Clinical Study Protocol	
Drug Substance	Verinurad / RDEA3170
Study Code	D5496C00005
Version	4.0
Date	20 September 2021

A Phase 2, Multicentre, Double-Blind, Placebo and Active Control Efficacy and Safety Study to Evaluate Verinurad combined with Allopurinol in Heart Failure with Preserved Ejection Fraction (AMETHYST)

Sponsor: AstraZeneca AB, 151-85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): USIND 146049, EudraCT 2019-004862-16

VERSION HISTORY

Version 4, 20 September 2021
Version 4 is a substantial amendment to the Clinical Study Protocol (CSP). The purpose of the substantial amendment is to inform of a decision to hold further study recruitment, remove the interim analysis, and remove a treatment arm (24 mg verinurad in combination with allopurinol) that was previously planned to be included (CSP version 3). There was a decision taken to hold recruitment at the original number of patients targeted for the interim analysis, i.e. reducing the sample size from n=435 to approximately 150 patients. This smaller sample size is considered to be enough for the evaluation of the primary efficacy objective, and the interim analysis is no longer needed. The reduction of the sample size and the removal of the treatment arm were not based on safety concerns, and the safety profile remains unchanged. Should results indicate a need for a larger study, as was originally planned, the CSP may be amended to restart recruitment, understanding the potential limitations of the added data. The substantial changes and all other changes in this amendment are summarised below. **Changes summarised below:** **Section 1.1, Schedule of Activities** • CCI [redacted] • Removed references to DECT and PET/CT from table and footnotes due to substudy cancellation. • Clarified that progression to Visit 2 can be performed before HLA-B results are available. **Section 1.2, Synopsis** • CCI [redacted]. • Removed text relating to 24 mg verinurad + allopurinol treatment arm and timing of Protocol Version 3.0 implementation. • Updated estimated date of the last visit of the last patient, number of patients that will be randomised/enrolled, and estimated screen-failure rate. • Removed dosing schedule (Table 1) relating to 24 mg verinurad + allopurinol treatment arm. • Removed text relating to planned analysis of pooled data from 24 mg verinurad + allopurinol treatment arm.

Section 1.3, Study Schema

- Updated labelling of Figure 1 study schema.
- Removed study schema labelled as Part (B) for 24 mg verinurad + allopurinol treatment arm.

Section 2.3, Benefit/Risk Assessment

- Removed reference to previous study of 24 mg verinurad dose (ER8 formulation) in healthy subjects.
- Updated total number of treatment arms to reflect removal of 24 mg verinurad + allopurinol treatment arm.

CCI

- CCI

Section 4.1.1, Overview

- Removed reference to 24 mg verinurad + allopurinol treatment arm and timing of Protocol Version 3.0 implementation, and reverted to 1:1:1 randomisation ratio.
- Related to the 24 mg verinurad + allopurinol treatment arm, removed the number of patients that would have been randomised/enrolled and the estimated screen-failure rate.

Section 4.1.2.2, Week -2 to -1 (Visit 2), Only if Eligibility Criteria Met as Assessed in Visit 1

- Clarified that patients can progress to Visit 2 before HLA-B results are available.

Section 4.1.2.3, Week 0 (Visit 3)

- CCI
- Removed references to DECT and PET/CT due to substudy cancellation.

Section 4.1.2.5, Week 8 (Visit 5)

- Removed reference to 24 mg verinurad + allopurinol treatment arm in final (titration step 3).

Section 4.1.2.6, Week 12 (Visit 6)

- CCI
- Removed reference to 24 mg verinurad + allopurinol treatment arm in final (titration step 3).

Section 4.1.2.7, Week 22 (Visit 7)

- Removed reference to 24 mg verinurad + allopurinol treatment arm in final (titration step 3).

Section 4.1.2.8, Week 32 (Visit 8)

- CCI [redacted]
- Removed references to DECT and PET/CT due to substudy cancellation.

Section 4.1.2.9, Week 36 (Visit 9)

- CCI [redacted]

Section 4.1.2.10, Premature Treatment Discontinuation Visit

- CCI [redacted]
- Removed references to DECT and PET/CT due to substudy cancellation

Section 4.3, Justification for Dose

- Removed clarification that 12-mg verinurad was the initially targeted dose and justification that doubling the initially targeted dose to 24 mg would occur at the last up-titration visit (Visit 5).

Section 5.2, Exclusion Criteria

- Removed exclusion criteria #26 due to substudy cancellation.

Section 5.3.1, Pregnancy

- Rearranged text for clarification.

Section 6.1.1, Investigational Products

- Removed text regarding dispensing of verinurad doses in separate treatment arms at study visit (24 mg and 12 mg).
- Removed clarification regarding how study treatments have changed and measures taken to ensure blinding in patients randomised after implementation of Protocol Version 3.
- Updated title of Table 4 and deleted Table 5.
- Removed clarification regarding implementation of Protocol Version 3.0 only when investigational products with updated labels are available and only at study sites where all necessary approvals are in place.

Section 6.3, Measures to Minimise Bias: Randomisation and Blinding

- Removed reference to 24 mg verinurad + allopurinol treatment arm and reverted to 1:1:1 randomisation ratio.

Section 8.1.3.9, Dual –emission Computed Tomography and PET Substudy

- Section deleted due to substudy cancellation.

CCI [redacted]

Section 8.6.1, Assessment of HLA-B Genotype

- Clarified ethnic groups with higher B*5801 allele frequency.

Section 8.7, Biomarkers

- Changed cross reference to biomarker section.
- Clarified that participation in future research is optional and contingent upon local regulations.

Section 9.2, Sample Size Determination

- Removed reference to 24 mg verinurad + allopurinol treatment arm and 1:1:1:1 randomisation ratio.
- Relating to 24 mg verinurad + allopurinol treatment arm, removed the number of patients that would have been randomised/enrolled and statistical power.

Section 9.4, Statistical Analysis

- Replaced reference to interim analysis with final data base lock.

Section 9.4.1.1, Analysis of the Primary Objective

- Removed references to planned analysis to include pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.
- Removed reference to new planned sensitivity analyses of the primary analysis with respect to the updated study design in Protocol Version 3.0.

Section 9.4.1.2, Analysis of the Secondary Objectives

- Removed reference to new planned analysis of pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.

Section 9.4.2, Safety Analyses

- Removed reference to new planned analysis of pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.

CCI [redacted]

CCI [redacted]

Section 9.5, Interim Analysis

- Removed section. Interim analysis replaced by final data base lock.

Section 10, References

- Removed references relating to cancelled DECT/PET substudy.

Version 3, 03 February 2021

Changes summarised below:

Clinical Study Protocol Title

- Updated title to remove text specifying a "3-arm" study because patients randomised after implementation of Protocol Version 3.0 are assigned to one of 4 treatment arms as part of modified study design.

Section 1.1, Schedule of Activities

- Updated timings when Patient Dosing Cards are given to patient (additionally at Visits 3, 6 and 7) and inserted cross-reference to new appendix describing Patient Dosing Cards.
- Updated to include additional ECG assessment at Visit 6.
- Clarified that, for patients who prematurely discontinued treatment, DECT should be performed only at the premature treatment discontinuation visit.
- CCI [redacted]

Section 1.2, Synopsis, Table – Objectives and Endpoints

- CCI [redacted]

Section 1.2, Synopsis

- Updated to include additional treatment arm (24 mg verinurad in combination with allopurinol), timing of Protocol Version 3.0 implementation, estimated date of the last

visit of the last patient, number of patients that will be randomised/enrolled and estimated screen-failure rate.

- Updated dosing schedule (Table 1) in-line with inclusion of additional treatment arm (24 mg verinurad in combination with allopurinol).
- Updated to include new planned analysis of pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.

Section 1.3, Study Schema

- Re-labelled Figure 1 as study schema as Part (A) (prior to implementation of Protocol Version 3.0) and corrected designation of KCCQ as secondary endpoint (not key secondary endpoint).
- Inserted new study schema labelled as Part (B) (after implementation of Protocol Version 3.0) to include additional treatment arm (24 mg verinurad in combination with allopurinol) and corrected designation of KCCQ as secondary endpoint (not key secondary endpoint) for consistency with wording throughout the CSP.

Section 2.3, Benefit/Risk Assessment

- Provided reference to previous study of 24 mg verinurad dose (ER8 formulation) in healthy subjects.
- Updated total number of treatment arms to reflect inclusion of additional treatment arm (24 mg verinurad in combination with allopurinol).

Section 4.1.1, Overview

- Updated to include additional treatment arm (24 mg verinurad in combination with allopurinol) and 1:1:1:1 randomisation ratio.
- Updated to include additional treatment arm (24 mg verinurad in combination with allopurinol), timing of Protocol Version 3.0 implementation, number of patients that will be randomised/enrolled and estimated screen-failure rate.

Section 4.1.2.3, Week 0 (Visit 3)

- Clarified that study treatment should be taken after blood drawn.
- Updated that Patient Dosing Card is given to patient.

Section 4.1.2.4, Week 4 (Visit 4)

- Clarified that patient should take IP from a new bottle at the end of the visit.

Section 4.1.2.5, Week 8 (Visit 5)

- Updated that final (titration step 3) verinurad doses will be dispensed in separate treatment arms at study visit (24 mg and 12 mg).

- Clarified that patient should take IP from a new bottle at the end of the visit.

Section 4.1.2.6, Week 12 (Visit 6)

- Updated that ECG will be performed at Visit 6.
- CCI [redacted]
- Clarified that dose, date and time of study treatment intake should be recorded in patient's medical records.
- Updated that final (titration step 3) verinurad doses will be dispensed in separate treatment arms at study visit (24 mg and 12 mg).
- Updated that Patient Dosing Card is given to patient.

Section 4.1.2.7, Week 22 (Visit 7)

- Clarified that dose, date and time of study treatment taken at home should be recorded in patient's medical records.
- Updated that final (titration step 3) verinurad doses will be dispensed in separate treatment arms at study visit (24 mg and 12 mg).
- Updated that Patient Dosing Card is given to patient.

Section 4.1.2.8, Week 32 (Visit 8)

- Clarified that, for patients who prematurely discontinued treatment, DECT should be performed only at the premature treatment discontinuation visit.
- Clarified that dose, date and time of study treatment intake should be recorded in patient's medical records.

Section 4.3, Justification for Dose

- Updated to clarify that 12-mg verinurad was the initially targeted dose and to justify doubling the initially targeted dose to 24 mg at the last up-titration visit (Visit 5).

Section 5.2, Exclusion Criteria

- Corrected text formatting error that grouped 2 separate exclusion criteria from CSP Version 1 (**#6** [HLA-B*58:01 allele carrier] and **#7** [TLS or LNS diagnosis]) into a single exclusion criterion in CSP Version 2 (**#6**). These are now relisted as separate criteria.
- Data collected from patients meeting exclusion criterion in CSP Version 2 (**#6**) will be retrospectively reviewed to confirm the specific exclusion criteria met and to revise exclusion criteria numbering (for consistency with that used in CSP Versions 1 and 3), which will then be updated in RAVE.
- Updated and simplified exclusion criterion **#17** (long QT syndrome), based on findings from recent verinurad thorough QT study.

Section 6.1.1, Investigational Products

- Updated verinurad doses dispensed in separate treatment arms at study visit (24 mg and 12 mg) and applied throughout the CSP.
- Re-labelled Table 4 (Study Treatments) to specify that this is applicable to patients randomised prior to implementation of Protocol Version 3.0. Inserted cross-reference to new appendix describing Patient Dosing Cards. Relabelled initial duplicate row category title "Dosing instructions" as "Dosage levels". Corrected timing when patients can receive their maintenance dose of study treatment (ie, Weeks 8 to 32).
- Clarified how study treatments have changed and measures taken to ensure blinding in patients randomised after implementation of Protocol Version 3 given the requirement to administer two verinurad capsules each day to achieve a dose of 24 mg. Highlighted that patients randomised prior to implementation of Protocol Version 3.0 will continue to receive only one verinurad capsule each day.
- Inserted new Table 5 (Study Treatments [applicable to patients randomised after implementation of Protocol Version 3.0]) to include additional treatment arm and provide important dosing instructions. Inserted cross-reference to new appendix describing Patient Dosing Cards.
- Clarified that Protocol Version 3.0 can be implemented only when investigational products with updated labels are available and only at study sites where all necessary approvals are in place.

Section 6.3, Measures to Minimise Bias: Randomisation and Blinding

- Updated to include additional treatment arm (24 mg verinurad in combination with allopurinol) and 1:1:1:1 randomisation ratio.
- Updated to provide details on down titration of study treatment at, or before, Visit 5.
- Clarified that sponsor will be blinded to post-randomisation sUA values in order that the study integrity is maintained.

Section 8.1.3.9, Dual-emission Computed Tomography and PET Substudy

- Changed wording of "termination visit" to "premature treatment discontinuation visit" for clarity and consistency of terminology in document.

Section 8.2.1, Clinical Safety Laboratory Assessments

- Clarified in Table 8 (Laboratory Safety Variables) that if a patient shows a total bilirubin value outside the normal range, direct bilirubin will be automatically evaluated by the central laboratory.

Section 9.2, Sample Size Determination

- Updated to include additional treatment arm (24 mg verinurad in combination with allopurinol), 1:1:1:1 randomisation ratio, number of patients that will be randomised/enrolled and statistical power.

Section 9.3, Populations for Analyses, Table 8 – Analysis Populations

- Corrected for consistency with wording stated in Section 9.4.2 describing the safety analysis set and analysis of patients according to their randomised IP assignment.

Section 9.4.1.1, Analysis of the Primary Objective

- Updated planned analysis to include pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.
- Updated to include new planned sensitivity analyses of the primary analysis with respect to the updated study design in Protocol Version 3.0.

Section 9.4.1.2, Analysis of the Secondary Objectives

- Updated to include new planned analysis of pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.

Section 9.4.2, Safety Analyses

- Updated to include new planned analysis of pooled data from the 24 mg verinurad + allopurinol and 12 mg verinurad + allopurinol treatment arms.

CCI

[redacted]

Appendix K, Patient Dosing Cards Information

- Inserted new appendix providing update of Patient Dosing Cards information for:
  (1) patients randomised prior to implementation of Protocol Version 3.0; and
  (2) patients randomised after implementation of Protocol Version 3.0.

Version 2, 30 July 2020

Changes summarised below:

Protocol summary, Section 1.1 Schedule of Activities

- Discrepancy related to footnote "f" has been corrected.
- Urinalysis has been added as one of the Safety Labs to correct discrepancy.
- Safety laboratory assessments have been removed from Visit 2.
- CCI [redacted]
- Clarification which visits can be performed in patients home due to pandemic has been added.
- Duration of titration and visits schedule have been changed.
- One additional week for patients screening has been added.

Protocol summary, Section 1.2 Synopsis

- Discrepancy between Synopsis and Inclusion 6 in number of weeks of patient´s symptoms before enrolment has been corrected.
- Estimated study timelines has been corrected.
- Estimated amount of sites and countries has been corrected.
- CCI [redacted]
- CCI [redacted]
- Duration of treatment titration has been changed.
- Dosing schedule (Table 1) has been updated.
- Statistical methods paragraph – timelines for study endpoint has been changed (from Week 28 to Week 32).
- Study scheme has been updated with extended titration period.
- Colchicine prophylaxis schedule has been modified due to extended titration.

Section 2.3 Benefit/Risk Assessment

- Colchicine prophylaxis schedule has been modified due to extended titration.

CCI [redacted]

Section 4.1.1 Overall design (overview)

- Estimated amount of sites and countries have been corrected.

Section 4.1.2 Study Procedures

- Urinalysis has been added as one of the Safety Labs to correct discrepancy in visits: 1, 3, 4, 5, 6, 7, 8, 9 and Premature Treatment Discontinuation Visit.
- Information related to providing cooler bag, two sterile 4oz./120ml collection containers and two urine collection pans has been added to visits: 2, 5, 7, 8.

Timing of visits' weeks has been changed based on updated titration and schedule of visits: 4, 5, 6, 7, 8, 9.

Section 4.1.2.1 Week -5 to -1 (Visit 1)

- Clarification related to timing of the visit has been added.
- One additional week for screening has been added.

Section 4.1.2.2 Week -2 to -1 (Visit 2)

- Clarification related to timing of the visit has been added.
- sCr has been removed.

Section 4.1.2.3 Week 0 (Visit 3)

- It has been clarified that two sequential CT scans are allowed for DECT sub study.

Section 4.1.2.4 Week 4 (Visit 4)

- Information about the time between visits 3 and 4 has been added.
- Information about Patient Dosing Card has been added.

Section 4.1.2.5 Week 8 (Visit 5)

- Information about the time between visits 4 and 5 has been added.
- Information about Patient Dosing Card has been added.

Section 4.1.2.8 Week 28 (Visit 8)

- CCI [redacted]
- It has been clarified that two sequential CT scans are allowed for DECT sub-study.

Section 4.1.2.10 Premature Treatment Discontinuation Visit

- It has been clarified that two sequential CT scans are allowed for DECT sub study.
- CCI [redacted]

Section 4.2 Scientific rationale for study design

- Duration of treatment titration has been changed.

Section 4.3 Justification of dose

- Duration of allopurinol titration has been changed.

Section 5.1 Inclusion Criteria, point 6d

- Discrepancy in NT-proBNP testing timing has been corrected.

Section 5.2 Exclusion Criteria

- Severe hepatic impairment (point 2) has been refined.
- Exclusion criterion (point 30) concerning hypersensitivity to allopurinol or any URAT1 inhibitor has been revised. Information about intolerance to lactose has been added. HLA-B allele testing (point 5) has been changed. Information about mandatory testing before randomisation has been added.

Section 5.3.1 Pregnancy

- Section has been updated as per new Clinical Study Template.

Section 6.0 Study Treatments

- It was clarified, what is considered IP and what non-IP in the study.
- Preferences related to IP administration has been added.

Section 6.1.1 Investigational Products

- Titration steps and its duration have been changed.
- It was clarified that titration to step 3 target dose will only be allowed if the patient's eGFR was ≥30 ml/min/1.73 m^2 at Visits 3 and 4.
- Table 4 – dosing instruction has been modified.
- Colchicine prophylaxis schedule has been modified due to extended titration.

Section 6.3 Measures to Minimise Bias: Randomisation and Blinding

- Requirement to contact Study Physician prior to dose down titration has been added.

Section 6.4 Treatment Compliance

- It was clarified what is acceptable patient's compliance level and what activities should be done to monitor and document it.

- The procedure of recording all administered study drugs in eCRF has been clarified.

Section 6.5 Concomitant Therapy, Table 5

- Information about ACEi therapy has been updated.

CCI [redacted]

Section 6.6 Dose modification

- Titration steps have been modified.

Section 7.1.1 Temporary Discontinuation

- Rules related to temporary treatment discontinuation has been clarified.

Section 7.3 Withdrawal From the Study

- Following sentence has been removed: "The patient will return electronic PRO devices."

Section 8.1.1 Peak VO2 and Other Cardiopulmonary Exercise Test Outcomes

- Time points related to CPET assessment have been corrected.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Section 8.1.3.9 Dual-emission Computed Tomography and PET Sub study

- Possibility of using two sequential CT scans if DECT is not available was added. Information about radiation exposure has been updated accordingly.
- It was clarified that second assessment will only be performed in patients who had evidence of uric acid crystal deposits at the baseline assessment.
- Time points related to DECT has been corrected.

Section 8.2. Safety Assessments, Table 7 - Laboratory Safety Variables

- Discrepancy related to testing urinalysis using dipstick has been corrected.

Section 8.2.4 Electrocardiograms

- Following sentence has been removed: "ECGs will be analysed centrally."

Section 8.3.2 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- Information related to SAE reporting has been clarified.

CCI [redacted]

Section 8.6.1 Assessment of HLA-B Genotype

- Information about mandatory testing before randomisation has been added.

Section 8.9 Guidelines, study assessments, and procedures during COVID-19 pandemic

- Section added.

Section 9.1 Statistical Hypotheses

- CCI [redacted]

CCI [redacted]

CCI [redacted]

Section 9.5 Interim Analysis

- Correction to the visit number (Week 28 changed to Week 32) has been corrected.

Section 9.3 Population for Analyses, Table 8 Analysis Populations

- Information in the table has been modified in order resolve inconsistent wording within the Protocol.

Section 9.4.2 Safety Analyses

- Section has been modified in order resolve inconsistent wording within the Protocol.

Appendix A3 Informed Consent

- Timelines related to reconsenting patients who are rescreened have been corrected.

Appendix F

Information related to CKD-EPI referenced formula has been corrected.

Version 1, 14 November 2019

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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1 PROTOCOL SUMMARY

1.1 Schedule of Activities

Table SoA Schedule of Activities

Period	Screening		Treatment period						Follow up		
Visit	**1** [a]	**2**	**3**	**4***	**5*** [b]	**6*** [c]	**7**	**8**	**9**	**Premature treatment discontinuation visit**	**Details in CSP section or Appendix**
Week (Day 1 of)	**-5 to -1**	**-2 to -1**	**0 (Randomisation)**	**4**	**8**	**12**	**22**	**32**	**36**		
Window			NA	±3d	±3d	±4d	±7d	±7d	±7d		
Informed consent	X										Appendix A 3
Informed consent for optional general genetics	X										Appendix D 2
Inclusion/exclusion criteria	X	X	X								Sections 5.1 and 5.2
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	X	X				Section 6.1
Dispense colchicine prophylaxis			X	X	X						Section 6.1
Study treatment returned				X	X	X	X	X		X	Section 6.2
CCI [redacted]		[redacted]					[redacted]				[redacted]
[redacted]			[redacted]								[redacted]

Table SoA Schedule of Activities

Period	Screening		Treatment period						Follow up		
Visit	**1** [a]	**2**	**3**	**4***	**5*** [b]	**6*** [c]	**7**	**8**	**9**	**Premature treatment discontinuation visit**	**Details in CSP section or Appendix**
Week (Day 1 of)	**-5 to -1**	**-2 to -1**	**0 (Randomisation)**	**4**	**8**	**12**	**22**	**32**	**36**		
Patient Dosing Card			X	X	X	X	X				Appendix K
Cooler bag, two sterile 4oz./120ml collection containers and two urine collection pans		X			X		X	X			
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	X		X	Section 8.2.2
Medical history and comorbid conditions	X										Sections 5.1 and 5.2
Vital signs	X	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	X	Section 8.2.2
ECG	X		X			X		X	X	X	Section 8.2.4
Concomitant medications	X		X	X	X	X	X	X	X	X	Section 6.5
Efficacy measurements											
Cardiopulmonary exercise test		X						X [h]			Section 8.1.1

Table SoA Schedule of Activities

Period	Screening		Treatment period						Follow up		
Visit	**1** [a]	**2**	**3**	**4***	**5*** [b]	**6*** [c]	**7**	**8**	**9**	**Premature treatment discontinuation visit**	**Details in CSP section or Appendix**
Week (Day 1 of)	**-5 to -1**	**-2 to -1**	**0 (Randomisation)**	**4**	**8**	**12**	**22**	**32**	**36**		
Kansas City Cardiomyopathy Questionnaire [i]			X				X	X		X	Section 8.1.2
Patient Global Impression of Severity [i]			X				X	X		X	Section 8.1.2
Patient Global Impression of Change [i]								X		X	Section 8.1.2
CCI											
sCr, eGFR	X		C								
Serum uric acid (sUA)	X		C								
CCI											
CCI											
CCI											
NT-proBNP	X										Section 8.7.1

Table SoA Schedule of Activities

Period	Screening		Treatment period						Follow up		
Visit	**1** [a]	**2**	**3**	**4***	**5*** [b]	**6*** [c]	**7**	**8**	**9**	**Premature treatment discontinuation visit**	**Details in CSP section or Appendix**
Week (Day 1 of)	**-5 to -1**	**-2 to -1**	**0 (Randomisation)**	**4**	**8**	**12**	**22**	**32**	**36**		
Routine safety measurements											
Adverse events	X (Only SAEs)	X (Only SAEs)	X	X	X	X	X	X	X	X	Section 8.3
Pregnancy test (serum or urine)	X								X		Section 5.1
Sample for HLA genotyping	X										Section 5.2 and 8.6.1
Safety laboratory assessments (including clinical chemistry, haematology, urinalysis)	X		X	X	X	X	X	X	X	X	Section 8.2.1
CCI [redacted]											
[redacted]						[redacted]					[redacted]
[redacted]							[redacted]	[redacted]			[redacted]

[a] Progression to Visit 2 screening is only for patients who fulfil eligibility based on Visit 1 screening; however, Visit 2 can be performed before HLA-B results are available.

[b] Patients should be reminded to not take study treatment in the morning before Visit 6

[c] Patients to take study treatment at clinic (time of study treatment intake should be recorded)

[d] CCI [redacted]

[h] All patients should perform CPET at this visit regardless of premature discontinuation of study treatment. CPET and EndoPAT should be performed before patients return study treatment

[i] All patient reported outcomes (PRO) will be administered using a site-based electronic device. To avoid bias in patient responses, all PRO questionnaires must be completed prior to any other study procedures

[j] Sub-study to randomise approximately 40 patients in selected sites

[k] Applicable only for patients that had UA crystals at baseline

[l] CCI [redacted]

* If a patient cannot be seen on site due to pandemic related restrictions (or any other restrictions due to civil crisis, natural disaster, or public health crisis), visit might be performed in the patient's home. See Section 8.9.

CSP Clinical Study Protocol; ECG Electrocardiography; eGFR estimated glomerular filtration rate; HLA Human leukocyte antigen; CCI [redacted]; sCr serum creatinine; CCI [redacted]; VO_2 Volume oxygen

1.2 Synopsis

International co-ordinating investigator; Dr Dalane Kitzman

Protocol title

A Phase 2, Multicentre, Double-Blind, Placebo and Active Control Efficacy and Safety Study to Evaluate Verinurad combined with Allopurinol in Heart Failure with Preserved Ejection Fraction

Short title: AMETHYST

Rationale

Evidence shows independent associations between hyperuricaemia and the risk of cardio-renal conditions, including heart failure (HF) (Anker et al 2003, Grayson et al 2011, Kodama et al 2009, Levya et al 1998, Nakagawa et al 2006). Serum uric acid (sUA) is also a strong prognostic factor and correlates with other markers of poor prognosis in HF patients with preserved ejection fraction (HFpEF), and an estimated 1/2-2/3 of HFpEF patients have hyperuricaemia (Odden et al 2014, Palazzuoli et al 2017). 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 is a novel URAT1 inhibitor in Phase 2 development for chronic kidney disease (CKD) and HF. 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 approximately 82%. HFpEF is a microvascular disease likely partly driven by endothelial dysfunction and inflammation in coronary vessel walls. Uric acid crystals have been identified in coronary vessel walls in some hyperuricaemic patients (Andrés et al 2016, Park et al 2014). The primary aim of this Phase 2 study is to evaluate the effects of substantial UA lowering on functional endpoints in hyperuricaemic HFpEF patients, using a combination of verinurad and allopurinol.

Objectives and endpoints

Primary objective:	**Endpoint/variable:**
To assess effect of verinurad + allopurinol compared to placebo on exercise capacity	Change from baseline at Week 32 in peak volume of oxygen (VO_2)
Secondary objectives:	**Endpoints/variables:**
To assess effect of verinurad + allopurinol compared to allopurinol monotherapy on exercise capacity	Change from baseline at Week 32 in peak VO_2
To assess effect of verinurad + allopurinol compared to placebo and compared to allopurinol monotherapy on Kansas City Cardiomyopathy Questionnaire (KCCQ)-total symptom score (TSS)	Change from baseline at Week 32 in KCCQ-TSS

Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of verinurad + allopurinol as compared to placebo and to allopurinol in patients with HFpEF.	Safety and tolerability will be evaluated in terms of adverse events (AEs), Vital signs, Clinical laboratory and electrocardiogram (ECG). Assessments related to AEs cover: • Occurrence • Relationship to study treatment as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of study treatment • Other action taken related to study treatment, including dose reductions and dose interruptions • AEs of special interest Vital signs parameters include systolic and diastolic blood pressure, pulse, temperature.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Overall design

A randomised, multicentre, global, double-blind, parallel arm, active- and placebo-controlled, Phase 2 study to assess safety and efficacy of 12 mg verinurad and 300 mg allopurinol on functional endpoints in patients with hyperuricaemia (sUA > 6 mg/dL) and HFpEF (left ventricular ejection fraction (LVEF) ≥ 45%). Patients who meet eligibility criteria will be randomised in a 1:1:1 ratio to verinurad/allopurinol combination, allopurinol, or placebo. There will be matching placebo for both the verinurad and allopurinol. The verinurad placebo will be identical in appearance to verinurad and likewise the allopurinol placebo to allopurinol.

Target patient population

The study will be conducted in male and female patients ≥ 40 years of age with HFpEF who provide informed consent to participate in the study and who are not pregnant and not lactating. Eligible patients will have New York Heart Association (NYHA) class II-III at enrolment, medical history of typical signs/symptoms of HF > 6 weeks before enrolment, and LVEF ≥ 45% (excluding history of a known, documented LVEF < 40%). Eligible patients will also have NT-proBNP ≥ 125 pg/mL or a history of pulmonary capillary wedge pressure ≥ 15 mmHg during rest or pulmonary capillary wedge pressure ≥ 20 mmHg during exercise. Apart from the above criteria, the following is necessary: sUA concentration > 6 mg/dL and peak VO_2 ≤ 75% of expected using treadmill, or peak VO_2 ≤ 68% of expected using cycle ergometer, based on normal values of peak VO_2. Individuals should be able to exercise to near exhaustion as exhibited by a respiratory exchange ratio (RER) ≥ 1.05.

Eligible patients should have an eGFR ≥ 30 mL/min/1.73 m^2.

Study period

The estimated date of first patient enrolled is Q2 2020. Patients will be followed until they complete 8 weeks of titration followed by 24 weeks of treatment at target dose plus 4 weeks of follow up. The estimated date of the last visit of the last patient is Q2 2022.

Number of patients

Approximately 150 patients (approximately 50 per arm) will be randomised at around 70 sites in approximately 12 countries. With an estimated screen-failure rate of 65%, up to 500 patients should be enrolled.

Treatments and treatment duration

Each patient will be randomised to 1 of the following three treatment arms: 12 mg verinurad plus 300 mg allopurinol; 300 mg allopurinol; or placebo. Study treatment will be titrated over 8 weeks. Once target dose has been reached, treatment will continue for 24 weeks. Titration is done in discrete steps of 4 weeks to reduce the risk of adverse reactions due to allopurinol. In order to prevent increase in inflammation due to rapid crystal dissolution, colchicine prophylaxis will be given during the titration period (8 weeks) and during the first 4 weeks of treatment at target dose (12 weeks total) and will be distributed as available, currently 500 µg within the European Union (EU) and 600 µg within the United States (US). For dosing, see the dosing schedule below (Table 1). The tablet and capsule will be taken orally in combination once daily.

Patients unable to tolerate the stepped dosage may be down-titrated only by reversing the assigned steps within treatment group. Verinurad and allopurinol cannot be unpaired from the titration schedule. Patients who cannot tolerate the step-1 dose will be discontinued from study treatment and be followed for the remainder of the study.

Table 1 Dosing Schedule

Treatment arm	Week 0-3 Step 1 - titration	Week 4-7 Step 2 - titration	Week 8-12 Step 3 - target dose	Week 13-32 Target dose
12 mg verinurad + allopurinol	Colchicine prophylaxis + 3 mg verinurad + 100 mg allopurinol	Colchicine prophylaxis + 7.5 mg verinurad + 200 mg allopurinol	Colchicine prophylaxis + 12 mg verinurad + 300 mg allopurinol	12 mg verinurad + 300 mg allopurinol
Allopurinol	Colchicine prophylaxis + 100 mg allopurinol	Colchicine prophylaxis + 200 mg allopurinol	Colchicine prophylaxis + 300 mg allopurinol	300 mg allopurinol
Placebo	Colchicine prophylaxis + placebo	Colchicine prophylaxis + placebo	Colchicine prophylaxis + placebo	Placebo

Data Monitoring Committee

The Data Monitoring Committee (DMC) will be responsible for monitoring the safety of the study patients and making appropriate recommendations based on the available data. The DMC will function independently of all other individuals associated with the conduct of the study, including AstraZeneca (AZ). The committee will operate in accordance with a DMC Charter.

Adjudication committee

The study will engage an independent clinical event adjudication (CEA) committee to independently review, interpret and adjudicate potential CV events that are experienced by the patients.

Statistical methods

The primary endpoint is absolute change from baseline in peak VO_2 at Week 32 and will be analysed using an analysis of covariance (ANCOVA) model with change from baseline in peak VO_2 at Week 32 as the dependent variable, treatment as the independent variable and baseline peak VO_2 included as a covariate. The analysis will include data from all patients at Week 32 irrespective of whether the patient has discontinued study treatment or received other medications. Missing peak VO_2 values at Week 32 will be imputed using a dropout reason-based multiple imputation approach.

The key secondary endpoint is change from baseline to Week 32 in KCCQ-TSS and will be analysed using a mixed model repeated measures (MMRM) model.

The primary and secondary objectives will be analysed using the Full analysis set.

A hierarchical test sequence will be used for the confirmatory analysis of the primary and secondary objectives in order to address the issue of multiple testing. Statistical significance will be assessed in the following sequence:

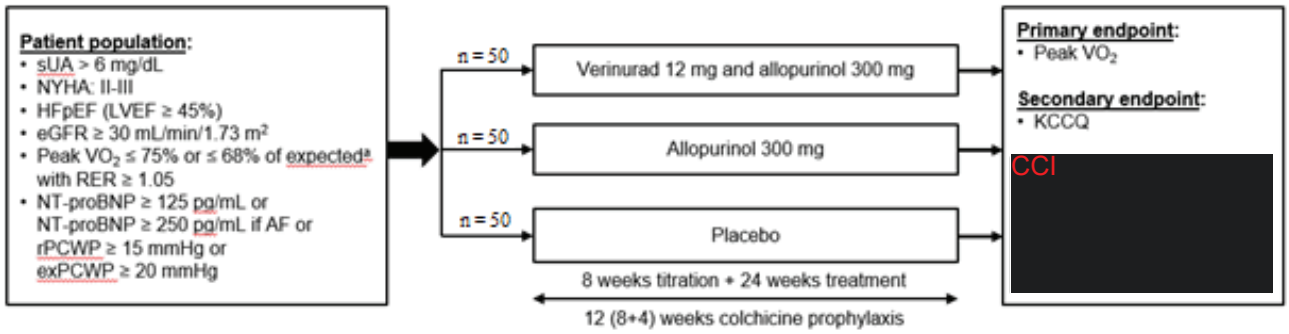
- Comparison between verinurad + allopurinol and placebo in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and placebo in change from baseline in KCCQ-TSS at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in KCCQ-TSS at Week 32

The testing procedure will continue down the hierarchy if the preceding endpoint is rejected at a two-sided 0.05 level and will stop if the preceding endpoint is not rejected at a two-sided 0.05 level.

1.3 Study Schema

The general study schema is summarised in Figure 1.

Figure 1 Study Schema



[a] Based on Fletcher et al 1995

AF Atrial fibrillation; eGRF estimated glomerular filtration rate; exPCWP Pulmonary capillary wedge pressure during exercise; HFpEF Heart failure with preserved ejection fraction; KCCQ Kansas City Cardiomyopathy Questionnaire; LVEF Left ventricular ejection fraction; NT-proBNP N-terminal pro b-type natriuretic peptide; NYHA New York Heart Association; RER Respiratory exchange ratio; rPCWP Pulmonary capillary wedge pressure during rest; sUA Serum uric acid; VO_2 Volume oxygen.

2 INTRODUCTION

2.1 Study Rationale

Chronic HF (CHF) is a major cause of mortality, hospitalisation and poor quality of life. Even with the best possible treatment, the five-year survival rate for HF patients is worse than for most cancers (Braunwald 2015). Moreover, the prevalence for CHF continues to increase globally. An estimated 38 million people are affected worldwide (Braunwald 2015) with over 1 million hospitalisations annually in both the US and Europe (Ambrosy et al 2014). The annual global economic burden in 2012 was estimated to be $108 billion (Cook et al 2014); this will increase dramatically as the population ages.

HF is characterised by dyspnoea, fatigue, and pulmonary congestion and/or peripheral oedema due to fluid retention. Patients with signs and symptoms of HF are categorised, based on measurement of LVEF, as having HF with reduced LVEF (HFrEF) or HF with preserved LVEF (HFpEF). Approximately half of all HF patients have HFpEF (Oktay et al 2013). The risk of death for HFpEF patients is high, with an annualised mortality rate up to 15% in community settings (Lam et al 2011). Patients with HFpEF have a particularly significant unmet medical need given that outcome studies hitherto performed have not resulted in any approved pharmacotherapy specifically for this condition. Conversely, outcome studies have provided evidence for treatments for HFrEF that can improve symptoms and haemodynamics and reduce hospitalisations for HF and mortality. These treatments include diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), ARB neprilysin inhibitors, mineralocorticoid receptor antagonists, and beta-blockers (Iwaz et al 2016).

Serum UA is a strong prognostic factor and correlates with other markers of poor prognosis in HFpEF patients. An estimated 1/2-2/3 of HFpEF patients have hyperuricaemia (Odden et al 2014, Palazzuoli et al 2017). Evidence shows independent associations between hyperuricaemia and the risk of hypertension, myocardial infarction, CKD, type 2 diabetes, HF, and metabolic syndrome, including obesity (Nakagawa et al 2006, Grayson et al 2011, Kodama et al 2009, Levya et al 1998, Anker et al 2003).

A recent prospective crossover trial suggested that HFpEF parameters improved in patients treated with UA-lowering therapy (Ogino et al 2019). The exact mechanism by which UA-lowering therapy may improve HFpEF remains to be established, but the presence of proinflammatory UA crystals in cardiac vessel walls (Andrés et al 2016) may contribute to endothelial dysfunction, a hallmark of HFpEF. Uric acid-lowering therapy has been proven to improve endothelial function, albeit not tested to date in subjects with HFpEF (SURPHER study presented by Dr Gaffo at European League Against Rheumatism [EULAR] 2019, data is in agreement with data from previous study with allopurinol in NYHA II/III subjects in Tousoulis et al (Tousoulis et al 2011)).

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 HF. 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 approximately 82% (see Investigator's Brochure [IB], Section 5.2.1).

The purpose of this Phase 2 study is to assess the effect of a combination of verinurad and allopurinol on exercise capacity and well-being in patients with HFpEF. CCI

Monotherapy with potent URAT1 inhibitors has been associated with creatinine elevation in some patients, potentially related to increased peak concentrations of urinary UA (uUA) in the proximal tubuli of the kidney. Verinurad is therefore given as an extended release formulation (ER8), as a low maximum concentration is expected to further reduce the risk of creatinine elevations. More importantly, verinurad is to be developed exclusively in a fixed-dose combination with an XOI, which will also reduce the production of UA. Treatment with verinurad combined with allopurinol or febuxostat has not been associated with an increased incidence of creatinine elevations compared to placebo in the studies conducted to date (see IB, Section 5.2.3.6).

The clinical evidence to date suggests that the combination of verinurad and allopurinol has an acceptable safety profile across multiple patient populations, and there may be a therapeutic benefit associated with UA-lowering therapy in HFpEF. Hence, a global, randomised, Phase 2 study is planned to evaluate the efficacy and safety of verinurad and allopurinol in patients with HFpEF and hyperuricaemia.

2.2 Background

Verinurad is a novel URAT1 inhibitor in Phase 2 development. Verinurad combined with the XOI allopurinol has been shown to lower sUA by > 70% in patients with recurrent gout in Phase 2 studies. A detailed description of the chemistry, pharmacology, efficacy, and safety of verinurad is provided in the IB.

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, 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. Serum UA 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 safety profile of verinurad may be found in the IB.

The study design aims to minimise potential risks to patients and to ensure adequate monitoring. A dual-inhibition approach using lower doses of two 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 > 1.5× 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 a 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 Phase 2a study D5495C00007, in which patients with diabetes and albuminuria were recruited, the combination of verinurad and febuxostat resulted in two creatinine elevation events in both the active treatment group and in the placebo control group.

The cumulative safety data observed in the clinical studies conducted in the verinurad clinical development programme indicate that verinurad in combination with allopurinol is generally well tolerated.

Patients with HFpEF are at increased risk to experience CV events. Furthermore, major CV events (MACE) have been identified as a potential risk for lesinurad, which is an approved drug with a similar mechanism of action as verinurad. The overall incidence of MACE in the lesinurad programme was low, with comparable rates for lesinurad 200 mg in combination with an XOI and an XOI alone. The rate was also low, but numerically higher, with lesinurad 400 mg; however, no causal relationship has been established. The small number of MACE observed in the pooled analysis of data from the pivotal Phase III combination therapy studies places limitations on assessment of treatment-associated differences in MACE risk and a post-approval prospective observational cohort study is planned to further evaluate this risk. There is no evidence of a CV safety signal in the verinurad clinical programme to date. 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. In addition, all potential CV events will be adjudicated by an independent, blinded adjudication committee.

The main risk from allopurinol, severe skin reactions, will be minimised by excluding patients carrying the high-risk human leukocyte antigen-B (HLA-B) *58:01 allele and by using a low starting dose and slow dose titration of allopurinol.

Patients with gout may experience an acute gout flare event with initiation of UA-lowering therapies (Borstad et al 2004). To prevent this, the manufacturer's prescribing information for UA-lowering therapies like lesinurad, allopurinol and febuxostat, as well as the EULAR, American College of Rheumatology, and British Society of Rheumatology treatment guidelines (Jordan et al 2007, Khanna et al 2012, Zhang et al 2006) recommend acute gout flare prophylaxis with colchicine, steroids, or a nonsteroidal anti-inflammatory drug (NSAID) when initiating or increasing the dose of such therapies. Thus, to prevent increased inflammation due to rapid crystal dissolution, and to reduce the risk of HFpEF exacerbation due to an inflammatory state, colchicine prophylaxis will be given during the titration period (8 weeks) and during the first 4 weeks of treatment at target dose (12 weeks total). Colchicine will be administered in all three treatment groups to ensure any difference in effect is not due to colchicine therapy.

There is a significant unmet medical need for HFpEF patients with hyperuricaemia as there are currently no available pharmacological therapies known to provide significant clinical benefit. Preliminary evidence suggests verinurad combined with allopurinol may demonstrate a meaningful benefit, but it cannot be assumed that recruited patients will derive any benefit from the treatment administered.

To further safeguard the interests of the patients, a DMC will be established. Refer to Section 9.4.5 and Appendix A for information regarding the DMC.

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 HFpEF 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 2 Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess effect of verinurad + allopurinol compared to placebo on exercise capacity	Change from baseline at Week 32 in peak VO_2
Secondary objectives:	**Endpoints/variables:**
To assess effect of verinurad + allopurinol compared to allopurinol monotherapy on exercise capacity	Change from baseline at Week 32 in peak VO_2
To assess effect of verinurad + allopurinol compared to placebo and compared to allopurinol monotherapy on KCCQ-TSS	Change from baseline at Week 32 in KCCQ-TSS
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of verinurad + allopurinol as compared to placebo and to allopurinol in patients with HFpEF.	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory and ECG. Assessments related to AEs cover: • Occurrence • Relationship to study treatment as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of study treatment • Other action taken related to study treatment, including dose reductions and dose interruptions • AEs of special interest Vital signs parameters include systolic and diastolic blood pressure, pulse, temperature.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 2 Objectives and Endpoints

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

4.1.1 Overview

This is a randomised, multicentre, double-blind, parallel arm, active- and placebo-controlled, global Phase 2 study to assess the efficacy and safety of verinurad and allopurinol in patients

with HFpEF and hyperuricaemia. Patients who meet the eligibility criteria will be randomised in a 1:1:1 ratio to 12 mg verinurad plus 300 mg allopurinol, 300 mg allopurinol, or placebo.

Approximately 150 patients (approximately 50 per arm) will be randomised at around 70 sites in approximately 12 countries. With an estimated screen-failure rate of 65%, up to 500 patients should be enrolled.

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 3 Objectives and Endpoints.

4.1.2 Study Procedures

All randomised patients should follow the visit scheme even if they discontinue treatment. (Section 7.1)

4.1.2.1 Week -5 to -1 (Visit 1)

First screening procedures should start maximum 35 days prior to randomisation (V3).

- Obtain signed informed consent form (ICF)
- Obtain signed informed consent for optional general genetics
- Assess inclusion/exclusion criteria
- Demography
- Full physical examination
- Medical history and comorbid conditions
- Vital signs
- Height
- Weight
- ECG
- Concomitant medications
- Collect serious AEs (SAEs)
- Pregnancy test (serum or urine)
- Sample for HLA genotyping
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- sUA, sCr, eGFR, NT-Pro-BNP

4.1.2.2 Week -2 to -1 (Visit 2), Only if Eligibility Criteria Met as Assessed in Visit 1

Progression to V2 screening is only for patients who fulfil eligibility based on V1 screening; however, V2 can be performed before HLA-B results are available. Subject should not meet

any of the exclusion criteria. V2 should be scheduled minimum 1 week prior to randomisation (V3).

- Assess inclusion/exclusion criteria
- Vital signs
- Weight
- Cardiopulmonary exercise test (CPET)
- CCI [redacted]
- Collect SAEs
- CCI [redacted]
- Hand out cooler bag, two sterile 4oz./120ml collection containers and two urine collection pans

4.1.2.3 Week 0 (Visit 3)

- Assess inclusion/exclusion criteria
- Brief physical examination
- Vital signs
- Weight
- ECG
- KCCQ
- PGIS
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Randomisation
- Titration step 1 dose dispensed: 3 mg verinurad plus 100 mg allopurinol, or 100 mg allopurinol plus verinurad placebo, or verinurad placebo and allopurinol placebo. **At Visit 3, study treatment should be taken after blood drawn.**
- Dispense colchicine prophylaxis
- Patient Dosing Card given to patient
- CCI [redacted]

4.1.2.4 Week 4 (Visit 4)

- Brief physical examination
- Vital signs
- Weight
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- Titration step 2 dose dispensed: 7.5 mg verinurad plus 200 mg allopurinol, or 200 mg allopurinol plus verinurad placebo, or verinurad placebo and allopurinol placebo
- Dispense colchicine prophylaxis
- Study treatment returned
- Patient Dosing Card given to patient

4.1.2.5 Week 8 (Visit 5)

- Brief physical examination
- Vital signs
- Weight
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- Final (titration step 3) dose dispensed: 12 mg verinurad plus 300 mg allopurinol, or 300 mg allopurinol plus verinurad placebo, or verinurad placebo and allopurinol placebo
- Dispense colchicine prophylaxis
- Study treatment returned
- Hand out two sterile 4oz./120ml collection containers and two urine collection pans
- Remind patient to not take study treatment in the morning before Visit 6
- Patient Dosing Card given to patient

4.1.2.6 Week 12 (Visit 6)

- Brief physical examination
- Vital signs
- Weight
- ECG
- Concomitant medications

- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- Patients take study treatment at clinic (dose, date and time of study treatment intake should be recorded in patient's medical records).
- CCI [redacted]
- CCI [redacted]
- Final (titration step 3) dose dispensed: 12 mg verinurad plus 300 mg allopurinol, or 300 mg allopurinol plus verinurad placebo, or verinurad placebo and allopurinol placebo
- Study treatment returned
- Patient Dosing Card given to patient

4.1.2.7 Week 22 (Visit 7)

- Brief physical examination
- Vital signs
- Weight
- KCCQ
- PGIS
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- Final (titration step 3) dose dispensed: 12 mg verinurad plus 300 mg allopurinol, or 300 mg allopurinol plus verinurad placebo, or verinurad placebo and allopurinol placebo
- Study treatment returned
- Patient Dosing Card given to patient
- CCI [redacted]
- Hand out two sterile 4oz./120ml collection containers and two urine collection pans

4.1.2.8 Week 32 (Visit 8)

- Brief physical examination
- Vital signs
- Weight

- CPET
- ECG
- KCCQ
- PGIS
- PGIC
- CCI [redacted]
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Study treatment returned
- Hand out two sterile 4oz./120ml collection containers and two urine collection pans

4.1.2.9 Week 36 (Visit 9)

- Full physical examination
- Vital signs
- Weight
- ECG
- Concomitant medications
- Collect AEs
- Pregnancy test (serum or urine)
- Safety laboratory assessment (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

4.1.2.10 Premature Treatment Discontinuation Visit

- Brief physical examination
- Vital signs

- Weight
- ECG
- KCCQ
- PGIS
- PGIC
- CCI [redacted]
- Concomitant medications
- Collect AEs
- Safety laboratory assessments (including clinical chemistry, haematology and urinalysis)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Study treatment returned

4.2 Scientific Rationale for Study Design

The purpose of this Phase 2 study is to evaluate the effect of substantial UA lowering on functional endpoints in hyperuricaemic HFpEF patients, using a combination of verinurad and allopurinol for 24 weeks, plus 8 weeks titration. The study will be a randomised, double-blind, placebo- and active-controlled study.

Since the URAT1 inhibitor verinurad plus a XOI such as febuxostat or allopurinol can lower sUA up to approximately 82%, the crystals formed due to high levels of UA are likely to be dissolved, which in turn is believed to lead to better clinical outcomes in HFpEF.

The duration of the study was set to approximately 8 months since microcrystals are expected to dissolve and hence inflammation to be reduced within that time. An 8-week titration was chosen for the safety of allopurinol. Colchicine prophylaxis will be used to prevent inflammation due to microcrystal dissolution.

4.2.1 Main Inclusion Criteria Rationale

In a study by Palazzouli et al (Palazzuoli et al 2017) where hyperuricaemia was defined as ≥ 6 mg/dL in women and ≥ 7 mg/dL in men, the results showed that the non-hyperuricaemic HFpEF group showed a statistically significant difference in the outcome of HF hospitalisation or death at 6 months as compared to the hyperuricaemic HFpEF group. Since we do not have a strong rationale for adjusting sUA levels for gender, the current study will

use 6.0 mg/dL as inclusion criteria to test what baseline levels of sUA would be associated with a meaningful benefit.

Since the primary endpoint is peak VO_2, a NYHA class II-III has been chosen. Class I was excluded since a benefit will be difficult to demonstrate since the class I patients by definition do not have any limitation of physical activity. Class IV patients are excluded since they will probably not be able to perform the CPET.

An NT-proBNP level of ≥ 125 pg/mL for patients without ongoing atrial fibrillation/flutter, and ≥ 250 pg/mL for patients with ongoing atrial fibrillation or flutter, with the alternative of documented pulmonary capillary wedge pressure during rest > 15 or pulmonary capillary wedge pressure during exercise > 20 , was chosen according to the European Society of Cardiology criteria (Ponikowski et al 2016) because of good sensitivity and specificity for identification of HFpEF (Ho et al 2019).

As there is currently no consensus within academia or industry, a LVEF of ≥ 45% was chosen as the definition of HFpEF for this trial. Patients who had a known history of a documented LVEF < 40% will be excluded from the study to enrich for patients with HFpEF-dominant disease.

4.2.2 Main Endpoint Rationale

Exercise capacity is severely limited in patients with HFpEF and is correlated with hospitalisation for HF and outcomes. At the same time, improving exercise capacity for patients with HFpEF is by itself clinically meaningful. In contrast to other methods to assess exercise capacity (eg, 6-minute walk test), CPET enables quantification of the effort the patient has applied during the test.

Patients with HF experience debilitating symptoms that substantially impact daily functioning, physical capacity and quality of life. For these reasons, it is important to measure the impact of new HF therapies on the HF patient's symptoms and functioning (Zannad et al 2013). The KCCQ instrument quantifies both the frequency of four cardinal HF symptoms (fatigue, peripheral oedema, dyspnoea, and orthopnoea) and how distressing are three of the cardinal HF symptoms (fatigue, peripheral oedema and dyspnoea). The KCCQ also assesses HF-related physical limitations, social limitations, self-efficacy, and health-related quality of life. First developed in 1996 (Green et al 2000, Spertus et al 2005), over the following two decades experience with the KCCQ has grown in industry-sponsored and academic studies and it is now the most common disease patient-reported outcome (PRO) instrument collected in HF studies.

4.3 Justification for Dose

The verinurad and allopurinol combination therapy doses and regimen selected for this study are based on the well-established dose-response relationship between verinurad in combination with allopurinol and sUA. The suggested verinurad dose (12 mg) was chosen based on PK, pharmacodynamic, and safety data from previous studies in healthy volunteers and Phase 2 studies in patients with gout or hyperuricaemia with albuminuria.

Verinurad combined with allopurinol (300 mg once daily) dose-dependently lowered 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. All doses tested in the study were considered tolerable and safe. Hence verinurad 12 mg dosed as the ER8 capsule was chosen to achieve significantly greater sUA lowering than with allopurinol monotherapy, while still being known to be safe and tolerable in earlier studies.

Verinurad monotherapy dose-dependently increases peak uUA excretion (Hall et al 2018), but peak uUA excretion is comparable to or lower than before any treatment when verinurad is given in combination with an appropriately dosed XOI (Fleischmann et al 2018a, Fleischmann et al 2018b). Verinurad is therefore combined with allopurinol 300 mg to reduce the peak uUA excretion, as high peak uUA excretion has been associated with creatinine elevations.

Allopurinol will be titrated every 4 weeks in the initial phase of the study 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 guideline recommendations for treatment of gout and recent literature (Khanna et al 2012, Stamp et al 2016, Richette et al 2017). Verinurad will be titrated along with allopurinol.

In parallel with this study, the Phase 2b SAPPHIRE study (D5495C00002) in patients with CKD is underway. The SAPPHIRE study is exploring the effects of 3, 7.5, 12 mg, and 24 mg verinurad ER8 in combination with allopurinol 300 mg.

4.4 End of Study Definition

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

A patient is considered to have completed the study when he or she has completed the last scheduled visit (Visit 9).

Refer to Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

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 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 screen failures (Section 5.4).

In this protocol, "enrolled" patients are defined as those who sign informed consent. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients, refer to Section 7.4.

5.1 Inclusion 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 ≥ 40 years of age at the time of signing the ICF.

Type of patient and disease characteristics

5 Patients with hyperuricaemia defined as sUA level of > 6 mg/dL.

6 Patients with documented diagnosis of symptomatic HFpEF according to all of the following criteria:

(a) Have NYHA functional class II-III at enrolment

(b) Have medical history of typical symptoms/signs of HF > 6 weeks before enrolment, which is stably treated medically, with at least intermittent need for diuretic

treatment. Typical symptoms of HF include breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, ankle swelling. Typical signs associated with HF include elevated jugular venous pressure, hepatojugular reflex, third heart sound (gallop rhythm). Less specific symptoms include: weight gain (> 2 kg/week), weight loss (in advanced HF), tissue wasting (cachexia), cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary crepitations, reduced air entry and dullness to percussion at lung bases (pleural effusion), tachycardia, irregular pulse, tachypnoea, Cheyne-Stokes respiration, hepatomegaly, ascites, cold extremities, oliguria, narrow pulse pressure.

(c) LVEF ≥ 45%

(d) NT-proBNP ≥ 125 pg/mL (≥ 14.75 pmol/L) at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at the time of sample collection, NT-proBNP must be ≥ 250 pg/mL (≥ 29.51 pmol/L) **OR** patients must have a history of pulmonary capillary wedge pressure ≥ 15 mmHg during rest or pulmonary capillary wedge pressure ≥ 20 mmHg during exercise.

7 Patients able to exercise to near exhaustion during a CPET as exhibited by RER ≥ 1.05 during CPET conducted during screening. If patient does not achieve RER ≥ 1.05 the CPET may be repeated once, at least 48 hours but less than 2 weeks (but before randomisation) after the initial test; in such cases the second test will serve as baseline.

8 Patients with peak VO_2 ≤ 75% of expected using treadmill, or peak VO_2 ≤ 68% of expected using cycle ergometer, based on normal values (Fletcher et al 1995).

9 Patients treated according to locally recognised guidelines on standard-of-care treatment for patients with HFpEF. Therapy should have been individually optimised and stable for ≥ 4 weeks (except diuretics) and include, unless contraindicated or not tolerated, treatment of high blood pressure (targeting a systolic blood pressure < 130 mmHg as suggested in 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines), ischaemic heart disease, and atrial fibrillation.

10 Patients treated with a sodium-glucose transport protein 2 inhibitor or sacubitril/valsartan must be on stable dose for ≥ 4 weeks before randomisation.

Sex

11 Male or female.

Reproduction

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

12 Negative pregnancy test (urine or serum) for female patients of childbearing potential. Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (with a failure rate of < 1% per year) 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. Refer to Section 5.3.1 for acceptable methods of contraception. Patients agreeing to total sexual abstinence can also be included, assuming it is their usual lifestyle.

5.2 Exclusion Criteria

Medical conditions

1 eGFR < 30ml/min/1.73 m^2 (based on CKD-EPI formula).

2 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.

3 Presence of any condition that precludes exercise testing such as:

(a) Claudication that limits exertion

(b) Uncontrolled bradyarrhythmia or tachyarrhythmia (according to Investigator judgement, pacemaker treatment is allowed as long as the same pacing mode/activity can be used at baseline and follow-up CPET)

(c) Clinically significant musculoskeletal disease or orthopaedic conditions that limit the ability to perform the CPET (eg, arthritis or injury in the foot, leg, knee or hip)

(d) Severe obesity (body mass index ≥ 50.0 kg/m^2)

(e) Amputation with artificial limb without stable prosthesis function for the past 3 months

(f) Any condition that, in the opinion of the Investigator, would contraindicate CPET assessment (eg, severe visual impairment)

(g) Any condition other than HF that, in the opinion of the Investigator, is the primary limitation to exercise.

4 Known history of a documented LVEF < 40%.

5 Probable alternative or concomitant diagnoses which in the opinion of the Investigator could account for the patient's HF symptoms and signs (eg, anaemia, hypothyroidism).

6 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.

7 Patients diagnosed with tumour lysis syndrome or Lesch-Nyhan syndrome.

8 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.

9 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.

10 Current acute decompensated HF or hospitalisation due to decompensated HF < 4 weeks prior to enrolment.

11 Myocardial infarction, unstable angina, coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial flutter/fibrillation, valve repair/replacement, implantation of a cardiac resynchronisation therapy device, stroke or transient ischemic attack within 6 months prior to enrolment.

12 Planned coronary revascularisation, ablation of atrial flutter/fibrillation and/or valve repair/replacement.

13 Atrial fibrillation with persistent resting heart rate > 110 beats per minute.

14 Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (ie, requiring home supplemental oxygen, chronic oral steroid therapy use at a dose equivalent to 10 mg prednisone or greater, or hospitalisation for exacerbation of COPD requiring ventilatory assist within 12 months prior to enrolment).

15 Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronisation therapy. Prior implantation of a ventricular assistance device or similar device, or implantation expected during the course of the study.

16 HF due to known infiltrative cardiomyopathy (eg, amyloid, sarcoid, lymphoma, endomyocardial fibrosis, haemochromatosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected severe primary valvular disease.

17 Patients diagnosed with long QT syndrome.

18 Uncontrolled hypertension with systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg.

19 History of blood dyscrasias: myelosuppression (eg, thrombocytopenia, leukopenia, granulocytopenia, pancytopenia) and aplastic anaemia.

20 Patients with the following bilateral upper or lower arm pathology can be randomised into the study, but are not allowed to participate in the reactive hyperaemia assessment:

(a) Presence of fistula / arteriovenous (AV) Shunt

(b) Other structural or vascular abnormality.

Prior/concomitant therapy

21 Treated with any drug for hyperuricaemia in the 6 months preceding randomisation. Drugs for hyperuricaemia include all XOIs (allopurinol, febuxostat and topiroxostat) and

URAT1 inhibitors (lesinurad, verinurad, probenecid, and benzbromarone) and urate oxidases (pegloticase, rasburicase).

22 Treated with strong or moderate organic anion transporting polypeptide (OATP) inhibitors (Entresto is not considered a strong or moderate OATP inhibitor).

23 Patients treated with strong P-glycoprotein and/or CYP3A4 inhibitors due to the potential drug-drug interaction with colchicine (Appendix J).

Prior/concurrent clinical study experience

24 Participation in another clinical study with an investigational product administered (currently or within 1 month prior to screening).

25 Participating in a structured exercise training programme in the 1 month prior to screening or planned to start during the trial.

Participants of DECT/PET substudy only (substudy cancelled)

26 Not applicable: Criterion removed due to DECT PET substudy cancellation.

Other exclusions

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

28 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.

29 Screened more than once or previous randomisation in the present study.

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

31 Patients who are pregnant (confirmed with pregnancy test), lactating, or planning to become pregnant.

5.3 Lifestyle Restrictions

5.3.1 Pregnancy

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

1 Male patients are not required to use contraception

2 Female patients of childbearing potential must follow the contraception requirement defined in Section 5.1 inclusion criterion 12.

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

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilised male partner must use an acceptable (ie, < 1% failure rate per year) effective method of contraception (Table 3) 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 (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All women of childbearing potential must have a negative serum pregnancy test result at Visit 1. Female patients should refrain from breastfeeding throughout this period.

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.
- 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.
- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Table 3 Highly Effective Methods of Contraception (< 1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Vasectomised partner • Bilateral tubal occlusion • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intrauterine device/levonorgestrel intrauterine system • 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®, Evra Patch™, Xulane™) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method.

5.3.2 Meals and Dietary Restrictions

It is recommended to take the study treatment with food.

5.3.3 Caffeine, Alcohol, and Tobacco

Study treatment should not be taken within an hour of ingesting alcohol. There are no restrictions on combining study treatment intake with caffeine or nicotine intake.

5.4 Screen Failures

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.

Individuals who do not meet the criteria for participation in this study (screen failure) at Visit 1 may be rescreened once. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

Screen failure 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 investigational product(s) (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, verinurad placebo and allopurinol 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.

Colchicine is considered as non-IP, should be used as a prophylaxis as per country label. Colchicine will not be supplied centrally by the Sponsor, but its cost will be reimbursed.

6.1 Treatments Administered

6.1.1 Investigational Products

Each patient will be randomised to receive 12 mg verinurad plus 300 mg allopurinol, 300 mg allopurinol, or placebo for 24 weeks at target dose after 8 weeks of titration (Table 4).

Titration will occur in discrete steps of 4 weeks to reduce the risk of skin reactions due to allopurinol. To prevent increase in inflammation due to rapid crystal dissolvement, colchicine prophylaxis will be given during the titration period and during the first 4 weeks of treatment at target dose (12 weeks total) and will be distributed as available, currently 500 µg within the EU and 600 µg within the US. For dosing, see the below dosing schedule (Table 4). The allopurinol/placebo tablet and verinurad/placebo capsule(s) will be taken orally together once daily.

Study treatments will be titrated in discrete steps as shown in Table 4. Titration steps will be spaced at 4-week (28 days ± 3 days) intervals to minimise the risk of adverse reactions to allopurinol. Patients unable to tolerate the stepped dosage may be down-titrated only by reversing the assigned steps within the 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 followed for the remainder of the study.

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

Table 4 Study Treatments

	Verinurad + allopurinol	Allopurinol	Placebo
Study treatment name	Verinurad + allopurinol	Verinurad placebo + allopurinol	Verinurad placebo + allopurinol placebo
Dosage formulation	Verinurad capsule, allopurinol tablet	Verinurad placebo capsule, allopurinol tablet	Verinurad placebo capsule, allopurinol placebo tablet
Dosage levels	Week 0-3: 3 mg verinurad, 100 mg allopurinol Week 4-7: 7.5 mg verinurad, 200 mg allopurinol Week 8-32: 12 mg verinurad, 300 mg allopurinol	Week 0-3: 100 mg allopurinol Week 4-7: 200 mg allopurinol Week 8-32 300 mg allopurinol	0 mg / 0 mg
Route of administration	Oral	Oral	Oral
Dosing instructions	All study treatment should be taken in the morning and will generally be better tolerated if taken in association with food.		
Packaging and labelling	Verinurad capsules and 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.	Verinurad placebo capsules and 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.	Verinurad placebo capsules and allopurinol placebo 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	AZ	AZ	AZ

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.

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).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All patients will be centrally assigned to randomised study treatment using an interactive web response system (IWRS). Randomisation to study treatment will be performed in balanced blocks to ensure approximate balance between the three treatment groups verinurad plus allopurinol, allopurinol alone, or placebo (1:1:1). The randomisation codes will be computer generated and loaded into the IWRS database. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

The IWRS system should ensure that a baseline peak VO_2 measurement is available for the patient before randomisation is allowed.

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

The 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 IWRS user manual that will be provided to each centre. For patients who need down titration, the Investigator will need to use the IWRS for allocation of new study drug kits for the lower dose.

Every effort should be taken to discuss the decision related to down titration with AZ Study Physician prior to IWRS allocation of new study drug kit.

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 AZ, without revealing the treatment given to patient to the AZ staff.

AZ retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study treatment 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 AZ study personnel will be blinded to post-randomisation sUA values (assessed using the central clinical laboratory) to maintain study integrity.

6.3.1 Emergency Unblinding

The 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 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF. 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.

6.4 Treatment Compliance

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

Assigned personnel at study site will be responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment. The Investigator(s) is responsible for ensuring that the patient has returned all unused study treatment.

Treatment compliance: The patient will be asked about compliance at each study visit starting from Visit 3 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 ≤120% of that prescribed. 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 SoA and Table 1, 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 drugs (including investigational products and colchicine prophylaxis) should be recorded in the appropriate sections of the CRF as well as any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations. Each time study drug/colchicine prophylaxis are dispensed, compliance will be reinforced. If any patient found to be non-compliant, he/she will be counselled on the importance of taking their IP/colchicine as prescribed.

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 route of administration, dose and frequency

Table 5 Restricted Medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations where 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	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 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) may 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.
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 probenicide, lesinurad or benzbromarone	
Strong or moderate OATP inhibitors [a] Examples: atazanavir, ritonavir, clarithromycin, cyclosporin, erythromycin, gemfibrozil, lopinavir, rifampin (single dose), simeprevir	
Any medication prohibited by the package insert of colchicine (Appendix J); applicable only while gout prophylaxis is being administered	

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

ACEi Angiotensin-converting enzyme inhibitor; ARBs Angiotensin receptor blockers; OATP Organic anion transport polypeptide; sUA serum uric acid; URAT1 Uric acid transporter 1; XOI Xanthine oxidase inhibitor

CCI

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 case report form (CRF).

6.6 Dose Modification

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

6.7 Treatment After the End of the Study

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

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of Study Treatment

Discontinuation from study treatment is not the same as withdrawal from the study. If the patient temporarily or permanently discontinues study treatment, the patient should remain in the study and it is important that the scheduled study visits and data collection continue according to the study protocol. Patients may be discontinued from study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- AE.
- Severe non-compliance with the Clinical Study Protocol (CSP).
- Skin reactions and hypersensitivity.
  - Study drug should be discontinued immediately at the first sign of a skin rash or other signs indicative of 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, including creatinine elevations.
  - Guidelines for assessing possible renal injury or kidney stone and altering treatment are in Appendix F.
- Development of aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3× upper limit of normal (ULN) together with total bilirubin ≥ 2× ULN as described in Section 8.3.8 and Appendix E.
- If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and an AZ representative notified.

See the schedule of activities (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 Discontinuation

Patients may temporarily interrupt study treatment administration, for instance based on criteria for Appendix F. In case temporary interruption happens, patient should stop taking both IPs (verinurad or placebo and allopurinol or placebo). Temporary interruption of study treatment does not mean discontinuation of follow-up or termination of study participation. Study assessments should continue. When study treatment is resumed, last dose level taken should be administered again. If temporary interruption of study treatment 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 study treatment must be re-titrated to avoid allopurinol induced hypersensitivity reactions, after communication with the sponsor or sponsor's representative.

7.1.2 Procedures for 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 eCRF. 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. 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 a modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

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 (study treatment **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).

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.

See SoA, 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.

7.4 Procedures for Handling Incorrectly Enrolled or Randomised Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on study treatment and must be withdrawn from the study. Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on study treatment, the following steps need to be taken:

- The Investigator or Study Monitor should inform the AZ study physician immediately, ensuring patient safety must always be the number one priority.
- Study Treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. A discussion should occur between the AZ study physician and the investigator; a decision may be reached on whether to continue or discontinue the patient from study treatment. The AZ study physician must ensure that all decisions are appropriately documented.
- In those cases where continuation of study treatment is judged not to present a concern related to safety and disease management, the rationale for continuing the study treatment must be clearly documented. The patient should continue follow up in accordance with defined study procedures.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the eCRFs.

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 CRFs. A copy of the completed CRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately 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.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

Primary and secondary efficacy assessments include peak VO_2 as assessed during CPET and patient-reported outcomes as assessed using the KCCQ (Total Symptom Score domain).

8.1.1 Peak VO_2 and Other Cardiopulmonary Exercise Test Outcomes

CPET will be used to assess the change from baseline at Week 32 in peak VO_2 consumption (primary objective). In addition, the following parameters will be assessed:Change from baseline in ventilatory efficiency as measured by V_E/V_{CO2}

- VO_2 at anaerobic threshold
- VO_2 kinetics at recovery phase
- Exercise time

All patients will undergo a CPET with gas-exchange analysis. The methodology will be standardised across all participating sites, as described in the CPET Manual. Testing will include continuous ECG monitoring by trained personnel and be performed in an area that is equipped for cardiopulmonary resuscitation. The primary modality for exercise tests will be either a motor-driven treadmill or cycle ergometer. Patients must use the same testing modality and the same exercise equipment for all exercise tests during the study.

Whenever possible, CPET should be administered by the same study personnel using the same piece of equipment and performed after the other study procedures on that visit day (including PROs, NYHA class, acute coronary syndrome signs and symptoms, vital signs, ECG, blood sampling, study treatment administration). Patients naïve to exercise protocols (cycle ergometer, treadmill, and measurement of oxygen consumption) will be familiarised with the technique during screening.All CPETs will be symptom-limited and patients will be strongly encouraged to perform a maximum test as indicated by a RER $\geq$ 1.05. Patients will be eligible for the study if they achieve a RER of $\geq$ 1.05. Eligible subjects must also have impaired peak VO_2. Peak VO_2 achieved must be $\leq$ 75% of predicted for age and gender when using a

treadmill or ≤ 68% when using a cycle ergometer, as based on normal values (Fletcher et al 1995). Eligibility will be determined by the CPET Core Lab.All study sites must be qualified by the CPET core laboratory prior to the initiation of screening. To qualify, sites will perform two exercise tests on the same healthy adult and submit them for core laboratory review. Centres may be required to submit additional normal exercise tests during the conduct of the study for review by the CPET core lab in order to confirm proper function of testing equipment.Data will be recorded and transmitted electronically to a core lab for analysis. The CPET manual will be developed for the study and sent to all sites.

8.1.2 Patient Reported Outcomes

Patients will perform the PRO assessments using an electronic tablet during clinic visits at the time points indicated in the SoA. All questionnaires must be completed using the electronic device; paper questionnaires are not allowed in this study.

Each site must allocate the responsibility for the administration of the PROs to a specific site personnel and, if possible, assign a backup person to cover if that individual is absent. A key aspect of study success is to have high PRO compliance. Therefore, it is essential that site personnel follow the SoA and ensure that the device is charged and set up properly before the first patient comes for PRO baseline visit (Visit 3) in order to minimise missing data.

If patients have any medical problems, they should discuss them with their doctor or research nurse separately from the PRO assessment.

The research nurse or appointed site staff must remind patients there are no right or wrong answers and that the value and relevance of PRO data is to hear directly from patients, without interpretation from health care professionals or others, how they function and feel.

The following best practice guidelines should be followed:

- The PRO questionnaires must be completed before any other study procedures are conducted, including being seen by the investigator.
- The appointed site personnel must show patients how to use the electronic PRO device, in accordance with the instructions provided.
- To avoid bias, patients must not receive help from relatives, friends or site staff to answer or to clarify the PRO questionnaires.
- The PRO questionnaires must be completed by the patient in private.
- The patient should be given enough time to complete the PRO questionnaires at his or her own speed.
- On completion of the questionnaires, the tablet should be handed back to the designated responsible person, who should check that all questionnaires, relevant for the specific visit (SoA), were completed. If any PRO questionnaire was not completed, the site

personnel must document the reason why a patient could not complete assessments in the REVPRDI module in the eCRF.

The following PROs will be used in this study:

- KCCQ
- PGIS
- PGIC

It will take approximately 10-15 minutes to complete.

Kansas City Cardiomyopathy Questionnaire

The KCCQ (Appendix G) is a 23-item, self-administered disease-specific instrument that has shown to be a valid, reliable and responsive measure for patients with HF (Green et al 2000, Spertus et al 2005).

The KCCQ was developed to measure the patients' perception of their health status independently, which includes HF-related symptoms (frequency, severity and recent change), impact on physical and social function, self-efficacy and knowledge, and how the patients' HF affects their quality of life. Scores are transformed to a range of 0 to 100. Higher scores represent a better outcome.

The 23 items in KCCQ can be merged into 10 summary scores. In this study, the KCCQ-Total Symptom Score (TSS), KCCQ-Clinical Summary Score (CSS) and KCCQ-Overall Summary Score (OSS) will be used.

Patient global impression of change

The PGIC (Appendix H) item is one question and assesses how a patient perceives his or her overall change in HF symptoms since the start of the study. Patients will choose from 7 response options, ranging from 'much worse' to 'much better.'

Patient global impression of severity

The PGIS (Appendix I) item is one question and assesses how a patient perceives his or her overall current severity of HF symptoms. Patients will choose from 6 response options, ranging from 'no symptoms' to 'very severe.'

CCI [redacted]

CCI

[redacted]

CCI [redacted]

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CCI

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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.

Refer to Table 7 for the list of clinical safety laboratory tests to be performed and 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 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 locally if clinically indicated at the discretion of the Investigator. The date and results of those additional samples will be collected on the appropriate eCRF.

Table 7 Laboratory Safety Variables

Haematology/haemostasis (whole blood)	Clinical chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)
	S/P Bicarbonate
	S/P Blood Urea Nitrogen
	S/P Phosphate

Note: In case a patient shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, please 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 total bilirubin value outside the normal range, direct bilirubin will be automatically evaluated by the central laboratory.

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 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, refer to 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 three blood pressure readings will be recorded on the eCRF.

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, QTcF) will be recorded in the eCRF. 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.

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 AEs refer to Section 8.3.3.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

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 Adverse Event and Serious Adverse Event Information

Adverse events will be collected from the time of the first dose of study treatment throughout the treatment period and including the follow-up period and last contact.

Serious AEs will be recorded from the time of signing of ICF throughout the treatment period and including the follow-up period and last contact.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours 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 Adverse Events and Serious Adverse Events

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 date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study treatment(s) (yes or no)
- Action taken with regard to study treatment(s)
- 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 Study treatment 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 study treatment?'

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 the CSP.

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/you were last asked?' 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 CSP mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory value or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study treatment.

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 ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

CCI [redacted]

8.3.10 Regulatory Reporting Requirements for Serious Adverse Events

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

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

For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or and will notify the IRB/IEC, if appropriate according to local requirements.

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study treatment, 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 AZ representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all the necessary information is provided to the AZ 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 AZ representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** 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 AZ representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AZ representative by telephone.

The AZ representative will advise the Investigator/study site staff how to proceed.

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

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study patient has received any study drug
- Pregnancies in the partner of male patients

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

Abnormal pregnancy outcomes (eg, spontaneous abortion, 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, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment 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 AZ representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

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 AZ study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AZ representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

- For overdoses associated with a SAE, the standard reporting timelines apply, refer to 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 AZ representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ 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 (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 Study Treatment-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 AEs) from the combination study treatment, dosage will be down-titrated to the highest previously-tolerated dosage.

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

An independent DMC will be appointed and will report to AZ. The DMC will be responsible for safeguarding the interests of the patients by assessing the safety of the study treatment during 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 AZ.

8.4.7 Clinical Event Adjudication Committee

The role of the CEA committee 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 or in the CEA process as specified in the CEA committee charter. The CEA committee member/s will not have access to individual treatment codes for any patient.

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

CCI [redacted]

- CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

8.6 Genetics

8.6.1 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 higher in Korean, Han Chinese, Thai, or African origin compared with Caucasian patients. In this study, HLA-B *5801 genotyping is mandatory prior to randomisation for all patients.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

8.7 Biomarkers

Samples will be collected and analysed for biomarkers as detailed CCI [redacted] in the SoA.

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 resource spend. Results of biomarker analyses may be reported separately from the CSR.

In addition to the biomarkers listed in CCI [redacted], urine, serum and plasma, from patients who have consented for future research, will be collected and stored in a biobank for future use. Participation is optional and contingent upon local regulations. The analysis may be performed on biomarker variants thought to play a role in inflammation, HF, CKD, endothelial function, and the safety of patients treated with study treatment including, but not limited to, plasma and urine analytes.

The samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to disease processes, pathways associated with HF or CKD, and/or mechanism of action of the study treatment.

CCI [redacted]

CCI [redacted]

8.8 Medical Resource Utilisation and Health Economics

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

8.9 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) 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.

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

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, investigational product 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) Visits 4, 5 and 6 may be conducted in the patient's home if site is closed or local regulations prohibit patients from travelling to site due to COVID-19. Safety laboratory tests are required. CCI [redacted]

(d) If labs collected for safety assessments cannot be collected 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 Study Physician how to re-start treatment and titrate the IP to maintenance treatment.

(e) Visits by phone or in patient's house might be performed solely due to COVID-19 pandemic. In any other cases, all the visits have to be performed at the site.

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9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

For all statistical tests, the null hypothesis is that there is no difference between treatment groups, with a two-sided alternative. Each hypothesis will be tested at a significance level of 5%. A multiplicity correction procedure will be applied (refer to Section 9.4.4 "Methods for multiplicity control" for details).

Objective	Hypothesis tested
Primary	
To assess effect of verinurad + allopurinol compared to placebo on exercise capacity	No difference in mean change from baseline at 32weeks in peak VO_2 consumption between treatment groups
Secondary	
To assess effect of verinurad + allopurinol compared to allopurinol monotherapy on exercise capacity	No difference in mean change from baseline at 32weeks in peak VO_2 consumption between treatment groups
To assess effect of verinurad + allopurinol compared to placebo and compared to allopurinol monotherapy on KCCQ-TSS.	No difference in mean change from baseline at 32 weeks in KCCQ total symptom score between treatment groups

9.2 Sample Size Determination

The study will employ a 1:1:1 randomisation ratio between 12 mg verinurad + allopurinol, allopurinol, and placebo. Based on this design with 50 patients randomised to the verinurad + allopurinol group and to the placebo group, respectively, and assuming a standard deviation for the primary endpoint of 2 mL/kg/min, the width of 95% confidence intervals for estimated differences between treatments will be about 1.57 ml/kg/min. The minimum detectable treatment difference for statistical significance in a two-group t-test with a two-sided significance level of 5% given the assumptions above is 0.794 mL/kg/min.

The assumed standard deviation of 2 mL/kg/min is derived from Borlaug (Borlaug et al 2018) and from Redfield (Redfield et al 2013).

For approximately 3 × 50 = 150 patients to be randomised, up to 500 patients should be screened, matching an assumed proportion of screening failures of up to 65%.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 8 Analysis Populations

Analysis set	Description
Enrolled	All patients who sign the main ICF
Full Analysis Set (FAS)	All patients who have been randomised to study treatment, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised study treatment assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary and secondary variables [redacted]

Table 8 Analysis Populations

Analysis set	Description
Safety analysis set	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment. Patients will be analysed according to their randomised study treatment assignment, irrespective of the treatment actually received. The Safety analysis set will be considered the primary analysis set for all safety variables.
CCI [redacted]	[redacted]

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 Contract Research Organisation designated by AZ. A comprehensive statistical analysis plan (SAP) for the analyses to be included in the CSR will be developed and finalised before the final data base lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 Efficacy Analyses

9.4.1.1 Analysis of the Primary Objective

The primary efficacy variable for the analysis of the primary objective is the absolute change from baseline in peak VO_2 at Week 32, calculated as the value at Week 32 minus the baseline value. This will be analysed using an ANCOVA model with change from baseline in peak VO_2 at Week 32 as the dependent variable, treatment as independent variable and baseline peak VO_2 included as a covariate. Baseline peak VO_2 will be the peak VO_2 value from the last exercise capacity test before randomisation.

The analysis will include data from all patients at Week 32 irrespective of whether the patient has discontinued study drug or received other medications. Missing peak VO_2 values at Week 32 will be imputed using a dropout reason-based multiple imputation approach; missing data in the verinurad + allopurinol group following the intercurrent events death, withdrawal of consent, loss to follow-up or premature discontinuation of study drug due to an AE will be imputed based on the peak VO_2 values in the placebo group whereas missing values for all other patients will be imputed assuming missing at random, ie, based on the peak VO_2 values in their own respective treatment group.

Estimated mean change from baseline per treatment group and difference between treatments (verinurad + allopurinol vs placebo) will be presented along with 95% confidence intervals and p-value.

Sensitivity analyses to assess the robustness of the primary analysis with respect to the handling of missing data will be performed and will include *i*) using the principles described above but imputing all missing values according to the placebo group *ii*) excluding patients with missing values from the analysis.

9.4.1.2 Analysis of the Secondary Objectives

Active treatment vs allopurinol monotherapy

The estimate of the treatment effect of verinurad + allopurinol vs allopurinol monotherapy will be extracted from the analysis described for the analysis of the primary objective in Section 9.4.1.1. For the assessment of statistical significance of this comparison, please see Section 9.4.4.

Kansas City Cardiomyopathy Questionnaire - KCCQ

The variable for the analysis of the secondary objective to assess the effect of verinurad + allopurinol compared to placebo and compared to allopurinol monotherapy on KCCQ-TSS will be the change from baseline at Week 32 of the KCCQ-TSS. Baseline is defined as the value at the randomisation visit. Change from baseline at each post-baseline KCCQ collection time point will be calculated as the value at the corresponding post-baseline time point minus the baseline value.

The analysis will include data from all patients irrespective of whether the patient has discontinued study drug or received other medications. Missing KCCQ-TSS values will be handled using the same method as described for the analysis of the primary objective in Section 9.4.1.1.

Change from baseline to Week 32 for KCCQ-TSS will be analysed in a MMRM model. The model will include terms for treatment group, visit, visit*treatment group, and baseline TSS measurement as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. The p-value for the treatment difference at Week 32 will be the basis for the confirmatory statistical testing (Section 9.4.4).

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Patients will be analysed according to their randomised study treatment assignment, irrespective of the treatment actually received. Patients who receive study treatment which is not consistent with the treatment he or she was randomised to will be listed.

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

Safety data will be summarised descriptively and will not be formally tested. 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.

CCI [redacted]

9.4.4 Methods for Multiplicity Control

In order to address the issue of multiple testing and control the Type I error rate at an overall two-sided 0.05 level, a hierarchical test sequence will be used for the confirmatory analysis of the primary and secondary objectives. Statistical significance will be assessed in the following sequence:

- Comparison between verinurad + allopurinol and placebo in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and placebo in change from baseline in KCCQ-TSS at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in KCCQ-TSS at Week 32

The testing procedure will continue down the hierarchy if the preceding endpoint is rejected at a two-sided 0.05 level and will stop if the preceding endpoint is not rejected at a two-sided 0.05 level.

9.4.5 Data Monitoring Committee

A DMC will be utilised for this study. Appendix A 5 provides more details on the rationale for and the remit of the committee.

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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 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 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 AZ 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.

CCI [redacted]

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 35 days from the previous ICF signature date.

CCI [redacted]

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 AZ clinical studies is closely monitored on an on-going basis by AZ 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 AZ. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the study treatment during 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 AZ. The DMC will ensure that the study meets high standards of ethics and patient safety.

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, 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. 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 Closure

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 AZ, 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 treatment,
- 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 eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patient's interests.

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 treatment development

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

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

B 2 Definitions of Serious Adverse Event

A serious adverse event 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-subject 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 subject or may require medical treatment to prevent one of the outcomes listed above

Adverse Events (AEs) 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 include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B 3 Life Threatening

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

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 subject 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 jeopardise the subject 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 subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- 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 AZ 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 IWRS errors)
- Wrong drug administered to participant (excluding IWRS errors)

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

- Errors related to or resulting from 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 AZ Biobank Team during the entire life cycle.

If required, AZ 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, AZ 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 AZ
- 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 AZ 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) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

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. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

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, C, D, and E viruses. 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 - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

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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 potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated 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 AZ clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the study treatment.

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 Aminotransferase (AST) or Alanine Aminotransferase (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 IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

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 (also sent to AZ 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 AZ representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory 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 (refer to Section 2 within this Appendix 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 AZ representative
- Determine whether the patient meets PHL criteria (refer to Section 2 Definitions within this Appendix 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:

- Inform the AZ representative that the patient has not met PHL criteria
- 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:

- Notify the AZ 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 patients that met PHL criteria prior to starting study treatment, the investigator is not required to submit a PHL SAE unless there is a significant change# in the patient's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) 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. Completes 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.

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 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 study treatment, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AZ Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

Where there is an agreed alternative explanation for the 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 study treatment:

- Send updated SAE (report term 'Hy's Law') according to AZ 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:

- Provides 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 study treatment 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 CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 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

REFERENCES

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H et al. Case definition and phenotype standardization in drug-induced liver injury. Clinical Pharmacology and Therapeutics. 2011;89(6):806-815.

FDA 2009
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 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.

F1 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.

F2 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 CKD-EPI formula (Levey et al) should be used to estimate GFR for enrolment criteria, baseline value and subsequent on-study measurements.

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

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 two 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 two 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

Levey et al 2009
Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of Internal Medicine 2009;150(9):604-12.

Appendix G Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1 Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2 Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of heart failure have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3 Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4 Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?

It has been...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all Bothersome	I've had no swelling
☐	☐	☐	☐	☐	☐

5 Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6 Over the past 2 weeks, how much has your fatigue bothered you?

It has been...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐	☐	☐	☐	☐	☐

7 Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8 Over the past 2 weeks, how much has your shortness of breath bothered you?

It has been...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
☐	☐	☐	☐	☐	☐

9 Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10 Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
☐	☐	☐	☐	☐

11 How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12 Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
☐	☐	☐	☐	☐

13 If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14 Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
☐	☐	☐	☐	☐

15 How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks?

Place an **X** in one box on each line

Activity	Severely Limited	Limited quite a bit	Moderately Limited	Slightly Limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationship with loved ones	☐	☐	☐	☐	☐	☐

Appendix H Patient Global Impression of Change (PGIC) for Heart Failure Symptoms

Overall, how would you rate the change in your heart failure symptoms since starting this study?

☐ Much better

☐ Moderately better

☐ A little better

☐ About the same

☐ A little worse

☐ Moderately worse

☐ Much worse

Appendix I Patient Global Impression of Severity (PGIS) for Heart Failure Symptoms

Overall, how would you rate the severity of your heart failure symptoms today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Appendix J Medication Requiring Adjustment for Co-administration with Colchicine

Table 1. COLCRYS Dose Adjustment for Coadministration with Interacting Drugs if no Alternative Available*

Strong CYP3A4 Inhibitors†

Drug	Noted or Anticipated Outcome	Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares			
		Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose
Atazanavir Clarithromycin Darunavir/ Ritonavir‡ Indinavir Itraconazole Ketoconazole Lopinavir/ Ritonavir‡ Nefazodone Nelfinavir Ritonavir Saquinavir Telithromycin Tipranavir/ Ritonavir‡	Significant increase in colchicine plasma levels*; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	0.6 mg twice a day 0.6 mg once a day	0.3 mg once a day 0.3 mg once every other day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)

Moderate CYP3A4 Inhibitors

Drug	Noted or Anticipated Outcome	Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares			
		Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose
Amprenavir‡ Aprepitant Diltiazem Erythromycin Fluconazole Fosamprenavir‡ (pro-drug of Amprenavir) Grapefruit juice Verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	0.6 mg twice a day 0.6 mg once a day	0.3 mg twice a day or 0.6 mg once a day 0.3 mg once a day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)

P-gp Inhibitors†

Drug	Noted or Anticipated Outcome	Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares			
		Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose	Original Intended Dosage	Adjusted Dose
Cyclosporine Ranolazine	Significant increase in colchicine plasma levels*; fatal colchicine toxicity has been reported with cyclosporine, a P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other P-gp inhibitors.	0.6 mg twice a day 0.6 mg once a day	0.3 mg once a day 0.3 mg once every other day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)

*For magnitude of effect on colchicine plasma concentrations *[see Pharmacokinetics (12.3)]*
†Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with strong CYP3A4 or P-gp inhibitors *[see Contraindications (4)]*
‡When used in combination with Ritonavir, see dosing recommendations for strong CYP3A4 inhibitors *[see Contraindications (4)]*

Table 2. COLCRYS Dose Adjustment for Coadministration with Protease Inhibitors

Protease Inhibitor	Clinical Comment	w/Colchicine - Prophylaxis of Gout Flares		w/Colchicine - Treatment of Gout Flares	w/Colchicine - Treatment of FMF
Atazanavir sulfate (Reyataz)	Patients with renal or hepatic impairment should not be given colchicine with Reyataz.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Darunavir (Prezista)	Patients with renal or hepatic impairment should not be given colchicine with Prezista/ritonavir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Fosamprenavir (Lexiva) with Ritonavir	Patients with renal or hepatic impairment should not be given colchicine with Lexiva/ritonavir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Fosamprenavir (Lexiva)	Patients with renal or hepatic impairment should not be given colchicine with Lexiva/ritonavir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg twice a day or 0.6 mg once a day 0.3 mg once a day	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
Indinavir (Crixivan)	Patients with renal or hepatic impairment should not be given colchicine with Crixivan.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Lopinavir/Ritonavir (Kaletra)	Patients with renal or hepatic impairment should not be given colchicine with Kaletra.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Nelfinavir mesylate (Viracept)	Patients with renal or hepatic impairment should not be given colchicine with Viracept.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Ritonavir (Norvir)	Patients with renal or hepatic impairment should not be given colchicine with Norvir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Saquinavir mesylate (Invirase)	Patients with renal or hepatic impairment should not be given colchicine with Invirase/ritonavir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Tipranavir (Aptivus)	Patients with renal or hepatic impairment should not be given colchicine with Aptivus/ritonavir.	**Original dose** 0.6 mg twice a day 0.6 mg once a day	**Adjusted dose** 0.3 mg once a day 0.3 mg once every other day	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)

Treatment of gout flares with COLCRYS is not recommended in patients receiving prophylactic dose of COLCRYS and CYP3A4 inhibitors.

Appendix K Patient Dosing Cards Information

All patients in the study will receive a Patient Dosing Card at each visit with IP dispensation (ie, Visits 3, 4, 5, 6 and 7). The Patient Dosing Cards information is only applicable to patients who follow the standard dose titration schedule (ie, dispensed dose of study treatment tolerated and no down-titration required).

Patient Dosing Card (Visit 3)

<table>
<tr><td colspan="2">During your visit today you will receive 2 bottles of Study Medication. This is enough Study Medication to last until Visit 4.</td></tr>
<tr><td>  </td><td>• 1 GREEN label bottle (100 mg allopurinol or matching placebo).
• Please take 1 tablet from the green label bottle every day.</td></tr>
<tr><td>  </td><td>• 1 WHITE label bottle (3 mg verinurad or matching placebo).
• Please take 1 capsule from the white label bottle every day.</td></tr>
<tr><td colspan="2">EACH DAY you will take your study medications in the morning (preferably with food) as follows:

• 1 TABLET from the GREEN label bottle.
• 1 CAPSULE from the WHITE label bottle.

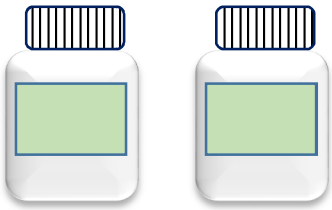
Please take colchicine as advised by your doctor.</td></tr>
<tr><td colspan="2">Important:

You should NEVER take more than one tablet or capsule from the same bottle in one day. You will NEVER take more than 2 pills in a single day.

You will continue to take your study medications each day for the remainder of the study as described above, unless you received other instructions from the study team.</td></tr>
</table>

Reminder **Before You Take Your Medication:** • Make Sure You Are Only Taking 2 Pills In Total (1 Pill From Each Label Colour Bottle).
If you ever have any questions about your study medications and how you should be taking them, contact your study doctor immediately.

Patient Dosing Card (Visit 4)

As per the standard dose titration schedule, during your visit today you will receive 3 bottles of Study Medication. This is enough Study Medication to last until Visit 5.	
	• 2 **GREEN** label bottles (100 mg allopurinol or matching placebo). • Please take **2 tablets** from the green label bottle **every day**.
	• 1 **WHITE** label bottle (7.5 mg verinurad or matching placebo). • Please take **1 capsule** from the white label bottle **every day**.
EACH DAY you will take your study medications in the morning (preferably with food) as follows: • **2 TABLETS from the GREEN label bottle** (always from the same bottle until it is empty, then from the next bottle of the same label colour). • **1 CAPSULE from the WHITE label bottle**. Please take colchicine as advised by your doctor.	
Important: **You should NEVER take more than 2 tablets and 1 capsule from the same bottle in one day.** The extra GREEN label bottle is to be opened when you run out. You will NEVER take more than 3 pills in a single day.	

You will continue to take your study medications each day for the remainder of the study as described above, unless you received other instructions from the study team.
Reminder **Before You Take Your Medication:** • Make Sure You Are Only Taking 3 Pills In Total (2 Pills From The Green Label Bottle And 1 Pill From The White Label Bottle). **Extra GREEN label bottle is ONLY used when you run out.**
If you ever have any questions about your study medications and how you should be taking them, contact your study doctor immediately.

Patient Dosing Card (Visit 5)

As per the standard dose titration schedule, during your visit today you will receive 2 bottles of Study Medication. This is enough Study Medication to last until Visit 6.	
	• 1 **BLUE** label bottle (300 mg allopurinol or matching placebo). • Please take **1 tablet** from the blue label bottle **every day**.
	• 1 **WHITE** label bottle (12 mg verinurad or matching placebo). • Please take **1 capsule** from the white label bottle **every day**.
EACH DAY you will take your study medications in the morning (preferably with food) as follows: • **1 TABLET from the BLUE label bottle**. • **1 CAPSULE from the WHITE label bottle**. Please take colchicine as advised by your doctor. **Remember to <u>NOT</u> take your study medications on the morning of your next study visit (Visit 6).**	

Important:

You should NEVER take more than one tablet or capsule from the same bottle in one day. You will NEVER take more than 2 pills in a single day.

You will continue to take your study medications each day for the remainder of the study as described above, unless you received other instructions from the study team.

Reminder

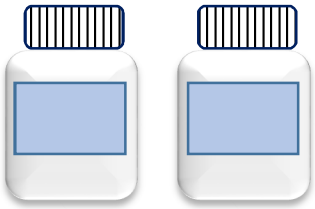
Before You Take Your Medication:

- Make Sure You Are Only Taking 2 Pills In Total (1 Pill From Each Label Colour Bottle).

If you ever have any questions about your study medications and how you should be taking them, contact your study doctor immediately.

Patient Dosing Card (Visit 6)

As per the standard dose titration schedule, during your visit today you will receive 5 bottles of Study Medication. This is enough Study Medication to last until Visit 7.

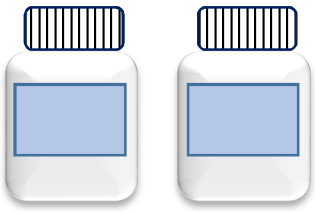
	• 2 **BLUE** label bottles (300 mg allopurinol or matching placebo). • Please take **1 tablet** from the blue label bottle **every day**.
	• 3 **WHITE** label bottles (12 mg verinurad or matching placebo). • Please take **1 capsule** from the white label bottle **every day**.

EACH DAY you will take your study medications in the morning (preferably with food) as follows:

- **1 TABLET from the BLUE label bottle** (always from the same bottle until it is empty, then from the next bottle of the same label colour).
- **1 CAPSULE from the WHITE label bottle (**always from the same bottle until it is empty, then from the next bottle of the same label colour).

Important: **You should NEVER take more than one tablet or capsule from the same bottle in one day.** Extra bottles are to be opened when you run out. You will NEVER take more than 2 pills in a single day. You will continue to take your study medications each day for the remainder of the study as described above, unless you received other instructions from the study team.
Reminder **Before You Take Your Medication:** • Make Sure You Are Only Taking 2 Pills In Total (1 Pill From Each Label Colour Bottle). **Extra bottles are ONLY used when you run out.**
If you ever have any questions about your study medications and how you should be taking them, contact your study doctor immediately.

Patient Dosing Card (Visit 7)

As per the standard dose titration schedule, during your visit today you will receive 5 bottles of Study Medication. This is enough Study Medication to last until Visit 8, your end of treatment visit.	
	• 2 **BLUE** label bottles (300 mg allopurinol or matching placebo). • Please take **1 tablet** from the blue label bottle **every day**.
	• 3 **WHITE** label bottles (12 mg verinurad or matching placebo). • Please take **1 capsule** from the white label bottle **every day**.
EACH DAY you will take your study medications in the morning (preferably with food) as follows:	

- **1 TABLET from the BLUE label bottle** (always from the same bottle until it is empty, then from the next bottle of the same label colour).
- **1 CAPSULE from the WHITE label bottle (**always from the same bottle until it is empty, then from the next bottle of the same label colour).

Important:

You should NEVER take more than one tablet or capsule from the same bottle in one day. Extra bottles are to be opened when you run out. You will NEVER take more than 2 pills in a single day.

You will continue to take your study medications each day for the remainder of the study as described above, unless you received other instructions from the study team.

Reminder

Before You Take Your Medication:

- Make Sure You Are Only Taking 2 Pills In Total (1 Pill From Each Label Colour Bottle).

Extra bottles are ONLY used when you run out.

If you ever have any questions about your study medications and how you should be taking them, contact your study doctor immediately.

Appendix L Abbreviations

Abbreviation or special term	Explanation
18-F-FDG	18F-fluorodeoxyglucose
ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate transaminase
AV	Arteriovenous
AZ	AstraZeneca
CEA	clinical event adjudication
CHF	chronic heart failure
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CRF	case report form (electronic/paper)
CPET	cardiopulmonary exercise test
CSP	clinical study protocol
CSR	clinical study report
CSS	clinical summary score
CT	computed tomography
CV	Cardiovascular
DECT	dual-emission computed tomography
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	Electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
E/E’	Ratio of the transmitral early peak velocity (E) over early diastolic mitral annulus velocity (E’)
eGFR	estimated glomerular filtration rate
ER8	verinurad extended release formulation
EU	European Union
FDG	Fluorodeoxyglucose
GDF15	growth/differentiation factor 15
GLS	global longitudinal strain

Abbreviation or special term	Explanation
HF	heart failure
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
HLA	human leukocyte antigen
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
hsTrop	high-sensitivity troponin
ICF	Informed consent form
IEC	independent ethics committee
IRB	institutional review board
IWRS	interactive web response system
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IWRS	interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	left atrial volume index
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MMRM	mixed model repeated measures
MSU	monosodium urate
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OSS	overall summary score
PET	positron-emission tomography
PGIC	patient global impression of change
PGIS	patient global impression of severity
PK	Pharmacokinetics
PRO	patient-reported outcome
QTcF	QT interval corrected by the Fridericia formula
RER	respiratory exchange ratio
CCI	[redacted]
RVSP	right ventricular systolic pressure
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or special term	Explanation
SoA	schedule of activities
sUA	serum uric acid
sCr	serum creatinine
sCystC	serum cystatin C
TSS	total symptom score
UA	uric acid
CCI	[redacted]
ULN	upper limit of normal
URAT1	uric acid transporter 1
US	United States
V_E/V_{CO2}	minute ventilation over carbon dioxide production
VO_2	volume of oxygen
XO	xanthine oxidase
XOI	xanthine oxidase inhibitor

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