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

ClinicalTrials.gov Identifier: NCT04550234

CSR Synopsis: 14 December 2021

Clinical Study Report

1 TITLE PAGE

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

Investigational Medicinal Products:	Test/Reference Product:	Verinurad prolonged release HPMC capsule 12 mg Verinurad prolonged release gelatin capsule 12 mg Verinurad/allopurinol FDC capsule 12/300 mg Allopurinol tablet 300 mg
Indication Studied:	Chronic kidney disease	
Parexel Study Number:	252258	
Sponsor Study Number:	D5495C00014	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Sodertalje Sweden	
Investigator Name and Address:	Thomas Körnicke, MD Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany Tel.: PPD Email: PPD	
Study Duration:	13 Apr 2021 (first subject first visit) to 15 Jul 2021 (last subject last visit)	
Version and Date of Report:	Final, dated 14 Dec 2021	

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

Confidentiality Statement

2 SYNOPSIS

Title of Study:	A Randomised, Single-dose, 5-period, 5-treatment, Crossover Study to Assess the Relative Bioavailability of 4 Different Formulations of Verinurad and Allopurinol in Healthy Subjects	
Study Numbers:	Parexel Study No.: 252258 Sponsor Study No.: D5495C00014	
Investigational Medicinal Products:	Test/Reference Product: Verinurad prolonged release HPMC capsule 12 mg Verinurad prolonged release gelatin capsule 12 mg Verinurad/allopurinol FDC capsule 12/300 mg Allopurinol tablet 300 mg	
Indication Studied:	Chronic kidney disease	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Sodertalje Sweden	
Principal Investigator:	Thomas Körnicke, MD	
Study Centre:	Parexel Early Phase Clinical Unit - Berlin	
Publication:	Not applicable	
Study Duration:	First subject first visit: 13 Apr 2021	Last subject last visit: 15 Jul 2021

Study Objectives:

Primary objective:

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

Secondary objectives:

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

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fasted conditions and of verinurad when administered as a prolonged release gelatin capsule 12 mg under fasted conditions.

Study Design:

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

The study comprised:

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

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

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

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

Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
25 subjects	25 subjects	25 subjects

Main Inclusion Criteria:

This study included healthy male and female subjects aged 18 to 50 years (inclusive) who had a body mass index between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive). Subjects had to have a negative pregnancy test at screening and on admission to the unit.

1 Females had to have a negative pregnancy test at screening and on admission to the unit and had to be:

(a) not pregnant or currently lactating or breastfeeding.

(b) of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:

(i) postmenopausal defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments and Follicle stimulating hormone levels in the postmenopausal range (FSH levels > 40 IU/mL).

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

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(c) OR if of childbearing potential had to be willing to use an acceptable method of contraception to avoid pregnancy for the entire study period.

2 Had to be able to swallow multiple capsules and tablets.

Investigational Medicinal Product(s): Verinurad and allopurinol

Formulation(s):	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
Verinurad prolonged release HPMC capsule 12 mg	12 mg	L016904	Not available
Verinurad prolonged release gelatin capsule 12 mg	12 mg	L016751	Not available
Verinurad/allopurinol FDC capsule 12/300 mg	Verinurad: 12 mg Allopurinol: 300 mg	L015636	Not available
Allopurinol tablet 300 mg	300 mg	L015572	02 2022

Duration of Treatment:

The planned duration of subject involvement was approximately 52 to 59 days.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit. The administration of all investigational medicinal products (IMPs) was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of IMP administration. After IMP administration, a check of the subject's mouth and hands was performed.

Criteria for Evaluation:

Pharmacokinetic Parameters:

The primary PK parameters were:

Area under plasma concentration-time curve from time zero to infinity (AUCinf), area under the plasma concentration time curve from time zero to time of last quantifiable concentration (AUClast) and maximum observed plasma (peak) drug concentration (Cmax) of verinurad, allopurinol and oxypurinol.

The secondary PK parameters were:

Time to reach maximum observed plasma concentration following drug administration (tmax), time delay between drug administration and the first observed concentration in plasma (tlag), terminal elimination rate constant (λz), Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve (t½λz), apparent total body clearance of drug from plasms after extravascular administration (parent drug only) (CL/F), mean residence time of the unchanged drug in the systemic circulation from zero to infinity (parent drug only) (MRTinf), volume of distribution (apparent) at steady state following extravascular administration (parent drug only) (Vss/F), and apparent volume of distribution during the terminal phase after extravascular administration (parent drug only) (Vz/F) of verinurad, allopurinol and oxypurinol.

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Pharmacodynamic Parameters:

Observed values and percentage change from baseline (CB) (time-matched, Day -1) in serum uric acids (sUA) concentrations at each time point up to and including 72 hours following administration of verinurad and allopurinol (verinurad only for Treatment 5) in each treatment period.

Emax, CB: Maximum percentage CB (time-matched, Day -1) in sUA concentrations up to and including 72 hours post-dose.

tEmax, CB: Time of maximum percentage CB (time-matched, Day -1) in sUA concentration up to and including 72 hours post-dose.

Safety Variables:

Adverse events (AEs), vital signs (systolic and diastolic blood pressure, pulse, tympanic temperature), resting 12-lead electrocardiograms (ECGs), physical examination, and laboratory assessments (haematology, clinical chemistry and urinalysis).

Statistical Methods:

Determination of Sample Size:

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

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

Analysis Populations

Randomised Set

The randomised set consisted of all subjects randomised into the study.

Safety Analysis Set

The safety analysis set included all subjects who received at least one dose of IMP and for whom any safety post-dose data were available. Unless otherwise stated, the safety analysis set was used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP was also presented using the safety analysis set.

Pharmacokinetics Analysis Set

The PK analysis set included all subjects in the safety analysis set who received a verinurad + allopurinol (or verinurad alone for Treatment 5) dose and who had at least one quantifiable post-dose plasma concentration. For the formal relative bioavailability evaluations, only subjects who provided eligible PK data for both Test and Reference treatments were included for each comparison.

Pharmacodynamic analysis data

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

Presentation and Analysis of Pharmacokinetic Data:

A listing of PK blood sample collection times, as well as derived sampling time deviations and all reportable concentrations was presented for verinurad and for allopurinol and oxypurinol for all dosed subjects. An additional listing of PK concentrations versus time was presented for those analytes based on the PK analysis set. Plasma concentrations were summarised for the PK analysis set for each time point by treatment for each analyte separately using scheduled times and appropriate descriptive statistics.

Inferential statistical analysis of PK parameters included the following:

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

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

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

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

Presentation and Analysis of Pharmacodynamic Data:

A listing of sUA sample collection times, as well as derived sampling time deviations was provided. Serum UA observed and time-matched percentage CB was listed by treatment and summarised descriptively by treatment and time point. Emax CB and tEmax CB data were listed by treatment. For observed and time-matched percentage change from baseline, the descriptive statistics included n, geometric mean, geometric coefficient of variation (CV), arithmetic mean, arithmetic standard deviation (SD), median, minimum, and maximum.

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

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (number of subjects [n], mean, SD, minimum, median, maximum) by treatment. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarised by preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA). Furthermore, listings of serious adverse events (SAEs) and AEs that led to withdrawal was made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and

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AEs with severe intensity were summarised. Adverse events that occurred from time of informed consent until first administration of IMP were reported separately.

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

Out-of-range values for safety laboratory tests, vital signs and ECGs were flagged in individual listings. However, there were no corresponding descriptive summaries generated.

Protocol Deviations:

No important protocol deviations, including COVID-19 related protocol deviations were identified (Table 14.1.2).

Pharmacokinetic Results:

- Compared to the prolonged release HPMC capsule (Treatment 1), the FDC capsule (Treatment 2) had higher Cmax (geometric mean ratio [GMR] of 131%) and similar AUCinf and AUClast of verinurad, similar Cmax, AUCinf and AUClast of allopurinol and lower Cmax (GMR of 95.2%) and similar AUCinf and AUClast of oxypurinol, under fasted condition.
- Compared to fasted condition (Treatment 2), the FDC capsule had lower Cmax (GMR of 57.7%) and similar AUCinf and AUClast of verinurad, lower Cmax, AUCinf and AUClast (GMR of 73.3%, 89.4% and 82.6%, respectively) of allopurinol and lower Cmax, AUCinf and AUClast (GMR of 86.9%, 91.2% 90.9%, respectively) of oxypurinol, under fed condition (Treatment 3).
- Compared to the prolonged release HPMC capsule (Treatment 4), the FDC capsule (Treatment 3) had higher Cmax, AUCinf and AUClast (GMR of 146%, 145%, and 147%, respectively) of verinurad, lower Cmax and AUClast (GMR of 66.3% and 87.1%, respectively) and similar AUCinf of allopurinol and lower Cmax (GMR of 92.3%) and similar AUCinf and AUClast of oxypurinol, under fed condition.
- Compared to fasted condition (Treatment 1), the prolonged release HPMC capsule had lower Cmax, AUCinf and AUClast (GMR of 52.1%, 76.7% and 76.7%) of verinurad, lower AUCinf and AUClast (GMR of 91.7% and 91.5%) and similar Cmax of allopurinol, and lower Cmax, AUCinf and AUClast (GMR of 89.5%, 90.1% and 89.2%) of oxypurinol under fed condition (Treatment 4).
- Compared to the FDC capsule (Treatment 3), the prolonged release gelatin capsule had similar Cmax, AUCinf and AUClast of verinurad under fasted condition (Treatment 5).

Pharmacodynamic Results:

The largest reduction in sUA occurred when 12 mg verinurad was given together with 300 mg allopurinol in Treatments 1, 2, 3 and 4 (arithmetic mean Emax, CB: -50.44 [Treatment 1], -53.84 [Treatment 2], -56.63 [Treatment 3], -54.43 [Treatment 4]) while the reduction was less pronounced when 12 mg Verinurad was given alone (Treatment 5, arithmetic mean Emax, CB: -38.15). There was no apparent difference in Emax, CB at fasting (Treatment 1 and 2) compared to fed state (Treatments 3 and 4).

The median time to reach tEmax, CB was 8 hours for Treatment 1, 6 hours for Treatment 2, and 12 hours each for Treatments 3, 4, and 5.

Food delayed the time to reach the maximum percentage reduction of sUA for both free combination and FDC of verinurad and allopurinol.

Safety Results:

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- A total of 13 of 25 subjects had AEs.
- There were no death or SAE reported in the study and no subject had AEs leading to discontinuation of study treatment or withdrawal from the study.
- The majority of AEs were mild in intensity and there were no severe AEs. No clinically relevant trends were observed for laboratory results, vital signs and no ECG findings were reported.
- Single doses of verinurad and allopurinol or verinurad alone were well tolerated and there were no safety concerns observed in the study.

Discussion and Conclusion:

This study was intended to evaluate the relative bioavailability between FDC and free combination formulations of verinurad and allopurinol in fasted and fed conditions. The study also assessed the relative bioavailability between a formulation only containing verinurad and the FDC capsule. For verinurad, all formulations had prolonged release profile whereas the two allopurinol formulations contained allopurinol with an immediate release profile.

Both the prolonged release HPMC capsule given in the free combination and the FDC capsule showed prolonged release of verinurad under both fasted and fed conditions. In the fasted state, both the verinurad prolonged release HPMC and FDC capsule formulations demonstrated the anticipated rate and extent of absorption. Whereas in the fed state, the relative bioavailability was higher for the verinurad FDC capsule compared to the prolonged release HPMC capsule. The absorption rate seemed to be slower resulting in a more variable plasma profile in the fed state for both the verinurad prolonged release HPMC and FDC capsule formulations compared to the fasted state. However, food intake affected the verinurad prolonged release HPMC and FDC capsule formulations to a different extent. The verinurad prolonged release HPMC capsule had lower AUC with food, whereas it was unchanged for the verinurad FDC capsule. This may suggest that the extent but not the rate of absorption of the verinurad prolonged release HPMC capsule is more sensitive to food intake than the FDC capsule.

The relative bioavailability of verinurad was similar for the prolonged release gelatin capsule and the FDC capsule in fasted condition, which indicates that the extent and rate of verinurad absorption is not affected by the presence of allopurinol in the FDC formulation.

Both the allopurinol tablet given in the free combination and the allopurinol FDC capsule showed immediate release of allopurinol under both fasted and fed conditions. In the fasted state, there was no difference in the relative bioavailability of allopurinol when comparing FDC capsule and the tablet given in the free combination. Similar results for allopurinol were seen with concomitant food intake, except for allopurinol Cmax, which was lower for the FDC capsule. Under fed conditions, allopurinol AUCinf and AUClast were slightly reduced for both the FDC capsule and the tablet given in the free combination, but Cmax was only reduced for the FDC capsule. In addition, a more variable plasma profile of allopurinol was seen for the FDC capsule in fed vs fasted state.

There was no observed difference in AUClast and AUCinf of oxypurinol, but a slight reduction in oxypurinol Cmax for the FDC capsule compared to the allopurinol tablet given in the free combination at both fasting and fed conditions. The plasma exposure of oxypurinol (AUClast, AUCinf and Cmax) was slightly reduced for

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both allopurinol formulations when given in fed vs fasted conditions. This finding is in line with the slight reduction in allopurinol exposure with concomitant food intake.

The sUA concentrations were reduced at all post-dose time points across all the treatment groups. Maximum reduction in sUA concentrations was observed between 6 h and 12 h and sUA levels increased thereafter but remained below pre-dose levels until the last time point. The largest reduction in sUA occurred when 12 mg verinurad was given together with 300 mg allopurinol for Treatments 1-4. Food did not impact the degree of reduction but delayed the time to reach the maximum percentage reduction of sUA for both free combination and FDC of verinurad and allopurinol.

A total of 13 of the 25 subjects had AEs. There were no SAEs, deaths, or AEs leading to IMP discontinuation. Majority of AEs were of mild intensity and none of the AEs were considered related to study treatment. There were no clinically significant mean changes in clinical laboratory parameters (haematology, clinical chemistry and urinalysis), vital signs, physical examination, and no ECGs findings.

Conclusion

- Compared to the prolonged release HPMC capsule (Treatment 1), the FDC capsule (Treatment 2) had higher Cmax GMR of 131%) and similar AUCinf and AUClast of verinurad, similar Cmax, AUCinf and AUClast of allopurinol and lower Cmax (GMR of 95.2%) and similar AUCinf and AUClast of oxyopurinol, under fasted condition.
- Compared to fasted condition (Treatment 2), the FDC capsule had lower Cmax (GMR of 57.7%) and similar AUCinf and AUClast of verinurad, lower Cmax, AUCinf and AUClast (GMR of 73.3%, 89.4% and 82.6%, respectively) of allopurinol and lower Cmax, AUCinf and AUClast (GMR of 86.9%, 91.2% 90.9%, respectively) of oxypurinol, under fed condition (Treatment 3).
- Compared to the prolonged release HPMC capsule (Treatment 4), the FDC capsule (Treatment 3) had higher Cmax, AUCinf and AUClast (GMR of 146%, 145%, and 147%, respectively) of verinurad, lower Cmax and AUClast (GMR of 66.3% and 87.1%, respectively) and similar AUCinf of allopurinol and lower Cmax (GMR of 92.3%) and similar AUCinf and AUClast of oxypurinol, under fed condition.
- Compared to fasted condition (Treatment 1), the prolonged release HPMC capsule had lower Cmax, AUCinf and AUClast (GMR of 52.1%, 76.7% and 76.7%) of verinurad, lower AUCinf and AUClast (GMR of 91.7% and 91.5%) and similar Cmax of allopurinol, and lower Cmax, AUCinf and AUClast (GMR of 89.5%, 90.1% and 89.2%) of oxypurinol under fed condition (Treatment 4).
- Compared to the FDC capsule (Treatment 3), the prolonged release gelatin capsule had similar Cmax, AUCinf and AUClast of Verinurad under fasted condition (Treatment 5).
- The mean Emax,CB of sUA was -50.44%, -53.84%, -56.63%, and -54.43% when 12 mg Verinurad + 300 mg allopurinol was given as a single-dose in different formulations under fed or fasting state to healthy subjects (Treatments 1-4, respectively). The mean Emax,CB of sUA was -38.15% when 12 mg verinurad was given as a single-dose under fasting state to healthy subjects (Treatment 5).
- Overall, single doses of verinurad and allopurinol or verinurad alone were well tolerated by all subjects that took part in this study and there were no safety concerns observed in the study.

Version and Date of Report: Final, dated 14 Dec 2021

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.

16.1.5 Approval Signatures

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

Parexel STUDY No.: PXL252258

SPONSOR STUDY No.: D5495C00014

Sponsor Signatory/Responsible Medical Expert

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of this study.

PPD

PPD

AstraZeneca BioPharmaceuticals R&D

PPD

Date

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SPONSOR STUDY No.: D5495C00014

Sponsor Signatory/Biostatistician

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of this study.

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Date

AstraZeneca R&D Gothenburg

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Principal Investigator

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of this study.

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Thomas Körnicke, MD
Parexel International
Early Phase Clinical Unit Berlin

Date

16.1.5 Approval Signatures

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Parexel STUDY No.: PXL252258

SPONSOR STUDY No.: D5495C00014

Deputy Principal Investigator

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of this study.

PPD

PPD

Parexel International

Early Phase Clinical Unit Berlin

PPD

Date