Clinical Study Protocol	
Drug Substance	Verinurad / RDEA3170
Study Code	D5495C00002
Version	5.0
Date	18 November 2020

A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled Study of Verinurad and Allopurinol in Patients with Chronic Kidney Disease and Hyperuricaemia

Sponsor: AstraZeneca AB, 151-85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): USIND 133978

VERSION HISTORY

Version 5, 17 November 2020
Changes to the protocol amendment are summarised below.

Most changes were implemented to allow 24 mg verinurad to be assessed in the study to fully explore the verinurad dose range, and to shorten the study treatment to 60 weeks in all patients due to shortage of investigational product (IP).

Section 1.1 Schedule of activities, Table 1

- Updated column header for Visit 10 to refer to EOT and FU visits in Table 2 and further clarified with updates of table footnotes for Visits 9 and 10
- Removed dispensation of IP, where appropriate, to shorten study treatment
- Added ECG assessment

Section 1.1 Schedule of activities, Table 2

- Updated column headers throughout the table to note which visits are applicable before and after implementation of the current protocol amendment, and included a description in the table footnotes
- Clarified the follow up visit will occur 4 weeks after end of treatment/early discontinuation/last scheduled, numbered visit, with an added footnote
- Included PK sample collection at the end of treatment visit and clarified with a footnote

Section 1.2 Synopsis, Section 4.1.1, Overview

- Updated to reflect overall changes to study design and clarified date of implementation of the protocol amendment
- Updated to describe new dosing regimen treatments
- Updated Figure 1 study design schema to reflect overall changes to the study design

CCI [redacted]

Section 2.3 Benefit/risk assessment, Section 4.3 Justification for dose

- Added text describing the blinded interim analysis results and justification for including higher verinurad dose

Section 4.1.2.9, Week 47 (Visit 9), Section 4.1.2.10, Week 60 (Visit 10), Section 4.1.2.11, At 12-week intervals after Visit 10 (Visits 11 through 14), Section 4.1.2.12, End of treatment, Section 4.1.2.13, End of study

- Updated to reflect overall changes to study design and to match changes in Schedule of Activities
- Clarified visit procedures based on implementation of the protocol amendment (prior to or after)

Section 6.1.1, Investigational products

- Revised to implement a new dosing regimen from Visit 9, allowing a blinded assessment of 24 mg verinurad treatment for 13 weeks
- Clarified eGFR criterion for switching to new dosing regimen treatments

Section 6.4, Treatment compliance

- Clarified dosing instructions for patients following the new dosing regimen treatment in the protocol amendment

Section 6.6, Dose modification

- Revised to provide detail on how to manage patients unable to tolerate the randomized dose under the new dosing regimen

Section 8.5 Pharmacokinetics

- Clarified a post dose PK sample will be collected at the Week 60 visit regardless of dosing regimen

Section 8.8 Biomarkers

- Added urine creatinine to Table 15 to allow normalisation of other analysed biomarkers through division by creatinine

Section 9.4 Statistical analyses

- Added description of treatment arms for the study
- Updated endpoints to reflect changes to the objectives section
- Updated secondary efficacy analyses section to reflect change in statistical methods

Version 4, 06 August 2020
Changes to the protocol amendment are summarised below:

Protocol summary, Section 1.1 Schedule of activities

- In Table 1, updated allele testing in to be mandatory for all patients prior to randomisation.

- In Table 2, for the end of treatment/early discontinuation visit, removed ±7 day window as it is not applicable. Corrected section reference in footnote a.
- In both Table 1 and Table 2, a footnote was added to final (titration step 3) dose dispensed at Visits 5 through 14, to state that titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.

Section 4.1.2.2, Week -4 to -0 – screening (Visit 2)

- Updated allele testing to be mandatory for all patients prior to randomisation.

Section 4.1.2.12, End of treatment

- Removed reference to patients who discontinue treatment. Added study drug return and accountability to end of treatment tasks.

Section 4.4, End of study definition

- Removed reference to Appendix A6.

Section 5.2, Exclusion criteria

- Exclusion criterion 3 was updated to require mandatory HLA testing for all patients prior to randomisation. This change was made to simplify the decision for the investigator to test for the allele on patients with mixed race that could carry the allele.
- Exclusion criterion 11 was updated to refine and clarify the criteria of hepatic impairment.

Section 6.1.1, Investigational products, Section 4.1.2.5, Week 8 (Visit 5), Section 4.1.2.6, Week 12 (Visit 6), Section 4.1.2.7, Week 20 (Visit 7), Section 4.1.2.8, Week 34 (Visit 8), Section 4.1.2.9, Week 47 (Visit 9), Section 4.1.2.10, Week 60 (Visit 10), Section 4.1.2.11, At 12-week intervals after Visit 10 (Visits 11 through 14)

- Limited up-titration steps in patients with low eGFR. This clarification was also added to the applicable study procedures section.

Section 6.1.1, Investigational products, Section 6.6, Dose modification

- Handling of up-titration in error

Section 7.1.3, Procedures for early discontinuation of study treatment

- Updated header to state "early" discontinuation.

Section 8.7.1, Assessment of HLA-B genotype

- Updated allele testing to be mandatory for all patients prior to randomisation.

Section 8.10, Guidelines, study assessments, and procedures during COVID-19 pandemic

- Clarified IP interruption and re-start by adding that IP could be re-started during the unscheduled visits and then study participant should return to regular visits as per the study protocol.

Version 3, 23 April 2020
Changes to the protocol amendment are summarised below:

Protocol summary, Section 1.1 Schedule of activities

- In Table 1, pregnancy test added to Visits 3, 6, 7, 8, 9, and 10, and procedure for pregnancy testing described in footnote c
- In Table 2, criterion for ending all study treatment provided and procedure for pregnancy testing described in footnote d

CCI [redacted]

- Criterion for ending all study treatment provided

CCI [redacted]

Sections 4.1.2.3 and 4.1.2.6 to 4.1.2.10

- Pregnancy tests added

Section 4.1.2.12, End of treatment

- Criterion for ending all study treatment provided

Section 5.1.2, Full eligibility criteria

- Definition of chronic kidney disease is further elaborated
- Table 5 is cross referenced to delineate an acceptable method of contraception

Section 5.2, Exclusion criteria

- Three syndromes of anti-neutrophil cytoplasmic antibody-associated vasculitis were provided
- Severe hepatic impairment was added as an exclusion criterion
- Urate oxidases were added as disallowed prior therapy

- Exclusion criterion concerning hypersensitivity to allopurinol or any uric acid transporter 1 inhibitor was revised

Section 5.3.1 Pregnancy

- Changed requirement of using at least 1 highly effective method of contraception to using an acceptable method as specified in Table 5
- In the title of Table 5, "Highly effective" was changed to "Acceptable"

Section 5.4, Pre-screen and screen failures

- Expanded the description of the pre-screening visit

Section 6.3, Measures to minimise bias: randomisation and blinding

- Noted exception that sUA and UACR would not be masked during pre-screening and screening

Section 6.4, Treatment compliance

- A paragraph on the procedure of assessing treatment compliance was added

Section 6.5, Concomitant therapy

- In Table 8, risk of concomitant angiotensin-converting enzyme inhibitor and allopurinol noted

CCI

Section 7.1.1, Temporary interruption of study treatment

- Section added

Section 7.3, Withdrawal from the study

- Two paragraphs on patients who failed to meet the eligibility criteria and one paragraph on follow-up were added

CCI

Section 8.2.1, Clinical safety laboratory assessments

- In the first footnote of Table 13, a cross-reference to Appendix F was replaced with a cross-reference to Appendix E

Section 8.5, Pharmacokinetics

- Number of patients to be sampled was increased

Section 8. 10, Guidelines, study assessments, and procedures during COVID-19 pandemic

- Section added

CCI [redacted]

Section 9.4.2, Efficacy analysis

- Formula for percent change from baseline was corrected
- Direction was provided to apply the same analyses for UACR to the endpoints sUA, estimated glomerular filtration rate (eGFR), creatinine, and cystatin-C

Section 9.5, Interim analyses

- Sentence specifying with first interim analysis will be performed was revised

Section 10, References

- The Summary of Product Characteristics for allopurinol was added to the list of references

Appendix A 9, Study and site start and closure

- This sub-appendix was added

Appendix B 2, Definitions of serious adverse event

- A paragraph on the reporting of malignant tumours was added

Appendix E 4.1, Potential Hy's Law criteria not met

- The sentence stating that the AstraZeneca representative has to be informed was deleted

Appendix E 4.2, Potential Hy's Law criteria met

- A sentence about determining whether potential Hy's Law criteria were met prior to starting study treatment was added

Appendix F 2.2.1, If eGFR drops to <75% of the baseline value

- All the signs ">" were replaced with "<" in the table of Examples of eGFR changes and triggered actions

Version 2, 11 March 2019
Changes to the protocol are summarised below:

Protocol summary, Section 1.1 Schedule of activities

- CCI [redacted]
- Provisions for a reminder phone call to patients regarding the pharmacokinetic procedures have been added
- Instructions for collection of urine samples for UACR and biomarkers were clarified as being separate from samples for safety monitoring
- Biomarker analyses were specified as being done with plasma rather than serum

Protocol summary, Section 1.2 Synopsis and other relevant sections

- Table of objectives and endpoints revised
- Study period dates have been revised
- Reduction of the sample size from 180 to 145 patients per arm
- Revision of the statement of statistical power
- Revision of methods of sequential testing

Section 6.1.1, Investigational products

- Specification of the allopurinol formulation was changed from over-encapsulated tablets to non-encapsulated tablets

CCI [redacted]

Section 8.2.1, Clinical safety laboratory assessments

- The list of haematology assessments has been updated and expanded

Section 8.5, Pharmacokinetics

- The number of patients in the PK substudy has been changed from 20 per arm to 15

Appendix E, Actions required in cases if increases in liver biochemistry and evaluation of Hy's Law, has been revised to meet current standards

Version 1, 1 November 2018

Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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Table 1 Schedule of activities (SoA), screening and treatment period

Visit	1 (Pre-Screening)	2 (Screening)	3 (Randomisation)	4	5	6	7	8 (Primary Analysis)	9[a]	10[a] See EOT visit in Table 2	Details in CSP section or Appendix
Week	**-6 to -1**	**-4 to 0**	**0**	**4**	**8**	**12**	**20**	**34**	**47**	**60**	
Window			**NA**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	
Informed consent for blood draw and urine collection	X										Appendix A3 page 95
Spot UACR	X										Sections 5.1.1 and 4.1.2.1
Blood test for creatinine, sUA, and eGFR	X										Sections 5.1.1 and 4.1.2.1
Full signed informed consent		X									Appendix A3 page 95
Inclusion /exclusion criteria		X	X								Sections 5.1 and 5.2
Dispense urine containers for FMV urine collection	X	X	X	X	X	X	X	X	X	X[b]	Section 8.1.1
Routine clinical procedures											
Demography		X									Section 5.1
Full physical examination		X								X	Section 8.2.2
Brief physical examination			X	X	X	X		X			Section 8.2.2
Medical history and comorbid conditions		X									Sections 5.1 and 5.2
Vital signs[c]		X	X	X	X	X	X	X	X	X	Section 8.2.3
Height		X									Section 8.2.2
Weight		X	X	X	X	X	X	X	X	X	Section 8.2.2

Table 1 Schedule of activities (SoA), screening and treatment period

Visit	1 (Pre-Screening)	2 (Screening)	3 (Randomisation)	4	5	6	7	8 (Primary Analysis)	9[a]	10[a] See EOT visit in Table 2	Details in CSP section or Appendix
Week	**-6 to -1**	**-4 to 0**	**0**	**4**	**8**	**12**	**20**	**34**	**47**	**60**	
Window			**NA**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	
ECG		X	X			X		X		X	Section 8.2.4
Concomitant medication		X	X	X	X	X	X	X	X	X	Section 6.5
Routine safety measurements											
Adverse events[d]		X	X	X	X	X	X	X	X	X	Section 8.3
Pregnancy test (serum or urine)[e]		X	X			X	X	X	X	X[b]	Section 5.1
Sample for HLA genotyping[f]		X									Sections 8.7.1 and 5.2
Safety laboratory assessments (including clinical chemistry, haematology, urinalysis)		X	X	X	X	X		X		X	Section 8.2.1
Biomarker analysis											
CCI [redacted]			[redacted]			[redacted]		[redacted]			[redacted]
Pharmacokinetic measurements[h]											
Phone call to PK participants						X	X	X	X	X	
Pre-dose blood sample in all patients						X					Section 8.5
Pre- and post-dose PK/sUA blood samples in sub-group						X					Section 8.5

Table 1 Schedule of activities (SoA), screening and treatment period

Visit	1 (Pre-Screening)	2 (Screening)	3 (Randomisation)	4	5	6	7	8 (Primary Analysis)	9[a]	10[a] See EOT visit in Table 2	Details in CSP section or Appendix
Week	**-6 to -1**	**-4 to 0**	**0**	**4**	**8**	**12**	**20**	**34**	**47**	**60**	
Window			**NA**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	
Post-dose blood sample in all patients							X	X	X	X	Section 8.5
Efficacy measurements											
sUA, creatinine, eGFR, Cystatin C, NT-proBNP		X	X	X	X	X	X	X	X	X	Section 8.1
UACR - First morning void samples from 3 days before visit		X	X	X	X	X	X	X	X	X	Section 8.1
CCI [redacted]			[redacted]					[redacted]			[redacted]
CCI [redacted]			[redacted]					[redacted]		[redacted]	[redacted]
CCI [redacted]			[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
Optional genetics sampling											
Blood sample			X								Section 8.7
Study treatment dispensing[i]											
Randomisation			X								Section 6.3
Titration step 1 dose dispensed			X								Section 6.1
Titration step 2 dose dispensed				X							Section 6.1
Final (Titration step 3) dose dispensed					X[j]	X[j]	X[j]	X[j]	X[j]	X[j,b]	Section 6.1

Table 1 Schedule of activities (SoA), screening and treatment period

Visit	1 (Pre-Screening)	2 (Screening)	3 (Randomisation)	4	5	6	7	8 (Primary Analysis)	9[a]	10[a] See EOT visit in Table 2	Details in CSP section or Appendix
Week	**-6 to -1**	**-4 to 0**	**0**	**4**	**8**	**12**	**20**	**34**	**47**	**60**	
Window			**NA**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	
Study treatment returned				X	X	X	X	X	X	X	Section 6.2

CSP Clinical study protocol; eGFR Estimated glomerular filtration rate; EOT End of treatment; FMV First morning void; FU follow up; IP Investigational product; CCI NA Not applicable; NT-proBNP N-terminal pro-brain natriuretic peptide; PK Pharmacokinetic; PWV Pulse wave velocity; sUA Serum uric acid; UACR urinary albumin to creatinine ratio

[a] At the time of implementation of Protocol Version 5.0 (refer to Section 4.1.1 for description of implementation), a new dosing regimen will be introduced to assess the higher dose of 24 mg verinurad. Patients in the 3 mg verinurad cohort who will have Visit 9 planned after the amendment is implemented in the respective country will be switched to 24 mg dose at Visit 9. Patients will only be allowed to switch to the new dosing regimen's treatments introduced under Protocol Version 5.0 if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visit 8. Management of patients with eGFR <30 mL/min/1.73m^2 at Visit 9 should be discussed with the medical monitor.
Patients who do not tolerate the new dosing regimen will be down-titrated to the initial dosing regimen (ie, patients on 24 mg will be down-titrated to 3 mg, and patients in other cohorts will not be dispensed the matching placebo capsule).
For the new dosing regimen, following Protocol Version 5.0 implementation, patients will be instructed thoroughly and receive new dosing card instructions at Visit 9. They will be instructed to take 1 tablet daily from one bottle of allopurinol/matching placebo and 1 capsule daily from each of two verinurad/matching placebo bottles that will be differentiated by the label colour.

[b] Only performed at Week 60 visit if this visit occurs before Protocol Version 5.0 implementation.

[c] Vital signs include temperature, pulse rate, blood pressure measurement.

[d] Serious adverse events will be collected from the time of signature of informed consent form at Visit 2, throughout the treatment period and including the follow-up period and last contact. Adverse events will be collected from the time of the first dose of IP. Changes in medical history between the time of signature of the informed consent form and the first dose of IP will be reported as medical history.

[e] For women of childbearing potential, pregnancy urine dipstick tests will be conducted on site. A serum pregnancy test will be done by central laboratory after 2 positive urine tests.

[f] Mandatory HLA-B*5801 allele testing prior to randomisation for all patients. Patients known to be positive for HLA-B*5801 cannot be randomised.

[g] CCI

[h] Verinurad, allopurinol and oxypurinol (active metabolite of allopurinol) plasma concentrations will be assayed.

[i] Study medication should be dispensed at end of visit

[j] At Visit 5 (approximately 8 weeks after randomisation) through Visit 9, titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.

Table 2 Schedule of activities – Extension treatment, end of treatment, and follow-up period (Visits 11 through 14 applicable only to patients who passed Week 60 prior to Protocol Version 5.0 implementation)

Visit	For patients who passed Week 60 prior to Protocol Version 5.0 implementation: Every 12 weeks till every randomised subject either has discontinued study or has reached 60 weeks after randomisation				For all patients: End of treatment (EOT)/early discontinuation [a]	For all patients: Follow up visit (4 weeks after EOT/early discontinuation/ last scheduled, numbered visit[b])	Details in CSP section or Appendix
	11	12	13	14			
Week	72	84	96	108			
Window	±7d	±7d	±7d	±7d		±7d	
Full physical examination					X	X	Section 8.2.2
Brief physical examination	X			X			Section 8.2.2
Vital signs [c]	X	X	X	X	X	X	Section 8.2.3
Weight	X	X	X	X	X	X	Section 8.2.2
ECG					X	X	Section 8.2.4
Concomitant medication	X	X	X	X	X	X	Section 6.5
Adverse events [d]	X	X	X	X	X	X	Section 8.3
Pregnancy test (serum or urine) [e]						X	Section 5.1
Safety laboratory assessments (including clinical chemistry, haematology, urinalysis)		X		X	X	X	Section 8.2.1
CCI [redacted]					[redacted]	[redacted]	[redacted]
Phone call to PK participants					X[g]		Section 8.5
PK post-dose blood sample in all patients					X[g]		Section 8.5
s-UA, creatinine, eGFR, Cystatin C, NT-proBNP	X	X	X	X	X	X	Section 8.1

Table 2 Schedule of activities – Extension treatment, end of treatment, and follow-up period (Visits 11 through 14 applicable only to patients who passed Week 60 prior to Protocol Version 5.0 implementation)

Visit	For patients who passed Week 60 prior to Protocol Version 5.0 implementation: Every 12 weeks till every randomised subject either has discontinued study or has reached 60 weeks after randomisation				For all patients: End of treatment (EOT)/early discontinuation [a]	For all patients: Follow up visit (4 weeks after EOT/early discontinuation/ last scheduled, numbered visit[b])	Details in CSP section or Appendix
	11	12	13	14			
Week	72	84	96	108			
Window	±7d	±7d	±7d	±7d		±7d	
UACR - First morning void samples from 3 days before visit	X	X	X	X	X	X	Section 8.1
CCI [redacted]					[redacted]	[redacted]	[redacted]
Final (Titration step 3) dose dispensed [h]	X[i]	X[i]	X[i]	X[i]			Section 6.1
Study treatment returned	X	X	X	X	X		Section 6.2

ECG Electrocardiogram; eGFR Estimated glomerular filtration rate; IP Investigational product; FMV First morning void; NT-proBNP N-terminal pro-brain natriuretic peptide; s-UA Serum uric acid; UACR Urinary albumin to creatinine ratio

Visits 11 through 14 in this table are only applicable to patients who had planned visits beyond Visit 10 occurring prior to the implementation of Protocol Version 5.0 (refer to Section 4.1.1 for description of implementation). After implementation of the amendment, patients who have passed Week 60 will discontinue IP at the subsequent visit (end of treatment visit).

An end of treatment visit and a numbered visit may be combined into a single visit if the last-dose date is within the planned time window for the numbered visit.

[a] Patients who discontinue study treatment will attend an end of treatment visit as soon as possible after treatment discontinuation. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol (see section 7.1.3). After implementation of Protocol Version 5.0, patients who have passed Week 60 will discontinue IP at the subsequent visit (end of treatment visit).

[b] The last scheduled, numbered visit is for patients who terminated IP early in the study and continued with scheduled visit without IP.

[c] Vital signs include temperature, pulse rate, blood pressure measurement.

[d] Serious adverse events will be collected from the time of signature of informed consent form, throughout the treatment period and including the follow-up period and last contact. Adverse events will be collected from the time of the first dose of IP. Changes in medical history between the time of signature of the informed consent form and the first dose of IP will be reported as medical history.

[e] For women of childbearing potential, pregnancy urine dipstick tests will be conducted on site. A serum pregnancy test will be done by central laboratory after 2 positive urine tests.

[f] CCI [redacted]

[g] Regardless of dosing regimen, a PK sample is to be collected post-dose during the visit.
[h] Study medication should be dispensed at end of visit.
[i] At Visit 5 (approximately 8 weeks after randomisation) through Visit 14, as applicable, titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.

1.2 Synopsis

Protocol title

A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled Study of VerinurAd and AlloPurinol in Patients with CHronic KIdney Disease and HyperuRicaEmia

Short Title: SAPPHIRE

Rationale

Evidence shows independent associations between hyperuricaemia (elevated serum uric acid [sUA]) and the risk of hypertension, myocardial infarction, chronic kidney disease (CKD), type 2 diabetes, heart failure, and metabolic syndrome, including obesity (Nakagawa et al 2006, Grayson et al 2011, Kodama et al 2009, Leyva et al 1998, Anker et al 2003). Furthermore, gout, an inflammatory arthritis caused by deposition of monosodium urate crystals in joints, is associated with an increased risk of all-cause death, as well as cardiovascular (CV) death (Iochimescu et al 2008, Kim et al 2008, Niizeki et al 2006, Jankowska et al 2007). Hyperuricaemia is a prerequisite for development of gout, thus linking high levels of sUA to gout and to poor outcomes. However, the causal relationship between hyperuricaemia and/or gout and the aforementioned diseases and outcomes remains to be proven.

Uric acid transporter 1 (URAT1) is responsible for reabsorption of uric acid (UA in the proximal tubule. Inhibition of URAT1 results in increased urinary excretion of UA. Verinurad (RDEA3170) is a novel URAT1 inhibitor in Phase 2 development for chronic kidney disease and heart failure. Verinurad combined with the xanthine oxidase (XO) inhibitors (XOI) febuxostat or allopurinol has been shown to lower sUA in patients with recurrent gout in Phase 2 studies by up to 80% (see Investigator's Brochure, Section 5.2.1.3-4 for details on Studies 204, 205, and 206). The extensive lowering of sUA delivered presents a unique opportunity to explore whether intensive urate lowering therapy can improve kidney function and/or cardiac health.

Potent URAT1 inhibition has been associated with creatinine elevation in some patients, potentially related to increased peak concentrations of urinary uric acid (uUA) in the proximal tubuli of the kidney. Verinurad is therefore given as an extended release formulation as a low maximum concentration is expected to further reduce or eliminate the risk of creatinine elevations. Moreover, verinurad is to be developed exclusively in a fixed-dose combination with an XOI, reducing also the production of UA.

The Phase 2a study D5495C00007 was performed using 9 mg verinurad given as the ER8 capsule and 80 mg febuxostat administered once daily in combination for 24 weeks. The primary endpoint was change in urinary albumin to creatinine ratio (UACR) at 12 weeks.

Sixty patients were randomised. At enrolment, the treatment arms in study D5495C00007 were generally balanced with regards to common clinical parameters.

The study met the primary endpoint at 12 weeks. UACR was significantly reduced by 39.4% for patients randomised to be treated with verinurad and febuxostat compared to placebo (p=0.0747). The comparison between the active arm and the control arm indicated statistical significance was achieved, considering the predetermined alpha (0.1). The effect on UACR was rapid, with full effect achieved at the first on-treatment assessment time point at 1 week, and did not appear to be driven by outliers.

Mean baseline estimated glomerular filtration rate (eGFR) in the trial was 59 and 68 mL/min/1.73 m^2 in the active and control arms, respectively. There were no changes in eGFR in either arm, either at the early or late assessment time points. However, considering the limited sample size, eGFR variability, and short duration of treatment, this is not unexpected.

For full data, including safety results, see the Investigator's Brochure.

Objectives and endpoints

Objectives	Endpoint/variable:
Primary objective:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 6 months	Change from baseline in UACR at 6 months
Secondary objectives:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 12 months	Change from baseline in UACR at 12 months
To assess the effects of verinurad and allopurinol, allopurinol alone, and placebo on sUA	Change from baseline in sUA at 6 and 12 months
To estimate the dose-response relationship among 3 doses of verinurad and allopurinol and placebo on UACR and sUA	Change from baseline in UACR and sUA at 6 months
To assess the effects of verinurad and allopurinol versus placebo on kidney function	Change from baseline in estimated glomerular filtration rate at 6 and 12 months Change from baseline in creatinine at 6 and 12 months Change from baseline in cystatin-C at 6 and 12 months
CCI [redacted]	
[redacted]	[redacted]

Objectives	Endpoint/variable:
CCI	

Objectives	Endpoint/variable:
CCI [redacted]	[redacted]
[redacted]	[redacted]
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of intensive UA lowering therapy with verinurad and allopurinol	Rates of AEs and SAEs, including CV events Changes in vital signs, electrocardiograms, and clinical laboratory parameters

AE Adverse event; ALT alanine transaminase; AST aspartate transaminase; CV cardiovascular; eGFR estimated glomerular filtration rate; NT-proBNP N-terminal pro-brain natriuretic peptide; PD pharmacodynamic; SAE serious adverse event; sUA serum uric acid; UA uric acid UACR urinary albumin to creatinine ratio
Months 6 and 12 are specified as elapsed time after the 8-week titration period. Thus, Month 6 is at 34 weeks of treatment and Month 12 is at 60 weeks of treatment.

Overall design

This is a randomised, double-blind, placebo-controlled, parallel, global, dose-finding, Phase 2b study to assess the efficacy and safety of verinurad and allopurinol in patients with CKD and hyperuricaemia. Patients who meet the eligibility criteria will be randomised in a 1:1:1:1:1 ratio to high, intermediate or low dose of verinurad plus allopurinol, allopurinol or placebo. CCI [redacted]

As of Protocol Version 5.0 and following a blinded interim analysis in September 2020, the study design was modified to include a new dosing regimen. All patients with Visit 9 (47 weeks) occurring after implementation of the amendment and investigational product (IP) is available (approximately 01 May 2021, ie, approximately half of planned patients randomized) will be treated with the new dosing regimen. Under the new dosing regimen all patients will continue with the same dose of verinurad and allopurinol as previously, except patients randomized to the low dose of verinurad (3 mg), which will be switched to treatment with 24 mg verinurad. Also, following implementation of the amendment, all subjects will discontinue therapy after 60 weeks (Visit 10). Patients that have conducted Visit 10 before the implementation of the amendment will discontinue therapy at their next scheduled visit.

The new treatment regimen will be dispensed to patients for which Visit 9 falls on or after the last of the following dates:

- the date of availability at site of IP suitable for the new treatment regimen,
- the date of the Regulatory Authority approval of Protocol Version 5.0 in the respective country, and
- the date of the Ethics Committee/Independent Review Board approval of Protocol Version 5.0 in the respective country/site.

A patient in the new dosing regimen who is still on treatment, who has not been down-titrated and has signed Informed Consent Form for the new dosing regimen, will receive the new treatment at Visit 9. Patients who do not consent should be discontinued from the study at a subsequent visit. If the patient has passed Visit 9 before the dates listed above, they will remain on the initial dosing regimen.

Additional details on treatment administration are included in Section 6.1.

Target patient population

The study will be conducted in male and female adults (≥18 years of age) with documented CKD who provide informed consent to participate in the study and are not pregnant. Eligible patients will have sUA concentrations ≥6.0 mg/dL, eGFR ≥25 mL/min/1.73 m^2 and a UACR between 30 mg/g and 5000 mg/g (inclusive). Patients should be receiving stable treatment of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 1 month prior to entry into the study.

Patients with a prior history of gout will receive gout prophylaxis treatment with colchicine up to 0.6 mg once daily, as outlined in gout guidelines. If intolerance or other sound medical rationale exists for not using colchicine, the investigator may instead prescribe gout flare prophylaxis with steroids or non-steroidal anti-inflammatory drugs (NSAIDs), or avoid administering prophylaxis altogether. Prophylaxis against flares will be fully explained and discussed with the patient.

Study period

Estimated date of first patient enrolled: Q3 2019

Estimated date of last patient completed: Q4 2021

Number of patients

Total of 725 patients (145 per arm [initial dosing regimen]) at around 200 sites in approximately 15 countries will be randomised with equal probability to 1 of 5 treatment arms.

Treatments and treatment duration

Each patient will be treated as randomised with placebo, allopurinol, and/or verinurad plus allopurinol (3 doses) for 26 weeks at target dose after 8 weeks of titration to allow for assessment of the primary endpoint, UACR at 6 months. After Protocol Version 5.0 is implemented, patients will continue treatment at target dose for approximately 12 weeks after Visit 9, and will discontinue therapy at Visit 10. Patients who have already had IP administered at Visit 9 or a subsequent visit before Protocol Version 5.0 is implemented will discontinue IP at the next subsequent visit.

Study treatments will be titrated in discrete steps as shown in Table 3. Titration steps will be spaced at 4-week intervals to minimise the risk of skin reactions to allopurinol. Patients unable to tolerate the stepped dosage may be down-titrated only by reversing the assigned steps within treatment group, and verinurad and allopurinol dosages cannot be unpaired from the titration schedule. Patients who cannot tolerate the step-1 titration will be discontinued from IP and be followed for the remainder of the study.

Table 3 Titration schedule

	Step 1 - titration (verinurad/ allopurinol)	Step 2 - titration (verinurad/ allopurinol)	Step 3 - target dose (verinurad/ allopurinol)
High Dose (mg)	3/100	7.5/200	12/300
Intermediate Dose (mg)	3/100	7.5/200	7.5/300
Low Dose (mg)	3/100	3/200	3/300
Allopurinol alone (mg)	0/100	0/200	0/300
Placebo (mg)	0/0	0/0	0/0

At the time of implementation of Protocol Version 5.0, a new dosing regimen will be introduced to assess a higher dose of 24 mg verinurad. Patients in the 3 mg verinurad cohort who will have Visit 9 planned after the amendment implementation in the country/site and who have signed ICF for the new dosing regimen will be switched to 24 mg dose at Visit 9.

Patients who do not consent should be discontinued from the study at a subsequent visit. To introduce the new 24 mg dose, a new dosing regimen will be initiated across treatment arms to maintain blinding. For verinurad dosing, all patients in the new dosing regimen will receive 2 capsules through addition of a matching placebo capsule, with the exception of those who switched from the 3 mg to 24 mg dose, where two 12-mg verinurad capsules will be given. Allopurinol dosing will remain the same.

When the new dosing regimen is introduced under Protocol Version 5.0, patients who were down-titrated due to intolerance in the initial dosing regimen will not switch treatment to the new dosing regimen. These patients will instead remain on the same treatment after Visit 9.

Patients who do not tolerate the new dosing regimen will be down-titrated to the initial dosing regimen (ie, patients on 24 mg will be down-titrated to 3 mg, and patients in other cohorts will not be dispensed the matching placebo capsule). If there is a need for further down-titration, patients will follow the down-titration steps outlined in the initial dosing regimen (Section 6.1). Additionally, patients in the initial dosing regimen will follow down-titration steps outlined for the initial dosing regimen (Section 6.1).

Data monitoring committee

An independent data monitoring committee (DMC) will be appointed and will report to AstraZeneca and the contract research organisation (CRO). The DMC will be responsible for ensuring patient safety by assessing the safety of the IP during the study, and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing.

Clinical event adjudication committee

The role of the clinical event adjudication committee (CEA) is to independently review, interpret and adjudicate potential CV events that are experienced by the patients. CV events will be identified preliminarily by the investigators, and also by AstraZeneca personnel, CRO personnel or in the CEA process as specified in the CEA charter. The CEA member/s will not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety event.

Statistical methods

The estimated sample size of 145 patients per arm (initial dosing regimen) will yield 80% power to detect a 25% reduction in UACR for the high dose of verinurad + allopurinol compared to placebo (treatment difference of approximately -0.29 on natural log scale) at the two-sided alpha level of 0.1, assuming a standard deviation of 1.0 on the natural log-scale. A total of 725 patients (145 patients per arm [initial dosing regimen]) need to be randomised.

The primary efficacy variable is the change from baseline in UACR at 6 months. The analysis of change in UACR from baseline to Week 34 (including the 8-week titration phase) will be conducted on the log-transformed UACR values using repeated measures model. This analysis will be performed on the Full Analysis Set (FAS).

Three hypotheses will be included in confirmatory testing for the primary objective. The following hypotheses will be tested sequentially at two-sided alpha = 0.1:

- Null hypothesis: No difference between high dose verinurad plus allopurinol compared to placebo on UACR at 6 months
- Alternative hypothesis: There is a difference between high dose verinurad plus allopurinol compared to placebo on UACR at 6 months

- Null hypothesis: No difference between high and intermediate dose verinurad combined plus allopurinol compared to allopurinol alone on UACR at 6 months
- Alternative hypothesis: There is a difference between high and intermediate dose verinurad combined plus allopurinol compared to allopurinol alone on UACR at 6 months

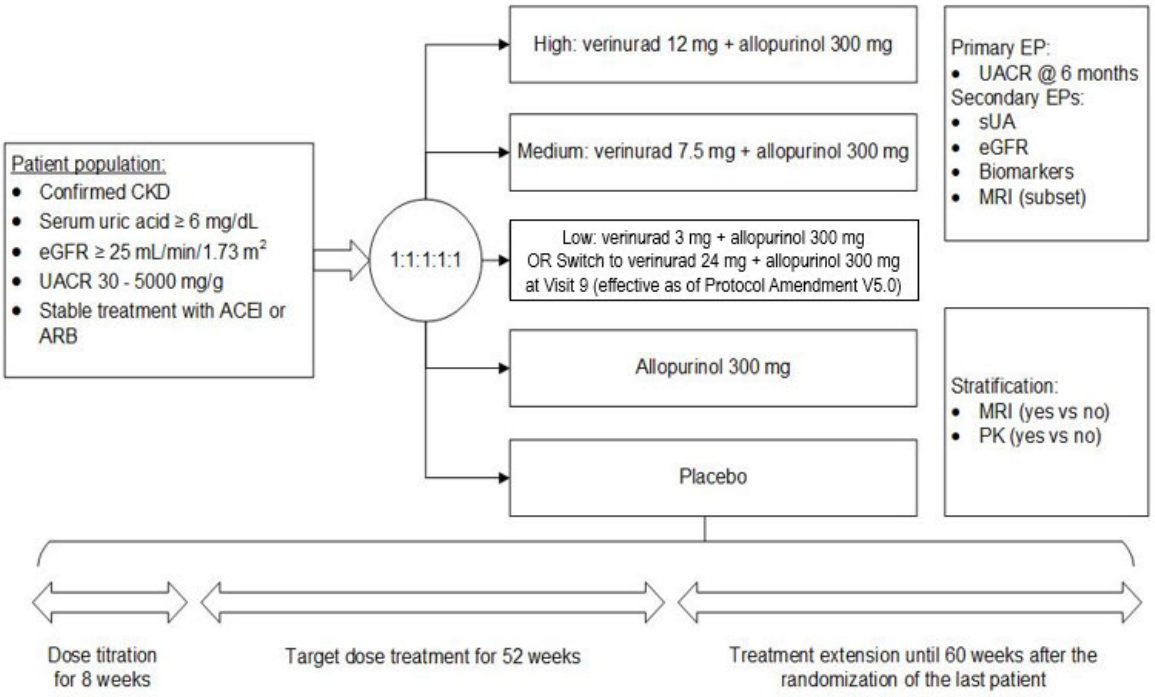
- Null hypothesis: No difference between allopurinol alone compared to placebo on UACR at 6 months
- Alternative hypothesis: There is a difference between allopurinol alone compared to placebo on UACR at 6 months

No other comparisons between treatment groups for the primary and secondary objectives will be adjusted for multiplicity.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; EP endpoint; MRI magnetic resonance imaging; PK pharmacokinetic; sUA serum uric acid; UACR urinary albumin to creatinine ratio

2 INTRODUCTION

Chronic kidney disease is a major public health problem, and its global burden is expected to further grow due to an aging population. Currently CKD management focuses on blood pressure, glycaemic control, and treatment with an ACEi or ARB. Although it is well accepted that hyperuricaemia is associated with CKD, the effects of UA-lowering therapy in patients with CKD remain uncertain.

Uric acid is a purine metabolite generated by the liver during turnover of nucleic acids. It is primarily excreted by the kidneys (two thirds) as well as the gastrointestinal tract (one third) (reviewed by Hyndman et al 2016). Numerous cross-sectional and epidemiological studies have shown the association of sUA level concentrations and CKD in both the general population and in patients with CKD (Mohandas and Johnson 2008). The harmful effects of sUA on kidneys are ascribed to direct cytotoxicity including the proximal tubule of the kidney due to its accumulation (and crystallisation) within cells, and activation and upregulation of inflammation by sUA (Mohandas and Johnson 2008).

UA-lowering therapy may prevent progression of CKD but the conclusion is very uncertain. Larger well-designed studies are required to study the effect of UA-lowering therapy on CKD progression.

2.1 Study rationale

Evidence shows independent associations between hyperuricaemia and the risk of hypertension, myocardial infarction, CKD, type 2 diabetes, heart failure, and metabolic syndrome, including obesity (Nakagawa et al 2006, Grayson et al 2011, Kodama et al 2009, Leyva et al 1998, Anker et al 2003). Furthermore, gout, an inflammatory arthritis caused by deposition of monosodium urate crystals in joints, is associated with an increased risk of all-cause death, as well as CV death (Iochimescu et al 2008, Kim et al 2008, Niizeki et al 2006, Jankowska et al 2007). Hyperuricaemia (elevated levels of urate in the circulation) is a prerequisite for development of gout, an inflammatory arthritis caused by deposition of monosodium urate crystals in joints. Gout occurs in patients with serum urate >6.8 mg/dL, which is the solubility limit of monosodium urate. The prevalence of gout increases with higher serum urate (Choi et al 2005). However, the causal relationship between hyperuricaemia / gout and the aforementioned diseases and outcomes remains to be proven.

URAT1 is responsible for reabsorption of UA in the proximal tubule. Inhibition of URAT1 results in increased urinary excretion of UA. Verinurad is a novel URAT1 inhibitor in Phase 2 development for CKD and heart failure. Verinurad combined with the XOIs febuxostat or allopurinol has been shown to lower sUA in patients with recurrent gout in Phase 2 studies by up to 80% (see Investigator's Brochure, Section 5.2.2.3 through Section 5.2.2.5 for details on Studies 204, 205, and 206). The extensive lowering of sUA delivered

presents a unique opportunity to explore whether intensive urate lowering therapy can improve kidney function and/or cardiac health. Currently no sUA-reducing drug is approved to treat CKD, thus presenting a potential to target a novel therapeutic pathway.

Potent URAT1 inhibition has been associated with creatinine elevation in some patients, potentially related to increased sUA peak concentrations of uUA in the proximal tubuli of the kidney. Verinurad is therefore given as an extended release formulation as a low maximum concentration is expected to further reduce or eliminate the risk of creatinine elevations. Moreover, verinurad is to be developed exclusively in a fixed-dose combination with an XOI, reducing also the production of UA.

The Phase 2a study D5495C00007 was performed using 9 mg verinurad given as the ER8 capsule and 80 mg febuxostat administered once daily in combination for 24 weeks. The primary endpoint was UACR at 12 weeks.

Sixty patients were randomised. At enrolment, the treatment arms in study D5495C00007 were generally balanced with regards to common clinical parameters.

The study met the primary endpoint at 12 weeks. UACR was significantly reduced by 39.4% for patients randomised to be treated with verinurad and febuxostat compared to placebo (p=0.0747). The comparison between the active arm and the control arm indicated statistical significance was achieved, considering the predetermined alpha (0.1). The effect on UACR was rapid, with full effect achieved at the first on-treatment assessment time point at 1 week, and did not appear to be driven by outliers. The therapeutic effect persisted with an LS mean of percent change from baseline in UACR compared to placebo (90% CI) -49.26 (-68.206, -19.009) at Week 24.

Mean baseline eGFR in the trial was 59 and 68 mL/min/1.73 m^2 in the active and control arms, respectively. There were no changes in eGFR in either arm, either at the early or late assessment time points. However, considering the limited sample size, eGFR variability, and short duration of treatment, this is not unexpected. Overall the treatment was well tolerated and safety findings in the study were consistent with the known safety profile of the drug.

The overall clinical evidence suggests that the combination of verinurad and XOI has clinical benefit and an acceptable safety profile in CKD patients and that further development is warranted. Hence, a global, randomised, Phase 2b study is planned to evaluate the efficacy and safety of verinurad and allopurinol in patients with CKD and hyperuricaemia.

2.2 Background

Verinurad is a novel URAT1 inhibitor in Phase 2 development. Verinurad combined with the XOI febuxostat has been shown to lower UACR in patients with diabetes and albuminuria,

and to lower sUA by >80% in patients with recurrent gout in Phase 2 studies. Please refer to the Investigator's Brochure for full details on safety and efficacy of verinurad.

2.2.1 Verinurad in combination with allopurinol

Study RDEA3170-206 was a Phase 2a, randomised, open-label, multicentre study to assess the pharmacokinetics (PK), pharmacodynamics (PD), and safety of verinurad administered in combination with allopurinol (300 mg qd) compared with allopurinol administered alone (300 mg once daily, 300 mg twice daily, or 600 mg once daily) in adult patients with gout. There were 40 male patients and 1 female patient randomised into the study. sUA was decreased in a dose-dependent manner in patients treated with multiple once daily doses of verinurad ranging from 2.5 to 20 mg given as the MR4 tablet in combination with allopurinol 300 mg. All verinurad and allopurinol 300 mg combination treatments resulted in greater reductions in sUA compared with allopurinol 300 mg dosed alone.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of verinurad and allopurinol may be found in the Investigator's Brochure.

The study design aims to minimise potential risks to patients and to ensure adequate monitoring. A dual-inhibition approach using lower doses of 2 agents with complementary mechanisms of action is expected to synergistically improve efficacy outcomes while reducing potential safety issues that would be of concern with higher doses of each agent alone.

The main toxicity of concern noted with verinurad monotherapy is creatinine elevations >1.5x baseline occurring in 6.2% of Caucasian patients in Study RDEA3170-201, and in 17.1% of Japanese patients in Study RDEA3170-203. When verinurad was combined with XOI in Studies RDEA3170-204, RDEA3170-205 and RDEA3170-206, no creatinine elevations were reported. In the current study, verinurad will therefore exclusively be administered in combination with allopurinol. In the CKD Phase 2a study D5495C00007, in which a similar patient population was recruited as in this study, the combination of verinurad and febuxostat resulted in the same rate of creatinine elevations in both the active treatment group and in the placebo control group.

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.

CKD with hyperuricaemia represents a significant unmet medical need and underlines the need for novel therapies for this patient population. Verinurad combined with allopurinol may demonstrate a meaningful clinical benefit and an acceptable safety profile. The overall

benefit-risk profile of verinurad combined with allopurinol is expected to be favourable, therefore supporting the current study design.

Patients with CKD are at increased risk to experience CV events, and several studies showed that both reduced renal function and proteinuria are associated with such events. Furthermore, CV events have been identified as a risk for lesinurad, which is an approved drug with a similar mechanism of action as verinurad. Few CV events were reported in the verinurad clinical programme. Important actions aiming to minimise the CV risk to patients in this study include using allopurinol instead of febuxostat, as allopurinol treatment is associated with a lower risk of CV death (White et al 2018). Also, high-risk patients such as patients with recent CV events or inadequate blood pressure control will be excluded.

The main risk from allopurinol, skin reaction, will be minimised by excluding patients carrying the high risk Human Leukocyte Antigen-B (HLA-B) *58:01 allele and administration of allopurinol via a slow dose titration.

Patients with gout may experience an acute gout flare event with initiation or an increase in dose of urate-lowering therapies (Borstad et al 2004). To prevent this, the manufacturer's prescribing information for urate-lowering therapies like lesinurad, allopurinol and febuxostat, as well as the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and British Society of Rheumatology treatment guidelines Zhang et al 2006; Jordan et al 2007; Khanna et al 2012), recommend acute gout flare prophylaxis with colchicine, steroids, or a NSAID when initiating or increasing the dose of such therapies. The protocol lists options for gout prophylaxis to the investigators to allow for appropriate management (Section 6.5.1).

Following a blinded interim analysis in September 2020, the study was modified (via Protocol Version 5.0) to explore a broader range of doses, and a 24 mg dose of verinurad will be introduced to a subset of patients in the 3 mg cohort. This subset will consist of patients randomized to 3 mg verinurad who have a planned Visit 9 after Protocol Version 5.0 is implemented in the respective territories and once IP is available.

Testing a higher dose of verinurad requires careful consideration. Based on the safety information from the blinded interim analysis, as well as the evidence accumulated throughout the verinurad clinical development program, there are no major concerns precluding testing 24 mg verinurad with regards to safety. Verinurad has previously been administered to healthy subjects for 7 days using the same formulation (ER8) at 12 and 24 mg in the JADE study (D5495C00006) without safety concerns (refer to Investigator's Brochure).

In the new dosing regimen, all subjects will end treatment at Visit 10, therefore no patients will be treated with 24 mg verinurad for longer than approximately 13 weeks.

Overall, the study has been designed to minimise the risks to participating patients by excluding patients at high risk of AEs and by applying appropriate safety monitoring of recruited study patients. The doses selected have been carefully considered in light of the target patient population. The potential benefits of developing a new treatment for CKD with hyperuricaemia therefore outweigh the limited risks to the patients exposed to treatment with verinurad and allopurinol in this trial.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and endpoints

Objectives	Endpoint/variable:
Primary objective:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 6 months	Change from baseline in UACR at 6 months
Secondary objectives:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 12 months	Change from baseline in UACR at 12 months
To assess the effects of verinurad and allopurinol, allopurinol alone, and placebo on sUA	Change from baseline in sUA at 6 and 12 months
To estimate the dose-response relationship among 3 doses of verinurad and allopurinol and placebo on UACR and sUA	Change from baseline in UACR and sUA at 6 months
To assess the effects of verinurad and allopurinol versus placebo on kidney function	Change from baseline in estimated glomerular filtration rate at 6 and 12 months Change from baseline in creatinine at 6 and 12 months Change from baseline in cystatin-C at 6 and 12 months
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 Objectives and endpoints

Objectives	Endpoint/variable:
CCI	
CCI	
CCI	
CCI	
CCI	

Table 4 Objectives and endpoints

Objectives	Endpoint/variable:
CCI [redacted]	[redacted]
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of intensive UA lowering therapy with verinurad and allopurinol	Rates of AEs and SAEs, including CV events Changes in vital signs, electrocardiograms, and clinical laboratory parameters

AE Adverse event; ALT alanine transaminase; AST aspartate transaminase; CV cardiovascular; eGFR estimated glomerular filtration rate; NT-proBNP N-terminal pro-brain natriuretic peptide; PD pharmacodynamic; SAE serious adverse event; sUA serum uric acid; UA uric acid UACR urinary albumin to creatinine ratio
Months 6 and 12 are specified as elapsed time after the 8-week titration period. Thus, Month 6 is at 34 weeks of treatment and Month 12 is at 60 weeks of treatment.

4 STUDY DESIGN

4.1 Overall design

4.1.1 Overview

This is a randomised, double-blind, placebo-controlled, parallel, global, dose-finding, Phase 2b study to assess the efficacy and safety of verinurad and allopurinol in patients with chronic kidney disease and hyperuricaemia. Patients who meet the eligibility criteria will be randomised in a 1:1:1:1:1 ratio to high, intermediate or low dose of verinurad plus allopurinol, allopurinol or placebo. CCI [redacted]

As of Protocol Version 5.0 and following a blinded interim analysis in September 2020, the study design was modified to include a new dosing regimen. All patients with Visit 9 (47 weeks) occurring after implementation of the amendment and IP is available (approximately 01 May 2021, ie, approximately half of planned patients randomized) will be treated with the new dosing regimen. Under the new dosing regimen all patients will continue with the same dose of verinurad and allopurinol as previously, except patients randomized to the low dose of verinurad (3 mg), which will be switched to treatment with 24 mg verinurad.

Also, following implementation of the amendment, all subjects will discontinue therapy after 60 weeks (Visit 10). Patients that have conducted Visit 10 before the implementation of the amendment will discontinue therapy at their next scheduled visit.

The new treatment regimen will be dispensed to patients for which Visit 9 falls on or after the last of the following dates:

- the date of availability at site of IP suitable for the new treatment regimen,
- the date of the Regulatory Authority approval of Protocol Version 5.0 in the respective country, and
- the date of the Ethics Committee/Independent Review Board approval of Protocol Version 5.0 in the respective country/site.

A patient in the new dosing regimen who is still on treatment, who has not been down-titrated and has signed Informed Consent Form (ICF) for the new dosing regimen, will receive the new treatment at Visit 9. Patients who do not consent should be discontinued from the study at a subsequent visit. If the patient has passed Visit 9 before the dates listed above, they will remain on the initial dosing regimen.

A total of 725 patients (145 per initial dosing regimen arm) at around 200 sites in around 15 countries will be randomised with equal probability to 1 of the initial dosing regimens 5 treatment arms.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 8, Study Assessments and Procedures.

4.1.2 Study procedures

4.1.2.1 Week -6 to -1 – prescreening (Visit 1)

- Obtain signed abbreviated ICF
- Obtain blood sample to assess sUA and eGFR, and spot UACR to determine eligibility
- Dispense containers for morning voids (patients not meeting criteria for enrolment will be notified before collection of morning voids begins)

4.1.2.2 Week -4 to -0 – screening (Visit 2)

- Collect first morning void samples from 3 days before visit
- Obtain signed full ICF
- Record serious adverse events (SAEs)
- Obtain demography information

- Obtain full medical history with note of comorbidities
- Record concomitant medication
- Perform full physical examination (PE)
- Obtain vital signs
- Obtain height and weight
- Obtain 12-lead electrocardiogram (ECG)
- Obtain blood samples for clinical chemistry and haematology, and efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Obtain blood sample for HLA-B*5801 allele genotyping for all patients prior to randomisation
- Obtain urine samples for safety assessment (dipstick urinalysis)
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- Evaluate all inclusion/exclusion criteria
- Confirm eligibility for renal MRI evaluation for patients who consented to participate in MRI sub-study prior to randomisation
- IVRS/IWRS (Interactive Voice/Web Response system) transaction
- Dispense containers for morning voids

4.1.2.3 Week 0 (Visit 3)

- Collect first morning void samples from 3 days before visit (for primary CCI [redacted] biomarkers)
- Review demography information
- Update concomitant medication
- Record medically important events as medical history
- Perform brief PE
- Record vital signs
- Record weight
- Obtain electrocardiogram (ECG)
- [redacted]
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP).CCI [redacted]
- Genetics sampling for some patients
- Obtain urine samples for safety assessment (dipstick urinalysis
- Conduct renal MRI and PWV evaluation for patients who consented to participate in MRI sub-study prior to randomisation
- Reactive hyperaemia evaluation

- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- Review inclusion/exclusion criteria
- Randomise patients via IVRS/IWRS transaction
- Dispense titration Step-1 dose
- Dispense containers for morning voids

4.1.2.4 Week 4 (Visit 4)

- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform brief PE
- Record vital signs
- Record weight
- Obtain blood samples for clinical chemistry and haematology, and efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Obtain urine samples for safety assessment (dipstick urinalysis)
- IVRS/IWRS transaction and dispense titration Step-2 dose
- Dispense containers for morning voids

4.1.2.5 Week 8 (Visit 5)

- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform brief PE
- Record vital signs
- Record weight
- [redacted]
- Obtain blood samples for clinical chemistry and haematology, and efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Obtain urine samples for safety assessment (dipstick urinalysis
- IVRS/IWRS transaction and dispense titration Step-3 dose (Note: Titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.)
- Dispense containers for morning voids

4.1.2.6 Week 12 (Visit 6)

- Place phone calls on the day before the visit to remind patients to not take drug at home before this visit and to record the time and date of the last dose taken
- Visit to be scheduled in the morning to permit PK blood collection
- Collect first morning void samples from 3 days before visit (for primary CCI biomarkers)
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform brief PE
- Record vital signs
- Record weight
- Obtain ECG
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP) CCI
- Obtain pre-dose PK blood samples (PK should be collected together with sUA) in all patients
- Patients take drug at clinic (time of drug intake should be recorded)
- Obtain post-dose PK and sUA blood samples in each of the four following time windows: (1) 3 to 4, (2) 4 to 5, (3) 5 to 6 and (4) 8 to 9 h in patients participating in the PK sub-study
- Collect untaken study medication
- Obtain urine samples for safety assessment (dipstick urinalysis
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- IVRS/IWRS transaction and dispense titration Step-3 dose (Note: Titration to step-3 target dose will only be allowed if the patient's eGFR was $\geq$30 mL/min/1.73m^2 at Visits 3 and 4.)
- Dispense containers for morning voids

4.1.2.7 Week 20 (Visit 7)

- Place phone calls on the day before the visit to remind patients to record the time and date of the study medication intake on the day of the visit
- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Record vital signs
- Record weight

- Obtain blood samples for post-dose PK and sUA (drug taken at home, date and time of drug intake should be recorded)
- Obtain blood samples for efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- IVRS/IWRS and dispense titration Step-3 dose (Note: Titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.)
- Dispense containers for morning voids

4.1.2.8 Week 34 (Visit 8)

- Place phone calls on the day before the visit to remind patients to record the time and date of the study medication intake on the day of the visit
- Collect first morning void samples from 3 days before visit (for primary CCI biomarkers)
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform brief PE
- Record vital signs
- Record weight
- Obtain ECG
- CCI
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP) CCI
- Obtain blood samples for post-dose PK and sUA (drug taken at home, date and time of drug intake should be recorded)
- Obtain urine samples for safety assessment (dipstick urinalysis
- Obtain results/confirm availability of MRI renal and PWV evaluation for some patients
- Reactive hyperaemia evaluation for some patients
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- IVRS/IWRS and dispense titration Step-3 dose (Note: Titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.)
- Dispense containers for morning voids

4.1.2.9 Week 47 (Visit 9)

At the time of implementation of Protocol Version 5.0, a new dosing regimen will be introduced to assess the higher dose of 24 mg verinurad. Patients in the 3 mg verinurad cohort

who will have Visit 9 planned after the amendment implementation in the respective country/site and who have signed ICF for the new dosing regimen will be switched to 24 mg dose at Visit 9. Patients who do not consent should be discontinued from the study at a subsequent visit.

To introduce the new 24 mg dose, a new dosing regimen will be initiated across treatment arms to maintain blinding. For verinurad dosing, all patients in the new dosing regimen will receive 2 capsules through addition of a matching placebo capsule, with the exception of those who switched from the 3 mg to 24 mg dose, where two 12-mg verinurad capsules will be given. Allopurinol dosing will remain the same.

Note: Patients will only be allowed to switch to the new dosing regimen's treatments introduced under Protocol Version 5.0 if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visit 8. Management of patients with eGFR <30 mL/min/1.73m^2 at Visit 9 should be discussed with the medical monitor.

- Place phone calls on the day before the visit to remind patients to record the time and date of the study medication intake on the day of the visit
- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Record vital signs
- Record weight
- Obtain blood samples for post-dose PK and sUA (drug taken at home, date and time of drug intake should be recorded)
- Obtain blood samples for efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- Prior to Protocol Version 5.0, IVRS/IWRS and dispense titration Step-3 dose (Note: Titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.)
- Dispense containers for morning voids

4.1.2.10 Week 60 (Visit 10) (prior to Protocol Version 5.0)

Prior to Protocol Version 5.0, patients were expected to continue treatment beyond Visit 10 with visits every 12 weeks. Patients who have conducted Visit 10 before the implementation of the amendment will continue the currently dispensed IP, and at the subsequent visit will conduct an end of treatment visit (see Section 4.1.2.12).

Patients who switch to the new dosing regimen, with Visit 9 planned after implementation of Protocol Version 5.0, will follow Visit 10 assessments as described in Section 4.1.2.12.

Patients not switching to the new dosing regimen will undergo the following assessments.

- Place phone calls on the day before the visit to remind patients to record the time and date of the study medication intake on the day of the visit
- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform full PE
- Record vital signs
- Record weight
- Obtain ECG
- [redacted]
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Obtain blood samples for post-dose PK and sUA (drug taken at home, date and time of drug intake should be recorded)
- Obtain urine samples for safety assessment (dipstick urinalysis)
- Reactive hyperaemia evaluation for some patients
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory
- Dispense containers for morning voids

4.1.2.11 At 12-week intervals after Visit 10 (Visits 11 through 14) (prior to Protocol Version 5.0)

Prior to Protocol Version 5.0, patients were expected to continue treatment beyond Visit 10 with visits every 12 weeks. After implementation of the amendment, patients who have passed Week 60 will discontinue IP at the subsequent visit (end of treatment visit) (see Section 4.1.2.12).

- Collect first morning void samples from 3 days before visit
- Collect untaken study medication
- Update concomitant medication
- Record AEs
- Perform brief PE (Visits 11 and 14)

- Record vital signs
- Record weight
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP)
- Dispense containers for morning voids

4.1.2.12 End of treatment (occurs at 60 weeks for patients on new dosing regimen following Protocol Version 5.0 implementation)/early discontinuation

Following the implementation of Protocol Version 5.0, all patients will discontinue treatment at Visit 10. The following assessments will be conducted at the end of treatment/early discontinuation visit.

- Collect first morning void samples from 3 days before visit (for primary CCI biomarkers)
- Record AEs
- Update concomitant medication
- Perform full PE
- Record vital signs
- Record weight
- CCI
- Obtain 12-lead ECG
- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP), PK, CCI
- Obtain urine for safety assessment (dipstick urinalysis)
- Study drug return and accountability

4.1.2.13 Follow up visit (4 weeks after end of treatment/early discontinuation/last scheduled, numbered visit)

- All patients (including any patients who have discontinued treatment with investigational product [IP]) should return for their Visit.
- Collect first morning void samples from 3 days before visit (for primary CCI biomarkers)
- Update concomitant medication
- Record AEs
- Perform full PE
- Record vital signs
- Record weight
- CCI
- Obtain 12-lead ECG

- Obtain blood samples for clinical chemistry and haematology, efficacy assessments (s-UA, creatinine, eGFR, Cystatin C, NT-proBNP) CCI
- Obtain urine samples for safety assessment (dipstick urinalysis)
- Perform pregnancy urine dipstick test for women of childbearing potential; after 2 positive urine tests, a serum pregnancy test is to be done by central laboratory

4.2 Scientific rationale for study design

The purpose of the study is to establish the dose of verinurad combined with allopurinol 300 mg once daily that will elicit the desired response; ie, reduction in UACR at 6 months. UACR is a measurement of albuminuria, it was chosen because changes in UACR can be detected early in response to treatment, and these changes, if substantial, correlate with progression of CKD, deterioration in eGFR, and hard outcomes. Therefore, change in UACR is regarded as an appropriate endpoint. In this study, change in UACR at 6 months of treatment is the primary endpoint for the efficacy evaluation of treatment with the combination of verinurad and allopurinol vs. placebo. A key secondary objective is evaluation of verinurad plus allopurinol on the reduction in UACR at 12 months. Additional secondary endpoints include changes from baseline in sUA, eGFR, cystatin C, creatinine and NT-proBNP. Further, standard safety parameters such as AEs, SAEs, and laboratory evaluations will be employed to assess the safety profile of the study drugs. Verinurad, allopurinol and oxypurinol plasma concentrations over time will also be measured.

4.3 Justification for dose

The verinurad and allopurinol combination therapy doses and regimen selected for this study are based on the goal of characterising the dose-response for UACR and evaluating safety in this patient population.

The suggested dose range (3 to 24 mg) of verinurad in this study is chosen to enable a test of a wide range of doses and is based on pharmacokinetic, pharmacodynamic, and safety data from previous studies in healthy volunteers and in patients with gout or hyperuricaemia with albuminuria. The lowest dose of 3 mg is selected to have limited effect on sUA and is therefore likely to have no or minimal effect on UACR. The highest dose of 24 mg is selected to maximise the effect on sUA and inhibition of URAT1.

A new dosing regimen of verinurad 24 mg will be introduced to patients in the 3 mg cohort at Visit 9 (47 weeks). Data from the SAPPHIRE interim analysis, indicate a lower than anticipated sUA reduction. The interim analysis also shows a slower rate of absorption of verinurad than anticipated with a maintained verinurad AUC but less than half the expected verinurad Cmax. To fully explore the hypothesis of inhibition of URAT1 inhibition, the highest verinurad dose assessed in the study is therefore increased to 24 mg.

Testing a higher dose of verinurad (24 mg) requires careful consideration. Based on the current safety information from the blinded SAPPHIRE interim analysis, as well as evidence accumulated throughout the verinurad clinical development program, there are no major concerns precluding testing verinurad 24 mg in this study. To maintain the scientific integrity of the SAPPHIRE study, further details of the interim analysis will not be shared at this time. Verinurad has previously been administered to healthy subjects for 7 days using the same formulation (ER8) at 12 and 24 mg in the JADE study (D5495C00006) without safety concerns (refer to the Investigator's Brochure). In the JADE study, the observed verinurad Cmax was higher than the verinurad Cmax expected to be achieved after 24 mg verinurad in the SAPPHIRE study. The verinurad AUC after 24 mg in the SAPPHIRE study is expected to be slightly above the observed AUC in the JADE study, as patients with low renal function have higher exposure compared to those with normal renal function. The highest observed verinurad Cmax and AUC are 760 ng/mL and 1270 ng*h/mL, respectively, after 40 mg verinurad given as an immediate-release formulation to healthy subjects. Details on Cmax and AUC achieved in earlier verinurad studies are provided in the Investigator's Brochure.

Verinurad combined with allopurinol (300 mg once daily) dose-dependently lower sUA from 47% up to 74% at verinurad doses of 2.5 to 20 mg (given as the MR4 tablet) in patients with recurrent gout (Fleischmann et al 2018a). A dose of 20 mg of the MR4 tablet is equivalent to 12 mg of the ER8 capsule used in this study. Allopurinol alone given as 300 mg once daily lowered sUA by 40% in the same study.

Verinurad dose-dependently increased the uUA excretion (Hall et al 2018). The uUA excretion is comparable to baseline when verinurad is given in combination with an XOI (Fleischmann et al 2018a, Fleischmann et al 2018b). Verinurad is therefore combined with allopurinol (XOI) to further reduce the peak uUA excretion, as high fractional excretion of UA has been associated with renal AEs in the setting of high UA production.

A dose of 9 mg verinurad (ER8 capsule) given in combination with 80 mg febuxostat reduced UACR (primary endpoint) by 39.4% compared to placebo (p=0.0747) at 12 weeks in the Phase 2a study D5495C00007.

Allopurinol will be titrated every 4 weeks in the initial phase of the study (Table 8) to minimise the risk for skin reactions. The starting dose of allopurinol will be 100 mg once daily, titrated up to 200 mg once daily, and finally titrated to 300 mg once daily, the target dose, which is in line with the guideline recommendation (Khanna et al 2012, Stamp et al 2016, Richette et al 2017). Verinurad will be titrated along with allopurinol (up to 300 mg allopurinol) in order to avoid oversaturation of urate in the urine.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the SoA.

5 STUDY POPULATION

The current protocol is intended to enrol a broad patient population with CKD and residual kidney function that is expected to benefit from the treatment while minimising risks for treatment-related AEs. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are defined as screen failures, refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who signed the full informed consent at Visit 2. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

5.1.1 Pre-screening criteria

(a) Provision of signed and dated, brief written ICF prior to any mandatory study-specific procedures, sampling, and analyses

(b) Enrol if:

– sUA ≥6 mg/dL and

– eGFR ≥25 mL/min/1.73 m^2 and

– UACR ≥30 mg/g and ≤5000 mg/g

5.1.2 Full eligibility criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling, and analyses.

3 Provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis

The ICF process is described in Appendix A 3.

Age

4 Patient must be ≥18 years of age at the time of signing the ICF.

Type of patient and disease characteristics

5 Patients with CKD. CKD as defined in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as abnormalities in kidney structure or function present for >3 months; ie, there must be a documented occurrence at least 3 months before randomisation of either of the following eGFR <60 mL/min/1.73 m^2, UACR ≥30 mg/g, and/or one or more other markers of kidney damage (including abnormalities detected by histology or imaging, urine sediments, urine protein dipstick ≥1+, positive urine albumin dipstick, or urinary protein to creatinine ratio ≥84 mg/g).

6 Patients should receive background standard of care treatment for albuminuria and/or T2DM and be treated according to locally recognised guidelines, as appropriate. Guideline-recommended medications should be used at recommended doses. Therapy should have been optimised and stable for ≥4 weeks before study entry and include an ACEi or an ARB, unless contraindicated, not tolerated, or in the opinion of the investigator not practically available or suitable.

7 If treated with a sodium-glucose transport protein (SGLT2) inhibitor, the SGLT2 inhibitor dose must have been stable for ≥4 weeks before randomisation.

8 Meeting screening criteria for sUA and eGFR (Visit 2)

(a) sUA ≥6.0 mg/dL

(b) eGFR ≥25 mL/min/1.73 m^2 (CKD-EPI formula)

9 Mean UACR between 30 mg/g and 5000 mg/g inclusive. At least 2 first morning void samples collected before randomisation will be required.

Sex

10 Male or female

Reproduction

11 Negative pregnancy test at investigation site (urine or serum) for female patients of childbearing potential.

12 Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (Table 5) for the duration of the study (from the time they sign consent) and for 4 weeks after the last dose of study treatment to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Patients agreeing to total sexual abstinence can also be included, assuming it is their usual lifestyle.

5.2 Exclusion criteria

Medical conditions

1 Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [Wegener's granulomatosis], microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis [Churg-Strauss syndrome]).

2 History of renal transplantation

3 Known carrier of the Human Leukocyte Antigen-B (HLA-B) *58:01 allele. HLA-B *58:01 genotyping is mandatory prior to randomisation for all patients.

4 Patients diagnosed with tumor lysis syndrome or Lesch-Nyhan syndrome

5 Patients who are severely physically or mentally incapacitated and who in the opinion of investigator are unable to perform the patients' tasks associated with the protocol

6 Presence of any condition which, in the opinion of the investigator, places the patient at undue risk or potentially jeopardises the quality of the data to be generated

7 History of stroke, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft in the past 6 months

8 Uncontrolled hypertension presenting with systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg

9 Diagnosed with heart failure and New York Heart Association Functional Classification (NYHA) Class IV (refer to Appendix E) at the time of randomisation

10 QT interval corrected by the Fridericia formula (QTc_F) >470 msec; patients diagnosed with long QT syndrome; patients with a family history of long QT syndrome

11 Evidence of significant liver disease (eg, aspartate transaminase [AST] or alanine transaminase [ALT] >3x the upper limit of normal [ULN]; or total bilirubin >1.5x ULN). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion.

Prior/concomitant therapy

12 Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within 6 months prior to enrolment

13 Treated with any drug for hyperuricaemia in the 6 months preceding randomisation. Drugs for hyperuricaemia include all XOIs (allopurinol, febuxostat, and topiroxostat), URAT1 inhibitors (lesinurad, verinurad, probenecid, and benzbromarone), and urate oxidases (pegloticase, rasburicase)

14 Dose of ACEi, ARBs, fenofibrate, guaifenesin, or SGLT2 inhibitors changed within 4 weeks of randomisation or further dose titration expected after randomisation

15 Treated with strong or moderate organic anion transporting polypeptide (OATP) inhibitors (See Table 10)

Prior/concurrent clinical study experience

16 Participation in another clinical study with an investigational product administered during the last month prior to randomisation

17 Known hypersensitivity to any URAT1 inhibitor, allopurinol, or any of its excipients. Known intolerance to lactose (an allopurinol excipient) due to hereditary defect.

Other exclusions

18 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

19 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

20 Previous randomisation in the present study.

21 Patients who are pregnant, lactating, or planning to become pregnant.

22 For the MRI substudy, patients unsuitable or unable to undergo MRI assessment for the following reasons are not allowed to participate in the optional MRI substudy:

- Body mass index >40 kg/m^2 or abdominal height in the supine position >30 cm
- Claustrophobia
- Pacemaker or aneurysm clips
- Other metallic implants or internal electrical devices (eg, cochlear implant, nerve stimulator, gastric pacemaker, bladder stimulator, defibrillator, artificial valves in heart, etc), or permanent makeup or tattoos which, in the investigator's opinion, might jeopardise the subject's safety or interfere with the imaging measurements
- Arrhythmia

– Pregnancy

23 Patients with bilateral upper or lower arm pathology are not allowed to participate in the vascular reactivity substudy:

– Presence of fistula / AV Shunt

– Other structural or vascular abnormality

5.3 Lifestyle restrictions

There are no life style restrictions, with the exception of contraceptive use and taking alcohol and investigational product at the same time.

5.3.1 Pregnancy

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after.

1 Female patient of childbearing potential

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use an acceptable method of contraception (Table 5) from the time of Screening throughout the total duration of the drug treatment and the drug washout period (4 weeks) after the last dose of study treatment. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2 Male patients are not required to use contraception

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.
- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Table 5 Acceptable methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly efficacious progesterone based pill

[a] This is also considered a hormonal treatment

5.3.2 Alcohol intake

Investigational product should not be taken within an hour of ingesting alcohol. There are no restrictions on combining IP intake with caffeine or nicotine intake, but it is recommended to take the IP with food.

5.3.3 MRI procedures:

Patients will be instructed to drink at least 250 mL water within 1 hour before the scan.

5.4 Pre-screen and screen failures

The study will include a two-step screening procedure:

- Pre-screening (Visit 1): Patients with sUA <6.0 mg/dL, eGFR <25 mL/min/1.73 m^2 or UACR <30 mg/g will be classified as pre-screen failures. A single repeat test is permitted if initial sUA, eGFR or UACR results are not in the eligible range.
  - Patients are eligible to pre-screen up to 2 times. There are no time restrictions between the two pre-screening visits.
  - The visit at which the pre-screening criteria are met should be within Weeks -6 to -1.
  - Once patients have met the criteria set in pre-screening, patients are eligible for screening.
  - If a patient passes pre-screening but does not yet satisfy the inclusion/exclusion criteria, the subject may wait to screen at the discretion of the investigator.
- Screening (Visit 2): Patients who do not meet all eligibility criteria based on the full Visit 2 assessment will be classified as Screen Failures.

- A single repeat of an out-of-eligibility range assessment is permitted.
- Patients can undergo screening up to 2 times.
- The same IXRS ecode should be used for the re(pre)screened patient.

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

These patients should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

6 STUDY TREATMENTS

Study treatment is defined as any IP (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to verinurad, allopurinol or placebo.

Study treatment is to be administered in the morning and will be generally better tolerated if taken in association with food. Patients should be advised to maintain adequate hydration.

6.1 Treatments administered

6.1.1 Investigational products

Table 6 Study treatments (prior to Protocol Version 5.0)

	IP 1	IP 2
Study treatment name:	Verinurad or matching placebo	Allopurinol or matching placebo
Dosage formulation:	Capsule	Tablet
Route of administration	Oral	Oral
Dosing instructions:	3, 7.5, or 12 mg to be taken, one time a day	100, 200, or 300 mg to be taken, one time a day
Packaging and labelling	Verinurad capsules will be packaged in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement	Allopurinol tablets will be packaged in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement
Provider	AstraZeneca	AstraZeneca

IP Investigational product

At the time of implementation of Protocol Version 5.0, a new dosing regimen will be introduced to assess the higher dose of 24 mg verinurad. Patients in the 3 mg verinurad cohort who will have Visit 9 after the amendment implementation in the prospective country/site and who have signed ICF for the new dosing regimen will be switched to 24 mg dose at Visit 9. Patients who do not consent should be discontinued from the study at a subsequent visit. To introduce the new 24 mg dose, a new dosing regimen across treatment arms will be initiated to maintain blinding in all study cohorts. All patients in the new dosing regimen will receive 2 capsules, as patients switched from 3 mg to 24 mg dose will receive two 12-mg verinurad capsules, and the bottles differentiated by colour, will be administered to all other patients. Patients on 24 mg verinurad need to take two 12-mg verinurad capsules. To match, patients in the other arms must take 2 capsules for blinding purposes. Patients will be instructed to take one capsule out of two different bottles every day. Allopurinol dosing will remain the same.

Table 7 Study treatments (after implementation of Protocol Version 5.0)

	IP 1	**IP 2**
Study treatment name:	Verinurad or matching placebo	Allopurinol or matching placebo
Dosage formulation:	Capsule	Tablet
Route of administration	Oral	Oral
Dosing instructions:	3*, 7.5, or 12 mg to be taken, one time a day from two differently coloured bottles Patients from 3 mg dose who will be switched to 24 mg will receive 24 mg as two 12-mg capsules**	100, 200, or 300 mg to be taken, one time a day
Packaging and labelling	Verinurad capsules will be packaged in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement	Allopurinol tablets will be packaged in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement
Provider	AstraZeneca	AstraZeneca

IP Investigational product
*3 mg verinurad capsules will only be used for down-titration for patients on the new dosing regimen as of Protocol Version 5.0.
**Patients on 24 mg verinurad need to take two 12-mg verinurad capsules. To match, patients in the other treatment arms must take 2 capsules to maintain the blind. Patients will be given two different bottles with differently coloured labels. Patients will be instructed to take one capsule from each of two different bottles every day. Patients who do not tolerate the new dosing regimen will be down-titrated to the initial dosing regimen (ie, patients on 24 mg will be down-titrated to 3 mg, and patients in other cohorts will not be dispensed the matching placebo capsule).

The verinurad capsules release verinurad over 8 h, hence the formulation is referred to as ER8 (Extended Release over 8 h).

Study treatments will be titrated in discrete steps as shown in Table 8. Titration steps will be spaced at 4-week (±1 week) intervals to minimise the risk of skin reactions to allopurinol. Patients unable to tolerate the stepped dosage may be down-titrated only by reversing the assigned steps within treatment group, and verinurad and allopurinol dosages cannot be unpaired from the titration schedule. Patients who cannot tolerate the step-1 dose will be discontinued from IP and be followed for the remainder of the study.

At Visit 5 (approximately 8 weeks after randomisation) through Visit 9, titration to step-3 target dose will only be allowed if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visits 3 and 4.

When the new dosing regimen is introduced under Protocol Version 5.0, patients who were down-titrated due to intolerance in the initial dosing regimen will not switch treatment to the new dosing regimen. These patients will instead remain on the same treatment after Visit 9.

Patients who do not tolerate the new dosing regimen will be down-titrated to the initial dosing regimen (ie, patients on 24 mg will be down-titrated to 3 mg, and patients in other cohorts will not be dispensed the matching placebo capsule).

Patients will only be allowed to switch to the new dosing regimen introduced under Protocol Version 5.0 if the patient's eGFR was ≥30 mL/min/1.73m^2 at Visit 8. Management of patients with eGFR <30 mL/min/1.73m^2 at Visit 9 should be discussed with the medical monitor.

In case patient down-titration was done in error, the patient can be up-titrated only after consultation with the medical monitor.

Table 8 Titration schedule

	Step 1 - titration (verinurad/allopurinol)	**Step 2 - titration (verinurad/allopurinol)**	**Step 3 - target dose (verinurad/allopurinol)**
High Dose (mg)	3/100	7.5/200	12/300
Intermediate Dose (mg)	3/100	7.5/200	7.5/300
Low Dose (mg)	3/100	3/200	3/300
Allopurinol alone (mg)	0/100	0/200	0/300
Placebo (mg)	0/0	0/0	0/0

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

A formal system for drug accountability will be implemented. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3 Measures to minimise bias: randomisation and blinding

All patients will be centrally assigned to randomised study treatment using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Patients who meet the eligibility criteria will be randomised in a 1:1:1:1:1 ratio to high, intermediate or low dose of verinurad plus allopurinol, allopurinol or placebo. CCI

[redacted]

Laboratory reports for sUA and UACR will be masked to guard against revealing group differences in treatment endpoints except during pre-screening and screening. The central laboratory will issue notifications to study sites if sUA or UACR values indicate potential health concerns.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

The IVRS/IWRS will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. For patients who need down titration, the investigator will need to use the IVRS/IWRS for allocation of new study drug kits for the lower dose.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the patient's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 h after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF) (electronic or paper), as applicable.

Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the personnel analysing the PK samples.

Provisions for interim analysis are described in Section 9.5.

6.4 Treatment compliance

Any change from the dosing schedule, dose interruptions, dose reductions, or dose discontinuations should be recorded in the eCRF.

The investigator is responsible for management of the IP from receipt by the study site until the destruction or return of all unused IP. The investigator(s) is responsible for ensuring that the patient has returned all unused IP. For the new dosing regimen, following Protocol Version 5.0 implementation, patients will be instructed thoroughly and receive new dosing card instructions at Visit 9. They will be instructed to take 1 tablet daily from one bottle of allopurinol/matching placebo and 1 capsule daily from each of two verinurad/matching placebo bottles that will be differentiated by the label colour.

Treatment compliance: The patient will be asked about compliance at each study visit starting from Visit 4 onwards. When study medication is returned, compliance will be assessed based upon patient's interview and a count of the tablets returned. Compliance should be between ≥80% and ≤100% of that prescribed. If the patient is not compliant with recording study drug doses during the study, then the period of non-compliance should be noted as a protocol deviation and the sponsor should be notified. Patients judged to be non-compliant may

continue in the study, but should be counselled on the importance of taking their study medication and applicable ancillary medications as prescribed. The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit as described in Table 1 and Table 2, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses, or overdose, must be recorded on the eCRF. The administration of all study medications (including IPs) should be recorded in the appropriate sections of the eCRF.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

An increased risk of hypersensitivity has been reported when allopurinol is given with ampicillin, amoxicillin, ACE inhibitors, or diuretics, in particular thiazides, especially in renal impairment. It is recommended that in patients receiving allopurinol an alternative therapy is used where available.

Table 9 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed):
Treatments known to lower albuminuria should be stable (consistent dosing for at least 4 weeks), eg, ACEi, ARBs, mineralocorticoid receptor antagonists, or sodium-glucose linked transporter-2 inhibitors.	Proteinuria-lowering therapies must not be started, and doses not changed, between screening and the end of the treatment period of the study unless required for patient safety. Patients on stable doses at study entry should continue on the same doses.
Any medication restricted by the allopurinol package insert; eg, vidarabine, uricosuric drugs such as probenicid and large doses of salicylate, chlorpropamide, warfarin, coumarin anticoagulants, phenytoin, theophylline, amoxicillin, ampicillin, cytostatics such cyclophosphamide, doxorubicin, bleomycin, procarbazine and alkyl halogenides, ciclosporin, didanosine, furosemide and other thiazide diuretics, ACEi, aluminium hydroxide.	Use in accordance with the allopurinol package insert. Case reports suggest concomitant ACEi therapy (eg, captopril and enalapril) enhance the risk of allopurinol-related hypersensitivity reactions. Hypersensitivity reactions can occur in the absence of ACEi therapy as in the presence of diuretics and renal dysfunction.

ACEi Angiotensin-converting enzyme inhibitor; ARBs Angiotensin receptor blockers

Table 10 Prohibited medications

Prohibited medication/class of drug:
Any other investigational drugs than provided in this study.
Any medication prohibited by the allopurinol package insert.
Mercaptopurine
Azathioprine
Any drug administered primarily to lower sUA, including XOIs such as febuxostat or topiroxostat, or URAT1 inhibitors such as lesinurad or benzbromarone.
Strong or moderate OATP inhibitors.[a] Examples: atazanavir, ritonavir, clarithromycin, cyclosporin, erythromycin, gemfibrozil, lopinavir, rifampin (single dose), simeprevir
CCI [redacted]

OATP Organic anion transport polypeptide; URAT1 Uric acid transporter 1; XOI Xanthine oxidase inhibitor

[a] Further information is available at: https://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2

CCI [redacted]

6.5.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

6.6 Dose modification

Study treatments will be titrated in discrete steps as shown in Table 8. Titration steps will be spaced at 4-week intervals to minimise the risk of skin reactions to allopurinol. Patients unable to tolerate the stepped dosage may be down-titrated only by reversing the assigned steps within treatment group, and verinurad and allopurinol dosages cannot be unpaired from the titration schedule. Patients who cannot tolerate the step-1 dose will be discontinued from IP and be followed for the remainder of the study.

When the new dosing regimen is introduced under Protocol Version 5.0, patients unable to tolerate the new dosing regimen will be down-titrated to the initial dosing regimen (ie, patients on 24 mg will be down-titrated to 3 mg, and patients in other cohorts will not be dispensed the matching placebo capsule). Additionally, patients who have been down-titrated and are receiving less than the randomized dose of verinurad/matching placebo at Visit 9 will not switch to the new dosing regimen introduced under Protocol Version 5.0.

In case patient down-titration was done in error, the patient can be up-titrated only after consultation with the medical monitor.

6.7 Treatment after the end of the study

After the end of the study patients can be treated with uric acid lowering therapy and/or other therapies for CKD or other conditions requiring treatment at the responsible physician's discretion.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event
- Severe non-compliance with the Clinical Study Protocol
- Skin reactions and hypersensitivity
  - Study drug should be discontinued immediately at the first sign of a skin rash or other signs which may indicate an allergic reaction. Skin rash is a commonly-reported AE in patients taking allopurinol. Skin reactions may be severe and can be fatal.
  - Extra vigilance for the signs of hypersensitivity syndrome or Stevens-Johnson syndrome / toxic epidermal necrolysis is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms.
- Development of signs/symptoms of nephrolithiasis or potential renal injury
  - Guidelines for assessing possible renal injury or kidney stone and altering treatment are in Appendix F
- Development of AST or ALT ≥3xULN together with total bilirubin ≥2xULN as described in Section 8.3.8 and Appendix E
- If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately and an AstraZeneca representative notified.

Patients who discontinue IP will be recommended to continue on the study and follow the original visit schedule without taking IP.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary interruption of study treatment

Patients may temporarily interrupt IP administration, for instance based on criteria for Appendix F. Temporary interruption of IP does not mean discontinuation of follow-up or termination of study participation. Study assessments should continue. When the IP is resumed, last dose taken should be administered again. If temporary interruption of IP occurred during titration step, the patient should resume titration with the last tolerable dose given. In the event of an interruption exceeding 1 month the administration of IP can be re-titrated to avoid allopurinol induced hypersensitivity reactions, after communication with the sponsor or sponsor's representative.

7.1.2 Study termination

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interest.

7.1.3 Procedures for early discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the CRF (electronic or paper). All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

Patients who discontinue study treatment will attend the end of treatment visit as soon as possible after treatment discontinuation. Discontinuation of study treatment, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol (including a follow-up visit, but no need to do another end of treatment visit). If the

patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately and an AstraZeneca representative notified.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin by, eg, repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to follow-up with unknown vital status at end of study.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (IP **and** assessments) at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). Circumstances of withdrawal will be documented either in writing by patient (ICF re-signature) or investigator.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up patients as medically indicated.

Patients who fail to meet the eligibility criteria must not, under any circumstances, be randomised or receive IP. There can be no exceptions to this rule.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician or representative immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician or representative must ensure all decisions are appropriately documented.

In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow-up in accordance with defined study procedures.

See SoA, Table 1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Laboratory efficacy assessments are shown in Table 11.

Table 11 Laboratory efficacy variables

UACR	Clinical chemistry (serum or plasma)
U-Albumin (mg/dL)[a]	S-Uric Acid (mg/dL)[b]
U-Creatinine (g/dL)[a]	S-Creatinine (mg/dL)[b]
	S-Cystatin C (mg/L)[b]
	S/P-NT-proBNP

[a] For derivation of UACR (primary outcome variable)
[b] Secondary outcome variables
NT-proBNP N-terminal pro-brain natriuretic peptide

Urine samples will be gathered as 3 consecutive daily morning void samples of urine for each visit.

8.1.1 Primary outcome - UACR

The ratio of urinary albumin to urinary creatinine (milligrams of albumin per grams of creatinine) will be assessed by a central laboratory. The mean ratio will be reported for each time point based on all samples collected (FMV sample 1, 2, and 3).

First morning void urine samples will be used for assessment of UACR. Patients will receive a urine sample collection kit allowing them to collect the first morning void urine on 3 consecutive days. Collected samples will be refrigerated until they can be brought to the study site for further processing in accordance with the laboratory manual. Ideally the urine samples should be collected 2 days before, the day before and on the day of a study visit to minimise storage and transportation of collected samples.

If a patient has forgotten to collect one or more of the samples before a visit, then the samples should be collected on the up-to-3 consecutive days following the visit instead (with exception for the randomisation visit urine samples, which must be collected before treatment is started).

In the absence of results from 3 analysed samples, the UACR for a time point will be calculated based on the available results.

Urine samples collected for assessment of UACR CCI must not be confused with urinalysis samples collected at study site during visits for assessment of safety parameters and pregnancy testing.

8.1.2 Secondary outcomes

Secondary outcome measures of renal function include:

- eGFR calculated using the CKD-EPI formula as previously published (Levey et al 2009). Details of the method are presented in Appendix F
- Serum cystatin C
- Serum creatinine

Secondary outcome measures for general metabolic effects include:

- sUA

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

earlier than 2 weeks before Visit 8 and Visit 10 and must be performed no later than on the

CCI

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI

[redacted]

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory.

See Table 14 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected and analysed by a central laboratory if clinically indicated at the discretion of the investigator. The date of collection will be recorded on the appropriate CRF.

Table 14 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Bilirubin, total
B-Leukocyte count	S/P-Alkaline phosphatase (ALP)
B-Leukocyte differential count (absolute count)	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
B-Haematocrit	S/P-Albumin
B-Haemoglobin A1c	S/P-Potassium
B-Red blood cell count (RBC)	S/P-Calcium, total
B-Mean corpuscular hemoglobin (MCH)	S/P-Sodium
B- Mean corpuscular hemoglobin concentration (MCHC)	S/P-Creatine kinase (CK)
B-Red blood cell morphology	S/P-Bicarbonate
B-Mean corpuscular volume (MCV)	S/P-Blood Urea Nitrogen
	S/P-Phosphate
Urinalysis (dipstick)	S/P-Creatinine
U-Hb/Erythrocytes/Blood	
U-Glucose	

Note: If a patient shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.
If a patient shows a creatinine value outside the normal range, refer to Appendix F 'Actions required in cases of a renal-related or kidney stone treatment-emergent adverse event or a serum creatinine elevation' for further instructions.

8.2.2 Physical examinations

Physical examination will be performed at timelines as specified in the SoA. Full physical examinations will include an assessment of the following: general appearance, respiratory, CV, abdomen, and musculoskeletal (including spine and extremities) systems, and the skin. Brief physical examinations are to be utilised by the investigator based on clinical observations and symptomatology, but must include an assessment of the patients' skin. Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

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 unless unequivocally related to the disease under study.

8.2.3 Vital signs

Temperature, pulse rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device with the patient in a seated position. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.4 Electrocardiograms

A 12-lead ECG will be performed after the patient has been lying down for 5 minutes at the times indicated in the SoA. The ECG assessment (normal, abnormal but not clinically significant, or abnormal and clinically significant; and QT interval, QTc_F) will be recorded in the CRF. Any clinically significant findings should be reported as AEs or in the Medical History, as appropriate.

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

An AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up on AEs, see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Serious adverse events will be collected from the time of signature of the ICF, throughout the treatment period and including the follow-up period and last contact. Adverse events will be collected from the time of the first dose of IP. Changes in medical history between the time of signature of the ICF and the first dose of IP will be reported as medical history.

All SAEs will be recorded and reported to the sponsor or designee within 24 h, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

'The following variables will be collected for each AE;

- AE (verbatim)
- The dates when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- Select the appropriate as required: AE caused patient'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'

8.3.5 Causality collection

The investigator will assess causal relationship between IP 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 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 B to this Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit?', or revealed by observation will be collected and recorded in the CRF. 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.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or qualify as AEs of interest.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses 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-mandated parameters should be reported as AE(s).

8.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

8.3.9 Adverse events of special interest

AEs of major CV events and acute changes in serum creatinine values which are clinically significant will be included as AEs of special interest in this study. To ensure that data on increased serum creatinine values are collected systematically, data will be recorded in the eCRF.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day; ie, immediately, but **no later than 24 h** of when he or she becomes aware of it.

The designated AstraZeneca representative works 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 is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day; ie, immediately, but **no later than 24 h** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of an SAE, see Appendix B of this Clinical Study Protocol.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study patient has received any study drug
- Pregnancy in a partner to the study subject

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy.

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

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, all study drugs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day; ie, immediately but **no later than 24 h** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT module is used to report the outcome of the pregnancy.

8.4.3 Overdose

For this study, any dose of verinurad or allopurinol greater than those specified in this protocol within the same day will be considered an overdose. If an overdose is suspected, the patient should be closely monitored, and treatment should consist of observation and general support measures, including adequate hydration. If considered necessary, haemodialysis may be used for allopurinol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 h** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

- For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate Covance representatives within 1 day; ie, immediately but no later than 24 h of when he or she becomes aware of it.

The designated Covance representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

Study drug should be discontinued immediately at the first sign of a skin rash or other signs which may indicate an allergic reaction, and patients should be maintained in the study for safety surveillance. In cases of intolerance (gastrointestinal, headache, or other mild AEs) from the combination IP, dosage will be down-titrated as described in Section 6.1.

Patients developing renal-related or kidney stone AEs, or creatinine elevations during treatment should be managed in accordance with Appendix F.

Patients developing elevated liver transaminase tests should be managed in accordance with Appendix E.

8.4.6 Data monitoring committee (DMC)

An independent DMC will be appointed and will report to AstraZeneca and the CRO. The DMC will be responsible for ensuring patient safety by assessing the safety of the IP during the study, and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing.

A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with AstraZeneca and the CRO.

8.4.7 Clinical event adjudication committee

The role of the clinical event adjudication committee (CEA) is to independently review, interpret and adjudicate potential CV events that are experienced by the patients. CV events will be identified preliminarily by the investigators, and also by AZ personnel, CRO personnel or in the CEA process as specified in the CEA charter. The CEA member/s will not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety event.

The Investigator's Manual or other investigator material will specify the information to be collected for potential CV events.

8.5 Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations of verinurad, allopurinol and oxypurinol (active metabolite of allopurinol) as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample and date and time (24-hour clock time) of previous dose taken will be recorded in the CRF (an electronic bottle cap or another method may be used to assist in capturing the information).

The PK blood samples will be taken at 5 different visits:

- (Visit 6) Week 12: pre-dose; ie, visit must take place in the morning and the patient must take the study medication at the clinic after pre-dose PK has been taken.
  - A subset of at least 95 patients (19 patients per arm, considering some patients may terminate the study before Visit 6) will have samples taken pre-dose followed by post-dose blood samples within 3 to 4, 4 to 5, 5 to 6, and 8 to 9 h windows (sample taken at each time window).
- (Visit 7) Week 20: study medication taken at home, PK blood sample during the visit.
- (Visit 8) Week 34: study medication taken at home, PK blood sample during the visit.
- (Visit 9) Week 47: study medication taken at home, PK blood sample during the visit.
- (Visit 10) Week 60: study medication taken at home, regardless of dosing regimen, PK blood sample will be collected post dose during the visit.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration will be analysed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Left-over PK samples may be used for analysis of safety, efficacy or biomarker laboratory parameters if samples drawn for that purpose at the same time point were insufficient for the analyses needed.

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

8.6 Pharmacodynamics

No further pharmacodynamic samples, apart from those described above and in Section 8.8, will be taken during the study.

8.7 Genetics

8.7.1 Assessment of HLA-B genotype

Skin reactions are the most common reactions for allopurinol, and rarely may include the drug hypersensitivity syndrome, Stevens–Johnson syndrome, and toxic epidermal necrolysis. HLA-B*5801 allele is an important genetic risk factor for these life-threatening conditions. HLA–B*5801 allele frequency is high in Korean (12%) and Han Chinese or Thai (6% to 8%) compared with Caucasian (2%) patients. In this study, HLA-B*5801 allele testing is mandatory in all patients prior to randomisation. If HLA-B*5801 allele is positive, the patient should not be included in the study.

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8.8 Biomarkers

Mandatory collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA and shown in Table 15.

Table 15 Biomarker collections

Urinalysis	Clinical chemistry (plasma)
Protein Urinary epidermal growth factor UA Urine creatinine Kidney injury markers such as: urinary kidney injury protein 1, Neutrophil gelatinase-associated lipocalin, etc	Hemodynamics such as: aldosterone, CHF biomarkers such as: NT-proBNP Inflammation biomarkers such as: interleukin 18, monocyte chemotactic protein 1, hsCRP, etc. Endothelial function such as: asymmetrical dimethylarginine, symmetrical dimethylarginine, L-arginine, etc CKD progression marker such as: soluble urokinase-type plasminogen activator receptor Others such as: fibroblast growth factor 23, etc

CHF congestive heart failure; CKD chronic kidney disease; hsCRP High-sensitivity C-reactive protein; NT-proBNP N-terminal pro-brain natriuretic peptide; UA uric acid

Urine and blood samples (plasma) will be collected, aliquoted and analysed or stored in a biobank for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. Some of the planned biomarker analyses may be performed only if the study provides evidence of efficacy and may be performed in a staggered fashion to minimise resources spend. Results of biomarker analyses will be issued separately from the CSR.

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Medical resource utilisation and health economics

Medical resource utilisation and health economics parameters are not evaluated in this study.

8.10 Guidelines, study assessments, and procedures during COVID-19 pandemic

In view of the ongoing and emerging novel coronavirus (COVID-19) pandemic spreading worldwide, the safety and well-being of our study participants is of primary importance. To protect the safety and well-being of study participants, this section will provide guidelines on study assessments and procedures during this period.

1 Every effort should be made to follow the clinical study protocol (CSP). Participant safety is paramount, and the investigator should continue to reassess the risk/benefit of continued study involvement for each study participant.

2 Investigational study sites must comply with local public health rules.

3 If a study participant is diagnosed with COVID-19 or is suspected to have COVID-19, they should follow the local area treatment and quarantine guidance.

   (a) Please accurately document all diagnoses, procedures, assessments, dosing interruptions, and sequelae in the eCRFs. All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP.

   (b) If a COVID-19 AE/SAE is reported, the investigator should determine whether the participant's investigational product should continue, be interrupted, or stopped in accordance with the CSP.

   (c) Patients with confirmed or suspected COVID-19 infection with moderate to severe symptoms may be at risk of dehydration or hypoxia. In case of such events the PI should consider IP interruption until symptoms improve.

4 If a study participant is unable to attend clinic visits, and/or receive study intervention, the site staff should keep in close contact with the study participant(s), preferably through telephone calls, to maintain awareness of their status.

5 If a patient cannot be seen on site, please consider the following options:

   (a) Conducting the visits in the patient's home by study personnel or other trained professionals. In addition, third party vendor personnel may be utilised to conduct assessments.

(b) Conducting the visit by phone, with urine samples, investigational product and urine sample collection containers shipped or otherwise transported between site and patient. The collection and analysis of safety blood samples at an alternative healthcare facility should be considered. Local lab results will not be collected or stored in the study database but will help the investigator to assess patient safety.

(c) If labs collected for safety assessments cannot be collected for more than two consecutive visits between Visit 3 and Visit 7 including Visit 7 or for more than one visit between Visit 7 and Visit 14, the IP should be temporarily interrupted. With the absence of safety labs as described in the above case, IP will not be dispensed. However, if it is interrupted for greater than one month, the investigator should discuss with the medical monitor how to re-start treatment and titrate the IP to maintenance treatment. IP could be re-started during the unscheduled visits and then study participant should return to regular visits as per the study protocol.

References:

https://www.fda.gov/media/136238/download

https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Three hypotheses will be included in confirmatory testing for the primary objective. See Section 9.4.4 for a description of multiplicity control. The following hypotheses will be tested sequentially at two-sided alpha = 0.1 (treatments refer to initial dosing regimen prior to Protocol Version 5.0):

- Null hypothesis: No difference between high dose verinurad plus allopurinol compared to placebo on UACR at 6 months
- Alternative hypothesis: There is a difference between high dose verinurad plus allopurinol compared to placebo on UACR at 6 months

- Null hypothesis: No difference between high and intermediate dose verinurad combined plus allopurinol compared to allopurinol alone on UACR at 6 months
- Alternative hypothesis: There is a difference between high and intermediate dose verinurad combined plus allopurinol compared to allopurinol alone on UACR at 6 months

- Null hypothesis: No difference between allopurinol alone compared to placebo on UACR at 6 months
- Alternative hypothesis: There is a difference between allopurinol alone compared to placebo on UACR at 6 months

No other comparisons between treatment groups for the primary and secondary objectives will be adjusted for multiplicity.

9.2 Sample size determination

The estimated sample size of 145 patients per arm (initial dosing regimen) will yield 80% power to detect a 25% reduction in UACR for the high dose of verinurad + allopurinol compared to placebo (treatment difference of approximately -0.29 on the natural log scale) at the two-sided alpha level of 0.1, assuming a standard deviation of 1.0 on the natural log-scale. A total of 725 patients (145 patients per arm [initial dosing regimen]) must be randomised. The standard deviation estimate is based on the results of Study D5495C00007.

For the MRI substudy, a sample size of 30 in each arm (initial dosing regimen) will have at least 80% power to detect a difference (high dose verinurad + allopurinol vs. placebo) in means of 0.05 in renal arterial resistive index assuming that the common standard deviation is 0.05 with a 0.05 two-sided significance level. The standard deviation of 0.05 is based on data published by Leoncini et al 2002.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined in Table 16:

Table 16 Analysis populations

Population	Description
Enrolled	All patients who sign the main ICF
Randomised set	All patients who are randomised
Full Analysis Set	All randomised patients
PPS	The per-protocol analysis set is a subset of the Full Analysis Set consisting of all patients who do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly. All decisions to exclude patients from the per-protocol analysis set will be made prior to the un-blinding of the study.
Efficacy analysis set	Full analysis set
Safety analysis set	All patients who had at least 1 dose of IP.
PK set	All patients who received allopurinol and verinurad treatment and have at least one post-dose plasma concentration measurement of verinurad at a scheduled time point

ICF Informed consent form; IP Investigational product; PK pharmacokinetic

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock.

Analyses will be performed by a CRO designated by AstraZeneca. A comprehensive statistical analysis plan (SAP) will be developed and finalised before the first interim analysis and will describe the subject populations to be included in the analyse and procedures for accounting for missing data. This section is a summary of the planned statistical analyses. Any deviations from this plan will be reported in the CSR.

9.4.1 Endpoints

9.4.1.1 Primary endpoint

- Change from baseline in UACR at 6 months

9.4.1.2 Secondary endpoints

- Change from baseline in UACR at 6 and 12 months
- Change from baseline in sUA at 6 and 12 months
- Change from baseline in estimated glomerular filtration rate at 6 and 12 months
- Change from baseline in creatinine at 6 and 12 months
- Change from baseline in cystatin-C at 6 and 12 months

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9.4.2 Efficacy analyses

All efficacy analyses will be performed using the Full Analysis Set (FAS) unless otherwise specified. In addition, the primary efficacy analysis will be performed using the Per Protocol Set as a sensitivity analysis.

Standard descriptive statistics comprise (but are not limited to) number of observations, mean value, standard deviation, coefficient of variation (or CV, for natural log-normal data), median value, minimum and maximum values.

9.4.2.1 Primary efficacy analysis

The primary efficacy variable is the change from baseline in UACR at 6 months (Week 34, ie, 26 weeks of treatment following an 8-week titration phase). Primary analyses will be performed on the FAS population, which consists of all randomised patients regardless of

treatment discontinuation. In other words, post-discontinuation data will be collected and included in the primary analysis. Details on how to handle missing data will be provided in the SAP.

In addition to analysis of the hypotheses in Section 9.1, the primary efficacy variable will be analysed comparing (initial dosing regimen):

- Intermediate dose verinurad plus allopurinol with placebo
- Low dose verinurad plus allopurinol with placebo
- High dose verinurad plus allopurinol with allopurinol alone
- Intermediate dose verinurad plus allopurinol with allopurinol alone
- Low dose verinurad plus allopurinol with allopurinol alone

The analysis of change in UACR from baseline to Week 34 will be conducted on the natural log-transformed UACR values using a repeated measures mixed model.

The analysis model will include the fixed categorical effects of treatment, week, DM status yes or no, microalbuminuria or macroalbuminuria, NT-proBNP < or ≥360 pg/mL, use of SGLT2 yes or no, and treatment-by-week interaction as well as the continuous fixed covariates of baseline log(UACR) and baseline log(UACR) by-week interaction. An unstructured matrix for the within patient error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the SAP in case of non-convergence of the preferred model or other issues.

The least squared mean change from baseline to 6 months in the log-transformed UACR will be calculated by treatment with its 95% confidence intervals. The least squared mean difference between the treatments will be calculated with its 95% confidence interval. P-values of the treatment differences between active treatment group and placebo/comparator will also be calculated.

The above least squared mean change from baseline (and the 95% confidence interval) for each treatment will be exponentiated to yield the geometric mean ratio from baseline for each treatment with its 95% confidence interval at the original scale of UACR. The least squared mean difference between the active treatments and placebo/comparator (and its 95% confidence interval) will also be exponentiated to yield the geometric mean ratio between the 2 treatments at each visit and its 95% confidence interval at the original scale of UACR. Percent change from baseline will be derived from the geometric estimated mean ratio by ([geometric mean ratio] - 1) × 100%.

9.4.2.2 Secondary efficacy analyses

For the secondary variables at 6 months, the following comparisons will be made (initial dosing regimen):

- High dose verinurad plus allopurinol with placebo
- Intermediate dose verinurad plus allopurinol with placebo
- Low dose verinurad plus allopurinol with placebo
- High dose verinurad plus allopurinol with allopurinol alone
- Intermediate dose verinurad plus allopurinol with allopurinol alone
- Low dose verinurad plus allopurinol with allopurinol alone
- Allopurinol with placebo

For the secondary variables at 12 months, the comparison "24 mg (double dose)" versus "Placebo (double dose)" will be made. If the model will not provide reliable results (eg, due to no convergence), descriptive statistics only will be considered sufficient.

All secondary variables will be log-transformed before analysis.

Analysis of secondary variables at 6 and 12 months will be performed using a model similar to that used for the primary efficacy variable. Change from baseline and treatment comparisons will also be estimated similarly.

The dose response of verinurad plus allopurinol on UACR and sUA will be evaluated using modelling, and the details will be provided in the SAP.

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9.4.2.4 Subgroup analyses

Subgroup analyses for the primary endpoint will be performed for the following subgroups:

- diabetics and non-diabetics at baseline
- CKD1, CKD2, and CKD3+CKD4 at baseline
- Microalbuminuria and macroalbuminuria at baseline
- <Median baseline sUA and ≥ median baseline sUA
- Baseline NT-proBNP < 360 pg/mL and NT-proBNP ≥360 pg/mL
- Baseline eGFR ≤60 mL/min/1.73 m^2 vs >60 mL/min/1.73 m^2
- Race of Black or African American, White, Asian, Other
- Age <65, and ≥65 years

- Gender of male, female
- Geographic region

The primary analysis model will be repeated for each subgroup adding factors for subgroup and treatment by subgroup interaction.

These analyses will be conducted only to the extent the results are considered reliable, eg, the analyses should converge.

9.4.3 Safety analyses

All safety analyses will be performed on the Safety Population.

The assessment of safety will be based on the analyses of AEs, vital signs, ECGs and laboratory evaluations.

All safety data will be summarised by treatment group based on the treatment received.

The number and percent of patients with at least one AE will be summarised for each treatment group, including summaries of AEs, SAEs, and AEs leading to discontinuation. Summaries will include the number of subjects with events by system organ class and preferred term. The incidence of laboratory abnormalities, to be defined in the SAP, will be summarised for each treatment group. Values and changes from baseline at each scheduled time point for clinical laboratory parameters and vital signs, including blood pressure and heart rate, will be summarised by treatment group using descriptive statistics. Additional analyses of creatinine will be specified in the SAP. The normality/abnormality of ECG tracings, as determined by the investigator, will be summarised by shift tables overall and by ECG tracing at baseline.

9.4.4 Methods for multiplicity control

The experiment-wise Type I error will be controlled at 10% by hierarchical testing of the hypotheses in Section 9.1. No other comparisons will be adjusted for multiplicity.

9.5 Interim analyses

Two interim analyses will be performed to support internal decisions of the programme development. No multiplicity adjustment is planned for the interim analyses because there is no provision to stop the trial early at the interim analyses to claim efficacy.

These interim analyses will be conducted by an independent team who are not involved in the conduct of the study. A communication plan will be developed to explain who will review the results from interim analyses. All necessary steps will be taken to ensure the integrity of the trial by keeping the study team blinded throughout the study.

The first interim analysis will be performed no later than when 90% of subjects have completed 12 weeks of treatment after titration (Visit 7). The second interim analysis will be conducted after all subjects complete 26 weeks of treatment after titration (Visit 8). The scope of data analysis will be specified in a SAP.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Institutional Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

If applicable, a separate informed consent will be submitted to the Ethical Committee for procedures concerning the MRI test persons that are scanned to ensure the correct implementation of imaging methods.

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Patients who are re-prescreened are required to sign a new brief ICF. The brief ICF is used to obtain patient consent for sUA, eGFR, and UACR assessments. Patients who are rescreened are required to sign a new full ICF. The full ICF is the master ICF for the study.

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A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

Data monitoring committee (DMC)

An independent DMC will be appointed and will report to AstraZeneca and the CRO. The DMC will be responsible for ensuring patient safety by assessing the safety of the IP during the study, and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing.

A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with AstraZeneca and the CRO.

Clinical event adjudication (CEA)

The role of the CEA is to independently review, interpret and adjudicate potential CV events that are experienced by the patients. CV events will be identified preliminarily by the investigators, and also by AZ personnel, CRO personnel or in the CEA process as specified in the CEA charter. The CEA member/s will not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety event. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site deemed “ready to enrol” and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before

submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment 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 hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B 3 Life threatening

'Life-threatening' means that the patient 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 patient'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).

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

Medical and scientific judgement 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 patient or may require medical treatment to prevent one 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 judgement must be used.

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

B 6 Intensity rating scale:

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient 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?
- De-challenge 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 another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

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

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

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognise that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING 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 eg, Ebola, Lassa fever virus:

- 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 eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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 650
  Exempt - 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**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient 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.

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Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 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 patient meets 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 TBL from a local laboratory.

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

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

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

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate transaminase (AST) or alanine transaminase (ALT) ≥3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥3 × ULN **together with** TBL ≥2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

E 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 patient who meets any of the following identification criteria in isolation or in combination:

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

Central laboratories being used:

When a patient meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (and also to the AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

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 patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits

- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section E 6)
- 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 Potential Hy's Law; 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 patients' follow-up and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete the follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
  - Complete the three Liver CRF Modules as information becomes available

E 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 IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

- Send an updated SAE (report term ‘Hy’s Law’) according to AstraZeneca standard processes.
  - The ‘Medically Important’ serious criterion should be used if no other serious 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 or not 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 Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria 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 the CSP process for SAE reporting, according to the outcome of the review amending, the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease)?

If **No**: Follow the process described in Appendix E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant# change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix E 4.2 for reporting PHL as an SAE

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

E 7 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory.

Some of the tests may also be considered for use with local laboratories that have respective testing capabilities. Any test results need to be recorded in the CRF

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR

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

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FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix F Actions required in cases of a renal-related or kidney stone 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.

F 1 Signs and symptoms suggestive of renal injury or kidney stone

After initiation of study medication, if a patient experiences signs or symptoms suggestive of nephrolithiasis (eg, flank pain or haematuria), he/she should be evaluated by a physician, and serum creatinine, blood urea nitrogen, and urinalysis should be measured via central laboratory testing (preferred) and/or local laboratory testing, as appropriate, to determine renal function. Imaging (intravenous urogram, renal ultrasound, or MRI) 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 the CRF.

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

F 2 Deterioration of renal function

This study will have at least 2 pre-dose serum creatinine measurements. The (higher) of all creatinine measurements collected before randomisation will be considered the baseline serum creatinine for renal safety monitoring.

This study enrols patients with chronic kidney disease (CKD). These patients may have changes in serum creatinine and estimated glomerular filtration rate (eGFR) that may be due to various causes such as: deterioration of renal function due to the underlying cause of CKD, volume depletion, hypotension, intercurrent medical conditions such as worsening heart failure, concomitant drugs that alter renal tubular creatinine secretion or reabsorption, or change in glomerular filtration rate via haemodynamic effects.

The investigator should assess each patient carefully to determine the most likely cause for the deterioration of renal function. Following a thorough assessment, the patient 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.

Patients on ACEi/ARB medication (CKD, heart failure) or on mineralocorticoid receptor antagonists or beta-blockers (heart failure) should not have these treatments reduced in dose or discontinued unless all other measures fail to improve the patient's situation.

F 2.1 Patients with baseline eGFR ≥40 mL/min/1.73 m^2

F 2.1.1 Serum creatinine increase to ≥1.5-fold from baseline

- Assess the patient to identify and manage any potential contributing factor. Correct any dehydration and ensure the patient is well hydrated prior to next renal safety monitoring visit.
- At the investigator's discretion, the patient may continue with study treatment, and retest of serum creatinine should be performed the following week. If the underlying cause (eg, dehydration) is still present at the next evaluation, the investigator should carefully consider if the retesting should be postponed for another week.
- Patient should attend the following week for repeat serum creatinine measurement. If an underlying potentially treatable cause (eg, dehydration) is still present, the investigator should treat this appropriately and postpone testing for up to a week.
- Subsequent management will depend on the repeat measurement(s):
  - If serum creatinine <1.5-fold of baseline value for two successive measurements, the patient may restart/continue with study treatment and the original study visit schedule.
  - If repeat serum creatinine is between ≥1.5 to <2.0-fold of baseline value, the patient should be evaluated every 1 to 2 weeks. During this evaluation period, the randomised treatment can be temporarily interrupted at the investigator's discretion. If serum creatinine is <1.5-fold of baseline value during the evaluation period, study treatment may be restarted/continued on the original study visit schedule.
  - If serum creatinine ≥2.0-fold of baseline value for 2 successive measurements (including the original high value if applicable), randomised treatment should be permanently discontinued and the patient should be followed up as per study schedule.

F 2.2 Patients with baseline eGFR <40 mL/min/1.73 m^2

The CKD-EPI formula (Michels et al 2010) should be used to estimate GFR for enrolment criteria, baseline value and subsequent on-study measurements.

More intense renal monitoring and discontinuation are based on % drop from the baseline value.

F 2.2.1 If eGFR drops to <75% of the baseline value

- Assess the patient to identify and manage any potential contributing factor. Correct any dehydration and ensure the patient is well hydrated prior any future evaluation.
- At the investigator's discretion, the patient may continue with study treatment and retest of serum creatinine should be performed within 7 days. If the underlying cause (eg, dehydration) is still present at the next evaluation, the investigator should carefully consider if the retesting should be postponed for another week.
- Subsequent management will depend on the repeat measurement(s):
  - If eGFR is >75% of the baseline value on **2** successive measurements, the patient may restart/ continue with study treatment on the original study visit schedule.
  - If the repeat eGFR value is between 60% and 75% of the baseline value, the patient should be evaluated every 1 to 2 weeks for serum creatinine measurements/ GFR estimation. During this evaluation period, the randomised treatment can be temporarily interrupted at the investigator's discretion. If eGFR returns to >75% of baseline value during the evaluation period, study treatment may be restarted/ continued on the original study visit schedule.
  - If eGFR is <60% of the baseline value on **2** successive measurements, randomised treatment should be permanently discontinued, and the patient should be followed up as per study schedule.

Examples of eGFR changes and triggered actions

Baseline eGFR (mL/min/1.73 m^2)	Intense renal monitoring ± temporary interruption of treatment eGFR (mL/min/1.73 m^2)	Permanently discontinue randomised treatment eGFR (mL/min/1.73 m^2)
39	23 to 29	<23
36	21 to 27	<21
32	19 to 24	<19
28	17 to 21	<17
25	15 to 19	<15

REFERENCE

Michels et al 2010
Michels WM1, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010 Jun;5(6):1003-9.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ARB	angiotensin receptor blocker
AST	aspartate transaminase
CKD	chronic kidney disease
CRF	case report form (electronic/paper)
CRO	contract research organisation
CSR	clinical study report
DMC	data monitoring committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal natriuretic peptide
OATP	organic anion transporting polypeptide
PD	pharmacodynamic
PK	pharmacokinetic
PWV	pulse wave velocity
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	sodium-glucose transport protein
sUA	serum uric acid
uUA	urinary uric acid
UACR	urinary albumin to creatinine ratio

Abbreviation or special term	Explanation
UA	uric acid
ULN	upper limit of normal
URAT1	uric acid transporter 1
XOI	xanthine oxidase inhibitor

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