2 SYNOPSIS

Title of Study:	A Single-Centre, Randomised, Double-Blind, Placebo-Controlled, 3-Period, Cross-Over Phase I Study to Investigate the Effect on the QTcF Interval of a Single Dose of 2 Different Doses of Verinurad, Each in Combination with Allopurinol 300 mg, Compared with Placebo In Healthy Volunteers	
Study Numbers:	Parexel Study No.: PXL244261 Sponsor Study No.: D5495C00012	
Investigational Medicinal Products:	Test Products: Verinurad extended-release capsule, 24 mg Verinurad immediate-release capsule, 40 mg Allopurinol tablet, 300 mg Reference Product: Placebo	
Indication Studied:	Chronic Kidney Disease	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Thomas Körnicke, MD	
Study Centre:	Parexel Early Phase Clinical Unit (Berlin) PPD 14050 Berlin Germany	
Publication:	None	
Study Duration:	First subject first visit: 03 Mar 2020 / restart on 24 Jun 2020 due to COVID-19 pandemic	Last subject last visit: 21 Sep 2020

Study Objectives:

Primary objective:

To assess the effect of a single dose of verinurad given as either a 24 mg extended-release (ER8) formulation (clinical exposure) or a 40 mg immediate-release (IR) formulation (exposure needed to waive positive control as per question 5.1 of International Council for Harmonisation Guideline E14 and associated Questions and Answers [ICH E14 Q&A]), both in combination with allopurinol 300 mg, on the QT interval corrected for heart rate (HR) using Fridericia's formula (QTcF) compared to placebo using a concentration-QTcF analysis.

Secondary objectives:

- To investigate the effect of verinurad given either as a 24 mg ER8 formulation (clinical exposure) or a 40 mg IR formulation (exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A), both in combination with allopurinol 300 mg, on HR and additional digital electrocardiogram (dECG) variables (PR, QRS, QT, and RR).
- To assess the pharmacokinetics (PK) of verinurad and its metabolites (M1 and M8) and allopurinol and its metabolite (oxypurinol) in healthy volunteers.

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- To assess the relationship between plasma concentrations of verinurad, allopurinol and the metabolites M1, M8, oxypurinol and dECG variables and HR.
- To examine the safety and tolerability of verinurad and allopurinol.

Study Design:

This study was conducted as a single-centre, randomised, placebo-controlled, double-blind, 3-period, cross-over study to assess the effect on the QTcF interval of a single oral dose of verinurad 24 mg ER8 formulation (clinical exposure) or verinurad 40 mg IR formulation (exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A), each in combination with allopurinol 300 mg, compared to placebo in healthy volunteers.

There were 3 study treatments:

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

All subjects were to receive a single dose of all 3 treatments (A, B, and C) in a cross-over design with wash-out periods of at least 7 days between each study dose administration.

Subjects were randomised to a treatment sequence (ABC, BCA, CAB, ACB, BAC, or CBA) using William's Latin square. The treatments were administered in a double-blind manner after an overnight fast of at least 10 hours.

The study comprised the following periods (visits):

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

Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
24 subjects	24 subjects	22 subjects

Main Inclusion Criteria:

This study included healthy male and female volunteers aged 18 to 50 years (inclusive) who had a body mass index between 18 and 30 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 100 kg (inclusive). Subjects were to have serum uric acid levels < 300 µmol/L at Screening (Visit 1) and < 330 µmol/L on Day −1 in every treatment period (Visits 2 to 4).

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Investigational Medicinal Products: Verinurad and Matching Placebo			
	Verinurad 12 mg ER8	**Verinurad 10 mg IR**	**Placebo**
Supplier:	AstraZeneca	AstraZeneca	AstraZeneca
Formulation:	Capsule	Capsule	Capsule
Strength/Concentration:	12 mg ER8	10 mg IR	Not applicable
Dose:	24 mg ER8	40 mg IR	Not applicable
Route of Administration:	Oral	Oral	Oral
Regimen:	2 × 12 mg verinurad ER8 capsule formulation	4 × 10 mg verinurad IR capsule formulation	2 × or 4 × placebo capsule matching verinurad*
Batch/Manufacturing Lot Numbers:	L013800	L013797	L013766
Expiry Dates:	07/2021	09/2020	01/2024
*Subjects receiving Treatment A received 2 placebo capsules matching verinurad; subjects receiving Treatment C received 4 placebo capsules matching verinurad.			
Investigational Medicinal Products: Allopurinol and Matching Placebo			
	Allopurinol	**Placebo**	
Supplier:	AstraZeneca	AstraZeneca	
Formulation:	Tablet	Tablet	
Strength/Concentration:	300 mg	Not applicable	
Dose:	300 mg	Not applicable	
Route of Administration:	Oral	Oral	
Regimen:	1 × 300 mg allopurinol tablet formulation	1 × placebo tablet matching allopurinol 300 mg	
Batch/Manufacturing Lot Numbers:	L013739	L013759	
Expiry Dates:	02/2022	03/2022	
Duration of Treatment: The planned duration of subject involvement in the study was approximately 53 days and included 5 study visits.			
Treatment Compliance: Dosing took place at the study centre (Parexel Early Phase Clinical Unit). Compliance was assured by direct supervision and witnessing of investigational medicinal product (IMP) administration.			

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Criteria for Evaluation:

Pharmacodynamic Parameters:

Note that 'Δ' refers to baseline-corrected values; 'ΔΔ' refers to baseline-corrected and placebo-corrected values.

- QTcF and maximum observed plasma concentration (Cmax) for the primary outcome measure ΔΔQTcF (derived from concentration-QTcF analysis)
- dECG variables HR, RR, PR, QRS, QT, and QTcF for baseline-corrected and placebo-corrected dECG variables (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval)
- Plasma concentration of each analyte at each time point and the time-matched dECG variables HR, RR, PR, QRS, QT, and QTcF for the outcome measure time-matched, baseline-corrected and placebo-corrected dECG variables (ΔHR, ΔΔHR, ΔRR interval, ΔΔRR interval, ΔPR interval, ΔΔPR interval, ΔQRS interval, ΔΔQRS interval, ΔQT interval, ΔΔQT interval, ΔQTcF interval, ΔΔQTcF interval)

Pharmacokinetic Parameters:

- For each analyte (verinurad, M1, M8, allopurinol, and oxypurinol): Area under plasma concentration-time curve from time zero extrapolated to infinity (AUC), area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC[0-t]), Cmax, time to reach maximum plasma concentration (tmax), time delay between drug administration and the first observed concentration in plasma (tlag), terminal half-life ($t_{½\lambda z}$), time of last quantifiable plasma concentration (tlast), apparent total body clearance of drug from plasma after extravascular administration (parent drug only) (CL/F), apparent volume of distribution during the terminal phase after extravascular administration (parent drug only) (Vz/F), apparent volume of distribution at steady state following extravascular administration (parent drug only) (Vss/F), and mean residence time of the unchanged drug in the systemic circulation from zero to infinity (MRT).
- Plasma concentration-time profile for each analyte.

Safety Variables:

Assessment of adverse events (AEs), laboratory variables (haematology, clinical chemistry, and urinalysis), vital sign variables (systolic and diastolic blood pressure, pulse rate, body temperature), electrocardiogram (ECG) variables, telemetry findings, and physical examination findings.

Statistical Methods:

Analysis Populations:

- Randomised Set: The Randomised Set consisted of all subjects randomised into the study.
- Safety Analysis Set: Included all subjects who received at least 1 dose of IMP (verinurad, allopurinol, and placebo) and for whom any safety post-dose data were available.
- Pharmacodynamic Analysis Set: Consisted of all subjects in the Safety Analysis Set for whom baseline and post-baseline QTcF results from smoothed dECG data were available for at least 1 treatment period and who had no major protocol deviations thought to impact the analysis of the dECG data.
- Pharmacokinetic Analysis Set: Consisted of all subjects in the Safety Analysis Set for whom at least 1 reportable PK parameter could be calculated and who had no major protocol deviations thought to impact the analysis of the PK data.

Presentation and Analysis of Pharmacodynamic Data:

Digital ECG variables (absolute values and change from baseline for: HR, RR, PR, QRS, QT, and QTcF) were listed by subject and time point and summarised by treatment group using appropriate descriptive statistics; in addition, exploratory plots were provided (such as time course for each dECG variable, changes from baseline for each dECG variable, by treatment group, mean with standard deviation [SD]) and time course for each

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dECG variable (RR, HR, PR, QRS, QTcF), baseline-corrected and placebo-corrected, for each treatment group.

A linear mixed-effect concentration-QTcF model was used as the primary analysis. Baseline-corrected and placebo-corrected QTcF (ΔΔQTcF), using individual time-matched placebo for a given subject, was the dependent variable and verinurad plasma concentration was the independent variable. Fixed effects were intercept in the absence of a treatment effect and slope of the assumed linear association between concentration and ΔΔQTcF and baseline QTcF. Random effects were included on the intercept term and the slope. ΔΔQTcF at the high clinical exposure scenario (76 ng/mL) was estimated. A prolonging effect as per regulatory guidance was excluded if the upper bound of the 2-sided 90% confidence interval (CI) for model-derived ΔΔQTcF was estimated to be < 10 msec at the highest clinically relevant exposure.

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

Presentation and Analysis of Pharmacokinetic Data:

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

Presentation and Analysis of Safety Data:

All AEs were coded using Medical Dictionary for Regulatory Activities vocabulary (MedDRA) (Version 23.0).

Safety data were presented in data listings. Continuous variables were summarised using descriptive statistics by treatment. Changes (and/or percentage change) from baseline were presented where applicable when baseline was defined. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment.

Tabulations and listings of data for vital signs and clinical laboratory tests were presented; 12-lead safety ECG data were listed only.

Adverse events were summarised by treatment and overall for all subjects, including tabulations by causality and severity (mild, moderate, and severe). All tabulations were presented by system organ class (SOC) and preferred term. An overview of all AEs was presented, separately for the number and percentage of subjects and the number of events. This included categories for any AE, serious adverse event (SAE), AE leading to discontinuation of IMP (DAE), and AE with outcome of death. Listings of all AEs, SAEs, DAEs, and AEs with outcome of death were presented.

Haematology and clinical chemistry values were listed by subject and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations including absolute value and changes from baseline were presented by treatment and time point for the Safety Analysis Set.

Vital signs measurements were listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements.

Determination of Sample Size:

The study sample size for a concentration-QTcF-based analysis is based on the recommendation from Garnett et al 2018 to have 16 to 32 subjects on drug and 8 to 16 subjects on placebo. The type-1 error rate has been

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shown to be controlled at around 5% when the true effect is 10 msec in small-sized studies of 6 to 12 subjects with multiple measurements per subject. A 3-period cross-over study, using concentration-QTcF-based analysis, with 2 verinurad doses and placebo in 20 evaluable healthy volunteers was expected to exceed the recommendations proposed by the scientific white paper on concentration-QTc modeling (Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-97).

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

Evaluable subjects were defined as subjects for whom baseline and post-baseline QTcF results from smoothed dECG data were available for at least 2 treatment periods (where 1 of the treatment periods needed to be the period in which the subject received placebo), and who had no major protocol deviation thought to impact the analysis of the dECG data.

Protocol Deviations:

No important protocol deviations were identified in this study.

Pharmacodynamic Results:

- Concentration-QT model (primary analysis):
  - Estimated mean ΔΔQTcF at the pre-specified verinurad concentration of 76 ng/mL (ie, high clinical exposure scenario which is the increase in Cmax considering intrinsic or extrinsic factors when the maximum therapeutic dose is given) was -2.7 msec (90% CI -4.6,-0.8); estimated mean ΔΔQTcF at the geometric mean Cmax after verinurad 24 mg ER8 formulation co-administered with 300 mg allopurinol (56.57 ng/mL) was -2.8 msec (90% CI -4.7,-0.9); and estimated mean ΔΔQTcF at the geometric mean Cmax after verinurad 40 mg IR formulation co-administered with 300 mg allopurinol (459.7 ng/mL) was -0.3 msec (90% CI -3.1,2.5).
  - The assumptions of the pre-specified concentration-QT model were met (no effect of verinurad on HR, lack of time delay between verinurad concentration and QTc [hysteresis], and a linear ΔΔQTc and verinurad concentration relationship). A linear model for describing concentration-QTc relationship was used.
- Throughout the post-dose measurements, after treatment with verinurad 24 mg ER8 co-administered with 300 mg allopurinol, the ΔΔQTcF values were below zero at all time points; after treatment with verinurad 40 mg IR formulation co-administered with 300 mg allopurinol, the ΔΔQTcF values fluctuated around zero. The shown pattern is compatible with normal diurnal variability of QTc data.
- The upper limit of the 2-sided 90% CI for the differences of QTcF from placebo for both doses of verinurad (clinical exposure [24 mg ER8 formulation] and exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A [40 mg IR formulation]) was < 10 msec at all time points.
- All limits of the 2-sided 90% CI for treatment with verinurad 24 mg ER8 co-administered with 300 mg allopurinol and treatment with verinurad 40 mg IR formulation co-administered with 300 mg allopurinol versus placebo were < 10 bpm at all time points and both treatments had a similar effect on HR as placebo.
- Exposure to verinurad at clinical exposure (24 mg ER8 formulation) and exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A (40 mg IR formulation) had a similar effect on cardiac conduction, ie, the RR, PR, and QRS intervals, as placebo.
- There was no apparent relationship between dECG variables (including HR, PR, QRS) and the concentrations of verinurad, allopurinol, and metabolites.

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Pharmacokinetic Results:

- The rate of absorption for verinurad was slower for the 24 mg ER8 formulation than for the 40 mg IR formulation, with median tmax of 5.00 and 1.02 hours for verinurad 24 mg ER8 and verinurad 40 mg IR, respectively.
- Verinurad exposure was higher when given as 40 mg IR compared to 24 mg ER8, shown by a geometric mean Cmax of 459.7 and 56.57 ng/mL and a geometric mean AUC of 918.7 and 393.8 h*ng/mL, for verinurad 40 mg IR and verinurad 24 mg ER8, respectively.
- The PK of metabolites M1 and M8 followed a pattern similar to the PK of verinurad.
- The PK profiles of allopurinol and oxypurinol were similar when allopurinol 300 mg was given in combination with verinurad 24 mg ER8 or verinurad 40 mg IR.

Safety Results:

- Overall, 11 (45.8%) of 24 subjects had at least 1 AE.
- The most frequently reported AE was headache, which was reported by 7 (29.2%) subjects overall.
- Overall, 7 (29.2%) subjects had at least 1 AE considered related to IMP according to Investigator's causality assessment.
- The majority of AEs was mild in intensity and there were no severe AEs.
- There were no AEs with outcome of death or other SAEs in this study.
- No clinically relevant findings were observed for laboratory results, vital signs, and ECGs and no safety concerns were raised.

Discussion and Conclusion:

- The upper bound of the 2-sided 90% CI of the mean QTcF effect of verinurad in combination with allopurinol as estimated by exposure-response analysis was -0.8 msec (90% CI -4.6,-0.8) at the high clinical exposure scenario (76 ng/mL).
- As the upper bound of the 2-sided 90% CI of the mean QTcF effect of verinurad in combination with allopurinol is well below the threshold for regulatory concern, ie, 10 msec, it can be concluded that verinurad does not have a prolonging effect on the mean QTcF at the highest clinically relevant exposures.
- The results from the primary analysis support a conclusion of a negative thorough QT study.
- Exposure to verinurad at clinical exposure and an exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A had a similar effect on HR and on cardiac conduction as placebo.
- Verinurad exposure was higher when given as 40 mg IR compared to 24 mg ER8 treatment, shown by a geometric mean Cmax of 459.7 and 56.57 ng/mL and a geometric mean AUC of 918.7 and 393.8 h*ng/mL, for 40 mg IR and 24 mg ER8, respectively.
- The PK profiles of allopurinol and oxypurinol were similar when allopurinol 300 mg was given in combination with verinurad 24 mg ER8 and 40 mg IR formulations.
- There was no apparent relationship between dECG variables (including HR, PR, QRS) and the concentrations of verinurad, allopurinol, and metabolites.
- Verinurad 24 mg ER8 formulation (clinical exposure) and 40 mg IR formulation (exposure needed to waive positive control as per question 5.1 of ICH E14 Q&A), both in combination with allopurinol 300 mg, were safe and well tolerated in healthy male and female volunteers and there were no new safety concerns observed.

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Version and Date of Report: Final, dated 28 Jan 2021	
This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.	