A Randomised, Single-dose, 3-period, 3-treatment, Crossover Study to Assess the Relative Bioavailability of 2 Different Formulations of Verinurad and Allopurinol in Healthy Subjects

ClinicalTrials.gov Identifier: NCT04550234

Original Protocol: 24 June 2020 (Version 1.0)
Amendment 1: 22 Feb 2021 (Version 2.0)

Clinical Study Protocol

A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 4 Different Formulations of Verinurad and Allopurinol in Healthy Subjects

Parexel Study No.:	PXL252258
Sponsor Study Code:	D5495C00014
EudraCT No:	2020-002720-36
Study Type:	Bioavailability
Test/Reference Product:	Verinurad/allopurinol FDC capsule 12/300 mg Verinurad prolonged release gelatin capsule 12 mg Verinurad prolonged release HPMC capsule 12mg Allopurinol tablet 300mg
Therapeutic Indication:	Chronic kidney disease
Pharmacological Class:	URAT1 inhibitor Xanthine oxidase inhibitor
Development Phase:	Phase 1
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel International GmbH PPD 14050 Berlin Germany
Date of Protocol:	Final 1.0, 24 June 2020
Protocol Amendment No. 1	Final, 22 February 2021

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

PROTOCOL AMENDMENTS

Protocol Amendment No. 1, dated 22 February 2021

The original protocol, Clinical Study Protocol Final 1.0 dated 24 June 2020, was amended for the following reasons:

- To have in the same study the relative bioavailability of verinurad, allopurinol, and its metabolite (oxypurinol) of both fixed-dose combinations (FDC, ie, verinurad/allopurinol FDC capsule 12/300 mg) and free combinations of verinurad (ie, verinurad prolonged release hydroxypropyl methylcellulose [HPMC] capsule 12 mg) and allopurinol (ie, allopurinol tablet 300 mg) tested under both fasted and fed conditions. Therefore, a fourth treatment period was added to evaluate the free combination formulations under fed conditions.
- Another capsule formulation containing only verinurad (verinurad prolonged release gelatin capsule 12 mg) will be administered under fasted conditions. Consequently, with the addition of Treatment 4 and Treatment 5, the sample size was increased to 25 randomized subjects to enable 20 evaluable subjects.
- To learn more about the pharmacokinetics (PK)-pharmacodynamics (PD) relationship of verinurad and allopurinol. Therefore, measurements of serum uric acid (sUA) were added as PD outcome measures. Consequently, the admission to the study site has been shifted from Day -1 to Day -2.
- To update the naming of the study drug for uniform naming of the different formulations.
- To implement corrections or clarifications of some study procedures.

The following sections were updated to reflect the addition of Treatment 4 (ie, verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free formulation combination, fed state) and Treatment 5 (ie, verinurad prolonged release gelatin capsule 12 mg, fasted state):

- Title Page (Study Title), Protocol Synopsis (Study Title, Study Design), Section 3.1 (Overall Study Design and Flow Chart), Study Flow Chart (Figure 3-1), Section 5.4.3 (Dose and Treatment Regimens): Changed text from ‘3-period, 3-treatment’ to ‘5-period, 5-treatment’, from ‘3 single-dose treatments’ to ‘5 single-dose treatments’, and from ‘Three/3 treatment periods’ to ‘Five/5 treatment periods’, where applicable.
- Protocol Synopsis (Secondary Study Objectives), Section 2.2 (Secondary Objectives): Added evaluation of Treatment 4 and Treatment 5 to objectives.
- Protocol Synopsis (Study Rationale), Section 1.3 (Rationale for Conducting this Study), Section 3.2.1 (Rationale for Study Design), Section 5.4.3 (Dose and Treatment Regimens): Added wording ‘in fasted and fed conditions’.
- Protocol Synopsis (Study Design, Investigational Medicinal Product), Section 3.1 (Overall Study Design and Flow Chart), Study Flow Chart (Figure 3-1), Section 5.4.1 (Table 5-1), Section 5.4.3 (Dose and Treatment Regimens): Added description of Treatment 4 and Treatment 5.

- Protocol Synopsis (Expected Duration of the Study), Section 3.1.3 (Expected Duration of the Study): Updated study duration from '46 to 53 days' to '52 to 59 days' to reflect the addition of Treatment Period 4 and Treatment Period 5.
- Protocol Synopsis (Number of Subjects Planned, Study Design, Sample Size Determination), Section 3.1 (Overall Study Design and Flow Chart), Section 5.1.1 (Procedures for Randomisation), Section 11.4 (Determination of Sample Size): Revised text of randomised subjects from '15' to '25' and evaluable subjects from '12' to '20'. Revised text of treatment sequences to reflect the addition of Treatment 4 and Treatment 5.
- Section 3.1 (Overall Study Design and Flow Chart): Added Treatment Period 4 and 5 (text box Figure 3-1, table heading Table 3-1). Added description of Treatment 4 and Treatment 5 in footnote (Figure 3-1). Updated definition of the residential period in footnotes (Table 3-1, Figure 3-1).
- Section 5.1.1 (Procedures for Randomisation): Updated randomisation ratio from '1:1:1' to '1:1:1:1:1'. Updated text for reference capsule and tables to include mention of Treatment 4 and Treatment 5.
- Protocol Synopsis (Presentation and Analysis of Pharmacokinetic Data), Section 11.2.7 (Inferential Statistical Analysis of Pharmacokinetic Data): Added text with regard to comparisons of relative bioavailability of the 5 treatments.
- Section 10.1.1 (Adverse Events): Added text with regard to assignment of adverse events to Treatment Period 4 and Treatment Period 5.

The following sections were updated to reflect the addition of measurement of sUA:

- Protocol Synopsis (Secondary Objectives, Statistical Methods), Section 2.2 (Secondary Objectives): Added new secondary objective and corresponding outcome measures, concerning PD of verinurad and allopurinol.
- Protocol Synopsis (Study Design), Section 3.1 (Overall Study Design and Flow Chart), Study Flow Chart (Figure 3-1), Schedule of Assessments (Table 3-1), Section 4.2 (Restrictions During the Study), Section 10.1.2 (Laboratory Assessments): Admission changed from 'Day -1' to 'Day -2'; some of the assessments that were previously scheduled for Day -1 of Treatment Period 1 were moved to Day -2 (Table 3-1).
- Protocol Synopsis: Added headings and text for 'Pharmacodynamic Endpoints' and 'Presentation and Analysis of Pharmacodynamic Data'.
- Section 3.1 (Overall Study Design and Flow Chart), Section 5.4.3 (Dose and Treatment Regimens): Revised text concerning the start of expected water intake from 'Day -1' to 'Day -2', due to change in admission.
- Schedule of Assessments (Table 3-1): Added assessment of sUA on Day -1 (Treatment Period 1) and Days 1 to 4 of each treatment period.
- Section 3.1.1 (Order of Assessments): Added PD and safety blood sampling.
- Section 3.2.1 (Rationale for the Study Design), Total Blood Volume (Table 7-1): Added sUA sample time, volume and number, updated sample numbers, updated total blood volume.

- Section 10.1.1 (Laboratory Assessments): Revised definition of baseline for laboratory assessments due to change in admission.
- Added Section 6.5 (Pharmacodynamics), Section 7.2.3 (Pharmacodynamic Samples): Added collection of the samples.
- Added Section 10.3 (Pharmacodynamic Parameters), Section 11.1.3 (Pharmacodynamic Analyses Set), and Section 11.2.8 (Presentation and Statistical Analysis of Pharmacodynamic Data): Added presentation and analysis of the sUA data.

The following sections were updated for correction or clarification:

- Protocol Synopsis (Targeted Study Population, Outcome Endpoints, Sample Size Determination), Section 11.4 (Determination of Sample Size): Added justification of sample size determination.
- List of Abbreviations updated according to updated text.
- Investigators and Study Administrative Structure: Telephone number for adverse event reporting was updated, details for Sponsor's lead physician was updated.
- Study Flow Chart (Figure 3-1): Removed text 'Admission Day -1' from text box of Treatment Period 3.
- Schedule of Assessments (Table 3-1): Corrected placement of marks 'X' that indicate assessment time points of tympanic temperature.
- Schedule of Assessments (Table 3-1), Section 4.2 (Restrictions During the Study), Section 10.1.2 (Laboratory Assessments): Added footnote that SARS-CoV-2 tests can be done unscheduled at the discretion of the investigator.
- Section 4.1.2: Added exclusion of subjects who had or planned to have the COVID-19 vaccination within 4 weeks prior to screening or during the study.
- Section 5.4.2 (Supply of Investigational Medicinal Product): Updated supply of IMP to bulk bottles with open labels.
- Section 0 (FDA Breakfast Menu): Corrected weight of hash-browned potatoes from '112 g' to '120 g'.
- Section 5.7 (Discontinuation of Investigational Product and Withdrawal from Study): Revised the wording 'drug-related' to 'IMP-related' to indicate a potential relationship with verinurad as well as allopurinol.
- Section 11.2.6 (Presentation of Pharmacokinetic Parameter Data): Removed the word 'period' from 'by treatment period'. Deleted reference to specific version of CPE TFL Corporate CSRHLD reporting standards, to cover if later version is used.
- Throughout: The terms 'Test' and 'Reference' were removed to avoid confusion with 'Test product' and 'Reference product'.

The following sections were updated for uniform naming of the different formulations:

- Title Page (Test/Reference Product), Synopsis (Study Rationale, Primary and Secondary Study Objectives, Study Design, Investigational Medicinal Product, Statistical Methods),

Section 1.3 (Rational for Conducting the Study). Section 2 (Study Objectives). Section 3.1 (Overall Study Design and Flow Chart), Section 3.2.1 (Rationale for Study Design), Section 5.1.1(Procedures for Randomisation), Section 5.4.1 (Table 5-1), Section 11.2.7 (Inferential Statistical Analysis of Pharmacokinetic Data): Updated the current study drug names to the proposed names for the clinical program as per below table.

Previous name in protocol	Proposed full name
12 mg verinurad ph2b capsule	Verinurad prolonged release HPMC capsule 12mg
N/A	Verinurad prolonged release gelatin capsule 12mg
12 mg verinurad + 300 mg allopurinol ph3 fixed-dose combination capsule	Verinurad/allopurinol FDC capsule 12/300 mg
300 mg allopurinol ph2b tablet	Allopurinol tablet 300mg

N/A: not applicable

In addition, the study period has been updated and some minor editorial and formatting changes were made.

PROTOCOL SYNOPSIS

Title of the Study
A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 4 Different Formulations of Verinurad and Allopurinol in Healthy Subjects.

Principal Investigator (PI)
Thomas Körnicke, MD

Study Centre
This study will be conducted at the Parexel Early Phase Clinical Unit Berlin.

Study Rationale
This study is intended to assess the relative bioavailability between the fixed-dose combination (FDC, ie, verinurad/allopurinol FDC capsule 12/300 mg) and free combination formulations of verinurad (ie, verinurad prolonged release HPMC capsule 12 mg) and allopurinol (ie, allopurinol table 300 mg) in fasted and fed conditions. The study will also assess the relative bioavailability between a formulation only containing verinurad (ie, verinurad prolonged release gelatin capsule 12 mg) and the FDC capsule. For verinurad, all formulations have prolonged release profile. For allopurinol, both formulations containing alopurinol have an immediate release profile.

Number of Subjects Planned
Twenty-five subjects will be randomised into this study to ensure at least 20 evaluable subjects complete the study.

Study Period
Estimated date of first subject enrolled: 2nd quarter of 2021 (signing of informed consent)
Estimated date of last subject completed: 3rd quarter of 2021

Study Objectives
The objectives of the study are:
Primary Objective:

- To evaluate the relative bioavailability of verinurad, allopurinol and oxypurinol after dosing with the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release hydroxypropyl methylcellulose [HPMC] capsule 12 mg) and allopurinol (allopurinol tablet 300 mg), under fasted conditions.

Secondary Objectives:

- To evaluate the relative bioavailability of verinurad, allopurinol and oxypurinol after dosing with the verinurad/allopurinol FDC capsule 12/300 mg under fed and fasted conditions and with free combination formulations (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg), under fed and fasted conditions.

- To evaluate the relative bioavailability of verinurad after dosing with the verinurad prolonged release gelatin capsule 12 mg and verinurad/allopurinol FDC capsule 12/300 mg under fasted conditions.
- To assess the pharmacokinetic profiles of verinurad, allopurinol and oxypurinol when administered as the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg) under fed and fasted conditions and of verinurad when administered as a prolonged release gelatin capsule 12 mg under fasted conditions.
- To assess the safety of single doses of verinurad and allopurinol.
- To assess the PD of verinurad, allopurinol and oxypurinol when administered as the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg) under fed and fasted conditions and of verinurad when administered as a prolonged release gelatin capsule 12 mg under fasted conditions.

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

- A Screening Period of maximum 28 days.
- Five treatment periods during which subjects will be resident from the morning of Day -2 until at least 72 hours after dosing in Treatment Period 5; discharged on the morning of Day 4 of Treatment Period 5.
- A Follow-up Visit 7 to 14 days after the last dosing.

There will be a minimum washout period of 5 days between each dose administration.
A total of 25 healthy male and female subjects will be randomised into one of 5 treatment sequences. Each subject will receive 5 single-dose treatments of verinurad and allopurinol or verinurad alone:

- Treatment 1: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state.
- Treatment 2: verinurad/allopurinol FDC capsule 12/300 mg, fasted state.
- Treatment 3: verinurad/allopurinol FDC capsule 12/300 mg, fed state.
- Treatment 4: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state.
- Treatment 5: verinurad prolonged release gelatin capsule 12 mg, fasted state.

Expected Duration of the Study
Each subject will be involved in the study for 52 to 59 days.

Targeted Study Population
This study will be conducted in healthy male and female subjects, 18 to 50 years of age.

Investigational Medicinal Product

Supplier:	AstraZeneca
Formulations:	Verinurad prolonged release HPMC capsule 12 mg Verinurad prolonged release gelatin capsule 12 mg Verinurad/allopurinol FDC capsule 12/300 mg Allopurinol tablet 300 mg
Strength/concentration:	Verinurad: 12 mg Allopurinol: 300 mg
Dose:	Verinurad: 12 mg Allopurinol: 300 mg
Route of administration:	Oral
Specific device for drug administration, if applicable:	Not applicable
Regimen:	Treatment 1: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state Treatment 2: verinurad/allopurinol FDC capsule 12/300 mg, fasted state Treatment 3: verinurad/allopurinol FDC capsule 12/300 mg, fed state Treatment 4: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state Treatment 5: verinurad prolonged release gelatin capsule 12 mg, fasted state

Outcome Endpoints

Safety and Tolerability Endpoints:

Safety and tolerability variables will include:

- Adverse events (AEs)
- Laboratory assessments (haematology, clinical chemistry and urinalysis).
- Physical examination
- Electrocardiogram (ECG)
- Vital signs (systolic and diastolic blood pressure, pulse, tympanic temperature)

Pharmacokinetic Endpoints:

The pharmacokinetic (PK) parameters will be determined for verinurad, allopurinol and oxypurinol using plasma concentrations.

- Primary PK parameters:
  - Area under plasma concentration-time curve from time zero to infinity (AUCinf)
  - Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUClast)
  - Maximum observed plasma (peak) drug concentration (Cmax)
- Secondary PK parameters:

- Time to reach maximum observed plasma concentration following drug administration (tmax)
- Time delay between drug administration and the first observed concentration in plasma (tlag)
- Terminal elimination rate constant (λz)
- Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve ($t_{½}λz$)
- Mean residence time of the unchanged drug in the systemic circulation from zero to infinity (parent drug only) (MRTinf)
- Apparent total body clearance of drug from plasma after extravascular administration (parent drug only) (CL/F)
- Apparent volume of distribution during the terminal phase after extravascular administration (parent drug only) (Vz/F)
- Volume of distribution (apparent) at steady state following extravascular administration (parent drug only) (Vss/F)

Additional PK parameters may be determined where appropriate.

Pharmacodynamic Endpoints:
The following PD variables will be assessed:

- Observed values and percentage change from baseline (CB) (time-matched, Day -1) in sUA concentrations at each time point up to and including 72 hours following administration of verinurad and allopurinol in each treatment period
- Emax, CB: Maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose
- tEmax, CB: Time of maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose

Statistical Methods
Presentation and Analysis of Safety and Eligibility Data:
All safety data will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment. 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.
Adverse events will be summarised by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities vocabulary.
Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs (listings only) will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

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

Presentation and Analysis of Pharmacokinetic Data:
Pharmacokinetic parameters will be summarised for each treatment using descriptive statistics. The descriptive statistics may include: n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum and maximum. For tmax, only n, median, minimum and maximum will be presented.
The geometric mean ratios of Cmax, AUCinf and AUClast will be calculated for each treatment comparison (Test treatment versus Reference treatment). Analyses will be performed using a linear mixed-effects analysis of variance model using the natural logarithm of Cmax, AUCinf and AUClast as the response variables, sequence, period and treatment as mixed-effects, subject nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for Cmax, AUCinf and AUClast will be calculated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented. Additionally, the 90% CI for the difference in tmax will be calculated and presented.
The following comparisons of relative bioavailability (Cmax, AUCinf and AUClast) for each analyte (verinurad, allopurinol and oxypurinol) will be performed:

- Treatment 2 versus Treatment 1, ie, “verinurad/allopurinol FDC capsule, fasted” versus “verinurad HPMC capsule and allopurinol tablet, free combination, fasted”.
- Treatment 3 versus Treatment 2, ie “verinurad/allopurinol FDC capsule, fed” versus “Verinurad/allopurinol FDC capsule. fasted”.
- Treatment 4 versus Treatment 1, ie. “verinurad HPMC capsule and allopurinol tablet, free combination, fed” versus “verinurad HPMC capsule and allopurinol tablet, free combination, fasted”.
- Treatment 3 versus Treatment 4, ie. “verinurad/allopurinol FDC capsule, fed” versus “verinurad HPMC capsule and allopurinol tablet, free combination, fed”.
- Treatment 5 versus Treatment 2 (for verinurad only), ie., “verinurad gelatin capsule, fasted” versus “verinurad/allopurinol FDC capsule, fasted”.

Presentation and Analysis of Pharmacodynamic Data:
Analyses of sUA will be based on log-transformed values (natural logarithm). Descriptive statistics will be presented for sUA observed and time-matched percentage change from baseline, Emax CB and tEmax CB by treatment. For observed and time-matched percentage change from baseline, the descriptive statistics will include n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum, and maximum. A listing of sUA sample collection times, as well as derived sampling time deviations will be provided.

Sample Size Determination
The sample size was chosen to obtain a reasonable assessment of relative bioavailability between different formulations of verinurad and allopurinol without exposing undue numbers of subjects to the compound at this phase of clinical development. It is estimated that 20 subjects randomised to 5 sequences in a reduced Latin square will provide a 90% CI within 0.7 and 1.43,

with a probability of > 90% if the estimated treatment ratio is 1 for Cmax. This is based on an intra-subject variability of 24% for Cmax of verinurad in Study D5495C00001. Similarly, it is estimated that 20 subjects will provide a 90% CI within 0.8 and 1.25, with a probability of > 95% if the estimated treatment ratio is 1 for AUC. This is based on an intra-subject variability of 14.7% for AUC of verinurad in Study D5495C00001.

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf
AUCinf	Area under plasma concentration-time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AV	Atrioventricular
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (The Federal Institute for Drugs and Medical Devices)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CB	Change from baseline
CI	Confidence interval
CKD	Chronic Kidney Disease
CL/F	Apparent total body clearance of drug from plasms after extravascular administration (parent drug only)
ClinBase™	Parexel's electronic source data capturing and information management system
Cmax	Maximum observed plasma (peak) drug concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DMP	Data management plan
DNA	Deoxyribonucleic acid
DRESS	Drug rash with eosinophilia and systemic symptoms

Abbreviation or special term	Explanation
DVS	Data validation specification
ECG	Electrocardiogram
eGRF	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
Emax, CB	Maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose
ER	Extended-release
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GGT	Gamma glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
gSD	Geometric standard deviation
Hb	Haemoglobin
HbsAg	Hepatitis B surface antigen
HCT	Haematocrit
HF	Heart Failure
HIV	Human immunodeficiency virus
HL	Hy's Law
HPMC	Hydroxypropyl methylcellulose
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobin G
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Immediate release
LLOQ	Lower limit of quantification
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MRTinf	Mean residence time of the unchanged drug in the systemic circulation from zero to infinity (parent drug only)
ms	milliseconds
N	Number of subjects
n	Number of data values
NA	Not applicable
NC	Not calculated
ND	Not determined
NQ	Not quantifiable
NR	No result
NS	No sample
OAE	Other significant adverse events
OTC	Over-the-counter
PDF	Portable Document Format
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event (see definition in Section 6.3.1.2).
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SJS	Stevens-Johnson syndrome
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee

Abbreviation or special term	Explanation
sUA	Serum uric acid
SUSAR	Suspected unexpected serious adverse reaction
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
TBL	Total bilirubin
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
tEmax, CB	Time of maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose
TEN	Toxic epidermal necrolysis
TFL	Table, Figure and Listing
tlag	Time delay between drug administration and the first observed concentration in plasma
tlast	Time of last observed (quantifiable) concentration
tmax	Time to reach maximum observed plasma concentration following drug administration
TSH	Thyroid-stimulating hormone
uUA	Urine uric acid
UA	Uric acid
ULN	Upper limit of normal
URAT1	Human urate transporter 1
US	United States
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration (parent drug only)
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration (parent drug only)
WAD	Windows Allowance Document
WBC	White blood cell
WHO	World Healthy Organisation
XO	Xanthine oxidase
XOI	Xanthine oxidase inhibitor
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
λz upper	Upper (later) t used for λz determination

Abbreviation or special term	Explanation
λzN	Number of data points used for λz determination

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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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 CSR.

1. INTRODUCTION

1.1. Background Information

Verinurad is a novel URAT1 inhibitor being developed by AstraZeneca to treat patients with CKD and/or HF. By inhibiting URAT1, verinurad prevents UA reabsorption, increases renal UA excretion, and thereby lowers sUA concentrations [1].

The initial development focus for verinurad was for the treatment of gout, which is caused by hyperuricaemia. Therefore, the initial clinical data accumulated on verinurad relate to gout. However, hyperuricaemia is also associated with an increased risk of CKD [2, 3, 4, 5] and HF [6, 7, 8] providing a rationale for developing verinurad in these indications. Despite the established association between hyperuricaemia and CKD and HF, a causal relationship between them remains to be proven.

Potent URAT1 inhibition has been associated with creatinine elevations in a fraction of patients, likely related to increased UA peak concentrations in the proximal tubuli of the kidney. Verinurad is to be developed exclusively in FDC with the XOI, allopurinol, thus also reducing the production of UA and thereby mitigating the risk of creatinine elevations.

The IB describes results from pre-clinical studies, clinical pharmacological studies, and clinical monotherapy and combination therapy with allopurinol [1].

1.1.1. Description of Verinurad

Verinurad 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.

1.1.1.1. 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 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 ([AUC] and Cmax) of verinurad increased in a dose proportional manner and the accumulation was minimal after once daily dosing. Subjects with an eGFR of 45 and 60 mL/min/1.73 m^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/1.73 m^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 PK findings (including PK parameters of the verinurad IR formulation) is available in the IB [1].

1.2. Background to COVID-19

There is currently an outbreak of 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 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 recent 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 EMA [9] and FDA [10], 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. The FDA have also issued guidance to provide recommendations on statistical considerations to address the impact of COVID-19 on meeting trial objectives for clinical trials conducted during the duration of the COVID-19 public health emergency [11]. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at a 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.

1.3. Rationale for Conducting this Study

This study is intended to assess the relative bioavailability between the fixed-dose combination (FDC, ie, verinurad/allopurinol FDC capsule 12/300 mg) and free combination formulations of verinurad (ie, verinurad prolonged release HPMC capsule 12 mg) and allopurinol (ie, allopurinol table 300 mg) in fasted and fed conditions. The study will also assess the relative bioavailability between a formulation only containing verinurad (ie, verinurad prolonged release gelatin capsule 12 mg) and the FDC capsule. For verinurad, all formulations have prolonged release profile. For allopurinol, both formulations containing alopurinol have an immediate release profile.

2. STUDY OBJECTIVES

2.1. Primary Objective

Table 2-1 Primary Objective and Outcome Measures

Primary Objective	Outcome Measures
• To evaluate the relative bioavailability of verinurad, allopurinol and oxypurinol after dosing with the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg), under fasted conditions.	• Primary pharmacokinetic parameters: AUCinf, AUClast and Cmax of verinurad, allopurinol and oxypurinol

2.2. Secondary Objectives

Table 2-2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
• To evaluate the relative bioavailability of verinurad, allopurinol and oxypurinol after dosing with the verinurad/allopurinol FDC capsule 12/300 mg under fed and fasted conditions and with free combination formulations (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg), under fed and fasted conditions	• Primary pharmacokinetic parameters: AUCinf, AUClast and Cmax of verinurad, allopurinol and oxypurinol
• To evaluate the relative bioavailability of verinurad after dosing with the verinurad prolonged release gelatin capsule 12 mg and verinurad/allopurinol FDC capsule 12/300 mg under fasted conditions	• Primary pharmacokinetic parameters: AUCinf, AUClast and Cmax of verinurad, allopurinol and oxypurinol
• To assess the pharmacokinetic profiles of verinurad, allopurinol and oxypurinol when administered as the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg) under fed and fasted conditions and of verinurad when administered as a prolonged release gelatin capsule 12 mg under fasted conditions	• Plasma concentration-time profiles of verinurad, allopurinol and oxypurinol. • Primary pharmacokinetic parameters: AUCinf, AUClast and Cmax of verinurad, allopurinol and oxypurinol • Secondary pharmacokinetic parameters: tmax, tlag, λz, t½λz, CL/F, MRTinf, Vss/F, and Vz/F of verinurad, allopurinol and oxypurinol
• To assess the safety of single doses of verinurad and allopurinol	• Adverse events, vital signs (systolic and diastolic blood pressure, pulse, tympanic temperature), resting 12-lead electrocardiograms, physical examination, and laboratory assessments (haematology, clinical chemistry and urinalysis)

Secondary Objectives	Outcome Measures
• To assess the PD of verinurad, allopurinol and oxypurinol when administered as the verinurad/allopurinol FDC capsule 12/300 mg and free combination formulations of verinurad (verinurad prolonged release HPMC capsule 12 mg) and allopurinol (allopurinol tablet 300 mg) under fed and fasted conditions and of verinurad when administered as a prolonged release gelatin capsule 12 mg under fasted conditions	• Observed values and percentage CB (time-matched, Day -1) in sUA concentrations at each time point up to and including 72 hours following administration of verinurad and allopurinol (verinurad only for Treatment 5) in each treatment period • Emax, CB: Maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose • tEmax, CB: Time of maximum percentage CB (time-matched, Day -1) in sUA concentration up to and including 72 hours post-dose

Refer to Section 6.4.1 for collection of PK samples and Section 6.3 for safety assessments.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

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

The study will comprise:

- A Screening Period of maximum 28 days.
- Five treatment periods during which subjects will be resident from the morning of Day -2 until at least 72 hours after dosing in Treatment Period 5; discharged on the morning of Day 4 of Treatment Period 5.
- A Follow-up Visit 7 to 14 days after the last dosing.

There will be a minimum washout period of 5 days between each dose administration.

A total of 25 healthy male and female subjects will be randomised into one of 5 treatment sequences to ensure at least 20 evaluable subjects at the end of the last treatment period. Each subject will receive 5 single-dose treatments of verinurad and allopurinol or verinurad alone:

- Treatment 1: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state.
- Treatment 2: verinurad/allopurinol FDC capsule 12/300 mg, fasted state.
- Treatment 3: verinurad/allopurinol FDC capsule 12/300 mg, fed state.
- Treatment 4: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state.
- Treatment 5: verinurad prolonged release gelatin capsule 12 mg, fasted state.

All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day, starting on Day -2 and throughout the stay at the clinic.

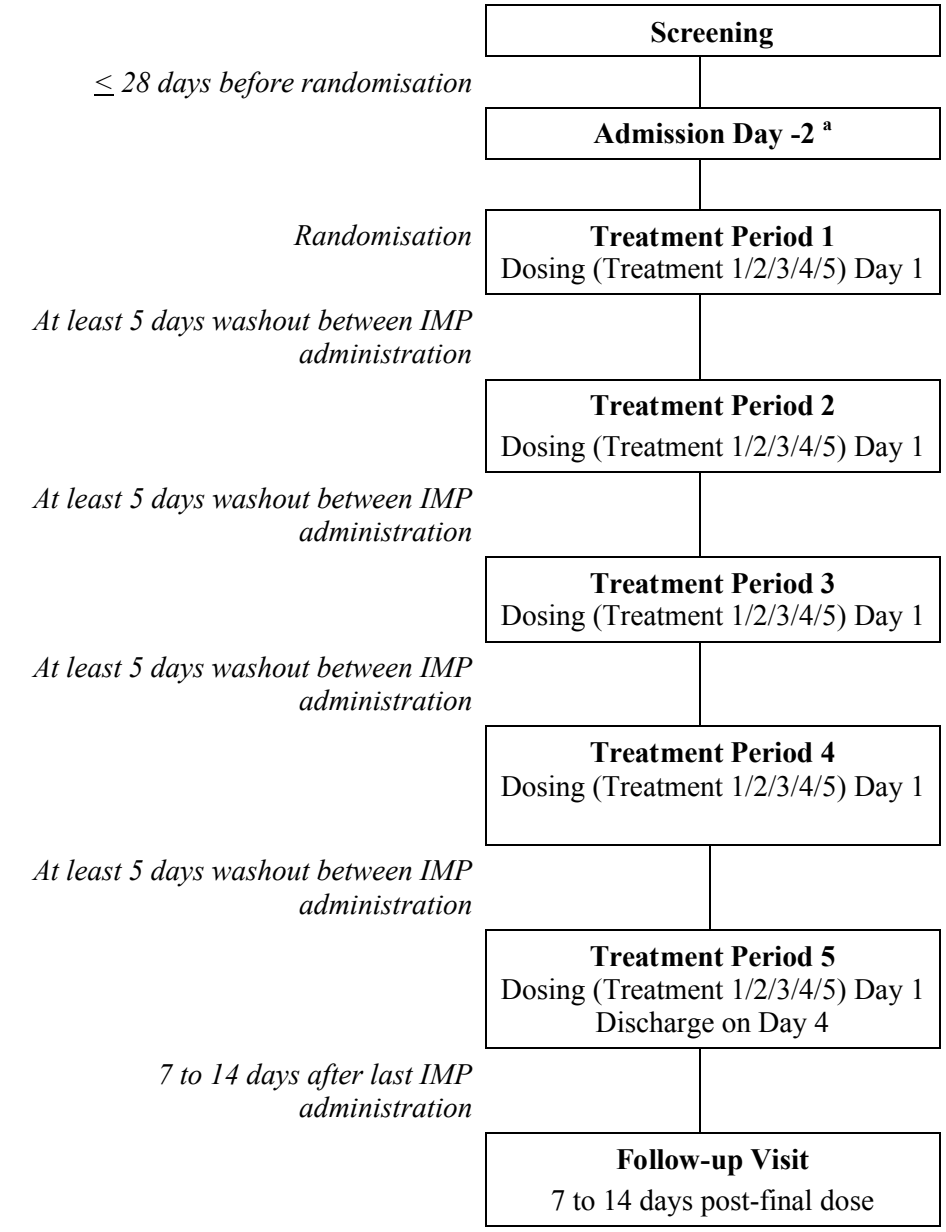
Subjects will follow an overnight fast of at least 10 hours before the dosing procedures: for the fed dosing, a high-fat, high-calorie breakfast (see Section 0) will be served 30 minutes before the planned administration of IMP, and is to be consumed in full at least 5 minutes before dosing; for the fasted dosing, no breakfast will be served. A meal can be given 4 hours after administration of IMP for both dosing states.

Details on IMP administration and food and fluid restrictions in relation to IMP administration are provided in Section 5.4.3.

The study flow-chart is presented in Figure 3-1. The SoA displaying assessments/tasks and time-points is presented in Table 3-1.

The study design is deemed appropriate for conduct in healthy volunteers during the COVID-19 pandemic (Section 3.3.3).

Figure 3-1 Study Flow Chart



Treatment 1: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state.
Treatment 2: verinurad/allopurinol FDC capsule 12/300 mg, fasted state.
Treatment 3: verinurad/allopurinol FDC capsule 12/300 mg, fed state.
Treatment 4: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state.
Treatment 5: verinurad prolonged release gelatin capsule 12 mg, fasted state.
IMP: Investigational Medicinal Product.

Table 3-1 Schedule of Assessments

	Screening	Admission	Treatment Periods 1, 2, 3, 4, and 5		Follow-up Visit	Corresponding Section in Protocol
Visit	**1**	**2**			**3**	
Study Day	**Day -28 to -3**	**Day -2**	**Day -1**	**Day 1 to 4**	**7 to 14 days post final dose**	
Inclusion/exclusion criteria	X	X	X [a]			Sections 4.1.1 and 4.1.2
Demographic data	X					Section 11.2.3.1
Medical history	X					Section 11.2.3.1
Urinary drug/alcohol/cotinine screen	X	X				Section 6.3.2.8
Serology	X					Section 6.3.2.6
Informed consent	X					Section 8.5
HLA-B*58:01 allele genotyping	X					Section 6.3.2.3
Randomisation			X [b]			Section 5.1.1
Study Residency: Check-in		X (in the morning) [c]				Section 3.1
Check-out				Day 4 (after 72 h post-dose assessments) [c]		Section 3.1
Non-residential visit	X				X	Section 3.1
Verinurad and Allopurinol (verinurad only for Treatment 5) **Administration:**				Day 1 (0 h)		Sections 3.1 and 5.4.3

	Screening	Admission	Treatment Periods 1, 2, 3, 4, and 5		Follow-up Visit	Corresponding Section in Protocol
Visit	**1**	**2**			**3**	
Study Day	**Day -28 to -3**	**Day -2**	**Day -1**	**Day 1 to 4**	**7 to 14 days post final dose**	
Safety and Tolerability:						
Tympanic temperature [d]	X	X	X [e]	X	X	Section 6.3.5
Adverse event questioning and reporting [f]	X	X	X [e]	Spontaneous plus Day 1: pre-dose, 3 and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose	X	Section 6.3.1
Prior and concomitant medications questioning	X	X	X [e]	X	X	Section 11.2.4.1
Blood pressure and pulse (supine)	X	X	X [e]	Day 1: Pre-dose Day 4: 72 h post-dose	X	Section 6.3.5
Safety 12-lead electrocardiograms	X				X	Section 6.3.4
Clinical laboratory evaluations [g]	X	X	X [e]		X	Section 6.3.2
Physical examination	X	X (brief)	X (brief) [e]	Day 4: 72 h post-dose (brief)	X	Section 6.3.3
Body weight and height, BMI	X					
Pregnancy test [h]	X	X			X	Section 6.3.2.5
COVID-19 Assessments						
Pre-visit phone call [i]	X	X			X	
SARS-CoV-2 RT-PCR		X [j]				Section 6.3.2.7
SARS-CoV-2 antibody	X					Section 6.3.2.7

	Screening	Admission	Treatment Periods 1, 2, 3, 4, and 5		Follow-up Visit	Corresponding Section in Protocol
Visit	**1**	**2**			**3**	
Study Day	**Day -28 to -3**	**Day -2**	**Day -1**	**Day 1 to 4**	**7 to 14 days post final dose**	
Pharmacokinetics						
Pharmacokinetic sampling for verinurad, allopurinol and oxypurinol [k]				Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h post-dose Day 2: 24 and 36 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose		Section 6.4.1
Pharmacodynamics						
Pharmacodynamic sampling for sUA			-24, -23, -22, -21, -20, -19, -18, -16, -14 and -12 h [l]	Day 1: Pre-dose, 1, 2, 3, 4, 5, 6, 8, 10 and 12 h post-dose Day 2: 24 h, Day 3: 48 h post-dose, Day 4: 72 h post-dose h post-dose		Section 6.5.1

[a] Eligibility criteria will be reconfirmed on Day -1 of Treatment Period 1, prior to randomisation.
[b] Randomisation will take place on Day -1 of Treatment Period 1, after eligibility has been reconfirmed.
[c] Subjects will be admitted to the Clinical Unit on Day -2 and will remain residential until they are discharged on Day 4 of Treatment Period 5.
[d] Tympanic temperature will be measured at least once daily (in the morning) on the days of assessment.
[e] Applicable to Day -1 of Treatment Periods 2 to 5 only.
[f] Adverse events will be collected from the start of randomisation throughout the treatment periods up to and including the Follow-up Visit. Serious adverse events will be recorded from the time of informed consent.
[g] Blood (clinical chemistry and haematology) and urine (urinalysis) sample collection. Samples will be collected following an overnight fast.
[h] Serum pregnancy tests will be performed at Screening. Urine pregnancy test will be performed at admission (Day -2 of Treatment Period 1) and the Follow-up Visit.

[i] 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 the reason for cancellation will be appropriately documented.
[j] At the discretion of the investigator, an unscheduled SARS-CoV-2 RT-PCR can be performed in case of any signs or symptoms of COVID-19.
[k] Samples for allopurinol and oxypurinol will not be collected for Treatment 5.
[l] Applicable to Treatment Period 1 only.

AE: Adverse event; BMI: Body mass index; COVID-19: Coronavirus disease 2019; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; sUA: Serum uric acid.

3.1.1. 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.
2 Vital signs (systolic and diastolic BP, pulse and tympanic temperature).
3 Pharmacokinetic blood sampling (will be drawn at the specified time point).
4 Pharmacodynamic and safety blood sampling.

Details of acceptable window allowance for the timing of safety and PK assessments will be included in a WAD which will be agreed upon and signed off before the start of the study.

3.1.2. End of Study

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

3.1.3. Expected Duration of the Study

Each subject will be involved in the study for 52 to 59 days.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

This study is intended to assess the relative bioavailability between the fixed-dose combination (FDC, ie, verinurad/allopurinol FDC capsule 12/300 mg) and free combination formulations of verinurad (ie, verinurad prolonged release HPMC capsule 12 mg) and allopurinol (ie, allopurinol table 300 mg) in fasted and fed conditions. The study will also assess the relative bioavailability between a formulation only containing verinurad (ie, verinurad prolonged release gelatin capsule 12 mg) and the FDC capsule. For verinurad, all formulations have prolonged release profile. For allopurinol, both formulations containing alopurinol have an immediate release profile.

Assessment of PD parameters will be done in a time-matched manner, to account for the diurnal effect of sUA.

3.2.2. Dose Rationale

Currently, the highest strength (12 mg) of the formulation being used in ongoing Phase 2 studies development of verinurad will be tested in this study. In Phase 2b, 300 mg allopurinol is given together with verinurad and is the planned dose of allopurinol in the verinurad/allopurinol FDC product.

3.3. 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. Subjects may experience slight skin irritation from the adhesive on the ECG electrodes. These procedural effects are generally mild and clear up completely within a few days.

The main toxicity concern noted with verinurad monotherapy in healthy subjects is serum 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 serum creatinine elevations and dose of verinurad. The creatinine elevations were primarily transient, and often resolved despite continued dosing with verinurad. In order to mitigate the risk in this study verinurad is administered with an XOI, except for Treatment 5, and appropriate hydration is mandated. Further information is provided in the IB [1].

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 noted 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 DRESS) and SJS/TEN. The 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 [1].

Overall, the study has been designed to minimise 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 CKD with hyperuricemia, therefore, outweigh the limited risks to the subjects exposed to verinurad and allopurinol single doses in this study.

3.3.1. Verinurad

3.3.1.1. Non-clinical Findings

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

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

Further information on non-clinical findings is available in the IB [1].

3.3.1.2. Clinical Studies

As of 01 May 2020, 19 clinical studies have been completed with verinurad, 12 Phase 1 studies and 7 Phase 2 studies. In these studies, verinurad was administered either as monotherapy or in combination with an XOI (allopurinol or febuxostat), and the studies were conducted in healthy subjects, in subjects with renal impairment, in patients with gout or asymptomatic hyperuricaemia, and in patients with diabetes and albuminuria [1].

Verinurad was initially developed as a treatment for gout. Therefore, the first Phase 2 studies recruited patients with gout or asymptomatic hyperuricemia and did not include renal endpoints such as albuminuria and eGFR. Nevertheless, they provide a body of data on the PD effects of verinurad (with and without concomitant XOI therapy) on sUA concentrations. Subsequent clinical studies incorporated renal endpoints [1].

3.3.2. 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 oxypurinol inhibit production of and thus lower the level of sUA.

Please refer to the product information sheet of allopurinol tablets [12] for information on PK, PD, and safety.

3.3.3. Risk Assessment for COVID-19 Pandemic

Verinurad is a potent and specific URAT1 inhibitor. Allopurinol is a well-known drug to treat hyperuricemia. The COVID-19 pandemic is not expected to impact the risk in this healthy volunteer study.

Therefore, the risk of the subjects being exposed to SARS-CoV-2 or suffering 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 start enrolling only when the Sponsor and 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 tympanic 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 face 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.

4. STUDY POPULATION

4.1. Selection of Study Population

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

Subjects who fail to meet 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. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

4.1.1. Inclusion Criteria

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

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Healthy male and female subjects aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venepuncture.

3 Have a body mass index between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive).

4 Females must have a negative pregnancy test at screening and on admission to the unit and must be:
   (1) not pregnant or currently lactating or breastfeeding.
   (2) of non-childbearing potential (as defined in Section 4.2.1.1), confirmed at screening by fulfilling one of the following criteria:
      (i) postmenopausal defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range (FSH levels > 40 IU/mL).
      (ii) documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
   (3) OR if of childbearing potential (as defined in Section 4.2.1.2) must be willing to use an acceptable method of contraception (as described in Section 4.2.1.2) to avoid pregnancy for the entire study period.

5 Must be able to swallow multiple capsules and tablets.

4.1.2. Exclusion Criteria

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

1 History of gout or any clinically significant disease or disorder which, in the opinion of the PI, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study.

2 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of verinurad.

3 History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

4 Any clinically important abnormalities in clinical chemistry, haematology or urinalysis results as judged by the Investigator at screening and first admission, including:
   (1) Alanine aminotransferase > 1.5 × ULN,
   (2) Aspartate aminotransferase > 1.5 × ULN,
   (3) Bilirubin (total) > 1.5 × ULN,
   (4) Gamma glutamyl transpeptidase > 1.5 × ULN.
   If any of these tests are out-of-range, the tests can be repeated once.

5 Any clinically significant abnormal findings in vital signs at the Screening Visit and/or admission to the Clinical Unit, including, but not limited to, any of the following:
   (1) Pulse (resting, supine) < 50 bpm or > 90 bpm,
   (2) Systolic BP < 90 mmHg or > 140 mmHg and/or diastolic BP < 50 mmHg or > 90 mmHg sustained for > 10 minutes while resting in a supine position.

6 Any clinically significant abnormalities on 12-lead ECG at the Screening Visit, including, but not limited to any of the following:
   (1) QTcF > 450 ms or < 340 ms or family history of long QT syndrome,
   (2) Any significant arrhythmia,
   (3) Conduction abnormalities:
   (4) Clinically significant PR (PQ) interval prolongation (> 240 ms); intermittent second or third degree AV block, or AV dissociation,
   (5) Complete bundle branch block and/or QRS duration > 120 ms.

7 Any positive result at the Screening Visit for serum HbsAg or anti-HBc antibody, hepatitis virus C antibody, and HIV antibody.

8 Suspicion or known Gilbert's and/or Lesch-Nyhan syndrome.

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

10 Has received another new chemical or biological entity (defined as a compound which has not been approved for marketing in the US) within 30 days or at least 5 half-lives (whichever is longer) of the first administration of verinurad in this study.
Note: subjects consented and screened, but not randomised in this study or a previous Phase 1 study, are not excluded.

11 Subjects who have previously received verinurad.

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

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

14 Hypersensitivity to verinurad, allopurinol or any drug with a similar chemical structure/class to verinurad and/or allopurinol.

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

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

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

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

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

20 Any AstraZeneca, Parexel or study site employee or their close relatives.

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

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

23 Vulnerable subjects, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

24 Subjects with any special dietary restrictions such as subjects that are lactose intolerant or are vegetarians/vegans.

25 Subject is a carrier of the HLA-B*58:01 allele.

26 Subject has a positive test result for SARS-CoV-2 RT-PCR before randomisation.

27 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.

28 History of severe COVID-19 (hospitalisation, extracorporeal membrane oxygenation, mechanically ventilated).

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.

30 Subjects who have had or are planning to have the COVID-19 vaccination within 4 weeks prior to screening or at any time during the study.

4.2. Restrictions During the Study

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

1 Subjects should not engage in any strenuous activity from 72 hours prior to check-in (Day -2) until after their Follow-up Visit.

2 Subjects should abstain from alcohol for the duration of the study from check-in (Day -2) 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.

3 Subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to check-in (Day -2) until the Follow-up Visit.

4 Subjects should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) from 7 days prior to check-in (Day -2) until after their Follow-up Visit.

5 During admission periods, subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages (except for water) must be consumed while in the Clinical Unit.

6 During the subjects' outpatient periods, subjects should abstain from consuming, high-energy drinks (eg, red bull), and food containing poppy seeds and any OTC medication or herbal preparations until after their Follow-up Visit has been completed.

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

8 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 food and fluid intake restrictions in relation to dosing please refer to Section 5.4.2.

For medication restrictions, please refer to Section 5.6.

4.2.1. Reproductive Restrictions

4.2.1.1. Women of Non-childbearing Potential

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

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

4.2.1.2. Women of Childbearing Potential

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

- A barrier method must be used in combination with one of the following methods, considered to be highly effective (failure rate < 1% per year when used consistently and correctly):
  - Hormonal contraception, ie, combined oral contraceptives, injectable [*] or implantable [*] hormonal contraceptives.
  - Hormonal or non-hormonal intrauterine device [*] (IUD, loop), established IUD [*] or intrauterine system (Note: The IUD must have a failure rate < 1%).

[*] These methods are considered to have low user dependency

  - Surgical sterilisation [*] (ie, bilateral tubal ligation for females; vasectomy for male partners [must have been vasectomised 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.

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

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

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

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

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 SoA (Table 3-1).

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/or child will be reported to the Sponsor after delivery.

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

[†] *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. 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.*

4.2.1.3. Male Subjects

Restrictions for Male Subjects

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

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

Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 3 months after the study Follow-up Visit.

Pregnancy

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.

4.3. Replacement of Subjects

Subjects who are withdrawn from the study due to AEs or changes in safety variables will not be replaced unless a specific sample size is to be met for statistical purposes and if the Sponsor's responsible physician and the PI agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for suspected or confirmed COVID-19 infection or other reasons may be replaced following discussion with the Sponsor.

5. STUDY CONDUCT

5.1. Subject Enrolment and Randomisation

The PI will ensure:

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

Randomisation will be done on Day -1 of 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 "1001" 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.

5.1.1. Procedures for Randomisation

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

Subjects will be randomised to treatment sequences in a ratio of 1:1:1:1:1 so that all subjects will receive all formulations. The reference product (capsule and tablet as free combination) (Treatments 1 and 4) and the test product (FDC or monotherapy capsule) (Treatments 2 and 3) and a prolonged release gelatin capsule (Treatment 5) will be given under fasted and/or fed conditions as per study design (see Section 3.1).

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 = 25) (see Section 11.4) as well as providing sufficient randomisation numbers for replacements. For this study, a total of

25 × 2 subject identifiers will be randomly assigned to the treatment sequences: 12345, 23451, 34512, 45123, and 51234.

5.2. 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 and has been dosed before the error is identified, the subject should be withdrawn and advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision made as to whether the subject should be replaced.

5.3. Blinding

This is an open-label study and blinding is not applicable.

5.4. TREATMENTS

5.4.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 5-1.

Table 5-1 Identity of the Investigational Medicinal Product

Supplier:	AstraZeneca
Formulations:	Verinurad prolonged release HPMC capsule 12 mg Verinurad prolonged release gelatin capsule 12 mg Verinurad/allopurinol FDC capsule 12/300 mg Allopurinol tablet 300 mg
Strength/concentration:	Verinurad: 12 mg Allopurinol: 300 mg
Dose:	Verinurad: 12 mg Allopurinol: 300 mg
Route of administration:	Oral
Specific device for drug administration, if applicable:	Not applicable

Supplier:	AstraZeneca
Regimen:	Treatment 1: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state Treatment 2: verinurad/allopurinol FDC capsule 12/300 mg, fasted state Treatment 3: verinurad/allopurinol FDC capsule 12/300 mg, fed state Treatment 4: verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state Treatment 5: verinurad prolonged release gelatin capsule 12 mg, fasted state

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

5.4.2. Supply of Investigational Medicinal Product

The IMP will be supplied by AstraZeneca and provided bulk bottles with study specific open labels.

If applicable, 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 Clinical Unit.

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

5.4.3. Dose and Treatment Regimens

Subjects will receive single doses of 4 different formulations of IMP under fasted and fed conditions during the 5 treatment periods.

Subjects will be fasted for 10 hours prior to dosing (or prior to receiving the FDA high-fat, high-calorie breakfast in fed dosing) until 4 hours after dosing on Day 1 of each treatment period. No fluids will be allowed apart from water which can be given until 1 hour prior to dosing and then from 1 hour after dosing, beverages provided with the high-fat, high-calorie breakfast with dosing under fed conditions and water given during administration. The IMP will be administered with 240 mL of water on Day 1 of each treatment period. All subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day, starting on Day -2 and throughout the stay at the clinic.

During fed dosing, subjects will be provided with an FDA high-fat, high-calorie breakfast 30 minutes before the scheduled dosing time (following the overnight fast as above), subjects should consume the breakfast within 25 minutes and finish the breakfast approximately 5 minutes before the scheduled dosing. During the fasted dosing, subjects will remain fasted for dosing. For both dosing states, no food will be allowed for at least 4 hours after dosing.

Following the restrictions above, each subject will receive a single-dose of 4 different formulations of IMP under fasted and/or fed conditions on 5 occasions:

Treatment 1	verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fasted state
Treatment 2	verinurad/allopurinol FDC capsule 12/300 mg, fasted state.
Treatment 3	verinurad/allopurinol FDC capsule 12/300 mg, fed state
Treatment 4	verinurad prolonged release HPMC capsule 12mg and allopurinol tablet 300mg, as a free combination, fed state
Treatment 5	verinurad prolonged release gelatin capsule 12 mg, fasted state

Other restrictions, including posture control are described in Section 4.2. Data of subjects may be excluded from the PK analysis set as described in Section 11.1.2.

5.4.4. FDA Breakfast Menu

The breakfast will constitute the following:

- Two eggs fried in butter
- Two slices of bacon
- One buttered English muffin
- 120 g of hash-browned potatoes
- 240 mL of whole milk

5.4.5. Labelling

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

The labels will fulfil GMP Annex 13 requirements and medical device directive for labelling.

5.4.6. Storage and Handling Procedures

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

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

5.5. 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 PI.

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

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

5.6. Treatment Compliance

Dosing will take place at the 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.

Drug Accountability, Dispensing and Destruction
The IMP provided for this clinical study will be used only as directed in the CSP.

In accordance with GCP, the investigational site will account for all supplies of IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

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

5.7. Discontinuation of Investigational Product and Withdrawal from Study

Dosing for any individual subject must be stopped if the subject experiences a possibly IMP-related SAE or a possibly IMP-related significant non-serious AE, which in the opinion of the Principal Investigator warrants discontinuation of the subject from the active protocol for his or her well-being.

Subjects must be discontinued from IMP in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to study protocol.

- Any significant and clinically relevant changes in the safety variables (eg, ECG, BP, pulse, tympanic temperature, laboratory assessments and AEs) making the continuation of IMP administration unjustified.
- Any case of PHL according to Appendix C.
- Study specific withdrawal criteria: If the subject reports symptoms which are considered unacceptable by the subject or the PI, he/she must be withdrawn from the study. In particular:
  - Any other severe or SAE that is judged as possibly related to verinurad by the Investigator.
  - Study treatment must be stopped if a subject has elevated serum creatinine levels greater than 1.5 times the pre-treatment value and retest of the creatinine should be performed as soon as possible (see Appendix D).
  - In subjects who report symptoms that indicate acute UA nephropathy including flank pain, nausea, or vomiting, treatment must be permanently discontinued. Appendix D contains guidelines on management of such subjects.
  - 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 CRF must be completed.

5.7.1. Procedures for Withdrawal of a Subject from the Study

If a subject withdraws or is withdrawn from the study, the subject will be encouraged to return to the Clinical Unit for an Early Termination Visit to ensure the subject's safety.

5.8. Premature Termination of the Study

The study must be terminated prematurely if:

- The PI and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study.
  For instance, when there is 1 case of SAE considered at least possibly related to the IMP by the PI and the Sponsor.
  The Sponsor considers the applied doses of the study drug to be no longer relevant.
- The Sponsor decides to discontinue the study.
- Data, 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 raises 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 PI and the Sponsor and must be documented. However, study results will be reported according to the requirements outlined in this CSP as far as applicable.

6. COLLECTION OF STUDY VARIABLES

6.1. Recording of Data

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

For timing of assessments refer to Table 3-1.

6.2. Enrolment and Screening Procedures

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

6.3. Safety and Eligibility Measurements

Safety and tolerability variables will include:

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

6.3.1. Adverse Events

6.3.1.1. 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 (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

6.3.1.2. Definitions of Serious Adverse Event

A SAE is an AE occurring during any study period (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 jeopardise 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 fulfil 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.

6.3.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or where relevant DAEs and withdrawal from the study. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered 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.

6.3.1.4. Recording of Adverse Events

Time Period for Collection of Adverse Events

Adverse events will be collected from the first administration of the IMP throughout the treatment periods up to and including the Follow-up Visit.

Serious adverse events will be recorded from the time of informed consent.

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.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (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 Appendix A.
- 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.

Causality Collection

The Investigator will assess causal relationship between investigational product 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 investigational product?"

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.

Adverse Events Based on Sign and Symptoms

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.

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 fulfils 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, anaemia 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.

Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ 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.

COVID-19

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

6.3.1.5. Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators 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.

Investigators 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.

6.3.1.6. 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 utilising medical devices investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to 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 or and will notify the IEC, if appropriate according to local requirements.

6.3.2. Laboratory Assessments

6.3.2.1. Haematology

Haematology	
White blood cell (WBC) count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Haemoglobin (Hb)	Monocytes absolute count
Haematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular haemoglobin (MCH)	Platelets
Mean corpuscular haemoglobin concentration (MCHC)	Reticulocytes absolute count

6.3.2.2. Serum Clinical Chemistry

Serum Clinical Chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total Bilirubin
Calcium	Unconjugated bilirubin
Phosphate	Creatine kinase
Glucose(fasting)	Uric acid
C-reactive protein (CRP)	
T_4 [a]	FSH [a,b]
TSH [a]	

[a] Screening only
[b] To confirm postmenopausal status of female subject

6.3.2.3. Genotyping

Genotyping	
HLA-B*58:01B	

6.3.2.4. Urinalysis

Urinalysis	
Glucose	pH
Protein	
Blood	

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.

6.3.2.5. Pregnancy Testing

Pregnancy test (females only)	
Beta human chorionic gonadotrophin (Serum)	Urine Assessment

6.3.2.6. Viral Serology

Viral Serology	
Human immunodeficiency virus (HIV) I and II	anti-HBc antibody
Hepatitis B surface antigen (HBsAg)	SARS-CoV-2 antibody
Hepatitis C Virus antibody	

6.3.2.7. SARS-CoV-2 Virology

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

6.3.2.8. Drugs of Abuse, Alcohol, and Cotinine

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

6.3.3. Physical Examination

Full (Complete)

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

Brief (Abbreviated)

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

6.3.4. Electrocardiograms

6.3.4.1. Resting 12-lead Electrocardiogram

At the time-points specified in the SoA (Table 3-1), a 10-second 12-lead safety ECG will be obtained after 10 minutes supine rest, using the site's own ECG machines.

The PI will judge the overall interpretation as normal or abnormal and this evaluation will be reported in ClinBase™. If abnormal, it will be further documented as to whether or not the

abnormality is clinically significant by the PI. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in ClinBase™. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

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

All ECG readings will be digitally stored as source documents.

6.3.5. Vital Signs

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

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

The measurement of vital signs will be carried out according to the relevant Parexel SOPs. Tympanic temperature will be measured at least once daily (in the morning) at every visit or during in-house stay.

6.4. Pharmacokinetics

6.4.1. Collection of Pharmacokinetic Samples

6.4.1.1. Plasma Samples

Blood samples for the determination of plasma concentrations of verinurad, allopurinol and oxypurinol will be collected for each treatment period as specified in the SoA (Table 3-1).

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

6.4.2. Pharmacokinetic Drug Assays

Blood samples for determination of verinurad, allopurinol and oxypurinol concentrations in plasma will be analysed by Covance Bioanalytical Service on behalf of AstraZeneca, using validated assays.

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

6.5. Pharmacodynamics

6.5.1. Collection of Pharmacodynamic Samples

Blood samples for the determination of sUA concentrations will be collected on Day -1 (Treatment Period 1) and for each treatment period as specified in the SoA (Table 3-1).

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

7. BIOLOGICAL SAMPLES PROCEDURES

All biological sample collections will be performed by trained staff and in accordance with the Clinical Unit's SOPs.

7.1. 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 7-1.

Table 7-1 Total Blood Volume

	Volume per Sample	Number of Samples	Total
Clinical Laboratory:			
Haematology	2.7 mL	7	18.9 mL
Clinical chemistry [a]	7.5 mL	7	52.5 mL
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:			
Verinurad sampling	2 mL	80	160 mL
Allopurinol, and oxypurinol sampling	2 mL	64	128 mL
Pharmacodynamics:			
sUA	1.1 mL	75	82.5 mL
Total			**447.7 mL**

[a] When applicable, serology, serum pregnancy (females only) and follicle stimulating hormone analyses will be performed on the sample collected for clinical chemistry analyses.
ELISA: enzyme-linked immunosorbent assay; HLA: human leukocyte antigen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; sUA: Serum uric acid.

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

7.2. Handling, Storage and Destruction of Biological Samples

7.2.1. Safety Samples

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

7.2.2. Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the bioanalytical report finalisation 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, 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.

7.2.3. Pharmacodynamic Samples

All PD samples collected during the study will be analysed locally. Samples will be collected and analysed per the processes of the local laboratory. Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalised, unless samples are retained for additional or future analyses.

7.3. Labelling and Shipment of Biohazard Samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B of this CSP "International Airline Transportation Association 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 labelling, shipment and containment provisions are approved.

7.4. Chain of Custody of Biological Samples

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

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

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

7.5. 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.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2. Subject Data Protection

The 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 PI and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

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

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

8.3. Ethics and Regulatory Review

The study will be submitted to the national regulatory agency, BfArM, for review and approval, by Parexel in accordance with local regulatory procedures.

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

Parexel will provide the IEC and PI with safety updates/reports according to local requirements, including 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.

8.4. 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.

8.5. 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, the current requirements of GCP (EMA/CHMP/135/1995) and local regulation which ever offers the greater subject protection.

8.6. Changes to the Protocol and Informed Consent Form

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

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

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

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

9. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

9.1. Quality Control and Source Data Verification

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

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

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

9.2. Audit/Inspections

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

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

9.3. Study Monitoring

The conduct of the study will be monitored by an independent Parexel 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.

9.4. 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 an 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 Clinical Unit. The PI 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™.

9.4.1. 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 PI for resolution.

9.4.2. Access to Source Documents

During the course of the clinical study, a study monitor will make Clinical Unit visits to review protocol compliance, compare 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 may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The PI assures the Sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilise 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 CFR Part 11 requirements.

A 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 finalised before first dose where possible but before database lock.

A DVS will be created to outline the validation checks to be performed during the study. The DVS must be finalised before data validation.

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

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the PI for review and resolution. Corrections resulting from these queries will be confirmed on the 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.

10. EVALUATION AND CALCULATION OF VARIABLES

10.1.1. 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:

- Treatment Period 1: AEs with start date/time at the time of or after dosing in Treatment Period 1 until the time of dosing in Treatment Period 2.
- Treatment Period 2: AEs with start date/time at the time of or after dosing in Treatment Period 2 until the time of dosing in Treatment Period 3.
- Treatment Period 3: AEs with start date/time at the time of or after dosing in Treatment Period 3 until the time of dosing in Treatment Period 4.
- Treatment Period 4: AEs with start date/time at the time of or after dosing in Treatment Period 4 until the time of dosing in Treatment Period 5.
- Treatment Period 5: AEs with start date/time at the time of or after dosing in Treatment Period 5 until the 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.

For purposes of the AE summaries, the following will apply:

- AEs with unknown intensity will be treated as "severe" for the tabulations.
- AEs with unknown relationship will be treated as "related" for the tabulations.
- AEs with unknown seriousness will be treated as "serious" for the tabulations

There will be no imputation of AE data for the data listings. All data will be listed as recorded in the CRF.

Adverse events with onset (start date/time) after dosing in Treatment Period 1 will be summarised by treatment (where treatments will be pooled across treatment periods) and overall for all subjects, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and Preferred Term with the exception of the causality and severity tables, which will be presented by Preferred Term only. Furthermore, separate listings of SAEs, DAEs and AEs that led to death will be presented.

Adverse events will be listed and 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.

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

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

10.1.2. 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 values and changes from baseline will be presented by time point for the safety analysis set. The baseline for the measurements in Treatment Period 1 will be the Day -2 assessment and for the measurements in Treatment Period 2, 3, 4, and 5, it will be the Day -1 assessment performed prior to dosing in each of the respective treatment periods. Shift tables will also be presented.

Any laboratory variables with results from the laboratory given as "< xx" or ">xx" in the database will be imputed with the absolute value of the number without the sign (eg, < 2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

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

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- The results of viral serology, SARS-CoV-2 virology, and the drugs of abuse, alcohol, and cotinine screen will not be listed in the CSR.

10.1.3. Physical Examination

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

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

10.1.4. Resting 12-lead Electrocardiogram

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

10.1.5. Vital Signs

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

10.2. Pharmacokinetic Parameters

The PK parameters will be estimated for verinurad, allopurinol and oxypurinol using plasma concentrations.

10.2.1. Plasma Parameters

The following PK parameters will be determined where data allow for verinurad, allopurinol and its metabolite oxypurinol for each treatment.

Primary PK parameters

AUCinf	Area under plasma concentration-time curve from time zero to infinity

AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
Cmax	Maximum observed plasma (peak) drug concentration

Secondary PK parameters

tmax	Time to reach maximum observed plasma concentration following drug administration
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
MRTinf	Mean residence time of the unchanged drug in the systemic circulation from zero to infinity (parent drug only)
λz	Terminal elimination rate constant
CL/F	Apparent total body clearance of drug from plasms after extravascular administration (parent drug only)
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration (parent drug only)
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration (parent drug only)

The following diagnostic parameters will also be provided:

λz upper	Upper (later) t used for λz determination
λz lower	Lower (earlier) t used for λz determination
tlast	Time of last observed (quantifiable) concentration
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

Additional PK parameters may be determined where appropriate.

10.2.2. Calculation or Derivation of Pharmacokinetic Parameters

The PK analyses of the plasma concentration data for verinurad, allopurinol and oxypurinol will be performed by Covance, on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca R&D and will be calculated according to the AstraZeneca standards (Guideline for PK Evaluations in Clinical Studies, v3, Feb 2020).

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

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

10.3. Pharmacodynamic parameters

The PD parameters will be assessed using sUA concentrations, calculating the percentage change from baseline (time-matched, Day -1) in sUA concentrations up to 72 hours post-dose at each timepoint following administration of IMP.

The following PD parameters will be derived from the calculated profiles using non-compartmental analysis with WinNonLin (Version 8.1 or higher):

Serum uric acid derived PD parameters

Emax, CB	Maximum observed percentage change from baseline (Time-Matched, Day -1 and pre-dose on each day) in serum uric acid concentrations
tEmax, CB	Time of maximum percentage change from baseline (Time-Matched, Day -1 and pre-dose on each day) in serum uric acid concentrations

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of the Analysis Sets

11.1.1. Safety Analysis Set

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

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

11.1.2. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the safety analysis set who received a verinurad + allopurinol (or verinurad alone for Treatment 5) dose and who have at least 1 quantifiable post-dose plasma concentration. In case of an important protocol deviation or event, affected PK data will be excluded from the descriptive and inferential statistical

analyses, but will still be included in the study result listings. For the formal relative bioavailability evaluations, only subjects who provide eligible PK data for both Test and Reference treatments can be included for each comparison.

Data for a subject may be excluded from the descriptive and inferential statistical analyses as a result of the following:

- Where a subject experienced vomiting at or before median tmax.
- Where the pre-dose concentration for an analyte is > 5% of Cmax in a specific PK sampling period

The exclusion of any subjects or any PK concentrations or parameters from the descriptive or inferential statistical analyses, or of any time-points from the PK parameter non-compartmental analysis, will be discussed and agreed with the AstraZeneca CPS prior to handover of the final PK parameters to programming.

11.1.3. Pharmacodynamic Analysis Set

The PD analysis set will consist of all subjects in the safety analysis set who received at least 1 of the verinurad and allopurinol (or verinurad alone for Treatment 5) doses and who have at least 1 quantifiable time-matched sUA concentration.

11.1.4. Randomised Set

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

11.2. Methods of Statistical Analyses

11.2.1. General Principles

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 SAP will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

All original and derived variables 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 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, SD, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$. If no subjects have data at a given time point, then only $n = 0$ will be presented. If $n < 3$, only the n, minimum and maximum will be presented. If $n = 3$, only the n, median, minimum and maximum will be presented. The other descriptive statistics will be left blank. Due to the explorative nature of this study, no adjustment for multiple testing of variables will be done.

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

- If the repeated measurement of a specific variable 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 3.1.1.

For safety assessments performed at screening and the follow-up, 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 higher.

11.2.2. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.1.1. Concentrations that are marked non-quantifiable in the PK data will be handled as described in the most recent version of the AstraZeneca CPE TFL Standards.

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

11.2.3. Subject Characteristics

A randomisation listing will be presented and include the following: each subject's randomisation number, the subject's full enrolment number and 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 analysis set 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.

11.2.3.1. 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, MedDRA SOC, MedDRA Preferred Term, start date and stop date (or ongoing if applicable).

11.2.4. Prior and Concomitant Medication and Drug Administration

11.2.4.1. 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, 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.

The duration will be calculated as:

Duration = end date/time – start date/time + 1

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

11.2.4.2. Drug Administration

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

11.2.5. Safety and Tolerability

All 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. 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.

Adverse events will be summarised by Preferred Term and SOC using MedDRA vocabulary. Furthermore, listings of SAEs and adverse events that led to withdrawal will be made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised. Adverse events that occurred from time of informed consent until first administration of IMP will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs (listings only) will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be 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. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting, and in Système International units in the CSR.

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

11.2.6. Presentation of Pharmacokinetic Parameter Data

A listing of PK blood sample collection times, as well as derived sampling time deviations and all reportable concentrations will be presented for verinurad and for allopurinol and

oxypurinol for all dosed subjects. An additional listing of PK concentrations versus time will be presented for those analytes based on the PK analysis set.

Plasma concentrations will be summarised for the PK analysis set for each time point by treatment for each analyte separately using CSP scheduled times and appropriate descriptive statistics.

All reportable PK parameters from the NCA will be listed for verinurad, allopurinol, and oxypurinol for subjects dosed.

Plasma PK parameters will be summarised for the PK analysis set by treatment for each analyte separately.

Further details on presentation of PK concentration and parameter data will be presented according to the most recent version of the AstraZeneca Corporate CSRHLD reporting standards, that includes applicable descriptive statistics, handling of individual concentrations below the LLOQ for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scale with the all dosed treatments overlaid on the same plot and separate plots for each subject and analyte. Plots will be based on all dosed subjects.

Combined individual plasma concentration versus actual times will be plotted based on the PK analysis set on both the linear and semi-logarithmic scale, with all subjects for the same treatment overlaid on the same plot and separate plots for each treatment and analyte.

Geometric mean (+/- geometric standard deviation [gSD]) plasma concentration versus nominal sampling time will be plotted on both the linear scale and semi-logarithmic (no gSD presented) with all treatments overlaid on the same plot and separate plots for each analyte. Plots will be based on the PK analysis set. Focus plots may be provided if there will be no clear distinction among profiles.

11.2.7. Inferential Statistical Analysis of Pharmacokinetic Data

For each individual relative bioavailability comparison, the ratios of Cmax, AUClast and AUCinf will be calculated for each treatment comparison (Test treatment versus Reference treatment) using log-transformed data.

The following comparisons of relative bioavailability (Cmax, AUCinf and AUClast) for each analyte (verinurad, allopurinol and oxypurinol) will be performed:

- Treatment 2 versus Treatment 1, ie, “verinurad/allopurinol FDC capsule, fasted” versus “verinurad HPMC capsule and allopurinol tablet, free combination, fasted”.

- Treatment 3 versus Treatment 2, ie "verinurad/allopurinol FDC capsule, fed" versus "Verinurad/allopurinol FDC capsule. fasted".
- Treatment 4 versus Treatment 1, ie. "verinurad HPMC capsule and allopurinol tablet, free combination, fed" versus "verinurad HPMC capsule and allopurinol tablet, free combination, fasted".
- Treatment 3 versus Treatment 4, ie. "verinurad/allopurinol FDC capsule, fed" versus "verinurad HPMC capsule and allopurinol tablet, free combination, fed".
- Treatment 5 versus Treatment 2 (for verinurad only), ie., "verinurad gelatin capsule, fasted" versus "verinurad/allopurinol FDC capsule, fasted".

The analyses will be performed using a linear mixed-effects analysis of variance model using the natural logarithm of Cmax, AUCinf and AUClast as the response variables, sequence, period and treatment as mixed-effects, volunteer nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for Cmax, AUCinf and AUClast will be estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented.

11.2.8. Presentation and Statistical Analysis of Pharmacodynamic Data

A listing of sUA sample collection times, as well as derived sampling time deviations will be provided. Serum UA observed and time-matched percentage change from baseline will be listed by treatment and summarized descriptively by treatment and time point. Emax CB and tEmax CB data will be listed by treatment. For observed and time-matched percentage change from baseline, the descriptive statistics will include n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum, and maximum. Geometric CV will be calculated as $100 \times$ (square root [$\exp(s^2)-1$]) where s is the SD of the log-transformed data.

Individual and mean (with corresponding error bars) serum concentration curves (both linear and log scale) will also be generated. All the results will be based on the PD analysis set.

11.3. 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 Clinical Unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification document. This will include a 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 8.6.

11.4. Determination of Sample Size

The sample size was chosen to obtain reasonable assessment of relative bioavailability between different formulations of verinurad and/or allopurinol without exposing undue numbers of subjects to the compound at this phase of clinical development. It is estimated that 20 subjects randomised to 5 sequences in a reduced Latin square will provide a 90% CI within 0.7 and 1.43, with a probability of >90% if the estimated treatment ratio is 1 for Cmax. This is based on an intra-subject variability of 24% for Cmax of verinurad in Study D5495C00001. Similarly, it is estimated that 20 subjects will provide a 90% CI within 0.8 and 1.25, with a probability of >95% if the estimated treatment ratio is 1 for AUC. This is based on an intra-subject variability of 14.7% for AUC of verinurad in Study D5495C00001.

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

12. LEGAL AND ADMINISTRATIVE ASPECTS

12.1. 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 authorised 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 25 years after completion of the study.

12.2. 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.

12.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of CSRs (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.

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14. APPENDICES

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

Life-threatening

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

Hospitalisation

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

A Guide to Interpreting the Causality Question

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

- Time course / Exposure to suspect drug:

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

- Consistency with known drug profile:

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

- Dechallenge experience:

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

- No alternative cause:

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

- Rechallenge experience:

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

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

- Laboratory tests:

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

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

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

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

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

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

Appendix B International Airline Transportation Association 6.2 Guidance Document

Labelling and Shipment of Biohazard Samples

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

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

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

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

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

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

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.**
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

C 1 Introduction

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

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

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

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

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

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

C 2 Definitions

Potential Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

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

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

C 3 Identification of Potential Hy's Law Cases

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

- AST ≥ 3 × ULN
- ALT ≥ 3 × ULN
- TBL ≥ 2 × ULN

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

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF module(s)

C 4 Follow-Up

C 4.1 Potential Hy's Law Criteria not met

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

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

C 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting

- For subjects that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[‡] in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
  - Subsequent to this contact the Investigator will:
    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used (if applicable).
    - Complete the 3 liver CRF modules as information becomes available.

C 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date the PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF module(s)

[‡] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRF entries accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes

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

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

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

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

C 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

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

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

* HCV RNA is only tested when anti-HCV is positive or inconclusive

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Appendix D Actions Required in Cases of a Renal-related or Urolithiasis Treatment-emergent Adverse Event or a Serum Creatinine Elevation

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

D 1 Signs and Symptoms Suggestive of Urolithiasis

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

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

D 2 Deterioration of Renal Function

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

Serum Creatinine Increase to ≥ 1.5-fold from Baseline

- Assess the subject to identify and manage any potential contributing factor. Correct any dehydration and ensure the subject is well hydrated prior any future evaluation.
- Contact the Sponsor's lead physician for advice and to discuss discontinuation of study medication.
- Assess creatinine daily if the elevation is detected while the subject is admitted to the Clinical Unit, and otherwise weekly.
- Subsequent management will depend on the repeat measurement(s):
  - If serum creatinine < 1.5-fold of baseline value for 2 successive measurements, the subject may restart/continue with study treatment on the original study visit schedule.

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