AstraZeneca

Statistical Analysis Plan

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A Phase 3 Multicenter Open-label Maintenance Study to Investigate the Long-term Safety of ZS (Sodium Zirconium Cyclosilicate) in Japanese Subjects With Hyperkalemia

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Study Statistician

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Global Product Statistician

[redacted] Date

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZ	AstraZeneca
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD	Chronic Kidney Disease
CP	Correction Phase
CPS	Calcium Polystyrene Sulfonate
DAE	Adeverse Event leading to discontinuation of study drug
DBP	dialystolic blood pressure
DM	Diabetes Mellitus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HF	Heart Failure
IC	Informed Consent
IP	investigational product
i-STAT	A portable blood analyser
ITT	Intent-to-Treat
IxRS	Interactive Voice/Web Response System
LSMean	Least sqaure mean
MedDRA	Medical Dictionary for Regulatory Activities
MP	Maintenance Phase
QD	once daily
QOD	every other day

Abbreviation or special term	Explanation
RAASi	Renin angiotensin aldosterone system inhibitors
SAE	Serious Adverse Event
SAF	Safety analysis set
SBP	Systolic blood pressure
SD	Standard Deviation
SE	Standard Error
S-K	Serum potassium
SPS	Sodium Polystyrene Sulfonate
TEAE	Treatment Emergent Adverse Event
TID	three times daily
UACR	Urine Albumin-to-Creatinine Ratio
UPCR	Urine Protein-to-Creatinine Ratio
ZS	Sodium Zirconium Cyclosilicate

AMENDMENT HISTORY

Date	Brief description of change
	N/A
18-Dec-2018	Update the following points : - Added search criteria for comorbidities and RAASi - Updated sensitivity analyses for Central lab assay change for S-K - Updated sensitivity analyses for iSTAT potassium - Added subgroup analyse of S-K and AEs - Updated the summary of exposure - Added analysis of RAASi dose change as per protocol amendment - Added analysis of Questionnaire for QOD or QD regimen - Added Adverse events of special interest - Clarified “on-treatment” definition, especially for under QOD regimen - Added detail of an approach to IA
5-Feb-2019	Update the following points : - Clarified visit aping rule for unscheduled visit - Age/weight cut-offs were updated - Deleted summary for days per dose period for which interpretation is difficult - Added subgroup evaluation for S-K and AEs - Added < 2.5 mmol/L category for hypokalemia summary - Updated compliance calculation to provide more precise value
17-Jun-2019	-Added clarification for the visit mapping and for number of normokalemic days derivation. -Removed descriptive summary of 3-component summary scores for SF36v2, and clarified that scoring will be done based on the standard algorithm.

1. STUDY DETAILS

1.1 Study objectives

Primary Objective:	Outcome Measure:
Maintenance Phase To assess open-label, long-term (12 months) safety and tolerability for ZS in Japanese subjects with hyperkalemia (serum potassium ≥ 5.1 mmol/L).	Safety and tolerability as measured by adverse events reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements.

Secondary Objectives:	Outcome Measures:
Maintenance Phase • To evaluate the proportion of ZS-treated subjects in whom normokalemia can be maintained over prolonged periods of time, using an individually titrated dose (5 g every other day [or 2.5 g once daily], 5 g once daily, 10 g once daily or 15 g once daily)	• Proportion of patients who can maintain normokalemia (defined as S-K level of ≥ 3.5 and ≤ 5.0 mmol/L, inclusive) on ZS at each Maintenance Phase study visit • Proportion of patients with average S-K ≤ 5.1 mmol/L • Proportion of patients with average S-K ≤ 5.5 mmol/L • Proportions of patients who were normokalemic (S-K ≥ 3.5 and ≤ 5.0 mmol/L), hypokalemic (< 3.5 mmol/L), or hyperkalemic (> 5.0 mmol/L) at each Maintenance Phase visit. • Subject-level average S-K over certain period of time • Observed values at visit and change from baseline in S-K over time • Number of normokalemic days during Maintenance Phase • Change in S-K level from the last on-treatment Maintenance Phase visit to the End of Study (EOS)
• To explore the time course of S-Aldosterone and S-Bicarbonate	• Change from baseline in S-Aldosterone over time • Proportion of patients with normal S-Aldosterone • Change from baseline in S-Bicarbonate • Proportion of patients with normal S-Bicarbonate

Secondary Objectives:	Outcome Measures:
• To evaluate the health state in the study population using SF-36 v2.	• SF-36 v2 questionnaire
Correction Phase To assess efficacy, safety and tolerability of 10 g TID ZS in Japanese patients with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L).	• Observed values and change from Correction Phase baseline in S-K • Proportion of patients who achieved normokalemia at 24, 48 and 72 hours after start of dosing • Safety and tolerability as measured by adverse events reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements during Correction Phase

Exploratory Objective:	Outcome Measure:
Maintenance Phase Patient reported outcomes: To evaluate if patients prefer ZS QOD or OD using the patient questionnaire.	Patient questionnaire
Treatment period To explore change in doses and reasonings of the change of RAAS inhibitors during the treatment period.	• Proportion of subjects increased RAASi doses • Proportion of subjects who decrease or discontinued RAASi doses • Proportion of subjects who increased at least once RAASi due to each reason • Proportion of subjects who decreased/discontinued at least once RAASi due to each reason • Time to first reduction/discontinuation of RAASi

1.2 Study design

The study is an open label, single arm study with flexible dose regimen focused on assessing long-term safety and tolerability of ZS in Japanese subjects with hyperkalemia.

Correction Phase: If the subject is normokalemic (i-STAT [A portable blood analyser] potassium between 3.5 and 5.0 mmol/L, inclusive) on the morning of Correction Phase Study Day 2 after 3 doses of ZS 10 g, they will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID treatment (6 total doses). If the subject's i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, on the morning of Correction Phase Study Day 3, the subject will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID

treatment (9 total doses). If the subject's i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, on the morning of Correction Phase Study Day 4, the subject will enter the Maintenance Phase. If the i-STAT potassium value is still < 3.5 mmol/L or ≥ 5.1 mmol/L on the morning of Correction Phase Study Day 4, after 72 hours of TID treatment, the subject will be withdrawn from the study and referred to their normal health care provider for standard of care treatment. Subjects withdrawn from the Correction Phase of the study will return to the clinic 7 (± 1) days after their last dose of ZS for an End of Study (EOS) visit.

Maintenance Phase: Patients will initially be dosed with ZS at a starting dose of 5g QD. During the Maintenance Phase, the ZS dose may be increased up to 15 g QD or decreased down to 5g QOD (or 2.5 g QD) based on i-STAT potassium measurements as outlined in Table 1.

Table 1 Dose Adjustment during MP

Current dose	i-STAT Potassium Value (mmol/L)	Dose Adjustment
5g QOD or 2.5 g QD	≤ 2.9	Discontinue dosing
	3.0-3.4	Discontinue dosing
	3.5-5.0	No change
	5.1-6.5	5g QD
	>6.5	Discontinue dosing
5g QD	≤ 2.9	Discontinue dosing
	3.0-3.4	5g QOD or 2.5 g QD
	3.5-5.0	No change
	5.1-6.5	10g QD
	>6.5	Discontinue dosing
10g QD	≤ 2.9	Discontinue dosing
	3.0-3.4	5g QD
	3.5-5.0	No change
	5.1-6.5	15g QD
	>6.5	Discontinue dosing
15g QD	≤ 2.9	Discontinue dosing
	3.0-3.4	10g QD
	3.5-6.5	No change
	>6.5	Discontinue dosing

Throughout all phases of the study, most potassium values will be measured at fasting before taking ZS. Nothing should be taken by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications, for a minimum of 8 hours prior to the blood collection. Potassium level should be determined by both i-STAT and the Central Laboratory on all occasions. Treatment decisions (eg, dose titration, stopping rules) will be made based on

i-STAT potassium values, as these provide clinical sites with a real-time measurement, according to dose modification rules. Statistical analyses on the study data will in principle be based on S-K values as measured by the Central Laboratory.

Safety and tolerability will be assessed on an ongoing basis. Standard study assessments including blood potassium, clinical chemistry (including calcium, magnesium, sodium, phosphate, creatinine, bicarbonate, and blood urea nitrogen [BUN]), aldosterone, renin and hematology parameters, urinalysis, vital signs, physical examinations, and electrocardiograms (ECGs) will be assessed. All women of childbearing potential will have a urine pregnancy test prior to enrollment and at their End of Study (EOS) visit.

Stopping rules will be implemented to ensure subjects discontinue the study treatment and receive alternative therapy in case of significant hyperkalemia, hypokalemia, arrhythmias, or development of congestive heart failure or end stage renal failure.

1.3 Number of subjects

Sample size of in total 150 subjects to be enrolled to this study was determined so that at least safety data of 100 subjects treated by ZS as long as one year will be collected, assuming 35% drop out rate.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Efficacy and safety analysis sets will be defined for each of correction phase and maintenance treatment phase.

2.1.1 Enrolled subjects

All subjects who signed informed consent.

2.1.2 Full analysis sets

All efficacy analyses will be performed using an Intent-to-Treat (ITT) principle based on the full analysis sets.

FAS-CP : For the correction phase (CP), the full analysis set will include all patients that receive at least one dose of ZS during the correction phase and have any post-baseline correction phase S-K values.

FAS-MP : For the subsequent long-term maintenance phase (MP), the full analysis set will include all patients who receive at least one dose of ZS during maintenance phase and have any post-baseline maintenance phase S-K values.

2.1.3 Safety analysis sets

SAF-CP: For the correction phase, the safety analysis set will include all patients treated with at least one dose of correction phase ZS and had any correction phase safety data.

SAF-MP: For the subsequent long-term maintenance phase, the safety analysis set will include all patients treated with at least one dose of maintenance phase ZS and had any maintenance phase safety data.

2.2 Protocol deviations

Protocol deviations will be identified programmatically or manually prior to database lock. Subjects who deviate from important protocol conditions (e.g. selected inclusion/exclusion criteria) will be reported as having important protocol deviations.

Important protocol deviations would include but not limited to:

- Patients who received ZS but did not meet Inclusion/Exclusion criteria
- Patients who received prohibited concomitant medication or non-drug therapy
- Patients who received wrong ZS dose regimen (including incorrect up-/down-titration)
- Study drug compliance < 80% or > 120%.

No protocol deviations will lead to exclude subjects from analysis. All the efficacy analyses will be based on the FAS and all the safety analyses will be based on SAF for each phase.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary variables (Safety)

Safety and tolerability of long-term ZS treatment (starting with 5g QD, flexible titration between 2.5g QD (5g QOD) and 15g QD) in patients with hyperkalemia will be evaluated by the following safety measures :

- Adverse Events (AEs)
- Safety clinical laboratory assessments
- Vital signs
- ECGs

3.2 Secondary variables

3.2.1 Efficacy in Maintenance phase

Efficacy of long-term ZS treatment in patients with hyperkalemia will be evaluated by the following efficacy measures:

- Proportion of patients who can maintain normokalemia (defined as S-K level of ≥ 3.5 and ≤ 5.0 mmol/L, inclusive) on ZS at each Maintenance Phase study visit
- Proportion of patients with average S-K ≤ 5.1 mmol/L
- Proportion of patients with average S-K ≤ 5.5 mmol/L
- Proportions of patients who were normokalemic (S-K ≥ 3.5 and ≤ 5.0 mmol/L), hypokalemic (< 3.5 mmol/L), or hyperkalemic (> 5.0 mmol/L) at each Maintenance Phase visit.
- Subject-level average S-K over the certain period of time (as specified below)
  - entire MP [Day 2 to Day 362]
  - Month 3 to Month 12 [Day 82 to Day 362]
  - Day 2 to Month 3[Day 2 to Day 82]
  - Month 4 to Month 6 [Day 110 to Day 166]
  - Month 7 to Month 9 [Day 194 to Day 278]
  - Month 10 to Month 12 [Day 306 to Day 362]
- Observed values at visit and change from baseline in S-K over time up to Week 52[Day 362]
- Number of normokalemic days during Maintenance Phase
- Change in S-K level from the last on-treatment Maintenance Phase visit to the End of Study
- Change from baseline in S-Aldosterone over time
- Proportion of patients with normal S-Aldosterone
- Change from baseline in S-Bicarbonate over time
- Proportion of patients with normal S-Bicarbonate
- SF-36 v2 questionnaire

3.2.2 Efficacy in Correction Phase

Efficacy in the Correction Phase ZS treatment in patients with hyperkalemia will be evaluated by the following efficacy measures:

- Observed values and change from Correction Phase baseline in S-K through to 72 hours
- Proportion (and cumulative proportion) of patients who achieved normokalemia at 24, 48 and 72 hours after start of dosing

3.2.3 Safety in Correction Phase

Safety in the Correction Phase ZS treatment will be evaluated by the same variables as described in section 3.1.

3.3 Exploratory variables

- Patient questionnaire
- Proportion of subjects increased RAASi doses
- Proportion of subjects who decrease or discontinued RAASi doses
- Proportion of subjects who increased at least once RAASi due to each reason
- Proportion of subjects who decreased/discontinued at least once RAASi due to each reason
- Time to first reduction/discontinuation of RAASi

4. ANALYSIS METHODS

4.1 General principles

The SAS® software, version 9.2 or higher, will be used in order to generate all the statistical outputs.

Unless otherwise specified, all efficacy analyses will be carried out on the FAS and all safety analyses will be based on the SAF, for each study phase (CP or MP).

4.1.1 Objectives and hypotheses

The objectives of this study is to assessing the safety, tolerability and efficacy of long-term treatment up to 52 weeks with ZS flexible dose regimen (starting with 5g QD, up-/down-titration between 2.5g QD (5g QOD) and 15g QD). There are no confirmatory statistical testing in this study and all analyses will be interpreted in a descriptive manner.

4.1.2 Definitions

4.1.2.1 Baseline Value

For S-K, Correction Phase (CP) baseline value will be established by the mean of 2 different S-K values, recorded 60 minutes apart (to confirm qualification for study entry) on the Correction Phase (CP) Day 1. Maintenance Phase (MP) baseline value will be defined as the measurement taken in the morning of the day of entering maintenance phase (Visit 6, MP Day 1). Note that two types of baseline (CP baseline and MP baseline) are defined only for S-K.

For the other variables (excluding S-K), baseline value of a parameter (eg, safety laboratory test, ECG or vital signs, etc) is defined as the last assessment of that parameter immediately prior to the start of the first dose of ZS during the Correction Phase. Typically, the baseline refers to the measurements obtained within 1 day (24 hours) of start of correction phase ZS treatment.

4.1.2.2 Change and Percent Change from Baseline

Change from baseline to any Time (Day or Hour) *t* in is defined as follows:

$$C_{Time\ t} = M_{Time\ t} - M_{baseline},$$

where:

- $C_{Time\ t}$ is the change from baseline at Time *t*,
- $M_{Time\ t}$ is the measurement at Time *t*,
- $M_{baseline}$ is the measurement at baseline.

Percent change from baseline to any Time (Day or Hour) *t* is defined as follows:

$$P_{Time\ t} = 100 \times (M_{Time\ t} - M_{baseline}) / M_{baseline}.$$

Where $P_{Time\ t}$ is the percent change from baseline at Time *t*, and $M_{Time\ t}$ and $M_{baseline}$ are defined as above.

4.1.3 Visit/Time windows

In principle, analyses will based on **nominal visit basis,** only if scheduled visit is available. In absence of scheduled visit, the unscheduled visits and discontinuation visit will be mapped according the below windows and utilized for by-visit analysis (Table 2 and Table 3).

If scheduled visit is missing,

- If an unscheduled visit exists for that visit window, it will be used.
- If two or more unscheduled visits are available for the same window, the one closes to nominal target day will be used.

- If two unscheduled observations are equally close to target day, the last observation will be used.

As outlined in the table, S-K measurement taken within 1 day (2 days on QOD regimen) after last dose will be regarded as on-treatment and used in analysis. Unscheduled S-K measurement taken more than 1 day (2 days on QOD regimen) after last dose of ZS could be mapped to EOS (Follow up) visit.

Table 2 Visit window for correction phase

Study Visit	Nominal Day	Target Day	From	To
1	Screening (CP Baseline)		-	-1
2	CP Day 1 (CP Baseline)	1	1	1
3	CP Day 2	2	2	2
4	CP Day 3	3	3	3
5	CP Day 4	4	4	4
EOS	CP Follow Up	10	5	17

Table 3 Visit window for maintenance phase

Study Visit	Nominal Day	Target Day	From	To*
6	MP Day 1 (MP Baseline)	1	1	1
7	MP Day 2	2	2	3
8	MP Day 5	5	4	8
9	MP Day 12	12	9	15
10	MP Day 19	19	16	22
11	MP Day 26	26	23	39
12	MP Day 54	54	40	67
13	MP Day 82	82	68	95
14	MP Day 110	110	96	123
15	MP Day 138	138	124	151
16	MP Day 166	166	152	179
17	MP Day 194	194	180	207
18	MP Day 222	222	208	235
19	MP Day 250	250	236	263
20	MP Day 278	278	264	291

Study Visit	Nominal Day	Target Day	From	To*
21	MP Day 306	306	292	319
22	MP Day 334	334	320	347
23	MP Day 362	362	348	Last dose + 1 day (2 days, on QOD regimen)
EOS	MP Follow Up	last dose + 7 days	last dose +2 days (+3 days, on QOD regimen)	last dose + 14 days

*S-K measurements more than 1 day (2 days, on QOD regimen) after last dose will be regarded off-treatment and will be mapped to the EOS visit.

Note : Any available measurements regardless of scheduled or unscheduled will be taken into account when summarizing the incidence of certain event based on most extreme (lowest or highest) values in safety evaluation (e.g. analysis of incidence of hypokalemia, etc).

4.1.4 Last on-treatment

The last on-treatment value is defined as the last measurements taken within 1 day (2 days, on QOD regimen) after last ZS dose (scheduled or unscheduled). For by-visit summary, the last on-treatment measurement during the respective phase will be additionally displayed.

4.1.5 Handling of drop outs and missing data

4.1.5.1 Missing central lab individual measurements of S-K

In the event of missing S-K data from the central laboratory, the i-STAT data will be used to replace missing data by adjusting for the average paired difference between the central and i-STAT levels collected at the same visit. As illustration of the change methodology, if the mean difference between central laboratory and i-STAT assessments for all patients with both values available at the relevant visit is 0.12 mmol/L higher for the central laboratory assessment, then 0.12 mmol/L will be added to the i-STAT level to impute the missing central laboratory assessment.

The above imputation procedure for missing central lab S-K based on non-missing i-STAT level will be carried out separately for samples tested on or before 3rd-December-2017 and for samples tested on or after 4th-December-2017.

If both central lab S-K and i-STAT are missing, the measurement at that visit/timepoint will be left as missing.

4.1.5.2 Handling of early study discontinuation

For subjects who discontinue the study medication before completion, the last assessment will be mapped according to the algorithm outlined in section 4.1.3.

4.1.6 Descriptive summary of continuous variables

Descriptive summary of continuous variables includes n, mean, standard deviation (SD), median, minimum and maximum). In the summary of change or percent change from baseline values, 95% confidence interval (95%CI) for the mean (percent) change from baseline will be calculated based on t-distribution.

4.1.7 Descriptive summary of categorical variables

Descriptive summary of categorical variables will consist of frequencies and percentages.

4.1.8 Descriptive summary and analysis of binomial proportions

For proportions of responders (e.g. patients with normokalemia), percentage and its exact (Clopper-Pearson) 95%CI will be provided.

4.1.9 Repeated measures mixed model for log-transformed S-K

A longitudinal repeated measures analysis using direct likelihood will be performed. The SAS procedure PROC MIXED will be used. The dependent variable will be the log-transformed S-K values measured post-baseline during the MP. The least square means (LSMeans) and its 95%CIs for each visit (time point) as well as the average over certain period of time will be derived from the model by specifying appropriate contrasts. The model estimates (LSMeans and 95%CIs) will be back transformed to original scale.

The model will include the fixed categorical effect of Visit and fixed continuous covariate of CP baseline S-K, MP baseline S-K and baseline eGFR. Age category (<55, 55-65, >= 65 years) and binary indicators for presence of Heart Failure, CKD, Diabetes and RAASi use will also be included. An unstructured matrix of within-subject error variance covariance will be used. The denominator degrees of freedom will be calculated according to Kenward-Roger method.

4.2 Analysis methods

4.2.1 Study patients

4.2.1.1 Disposition of patients

The disposition of subjects for the enrollment period, correction phase treatment period, the maintenance phase treatment period and follow-up period will be summarized.

The summary of disposition for the enrolment period will include all Enrolled subjects (who signed informed consent).

The summary of disposition for correction phase will include SAF-CP. This summary will include subjects completing and discontinuing the correction phase treatment period.

The summary of disposition in the maintenance phase treatment will include SAF-MP. This summary will include subjects completing and discontinuing the maintenance treatment

period up-to Visit 17 (MP Day 194) and up-to Visit 23 (MP Day 362), broken down by reasons for discontinuation.

The summary of disposition in CP follow up period will include all subjects who discontinued correction phase or completed correction phase but did not enter MP. The summary of disposition in MP follow up period will include all subjects who discontinued or completed MP. For each, summary will include subjects completing and discontinuing the follow up period, broken down by reason for discontinuation.

4.2.2 Demographics and baseline characteristics

Demographic and other baseline characteristics, including disease-related characteristics will be summarized, using the SAF-CP as well as SAF-MP.

Demographic and baseline characteristics are listed in Table 4. Disease-related common baseline characteristics are listed in Table 5.

Table 4 Demographics

Characteristics	Summarized as	Categories
Sex	Categorical	Male, Female
Age	Categorical and Continuous	<65, >= 65 years <75, >= 75 years
Body Weight	Categorical and Continuous	< 65, >= 65 kg
BMI	Continuous	
Height	Continuous	
Race	Categorical	Asian, Other

Table 5 Disease-related characteristics

Characteristics	Summarized as	Categories
CP Baseline S-K	Categorical and Continuous	< 5.5 mEq/L, 5.5-< 6.0 mEq/L, >= 6.0 mEq/L
Baseline eGFR*	Categorical and Continuous:	<15 mL/min/1.73m2, 15-<30 mL/min/1.73m2 30-<60 mL/min/1.73m2 >= 60 mL/min/1.73m2
Comorbidity – Heart Failure	Categorical	Yes, No
Comorbidity - Diabetes	Categorical	Yes, No
Comorbidity - CKD	Categorical	Yes, No

Characteristics	Summarized as	Categories
RAAS Inhibitor Use	Categorical	Yes, No
Diuretic Use	Categorical	Yes, No
On peritoneal dialysis	Categorical	Yes, No

*eGFR derived by Japan guideline formula;

$$\text{eGFR}[\text{mL/min/1.73m}^2] = \text{SCr}[\text{mg/ dL}]^{-1.094} \times \text{Age}[\text{years}]^{-0.287} \left(\times 0.739 \text{ for female}\right)$$

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages will be calculated out of the total number of subjects in the analysis set (ie, each denominator includes the number of subjects with missing/unknown values for the characteristic).

Comorbidities will be based on medical history (ongoing), using the following search criteria:

- HF will be searched by standardised MedDRA query (SMQ) (narrow) “Cardiac failure”.
- DM will be searched by SMQ (narrow) “Hyperglycaemia/new onset diabetes mellitus”.
- CKD will be searched by SMQ (narrow) “Chronic kidney disease”.

Current medications were based on concomitant medication used at the time of 1st dose of ZS, using the following search criteria :

- Current RAASi use will be searched by anatomical therapeutic chemical (ATC) class ‘C09’ or ‘C03DA’
- Current Diuretic use will be ATC class ‘C03’, 'C02LG', 'C07CB', 'C09BA', or 'C09DA'

Medical history

The number (%) of subjects with each past and current medical histories as well as surgical history will be summarized by system organ class (SOC) and preferred term (PT) using SAF-CP as well SAF-MP.

4.2.3 Extent of Exposure

4.2.3.1 Study Medication

Correction phase

Duration of exposure (defined as the last CP dose date – first CP dose date + 1), and number of doses taken (at most 9) will be summarized by categorical/continuous descriptive statistics, using SAF-CP.

Maintenance phase

The following summary will be provided using SAF-MP.

The extent of exposure to study medication during the MP (defined as the last MP dose date – first MP dose date + 1) will be summarized with number (%) of subjects with certain duration, where the categorization would be 1-7, 8-30, 31-90, 91-180, 181-270, 271-360, and > 360. The mean (SD), median, and range of the number of days of exposure will also be presented. In addition, total subject-years/days will be calculated using the sum of the exposure to study medication for all subjects.

The extent of exposure to each ZS dose level during the MP will be defined as sum of the dose intervals (end date - start date + 1) during which that dose level is given. The extent of exposure to each ZS dose level will also be summarized using continuous summary statistics and total subject-years/days to each dose level. The summary will be presented also by subjects' maximum dose level.

Following summaries of exposure during MP will be provided to describe the distribution of dose level actually administered in the study:

- number (%) of subjects with at least one dose taken by dose level
- number (%) of subjects by mode dose level (dose level used for longest duration per subject), by maximum dose level, and by last dose level
- Summary statistics of mean daily dose (sum of all administered dose (g) divided by duration of exposure (day)) during entire maintenance phase
  Note: the drug interruption period will also be considered as part of duration of exposure (denominator) but will add "0" dose to the numerator.

Further, dose regimen on the target day of scheduled visit will be summarized with proportions of patients treated by each dose regimen on that day to show the general distribution of dose regimen over time. In addition, proportion of subjects with each sequence of dose change will be summarized, if considered meaningful.

4.2.3.2 Prior and concomitant medication

Prior medications are defined as medications taken with a start date that falls before the first dose of study medication (ZS) of Correction Phase.

Concomitant medications include medications that started prior to, but continued after, the first day of a study phase, or medication changes (including newly initiated medications) during a study phase.

All prior medication and concomitant medications will be coded with the WHO Drug Dictionary, and summarised by phase for their respective safety analysis sets.

4.2.3.3 Measurements of Treatment Compliance

Percent treatment compliance is calculated for the maintenance phase. For each type of medication, percent compliance is defined as the sum of ZS doses actually taken divided by the sum of dispensed ZS doses that should have been taken. A subject is considered compliant if percent compliance is ≥ 80% and ≤ 120%. In this calculation, period of temporary interruption will also be counted in the period when ZS should have been taken as assigned by IxRS.

4.2.4 Efficacy

4.2.4.1 Efficacy in the Maintenance Phase

Analysis of S-K related variables

- Proportion of patients who can maintain normokalemia (defined as S-K level of ≥ 3.5 and ≤ 5.0 mmol/L, inclusive) on ZS at each Maintenance Phase study visit

Number (%) of subjects who can maintain normokalemia at each Mainteance Phase study visit and last on treatment visit will be tabulated with binomial proportion and its 95%CI.

- Proportions of patients who were hypokalemic (< 3.5 mmol/L) or hyperkalemic (> 5.0 mmol/L) at each Maintenance Phase visit.

For each visit and last on treatment, patients will be classified to either normokalemic, hypokaelmic or hyperkalemic by their S-K value. Number and proportion for each category will be tabulated.

- Observed values at visit and change from baseline in S-K over time

Observed S-K values at each visit/last on treatment and changes from CP baseline and from MP baseline will be summarized by descriptive summary statistics. For changes from baseline, 95%CI will be also presented.

- Subject-level average S-K over certain period of time
- Proportion of patients with average S-K ≤ 5.1 mmol/L
- Proportion of patients with average S-K ≤ 5.5 mmol/L

Average S-K level per subject will be calculated over the certain period of time (as specified in section 3.2.1). Continuous summary statistics will be provided for each. In addition, number (%) of subjects meeting <= 5.1 or <=5.5 mmol/L will also be summarized with binomial proportion and its 95%CI.

- Model-based estimates for S-K over time as well as average S-K levels over certain period of time

The log-transformed S-K data will be analysed with mixed model as described in section 4.1.9. All post-baseline data will be included into the model. The LSMean and 95%CI at each timepoint as well as over certain period of time (as specified in section 3.2.1) will be produced using appropriate contrasts. The estimates and 95%CIs will back-transformed to original scale and tabulated.

- Number of normokalemic days during Maintenance Phase

The number of normokalemic days during the MP will be calculated assuming that the time interval between assessments is normokalemic only if both the beginning and end assessments for that time interval display normal S-K values. If an intermediate scheduled assessment time point is missing, then the scheduled assessment is regarded as not normokalemic. In order to determine this variable all scheduled or unscheduled fasting S-K will be take into calculation. Descriptive statistics and 95%CI for mean for the number of normokalemic days will be provided.

- Change in S-K level from the last on-treatment Maintenance Phase visit to the End of Study

To investigate if S-K increases after stopping treatment, change in S-K from last on-treatment visit to MP EOS (MP follow up) visit will be summarized with continuous summary statistics and 95%CI for mean.

Sensitivity analysis for missing S-K values

For the mean S-K over time, longitudinal repeated measures model specified above will serve as a sensitivity check to missing S-K values. It provides estimates of S-K over time *had subjects remained on ZS for planned 52 weeks* under the Missing At Random assumption.

Further sensitivity analyses may be conducted depending on the volume of missing data as well as on the reason of study discontinuation.

Sensitivity analysis with iSTAT potassium measurements

Since the ZS dose adjustment during study is based on iSTAT measurement, analyses with categorized values (e.g. proportion of subjects with normokalemia) are expected to be sensitive to which of S-K or iSTAT K are analysed.

Summary of Potassium value over time, proportion of subjects with normokalemia and number of normokalemic days will be repeated using iSTAT potassium measurements instead of S-K values provided by Central lab. Only observed iSTAT values measured within last ZS dose + 1 day (+ 2days on QOD regimen) will be used.

Sensitivity analyssi with iSTAT potassium measurements for Correction Phase will be also carried out as outlined in section 4.2.5

Analysis with S-K adjusted for assay change bias

Assay for S-K in Covance was updated during the study, on 4th December 2017. A sensitivity analysis will be performed by subtracting the average bias (0.208 mmol/L) between the old and the new assays from all the Central lab S-K measurements analysed by the new assay. Primary analysis will be repeated on this new dataset containing all original S-K measurements analysed by the old assay and the adjusted measurements analysed by the new assay, i.e.

- S-K (adjusted) =S-K (reported) for data measured by old assay
- S-K (adjusted) =S-K (reported) – 0.208 mmol/L for data measured by new assay

By doing this, the adjusted measurements will be on the same "level" as the S-K measurements analysed by the old assay, and results will reflect what could have been observed had the assay not been changed.

Summary of S-K over time as well as proportion of subjects (normokalemia, hyperkalemia, hypokalemia) will be repeated using S-K adjusted for assay change instead of S-K values provided by Central lab.

Subgroup analysis of S-K related variables

The summary of proportions (normokalemia, hyperkalemia, hypokalemia) by visit and mean change from baseline will be provided by the following subgroups :

- By Heart Failure (Yes, No)
- By CKD (Yes, No)
- By DM (Yes, No)
- By Baseline RAASi use (Yes, No)
- By Baseline Diuretics use (Yes, No)
- By Baseline eGFR (<30, 30-<60, >= 60)
- By Baseline S-K (< 5.5, 5.5 -< 6.0, >=6.0 mmol/L)
- By Baseline Weight (<65. >= 65 kg)
- By Age (<65, >= 65 years, < 75, >= 75 years)
- By Gender

Analysis of S-Aldosterone and S-Bicarbonate

- Change from baseline in S-Aldosterone over time

- Change from baseline in S-Bicarbonate over time

Observed values at each visit (including last on treatment) and changes from baseline will be summarized by descriptive summary statistics. For change from baseline, 95%CI will be also presented.

- Proportion of patients with normal S-Aldosterone

- Proportion of patients with normal S-Bicarbonate

Number (%) of subjects who can maintain normal S-Aldosterone levels and S-Bicarbonate, respectively, at each Maintenance Phase study visit and last on treatment visit will be tabulated with binomial proportion and its 95%CI. Normal reference ranges provided by Central laboratory vendor will be used for these analyses.

- SF-36 v2 questionnaire

In the CSR, only descriptive summary will be provided. Any further analyses of SF-36 v2 questionnaire will be reported outside the CSR. Note that the scoring for SF-36v2 will be based on standard algorithm using the validated software by OPTUM.

Descriptive summary at baseline and Week 52 will be provided for the following variables

  - eight subscale composite scores (Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH))

  - physical component summary (PCS) score and mental component summary (MCS) scores from standard 2-component model

Number (%) of patients with each category will be provided for the following variable :

  - Reported Health Transition score (HT) (compared to 1 year ago)

4.2.5 Efficacy in the Correction Phase

- Observed values and change from Correction Phase baseline in S-K

Descriptive summary for observed values and changes from baseline through to 24, 48 and 72 hours post dose as well as last on treatment value will be descriptively summarized.

- Proportion of patients who achieved normokalemia at 24, 48 and 72 hours after start of dosing

Number (%) of patients achieved normokalemia at 24, 48 and 72 hours post dose as well as last on treatment value with its 95%CIs will be provided.

Both analyses will be repeated with iSTAT potassium measurements.

4.2.6 Exploratory

- Patient questionnaire

Number (%) of patients falling in each questionnaire category will be presented.

RAASi dose change related variables

Baseline RAASi user will be determined based on the information collected on CRF (CM module). A patient is considered to be on RAASi, if (s)he used RAASi on the day of first CP dose (Day1) of ZS.

RAASi use at end of treatment will be determined based on the information collected on CRF(CM module). Patients are regarded as discontinued RAASi, if (s)he is no longer on RAASi at the end of treatment (last ZS dose date).

During the study, any dose change of RAASi will be recorded on the separate CRF module (RAASIT), with the corresponding reason for changes. While it is anticipated there will be various pattern of RAASi changes, investigators are guided to choose either of "increase", "decrease" or "no change", *relative to previous RAASi intensity*, based on whether their intention of treatment change was to intensify, to diminish, or neither.

Table 6 RAASi dose changes

For	Variable	Condition
Baseline RAASi user	Subjects who discontinued RAASi	- No RAASi medication at the end of ZS treatment
Baseline RAASi user	Subjects who increased RAASi doses	- at least one dose increase events - no dose decrease events
Baseline RAASi user	Subjects who decreased/discontinued RAASi doses	- at least one dose decrease events - no dose increase events
Baseline RAASi user	Subjects who did not change RAASi intensity	- no records of "increase" or "decrease" events during study.
Baseline RAASi user	Subjects who increased at least once RAASi due to each reason	at least one cause-specific increase events (e.g. "titration") regardless of trajectory of RAASi changes before or after that increase.

Table 6 RAASi dose changes

For	Variable	Condition
Baseline RAASi user	Subjects who at least once decreased/discontinued due to each reason	- at least one cause-specific decrease events (e.g. "high potassium") - regardless of trajectory of RAASi changes before or after that decrease
Baseline RAASi non-user	Subject who initiated RAASi	- at least one dose increase events - regardless of the trajectory of after that dose increase

For each of above category, proportion of subjects will be calculated.

Further, time to first reduction/discontinuation of RAASi will be presented with Kaplan Meier plot for baseline RAASi user. Subjects will be censored at the last day of ZS dose.

4.2.7 Safety

4.2.7.1 Adverse events

Adverse events will be classified by the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be considered Treatment-Emergent if onset is on or after first dose of ZS and on or before last dose of ZS + 1 day (+ 2days, on QOD regimen). AEs starting before 1st AEs with onset during correction phase and those with onset during maintenance phase will be separately summarized, unless otherwise specified. Adverse events starting before first dose of ZS or more than 1 day (+2days, on QOD regimen) after last dose of ZS will only be listed.

All Adverse events (including SAEs)

Summary of following TEAEs will be separately presented for Correction Phase as well as for Maintenance Phase by SOC and PT. Number and proportion of subjects with these events as well as the events rates will be provided.

- Most common AEs (i.e. reported by >= 2% of patients based on Preferred Term)
- Any AEs
- Deaths
- Serious AEs (SAEs)
- AEs leading to drug discontinuation (DAEs)
- AEs by maximal intensity

- AEs related to study drug

In addition, incidence of AEs by MP study period (Day 1-7, Day 8-30, Day 31-90, Day 91-180, Day 181-270, Day 271-360, After Day 360) will be presented.

Adverse events of special interest (AEOSI)

Oedema-related events

Oedema related event will be defined as any of the following events (PT): Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral and Peripheral swelling.

Cardiac Failure

Cardiac Failure will be searched by SMQ "Cardiac Failure" (narrow).

Hypertension

Hypertension will be searched by SMQ "Hypertension" (narrow).

Treatment-emergent Oedema-related events, Cardiac Failure and Hypertension will be summarized by PT using as number (%) of subjects with events as well as exposure corrected event rates.

Subgroup analysis of Adverse Events

Any treatment-emergent AEs stratified by age (<65, >= 65 years, <75, >= 75 years), gender, comorbidities (HF, CKD and DM), use of medications (RAASi and Diuretics), baseline S-K (<5.5, 5.5-<6.0, >= 6.0 mmol/L), baseline eGFR (<30, 30-< 60, >= 60 mL/min/1.73m^2) and baseline weight (<65, >= 65kg) will be provided by SOC and PT.

4.2.7.2 Clinical Laboratory evaluation

Change from baseline over time

For continuous variables, observed values and changes from baseline to each post-baseline visit (including last on-treatment value) will be summarized by descriptive statistics.

For categorical variables, shift table from baseline to post-baseline visit (including last on treatment value) will be summarized by number (%) of subjects with each category.

Laboratory abnormalities

The incidence of hypokalemia will be evaluated by tabulating the proportion of subjects in each study phase with a lowest S-K assessment (regardless of scheduled or unscheduled) <3.5 mmol/L (mild hypokalemia) and will be repeated for a more severe definition of < 3.0 mmol/L (moderate hypokaelmia) and of < 2.5 mmol/L (severe hypokalemia).

Other potentially clinically significant laboratory abnormalities will also be identified based on the most extreme (lowest and/or highest) post-baseline values and tabulated with number and proportion of subjects meeting each criterion.

Table 7 Potentially Clinically Significant Abnormalities for Laboratory Values

Variable	Unit	Low	High
Chemistry			
Calcium	mg/dL	< 7.0	> 11.0
Inorganic Phosphorus	mg/dL	< 2.0	> 6.5
Albumin	g/dL	< 2.0	> 6.0
Bicarbonate	mmol/L	< 15	> 35
Glucose	mg/dL	< 60	> 300
Potassium	mmol/L	< 3.0	> 6.0
Sodium	mmol/L	< 120	> 160
Total Protein	g/dL	< 4.0	> 10.0
Magnesium	mg/dL	< 0.9	> 4.0
ALP	IU/L	-	> 3xULN
GGT	IU/L	-	> 3xULN
AST	IU/L	-	> 3xULN
ALT	IU/L	-	> 3xULN
Total Bilirubin	mg/dL	-	> 3xULN
Hematology			
Hematocrit	%	< 28	> 55
Hemoglobin	g/dL	< 8	> 20
Platelet Count	x 10^9/L	< 50	> 600
WBC	x 10^9/L	< 2.0	> 14

Additional laboratory data summaries

Shift table for UACR categories

Shift table form subjects with UACR in categories of 0-< 30 mg/g (normoalbuminuria), 30-< 300 mg/g (microalbuminuria) and >= 300 mg/g (macroalbuminuria) will be summarized using baseline and last on-treatment values.

Shift table for eGFR categories

Shift tables for subjects with eGFR in categories of 0-< 15 mL/min/1.73 m^2, 15-<30 mL/min/1.73 m^2, 30-< 60 mL/min/1.73 m^2, >= 60 mL/min/1.73 m^2 will be summarized using baseline and last on-treatment values.

4.2.7.3 Vital signs

Summary statistics for changes from baseline over time (including last on treatment) for each parameters (SBP, DBP and body weight) will be provided.

In addition, potentially clinically significant abnormal changes at any time post-baseline will be summarized with number of subjects and proportions.

Table 8 Potentially Clinically Significant Abnormalities for Vital Signs

Parameter	Direction	Criterion
SBP	Low	Value <= 90 mmHg and decreased >= 20 mmHg from baseline
	High	Value >= 180 mmHg and increased >= 20 mmHg from baseline
DBP	Low	Value <= 50 mmHg and decreased >= 15 mmHg from baseline
	High	Value >= 105 mmHg and increased >=15 mmHg from baseline

4.2.7.4 ECGs

Number of subjects with clinically significant abnormality (as assessed by investigator) will be summarized for baseline and post-baseline visits. Summary for most extreme value and last on treatment evaluation will also be presented.

Summary statistics for changes from baseline over time (including last on treatment value) for each parameter (heart rate (HR), P, PR, QRS, QT and QTcF) will be provided. Here QTcF will be derived by below formula.

$$QTcF = \frac{QT}{(60 / \mathrm{HR})^{1/3}}$$

where, QT is in msec and HR is in bpm.

Abnormal prolongation of QTc (QTcF) will be summarized based on criteria specified in the table below. The most extreme (highest) value for a subject during treatment will be used this summary.

Table 9 Categorical evaluation of QTc prolongation

Parameter	Criterion
QTcF	>450 msec
	>480 msec
	>500 msec
Change from baseline in QTcF	>30 msec
	>60 msec

5. INTERIM ANALYSES

An interim analysis is planned in this study for the purpose of regulatory submission. The data cut-off for interim analysis will be when the last subject passed the Visit 17. The interim analysis will include safety/efficacy evaluation for the correction phase as well as safety/efficacy evaluation for maintenance phase up to Visit 17.

6. CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

7. REFERENCES (NOT APPLICABLE)

8. APPENDIX

8.1 Focus of Interim Analysis

As in section 5, one interim analysis (IA) including data up to Visit 17 is planned.

In principle, all planned analysis for safety and efficacy analyses will be carried out with the subset of data up to Visit 17, hence the target time period should be replaced as such.

In addition, the following variables will be scoped out since the data is expected to be immature at the time of IA.

- S-K analysis - change from last maintenance visit to follow up visit
- Questionnaire related to low dose regimen (5g QOD or 2.5g QD)
- SF36v2

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