referred to the local health care system for further follow-up and treatment.

- Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house stay.
- Where physical distancing is not possible, personal protective equipment will be used by subject (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

6. STUDY OBJECTIVES

6.1. Primary Objective

Table 6-1 Primary Objective and Outcome Measures

Primary Objectives	Outcome Measures
To assess the effect of a single dose of verinurad given as either a 24 mg ER8 formulation (therapeutic exposure) or a 40 mg IR formulation (supra-therapeutic exposure), both in combination with allopurinol 300 mg, on the QTcF interval compared to placebo using a concentration-QTcF interval analysis.	• The primary outcome measure is ΔΔQTcF (derived from concentration-QTcF modeling). • Parameters for this outcome measure are QTcF and Cmax.

See Section 2 for abbreviations.

6.2. Secondary Objectives

Table 6-2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
To investigate the effect of verinurad given either as a 24 mg ER8 formulation (therapeutic exposure) or a 40 mg IR formulation (supra-therapeutic exposure), both in combination with allopurinol 300 mg, on HR and additional dECG variables (PR, QRS, QT and RR).	• Baseline-corrected and placebo-adjusted dECG parameters (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval). • Parameters for this outcome measure are the dECG variables HR, RR, PR, QRS, QT and QTcF.
To assess the PK of verinurad and its metabolites (M1 and M8) and allopurinol and its metabolite (oxypurinol) in healthy subjects.	• As appropriate and where possible, the following PK parameters will be assessed for verinurad, M1, M8, allopurinol, and oxypurinol: AUC, AUC0-t, Cmax, tmax, tlag, t½λz, tlast, CL/F, Vz/F, Vss/F and MRT. • Plasma concentration-time profile for each analyte.
To assess the relationship between plasma concentrations of verinurad, allopurinol and the metabolites M1, M8, oxypurinol and dECG variables and HR.	• Plasma concentrations of verinurad, M1, M8, allopurinol, and oxypurinol and time-matched, baseline-corrected and placebo-adjusted dECG parameters (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval). • Parameters for this outcome measure are the plasma concentration of each analyte at each time point and the time-matched dECG variables HR, RR, PR, QRS, QT and QTcF.
To examine the safety and tolerability of verinurad and allopurinol	• Assessment of AEs, laboratory variables (haematology, clinical chemistry and urinalysis), vital sign variables (systolic and diastolic blood pressure, pulse rate, body temperature), ECG parameters, telemetry findings and physical examination findings.

See Section 2 for abbreviations.

6.3. Exploratory Objective(s): Not Applicable

7. STUDY POPULATION

7.1. Selection of Study Population

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

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.

This study will be conducted in healthy male and female subjects. The study may not necessarily be balanced regarding gender. It is not planned to perform sub-analyses on gender.

7.1.1. Inclusion Criteria

For inclusion in the study subjects should fulfill 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 venipuncture.

3 Females must have a negative pregnancy test at Screening and on admission to the study centre must be:

(1) Not pregnant or currently lactating or breast-feeding.

(2) Of non-childbearing potential (as defined in Section 7.2.1.1), confirmed at the Screening Visit by fulfilling one of the following criteria:

(i) Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels in the post-menopausal range (FSH >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, must be willing to use an acceptable method of contraception (see Section 7.2.1.2) to avoid pregnancy for the entire study period and 3 months after the Follow-up Visit.

4 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.

5 sUA <300 µmol/L at Screening (Visit 1) and sUA <330 µmol/L on Day −1 in every treatment period (Visit 2 to 4). Note: Since sUA levels might vary on a daily basis, subjects with sUA ≥330 µmol/L on Day −1 will be retested. Treatment on Day 1 will only be administered when the sUA level on Day −1 is <330 µmol/L upon retesting.

Subjects with sUA ≥330 µmol/L despite retesting, may conduct the treatment period at a later date when they have sUA <330 µmol/L.

6 Must be able to swallow multiple capsules/tablets.

7.1.2. Exclusion Criteria

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

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2. 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.
3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.
4. Subject has a positive test result for SARS-CoV-2 RT-PCR before randomisation.
5. Subject has clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnoea, sore throat, fatigue or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission.
6. History of severe COVID-19 (hospitalisation, extracorporeal membrane oxygenation, mechanically ventilated).
7. Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results, at Screening (Visit 1) as judged by the Investigator, including:
   (1) Alanine aminotransferase (ALT) >1.5 × ULN
   (2) Aspartate aminotransferase (AST) >1.5 × ULN
   (3) Bilirubin (total) >1.5 × ULN
   (4) Gamma glutamyl transpeptidase (GGT) >1.5 × ULN

   If any of these tests are out of range, the test can be repeated once at the Screening Visit at the discretion of the Investigator.
8. Any clinically significant abnormal findings in vital signs at Screening as judged by the Investigator, including:
   (1) Systolic blood pressure <90 mmHg or >140 mmHg
   (2) Diastolic blood pressure <50 mmHg or >90 mmHg
   (3) Heart rate <50 or >90 bpm

   If any of these tests are out of range, the test can be repeated once at the Screening Visit at the discretion of the Investigator.
9. Carrier of the HLA-B*58:01 allele.
10. Any clinically important abnormalities in rhythm, conduction or morphology of the 12-lead safety ECG and any clinically important abnormalities in the 12-lead safety ECG as considered by the Investigator that may interfere with the interpretation of QT

interval corrected for heart rate using Fridericia's formula (QTcF), including abnormal ST-T-wave morphology, particularly in the Clinical Study Protocol (CSP)-defined primary lead for dECG analysis or left ventricular hypertrophy:

(1) Prolonged QTcF >450 ms or shortened QTcF <340 ms or family history of long QT syndrome.

(2) PR (PQ) interval shortening <120 ms (PR >110 ms but <120 ms is acceptable if there is no evidence of ventricular pre-excitation).

(3) PR (PQ) interval prolongation (>220 ms) intermittent second (Wenckebach block while asleep is not exclusive) or third degree atrioventricular (AV) block, or AV dissociation.

(4) Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with QRS >110 ms. Subjects with QRS >110 ms but <115 ms are acceptable if there is no evidence of ventricular hypertrophy or pre-excitation.

11. Any positive result on Screening for serum hepatitis B surface antigen OR anti-HBc antibody, hepatitis C antibody, and human immunodeficiency virus (HIV) antibody.
12. Suspected or known Gilbert's syndrome.
13. Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the 3 months prior to Screening.
14. Known or suspected history of alcohol abuse or excessive intake of alcohol as judged by the Investigator. Excessive intake of alcohol defined as the regular consumption of more than 24 g of alcohol per day for men or 12 g per day for women.
15. Positive screen for drugs of abuse, cotinine (nicotine) or alcohol at the Screening Visit or on each admission to the study centre.
16. Excessive intake of caffeine-containing drinks or food (eg, coffee, tea, chocolate) as judged by the Investigator. Excessive intake of caffeine defined as the regular consumption of more than 600 mg of caffeine per day (eg, >5 cups of coffee) or would likely be unable to refrain from the use of caffeine-containing beverages during in-house stay at the study site.
17. Previous hypersensitivity reaction to allopurinol or any URAT1 inhibitor.
18. Subjects who are pregnant, breast-feeding or planning to become pregnant (pregnancy is to be avoided for the entire study period and 3 months after the Follow-up Visit).
19. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.
20. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 × the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or within 5 half-lives (whichever is longer). Hormone replacement therapy is allowed for females.
21. Plasma donation within 1 month of Screening or any blood donation/blood loss >500 mL during the 3 months prior to Screening.

22. Has received another new chemical or biological entity (defined as a compound which has not been approved for marketing in the US) within 30 days or within 5 half-lives (whichever is longer) of the first administration of IMP in this study.

    Note: Subjects consented and screened, but not randomised in this study or a previous Phase I study, are not excluded.
23. Involvement of any AstraZeneca, Parexel or study site employee or their close relatives.
24. Subjects who have previously received verinurad.
25. Subjects who cannot communicate reliably with the Investigator and/or are not able to read, speak and understand the German language.
26. Judgment by the Investigator that the subject should not participate in the study if there are any ongoing or recent (ie, during the Screening Period) minor medical complaints that may interfere with the interpretation of the study data or are considered unlikely to comply with study procedures, restrictions and requirements.
27. Subjects who are vegans or have medical dietary restrictions.
28. Vulnerable subjects, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.
29. Subjects who are regularly exposed to COVID-19 (eg, health care professionals working in COVID-19 wards or at emergency departments) as part of their daily life.

7.2. Restrictions During the Study

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

1 Subjects will be fasted for 10 hours prior to dosing (starting from Day −1). The IMPs will be administered with 240 mL of water. No food will be allowed for at least 3 hours post-dose. Water will be allowed as desired except for 1 hour before and after drug administration (see Section 9.6).

2 Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after dosing.

3 Subjects should not engage in any strenuous activity from 72 hours prior to check-in until after their final Follow-up Visit.

4 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.

5 Prior to each treatment period, subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to check-in until discharge from the study centre.

6 Subjects should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) from 7 days prior to check-in on Day -1 until after their Follow-up Visit.

7 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 study centre.

8 Standardised meals, water intake and timing: Subjects will receive standardised meals, scheduled at the same time in each study period, to avoid the impact of food on the ECG.

- On Day 1: (1) a very light snack immediately after 3-hour sample, (2) meal immediately after 6-hour sample, and (3) dinner after 10-hour sample.
- On Days 2 and 3, subjects should not eat any food up to 2 hours before the 36-hour and 48-hour samples.
- The dose will be administered after an overnight fast of at least 10 hours with 240 mL of water. Subjects should drink 3 to 3.5 L of water on Day −1 and again on Day 1. To prevent dehydration, subjects will be allowed to drink water until 1 hour before dosing. Water will be allowed ad libitum from 1 hour after dosing.

9 During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (eg, red bull), and food containing poppy seeds and any over-the-counter medication or herbal preparations until after their Follow-up Visit has been completed. Subjects should also limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup=330 mL soda, 180 mL coffee, or 240 mL tea).

10 Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the Follow-up Visit.

11 Subjects are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. All subjects are called 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. In addition, subjects are asked for any contact with a person who has confirmed infection. If applicable, subjects will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to subjects while staying at the study site. Where physical distancing is not possible, subjects will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

For medication restrictions, please refer to Section 9.7.

7.2.1. Reproductive Restrictions

Verinurad is not genotoxic, has no effect on fertility in animal studies, and carries a low risk for foetal harm at maternally nontoxic doses in animal studies.

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

- Be of non-childbearing potential, that is, she must be surgically sterilized or post-menopausal as described in Section 7.2.1.1, OR

- If of childbearing potential, must be using highly effective methods of birth control as described in Section 7.2.1.2.

7.2.1.1. Women of Non-Childbearing Potential

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

Acceptable methods of sterilization include:

- Surgical bilateral oophorectomy (with or without hysterectomy) at least 6 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 6 weeks before Screening.
- Bilateral salpingectomy.

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

7.2.1.2. Women of Childbearing Potential

A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Women of childbearing potential who are sexually active must agree to use, with their partner, an approved method of highly effective contraception from the time of IMP administration until 3 months after the 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, ie, 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] (ie, 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]).
- 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 after receiving 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. Periodic abstinence (eg, 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 childbearing potential can be included only after a negative highly sensitive serum pregnancy test. Additionally, urine pregnancy testing will be done as per the Schedule of Assessments.

Pregnancy

If the subject becomes pregnant during the study this should be reported to the Investigator. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. The pregnancy will be followed and the status of mother and child will be reported to the Sponsor after delivery.

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

7.2.1.3. 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. There is inadequate evidence of safety of allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence.

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 of a highly effective method of contraception (see definition above), together with their female partner, starting from the time of IMP administration until at least 3 months after the Follow-up Visit.

Pregnancy

Male subjects will be instructed that, if their partner becomes pregnant during the study, this should be reported to the Investigator. The Investigator 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 Investigator agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for suspected or confirmed COVID-19 infection or other reasons may be replaced following discussion with the Sponsor.

8. STUDY STOPPING RULES

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

Subjects must be discontinued from treatment in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe noncompliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, body temperature, laboratory assessments and AE) making the continuation of IMP administration unjustified.
- Study-specific withdrawal criteria: If a subject reports any event/symptoms that are considered unacceptable by the subject or the Investigator, he/she will be withdrawn from the study. In particular:
  - Any severe or serious AE that is judged as possibly related to the IMP by the Investigator.
  - Any case of Potential Hy's Law (PHL) according to Appendix C.
  - QTc prolongation defined as QTcF >500 ms, or a prolongation from baseline of >60 ms, confirmed (persistent for at least 5 minutes) and determined post-dose either during continuous 12-lead safety ECG monitoring or on a repeat 12-lead safety ECG.
  - See Appendix D 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.
  - Any confirmed COVID-19 case that warrants discontinuation in the judgment of the Investigator or Sponsor to protect the safety of the subject, other study participants or study site staff.

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

8.1.1. 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 IMP:

- A "serious" adverse reaction (ie, an SAE considered at least possibly related to IMP administration as per guideline EMEA/CHMP/SWP/28367/07 Rev. 1 [22]) in 1 subject;
- "Severe" non-serious adverse reactions (ie, 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 will be terminated prematurely if:

- The Investigator and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance, when there is at least 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered related to the IMP by the Investigator and the Sponsor.
- The Sponsor considers the applied doses of the IMPs to be no longer relevant.
- The Sponsor decides to discontinue the study.
- Data, that were not known before, become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.
- New data become available regarding COVID-19, which raise concern for the safe study conduct so that continuation would pose potential risks to the subjects or the study site staff.

Premature termination of the study must be mutually agreed upon by the Investigator 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 test products (verinurad, allopurinol) and reference product (placebo) are presented in Table 9-1 and Table 9-2. The capsules of verinurad ER8 12 mg, verinurad IR 10 mg and verinurad placebo are all of the same size and shape.

Table 9-1 Identity of the Investigational Medicinal Products - Verinurad 12 mg ER8, Verinurad 10 mg IR and Matching Placebo

	Verinurad 12 mg ER8	Verinurad 10 mg IR	Placebo
Supplier:	AstraZeneca	AstraZeneca	AstraZeneca
Formulation:	Capsule	Capsule	Capsule
Strength/concentration:	12 mg ER8	10 mg IR	NA
Dose:	24 mg ER8	40 mg IR	NA
Route of administration:	Oral	Oral	Oral
Regimen:	2×12 mg verinurad ER8 capsule formulation	4×10 mg verinurad IR capsule formulation	2× or 4× placebo capsule matching verinurad*
Special handling requirements:	None	None	None

ER8: Extended-release; IR: Immediate-release; NA: Not applicable.
* Subjects receiving Treatment A will receive 2 placebo capsules matching verinurad; subjects receiving Treatment C will receive 4 placebo capsules matching verinurad.

Table 9-2 Identity of the Investigational Medicinal Products - Allopurinol and Matching Placebo

	Allopurinol	Placebo
Supplier:	AstraZeneca	AstraZeneca
Formulation:	Tablet	Tablet
Strength/concentration:	300 mg	NA
Dose:	300 mg	NA
Route of administration:	Oral	Oral
Regimen:	1× 300 mg allopurinol tablet formulation	1× placebo tablet matching allopurinol 300 mg
Special handling requirements:	None	None

NA: Not applicable.

Details of the batch numbers will be included in the Trial Master File and the final CSR.

9.2. Supply of Investigational Medicinal Product

Verinurad, allopurinol and the matching placebos will be supplied by AstraZeneca and provided in study-specific labeled bottles.

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

A release document signed by a legally authorized Qualified Person at the study centre will be placed in the appropriate section of the Trial Master File to document labeling and dispensing of the IMPs to the subject.

9.3. Storage and Handling Procedures

All study treatment will be stored in a secure facility, details of storage conditions will be provided on the respective labels of the IMP.

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. Labeling

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

The labels will fulfill GMP Annex 13 requirements and medical device directive for labeling.

9.5. Drug Accountability, Dispensing and Destruction

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

In accordance with GCP, the study centre will account for all supplies of verinurad, allopurinol, and placebo. Details of receipt and storage, dispensing and return will be recorded.

All unused supplies of verinurad, allopurinol, and placebo 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

In the respective treatment periods, subjects will receive single doses of verinurad, allopurinol, and placebo under fasted conditions. In order to blind the treatments, each subject will receive 4 verinurad capsules and 1 allopurinol tablet at each dispensation. The capsules of verinurad 12 mg ER8, verinurad 10 mg IR and verinurad placebo are all of the same size and shape. In total, 5 capsules/tablets will be administered per dispensing visit according to the scheme in Table 9-3.

Table 9-3 Treatment Regimens

IMP	Number of Capsules/Tablets Administered		
	Treatment A[a]	**Treatment B[b]**	**Treatment C[c]**
12 mg verinurad ER8 capsule	2	0	0
10 mg verinurad IR capsule	0	4	0
Verinurad placebo	2	0	4
300 mg allopurinol tablet	1	1	0
Allopurinol placebo	0	0	1
Total number of tablets/capsules	**5**	**5**	**5**

ER8: Extended-release; IMP: Investigational Medicinal Product; IR: Immediate-release.
[a] Treatment A: Verinurad 24 mg ER8 formulation co-administered with 300 mg allopurinol
[b] Treatment B: Verinurad 40 mg IR formulation co-administered with 300 mg allopurinol
[c] Treatment C: Matched placebos for both verinurad and allopurinol

Requirements for hydration are described in Section 7.2.

After dosing, subjects will remain semi-supine on their bed or sitting (except when necessary for study procedures) until completion of the 3-hour assessments.

Other restrictions, including posture control are described in Section 7.2. Data of subjects may be excluded from the PK Analysis Set as described in Section 12.3.4.

9.7. Concomitant and Post-study Treatment(s)

Apart from paracetamol/acetaminophen, hormone replacement therapy, 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 over-the-counter products, without the consent of the Investigator.

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

When any medication is required, it should be prescribed by the Investigator. Following consultation with AstraZeneca Lead Physician, the Investigator 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 must be documented as a protocol deviation after consultation of the Investigator with AstraZeneca Lead Physician

9.8. Treatment Compliance

Dosing will take place at the study centre (Parexel Early Phase Clinical Unit).

The administration of all IMPs will be recorded in ClinBase™.

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

In addition, bioanalysis of the time at predicted Cmax plasma sample from all presumed placebo-treated subjects may be used to confirm lack of verinurad, M1, M8, allopurinol or oxypurinol in the plasma.

9.9. Randomisation

9.9.1. Subject Enrolment and Randomisation

The Investigator will ensure that:

- 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 randomisation code.

Randomisation to the cross-over treatment sequence will be done on the evening prior to the day of first dose (Treatment Period 1).

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation (codes to be used without leading zero(s)).

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

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

9.9.2. Procedures for Randomisation

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

Subjects will be randomised according to a randomised William's Latin square to receive the 3 study treatments (Treatment A: verinurad 24 mg ER8 + allopurinol; Treatment B: verinurad 40 mg IR + allopurinol, Treatment C: placebo) in 1 of 6 treatment sequences: ABC, BCA, CAB, ACB, BAC, or CBA.

The randomisation will be completed using consecutive randomisation codes.

The number of subject identifiers generated for the study will account for the number of randomised subjects per the sample size calculation (N=24; see Section 12.4) as well as providing sufficient randomisation numbers for replacements. For this study, a total of 48 subject identifiers will be randomly assigned to the treatment sequences (ABC, BCA, CAB, ACB, BAC, CBA).

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 Investigator 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

9.11. Methods for Ensuring Blinding

This study is double-blind with regard to IMP (verinurad and allopurinol or the matching placebos).

Placebos will be matched with their respective test product (verinurad or allopurinol) for formulation, appearance, and amount.

Any clinical staff involved in the preparation or administration of the IMP and who become unblinded will take no further part in the study.

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

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

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

The following personnel will have access to the randomisation list:

- The AstraZeneca personnel carrying out the labeling and packaging of subject-specific treatments

- The pharmacy personnel preparing IMP at the site
- The personnel performing the bioanalyses of the plasma/urine samples.

9.12. Methods for Unblinding the Study

As the study will be conducted double-blinded, individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator and the pharmacist.

In most of the studies using blinding, the treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the subject to the AstraZeneca staff. In the event of a medical emergency when management of a subject's condition requires knowledge of the study medication, the treatment received may be revealed by personnel authorized by the Investigator. If possible, such emergencies are to be discussed with AstraZeneca prior to disclosure of the treatment allocation. Reasons for breaking a code will be clearly explained and justified in the subject's CRF. The date on which the code was broken together with the identity of the person responsible will also be documented.

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 and allopurinol planned to be given during this study, no safety issues are expected.

For timing of assessments refer to Table 5-2.

10.2. Enrolment and Screening Procedures

Viral serology and urine tests for drugs of abuse, alcohol and cotinine will be done to assess eligibility. Laboratory tests for FSH (females only) and pregnancy (females only) will be done. The use of concomitant medication will be recorded and reported.

10.3. Pharmacokinetics

10.3.1. Collection of Pharmacokinetic Samples

Blood samples for the determination of plasma concentrations of verinurad, verinurad metabolites (M1 and M8), allopurinol, and allopurinol metabolite (oxypurinol) will be collected for each treatment period as specified in the Schedule of Assessments (Table 5-2).

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

10.3.2. Pharmacokinetic Drug Assays

Blood samples for determination of verinurad, M1, M8, allopurinol, and oxypurinol concentrations in plasma will be analysed by Covance Bioanalytical Services on behalf of AstraZeneca, using validated assays. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Placebo samples will not be analysed, unless there is a need to confirm that correct treatment has been given to study subjects.

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

10.4. Safety Measurements

Safety and tolerability variables will include:

- Adverse events
- Laboratory variables (haematology, clinical chemistry and urinalysis), tested locally
- Vital sign variables (systolic and diastolic blood pressure, pulse rate, body temperature)
- ECG parameters

- Telemetry findings
- Physical examination findings

10.4.1. Adverse Events

Refer to Section 13.

10.4.2. Laboratory Assessments

10.4.2.1. Haematology

Haematology	
WBC count	Neutrophils absolute count
RBC count	Lymphocytes absolute count
Hb	Monocytes absolute count
HCT	Eosinophils absolute count
MCV	Basophils absolute count
MCH	Platelets
MCHC	Reticulocytes absolute count

Hb: Haemoglobin; HCT: Haematocrit; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; RBC: Red blood cell; WBC: White blood cell.

10.4.2.2. Serum Clinical Chemistry

Serum Clinical Chemistry	
Sodium	ALP
Potassium	ALT
Urea	AST
Creatinine	GGT
Albumin	Total Bilirubin
Calcium	Unconjugated bilirubin
Phosphate	sUA
Glucose (fasting)	
CRP	
TSH[a]	FSH[b]

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; FSH: Follicle-stimulating hormone; GGT: Gamma glutamyl transpeptidase; sUA: Serum uric acid; TSH: Thyroid-stimulating hormone.

[a] Screening only
[b] Females only

10.4.2.3. Genotyping

Genotyping	
HLA-B	

HLA-B: Human leukocyte antigen B

10.4.2.4. Urinalysis

Urinalysis[a]	
Glucose	pH
Protein	
Blood	

[a] 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.

10.4.2.5. Pregnancy Testing

Pregnancy test (females only)	
β-hCG	

β-hCG: Beta human chorionic gonadotropin.

10.4.2.6. Viral Serology

Viral Serology	
HIV I and II	SARS-CoV-2 antibody
HBsAg	
HCV antibody	
Anti-HBc antibody	

HBc: Hepatitis B core; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

10.4.2.7. SARS-CoV-2 Virology

SARS-CoV-2 Virology	
SARS-CoV-2 RT-PCR	

RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

10.4.2.8. Drugs of Abuse and Alcohol

Drugs of Abuse and Alcohol	
Amphetamine / Ecstasy	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine Creatinine
Cotinine	
TCA	

TCA: Tricyclic anti-depressants

10.4.3. Vital Signs

The following variables will be collected after the subject has rested in the supine position for at least 10 minutes:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (bpm)
- Tympanic body temperature (°C)

Supine pulse (bpm) and blood pressure (mmHg) will be measured at the time points indicated in Table 5-2. Measurements will be performed according to Parexel standard operating procedures (SOP), subsequent to at least a 10-minute rest. Systolic and diastolic blood pressure will be measured using the same cuff size, appropriate for arm circumference, in triplicates and then averaged, throughout the study. Body temperature will be measured at least once daily (in the morning) at every visit or during in-house stay.

10.4.4. Electrocardiography

10.4.4.1. 12-lead Safety Electrocardiogram

At the time points specified in Table 5-2, a 10-second 12-lead safety ECG for safety review by the Investigator will be obtained after 10 minutes supine rest. These 12-lead safety ECG recordings will be performed prior to the dECG recordings and at additional intervals if required.

When 12-lead safety ECG time points coincide with dECG or telemetry time points, the 12-lead safety ECG will be printed out directly from the device used for dECG or telemetry. When 12-lead safety ECG time points do not coincide with dECG or telemetry time points, the 12-lead safety ECGs will be obtained using the study centre's own ECG device.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded.

The date/time and the physician interpretation (normal, abnormal clinically significant, abnormal not clinically significant) for the 12-lead safety ECGs will be recorded in the source, with any abnormalities specified. The outcome of the overall evaluation is to be recorded as normal/abnormal in the electronic source, with any abnormalities specified.

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

All ECG readings will be digitally stored as source documents.

10.4.4.2. Electronic Capture of 12-lead Continuous Digital Electrocardiogram

The AstraZeneca ECG Centre will perform the dECG analysis in this study, using the EClysis© system, version 4.0, or higher.

At the time points specified in Table 5-3, 12-lead continuous dECG files will be recorded using the site's Mortara Telemetry Surveyor equipment according to AstraZeneca ECG Centre´s standard procedures for settings, recording and transfer of dECGs.

The same recording device will be used for each subject at all time points, when possible. Date and time settings must be checked on the Mortara Telemetry Surveyor at the start of each study day and aligned with an official timekeeper.

The metadata of each file will be checked by the responsible personnel at the study site to ensure that the files transferred to the AstraZeneca central dECG files repository are correct.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead safety ECG placement. Electrode positions will be marked with an indelible pen at the start of each study day to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration of each relevant study day.

Subjects will rest in a supine position for at least 10 minutes before the start of each recording. The subject should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

From the continuous dECG files received at the AstraZeneca ECG Centre, the EClysis© system will extract continuous files of at least 5 minutes length at the time points indicated in Table 5-3. The extraction window can be adjusted based on the clinical logs received from the site. As standard, from each dECG extracted window, 10-second ECGs will be extracted by the EClysis© system twice per minute and will be initially automatically analysed by the software.

The dedicated ECG Scientific Advisor(s) with Importer role in the EClysis© system will evaluate the files for signal quality and provide timely feedback to the study centre. They will ensure that all recorded protocol-defined dECGs have been extracted and imported and then will make these available to the dedicated ECG Scientific Advisors with the Analyst role.

The ECG Scientific Advisor(s) with Analyst role, as well as the Reviewing Cardiologist, will perform the semi-automated analysis in a fully blinded manner (to treatment, time, sequence and subject identifier). All dECGs from one subject will be analysed by a single reader.

Lead V2 will be used as the primary lead, with lead V5 as the primary backup lead and lead II as the secondary backup lead, for all time points when lead V2 is found to be unsuitable for analysis or evaluation.

The ECG Scientific Advisor will perform all necessary manual corrections to the ECG annotations provided automatically by EClysis©.

Finally, the Reviewing Cardiologist will review the data and perform all necessary adjustments before locking the data into a read-only state. From the locked data, the numerical values for the ECG intervals and amplitudes will then be made accessible on a secure file share of the AstraZeneca dECG central repository to accredited data management specialists for conversion into SAS files®.

The following dECG variables will be reported by the AstraZeneca ECG Centre: RR, PR, QRS and QT intervals from the lead defined as primary analyses lead, as well as potential T-wave morphology changes. For T-wave morphology, treatment-emergent changes will be assessed, ie, changes not present at baseline, and will be reported as part of the ECG analysis results text in the CSR. Derived parameters (QTcF, HR and others, as applicable) are calculated by the study statistician or delegate.

10.4.5. Telemetry

A 12-lead real-time cardiac telemetry will be performed for 4 to 6 hours on Day -1 and from at least 30 minutes pre-dose until 24 hours post-dose on Day 1 using the Mortara Surveyor Telemetry 12-leads system.

The telemetry monitoring system will be reviewed by the Investigator or research nurse and paper printouts of any clinically important events will be stored as source data.

10.4.6. Physical Examination

At the time points specified in the Schedule of Assessments (Table 5-2), a full or brief physical examinations will be performed.

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

10.5. Exploratory Assessments – Not Applicable

10.6. Procedures for Handling of Biological Samples

10.6.1. 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.

10.6.1.1. Pharmacokinetic Samples

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

Pharmacokinetic samples may be disposed of or 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.

10.6.1.2. Pharmacodynamic Samples – Not Applicable

10.6.1.3. Pharmacogenetic Samples – Not Applicable

10.6.2. Labeling and Shipment of Biohazard Samples

Samples will be labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B, 'IATA 6.2 Guidance Document'.

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 labeling, shipment and containment provisions are approved.

10.6.3. Chain of Custody of Biological Samples

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

The Investigator will ensure full traceability of collected biological samples from the subjects while in storage at the study 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.

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

10.6.4. 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, the subject is then withdrawn from further study participation. If the subject withdraws consent for the genetic component of the study, then they may continue in the study.

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

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 study centre 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 study centre.

11.2. Audit/Inspections

The study centre facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The Investigator must allow the applicable persons access to all relevant facilities and data/documents. The Investigator 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.

Monitoring visits at site will be limited to a minimum, required as deemed appropriate during COVID-19 pandemic.

11.4. Data Collection

The ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase™. 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 study centre. The Investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase™ by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase™.

11.4.1. Case Report Forms and Source Documents

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

The original ClinBase™ 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 Investigator for resolution.

11.4.2. Access to Source Documents

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

Checking of the ClinBase™ 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/Institutional Review Boards (IRB)s 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 Investigator assures the Sponsor of the necessary support at all times.

11.5. Data Management

Parexel will utilize standardised 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 Code of Federal Regulations 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 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 Investigator for review

and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). 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 concentration-QT (C-QT) analysis plan for the primary C-QT analysis will be written for the study. A brief description of the primary analysis is provided in Section 12.9. All other analyses are described within this protocol. 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 statistical analysis plan, if appropriate. The verification and review of all statistical modeling assumptions will be documented appropriately.

12.2. General Statistical Methodology

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

Demographic and baseline data will be summarised for all randomised subjects. Pharmacokinetic data will be summarised by treatment. Safety and tolerability data (see Section 10.4 for definition of safety and tolerability variables) will be summarised by treatment, if applicable.

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

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

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

The planned sequence for measurement of multiple assessments at the same time point is described in Section 5.3.5.

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

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

All statistical analyses and production of tables, figures and listings will be performed using 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 12.12.2. Concentrations that are not quantifiable (NQ) in the PK data will be handled as described in Section 12.10.2.

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

12.3. Study Populations

12.3.1. Randomised Set

The Randomised Set will consist of all subjects randomised into the study.

12.3.2. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose of IMP (verinurad, allopurinol and placebo) 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.

12.3.3. Pharmacodynamic Analysis Set

The PD Analysis Set will consist of all subjects in the Safety Analysis Set for whom baseline and post-baseline QTcF results from smoothed dECG data are available for at least 2 treatment periods (where 1 of the treatment periods needs to be the period in which the subject received placebo) and who have no major protocol deviations thought to impact on the analysis of the dECG data.

12.3.4. Pharmacokinetic Analysis Set

The PK Analysis Set will consist of all subjects in the Safety Analysis Set for whom at least 1 reportable PK parameter can be calculated and who have no major protocol deviations thought to impact on the analysis of the PK data.

Pharmacokinetic data for a subject during any Treatment Period may be excluded from descriptive statistics as a result of the following:

- An AE of vomiting that occurred at or before median tmax for that specific treatment
- The pre-dose concentration being >5% of Cmax for an analyte in a specific treatment period

A subject may be excluded from the analysis only for the specific Treatment Period in which the above occurred. If there are no other reportable PK data for the subject, then the subject may 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 pharmacokineticist will document and include the reason(s) for exclusion of the following:

- Exclusion of any subjects from the PK Analysis Set.
- Exclusion of any individual concentration-time points from the calculation of the PK parameters or from the statistical analyses and corresponding figures.
- Exclusion of any individual PK parameters from the statistical analyses and corresponding figures.

All available concentration data and PK parameter data will be listed for the Safety Analysis Set. Concentration or parameter data for subjects excluded from the descriptive statistics or analysis will be presented in the individual concentration versus time plots or PK parameter figures, but not in the corresponding summary figures.

12.4. Determination of Sample Size

Study sample size for a concentration-QTcF (C-QTcF)-based interval analysis is based on the recommendation from Garnett et al 2018 [21] to have 16 to 32 subjects on drug and 8 to 16 subjects on placebo. The type-1 error rate has been shown to be controlled at around 5% when the true effect is 10 ms in small-sized studies of 6 to 12 subjects with multiple measurements per subject.

A 3-period cross-over study, using C-QTcF-based interval analysis, with 2 verinurad doses and placebo in 20 evaluable healthy volunteers is expected to exceed the recommendations proposed in Garnett et al 2018 [21].

Twenty-four subjects will be randomised to a 6-sequence William's design for 3 periods and 3 treatments to achieve 20 evaluable subjects based on an expected dropout of 17%.

Evaluable subjects are defined as subjects for whom baseline and post-baseline QTcF results from smoothed dECG data are available for at least 2 treatment periods (where 1 of

the treatment periods needs to be the period in which the subject received placebo), and who have no major protocol deviation thought to impact on the analysis of the dECG data.

12.5. Protocol Deviations

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

- Inclusion/exclusion criteria deviations
- Dosing deviations (eg, 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 study centre on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification (PDS) document. This will include a WAD 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.

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 (missing assessments/visits) related to COVID-19 will be listed separately.

Protocol deviations will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 3.6.

12.6. Subject Disposition

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

Subjects and/or data excluded from the PK and PD analysis sets will be listed including the reason for exclusion. Subject disposition will be summarised 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.

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 summarised separately 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) 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 ClinBase™.

Prior and concomitant medication will be listed by subject and will include the following information: reported name, preferred term (PT), 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.

12.9. Pharmacodynamic Analysis

Note: In this study, the PD data collected refer to dECG data.

Primary analysis:

A linear mixed-effect concentration-QTcF model will be used as the primary analysis. Baseline-corrected and placebo-adjusted QTcF (ΔΔQTcF), using individual time-matched placebo for a given subject, will be the dependent variable and verinurad plasma concentrations will be the independent variable. Fixed effects will be: intercept in the absence of a treatment effect, slope of the assumed linear association between concentration and ΔΔQTcF and baseline QTcF. Random effects will be included on the intercept term and the slope. ΔΔQTcF at the concentration of interest will be estimated. A prolonging effect will be excluded if the upper bound of the two-sided 90% confidence interval for model-derived ΔΔQTcF is estimated to be <10 ms at the highest clinically

relevant exposure. Details of the concentration-QTcF modeling will be provided in a separate document (C-QT analysis plan).

Relevant exploratory plots will also be provided such as mean change from baseline QTcF vs. drug concentration, QTcF vs. RR and other dECG variables.

Calculations related to the PD variables will be performed by Parexel International. Parexel SOPs and Work Instructions will be used as the default methodology if not otherwise specified.

For dECGs the lead V2 is used as the primary lead, with lead V5 as the primary backup lead and lead II as the secondary backup lead, for all time points when lead V2 is found to be unsuitable for analysis or evaluation. Prior to the statistical analysis and summary, the ECG intervals will be smoothed into target time point values.

After the smoothing of QT and RR into target time point values, the HR-corrected QT will be calculated (QTcF) using the standard formula. All the statistical analyses will be performed using smoothed data.

The QTcF versus RR intervals will be plotted to confirm if HR-correction has been appropriate.

Digital ECG variables (absolute values and change from baseline for: HR, RR, PR, QRS, QT and QTcF) will be listed by subject and time point and summarised by treatment group using appropriate descriptive statistics (eg, n, geometric mean, arithmetic mean, SD, min, median, max, etc.); in addition, exploratory plots will be provided (such as time course for each dECG variable, changes from baseline for each dECG variable, by treatment group, mean with SD) and time course for ΔΔ: RR, HR, PR, QRS, QTcF for each treatment group.

The QT and QTcF outliers (defined as values following dosing that are greater than 450 ms or increases from baseline greater than 30 ms) will be summarised using cumulative counts and percentage under the following categories:

1 absolute value >450 ms,
2 absolute value >480 ms,
3 absolute value >500 ms,
4 increase from time-matched baseline >30 ms,
5 increase from time-matched baseline >60 ms,
6 absolute value >450 ms and increase from time-matched baseline >30 ms,
7 absolute value >500 ms and increase from time-matched baseline >60 ms.

All PD analyses will be done on the PD Analysis Set. The analysis population of the primary analysis will be defined in the C-QT analysis plan.

Additional analyses of the dECG data will be performed and a corresponding summary table will be presented according to the guidance for the analysis and review of QT/QTc interval data published by Health Canada [23].

12.10. Pharmacokinetic Analysis

12.10.1. Pharmacokinetic Parameters

As appropriate and where possible, the following PK parameters will be assessed for verinurad, M1, M8, allopurinol, and oxypurinol using plasma concentrations.

AUC	Area under plasma concentration-time curve from time zero to infinity
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
Cmax	Maximum observed plasma concentration
tmax	Time to reach maximum observed plasma concentration
tlag	Time delay between drug administration and the first observed concentration in plasma
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
tlast	Time of last quantifiable plasma concentration
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug)
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration (parent drug)
Vss/F	Apparent volume of distribution at steady state
MRT	Mean residence time of the unchanged drug in the systemic circulation from zero to infinity

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

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 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.

12.10.2. Derivation of Pharmacokinetic Parameters

The PK analyses of the plasma concentration data for verinurad, M1, M8, allopurinol, and oxypurinol will be performed by Covance Clinical Pharmacokinetic Alliance (CPKA), on behalf of AstraZeneca Research and Development (R&D).

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher. All descriptive and inferential statistical analyses 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, tlag, tlast, t lower and t upper 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 and agreement reached with the Sponsor regarding exclusion of λz and dependent parameters (t½, λz, AUC, CL/F, MRT, Vz/F and Vss/F) from the corresponding statistical analyses.

The Rsq-adj value will also be calculated to show the goodness-of-fit of the choice of datapoints taking into consideration the number of points used in the estimation. Where the Rsq-adj value is <0.8 it will be flagged and commented upon in the CSR and agreement reached with the Sponsor regarding exclusion of λz and dependent parameters from the statistical analyses.

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.

12.10.3. Presentation of Pharmacokinetic Data

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations will be summarised for the PK Analysis Set for each time point by analyte and 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 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 summarised. 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, analyte, and treatment. A separate listing will be provided for the diagnostic PK parameters.

Plasma PK parameters will be summarised for the PK Analysis Set by analyte and treatment using the following descriptive statistics:

- Cmax, AUC, and AUC0-t: 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, tlag, and tlast: present n, median, min and max.
- Diagnostic parameters (eg, λz, t upper, t lower, λzN, Rsq-adj and %AUCextr): listed only and not summarised.

Three values are required as a minimum for PK parameters to be summarised. 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, tlag, tlast, t lower and t upper time limit: present as received in the data, usually to 2 decimal places
- AUC, AUC0-t, t½λz, CL/F, Vz/F, Vss/F, MRT, λz, %AUCextr, Rsq-adj: present to 3 significant figures
- n and λzN: present 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, tlag, 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, as appropriate.

Individual subject plasma concentrations versus actual time will be plotted for each analyte 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 analyte and treatment.

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

All gmean plots or combined plots showing all subjects by analyte and 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.

12.10.4. Statistical Analysis of Pharmacokinetic Data

No inferential statistical analysis of PK parameters will be conducted.

12.11. Pharmacokinetic/Pharmacodynamic Analysis

Additional population PK/PD analysis may be conducted in case of non-linear concentration-QTc relationship, large HR effect, or time delay between drug concentration and QTcF effect.

A detailed analysis plan of the primary C-QTc analysis will be prepared prospectively as a separate document (C-QTc analysis plan). It will include all technical details of the primary analysis modeling approach.

12.12. Analysis of Safety Data

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Changes (and/or percentage change) from baseline will be presented where applicable when baseline is defined. Categorical variables will be summarised 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 and clinical laboratory tests will be presented. Data will be summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline is defined. 12-lead safety ECG data will be listed only. Out-of-range values will be flagged in individual listings for safety laboratory findings, vital signs and 12-lead safety ECGs findings. Furthermore, out-of-range values will be summarised descriptively for safety laboratory findings and vital signs using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, program, or laboratory ranges).

12.12.1. 12-lead Safety Electrocardiogram

The 12-lead safety ECG results will be listed for each subject and out-of-range results will be flagged. Abnormal findings may be classified as AEs if considered clinically significant by the Investigator. See Section 13.2.6 for AE reporting.

12.12.2. Adverse Events

All AEs will be coded using MedDRA vocabulary and will be listed for each subject. Adverse events will be assigned to a treatment based on the start date/time of the AE in relation to dosing in that period; for tabulation purposes the AE will then be assigned to the treatment received in the respective treatment period as follows:

- Screening: all AEs with start date/time prior to dosing in Treatment Period 1 (from time of randomisation for AEs and from time of signed ICF for SAEs).
- 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 final 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 (ie, 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 (ie, 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 (ie, 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 summarised by treatment and overall for all subjects, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT.

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, SAEs, AEs leading to discontinuation of IMP (DAE) and AEs with outcome of death.

Listings of all AEs, SAEs, DAEs and AEs with outcome of death will be presented. Adverse events that occur before dosing will be presented separately.

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

12.12.3. 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 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 out of range (eg, AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in Systeme International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- Potential Hy's law case
- The results of viral serology, SARS-CoV-2 PCR and drugs of abuse and alcohol screen will not be listed in the CSR.

12.12.4. 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 and out-of-range values. 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. Shift tables will also be presented.

12.12.5. Physical Examination

The baseline/Screening results of the physical examination will be documented in medical history for each subject. These results will not be listed or summarised.

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

13. ADVERSE EVENTS

13.1. Definitions

13.1.1. Definition of Adverse Events

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

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

13.1.2. Definitions of Serious Adverse Event

A serious AE is an AE occurring during any study phase (ie, run-in, treatment, wash-out, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- 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 a SAE, see Appendix A of this CSP.

Adverse events for malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'important medical event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a non-serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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 adverse events 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 randomisation throughout the treatment period and up to and including the Follow-up Visit.

Serious adverse events 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 Investigator for as long as medically indicated, but without further recording in ClinBase™.

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:

- Adverse event diagnosis/description
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP (yes or no)
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to

- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The following intensity ratings will be used:

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

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 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 a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

13.2.4. Causality Collection

The Investigator will assess causal relationship between IMP and each AE, 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 A 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 ClinBase™.

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 summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AE if it fulfills any of the SAE criteria, is clinically significant according to Investigator judgment, or is the reason for discontinuation of treatment with the IMP.

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

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

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-protocol-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 elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

13.2.8. COVID-19

Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded as AEs.

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 ClinBase™.

If any SAE occurs in the course of the study, then the Investigator 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 Investigator to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry site

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

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

The Investigator 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 for the AstraZeneca drug.

13.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC, and Investigators.

For all studies, except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to the Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IEC, if appropriate according to local requirements.

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 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 CSP 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 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. LIST OF REFERENCES

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. American College of Physicians; American Physiological Society. 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 and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids 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-S19.

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 Verinurad Investigator's Brochure, Edition 3, dated 01 November 2019.

16 European Medicines Agency. Guidance on the Management of clinical trials during the COVID-19 (Coronavirus) pandemic, Version 3, dated 28 April 2020. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

17 Food and Drug Administration; FDA Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency, dated March 2020, updated on 16 April 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

18 Summary of Product Characteristics - Allopurinol 300 mg Tablets. Revision date: 17 December 2018 [cited 25 Oct 2019]. Available from: https://www.medicines.org.uk/emc/product/6006/smpc

19 ICH Harmonised Tripartite Guideline E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. May 2005 [cited 25 Oct 2019]. Available from: https://database.ich.org/sites/default/files/E14_Guideline.pdf

20 E14 Implementation Working Group, ICH guideline E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non antiarrhythmic drugs - Questions and Answers(R3). December 2015 [cited 25 Oct 2019]. Available from: https://database.ich.org/sites/default/files/E14_Q%26As_R3_Q%26As.pdf

21 Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-97.

22 European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 Rev. 1. Feb 2018 [cited 07 Nov 2019]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

23 Health Canada. Guidance Document - Guide for the analysis and review of QT/QTc interval data. Mar 2010 [cited 25 Oct 2019]. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/qtqtc/qt_review_examen-eng.pdf

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