An Open-label, 3-Treatment, 3-Period, Fixed Sequence Study in Healthy Subjects to Assess the Pharmacokinetics of Verinurad and Allopurinol when Administered Alone, and in Combination with Single Doses of Cyclosporine or Rifampicin

ClinicalTrials.gov Identifier: NCT04532918

Date of Protocol: 19 May 2020

Clinical Study Protocol

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Parexel Study No.:	CCI [redacted]
Sponsor Study Code:	D5495C00013
Eudra CT No:	2020-000937-42
Study Type:	Drug-drug interaction (DDI) study
Test Product:	Verinurad, Allopurinol
Interaction Products:	Cyclosporine and Rifampicin
Therapeutic Indication:	Chronic kidney disease
Pharmacological Class:	URAT1 transporter inhibitor and xanthine oxidoreductase inhibitor
Development Phase:	Phase 1
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel International GmbH CCI [redacted], CCI [redacted] CCI [redacted] 14050 Berlin Germany
Date of Protocol:	Final 1.0, 19 May 2020

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

PROTOCOL SYNOPSIS

Title of the Study
An Open-label, 3-Treatment, 3-Period, Fixed Sequence Study in Healthy Subjects to Assess the Pharmacokinetics of Verinurad and Allopurinol when Administered Alone, and in Combination with Single Doses of Cyclosporine or Rifampicin

Principal Investigator (PI)
Thomas Körnicke, MD

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

Study Rationale
Verinurad exposure has been hypothesized, based on in vitro data, to increase if co-administered with compounds that inhibit transporters, such as OATP1B1 and OATP1B3, involved in the disposition of verinurad. The proposed study aims to quantify the effects of cyclosporine, a broad transporter inhibitor, and rifampicin, an OATP1B1/3 inhibitor, on verinurad PK (FDA Guidance on Clinical Drug Interaction Studies, 2020).

Number of Subjects Planned
A total of 14 healthy subjects will be enrolled to ensure at least 12 evaluable subjects at the end of the last treatment period.

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

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

- To assess the effect of a single dose of cyclosporine on the PK of verinurad.
- To assess the effect of a single dose of rifampicin on the PK of verinurad.

Secondary Objectives:

- To assess the effect of a single dose of cyclosporine or rifampicin on the PK of verinurad metabolites M1 and M8.
- To assess the effect of a single dose of cyclosporine or rifampicin on the PK of allopurinol and oxypurinol.
- To describe the PK parameters and the PK profiles for verinurad, M1, M8, allopurinol and oxypurinol when verinurad+allopurinol is administered alone or in combination with cyclosporine or rifampicin.
- To assess the safety and tolerability of verinurad and allopurinol in combination with a single dose of cyclosporine or rifampicin.

Exploratory Objective:

- To collect and store samples for potential future measurement of cyclosporine and/or rifampicin plasma levels.
- To collect blood and urine samples for additional clinical chemistry and urinalysis.

Study Design

This study will be an open-label, 3-period, 3-treatment, fixed-sequence study in healthy subjects (males and females of non-childbearing potential), performed at a single Clinical Unit.

The study will comprise of the following periods (visits):

- A Screening Period of maximum 28 days (Visit 1);
- A fixed sequence of 3 Treatment Periods during which subjects will be resident at the Clinical Unit from one day prior to administration of verinurad+allopurinol (Day -1) of Treatment Period 1 until the morning of Day 5 of the Treatment Period 2, and similarly between Day -1 to Day 5 of Treatment Period 3. There will be a washout period of 14 days between Treatment Periods 2 and 3 dosing. The 3 Treatment Periods, including the washout period, will be a total of up to 36 days (Visits 2 and 3);
- A Follow-up Visit within 7 to 14 days after the last administration of verinurad+allopurinol (Visit 4).

Subjects will be resident at the Clinical Unit from Day -1 of Treatment Period 1 (Visit 2), ie, prior to the evening meal the night before first dosing with verinurad+allopurinol, until the morning of Day 5 of Treatment Period 2, ie, at least 96 hours after the second dosing with verinurad+allopurinol. There will be no washout between Treatment Period 1 and Treatment Period 2. Subjects will be resident continuously for the full duration of Treatment Periods 1 and 2. There will be a minimum washout period of 14 days between dosing in Treatment Period 2 and dosing in Treatment Period 3. Subjects will not be required to be resident at the Clinical Unit for around 10 days during the washout period. Subjects will be resident again from Day -1 of Treatment Period 3 (Visit 3), ie, prior to the evening meal the night before third (last) dosing with verinurad+allopurinol, until the morning of Day 5 of Treatment Period 3, ie, at least 96 hours after the last dosing with verinurad+allopurinol. The subjects will return for a Follow-up Visit in 7-14 days after the last verinurad+allopurinol dose.

Each subject will receive a single dose of verinurad+allopurinol on 3 occasions, under fasted conditions. Each subject will also receive a single dose of cyclosporine on 1 occasion and a single dose of rifampicin on 1 occasion, with cyclosporine and rifampicin being dosed on separate occasions and always together with verinurad+allopurinol.

Expected Duration of the Study

Each subject will be involved in the study for approximately 9 weeks and have 4 study visits.

Targeted Study Population
This study will be conducted in healthy males and females of non-childbearing potential, 18 to 55 years of age (inclusive).

Investigational Medicinal Product

Investigational Medicinal Product Name	**Verinurad**	**Allopurinol**	**Cyclosporine**	**Rifampicin**
Trade Names:	Verinurad	Allopurinol	Sandimmun Optoral	Eremfat
Manufacturer:	AstraZeneca	Teva Pharmaceutical	Novartis Pharma GmbH	RIEMSER Pharma GmbH
Formulation:	Capsule	Tablet	Soft Capsule	Film coated Tablets
Strength/concentration:	7.5 mg	300 mg	100 mg	600 mg
Dose:	7.5 mg	300 mg	600 mg	600 mg
Route of administration:	Oral	Oral	Oral	Oral
Specific device for drug administration, if applicable:	Not applicable	Not applicable	Not applicable	Not applicable
Regimen:	Single dose of 7.5 mg	Single dose of 300 mg	Single dose of 600 mg	Single dose of 600 mg
Special handling requirements:	Not applicable	Not applicable	Not applicable	Not applicable

Outcome Endpoints
The primary outcome measures are:

- Verinurad Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone).
- Verinurad Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).

The secondary outcome measures are:

- M1 and M8 Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone).
- M1 and M8 Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).
- Allopurinol and oxypurinol Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone).

- Allopurinol and oxypurinol Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).
- Where possible the following PK parameters of verinurad, M1, M8, allopurinol and oxypurinol will be assessed: Cmax, AUCinf, AUClast, AUC(0-24), tmax, t½λz, λz, CL/F (parent only), MRTinf (parent only), Vss/F (parent only), Vz/F (parent only) and metabolite:parent (MP) ratios of M1 and M8: verinurad for Cmax, AUCinf and AUClast. Plasma concentration time profile for each analyte.
- Incidence of AEs, 12-lead ECGs, vital signs, physical examination, and clinical laboratory assessment.

Statistical Methods

Presentation and Analysis of Safety Data:

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 PT 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 occur before dosing 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 from the baseline when baseline is defined.

Inferential Analysis of Pharmacokinetic Data:

The pharmacokinetic parameters (Cmax, AUCinf and AUClast) of verinurad, M1, M8, allopurinol and oxypurinol will be analysed using an analysis of variance model following a natural logarithmic transformation, with fixed effects for treatment and subject. Least-squares geometric means, 2-sided 95% confidence intervals, ratios of geometric means together with 2-sided 90% confidence intervals of test treatment (verinurad+allopurinol+cyclosporine or verinurad+allopurinol+rifampicin), and reference treatment (verinurad+allopurinol) will be estimated and presented. Descriptive statistics will be presented for PK concentration-time data and PK parameters for verinurad, M1, M8, allopurinol and oxypurinol.

Presentation and Analysis of Exploratory Data:

Results from exploratory data will not form part of the CSR and will not be included in the tables, figures or listings of this study.

Sample Size Determination

The number of subjects is based on the desire to gain adequate information on the primary endpoints while exposing as few subjects as possible to study procedures. Interpretation of the results will be based on the size of the treatment ratio and associated 90% CI. It is estimated

that 12 subjects will provide a CI within 1.58 to 2.53 with a probability of 80% if the calculated treatment ratio is 2. This is based on an intra-subject CV of 24% for verinurad.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Please note: definitions of abbreviations for pharmacokinetic variables are also presented in Section 10.2.1 of this protocol.

Abbreviation or special term	Explanation
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
AE	Adverse event (see definition in Section 6.3.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC(0-24)	Area under plasma concentration-time curve from zero to 24 hours post-dose
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as a percentage of AUCinf
AUCinf	Area under plasma concentration-time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from zero to time of last quantifiable concentration
AZ	AstraZeneca
BMI	Body mass index
bpm	Beats per minute
CKD	Chronic kidney disease
CI	Confidence interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
ClinBase™	Parexel's electronic source data capturing and information management system
Cmax	Maximum observed plasma peak 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

Abbreviation or special term	Explanation
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ER	Extended release
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HF	Heart failure
HIV	Human immunodeficiency virus
HL	Hy's Law
HLA-B	Human leukocyte antigen B
HR	Heart rate
IATA	International Airline Transportation Association
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IR	Immediate release
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MRAUCinf	Ratio of metabolite AUCinf to parent AUCinf
MRAUClast	Ratio of metabolite AUClast to parent AUClast
MRCmax	Ratio of metabolite Cmax to parent Cmax
MRTinf	Mean residence time of the unchanged drug in the systemic circulation
ms	milliseconds
n	Number of data values
N	Number of subjects
NA	Not applicable
NC	Not calculated
NR	No result
NQ	Not quantifiable
NS	No sample
OAE	Other significant adverse events
OATP	Organic anion transporting polypeptide
OTC	Over-the-counter
PD	Pharmacodynamics
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PT	Preferred term
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
RCTC	Rheumatology Common Toxicity Criteria
Rsq-adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
RT-PCR	Real-time Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious adverse event (see definition in Section 6.3.1.2).
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan

Abbreviation or special term	Explanation
sCr	Serum creatinine
SD	Standard deviation
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
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
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TCA	Tricyclic anti-depressant
tlast	Time of last observed (quantifiable) plasma concentration
tmax	Time to reach peak or maximum observed plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
URAT1	Novel uric acid transporter 1
UA	Uric acid
USA/US	United States of America
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)
WAD	Windows Allowance Document
WBC	White blood cell
XOI	Xanthine oxidase inhibitor

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	PPD AstraZeneca R&D Gothenburg PPD 431 83 Mölndal Sweden PPD PPD PPD
Sponsor's Biostatistician:	PPD AstraZeneca R&D Gothenburg PPD 431 83 Mölndal Sweden PPD
Principal Investigator:	Thomas Körnicke Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany PPD
Deputy PI:	PPD Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany PPD

Contract Research Organization (CRO):	Parexel Early Phase Clinical Unit Berlin PPD PPD 14050 Berlin Germany PPD
Clinical Laboratory:	Synlab Clinical Trial GmbH PPD 10559 Berlin Germany **Contact:** PPD
Analytical Laboratory: (pharmacokinetic [PK] sample analysis)	Covance Bioanalytical Services, LLC PPD Indianapolis, IN 46214 United States of America **Contact:** PPD
Human leukocyte antigen (HLA) sample analyses	DNA Identification Testing Division Laboratory Corporation of America Holdings PPD Burlington, NC 27215-3361 United States of America **Contact:** PPD
Pharmacy:	Hubertus-Apotheke PPD 10587 Berlin Germany Contact: PPD

Parexel Laboratory Contact:	Parexel International GmbH, PPD 8 PPD 14050 Berlin Germany Contact: PPD
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services 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

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 [8, 9, 10], 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.

Verinurad is administered in combination with the xanthine oxidase inhibitor (XOI) allopurinol, which reduces the production of UA. By dosing verinurad with allopurinol, patients have a substantially decreased risk of the creatinine elevations noted with URAT1 inhibitor monotherapy. The combination also provides a dual-mechanism approach to lowering sUA concentrations, by targeting both production and excretion. Clinical studies with verinurad have been performed using 2 XOIs: febuxostat and allopurinol, each administered concomitantly with verinurad. In progressing to Phase 2b, allopurinol has been selected as the XOI for co-administration with verinurad because it may have a better cardiovascular side effect profile than febuxostat.

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

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 time to maximum plasma concentration (tmax). The degree of protein binding of verinurad in human plasma was 97%. Glucuronidation is the major metabolic pathway of verinurad with oxidation as the minor pathway. The major metabolites observed in humans after oral verinurad dosing are the acyl glucuronides M1 and M8 which are renally cleared. The amount of verinurad in urine is small (<2% of given dose). The terminal half-life (t½) of verinurad was 13 hours in subjects with normal renal function and 21 hours in those

with moderate renal impairment. The exposure ([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/1.73m^2 are predicted to have a 1.4 and 1.2-fold higher verinurad exposure, respectively, compared to those with normal renal function (eGFR of 90 mL/min/1.73m^2). Asian subjects are predicted to have about 44% higher exposure compared to non-Asians after accounting for differences in renal function and body weight.

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

Both EMA [2] and FDA [3] as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

1.3. Rationale for Conducting this Study

It has been hypothesized based on in vitro data that verinurad exposure could increase if it is co-administered with compounds that inhibit transporters which are involved in disposition of verinurad, such as OATP1B1 and OATP1B3 [1]. The study outlined in this protocol aims to quantify the effects on verinurad PK when co-administered with cyclosporine, a broad transporter inhibitor, or rifampicin, a more specific OATP1B1/3 inhibitor when given as a single dose. The study is conducted in accordance with FDA guidance on Clinical Drug Interaction Studies, 2020 [11]. Verinurad will be developed as a fixed combination since it will always be administered together with allopurinol.

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

2. STUDY OBJECTIVES

2.1. Primary Objectives

Table 2-1 Primary Objectives and Outcome Measures

Primary Objectives	Outcome Measures
To assess the effect of a single dose of cyclosporine on the PK of verinurad	Verinurad Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone).
To assess the effect of a single dose of rifampicin on the PK of verinurad	Verinurad Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).

See List of Abbreviations for definition of abbreviations in Table 2-1

2.2. Secondary Objectives

Table 2-2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
To assess the effect of a single dose of cyclosporine or rifampicin on the PK of verinurad metabolites M1 and M8	M1 and M8 Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone). M1 and M8 Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).
To assess the effect of a single dose of cyclosporine or rifampicin on the PK of allopurinol and oxypurinol	Allopurinol and oxypurinol Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with cyclosporine), relative to reference treatment (verinurad+allopurinol alone). Allopurinol and oxypurinol Cmax, AUCinf and AUClast ratios of geometric means of test treatment (verinurad+allopurinol with rifampicin), relative to reference treatment (verinurad+allopurinol alone).

Secondary Objectives	Outcome Measures
To describe the PK parameters and the PK profiles for verinurad, M1, M8,allopurinol and oxypurinol when verinurad+allopurinol is administered alone or in combination with cyclosporine or rifampicin.	Where possible the following PK parameters of verinurad, M1, M8, allopurinol and oxypurinol will be assessed: Cmax, AUCinf, AUClast, AUC(0-24), tmax, t½λz, λz, CL/F (parent only), MRTinf (parent only), Vss/F (parent only), Vz/F (parent only) and metabolite:parent (MP) ratios of M1 and M8: verinurad for Cmax, AUCinf and AUClast. Plasma concentration time profile for each analyte.
To assess the safety and tolerability of verinurad and allopurinol in combination with cyclosporine or rifampicin	Incidence of AEs, 12-leadECGs, vital signs, physical examination, and clinical laboratory assessment.
See List of Abbreviations for definitions of abbreviations in Table 2-2	

2.3. Exploratory Objective

Table 2-3 Exploratory Objective and Outcome Measures

Exploratory Objectives	Outcome Measures
To collect and store blood samples for potential future measurement of cyclosporine and/or rifampicin plasma levels.	If samples are analysed: cyclosporine and rifampicin plasma concentrations.
To collect blood and urine samples for additional clinical chemistry and urinalysis.	Collected on Days 1, 2 and 3 in Treatment Period 1.
Exploratory data will not form part of the CSR and will not be included in the tables, figures or listings of this study.	

Refer to Section 10.2 for PK variables and Section 6.3 for safety variables.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

This study will be an open-label, 3-period, 3-treatment, fixed-sequence study in healthy subjects (males and females of non-childbearing potential), performed at a single Clinical Unit.

The study will comprise of the following periods (visits):

- A Screening Period of maximum 28 days (Visit 1);
- A fixed sequence of 3 Treatment Periods during which subjects will be resident at the Clinical Unit from one day prior to administration of verinurad+allopurinol (Day -1) of Treatment Period 1 until the morning of Day 5 of the Treatment Period 2, and similarly between Day -1 to Day 5 of Treatment Period 3. There will be a washout period of 14

days between Treatment Periods 2 and 3 dosing. The 3 Treatment Periods, including the washout period, will be a total of up to 36 days (Visits 2 to3);

- A Follow-up Visit within 7 to 14 days after the last administration of verinurad+allopurinol (Visit 4).

Subjects will be resident at the Clinical Unit from Day -1 of Treatment Period 1 (Visit 2), ie, prior to the evening meal the night before first dosing with verinurad+allopurinol, until the morning of Day 5 of Treatment Period 2, ie, at least 96 hours after the second dosing with verinurad+allopurinol. There will be no washout between Treatment Period 1 and Treatment Period 2. Subjects will be resident continuously for the full duration of Treatment Periods 1 and 2. There will be a minimum washout period of 14 days between dosing in Treatment Period 2 and dosing in Treatment Period 3. Subjects will not be required to be resident at the Clinical Unit for around 10 days during the washout period. Subjects will be resident again from Day -1 of Treatment Period 3 (Visit 3), ie, prior to the evening meal the night before third (last) dosing with verinurad+allopurinol, until the morning of Day 5 of Treatment Period 3, ie, at least 96 hours after the last dosing with verinurad+allopurinol. The subjects will return for a Follow-up Visit in 7-14 days after the last verinurad+allopurinol dose.

Each subject will receive a single dose of verinurad+allopurinol on 3 occasions, under fasted conditions. Each subject will also receive a single dose of cyclosporine on 1 occasion and a single dose of rifampicin on 1 occasion, with cyclosporine and rifampicin being dosed on separate occasions and always together with verinurad+allopurinol.

Details on IMP administration is provided in Section 5.4.3.

Figure 3-1 Study Flow Chart

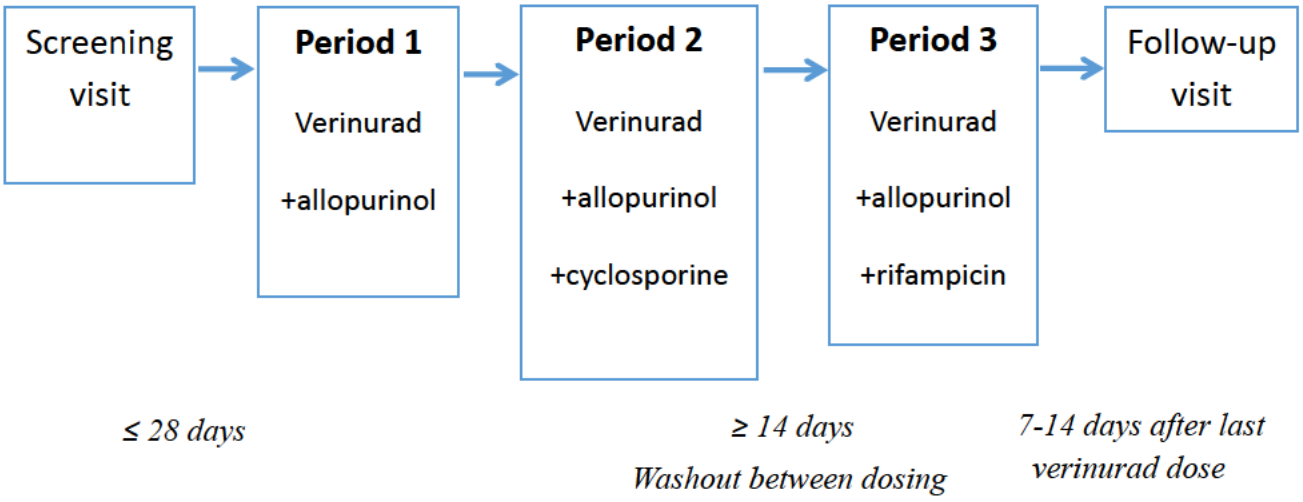

Table 3-1 Schedule of Assessments

Study Assessments	Visit 1	Visit 2			Visit 3		Visit 4	Corresponding Section in Protocol
	Screening	Treatment Period 1		Treatment Period 2	Treatment Period 3		Follow-up or Early Termination	
	Day -28 to -2	Day -1	Days 1 to 5	Days 1 to 5	Day -1	Days 1 to 5	7-14 days after last verinurad dose	
Informed consent	X							Section 8.5
Inclusion/exclusion criteria	X	X						Section 4.1
Eligibility Assessment					X			Section 4.1
Demographic data	X							Section 11.2.3.1
Weight, height and BMI	X							Section 11.2.3.1
Medical/surgical history	X							Section 11.2.3.1
Concomitant medication	X	X	X	X	X	X	X	Section 11.2.4.1
Urine drug, alcohol and cotinine screen	X	X			X			Section 6.3.2.6
FSH test	X							Section 6.3.2.2
HIV status/hepatitis B and C screen, anti-HBc antibody	X							Section 6.3.2.5
HLA-B*58:01 allele genotyping	X							Section 6.3.2.3
Study residency								
Check-in		X			X			Section 3.1
Check-out				X[a]		X[a]		Section 3.1

Study Assessments	**Visit 1**	**Visit 2**			**Visit 3**		**Visit 4**	**Corresponding Section in Protocol**
	Screening	**Treatment Period 1**		**Treatment Period 2**	**Treatment Period 3**		**Follow-up or Early Termination**	
	Day -28 to -2	**Day -1**	**Days 1 to 5**	**Days 1 to 5**	**Day -1**	**Days 1 to 5**	**7-14 days after last verinurad dose**	
Non-residential visit	X						X	Section 3.1
Verinurad + allopurinol administration			X[b]	X[b]		X[b]		Section 3.1 and 5.4.3
Cyclosporine administration				X[b]				Section 3.1 and 5.4.3
Rifampicin administration						X[b]		Section 3.1 and 5.4.3
Safety/tolerability								
Phone call to assess symptoms	X[c]	X[c]			X[c]		X[c]	Section 4.1.2
SARS-CoV-2 antibody	X							
SARS-CoV-2 RT-PCR		X			X			
Adverse event questioning (AEs and SAEs)	X[d]	X[d]	X	X	X	X	X	Section 6.3.1
Blood pressure, pulse rate (supine) and temperature (tympanic)	X	X	X[e]	X[e]	X	X[e]	X	Section 6.3.5
Safety 12-lead ECG	X						X	Section 6.3.4

Study Assessments	Visit 1	Visit 2			Visit 3		Visit 4	Corresponding Section in Protocol
	Screening	Treatment Period 1		Treatment Period 2	Treatment Period 3		Follow-up or Early Termination	
	Day -28 to -2	Day -1	Days 1 to 5	Days 1 to 5	Day -1	Days 1 to 5	7-14 days after last verinurad dose	
Clinical laboratory evaluations:								Section 6.3.2
Clinical Chemistry and urinalysis	X	X	X[f]		X		X	
Haematology	X	X	X[g]	X[g]	X	X[g]	X	
Physical examination	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	Section 6.3.3
Pharmacokinetics								
Blood sampling for analysis of verinurad, M1, M8, allopurinol and oxypurinol plasma concentrations			X[i]	X[i]		X[i]		Section 6.4.2
Exploratory blood sampling for analysis of cyclosporine blood concentrations				X[i]				Section 6.4.2
Exploratory blood sampling for analysis of rifampicin plasma concentrations						X[i]		Section 6.4.2

Abbreviations: AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; FSH = Follicle stimulating hormone; HBc = Hepatitis B core; HIV = Human immunodeficiency virus; HLA-B = Human leukocyte antigen B; SAE = Serious adverse events;

Study Assessments	Visit 1	Visit 2			Visit 3		Visit 4	Corresponding Section in Protocol
	Screening	Treatment Period 1		Treatment Period 2	Treatment Period 3		Follow-up or Early Termination	
	Day -28 to -2	Day -1	Days 1 to 5	Days 1 to 5	Day -1	Days 1 to 5	7-14 days after last verinurad dose	

[a] Subjects will be allowed to leave (discharged from) the clinical unit after the last PK sample is taken at 96 hours after dosing (Day 5).

[b] Occurs on Day 1, in each Treatment period (considered as the 0 hour time point)

[c] Subjects will be contacted within 24 hours before a scheduled visit to the Clinical Unit to confirm that no signs and/or symptoms of COVID-19 are present and that no subject had any contact with a known SARS-CoV-2 positive tested person within the last 14 days. In the case that a subject confirms signs and/or symptoms or has had contact with a SARS-CoV-2 positive person, the visit will be canceled and the reason for the cancellation will be appropriately documented.

[d] Only SAEs will be recorded during the Screening period and on Day -1 Treatment Period 1 (Visit 1)

[e] Blood pressure, pulse rate (supine) and temperature (tympanic) will be taken at pre-dose and 1.5, 4, and 6 hours after dosing on Day 1 and on Days 2, 3, 4 and 5 in each Treatment Period.

[f] In Treatment Period 1, urine samples and blood for clinical chemistry will be collected on Days 1, 2 and 3. Urine samples will include only the measurement of sodium, creatinine, lactic acid, potassium, aldosterone and pH. Blood samples will include only the measurement of creatinine, cystatin-C and sodium.

[g] Blood for haematology will be collected on Day 3 only.

[h] A full physical exam will occur at the Screening and Follow-up Visits. A brief physical exam will occur on Day -1 and Day 3 in each Treatment Period.

[i.] Blood samples will be taken at the following time points: up to 30 minutes pre-dose and at 30 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours post-dose.

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 Vital signs (systolic and diastolic blood pressure, pulse rate and tympanic temperature)

2 PK blood sampling (will be drawn at the specified time points)

3 Safety laboratory blood sampling

Tolerance windows for the assessments will be detailed in the WAD.

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 approximately 9 weeks and have approximately 4 study visits.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

This study has been designed to quantify the effects on verinurad PK when co-administered with cyclosporine, a broad transporter inhibitor, or rifampicin, an OATP1B1/3 inhibitor when given as a single dose.

A fixed-sequence design allows to determine whether cyclosporine or rifampicin affects the PK of verinurad. Verinurad is given in combination with allopurinol, since verinurad is developed as a fixed dose combination with allopurinol. This design is consistent with regulatory guidelines for drug interaction studies [11].

The 14-day washout period between Treatment Periods 2 and 3 dosing, is considered sufficient to avoid carry-over effects between Treatment Periods 2 and 3. The 7-14 days washout period between rifampicin administration and the Follow-up Visit is also considered a sufficient time period [18].

The PK sampling time points in all periods (up to 96 hours) are based on the plasma half-lives of the IMP as well as previous experience in assessing PK profiles of verinurad, allopurinol and their metabolites [1, 16].

3.2.2. Dose Rationale

A single dose of 7.5 mg verinurad, formulated as an extended release capsule (ER8) is selected for this study. This is the middle dose currently tested in a Phase 2b study. The AUC and Cmax of verinurad increases in a dose proportional manner after administration of single doses of 4.5 to 12 mg ER8 verinurad capsule. Multiple dosing of 24 mg ER8 verinurad once daily doses, and single doses of 40 mg verinurad as immediate release tablets, have been assessed previously in healthy volunteers and been found to be well tolerated.

A single dose of 300 mg of allopurinol was selected because it is the intended clinical dose in the verinurad+allopurinol fixed-dose-combination.

A single dose of 600 mg cyclosporine reflects daily doses in transplant patients and has been used in similar drug-drug interaction studies in the past [12, 13].

A single dose of 600 mg rifampicin is the highest daily recommended dose and has been used for both single and multiple dosing in drug-drug interaction studies in the past [14, 15].

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.

The main toxicity concern noted with verinurad monotherapy in healthy subjects is creatinine elevations >1.5 × baseline which occurred in 1.7% of healthy subjects. A change from baseline of ≥0.3 mg/dL was reported for 6.8% of all subjects. There was no apparent relationship between sCr elevation and dose of verinurad. The creatinine elevations were primarily transient, and often resolved despite continued dosing with verinurad. This risk is mitigated by combining verinurad with an XOI, excluding subjects with high uric acid and mandating hydration. Further information is provided in the IB [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 identified in the prescribing information are rash and blood thyroid-stimulating hormone increased. Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as drug rash with eosinophilia and systemic symptoms [DRESS]) and SJS/TEN. The human leukocyte antigen B (HLA-B)*58:01 allele has been shown to be associated with increased risk of developing allopurinol-related hypersensitivity

syndrome and SJS/TEN. The frequency of the HLA-B*58:01 allele varies widely between ethnic populations: up to 20% in the Han Chinese population, 8 to 15% in the Thai population, about 12% in the Korean population and 1 to 2% in individuals of Japanese or European origin. At the Screening Visit, the subject's HLA-B*58:01 status will be tested and carriers of HLA-B*58:01 will be excluded [16].

Overall, the study has been designed to minimize the risks to participating subjects by excluding subjects at high risk of AEs and by applying appropriate safety monitoring of recruited study subjects. This is a single dose study and subjects will only be exposed to 1 dose of each treatment (verinurad+allopurinol, verinurad+allopurinol+cyclosporine and verinurad+allopurinol+rifampicin). The dose selected has been carefully considered in light of the target subject population. The potential benefits of developing a new treatment for chronic kidney disease with hyperuricemia, therefore, outweigh the limited risks to the subjects exposed to verinurad and allopurinol single doses in this study.

3.3.1. Adverse Events, Contraindications and Warnings of Verinurad

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

Safety in healthy subjects was assessed in a pooled analysis of 8 Phase I (Studies 101, 103, 104, 105, 106, 110, 111, and 112) and in a single Phase I study (D5495C00006). A summary of information on clinical safety findings in healthy subjects is provided below; further details are available in the IB [1].

Adverse Events

The 8 pooled Phase I studies collectively enrolled 293 male subjects, treated at doses ranging from 5 to >15 mg; 94.5% of the subjects completed the planned treatment. Overall, 86 subjects (29.4%) experienced AEs. The incidence of AEs was similar among the pooled verinurad groups and pooled placebo groups. The most common AE was headache, which occurred in 12 subjects (4.1%). There was no apparent relationship between the incidence of these AEs and verinurad dose. Most AEs were RCTC toxicity Grade 1. Only 2 AEs had an RCTC toxicity >Grade 2, consisting of Grade 3 blood creatinine increased and Grade 3 tooth infection, both reported in subjects treated with verinurad doses ranging from 5 to <10 mg. There were no SAEs. Three subjects withdrew from the study due to AEs: 2 subjects who had received verinurad 5 mg (dehydration and influenza, respectively) and 1 subject who had received verinurad 15 mg and experienced urticaria.

Study D5495C00006 was a double-blind safety and PK study in healthy Asian and Chinese subjects who were randomised to receive verinurad + allopurinol or placebo. No deaths or

SAEs were reported in the study and no subject discontinued IMP due to an AE. All AEs reported on IMP were mild in intensity.

Laboratory Evaluations

In the pooled analysis of the 8 Phase I studies, sCr elevations ≥1.25 × baseline and ≥1.5 × baseline were reported for 13.7% and 1.7% of subjects, respectively. A change from baseline ≥0.3 mg/dL was reported for 6.8% of all subjects. There was no apparent relationship between sCr elevation and dose of verinurad. Furthermore, 18.4% of all subjects treated with verinurad experienced ALT elevations ≥1.5 × baseline, 5.1% experienced elevations ≥2.0 × baseline, and 2.0% experienced elevations ≥3.0 × baseline. There was no clear relationship with dose. Aspartate aminotransferase elevations ≥1.5 × baseline were reported for 6.1% of all subjects, while <1.5% of subjects experienced AST elevations ≥2.0 or ≥3.0 × baseline.

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

Vital Signs, Physical Findings, and Other Observations

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

Electrocardiogram Data

In 8 of the Phase I studies in healthy subjects there were no apparent treatment or dose-related trends in the 12-lead ECG parameters and no clinically important findings in the morphology of the 12-lead ECG for individual subjects. However, in 1 study (Study 101), prolongations in QT interval corrected for QTcB of >60 ms occurred in 2 subjects in the 1 mg fasted dose group; yet, no subjects had prolonged QTcB intervals >450 ms. Three subjects in the 1 mg fasted dose group and 1 subject in the 5 mg fasted dose group had prolonged QT intervals corrected for QTcF (>450 to 480 ms) although no subjects had a QTcF interval >480 ms. All episodes of QTcF >450 ms occurred at HRs <50 bpm.

Subjects with Gout or Asymptomatic Hyperuricemia

Information on clinical safety findings in subjects with gout or asymptomatic hyperuricemia is available in the IB [1].

3.3.2. Allopurinol

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

Please refer to the product information sheet of allopurinol tablets for information on PK, PD and safety [16].

3.3.3. Cyclosporine

Cyclosporine is a commercially available systemic immunosuppressant with a known safety and efficacy profile.

Although the mode of action is not fully understood, studies suggest that cyclosporine inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease, and also T-cell dependent antibody production. At the cellular level it inhibits production and release of lymphokines including interleukin 2 (T-cell growth factor, TCGF). Cyclosporine appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen-triggered release of lymphokines by activated T-cells. All available evidence suggests that cyclosporine acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not depress haemopoiesis and has no effect on the function of phagocytic cells.

Cyclosporine has a half-life of 6 hours in healthy volunteers, and discharge from the Clinical Unit at 96 hours post-dose deemed appropriate.

Some cyclosporine side effects are related to the cardiovascular system (hypertension) and central nervous system (tremor, headache, convulsions, paraesthesia, encephalopathy) and would theoretically influence the subject who has COVID-19 but these effects would pose minimal risks in healthy volunteers and short duration of treatment (such as a single dose of 600 mg cyclosporine).

Cyclosporine has been reported to inhibit the replication of diverse coronaviruses in vitro but this effect is not confirmed for SARS-CoV-2. In addition, cyclosporine may be beneficial in severe stages of COVID-19 based on inhibition on pro-inflammatory IL-2.

On consideration of the benefit/risk due to the COVID-19 pandemic, the single dose of cyclosporine is not considered to add any additional risk to the subjects, such as a reduction of the efficacy of the immune system.

Please refer to the Summary of Product Characteristics of cyclosporine capsules for details on PK, PD and safety [17].

Reports suggest that the plasma concentration of cyclosporine may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporine toxicity should be considered if the drugs are co-administered [1].

3.3.4. Rifampicin

Rifampicin is a commercially available semisynthetic antibiotic with a known safety and efficacy profile.

Please refer to the Summary of Product Characteristics of rifampicin for details on PK, PD and safety [18].

3.3.5. Risk Assessment for COVID-19 Pandemic

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, dyspnea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by subjects, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during in-house stay and outpatient visits will be implemented.
- The investigator will not dose subjects upon identification of any signs of COVID-19 infection.
- Confirmation of COVID-19 infection by optional 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 one 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 study participant (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

4. STUDY POPULATION

4.1. Selection of Study Population

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

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

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

4.1.1. Inclusion Criteria

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

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

2 Healthy male or female subjects aged 18 – 55 years (inclusive) with suitable veins for cannulation or repeated venipuncture.

3 Females must be either

(1) Of non-childbearing potential, confirmed at Screening by fulfilling one of the following criteria

(i) Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the post-menopausal range (FSH >40 IU/mL).

(ii) Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

4 Male subjects must adhere to the contraception methods in details in Section 4.2.1.2.

5 Have a BMI between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive).

6 Must be able to swallow multiple capsules/tablets.

4.1.2. Exclusion Criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled (for values deviating from the reference or specified range, one retest is allowed):

1 History of any clinically significant disease or disorder which, in the opinion of the Investigator, 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 Subject has a positive test result for SARS-CoV-2 before dosing in Treatment Period 1.

3 Has clinical signs and symptoms consistent with COVID-19 infection, eg fever, dry cough, dyspnea, sore throat, fatigue or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission.

4 History of severe COVID-19 (ECMO, mechanically ventilated).

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

6 Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks prior to the first administration of verinurad.

7 Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results, at Screening (Visit 1) and on first admission (Day –1 in Treatment Period 1) as judged by the Investigator, including:

   1) ALT >1.5 × ULN
   2) AST >1.5 × ULN
   3) Bilirubin (total) >1.5 × ULN
   4) GGT >1.5 × ULN

   If any of these tests are out of range, the test can be repeated once at the Screening Visit at the discretion of the Investigator.

8 Any clinically significant abnormal findings in vital signs at Screening Visit and/or on admission (Day -1 in Treatment Period 1) to the Clinical Unit, including, but not limited to, any of the following:

   1) Systolic blood pressure <90 mmHg or >140 mmHg and/or diastolic blood pressure <50 mmHg or >90 mmHg sustained for more than 10 minutes while resting in a supine position
   2) Heart rate (resting, supine) <50 or >90 bpm

9 Any clinically significant abnormalities on 12-lead ECG at Screening Visit, as judged by the Investigator, including, but not limited to any of the following:

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

10 Any positive result at Screening Visit for serum hepatitis B surface antigen or anti-HBc antibody, hepatitis C antibody, and HIV antibody.

11 Suspicion or known Gilbert’s and/or Lesch-Nyhan syndrome.

12 History of hypersensitivity to drugs with a similar chemical structure or class to verinurad, allopurinol, cyclosporine or rifampicin or excipients.

13 Subjects who wear soft contact lenses (due to possible staining from rifampicin), unless the subject is prepared to refrain from wearing soft lenses throughout Treatment Period 3 until after the last PK sample collection.

14 Women of childbearing potential.

15 Carrier of the HLA-B*58:01 allele.

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

Note: subjects consented and screened, but not randomised in a previous Phase I study, are not excluded.

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

18 History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to URAT1 transporter inhibitor & XOI.

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

20 Positive screen for drugs of abuse, cotinine (nicotine) or alcohol at Screening or on each admission to the Clinical Unit.

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

22 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 IMP or longer if the medication has a long half-life.

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

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

25 Involvement of any AstraZeneca, Parexel or Clinical Unit employee or their close relatives.

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

27 Subjects who are vegans or have medical dietary restrictions.

28 Subjects who cannot communicate reliably with the Investigator and/or are not able to read, speak and understand the German language.

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

4.2. Restrictions During the Study

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

1 On Day 1 of each treatment period (Period 1, Period 2 and Period 3), subjects will be fasted for at least 10 hours prior to dosing until 4 hours after dosing. Water will be allowed except from 1 hour before and after dosing. (excluding water used in conjunction with dosing; see Section 5.4.3).

2 Subjects will be instructed to drink approximately 2 L to 2.5 L of liquid a day (including Day -1) throughout the duration of the study.

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

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

5 Subjects should abstain from alcohol for 72 hours from the first check-in (Day -1 of Treatment Period 1) until after their last PK sampling visit. Subjects should also abstain from alcohol for 72 hours before the Screening Visit and their final Follow-up Visit.

6 Prior to each treatment period, subjects should abstain from caffeine-containing foods and beverages (eg, coffee, tea, chocolate) for 24 hours prior to check-in until discharge from the Clinical Unit.

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

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

9 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 final Follow-up Visit has been completed. Subjects

should also limit their caffeine intake to equivalent of 3 servings of coffee per day (1 serving = 330 mL cola, 180 mL coffee, or 240 mL tea).

10 Subjects who wear soft contact lenses, unless the subjects is prepared to refrain from wearing soft lenses from check-in (Day -1 in Treatment Period 1) until after the last PK sample collection.

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

12 Subjects are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. All subjects are called one 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 study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

For medication restrictions, please refer to Section 11.2.4.1.

4.2.1. Reproductive Restrictions

Verinurad is not genotoxic, has no effect on fertility in animal studies, and carries a low risk for foetal harm at maternally nontoxic doses in animal studies. 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 [1].

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

Cyclosporine and rifampicin have both been shown to have reproductive toxicity in animal studies and falls under the FDA Pregnancy category C [17, 18].

Therefore, a female subject who participates in the clinical trial must either:

- Be of non-childbearing potential, that is, must be surgically sterilised or
- Be post-menopausal as described in Section 4.2.1.1

4.2.1.1. Women of Non-Childbearing Potential

Only women who are of non-childbearing potential will be allowed to participate in this study. Women of non-childbearing potential are defined as female subjects who are permanently surgically sterilised or post-menopausal.

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

4.2.1.2. Male Subjects

Restrictions for Male Subjects

Verinurad had no effects on fertility or embryo-foetal development in rats at doses up to 300 mg/kg/day and did not affect embryo-foetal development in rabbits at doses up to 30 mg/kg/day. Therefore, it is important that women of childbearing potential, who are the partners of male subjects, do not become pregnant during the study and for a total period of 3 months after the male subject has attended the study Follow-up Visit.

Male subjects who have been sterilised are required to use one barrier method of contraception (condom) from the time of IMP administration until after the follow-up visit. The subject must have received medical assessment of the surgical success.

As a precaution, all non-sterilised male subjects should avoid fathering a child by either true abstinence[1] or use a condom and their female partner/spouse has to be either of non-childbearing potential or has to use a highly effective contraception form of birth control, starting from the time of IMP administration until 3 months after the study follow-up visit. The female partner/spouse should be stable on their chosen method of birth control for at least 3 months first dosing.

Highly effective contraception form of birth control, ie. a form of birth control with a failure rate of less than 1% per year when used consistently and correctly, are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

[1] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the subject.

  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine system
- Bilateral tubal occlusion of female partner

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

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

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

4.3. Replacement of Subjects

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

5. STUDY CONDUCT

5.1. Subject Enrolment and Randomisation

As this is a fixed sequence study, randomisation does not apply.

The Investigator will ensure:

- Signed ICF 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 ICF.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique enrolment code.

When using unique enrolment number, the specific format must be followed (i.e., 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 code cannot be reused. If a replacement is mandated, replacement subjects will receive a new enrolment number.

5.2. Procedures for Handling Incorrectly Enrolled Subjects

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

Where a subject, who does not meet the selection criteria, is enrolled 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 Investigator 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 test products (verinurad, allopurinol) and interaction products (cyclosporine and rifampicin) are presented in Table 5-1.

Table 5-1 Identity of the Investigational Medicinal Product

Investigational Medicinal Product Name	**Verinurad**	**Allopurinol**	**Cyclosporine**	**Rifampicin**
Trade Names:	Verinurad	Allopurinol	Sandimmun Optoral	Eremfat
Manufacturer:	AstraZeneca	Teva Pharmaceutical	Novartis Pharma GmbH	RIEMSER Pharma GmbH
Formulation:	Capsule	Tablet	Soft Capsule	Film coated Tablets
Strength/concentration:	7.5 mg	300 mg	100 mg	600 mg
Dose:	7.5 mg	300 mg	600 mg	600 mg
Route of administration:	Oral	Oral	Oral	Oral
Specific device for drug administration, if applicable:	Not applicable	Not applicable	Not applicable	Not applicable
Regimen:	Single dose of 7.5 mg	Single dose of 300 mg	Single dose of 600 mg	Single dose of 600 mg
Special handling requirements:	Not applicable			

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

Verinurad and allopurinol will be supplied by AstraZeneca and provided in study-specific labeled bottles. Cyclosporine and rifampicin will be sourced by Parexel.

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

5.4.3. Dose and Treatment Regimens

Subjects will receive single oral doses of verinurad, allopurinol, cyclosporine and rifampicin in the following Treatment Periods under fasted conditions.

- Treatment Period 1: 7.5 mg verinurad and 300 mg allopurinol, fasted state (>10 h)

- Treatment Period 2: 7.5 mg verinurad, 300 mg allopurinol and 600 mg cyclosporine, fasted state (>10 h)
- Treatment Period 3: 7.5 mg verinurad, 300 mg allopurinol and 600 mg rifampicin, fasted state (>10 h)

The dose will be administered after an overnight fast of at least 10 hours and will be taken with 240 mL of water.

Subjects will be allowed to drink water to prevent dehydration until 1 hour before dosing.

Water will be allowed ad libitum from 1 hour after dosing and a standard meal will be given 4 hours after dosing.

After dosing, subjects will remain semi-supine on their bed or sitting (except when necessary for study procedures) until completion of the 4 hour vital sign assessments.

Subjects will receive the following IMPs in each Treatment Period, respectively:

Table 5-2 IMP in each Treatment Period

Treatment Period	IMP	Formulation	Dose
Period 1	Verinurad	Capsule	1 x 7.5 mg
	Allopurinol	Tablet	1 x 300 mg
Period 2	Verinurad	Capsule	1 x 7.5 mg
	Allopurinol	Tablet	1 x 300 mg
	Cyclosporine	Soft Capsule	6 x 100 mg
Period 3	Verinurad	Capsule	1 x 7.5 mg
	Allopurinol	Tablet	1 x 300 mg
	Rifampicin	Film coated Tablet	1 x 600 mg

Other restrictions, including posture control are described in Section 29. Data of subjects may be excluded from the PK analysis set as described in Section 11.1.3.

5.4.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines.

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

5.4.5. Storage and Handling Procedures

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

5.5. Concomitant and Post-study Treatment(s)

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed.

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

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

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

5.6. Treatment Compliance

Dosing will take place at the Parexel Early Phase Clinical Unit – Berlin site.

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.

5.6.1. Drug Accountability, Dispensing and Destruction

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

In accordance with GCP, the investigational site will account for all supplies of verinurad, allopurinol, cyclosporine and rifampicin. Details of receipt, storage, dispensing and return will be recorded.

All unused supplies of verinurad, allopurinol, cyclosporine and rifampicin 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 will be stopped if the subject experiences a possibly drug-related SAE or a possibly drug-related significant non-serious AE, which in the opinion of the Investigator warrants discontinuation of the subject from the active protocol for his or her well-being.

Subjects must be discontinued from treatment in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, laboratory assessments and AE) making the continuation of IMP treatment administration unjustified.
- Study specific withdrawal criteria: If a subject reports symptoms which are considered unacceptable by the subject or the Investigator, he/she will be withdrawn from the study. In particular:
  - Any other severe or serious adverse event (SAE) that is judged as possibly related to the treatment by the Investigator
  - Any case of Potential Hy's Law (PHL) according to Appendix C
  - 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.
  - Any suspected or confirmed COVID-19 case will be immediately discontinued from study treatment

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 subjects safety.

5.8. Premature Termination of the Study

The study must be terminated prematurely if:

- The Investigator and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance, when there is 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered at least possibly related to the IMP by the Investigator and the Sponsor.
- The Sponsor considers the applied doses of the IMP to be no longer relevant.

- The Sponsor decides to discontinue the study.
- Data, that was now known before, becomes available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.
- New data become available regarding COVID-19, which raise concern for the safe study conduct so that continuation would pose potential risks to the subjects or the study site staff.

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

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 verinurad, allopurinol, cyclosporine and rifampicin 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

There will be 12-lead ECG, measurement of blood pressure, pulse rate and tympanic temperature, clinical laboratory evaluations, and a physical examination during the Screening Visit. Viral serology and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility. Follicle-stimulating hormone (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
- 12-lead ECG
- Vital signs (systolic and diastolic blood pressure, pulse rate and 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 unfavorable 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 IMP has been administered.

6.3.1.2. Definitions of Serious Adverse Event

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

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

Adverse events for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement 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 hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

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

6.3.1.4. Recording of Adverse Events

Time Period for Collection of Adverse Events

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

Serious adverse events will be recorded from the time of ICF.

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

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)
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed

- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The following intensity ratings will be used:

1 Mild (awareness of sign or symptom, but easily tolerated)

2 Moderate (discomfort sufficient to cause interference with normal activities)

3 Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.1.2.
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

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 AEs if they fulfill any of the SAE criteria, is clinically significant according to the Investigator judgment, or are the reason for discontinuation of treatment with the investigational product.

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 ≥ 3 x ULN together with total bilirubin ≥ 2 x 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.

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 in the IB for the AstraZeneca drug.

6.3.1.6. Regulatory Reporting Requirements for SAEs

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

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

For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSAR 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
Hemoglobin (Hb)	Monocytes absolute count
Hematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular hemoglobin (MCH)	Platelets
Mean corpuscular hemoglobin concentration (MCHC)	Reticulocytes absolute count

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 (TBL)
Calcium	Unconjugated bilirubin
Phosphate	Cystatin-C
Glucose(fasting)	Uric acid
C-reactive protein (CRP)	Follicle-stimulating hormone (FSH[a,b])
Thyroxine (T_4[a])	Thyroid stimulating hormone (TSH[a])

[a] Screening only
[b] All women

6.3.2.3. Genotyping

Genotyping	
HLA-B*58:01	

HLA-B: Human leukocyte antigen B

6.3.2.4. Urinalysis

Urinalysis[a]	
Glucose	pH
Protein	Potassium
Blood	Sodium
Creatinine	Lactic Acid
Aldosterone	

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

6.3.2.5. Viral Serology

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

6.3.2.6. SARS-CoV-2 Serology

SARS-CoV-2 Serology	
SARS-CoV-2 RT-PCR*	

* A nasopharyngeal or oropharyngeal swab will be collected

6.3.2.7. Drugs of Abuse, Alcohol and Cotinine

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

6.3.3. Physical Examination

Full

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

Brief (Abbreviated)

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

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 sites' own ECG machines.

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

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

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

All ECG readings will be digitally stored as source documents.

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 blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Temperature (tympanic)

Supine pulse (bpm), temperature (tympanic) and blood pressure (mmHg) will be measured at the time points indicated in Table 3-1. Measurement will be performed according to the relevant Parexel SOPs, subsequent to at least a 5-minute rest. Systolic and diastolic blood pressure will be measured using the same cuff size, appropriate for arm circumference. Body temperature will be measured at least once daily on every visit or during in-house stay.

6.4. Pharmacokinetics

6.4.1. Collection of Pharmacokinetic Samples

6.4.1.1. Whole Blood Samples

Blood samples for the determination of concentrations of verinurad, M1, M8, allopurinol and oxypurinol will be collected for each treatment period as specified in the SoA (Table 3-1). Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual.

Blood samples for the determination of concentrations of cyclosporine and rifampicin will be collected for each treatment period as specified in the SoA (Table 3-1). If the concentration analysis is done, it will be reported separately from the CSR.

6.4.2. Pharmacokinetic Drug Assays

Blood samples for determination of verinurad, M1, M8, allopurinol and oxypurinol concentrations in plasma will be analysed by Covance Bioanalytical Services on behalf of AstraZeneca, using validated assays.

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

Exploratory blood samples for cyclosporine and rifampicin will be stored by Covance Bioanalytical Services on behalf of AstraZeneca until the decision for analysis is made. Full details of the analytical method and analyses performed will be described separately to this document.

6.5. Pharmacodynamics

This section is not applicable as there are no pharmacodynamic assessments in this study.

6.6. Pharmacogenetics

This section is not applicable as there are no pharmacodynamic assessments in this study.

6.7. Biomarkers

This section is not applicable as there are no biomarker assessments in this study.

6.8. Immunogenicity

This section is not applicable as there are no immunogenicity assessments in this study.

6.9. Metabolites

No additional blood samples will be collected for metabolite identification.

7. BIOLOGICAL SAMPLES PROCEDURES

All biological samples will be 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
Haematology	2.7 mL	7	18.9 mL
Clinical chemistry[a]	7.5 mL	4	30.0 mL
	2.6 mL	3	7.8 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
PK blood draws for verinurad and metabolites	3.0 mL	51	153.0 mL
PK blood draws for allopurinol	2.0 mL	51	102.0 mL

	Volume per Sample	Number of Samples	Total
Exploratory PK blood draws for cyclosporine	1.0 mL	17	17.0 mL
Exploratory PK blood draws for rifampicin	1.0 mL	17	17.0 mL
Total			351.3 mL

ELISA: Enzyme-linked immunosorbent assay; HLA-B: Human leukocyte antigen B; FSH: Follicle-stimulating hormone.
[a] When applicable, serology and FSH (females only) analyses will be performed on the sample collected for clinical chemistry analyses.

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

7.2. Handling, Storage and Destruction of Biological 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.

7.2.1. Pharmacokinetic Samples

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

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

Incurred sample reproducibility analysis or additional assay development work, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

7.2.2. Pharmacodynamic Samples – Not Applicable

7.2.3. Pharmacogenetic Samples – Not Applicable

7.3. Labeling and Shipment of Biohazard Samples

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

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

7.4. Chain of Custody of Biological Samples

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

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

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

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

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.

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

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

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 (version 1996) 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 Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

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

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

8.3. Ethics and Regulatory Review

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

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

Parexel will provide the IEC and Investigator with safety updates/reports according to local requirements, including 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 ICF will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his/her free ICF, prior to the start of the study.

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

8.6. Changes to the Protocol and Informed Consent Form

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

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

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

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

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 Investigator must allow the applicable persons access to all relevant facilities and data/documents. The Investigator must be available to discuss any findings/issues.

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

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 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 Investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase™ by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase™.

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 Investigator 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 Investigator assures the Sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 Code of Federal Regulations 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 Investigator 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. Safety Variables

10.1.1. Adverse Events

All AEs will be coded using the latest version of the 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 treatment 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 Follow-up Visit,

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

- Adverse events with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- Adverse events with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- Adverse events with partially known start dates/times will be treated as follows:
  - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
  - If only the month is missing and the year is a year in which IMP was administered, then the month will be imputed with the first month in which IMP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IMP was administered, then the month will also be imputed with JAN.
  - If both the day and month is missing and the year is a year in which IMP was administered, then the day and month will be imputed with the day and month of dosing. If this results in a start date after end date, then the day and month will be

imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.

– If only the year is missing, then the year will be imputed with the year of dosing.

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 CRFs.

Adverse events with onset (start date/time) after dosing in Treatment Period 1, up to and including the final Follow-up visit will be summarised by treatment period 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 (PT). Furthermore, separate listings of SAEs, AEs that led to discontinuation (DAEs) and AEs that led to death will be presented.

Adverse events will be listed by subject and treatment, including the following information: 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 value and changes from baseline will be presented by treatment period and time point for the safety analysis set. The baseline for the measurements will be the last assessment performed prior to dosing in Treatment Period 1. Changes from baseline will be calculated and presented for all post-baseline time points including the Follow-up Visit. Shift tables will also be presented.

Any laboratory parameters 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)
- The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

10.1.3. Physical Examination and Body Weight

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

For each subject, 12-Lead ECG results will be listed, including classifications as "Normal", "Abnormal, clinically significant" and "Abnormal not clinically significant".

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 last assessment prior to dosing in Treatment Period 1. Descriptive statistics will be presented by treatment and time point for both observed values and changes from baseline.

10.2. Pharmacokinetic Variables

Where possible, the following PK parameters will be determined for verinurad, its metabolites M1 and M8, allopurinol and oxypurinol using plasma concentrations for Treatment Period 1 (reference treatment), Treatment Period 2 (test treatment 1) and Treatment Period 3 (test treatment 2).

10.2.1. Plasma Parameters

Primary PK parameters

Cmax	Maximum observed plasma peak concentration
AUCinf	Area under plasma concentration-time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from zero to time of last quantifiable concentration

Secondary PK parameters

AUC(0-24)	Area under plasma concentration-time curve from zero to 24 hours post-dose
tmax	Time to reach peak or maximum observed concentration following drug administration
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
λz	Terminal elimination rate constant
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug only)
MRTinf	Mean Residence Time of the unchanged drug in the systemic circulation
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)
MRCmax	Ratio of metabolite Cmax to parent Cmax
MRAUCinf	Ratio of metabolite AUCinf to parent AUCinf
MRAUClast	Ratio of metabolite AUClast to parent AUClast

Diagnostic PK Parameters

The following diagnostic parameters for plasma PK analysis will apply:

tlast	Time of last observed (quantifiable) concentration
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
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 (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as a percentage of AUCinf

10.2.2. Calculation or Derivation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived from the plasma concentration data for verinurad, M1, M8, allopurinol and oxypurinol using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher. All descriptive and inferential statistical computations will be performed using SAS® Version 9.3, or higher.

The PK parameters are calculated/estimated according to AZ standards [19].

Pharmacokinetic analysis for each analyte will, where data allows, be carried out using actual times determined from the PK sampling and dosing times recorded in the database. If actual times are missing, nominal times may be used.

10.3. Pharmacodynamic variable(s) – Not Applicable

10.4. Pharmacogenetics – Not Applicable

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of the Analysis Sets

11.1.1. Enrolled Set

The enrolled set will consist of all subjects who were enrolled and assigned to treatment.

11.1.2. Safety Analysis Set

The safety analysis set will include all subjects who received at least the dose of verinurad+allopurinol in Treatment Period 1 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.

11.1.3. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the Safety Analysis Set who receive verinurad+allopurinol 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.

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

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

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 modeling assumptions will be documented appropriately.

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

Demographic and baseline data will be summarised overall for all dosed subjects. Pharmacokinetic data will be summarised by treatment. Safety and tolerability data will be summarised by treatment period, if applicable.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics for safety data (n, mean, SD, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n > 3$. 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, minimum and maximum will be presented; the other descriptive statistics will be left blank.

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

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

The planned sequence for measurement of multiple assessments at the same time point is described in Section 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 9.3 or later.

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 non-quantifiable (NQ) in the PK data will be handled as described in Section 11.2.6.

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

11.2.3. Subject Characteristics

An enrollment listing will be presented and include each subject's full enrolment number and the country where the Clinical Unit 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 enrolled and dosed, number and percentage of subjects completing each ttreatment period of the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all dosed subjects.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of ICF 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 overall. The denominator for percentages will be the number of all subjects dosed.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA SOC, MedDRA PT, 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 AstraZeneca dictionary.

The duration of medication use 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.

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 PT 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 occur before dosing 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 from the baseline when baseline is defined. Clinical laboratory data will be reported in Système International units in the CSR.

Out-of-range values for safety laboratory 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 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, M1, M8, 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 period for each analyte separately using CSP scheduled times and appropriate descriptive statistics.

Further details on presentation of PK concentration and parameter data will be presented according to the most recent version of the AZ CPE TFL 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 concentrations with time deviations of greater than ±10% from the CSP scheduled time will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scale with the test and reference 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.

Gmean (+/- 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 Analysis of Pharmacokinetic Data

The PK parameters (Cmax, AUCinf and AUClast) of verinurad, M1, M8, allopurinol and oxypurinol will be analysed using an analysis of variance model following a natural logarithmic transformation, with fixed effects for treatment and subject. Least-squares geometric means, 2-sided 95% confidence intervals, ratios of geometric means together with 2-sided 90% confidence intervals of test treatment (verinurad+allopurinol+cyclosporine or verinurad+allopurinol+rifampicin), and reference treatment (verinurad+allopurinol) will be estimated and presented. Descriptive statistics will be presented for PK concentration-time data and PK parameters for verinurad, M1, M8, allopurinol and oxypurinol.

11.2.8. Pharmacodynamics – Not Applicable

11.2.9. Pharmacogenetics – Not Applicable

11.2.10. Exploratory Data

Results from exploratory data will not form part of the CSR and will not be included in the tables, figures or listings of this study.

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.

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

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 8.6.

11.4. Determination of Sample Size

The number of subjects is based on the desire to gain adequate information on the primary endpoints while exposing as few subjects as possible to study procedures. Interpretation of the results will be based on the size of the treatment ratio and associated 90% CI. It is estimated that 12 subjects will provide a CI within 1.58 to 2.53 with a probability of 80% if the calculated treatment ratio is 2. This is based on an intra-subject CV of 24% for verinurad.

A total of 14 healthy subjects will be enrolled to ensure at least 12 evaluable subjects at the end of the last treatment period.

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1. Medical emergencies and AstraZeneca contacts

In case of medical emergency, the primary contact is the Investigator. The Investigator may contact the Sponsor's Lead Physician. If the Investigator cannot be reached, the site's staff will contact the Investigator's deputy or may contact Sponsor's Lead Physician.

Name	Role in the Study	Contact Details
Thomas Koernicke	Principal Investigator	Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany PPD
PPD	Sponsor's Lead Physician	AstraZeneca R&D Gothenburg PPD 431 83 Mölndal Sweden PPD

12.2. Pregnancy

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

- If the pregnancy is discovered before the study patient has received any IMP.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Please refer to Section 4.2.1 for further details.

12.2.1. Paternal exposure

Male subjects should refrain from fathering a child during the study and for 3 months after the Follow-up Visit.

In case of pregnancy of the partner of a male patient, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the patient's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be obtained and documented.

Please refer to Section 4.2.1.2 for further details.

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the 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 15 years after completion of the study.

13.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, 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.

13.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the 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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15. 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 edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the 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 jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anemia 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 recognized feature of overdose of the drug?
- Is there a known mechanism?

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

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

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

Appendix B International Airline Transportation Association 6.2 Guidance Document

Labeling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) 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 Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

The Investigator will also review adverse event (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 Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious adverse events (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

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

Hy's Law

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

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

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 x ULN
- ALT ≥ 3 x ULN
- TBL ≥ 2 x 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 C 4 below 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.

[#] 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 TBL) 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.

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)
- 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 tests	GGT LDH	
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

Appendix D Actions Required in Cases of a Renal-related 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.

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 hematuria), 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 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.

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):
  1. 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.

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

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