
Statistical Analysis Plan

Study Code	D5495C00002
Edition Number	3.0
Date	16 July 2021

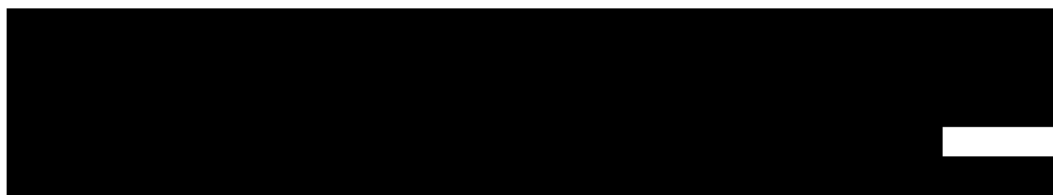
A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled Study of Verinurad and Allopurinol in Patients with Chronic Kidney Disease and Hyperuricaemia

TABLE OF CONTENTS

1	STUDY DETAILS	16
1.1	Study objectives.....	16
1.2	Study design	17
1.3	Number of subjects	17
1.4	This statistical analysis plan.....	18
2	ANALYSIS SETS	18
2.1	Definition of analysis sets	18
2.2	Violations and deviations.....	18
2.3	Switching to two-capsule regimen.....	18
3	PRIMARY AND SECONDARY VARIABLES	19
3.1	Baseline. On treatment. In study	19
3.2	Missing values	20
3.3	Endpoints.....	20
3.3.1	Primary endpoint	20
3.3.2	Secondary endpoints	20
CCI	[REDACTED]	
3.3.4	Safety endpoints	22
3.4	How to identify the end-of-treatment (EOT) visit and the follow-up visit	23
4	ANALYSIS METHODS.....	25
4.1	General principles.....	25
4.1.1	Descriptive statistics	25
4.1.2	Handling of laboratory values that (1) are not reportable, (2) are reported as “No sample” or are otherwise missing, or (3) are below LLOQ.....	26
4.1.3	Handling of laboratory values that are above the upper limit of quantification (ULOQ).....	26
4.2	Analysis methods.....	26
4.2.1	Primary endpoint: Change from baseline in UACR at 6 months (V8): “High” vs. “Placebo”	26
4.2.1.1	Main analysis.....	26
4.2.1.2	Sensitivity analysis: Jump to placebo arm	28
4.2.1.3	Supplementary subgroup analyses.....	30
4.2.2	Primary endpoint: Change from baseline in UACR at 6 months (V8): other comparisons.....	31
4.2.3	Secondary endpoints at 6 months (V8) and 12 months (V10)	32
4.2.3.1	Secondary endpoints at 6 months (V8).....	32
4.2.3.2	Secondary endpoints at 12 months (V10).....	32
4.2.4	[Removed]	33

CCI

CCI



4.2.6	Safety assessments.....	36
4.2.6.1	Adverse events (AE).....	36
4.2.6.2	Adjudicated events.....	37
4.2.6.3	S-creatinine elevations.....	38
4.2.6.4	Potential Hy's law.....	38
4.2.6.5	The COVID-19 pandemic.....	39
4.2.6.6	Patient narratives.....	39
4.2.6.7	Overdoses.....	40
4.2.6.8	Vital signs, electrocardiogram (ECG), haematology, clinical chemistry, and urinalysis.....	40
4.2.7	Other analyses.....	41
4.2.7.1	Demographics and baseline characteristics.....	41
4.2.7.2	Subject disposition.....	41
4.2.7.3	Prior medications and concomitant medications.....	42
4.2.7.4	Medical history and comorbid conditions.....	43
4.2.7.5	Compliance.....	43
4.2.7.6	Exposure.....	43
4.2.7.7	Important protocol deviations.....	43
4.2.7.8	Change from baseline in UACR vs. baseline sUA.....	44
4.2.9	Dose-response analysis.....	46
4.2.10	Formal testing and multiplicity.....	46
4.2.11	Some definitions.....	47
4.2.11.1	Albuminuria status.....	47
4.2.11.2	Geographic region.....	47
4.2.11.3	Hypertension status at baseline.....	47
4.2.11.4	eGFR status.....	48
4.2.11.5	sUA status.....	49
4.2.11.6	NT-proBNP status.....	49
4.2.11.7	Use of ACEi and ARB.....	49
4.2.11.8	Study periods.....	49
4.2.12	Albuminuria status over time.....	49
4.2.13	High-level results.....	50
5	INTERIM ANALYSES.....	50
5.1	The first interim analysis.....	50
5.2	The second interim analysis.....	51
6	CHANGES OF ANALYSIS FROM PROTOCOL.....	52
6.1	Analysis sets.....	52
6.2	Dose-response modelling.....	52
6.3	[Removed].....	52

6.4	Clarification regarding ‘treatment received’	52
6.5	Change in physical examination.....	53
6.6	Subgrouping variables for the supplementary analyses of the primary endpoint	53
6.7	Incidence of laboratory abnormalities	53
6.8	Secondary endpoints at 12 months (V10)	53
6.9	[Removed]	54
6.10	eGFR slope at V9 and at end-of-treatment (EOT)	54
7	APPENDIX	55
7.1	References	55

LIST OF TABLES

CCI

LIST OF FIGURES

No table of figures entries found.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
A1c	<i>a glycated form of haemoglobin A1</i>
ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
AEoSI	adverse event of special interest
AI	augmentation index
CCI	
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance (<i>statistical model</i>)
ARB	angiotensin receptor blocker
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AZ	AstraZeneca
CCI	
CI	confidence interval
CK	creatinine kinase
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CSR	clinical study report
CSRHLD	clinical study report or higher level document
CV	cardiovascular
CV	coefficient of variation
DAE	discontinuation of study drug due to an adverse event
DBL	database lock
DBP	diastolic blood pressure
DM	diabetes mellitus
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
CCI	
EOS	end of study
EOT	end of treatment
exp	exponential (<i>function</i>)

Abbreviation or special term	Explanation
FAS	full analysis set
G1, G2, G3, G3a, G3b, G4, G5	KDIGO 2012 GFR categories 1, 2, 3, 3a, 3b, 4, 5, <i>see KDIGO 2013</i>
GFR	glomerular filtration rate
gCV	geometric coefficient of variation
gmean	geometric mean
gSD	geometric standard-deviation
Hb	haemoglobin
HLR	high-level results
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IPD	important protocol deviation
KDIGO	Kidney Disease: Improving Global Outcomes
LLOQ	lower limit of quantification
log	logarithm(ic)
LSMean	least squares mean
MACE	major cardiovascular even
MAR	missing at random
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model (for) repeated measure(ment)s (<i>statistical model</i>)
MNAR	missing not at random
CCI	[REDACTED]
NC	not calculable
NQ	<i>below LLOQ</i>
NR	not reported
NS	no sample
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PA5	protocol amendment 5 (<i>same as protocol version 5.0</i>)
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	<i>MedDRA preferred term</i>

Abbreviation or special term	Explanation
QTcF	QT interval corrected for heart rate according to Fridericia
R1, R2, R2*	specifiers to some kidney endpoints
CCI	
RBC	red blood cell count
CCI	
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SGLT2	sodium/glucose cotransporter 2
SGLT2i	sodium/glucose cotransporter 2 inhibitor
SMQ	standardised MedDRA query
SOC	MedDRA system organ class
sqrt	square root (<i>function</i>)
sUA	serum uric acid
TIA	transient ischaemic attack
UACR	urinary albumin to creatinine ratio
UA	uric acid
ULN	upper limit of normal
ULN _{ALT}	upper limit of normal for ALT
ULN _{AST}	upper limit of normal for AST
ULN _{total bilirubin}	upper limit of normal for total bilirubin
ULOQ	upper limit of quantification
v	version
V1, V2, ..., V14	visit 1, visit 2, ..., visit 14
V _x	visit <i>x</i> , a placeholder for any numbered visit
WHO	World Health Organization
WHO DD	WHO Drug Dictionary
	Sample matrices
B-	blood
P-	plasma
S-	serum
S/P-	serum or plasma (<i>undecided</i>)
U-	urine

VERSION HISTORY

Version 2.0, 2 March 2021

General

- Minor issues regarding spelling, grammar, wording, and layout have been resolved ad hoc and in a way that does not change the information conveyed.
- Changed names to “Albuminuria status” for the variable previously called “microalbuminuria/macroalbuminuria”, “microalbuminuria or macroalbuminuria”, “micro-/macroalbuminuria”, “micro- or macroalbuminuria”, or the like.
- Specification of which categories to be used for demographics variable ‘race’ removed.
- References updated to version 4.0 of the protocol, and also to version 5.0 where needed.

Version history

- Version history added.

CCI

Subsection 1.4

- Subsection added, “This statistical analysis plan”.

Subsection 3.1

- Definition of baseline changed to one more easy to follow when implemented.
- Information on in-study and on-treatment added.

Subsection 3.3

- Sentences added on interpretation of “end of treatment” and “end of study”.

CCI

Subsection 4.1.1

- Whole subsection gently revised.
- Paragraph on logarithmised endpoints removed.

Subsection 4.1.2

- Subsection added, “Handling of laboratory values that (1) are not reportable, (2) are reported as ‘No sample’ or are otherwise missing, or (3) are below LLOQ”.

Subsection 4.1.3

- Subsection added, “Handling of laboratory values that are above the upper limit of quantification (ULOQ)”.

Subsection 4.2.1.1

- Added that only response values from (V3,) V4, V5, V6, V7, V8, and V9 will contribute; for second interim analysis only values from (V3,) V4, V5, V6, V7, and V8 will contribute.
- Paragraph on missing explanatory variables moved to Subsection 4.2.1.2.

Subsection 4.2.1.2

- Added that only response values from (V3,) V4, V5, V6, V7, V8, and V9 will contribute; for second interim analysis only values from (V3,) V4, V5, V6, V7, and V8 will contribute.
- Paragraph on missing explanatory variables moved here from Subsection 4.2.1.1.

Subsection 4.2.1.3

- New subgroup analyses added: hypertension status at baseline; six-category eGFR status at baseline ; use of ACEi and ARB at baseline; use of SGLT2i at baseline.

Subsection 4.2.3

- Paragraph on missing explanatory variables removed.
- Paragraph added where dose-response analyses are mentioned.
- Only descriptive statistics will be provided for secondary endpoints at 12 months (V10).
- Subsection split in two
 - 4.2.3.1 “Secondary endpoints at 6 months (V8)”
 - 4.2.3.2 “Secondary endpoints at 12 months (V10)”

Subsection 4.2.4

- Paragraph on missing explanatory variables removed.
- Clarification on time to EOT visit added.
- 95 % CI added to estimates of change-from-baseline for each treatment.

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

Subsection 4.2.6

- Added minimum requirements for vital signs, ECG, haematology, clinical chemistry, laboratory, and urinalysis.
- Added what safety tables and key-subject-information listings not to be included for the time being.

Subsection 4.2.6.1

- Whole subsection reworded.
- AEs with “AEs within MedDRA SMQ = ‘Acute renal failure’” removed.
- CV events “for adjudication (as determined from the AE form)” removed
- CCI [REDACTED]
- On-treatment AEs will be summarised too.
- Non-serious AEs added (see item 10 under C).
- Key subject information will be provided for AEs with outcome death, SAEs, and AEs leading to discontinuation of IP (see F).

Subsection 4.2.6.2

- Whole subsection reworded.
- Has been added a more detailed specification of what adjudicated-event information to be presented.
- On-treatment adjudicated events will be summarised too.

Subsection 4.2.6.3

- Clarification that only *in-study* S-creatinine elevations are in scope.
- Changed from ‘mean’ to ‘maximum’ in the definition of baseline for S-creatinine elevations.
- Clarification that the S-creatinine elevations will also be listed.

Subsection 4.2.6.4

- Clarification that only *in-study* cases of potential Hy’s law are in scope.
- The limit for total bilirubin in first paragraph corrected.
- Clarification that the cases of potential Hy’s law will also be listed and that individual subject data will be presented.
- The description of the plots is corrected.

Subsection 4.2.6.5

- Subsection added, “COVID-19”.

Subsection 4.2.6.6

- Subsection added, “Patient narratives”.

Subsection 4.2.7.1

- Added to list: baseline UACR; baseline cystatin-C; hypertension status at baseline; six-category eGFR status at baseline.

Subsection 4.2.7.2

- List of items in subject disposition updated.

Subsection 4.2.7.3

- Changed from “randomisation day” to “day of randomisation visit”.
- Added paragraph on *allowed* concomitant medication and *disallowed/prohibited* concomitant medication.
- Analysis set changed to the FAS.

Subsection 4.2.7.4

- Analysis set changed to the FAS.

Subsection 4.2.7.5

- Analysis set changed to the safety analysis set.

Subsection 4.2.7.6

- Analysis set changed to the safety analysis set.

CCI

Subsection 4.2.9

- Type of plot specified: “a mean plot (as a line plot)”.

Subsection 4.2.11.1

- Whole subsection reworded, including header (“Albuminuria status”).

Subsection 4.2.11.2

- ‘China’ removed.

Subsection 4.2.11.3

- Subsection added, “Hypertension status at baseline”.

Subsection 4.2.11.4

- Subsection added, “eGFR status”. Specification of eGFR groupings.

Subsection 4.2.11.5

- Subsection added, “sUA status”. Specification of sUA groupings.

Subsection 4.2.11.6

- Subsection added, “NT-proBNP status”. Specification of NT-proBNP grouping.

Subsection 4.2.11.7

- Subsection added, “Use of ACEi and ARB”

CCI

Subsection 4.2.12

- Subsection added, “Albuminuria status over time”.

Subsection 4.2.13

- Subsection added, “High-level results”.

Section 5

- Adapted second paragraph to version 4.0 of the protocol (time for first interim).
- Added sentence “The analyses below will be done to the extent there is enough data for a meaningful interpretation”.

Subsection 5.1

- List updated.

Subsection 5.2

- Whole subsection revised.

Subsection 6.1

- Definition of PK analysis set changed to better fit the study’s design.

Subsection 6.3

- Whole subsection reworded.

Subsection 6.6

- Added to list: hypertension status at baseline; six-category eGFR status at baseline; use of ACEi and ARB at baseline; use of SGLT2i at baseline.

Subsection 6.7

- Subsection added, “Incidence of laboratory abnormalities”.

Subsection 6.8

- Subsection added, “Secondary endpoints at 12 months (V10)”.

Subsection 6.9

- Subsection added, “Secondary endpoints at End-of-treatment visit [EOT] and at Follow-up visit (End-of-study visit) [EOS]”.

Draft version 2.3 (3.0 to be), 15 July 2021

General

- References updated to version 5.0 of the protocol, and also to version 4.0 where needed.
- ‘End-of-treatment follow-up (End-of-study) [EOS]’ renamed to ‘follow-up’.
- List of abbreviations updated

Version history

- Version history updated.

Subsection 1.2

- Reference to version 5.0 of the protocol.

Subsection 1.4

- Subsection rewritten: Reference to version 5.0 of the protocol.

Subsection 2.1

- Definition of the PK (analysis) set changed from “All patients who received allopurinol and verinurad treatment and have at least one post-dose plasma concentration measurement of verinurad at a scheduled time point” to “All subjects who received investigational allopurinol or verinurad and have at least one post-baseline concentration measurement of verinurad, allopurinol, or oxypurinol at a scheduled time point”.

Subsection 2.3

- Subsection added, “Switching to two-capsule regimen”.

Subsection 3.3

- Reference changed to version 5.0 of the protocol.
- References to version 5.0 of the protocol added.

Subsection 3.3.2


- Change from baseline in UACR at 6 months added as endpoint.

CC

CCI

CC

CC



Subsection 3.4

- Added subsection, “How to identify the end-of-treatment (EOT) visit and the follow-up visit”.

Subsection 4.1.1

- Added paragraph that four (4) significant digits are required for geometric means, values of gmean/gSD , values of $\text{gmean}\times\text{gSD}$, geometric coefficients of variation, (estimated) geometric-mean ratios, and upper and lower limits of confidence intervals for (estimated) geometric-mean ratios.
- Text gently revised here and there.

Subsection 4.1.2

- Added that, whenever the LLOQ rule (i.e. a value reported as below LLOQ is replaced by $\text{LLOQ}/2$ in all analyses) is applied, it must be clearly stated so in, e.g., the footer of the output in question, preferably together with the number, and proportion, of subjects subceeding LLOQ.

Subsection 4.1.3

- Added that, in statistical analyses, values below ULOQ will be replaced by the value of the ULOQ.
- Added that, whenever the ULOQ rule above is applied, it must be clearly stated so in, e.g., the footer of the output in question, preferably together with the number, and proportion, of subjects exceeding ULOQ.

Subsection 4.2.1.2

- Heading shortened to “Sensitivity analysis. Jump to placebo arm”.
- Imputation rules for missing $\log(\text{UACR})$ values totally revised and text rewritten accordingly.
- Imputation rules for missing covariates revised. Now randomness is added to the process.

Subsection 4.2.1.3

- No imputation of missing grouping variables required anymore.

Subsection 4.2.3.1

- Correction: The analysis time point (V8) is not supposed to be changed.

Subsection 4.2.3.2

- Formal analysis suggested for the comparison double-capsule 24 mg vs double-capsule Placebo.

Subsection 4.2.4

- Subsection removed. It dealt with previously secondary endpoint at end-of-treatment visit and at follow-up visit (end-of-study visit), cf. superseded version 4.0 of the protocol. Updated contents moved to Subsection 4.2.5.6.

CCI

CCI

Subsection 4.2.6

- Removed minimum requirements for tables for vital signs, ECG, haematology, clinical chemistry, laboratory, and urinalysis. Moved to Subsection 4.2.6.8

Subsection 4.2.6.4

- Sentence “A separate summary of individual subject data is also required” removed.

Subsection 4.2.6.5

- Heading changed to “The COVID-19 pandemic”.
- Subsection completely rewritten.

Subsection 4.2.6.7

- Subsection added, “Overdoses”.

Subsection 4.2.6.8

- Subsection added, “Vital signs, electrocardiogram (ECG), haematology, clinical chemistry, and urinalysis”.
- Moved minimum requirements for tables for vital signs, ECG, haematology, clinical chemistry, laboratory, and urinalysis to here from beginning of Subsection 4.2.6.
- Added quite some more items to the list of minimum requirements for tables.

Subsection 4.2.7.2

- Added reasons for not randomised
- Added reasons for not being treated, when randomised.
- COVID-19 pandemic added as a reason for not being randomised, for not being treated once randomised, for discontinuing treatment, and for discontinuing study.
- Added status w r t double-capsule regimen according to PA5.

Subsection 4.2.7.3

- Reference changed to Table 10 of version 5 of the protocol.

Subsection 4.2.7.7

- Subsection rewritten: Reference to template AZTSP06 in the AZ Study-population table-templates (1 April 2021) replaced previous text.
- Request for number of IPDs, not only number and proportion of subjects experiencing at least one IPD.
- COVID-19 pandemic addressed: Added reference to template ‘COVID-summary2’ in AZ Corporate Pandemic CSRHLD standard.

CCI

Subsection 4.2.11.8

- Added period V3—V8.

Subsection 5.2

- ‘EOS visit’ renamed ‘follow-up visit’.

• CCI

CCI

Subsection 6.9

- Subsection removed. It dealt with previously secondary endpoint at End-of-treatment visit and at Follow-up visit (End-of-study visit), cf. superseded version 4.0 of the protocol.

Subsection 6.10

- Subsection added, “eGFR slope at V9 and at end-of-treatment (EOT)”.

1 STUDY DETAILS

1.1 Study objectives

According to the protocol, the objectives are:

Primary objective

1. To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 6 months.

Secondary objectives

2. To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on UACR at 12 months.
3. To assess the effects of verinurad and allopurinol, allopurinol alone, and placebo on sUA.
4. To estimate the dose-response relationship among 3 doses of verinurad and allopurinol and placebo on UACR and sUA.
5. To assess the effects of verinurad and allopurinol versus placebo on kidney function.

CCI



Safety objective

13. To assess the safety and tolerability of intensive UA lowering therapy with verinurad and allopurinol.

1.2 Study design

This is a randomised, double-blind, placebo-controlled, parallel, global, dose-finding, phase 2b study to assess the efficacy and safety of verinurad and allopurinol in subjects with chronic kidney disease and hyperuricaemia. Subjects who meet the eligibility criteria will be randomised 1:1:1:1:1 to, respectively,

- high dose of verinurad plus allopurinol (“High”),
- intermediate dose of verinurad plus allopurinol (“Intermediate”),
- low dose of verinurad plus allopurinol (“Low”),
- allopurinol only (“Allopurinol alone”), or
- placebo (“Placebo”).

Two sub-studies, the one on magnetic resonance imaging (MRI) and the other on pharmacokinetics (PK), are planned that together will form four strata according to a subject’s participation in the sub-studies. The four strata are: Participation (1) in none of the sub-studies, (2) in MRI only, (3) in PK only, and (4) in both MRI and PK. For each subject, participation is optional. Randomization will be stratified to ensure approximate balance between treatment groups within each sub-study.

CCI

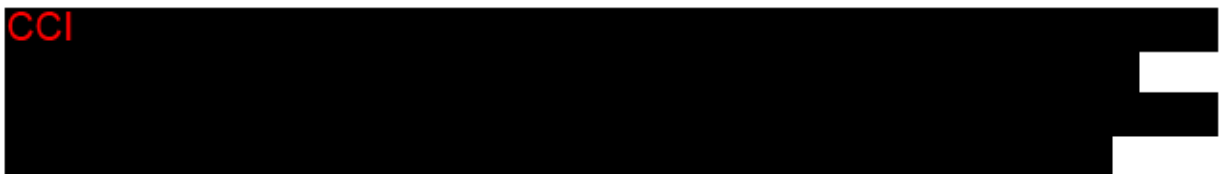


For further details, please see the protocol.

1.3 Number of subjects

With 145 randomised subjects in each arm and a between-subject standard-deviation of 1.0 on log-scale (natural logarithm), a relative treatment difference of –25 % between high-dose and placebo in geometric-mean ratio of UACR at 6 months over baseline will be detected with close up to 80 % power, based on a two-sided t-test with significance level 0.1. Assuming the same number in all arms, $5 \times 145 = 725$ subjects must be randomised in total. The estimated value of 1.0 for the standard deviation on log-scale is derived from the results from the AstraZeneca clinical-study D5495C00007.

CCI



CCI

1.4 This statistical analysis plan

This statistical analysis plan (SAP) covers v 5.0 of the protocol.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Full analysis set (FAS): All randomised subjects. Subjects will be analysed by randomised treatment.

Safety analysis set: All subjects who had at least one dose of investigational product. A subject will be analysed by his/her randomised treatment, unless the subject (erroneously) was given *another* specific investigational treatment *for the whole duration of the study*, in which case the subject will be analysed by that other treatment instead.

PK (analysis) set: All subjects who received investigational allopurinol or verinurad and have at least one post-baseline concentration measurement of verinurad, allopurinol, or oxypurinol at a scheduled time point.

The protocol also mentions the **per-protocol analysis set**, the **enrolled (analysis set)**, the **randomised (analysis) set**, and the **efficacy analysis set**. None of these four analysis sets will be used in this SAP.

2.2 Violations and deviations

The identified types of important protocol deviations (IPD) as well as non-important protocol deviations are found in the protocol-deviation list accompanying the current version of the Protocol Deviation Plan. For the display, please see Subsection [4.2.7.7](#).

2.3 Switching to two-capsule regimen

As per version 5.0 of the protocol (protocol amendment 5, PA5), the last planned, numbered visit will be V10. Most of those subjects that have reached V9 have been asked to switch to two-capsule regimen from the previous one-capsule regimen, but some have declined and therefore continued on one-capsule regimen until V10 and discontinued study there. Other subjects may have passed V10 when version 5 of the protocol took effect; these subjects will stay on one-capsule treatment until next planned, numbered visit and discontinue study there.

With respect to “switching status”, we thus need to identify these subsets of subjects:

1. PA5 consenters: All randomised subject who have signed the informed consent at V9 according to PA5.
2. Non-PA5-consenters: All randomised subjects who are not PA5 consenters.
3. All: All randomized subjects.

The basic principle is that, in an analysis (table, figure, formal statistical analysis) where

- at least one of the involved visits
 - is strictly beyond V9 or
 - is the EOT visit or the follow-up visit, or
- at least one of the involved study periods
 - partly or in total falls strictly beyond V9, like V3V10 or V3 (whole study), or
 - involves the EOT visit or the follow-up visits, like V3EOT,

the presented “switching status” groups should be PA5-consenters, Non-PA5-consenters. If – on the other hand – all involved visits of analysis and all involved study periods neither go beyond V9, nor involve the EOT visit or the follow-up visit, then the appropriate group is All. An exception is summaries and displays of baseline data, where all three groups should be considered.

Subject dispositions (see Subsection 4.2.7.2) must take switching into double-capsule regimen into account. Listings must also be adjusted to meet the “switching status”

In output where the group of PA5-consenter (or non-PA5-consenters) is taken into account, it could be wise to clearly indicate – in one way or another, e.g. in the treatment label – that the “Low” arm does not necessarily takes its label from the lowest planned dose of verinurad, 3 mg, but could very well connote the very highest planned dose of verinurad, 24 mg, this to avoid grave misreading with ensuing misinterpretation.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Baseline. On treatment. In study

For all longitudinal series of measurements of the same kind, the *baseline* is derived – if not otherwise specified – as the latest non-missing value with a date on, or prior to, the date of the randomization visit. If no such value exists, the baseline assessment will be set to missing. For baseline S-creatinine used for determining S-creatinine elevations, in particular, another rule applies, see Subsection 4.2.6.3.

A subject is *on treatment* from the first dosing day until five (5) whole days after last dosing day (both end-days included).

A subject is *in study* from the day of V3 until the day of last attended scheduled visit, i.e. one of the visits V3, V4, ..., V14 (or beyond), the end-of-treatment (EOT) visit, and the follow-up visit.

3.2 Missing values

No missing values will be imputed unless otherwise stated in Subsection 4. All statistical analyses (particularly the formal statistical analyses of UACR, sUA, eGFR, S-creatinine, and S/P-cystatin C) are based on a treatment-policy strategy for intercurrent events, so all in-study values for all subjects are valid, regardless of any intercurrent event.

3.3 Endpoints

The formal endpoints, as stated in the protocol, are listed below. “At 6 months” is defined as V8. “At 12 months” is defined as V10. “End of treatment” is defined as the end-of-treatment (EOT) visit. “Follow-up” is defined as the follow-up visit. These are the endpoints (for Subsections 3.3.1, 3.3.2, and 3.3.3 below, reference is Subsection 9.4.1 in v 5.0 of the protocol; for Subsection 3.3.4 below it is Table 4 in Section 3 of v 5.0 of the protocol; for Table 1 below it is Table 12 [modified] in Subsection 8.1.3.1 in v 5.0 of the protocol):

3.3.1 Primary endpoint

- Change from baseline in UACR at 6 months

3.3.2 Secondary endpoints

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

CC|

[REDACTED]

Electrocardiogram (ECG) assessments for safety are:

- Overall ECG evaluation
- QT interval
- QTcF interval

Clinical-laboratory assessments for safety are:

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

3.4 How to identify the end-of-treatment (EOT) visit and the follow-up visit

Because V10 for quite many (most?) subjects will – according to updated protocol version 5.0 – also be the EOT visit, and because the EOT visit therefore will carry the label ‘V10’ rather

than ‘EOT’ in the datasets, there must be a rule for identifying the EOT visit when it cannot be found. Such a rule could very well be useful in other situations when the EOT visit is missing. An EOT visit, or rather the requested data for it, is identified like this:

1. If data of the requested kind is collected (missing or non-missing) at a visit termed “EOT” then that data will – of course – be identified as the EOT-visit data.
2. Else, if there are strong indications that V10 has coincided with the EOT visit, then the V10 data will be identified as the EOT-visit data, if data of the requested kind is collected (missing or non-missing) at ‘V10’.
3. Else, if last day of treatment falls within the planned time window of a numbered visit, then the data from that numbered visit will be identified as the EOT-visit data, if data of the requested kind is collected (missing or non-missing) at that visit, and as long as the numbered visit actually occurs *after* the last treatment day.
4. Else, data obtained on the visit closest to, or on, but not preceding, the last treatment day – be this visit scheduled or unscheduled – will be identified as the EOT-visit data, if data of the requested kind is collected (missing or non-missing) at that visit. However, to be eligible, that visit must not fall more than two weeks after last treatment day.
5. Else, EOT visit data will be set to missing.

Also we could use a rule to identify the follow-up visit when it cannot be readily found. Typically, this would be the case when a subject has permanently discontinued treatment early. Requested data for a follow-up visit is identified like this:

1. If data of the requested kind is collected (missing or non-missing) at a visit termed “Follow-up”, then that data will – of course – be identified as the follow-up-visit data.
2. Else, if the subject permanently discontinued treatment early, the data will be the data for the last scheduled, numbered visit after last treatment day, if data of the requested kind is collected (missing or non-missing) at that visit.
3. Else, again if the subject permanently discontinued treatment early, the data will be the data for the last visit, scheduled or unscheduled, after last treatment day, if data of the requested kind is collected (missing or non-missing) at that visit
4. Else, be it scheduled or unscheduled, closest to four weeks after last treatment day will be identified as the follow-up data, if the requested kind of data is collected (missing or non-missing) at that visit, and as long as the visit takes place between three and five weeks after last treatment day.
5. Else, the follow-up-visit data will be set to missing.

4 ANALYSIS METHODS

4.1 General principles

4.1.1 Descriptive statistics

All variables in this SAP will be summarised in tables and graphs, as appropriate.

In tables, numerical variables will be summarized by the number of observations, arithmetic mean, (arithmetic) standard-deviation, median, minimum, and maximum. However, if best analysed on log scale (like UACR, sUA, eGFR, S-creatinine, and S/P-cystatin C), the variables will be summarised by number of observations, geometric mean (gmean), coefficient of variation (CV), median, minimum, and maximum. Categorical variables will be summarized by number of observations, frequency counts for each category, and percentages for each category. All variables will be summarised by visit and by treatment.

Numerical variables assessed at several visits will, when needed, be displayed graphically as arithmetic-mean, geometric-mean, or median curves (line plot) over time (visit), by treatment.

Numerical variables that are derived change-from-baseline variables will, when needed, have tables and graphs as above for both the raw values and the change-from-baseline values. Change from baseline in categorical variables will, when deemed needed, be summarised in shift tables.

CCI [REDACTED]

Geometric means, CCI [REDACTED], geometric coefficients of variation, (estimated) geometric-mean ratios, and the upper and lower limits of confidence intervals for (estimated) geometric-mean ratios must be presented with at least four (4) significant digits.

4.1.2 Handling of laboratory values that (1) are not reportable, (2) are reported as “No sample” or are otherwise missing, or (3) are below LLOQ

For all laboratory variables **CCI**: Values reported as ‘Not Reportable’, or the like, will, if feasible, be listed as NR (not reported), otherwise as missing. Missing values, some of them perhaps reported as ‘No Sample’ or the like, will in listings, if feasible, be presented as NS (no sample), otherwise as missing. Numerical values below LLOQ will in listings preferably be presented as “< {LLOQ}”, where “{LLOQ}” is replaced by the numerical value of the LLOQ in question, e.g., “< 51”, otherwise as “< LLOQ”, “NQ”, or the like. If reported as “< LLOQ” or “NQ”, then the value of LLOQ must be stated in a footnote (or the like) of the listing. Values that are not reportable (NR) or non-sample (NS) will be considered missing in all statistical analyses, both descriptive and inferential. Numerical values that are below LLOQ (NQ) will in all statistical analyses, both descriptive and inferential, be replaced by a value which is half the value of the LLOQ, i.e., by LLOQ/2; this rule must – wherever applied – be flagged in a footnote (or the like) in the output report in question, preferably together with the number, and fraction, of values below LLOQ.

CCI

4.1.3 Handling of laboratory values that are above the upper limit of quantification (ULOQ)

Numerical values above the upper limit of quantification (ULOQ) will preferably be listed as “> {ULOQ}”, where “{ULOQ}” is replaced by the numerical value of the ULOQ in question, e.g., “> 500”, otherwise as “> ULOQ”. If reported as “> ULOQ”, then the value of ULOQ must be stated in a footnote (or the like) of the listing.

Numerical values that are above ULOQ will in all statistical analyses, both descriptive and inferential, be replaced by the value of the ULOQ; this rule must – wherever applied – be flagged in a footnote (or the like) in the output report in question, preferable together with the number, and fraction, of subjects exceeding ULOQ.

4.2 Analysis methods

4.2.1 Primary endpoint: Change from baseline in UACR at 6 months (V8): “High” vs. “Placebo”

4.2.1.1 Main analysis

The natural log-transformed UACR values for V4, V5, V6, V7, V8, and V9 (for the second interim analysis: V4, V5, V6, V7, and V8) will be analysed using a repeated measures mixed model (MMRM) where $\log(\text{UACR})$ would depend on the fixed categorical effects of randomised treatment, visit, diabetes mellitus (DM) status (yes/no) at baseline, albuminuria

status (see Subsection 4.2.11.1) at baseline, NT-proBNP status (see Subsection 4.2.11.6) at baseline, use of sodium/glucose cotransporter 2 inhibitor (SGLT2i) (yes/no) at baseline, and treatment-by-visit interaction, as well as the continuous fixed covariate of baseline $\log(\text{UACR})$ and its baseline- $\log(\text{UACR})$ -by-visit interaction. An unstructured matrix for the within subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. If the estimating algorithms will not converge, the following steps will be taken to simplify the model until convergence is achieved:

1. As a first step, try in order these three covariance structures: Toeplitz, the first-order autoregressive, and compound symmetry.
2. If step 1 does not work, the baseline- $\log(\text{UACR})$ -by-visit interaction will be removed from the last model in step 1, i.e. from the model with compound symmetry.
3. If step 2 does not work either, then instead the treatment-by-visit interaction will be removed from the last model in step 1, i.e. from the model with compound symmetry.
4. If step 3 does not work either, then both the baseline- $\log(\text{UACR})$ -by-visit interaction and the treatment-by-visit interaction will be removed from the last model in step 1, i.e. from the model with compound symmetry.
5. If step 4 did not work either, then (a) NT-proBNP-status factor, (b) the DM-status factor, and (c) the albuminuria-status factor will be removed, one at a time, in this order, starting with the model in step 4, until convergence.

The least squares mean (LSmean) change from baseline to 6 months (V8) in the log-transformed UACR will be calculated by treatment (“High” and “Placebo”) with its 95 % confidence intervals (CI). The LSMeans difference between the two treatments (“High” vs. “Placebo”) will be calculated with its 95 % CI. A p-value for the treatment difference between “High” and “Placebo” will also be calculated. The above LSMeans change from baseline (and the 95 % CI) for each of the two treatments will be exponentiated to yield the geometric mean ratio from baseline for each treatment with its 95 % CI at the original scale of UACR. Percent change from baseline with 95 % CI for each of the two treatments will in turn be derived from the geometric estimated mean ratio, and CI, by $([\text{geometric mean ratio}] - 1) \times (100 \%)$. The LSMeans difference between “High” and “Placebo” (and its 95 % CI) will also be exponentiated to yield the geometric mean ratio between the two treatments at V8 and its 95 % CI at the original scale of UACR.

All available in-trial UACR values at (V3, V4, V5, V6, V7, V8, and V9) will be used (for the second interim analysis: [V3, V4, V5, V6, V7, and V8]), regardless of any intercurrent events. Missing values will not be imputed. In this analysis it is thus assumed that any missing UACR values are missing at random (MAR).

Missing explanatory covariates and factors will not be imputed either.

The analysis set will be the FAS.

4.2.1.2 Sensitivity analysis: Jump to placebo arm

A sensitivity analysis will be conducted, a multiple-imputations analysis with an assumption of “unconditional jump to placebo arm” for off-treatment subjects.

All available in-trial values for UACR at (V3,) V4, V5, V6, V7, V8, and V9 (for the second interim analysis: [V3,] V4, V5, V6, V7, and V8) will be used in the sensitivity analysis, regardless of any intercurrent events.

Missing values of $\log(\text{UACR})$ from V4, V5, V6, V7, V8, and V9 (for the second interim analysis: V4, V5, V6, V7, and V8) will be imputed recursively by means of simulation, visit by visit, starting with the imputations at V4. Missing $\log(\text{UACR})$ data at a visit x (V_x) will be simulated like this:

- A. Missing off-treatment values will be simulated from an ANCOVA where non-missing $\log(\text{UACR})$ at V_x depends on baseline $\log(\text{UACR})$ and on the last post-baseline, non-missing or previously imputed $\log(\text{UACR})$ -value before V_x (if any) as covariates and DM status at baseline, albuminuria status at baseline, NT-proBNP status at baseline, and use of SGLT2i at baseline as factors. Only subjects in the placebo arm (on or off treatment) will contribute to the ANCOVA, and they do it as long as they have non-missing $\log(\text{UACR})$ at V_x and has a full set of explanatory variables.
- B. Missing on-treatment values will be simulated form an ANCOVA where non-missing $\log(\text{UACR})$ at V_x depends on baseline $\log(\text{UACR})$ and all post-baseline, non-missing or previously imputed $\log(\text{UACR})$ -values before V_x (if any) as covariates and randomised treatment, DM status at baseline, albuminuria status at baseline, NT-proBNP status at baseline, and use of SGLT2i at baseline as factors and baseline- $\log(\text{UACR})$ -by-treatment as interaction. Only subjects with non-missing, on-treatment $\log(\text{UACR})$ -value at V_x and with a full set of explanatory variables will contribute to the ANCOVA.

A simulated $\log(\text{UACR})$ value from one of the ANCOVAs above is its predicted mean-value plus the estimated standard-deviation times a random number from a standard-normal distribution. We will conduct the simulations in [A](#) and [B](#) above not just once but multiple times (a kind of *multiple imputations*). In this way, we will simulate 500 independent data-sets where *all* missing $\log(\text{UACR})$ values from V4 until V9 (V8 for second interim) have been imputed with simulated values.

In case of missing covariates and factors, all of what is laid down above must – for each of the 500 data-sets – be preceded by one cycle of imputation by chained equations, where the missing covariates and factors are imputed, one covariate/factor after the other:

- A. First, the covariate $\log(\text{UACR})$ at baseline (V3) will, if missing, be simulated from an ANCOVA where $\log(\text{UACR})$ at baseline depends on $\log(\text{UACR})$ at V4, treatment, and treatment-by- $\log(\text{UACR})$ -at-V4. All subjects with non-missing $\log(\text{UACR})$ at baseline and at V4 will contribute to the ANCOVA. The imputed $\log(\text{UACR})$ value from the ANCOVA is its predicted mean-value plus the estimated standard-deviation times a random number from a standard-normal distribution. For those subjects where $\log(\text{UACR})$ is missing also at V4, $\log(\text{UACR})$ at baseline will, if missing, instead be imputed as random numbers from a normal distribution with mean and standard-deviation set to the observed mean and standard-deviation for the non-missing $\log(\text{UACR})$ values at baseline. Hereafter, the covariate $\log(\text{UACR})$ at baseline is complete. Please note that by now, we can form change-from-baseline in $\log(\text{UACR})$ for those subjects where $\log(\text{UACR})$ was missing at baseline; this was unfeasible before.
- B. Next, the factor albuminuria status at baseline will, when missing, be imputed. The imputed value will be derived from imputed baseline $\log(\text{UACR})$ values, obtained as in step A, according to the definition in Subsection 4.2.11.1. Hereafter, also the factor albuminuria status at baseline is complete.
- C. Next, $\log(\text{NT-proBNP})$ at baseline will, when missing, be simulated from an ANCOVA where $\log(\text{NT-proBNP})$ at baseline depends on $\log(\text{UACR})$ at baseline and albuminuria status at baseline (both either non-missing or imputed). All subjects with non-missing $\log(\text{NT-proBNP})$ at baseline at baseline will contribute to the ANCOVA model. The imputed $\log(\text{NT-proBNP})$ value from the ANCOVA is its predicted mean-value plus the estimated standard-deviation times a random number from a standard-normal distribution.
- D. Next: Back-transformation of the imputed values of $\log(\text{NT-proBNP})$ at baseline in step C above, and then categorisation, makes the factor NT-proBNP status (see Subsection 4.2.11.6) at baseline complete too.
- E. Next, the factor DM status at baseline will, when missing, be simulated from a logistic-regression model where “yes” (vs. “no”) for DM status at baseline depends on $\log(\text{NT-proBNP})$ at baseline, $\log(\text{UACR})$ at baseline, and albuminuria status at baseline (all three either non-missing or imputed). All subjects with a non-missing DM status at baseline, with a non-missing $\log(\text{NT-proBNP})$ at baseline, and a non-missing $\log(\text{UACR})$ at baseline will contribute to the logistic-regression model. The imputed DM status at baseline will be a random outcome from a binomial distribution with the probability of DM status at baseline being ‘yes’ is set to the estimated probability of DM status at baseline being ‘yes’, given by the logistic-regression model. Hereafter the factor DM status at baseline is also complete.
- F. Eventually, the factor SGLT2i use at baseline: It is not expected that the value of SGLT2i use at baseline be missing, so all covariates and factors are complete by now.

The 500 datasets will each be analysed with the same MMRM model as for the main analysis in Subsection 4.2.1.1. However, before being applied to the 500 datasets, the MMRM must be simplified to the same extent as was needed for the main analysis to converge, in terms of the simplification steps 1 to 5 in Subsection 4.2.1.1.

The MMRM will leave us with 500 regression results (regression-parameter estimates with standard-error). Before back-transformation from log-scale, Rubin's formulae will be applied to the 500 results and compile them into one estimate of the log-scale treatment-difference for "High" vs. "Placebo", together with a 95 % CI. Back-transformation from log-scale will then give an estimate, with a 95 % CI, of the treatment ratio for "High" vs. "Placebo". Yet another transformation will eventually give an estimate, with 95 % CI, of the relative treatment difference for "High" vs "Placebo", $([\text{treatment ratio}] - 1) \times (100 \%)$.

No p-value will be provided.

The analysis set will be the FAS.

Since off-treatment subjects without assessment in this analysis are assumed to behave basically as placebo subjects, missing UACR values are automatically modelled as missing not at random (MNAR), and from that aspect, this analysis challenges the main analysis, which assumes MAR. If the result from the main analysis and the ones from the sensitivity analysis will not sensibly match, the robustness of the results from the main analysis will be questionable.

4.2.1.3 Supplementary subgroup analyses

The following 16 subgroupings will be investigated:

- DM status at baseline
- Hypertension status at baseline (see Subsection 4.2.11.3)
- eGFR status, two categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, three categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, four categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, six categories, (see Subsection 4.2.11.4) at baseline
- Albuminuria status (see Subsection 4.2.11.1) at baseline
- sUA status, two categories, median-based, (see Subsection 4.2.11.5) at baseline
- sUA status, four categories, (see Subsection 4.2.11.5) at baseline
- NT-proBNP status (see Subsection 4.2.11.6) at baseline
- Race
- Age group (< 65 yr; ≥ 65 yr) at baseline
- Sex
- Geographic region (see Subsection 4.2.11.2)
- SGLT2i use at baseline
- Use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) (see Subsection 4.2.11.7) at baseline.

Each of the 16 subgroup analyses will be carried out exactly as for the main analysis in Subsection 4.2.1.1, except

1. that the subgrouping factor itself and the subgrouping-by-treatment interaction both will be added to the list of explanatory variables of the MMRM (if the subgrouping factor is already included, then only the interaction will be added), and
2. that a p-value for the subgrouping-by-treatment interaction will be given, and
3. that measures must be taken in case scarcity in any of the subgroups precludes convergence (collapsing of subgroups is not advisable, removing small subgroups is better), and
4. that measures must be taken in Step 5 in the model-simplification in Subsection 4.2.1.1 to prevent that the current subgrouping's main factor is not removed, and
5. that the subsequent estimates and CIs all are reported subdivided by current subgroups, and
6. that the corresponding p-values related to treatment differences will not be provided.

The CIs in item 5 above will, besides in one or more tables, also be presented in a forest plot.

Those subjects for which the grouping variable is missing will be excluded from the corresponding analysis.

The analysis set will be the FAS.

4.2.2 Primary endpoint: Change from baseline in UACR at 6 months (V8): other comparisons

The analyses of change from baseline in UACR at 6 months (V8) in this subsection focus on the following comparisons:

- “High” and “Intermediate” combined vs. “Allopurinol alone” **
- “Intermediate” vs. “Placebo”
- “Low” vs. “Placebo”
- “High” vs. “Allopurinol alone”
- “Intermediate” vs. “Allopurinol alone”
- “Low” vs. “Allopurinol alone”
- “Allopurinol alone” vs. “Placebo” **

Each of these seven (7) analyses will be carried out exactly as the main analysis in Subsection 4.2.1.1 except that the comparison “High” vs. “Placebo” is replaced by the current comparison.

For the comparison “High” and “Intermediate” combined vs. “Placebo”, the two treatment categories of “High” and “Intermediate” will be merged, forming one new temporary category.

The double asterisks (**) in the list above indicate where the tests of no treatment difference, together with the test of no treatment difference in Subsection 4.2.1.1 (“High” vs. “Placebo”), are controlled for multiplicity. See Subsection 4.2.10 below.

4.2.3 Secondary endpoints at 6 months (V8) and 12 months (V10)

4.2.3.1 Secondary endpoints at 6 months (V8)

For the secondary endpoints at 6 months (V8), there are four (4) endpoints, specifically

- Change from baseline in sUA at 6 months (V8),
- Change from baseline in eGFR at 6 months (V8),
- Change from baseline in S-creatinine at 6 months (V8), and
- Change from baseline in S/P-cystatin C at 6 months (V8).

and there are seven (7) comparisons requested for each endpoint, namely

- “High” vs. “Placebo”,
- “Intermediate” vs. “Placebo”,
- “Low” vs. “Placebo”,
- “High” vs. “Allopurinol alone”,
- “Intermediate” vs. “Allopurinol alone”,
- “Low” vs. “Allopurinol alone”, and
- “Allopurinol alone” vs. “Placebo”.

Thus, in this subsection, 28 analyses are laid down. Each such analysis will be carried out exactly as the main analysis in Subsection 4.2.1.1, except that the analyte “UACR” and the comparison “High” vs. “Placebo” are replaced by the current analyte and comparison, respectively.

The comparison “High” vs. “Placebo” for change from baseline in sUA at 6 months (V8) will also be analysed as in Subsection 4.2.1.3.

Please note that the two endpoints change from baseline in UACR at 6 months (V8) and change from baseline in sUA at 6 months (V8) also are secondary endpoints in the dose-response analyses. Instructions for the dose-response analyses are found in Subsection 4.2.9 below.

4.2.3.2 Secondary endpoints at 12 months (V10)

For the secondary endpoints at 12 months (V10), there are five (5) endpoints, specifically

- Change from baseline in UACR at 12 months (V10),
- Change from baseline in sUA at 12 months (V10),
- Change from baseline in eGFR at 12 months (V10),
- Change from baseline in S-creatinine at 12 months (V10), and
- Change from baseline in S/P-cystatin C at 12 months (V10),

These endpoints will be analysed with descriptive statistics only, except for change from baseline in UACR at 12 months (V10), where the treatment difference between double-capsule 24 mg treatment and double-capsule placebo treatment is estimated in the same way as the primary analysis, see Subsection 4.2.1.1 above,

1. except that the valid visits will be (V3), V4, V5, V6, V7, V8, V9, and V10,
2. except that a variable which is 1 at V10 if the subject was transferred to double-capsule regimen at V9, and 0 otherwise, will now be added to the model as an explanatory variable (modelling PA5-consenters vs non-PA5-consenters),
3. except that a variable which is 1 at V10 if the subject was transferred from a 3 mg single-capsule treatment to 24 mg double-capsule treatment at V9, and 0 otherwise, will also be added to the model as an explanatory variable (modelling the contribution from the ultimate dose 24 mg, vs 3 mg verinurad),
4. except that no p-value will be provided for the treatment difference (it is sufficient with a point estimate and a 95 % CI), and
5. except that there will be provided a p-value for a test of no double-capsule-vs-single-capsule effect.

Analysis set will be the FAS.

4.2.4 [Removed]

CCI

[Redacted]

[Redacted]

CCI

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

4.2.6 Safety assessments

All safety endpoints (see Subsection 3.3.4) will be analysed descriptively only. The analysis set will be the safety analysis set, unless otherwise specified.

4.2.6.1 Adverse events (AE)

- A. All serious adverse events (SAE) *occurring before day of randomisation visit (V3)* will be displayed in listings. This will be done for all subjects, not just for the subjects in the safety analysis set.
- B. All *in-study* AEs will be listed. The analysis set will be the safety analysis set.
- C. All *in-study* AEs will be summarised, by allocated treatment (see Subsections 2.1 above [safety analysis set] and 6.4 below). This will be summarised:
 1. all AEs,
 2. all AEs, by system organ class (SOC)/preferred term (PT),
 3. all AEs, most common (> 5 %), by SOC/PT,
 4. all AEs, most common (> 5 %), by PT,
 5. all AEs, by PT and maximum reported intensity,
 6. all AEs, by PT and relationship to investigational product (IP)
 7. all SAEs, by SOC/PT,
 8. all AEs with outcome death, by SOC/PT,
 9. all AEs leading to permanent discontinuation of IP, by SOC/PT, and
 10. all non-serious AEs, most common (> 5 %)

Presented will be the number and percentage of subjects with at least one AE of the type in question. The number that the percentage relates to (“the denominator”) will always be the total number of subjects allocated to the treatment in question. For items 1, 2, 7, and 10 above, the number of events of the type in question will also be presented.

For items 3 and 4 above, the PTs should be sorted, first after descending frequency, and then (i.e. when there is a tie) alphabetically.

When the AEs are to be summarised by SOC/PT of the Medical Dictionary for Regulatory Activities (MedDRA), then the latest version of the MedDRA dictionary must be used for the coding of the AEs.

The analysis set will be the safety analysis set.

- D. All *in-study* AEs will also be summarised in a separate overview table, by study period (see Subsection 4.2.11.8 below), and allocated treatment (see Subsections 2.1 above [safety analysis set] and 6.4 below). These categories of AEs will be summarised:
 1. all AEs,
 2. all SAEs,
 3. all AEs with outcome death,
 4. all AEs leading to permanent discontinuation of IP, and

5. all AEs with dose reduction.

Presented will be the number and percentage of subjects with at least one AE of the type in question. The number that the percentage relates to (“the denominator”) will always be the total number of subjects allocated to the treatment in question. Presented will also be the number of events of the type in question, except for items 3 (death) and 4 (IP discontinuation) [above](#). The analysis set will be the safety analysis set.

- E. In the same way as for the *in-study* AEs in item [D above](#), all *on-treatment* AEs will be summarised, by study period and allocated treatment. The analysis set will be the safety analysis set.
- F. Key subject information will be provided for all *in-study*
1. AEs with outcome death,
 2. SAEs, and
 3. AEs leading to permanent discontinuation of IP.
- The analysis set will be the safety analysis set.

4.2.6.2 Adjudicated events

- A. All adjudication-confirmed events *occurring before day of randomisation visit (V3)* will be listed. This will be done for all subjects, not just for the subjects in the safety analysis set.
- B. All *in-study* adjudication-confirmed events will be listed. The analysis set will be the safety analysis set.
- C. All *in-study* CV events sent for adjudication will be summarised by type of CV events, by allocated treatment (see Subsections [2.1 above](#) [safety analysis set] and [6.4 below](#)), and by time period (see Subsection [4.2.11.8 below](#)). Types of events sent for adjudication that are not AEs, include thromboembolic events and all planned cardiac surgery (modules ‘PROCCA’, ‘PROCNCVI’, ‘CERVENT’, ‘CIEVENT’). Presented will be the number and percentage of subjects with at least one event. The number that the percentage relates to (“the denominator”) should always be the total number of subjects allocated to the treatment in question. Presented will also be the number of events. The analysis set will be the safety analysis set.
- D. All *in-study* adjudication-confirmed events will also be summarised by allocated treatment (see Subsections [2.1 above](#) [safety analysis set] and [6.4 below](#)) and time period (see Subsection [4.2.11.8 below](#)). These categories of adjudicated events will be summarised:
1. all adjudication-confirmed events, by reported categories of adjudication-confirmed events,
 2. all adjudication-confirmed major CV events (MACE), by reported categories of MACEs,
 3. all adjudication-confirmed deaths (any type), by reported type of death,
 4. all adjudication-confirmed CV deaths, by reported type of CV death,

5. all adjudication-confirmed non-CV deaths, by reported type of non-CV death. Presented will be the number and percentage of subjects with at least one event of the kind in question. The number that the percentage relates to (“the denominator”) should always be the total number of subjects allocated to the treatment in question. Presented will also be the number of events of the type in question. The analysis set will be the safety analysis set.

E. In the same way as for the *in-study* events in items C and D above, all *on-treatment* adjudicated events will be summarised. The analysis set will be the safety analysis set.

4.2.6.3 S-creatinine elevations

In-study S-creatinine elevations will be summarised, by visit, with number and percentage of subjects in each category of S-creatinine elevations. The categories of S-creatinine elevations are:

- $1.5 \times \text{baseline} \leq \text{S-creatinine}$
- $1.5 \times \text{baseline} \leq \text{S-creatinine} < 2.0 \times \text{baseline}$
- $2.0 \times \text{baseline} \leq \text{S-creatinine} < 3.0 \times \text{baseline}$, or $\text{S-creatinine} \geq 3.0 \text{ mg/dL}$
- $\text{S-creatinine} \geq 3.0 \times \text{baseline}$, or $\text{S-creatinine} > 4.0 \text{ mg/dL}$

Here, ‘baseline’ refers to a baseline S-creatinine defined as the maximum non-missing S-creatinine value observed within 14 days prior to the first dose of randomized study medication; if no S-creatinine values exist in that time period, baseline S-creatinine will be set to missing. Please note that the four categories above are not mutually exclusive. The elevations will be both listed and summarised for the time periods in Subsection 4.2.11.8 below. S-creatinine elevations will also be listed.

Analysis set will be safety analysis set.

4.2.6.4 Potential Hy’s law

Elevated hepatic biochemistry could be identified by means of potential Hy’s law: $\text{AST} \geq 3 \times \text{ULN}_{\text{AST}}$ or $\text{ALT} \geq 3 \times \text{ULN}_{\text{ALT}}$, together with $\{\text{total bilirubin}\} \geq 2 \times \text{ULN}_{\text{Total bilirubin}}$. The ULN values will be provided by the laboratory.

Cases of *in-study* potential Hy’s law will be both listed and summarised. Plots will also be provided: each plot is a log-log scatter plot of maximum in-study (until V8 or V10) total bilirubin vs. maximum in-study (until V8 or V10) ALT, both in multiples of upper limit of normal (ULN), with horizontal and vertical lines indicating potential Hy’s law thresholds, i.e. $\text{ALT} = 3 \times \text{ULN}_{\text{ALT}}$ and $\{\text{total bilirubin}\} = 2 \times \text{ULN}_{\text{total bilirubin}}$. There will be provided five such plots, one per treatment arm, arranged in a panel if feasible, and there will be one such panel for V8 and one for V10. All the plots must have same size and axis ranges, for comparability.

The analysis set will be the safety analysis set.

4.2.6.5 The COVID-19 pandemic

The AZ Corporate Pandemic CSRHLD Table and Listing Templates will be followed.

Firstly, COVID-19 pandemic will be given as a reason for not randomized, for not treated once randomized, for treatment discontinuation, and for study discontinuation in the subject disposition, see Subsection 4.2.7.2 below. As for the subject-disposition summary-table in general, the analysis set will be the FAS.

Secondly, important protocol deviations (IPD) related to COVID-19 pandemic will be part of the IPD summary in Subsection 4.2.7.7 below. As for the IDP summary-table in general, the analysis set will be the FAS.

Thirdly, summary of COVID-19 disruptions will be provided, please cf. template ‘COVID summary3’ in the AZ Corporate Pandemic CSRHLD Table and Listing Templates. A COVID-19-related study-disruption is *any* change in the study conduct or data collection due to the COVID-19 pandemic. *Examples* of COVID-19 related study disruptions include

- the introduction of alternative monitoring approaches,
- changes to visit schedules, missed visits, changes to study procedures, and
- discontinuation of IP or distribution of IP to patients.

The analysis set will be the FAS.

Fourthly, subjects affected by the COVID-19 pandemic will be listed, cf. template ‘APL-COVID1’ in the AZ Corporate Pandemic CSRHLD Table and Listing Templates. The analysis set will be the FAS.

Fifthly, subjects with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic will also be listed, cf. template ‘APL-COVID2’ in the AZ Corporate Pandemic CSRHLD Table and Listing Templates. The analysis set will be the FAS.

4.2.6.6 Patient narratives

Programmed patient narratives will be produced for the following AEs and other events, irrespective of the events occurred before randomization, on treatment, or off treatment:

- all deaths,
- all other SAEs,
- all AEs leading to permanent discontinuation of IP,
- all AEs specifically targeted in the study and/or project (to be decided after DBL),
- all S-creatinine elevations (see Subsection 4.2.6.3),
- all cases of Hy’s law,
- all cases of potential Hy’s law (see Subsection 4.2.6.4),

- all cases of hypersensitivity (MedDRA SMQ *Hypersensitivity* broad),
- all cases of renal failure (MedDRA SMQ *Acute renal failure* broad) and
- all cases of down-titration.

The narratives are to be presented ‘by patient’, not ‘by event’. More guidance can be found in the AZ global guideline LDMS_001_00071172 *Patient safety narratives*.

4.2.6.7 Overdoses

Overdoses will be listed. The analysis set will be the FAS.

4.2.6.8 Vital signs, electrocardiogram (ECG), haematology, clinical chemistry, and urinalysis

Vital signs, ECG, haematology, clinical chemistry, and urinalysis data will be listed.

For tables, the following is minimum for vital signs, ECG, haematology, clinical chemistry, and urinalysis:

1. Vital signs over time (*in-study*).
2. ECG variables over time (*in-study*).
3. ECG evaluation over time (*in-study*).
4. ECG evaluation, last observation (not beyond V9) vs. baseline, shift tables (*on-treatment*).
5. ECG: QTcF and QTcF intervals, increase from baseline to last timepoint (not beyond V9) (*on-treatment*); not for 2nd interim analysis.
6. Haematology variables over time (*in-study*).
7. Clinical-chemistry variables over time (*in-study*).
8. Urinalysis variables over time (*in-study*).
9. Urinalysis, increase from baseline, not beyond V9 (*on-treatment*); for 2nd interim analysis only; [item 10 below](#) is for the CSR.
10. Urinalysis, maximum value vs. baseline, shift tables (*on-treatment*); for the CSR only; [item 9 above](#) is for 2nd interim analysis.
11. Haematology, changes outside predefined criteria – key subject information (*on-treatment*).
12. Haematology, changes vs. baseline, w r t extended reference limits – summary (*on-treatment*).
13. Clinical chemistry, changes outside predefined criteria – key subject information (*on-treatment*).
14. Clinical chemistry, changes vs. baseline, w r t extended reference limits – summary (*on-treatment*).
15. Urinalysis, changes outside predefined criteria – key subject information (*on-treatment*).
16. Urinalysis, changes vs. baseline, w r t extended reference limits – summary (*on-treatment*).

Suitable graphs will also be produced.

Analysis set will be the safety analysis set.

4.2.7 Other analyses

4.2.7.1 Demographics and baseline characteristics

This should be presented in the summary by randomised treatment (and total) of demographics and baseline characteristics:

- Age (yr)
- Age group (<65 yr, and ≥65 yr)
- Sex
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race
- Country
- Geographic region (see Subsection 4.2.11.2)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (kg/m²) at baseline
- Use of SGLT2i at baseline
- Use of ACEi and ARB (see Subsection 4.2.11.7) at baseline
- DM status at baseline
- Hypertension at baseline (see Subsection 4.2.11.3)
- UACR at baseline
- Albuminuria status (see Subsection 4.2.11.1) at baseline
- NT-proBNP at baseline
- NT-proBNP status (see Subsection 4.2.11.6) at baseline
- eGFR at baseline
- eGFR status, two categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, three categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, four categories, (see Subsection 4.2.11.4) at baseline
- eGFR status, six categories, (see Subsection 4.2.11.4) at baseline
- sUA at baseline
- sUA status, two categories, median based,(see Subsection 4.2.11.5) at baseline
- sUA status, four categories, (see Subsection 4.2.11.5) at baseline
- S-creatinine at baseline
- S/P-cystatin C at baseline
- Sub-study participation (stratifying sub-studies only; not the vascular-reactivity sub-study), four categories: No sub-study, Only MRI, Only PK, Both MRI and PK.

The analysis set will be the FAS.

4.2.7.2 Subject disposition

The subject disposition will include *at least* the following.

- Pre-screened

- Screened (defined as signed the screening informed consent)
- Randomised
- Not randomised and reasons for not randomised, including COVID-19 pandemic
- Randomised and treated
- Randomised and not treated and reasons for not treated, including COVID-19 pandemic
- Completed treatment
- Discontinued treatment and reasons for discontinuation, including COVID-19 pandemic
- Completed study
- Discontinued study and reasons for discontinuation, including COVID-19 pandemic
- Status w r t double-capsule regimen in PA5

Subject disposition (all subjects) will be given in a table, with number of subjects and percentage. For the interim analyses (Section 5), it must also be accounted for subjects still in the trial.

Regarding the COVID-19 related reasons for not randomised, for not treated once randomised, for treatment discontinuation, and for study discontinuation in the list above, please cf. template ‘COVID-summary1’ in the AZ Corporate Pandemic CSRHLD Table and Listing Templates.

4.2.7.3 Prior medications and concomitant medications

All medication will be coded with latest version of the WHO Drug Dictionary (WHO DD) code. Prior medication and concomitant medication will be summarised in tables (number and percentage of subjects), by treatment, anatomical-therapeutic-chemical (ATC) code, and generic name.

Partially missing medication start and stop dates will be imputed:

- If the year is present but the month and day are missing, then 01JAN will be imputed for the start date and 31DEC for the stop date.
- If the year and month are present but the day is missing, then 01 will be imputed for the start date and the last day of the month (28, 29, 30, or 31) for the stop date.

Medication start-dates and stop-dates with other missing-patterns will not be imputed and are deemed missing.

- If the medication start-date is missing or, else, falls strictly before the day of randomisation visit, then the medication in question is *prior*.
- Again, if the start-date is missing or, else, falls strictly before the day of randomisation visit, then the medication in question is *concomitant* if the stop-date is missing or, else, falls on the day of the randomisation visit or thereafter.

- If, on the other hand, the start-value is not missing and falls on the day of randomisation visit, on the last day on study, or between, then the medication in question is *concomitant*.
- A medication can thus be both *prior* and *concomitant*.

Concomitant medication (not prior medication) will be separated into two tables, allowed concomitant medications and disallowed/prohibited concomitant medications. Disallowed/prohibited medications are found in Table 10 of the protocol, v 5.0.

Analysis set will be the FAS.

4.2.7.4 Medical history and comorbid conditions

All medical conditions will be coded with latest version of the MedDRA code. Medical history and comorbid conditions will be summarised (number and percentage of subjects), by treatment, MedDRA system organ class (SOC), and MedDRA preferred term (PT).

Partial start-dates and stop-dates will be imputed as in [4.2.7.3](#)

Analysis set will be the FAS.

4.2.7.5 Compliance

Compliance rate for verinurad (allopurinol) for a subject will be obtained by summing up the estimated number of capsules (tablets) taken by the subject during the study and dividing it by the number of capsules (tablets) planned to be administered to the subject (expressed as a percentage), where the number to be administered is calculated over the subject's actual duration in the study and not the planned duration. A subject's actual duration is adjusted for potential dose reductions/interruptions and early treatment stopping.

Compliance rate will be summarised in table(s), by treatment.

The analysis set will be the safety analysis set

4.2.7.6 Exposure

Exposure for a subject will be derived as last dose date minus first dose date plus one day. It will be summarised in table(s), by treatment. The analysis set will be the safety analysis set.

4.2.7.7 Important protocol deviations

IPDs will be summarised in a table, specified in template AZTSP06 in the AstraZeneca Study-population table-templates (1 April 2021). Entries shall be adapted to match the COVID-19 entries in the 'COVID-summary2' template of the AZ Corporate Pandemic CSRHLD Table and Listing Templates.

Besides number and proportion of subjects experiencing at least one IPD (of various kinds), the number of IPD should also be given.

The analysis set will be the FAS.

4.2.7.8 Change from baseline in UACR vs. baseline sUA

Scatter plots will be provided at visits V4 through V10, where change from baseline UACR is plotted against baseline sUA, for each treatment arm at a time. Correlation coefficients will be given, but no inference related to them. For V8, the analyses will be sub-grouped by the following subgrouping variables:

- DM status at baseline,
- eGFR status, four categories, (see Subsection 4.2.11.4) at baseline,
- sUA status, four categories, (see Subsection 4.2.11.5) at baseline,
- Albuminuria status (see Subsection 4.2.11.1) at baseline.

Analysis set will be the FAS.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

4.2.9 Dose-response analysis

The dose-response relationship will be analysed only descriptively. The descriptive statistics will include, e.g., a mean plot (as a line plot) of observed response vs. dose, with superimposed box plots of the response variable at each dose level. The dose variable is dose (unit: 1 mg) of verinurad on top of 300 mg allopurinol. Thus, four (4) dose levels of verinurad are in scope here, namely 0 mg, 3 mg, 7.5 mg, and 12 mg. Here, the zero dose, i.e. 0 mg of verinurad, will be represented by the 300 mg allopurinol-monotherapy arm. The placebo arm will not contribute to this plot, but a boxplot of the observed responses in the placebo arm could be juxtaposed to the plot, relating to the same response axis as the plot, for reference.

The two endpoints to be investigated in the aforementioned dose-response analysis are change from baseline in log(UACR) at 6 months (V8) and change from baseline in log(sUA) at 6 months (V8). Both are secondary endpoints.

Analysis set will be the FAS.

CCI [REDACTED]

4.2.10 Formal testing and multiplicity

As said above, the following three tests will be conducted sequentially, each at significance level 0.1 (cf. Subsections 4.2.1.1 and 4.2.2), in this order:

- Change from baseline in UACR at 6 months (V8); “High” vs. “Placebo”; test of no treatment difference.
- Change from baseline in UACR at 6 months (V8); “High” and “Intermediate” combined vs. “Allopurinol alone”; test of no treatment difference.
- Change from baseline in UACR at 6 months (V8); “Allopurinol alone” vs. “Placebo”; test of no treatment difference.

The test sequence will stop as soon as a null hypothesis in the test sequence was not rejected. The first null hypothesis not rejected in the sequence and all null hypotheses not yet tested thereafter will be considered not rejected regardless their p-values, whereas all null hypotheses before that will be considered rejected. In this way the familywise error rate in the strong sense is kept under control, below 0.1. A separate table will display the course of this sequence of tests.

Multiplicity will not be controlled for in any other test in this study.

4.2.11 Some definitions

4.2.11.1 Albuminuria status

Albuminuria status is a dichotomous variable, based on the UACR value, with these categories:

1. **Microalbuminuria:** $30 \text{ mg/g} \leq \text{UACR} < 300 \text{ mg/g}$.
2. **Macroalbuminuria:** $\text{UACR} \geq 300 \text{ mg/g}$.

All randomized subjects should have either microalbuminuria or macroalbuminuria at baseline, so in all model-based analyses, the explanatory variable ‘albuminuria status at baseline’ should be truly dichotomous. However, for observations of albuminuria status outside baseline, a third category may be needed:

3. **Normal:** $\text{UACR} < 30 \text{ mg/g}$.

4.2.11.2 Geographic region

There are three (3) geographic regions defined in this study:

- **Europe:** Czech Republic, France, Hungary, Israel, Italy, Poland, Romania, Slovakia, Spain.
- **South Africa:** South Africa.
- **North America:** Mexico, USA.

China is not part of the trial anymore.

4.2.11.3 Hypertension status at baseline

The trichotomous variable “Hypertension status at baseline” has these three categories:

1. **No hypertension**

2. **Hypertension, controlled**
 3. **Hypertension, uncontrolled**
- (all at baseline).

‘**No hypertension**’ is when ‘Hypertension’ is not set to ‘Yes’ in ‘SPECHIS’ module.

‘**Hypertension, controlled**’ is when ‘Hypertension’ is set to ‘Yes’ in ‘SPECHIS’ module AND $SBP@baseline \leq 140$ mmHg AND $DBP@baseline \leq 90$ mmHg.

‘**Hypertension, uncontrolled**’ is when ‘Hypertension’ is set to ‘Yes’ in ‘SPECHIS’ module AND ($SBP@baseline > 140$ mmHg OR $DBP@baseline > 90$ mmHg).

We have to ignore that we, in principle, do not know if the hypertension, as assessed in the ‘SPECHIS’ module, is ongoing or not at baseline. However, it is considered highly unlikely that one recovers from hypertension. So, all hypertension assessed as such in the ‘SPECHIS’ module will be assumed to be ongoing at baseline.

4.2.11.4 eGFR status

eGFR values can be grouped into four different eGFR-status groupings (see [KDIGO 2013](#) for underlying groups G1, G2, G3, G3a, G3b, G4, G5):

- eGFR status with two categories:
 - $eGFR < 60$ mL/min/1.73m² (G3+G4+G5),
 - $eGFR \geq 60$ mL/min/1.73m² (G1+G2).
- eGFR status with three categories:
 - $eGFR < 60$ mL/min/1.73m² (G3+G4+G5),
 - 60 mL/min/1.73m² \leq $eGFR < 90$ mL/min/1.73m² (G2),
 - $eGFR \geq 90$ mL/min/1.73m² (G1).
- eGFR status with four categories:
 - $eGFR < 30$ mL/min/1.73m² (G4+G5),
 - 30 mL/min/1.73m² \leq $eGFR < 60$ mL/min/1.73m² (G3),
 - 60 mL/min/1.73m² \leq $eGFR < 90$ mL/min/1.73m² (G2),
 - $eGFR \geq 90$ mL/min/1.73m² (G1).
- eGFR status with six categories:
 - $eGFR < 30$ mL/min/1.73m² (G4+G5),
 - 30 mL/min/1.73m² \leq $eGFR < 45$ mL/min/1.73m² (G3b),
 - 45 mL/min/1.73m² \leq $eGFR < 60$ mL/min/1.73m² (G3a),
 - 60 mL/min/1.73m² \leq $eGFR < 75$ mL/min/1.73m² (G2),
 - 75 mL/min/1.73m² \leq $eGFR < 90$ mL/min/1.73m² (G2),
 - $eGFR \geq 90$ mL/min/1.73m² (G1).

4.2.11.5 sUA status

sUA values can be grouped into two different sUA-status groupings:

- sUA status with two categories, median-based and thus data-driven:
 - $sUA < \{\text{median of baseline sUA}\}$,
 - $sUA \geq \{\text{median of baseline sUA}\}$.
- sUA status with four categories:
 - $0 \text{ mg/dL} \leq sUA < 6 \text{ mg/dL}$,
 - $6 \text{ mg/dL} \leq sUA < 8 \text{ mg/dL}$,
 - $8 \text{ mg/dL} \leq sUA < 10 \text{ mg/dL}$,
 - $sUA \geq 10 \text{ mg/dL}$.

4.2.11.6 NT-proBNP status

NT-proBNP values can be grouped into a NT-proBNP-status grouping with two categories:

- $NT\text{-proBNP} < 360 \text{ pg/mL}$,
- $NT\text{-proBNP} \geq 360 \text{ pg/mL}$.

4.2.11.7 Use of ACEi and ARB

The use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is in this SAP to be interpreted as a categorical variable with four categories:

- Neither ACEi nor ARB,
- ACEi but not ARB,
- ARB but not ACEi,
- Both ACEi and ARB at the same time.

4.2.11.8 Study periods

Study periods for **CCI** AEs, adjudicated events, and S-creatinine elevations are:

1. V3—, i.e. the whole in-study period from day of V3 (included) and onward,
2. V3—V4, i.e. in-study from day of V3 (included) to day of V4 (excluded),
3. V3—V5, i.e. in-study from day of V3 (included) to day of V5 (excluded),
4. V3—V8, i.e. in-study from day of V3 (included) to day of V8 (excluded),
5. V3—V9, i.e. in-study from day of V3 (included) to day of V9 (excluded), and
6. V3—V10, i.e. in-study from day of V3 (included) to day of V10 (excluded).

4.2.12 Albuminuria status over time

Shift tables for albuminuria status (see Subsection 4.2.11.1 above) from baseline to visits V5, V8, V10, and EOT visit will be provided. Please note that, at baseline, there should be no subjects with albuminuria status “Normal”, but at any other visit, the status could very well be “Normal”.

Analysis set will be the FAS.

4.2.13 High-level results

After the second interim there may come a request for high-level results (HLR), together with a specification thereof.

5 INTERIM ANALYSES

Two interim analyses are planned to support internal decisions of the program development. These analyses will be unblinding, therefore, an independent team at Covance will conduct these analyses. These interim analyses are supposed to have no impact on the conduct of the study, and since there is no provision to stop the trial early because of any results from the interim analyses, no multiplicity adjustment will be required.

The first interim analysis will be performed no later than when 90 % of the subjects have completed 12 weeks of treatment after titration (V7). The second interim analysis will be conducted after all subjects complete 26 weeks of treatment after titration (V8).

The analyses below will be done to the extent there is enough data for a meaningful interpretation

5.1 The first interim analysis

The following analyses will be carried out in the first interim analysis.

- Demographics and baseline characteristics (Subsection 4.2.7.1), except UACR at baseline and cystatin-C at baseline if not in place at the first interim.
- Prior medications and concomitant medications (Subsection 4.2.7.3).
- Medical history and comorbid conditions (Subsection 4.2.7.4).
- Subject disposition (Subsection 4.2.7.2) which will have to account also for subjects who are still in the trial at the time for the first interim analysis.
- UACR will be analysed as in Subsection 4.2.1.1, except that the evaluation visit will be V7 and that the comparisons will be not only “High” vs. “Placebo” (as in 4.2.1.1), but also “High” and “Intermediate” combined vs. “Allopurinol alone” (as in 4.2.2) and “Allopurinol alone” vs. “Placebo” (also as in 4.2.2).
- Subgroup analyses of UACR as in Subsection 4.2.1.3 will be carried out for at least the subgrouping variables eGFR category (four categories) at baseline, sUA category (four categories) at baseline, DM status at baseline, and albuminuria status at baseline, if numerically feasible. Then forest plots could be useful. P-values should be avoided. Other subgrouping variables, as well as other comparisons than “High” vs. “Placebo”, may be investigated as needed.

- UACR, as well as sUA, eGFR, S-creatinine, and S/P-cystatin C, will also be summarized descriptively, in the same way as any other lab variable. UACR, and other variables too if deemed necessary, will have their tables subdivided by subgroups, at least for the subgrouping variables eGFR status (four categories) at baseline, sUA status (four categories) at baseline, DM status at baseline, and albuminuria status at baseline (see Subsection 4.2.1.3 for definitions and a list of subgrouping variables).
- All analyses on change-from-baseline UACR vs. baseline sUA in Subsection 4.2.7.8.
- All lab, descriptive statistics only.
- All PK as described in Subsection 4.2.8, descriptive statistics only (This was not carried out in the first interim).
- All AE, descriptive statistics only (Subsection 4.2.6.1), except on-treatment analyses (See item E in Subsection 4.2.6.1).
- All S-creatinine elevations, descriptive statistics only (Subsection 4.2.6.3)
- All ECG, descriptive statistics only
- Exposure, descriptive statistics only (Subsection 4.2.7.6)

The evaluation visits specified in Section 4 may have to be adjusted to best match the place in time for the interim. For instance, the first panel of plots in Subsection 4.2.6.4 may have to be moved from V8 to V6 to best mirror the status at the interim.

Any other analysis may be carried out on request, if feasible.

5.2 The second interim analysis

The analyses of the second interim analysis will comprise all analyses in Section 4, *except*

- all analyses where the evaluation visit is explicitly V10, the EOT visit, or the follow-up visit,
- all analyses where the study period (if any) is “V3–” (whole study period) or “V3–V10”, see items 1 and 6 in Subsection 4.2.11.8 (these intervals should instead be shortened to “V3–V9” or “V3–V8”, depending on the schedule of assessments in the protocol, when feasible),
- the sensitivity analysis in Subsection 4.2.1.2 (however, this sensitivity analysis should preferably not be excluded),
- the eGFR-slope analyses in Subsection 4.2.5.1,
- **CCI** [REDACTED]
- all analyses of tophi,
- all analyses of non-serious AEs, most common, in item C.10 in Subsection 4.2.6.1,
- the separate summary table of AEs in item D in Subsection 4.2.6.1,

- all analyses of adjudication-confirmed events (see item D in Subsection 4.2.6.2), unless already provided to the first interim analysis,
- key-subject-information for SAEs (see item F.2 in Subsection 4.2.6.1) and for AEs leading to permanent discontinuation of IP (see item F.3 in Subsection 4.2.6.1).
- all *on-treatment* analyses of AEs (item E in Subsection 4.2.6.1) and adjudicated events (item E in Subsection 4.2.6.2),
- all analyses of IPDs (see Subsection 4.2.7.7), but listings should be included,
- all patient narratives (see Subsection 4.2.6.6),
- all COVID-19 reports (see Subsection 4.2.6.5), and
- the subgrouping at V8 in the analysis of change-from-baseline UACR vs baseline sUA in Subsection 4.2.7.8.

Any reporting containing assessments/measurements beyond V9 should be avoided, except in listings. The sensitivity analysis in Subsection 4.2.1.2 should preferably be part of the second interim but may be excluded from the second interim because of its complexity. The number of tables, figures, and listings to be presented at the interim may be reduced ad hoc. As for the first interim analysis, the subject disposition will have to account also for subjects who are still in the trial at the time for the second interim analysis.

CCI



6 CHANGES OF ANALYSIS FROM PROTOCOL

6.1 Analysis sets

The protocol mentions the **per-protocol analysis set**, the **enrolled (analysis set)**, the **randomised (analysis) set**, and the **efficacy analysis set**. These four analysis sets will not be used in this SAP.

6.2 Dose-response modelling

Formal dose-response modelling will not be detailed in this SAP, as suggested in the protocol, but in a separate analysis-plan authored by AstraZeneca. AstraZeneca will be responsible for the formal dose-response modelling in this trial.

6.3 [Removed]

6.4 Clarification regarding ‘treatment received’

In Section 9.4.3 of the protocol (v 4.0) it says that all safety data will be summarised by treatment group based on the treatment received. In this SAP, we will let that mean that a subject – for the safety analyses – will be allocated to his/her randomised treatment, unless the

subject (erroneously) was given *one* other specific investigational treatment *for the whole duration of the study*, in which case the subject will be allocated to that other treatment instead. For instance, if a subject was randomised to “High” and received “Low”, the subject will be allocated to “Low” for the safety analyses if the subject received “Low” for the whole duration of the study, otherwise to “High”, the randomised treatment. Consequently, a subject that is switched from a treatment A to a treatment B during the trial will always be allocated to the randomised treatment for the safety analyses, regardless what treatments A and B may be.

6.5 Change in physical examination

The endpoint “change (deterioration) in physical examination” is an event endpoint and is supposed to be reported as an AE on the AE form of the eCRF. However, the AE form does not distinguish between physical-examination-related AEs and other AEs. Thus, no analyses will be suggested for this endpoint in this SAP.

6.6 Subgrouping variables for the supplementary analyses of the primary endpoint

The following assessments have been added to the list of subgrouping variables in Subsection [4.2.1.3](#).

- Hypertension status at baseline (see Subsection [4.2.11.3](#))
- eGFR status, four categories, (see Subsection [4.2.11.4](#)) at baseline
- eGFR status, six categories, (see Subsection [4.2.11.4](#)) at baseline
- sUA status, four categories, (see Subsection [4.2.11.5](#)) at baseline
- Use of ACEi and ARB (see Subsection [4.2.11.7](#)) at baseline
- SGLT2i use at baseline

The two subgroups $eGFR \leq 60 \text{ mL/min/1.73m}^2$ and $eGFR > 60 \text{ mL/min/1.73m}^2$ for the subgrouping variable ‘baseline $eGFR \leq 60 \text{ mL/min/1.73m}^2$ vs. $eGFR > 60 \text{ mL/min/1.73m}^2$ ’, mentioned in Subsection 9.4.2.4 of the protocol (version 0.3), are changed to $eGFR < 60 \text{ mL/min/1.73m}^2$ (G3+G4+G5) and $eGFR \geq 60 \text{ mL/min/1.73m}^2$ (G1+G2), respectively. This new categorisation adapts to the KDIGO 2012 GFR categories G1 through G5 (see [KDIGO 2013](#)), which the previous one does not.

6.7 Incidence of laboratory abnormalities

Incidence of laboratory abnormalities will not be summarised.

6.8 Secondary endpoints at 12 months (V10)

There are five (5) secondary endpoints at 12 month (V10), viz

- Change from baseline in UACR at 12 months (V10),
- Change from baseline in sUA at 12 months (V10),

- Change from baseline in eGFR at 12 months (V10),
- Change from baseline in S-creatinine at 12 months (V10), and
- Change from baseline in S/P-cystatin C at 12 months (V10).

In this SAP, they will all be considered exploratory endpoints, and they will be analysed with descriptive statistics only (see Subsection [4.2.3.2](#)).

6.9 [Removed]

6.10 eGFR slope at V9 and at end-of-treatment (EOT)

In this SAP, eGFR slope at V9 has been added as an endpoint. eGFR slope at end-of-treatment will not be considered an endpoint anymore, contrary to what is said in the protocol.

7 APPENDIX

7.1 References

1. **Leoncini et al 2002**

Leoncini G, Martinoli C, Viazzi F, Ravera M, Parodi D, Ratto E, et al: *Changes in renal resistive index and urinary albumin excretion in hypertensive patients under long-term treatment with lisinopril or nifedipine GITS*. – *Nephron*. 2002; 90(2):169—173.

2. **KDIGO 2013**

KDIGO: *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. – *Kidney Int., Supplements*; 2013, Vol 3, Issue 1.