AstraZeneca

Statistical Analysis Plan

Study Code	D9482C00002
Edition Number	2.0
Date	19-Feb-2018

A Phase 2/3 Multicenter, Dose-response Study to Assess Efficacy and Safety of ZS (Sodium Zirconium Cyclosilicate), in Japanese Patients With Hyperkalemia

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Study Statistician [redacted]

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Global Product Statistician [redacted]

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
CI	Confidence Interval
CKD	Chronic Kidney Disease
DM	Diabetes mellitus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
ITT	Intent-to-Treat
IP	Investigational Product
RAAS	Renin-angiotensin-aldosterone system
SAE	Serious Adverse Event
SAF	Safety Analysis Set
S-K	Serum potassium
S-Mg	Serum magnesium
S-Na	Serum sodium
S-PO4	Serum phosphate
TEAEs	Treatment-emergent Adverse Events
TID	Three times a day
ZS	Sodium Zirconium Cyclosilicate

AMENDMENT HISTORY

Date	Brief description of change
19-February-2018	- Baseline eGFR category (<60, >=60 mL/min/1.73 m^2) is taken out from primary and key secondary analysis models and from some subgroup analyses since the expected number of subjects in eGFR >= 60 mL/min/1.73 m^2 is quite small. - Imputation rule for missing central lab S-K based on non-missing i-STAT level is modified to reflect assay change in Central lab. - Sensitivity analysis to check the impact of S-K assay change are added. - Cardiac events and Hypertension are added as the AEs of special interest. - Heart Rate was taken out from vital sign section, as it is evaluated as one of the ECG parameters.

1. STUDY DETAILS

1.1 Study objectives

Primary Objective:	**Outcome Measure:**
To assess efficacy of 5 g three times daily (TID) and 10 g TID ZS versus placebo in Japanese patients with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L and ≤ 6.5 mmol/L).	Exponential rate of change in S-K values during the initial 48 hours of study drug treatment.

Secondary Objectives:	**Outcome Measures:**
Key secondary objective To evaluate the proportion of subjects who achieved normokalemia at 48 hours after start of dosing in ZS 5 g TID and 10 g TID groups when compared with placebo.	Key secondary variable Proportion of patients who achieved normokalemia at 48 hours after start of dosing
Other secondary objective To evaluate the efficacy of ZS 5 g TID and 10 g TID compared with placebo from various aspects.	Other secondary variables • Exponential rate of change in S-K values during the initial 24 hours of study drug treatment • Proportion of patients who achieved normokalemia at 24 hours after start of dosing • Proportion of patients who achieved normokalemia at each scheduled potassium assessment time-point after start of dosing • Mean change and mean percent change from baseline in S-K values at all measured time intervals post dose • Time to normalization in S-K values (normalization defined as S-K values between 3.5 and 5.0 mmol/L, inclusive).

Safety Objective:	**Outcome Measures:**
To assess safety and tolerability of 5 g TID and 10 g TID ZS versus placebo in Japanese patients with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L and ≤ 6.5 mmol/L).	Safety and tolerability as measured by adverse event reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements.

1.2 Study design

This is a randomized, double-blind, parallel group, multicentre, Phase 2/3 study to determine the efficacy and safety of ZS 5g TID and 10g TID versus placebo for correction of hyperkalemina in Japanese patients.

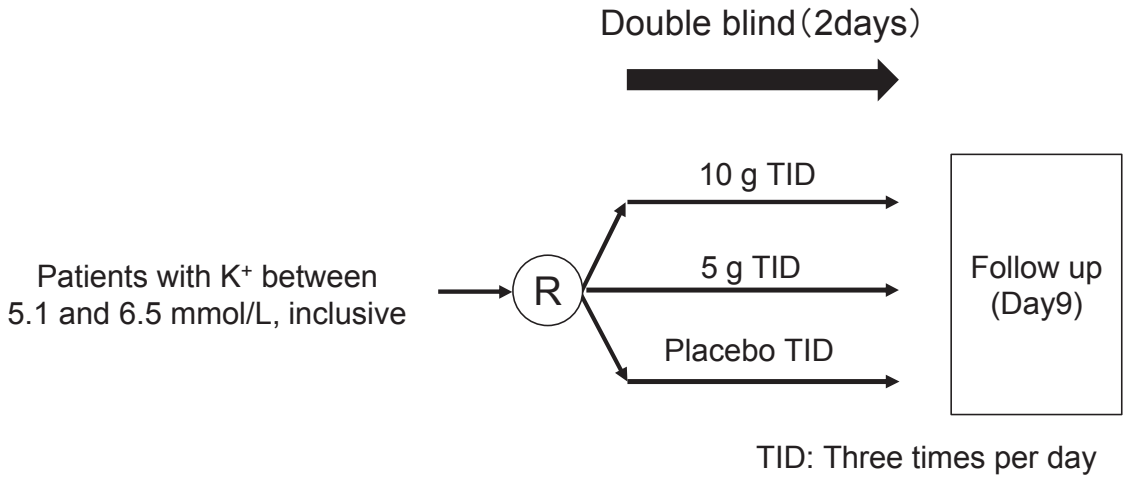
Patients not receiving any therapy for hyperkalemia and with 2 consecutive i-STAT (A portable blood analyser) potassium values of ≥ 5.1 mmol/L and ≤ 6.5 mmol/L will be enrolled and randomized 1:1:1 to receive ZS 5 g, ZS 10 g, or placebo TID for 48 hours. Randomization will be stratified by screening eGFR (< 60, >=60 mL/min/1.73m2) so that proportion of subjects with eGFR >= 60 mL/min/1.73m2 will not exceed 25% of the entire randomized subjects.

Throughout the study most potassium values will be measured at fasting before taking study drug. Nothing should be taken by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications, prior to the blood collection for a minimum of 8 hours. Potassium level should be determined by both i-STAT and the Central Laboratory on all occasions. Treatment decisions (eg, stopping rules) will be made based on i-STAT potassium values, as these provide clinical sites with a real-time measurement. Statistical analyses on the study data will in principle be based on serum potassium (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]) and hematology parameters, urinalysis, vital signs, physical examinations, and electrocardiograms (ECGs) will be assessed during the study at the time points specified in the assessments schedule. 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, or significant cardiac arrhythmias.

Figure 1 Study flow chart



1.2.1 Study Plan

Table 1 provides an overview of the procedures at each visit in this study. Further details are provided in the protocol.

Table 1 Study Plan

Study Visit	**Visit 1**	**Visit 2[6]**	**Visit 3**	**Visit 4**	**EOS[5]**
Study Day	**Screening**	**Day 1[6]**	**Day 2**	**Day 3**	**Day 9[5]**
Written informed consent	X				
Eligibility criteria		X			
Demographics	X				
Medical History		X			
Physical exam including weight		X			X
Randomization		X			
Access IVRS/IWRS	X	X			
Study drug (IP) dispensation		X			
Study drug (IP) administration		X	X		
ECG		X		X	X
Vital signs		X		X	X
Concomitant medications		X	X	X	X
Adverse events		X[7]	X	X	X
eGFR	X				
Potassium[1]		X[2]	X[3]	X	X

Table 1 Study Plan

Study Visit	Visit 1	Visit 2[6]	Visit 3	Visit 4	EOS[5]
Serum Chemistry[1]		X		X	X
Hematology[1]		X		X	X
Urinalysis[1]		X		X	X
Urine HCG		X[4]			X[4]
IP Reconciliation				X	

1. All blood potassium samples are analyzed by i-STAT and by the Central Laboratories on all occasions. Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting and before administration of study drug. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible
2. Potassium will be measured twice 60 (±10) minutes apart within 1 day prior to first dose administration, and prior to, 1, 2 and 4 hours (±15 min) after administration of the first dose of study drug on Day 1. Potassium will be measured again at 90 minutes after taking the second dose for patients with i-STAT potassium ≥6.1 mmol/L or <4.0 mmol/L 4 hours after the first dose
3. Potassium will be measured predose (0 hour), 1 and 4 hour (±15 min) after the first dose on Day 2 (Visit 3)
4. U-HCG will be performed exclusively for women of childbearing potential. Samples will be analysed locally, and the data will not need to be collected in the database. Pregnant women are excluded from the study.
5. The End of Study (EOS) visit will occur 7±2 day after the last administration of IP.
6. Baseline parameters should be measured/collected no earlier than 1 day prior to administration of the 1st dose of study drug on Day 1 (Visit 2). Visits 1 and 2 may be combined into a single visit on the same day.
7. AEs will be collected after the patient has signed informed consent, so during the Day 1 (Visit 2), investigator need to check if any AE happened since from inform consent

1.2.2 Assessment schedule of S-K

Blood samples for determination of potassium will be taken at the times indicated in the Study Plan (see Table 1). Potassium samples will be analyzed locally using i-STAT devices, and serum samples will be prepared and shipped to the Central Laboratory. All serum samples should be examined and any hemolyzed samples MUST be redrawn. In the event that hemolyzis or other artefacts are suspected based on the reported i-STAT result the sample may be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF. Table 2 shows the collection times of serum Potassium.

Table 2 Summary of Serum Potassium Collection Times

Study Day	Time	Central Laboratory	i-STAT
-1 ~ 1	1st assessment to confirm qualification (within 1 day of the first administration of study drug)	X	X
	1 hour post 1st assessment	X[1]	X

Table 2 Summary of Serum Potassium Collection Times

Study Day	Time	Central Laboratory	i-STAT
1	0 hour (pre-dose)	X	X
	1 hour post Dose 1	X	X
	2 hours post Dose 1	X	X
	4 hours post Dose 1	X	X
	90 minutes post Dose 2	X[2]	X[2]
2	0 hour (pre-dose)	X	X
	1 hour post Dose 1	X	X
	4 hours post Dose 1	X	X
3	0 hour	X[1]	X
EOS	0 hour	X[1]	X

1 S-K analyzed as part of the serum chemistry assessment.
2 Sample only collected if i-STAT potassium value at the 4-hour post Dose 1 time point was ≥ 6.1 or <4.0 mmol/L.

1.3 Number of subjects

Approximately 102 patients will be randomized to ZS 5g TID, ZS 10g TID, and Placebo with 1:1:1 ratio.

Sample size for the exponential rate of change during the study is calculated based on a random slope model, with parameters estimates based on the ZS-003 data, and here it is assumed that K measurement schedule is same as that in study 003 correction phase, i.e. K is measured at Baseline(0),1,2,4,24,25,28 and 48 hours post first dose. When the model is fit to the ZS-003 data (for only Placebo, ZS5g TID, ZS10g TID groups), with time measured in days, the variance of the slope was 0.001053, the variance of intercept was 0.004237, and covariance between intercept and slope was -0.00065, and the residual variance was 0.003980. Based on these parameters, 34 patients in each ZS dose and Placebo group would provide more than 95% power to detect difference of slopes of 0.055/day (assumed for ZS 10g TID vs. Placebo) and approximately 83% power to detect the difference in slopes of 0.030/day (assumed for ZS 5g TID vs. Placebo), respectively.

For the proportion of normokalemic patients at the end of dosing, 34 patients in each ZS dose and Placebo would provide approximately 90% and 66% power to detect the difference in 10g TID vs. Placebo and 5g TID vs. Placebo with nominal significance level of 0.05, respectively, according to Fisher's exact test. Here it was assumed that proportion of normokalemic patients at 48 hours are 47.8%, 77.6% and 86.4% for Placebo, ZS 5g TID, and ZS 10g TID, respectively.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Enrolled subjects

All subjects who signed informed consent.

2.1.2 Full analysis set (FAS)

The FAS includes all patients randomized in the study. Patients will be analysed according to their randomized treatment assignment. Patients without any post randomization data will not be used in any of the inferential analyses, but will be accounted for in summary statistics tables.

All efficacy analyses will be performed using the full analysis set (FAS).

2.1.3 Safety analysis set (SAF)

The safety analysis set will include all patients who took at least one dose of investigational products (IP) during the study. Patients will be analysed according to the actual treatment they received.

2.2 Protocol deviations

Protocol deviations will be identified programmatically or manually and reviewed in a blinded fashion and documented prior to the un-blinding the study. Subjects who had any important protocol deviations will be summarized by treatment group. Important protocol deviations will include but not limited to:

Important protocol deviations would include but not limited to:

- Patients who received study drug but did not meet Inclusion/Exclusion criteria
- Patients who received prohibited concomitant medication or non-drug therapy
- Patients who received wrong study drug
- Study drug compliance < 80% or > 120%.

No protocol deviations will lead to exclusion of randomized subjects from FAS. All efficacy analysis will be carried out with FAS following Intent-to-treat principle.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary efficacy variable

Primary efficacy variable is the exponential rate of change in S-K values during the initial 48 hours of study drug treatment.

3.2 Key secondary efficacy variable

Key secondary efficacy variable is proportion of patients who achieved normokalemia (S-K between 3.5 and 5.0, inclusive) at 48 hours after start of dosing.

3.3 Other secondary efficacy variables

Following secondary efficacy variables will be evaluated.

- Exponential rate of change in S-K values during the initial 24 hours of study drug treatment
- Proportion of patients who achieved normokalemia at 24 hours after start of dosing
- Proportion of patients who achieved normokalemia at each scheduled potassium assessment time-point after start of dosing
- Mean change and mean percent change from baseline in S-K values at all measured time intervals post dose
- Time to normalization in S-K values (normalization defined as S-K values between 3.5 and 5.0 mmol/L, inclusive).

3.4 Safety variables

Safety evaluation will be done with the following variables.

- Adverse events
- Safety Laboratory parameters
- ECGs
- Vital Signs

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 Safety set. Efficacy summary results during the treatment phase will be presented based on randomized treatment group (ZS 10g TID, ZS 5g TID or placebo). Safety summary results will be presented based on treatment they actually received. For Safety analysis, if a patient receives more than one treatment, they will be analysed according to the highest dose of study medication received.

Continuous variables will be summarized by descriptive statistics, including number of non-missing observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages. Results of statistical analyses will be presented using a 95% confidence interval (CI) and two-sided p-value, unless otherwise stated.

4.1.1 Objectives and hypotheses

The primary objective of this study is to demonstrate the superiority of ZS 10g TID and 5g TID to placebo in correction of hyperkalemia, as measured by the exponential rate of change through to 48 hours. Here, the exponential rate of change refers to the slope coefficient when longitudinal S-K measurements in log scale were regressed on time. The detail about model specification is provided in section 4.1.5.

The null hypothesis family is composed of two elementary hypotheses.

$H_{0,L}: \beta_P = \beta_L$ $H_{0,H}: \beta_P = \beta_H$

The alternative hypotheses are complements of them.

$H_{A,L}: \beta_P \neq \beta_L$ $H_{A,H}: \beta_P \neq \beta_H$

, where β_P , β_L , and β_H are exponential rate of change in Placebo, ZS 5g TID group, and ZS 10g TID group, respectively.

To protect family wise error rate (FWER) at 5%, hierarchical testing strategy will be employed. Confirmatory testing will proceed with the sequential order as specified below. Each individual statistical comparison will be conducted with two-sided significance level of 0.05.

Step 1: Compare exponential rate of change through 48 hours between ZS 10g TID vs. Placebo,

Step 2: Compare exponential rate of change through 48 hours between ZS 5g TID vs. Placebo.

4.1.2 Definitions

4.1.2.1 Baseline Value

For S-K, baseline value will be established by taking the mean of 2 different S-K values, recorded 60 minutes apart (to confirm qualification for randomization) and then averaged with the last S-K value taken just before administration of the first dose (0-hr) on Study Day 1.

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 prior to the start date and time of the first dose of the double-blind study medication.

4.1.2.2 Change and Percent Change from Baseline

Change from baseline to any Time *t* in correction phase double-blind treatment period 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 *t* in correction phase double-blind treatment period 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 windows and Time mapping

In principle, efficacy analyses will be based on nominal scheduled visit/time basis in efficacy evaluation. For the safety evaluation of incidence of events (e.g. hypokalemia) any post-baseline measurements regardless of scheduled or unscheduled will be included in analyses.

The scheduled S-K time will be mapped to time in hours relative to first dose of ZS to include in efficacy analysis model. S-K Measurements taken after Hour 48 (Day 3, 0 hour) will not be included in main efficacy analysis, but EOS (Day 9) visit will be separately presented.

Table 3 Time mapping for serial S-K measurements

Study Day	Time	Mapped time (Hours) for Analysis
-1 ~ 1	1st assessment to confirm qualification (within 1 day of the first administration of study drug)	0*
-1 ~ 1	1 hour post 1st assessment	(Baseline)
1	0 hour (pre-dose)	
1	1 hour post Dose 1	1
1	2 hours post Dose 1	2
1	4 hours post Dose 1	4
1	90 minutes post Dose 2	5.5
2	0 hour (pre-dose)	24
2	1 hour post Dose 1	25
2	4 hours post Dose 1	28
3	0 hour	48

* Baseline S-K will be derived as outlined in section 4.1.2.1

4.1.4 Handling of drop outs and missing data

4.1.4.1 Missing central lab 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 timepoint. 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.

4.1.4.2 Handling early study discontinuation

Whether subjects completed or discontinued the study, all available data taken up to Hour 48 (Day 3, 0 hour) will be included in the efficacy analysis. The EOS visit (Day 9 or last dose + 7 days) will be additionally displayed in the by-visit summary.

4.1.5 Random slope (coefficient) model for log-transformed S-K

Exponential rate of change in S-K through to T (=48 or 24) hours will be analysed with the following mixed effect model (random slope model). SAS procedure PROC MIXED will be used.

$$Ln(Y_{ijk}) = (\alpha + a_{ij}) + (\beta_0 + \beta_1 L_i + \beta_2 H_i + b_{ij}) \cdot t_k + \varepsilon_{ijk}$$

Where

- Y_{ijk} is the k_{th} measurement (at Time t_k) of subject j in treatment group i
- α is the fixed intercept
- a_{ij} is random intercept for subject j in treatment i
- β_0 is fixed slope on time t for reference group (Placebo)
- β_1 is fixed slope difference of ZS 5g TID to reference group (Placebo)
- β_2 is fixed slope difference of ZS 10g TID to reference group (Placebo)
- L_i =1 if subject is in ZS 5g TID and L_i=0 otherwise.
- H_i = 1 if subject is in ZS 10g TID and H_i=0 otherwise
- b_{ij} is random slope on time t for subject j in treatment i
- Discrete Time t_k spans as follows, and will be regarded as continuous variable in the models.
  - from 0 to 48 hours (0, 1, 2, 4, 5.5,24, 25, 28, and 48 hours) in primary analysis model,
  - from 0 to 24 hours (0, 1, 2, 4, 5.5, and 24 hours) in secondary analysis model

Subject-level random effects (a_{ij} and b_{ij}) are assumed to be bivariate normally distributed with mean zeros, independent of random error. An unstructured covariance will be specified in MIXED procedure. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The estimate of treatment difference in slopes (coefficients for the time x treatment interaction for each dose) with its 95%CI as well as two-sided p-values for pairwise comparison to placebo will be presented for both ZS 10g TID and ZS 5g TID groups.

4.1.6 Logistic regression model for responder analysis

Dichotomous variables (e.g. proportion of patients who achieved normokalemia at 48 hours after start of dosing) will be analysed with logistic regression model, including treatment as a factor and baseline S-K as a covariate. Subjects with missing S-K at that time point will be counted as non-responders. Odds ratio and its 95%CI as well as nominal two-sided p-values will be presented for each pairwise comparison (ZS 10g TID vs. Placebo and ZS 5g TID vs. Placebo).

4.1.7 Kaplan Meier plots

Kaplan-Meier plots of time to event variables (e.g. time to normokalemia) will be displayed by treatment group.

4.1.8 Nonparametric test for time to event variables

Time to event variables (e.g. time to normokalemia) will be analysed with log-rank test and nominal p-value will be provided for pairwise comparisons for each ZS dose vs. Placebo.

4.1.9 Descriptive summary of continuous variables

Descriptive summary of continuous variables includes n, mean, standard deviation (SD), median, minimum and maximum.

4.1.10 Descriptive summary of categorical variables

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

4.2 Analysis methods

4.2.1 Populations

4.2.1.1 Disposition

The disposition of subjects for the enrollment period, double-blind 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 double-blind treatment period will include FAS. This summary will include subjects completing and discontinuing the double-blind treatment period, broken down by reason for the discontinuation.

The summary of disposition for follow up period will include FAS. This summary will include subjects completing and discontinuing the follow up period, broken down by reason for discontinuation.

4.2.1.2 Demographics and baseline characteristics

Demographic and other baseline characteristics, including disease-related characteristics will be summarized by treatment group and overall, using the FAS.

Demographic and baseline characteristics are listed in Table 4. Other disease related baseline characteristics are listed in Table 5.

Table 4 Demographics

Characteristic	Summarized as	Categories
Sex	Categorical	Male, Female
Age	Categorical and Continuous	< 55 years 55-64 years >= 65 years
Body Weight	Categorical and Continuous	< 50, >= 50 kg
BMI	Continuous	-
Height	Continuous	-
Race	Categorical	Asian, Other

Table 5 Other baseline characteristics

Characteristic	Summarized as	Categories
Baseline S-K	Categorical and Continuous	<= 5.3 mmol/L 5.4-5.5 mmol/L > 5.5 mmol/L
Baseline eGFR	Categorical and Continuous	< 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 < 60 mL/min/1.73 m^2 >= 60 mL/min/1.73 m^2
Comorbidity –Heart Failure	Categorical	Yes, No
Comorbidity – Diabetes	Categorical	Yes, No
Comorbidity – CKD	Categorical	Yes, No
RAAS Inhibitor Use	Categorical	Yes, No
Diuretic Use	Categorical	Yes, No

*eGFR derived by Japan guideline formula;

$$\mathrm{eGFR[mL/min/1.73m^2]} = 194 \times \mathrm{SCr[mg/dL]}^{-1.094} \times \mathrm{Age[years]}^{-0.287} \left(\times 0.739 \text{ for female}\right)$$

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).

4.2.1.3 Medical history/Surgical 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.

4.2.2 Extent of Exposure

4.2.2.1 Study medication

Duration of exposure (defined as the last dose date – first dose date + 1), and number of doses taken (for overall and for each of Day 1 and 2) will be summarized by categorical/continuous descriptive statistics, using SAF.

4.2.2.2 Prior- and concomitant medications

Prior medications are defined as medications taken within 1 week before the first dose of study medication. Concomitant medications are defined as treatments taken during treatment period (any medications taken between the first dose of ZS and EOS visit). The medications continuing before 1st dose of ZS will be counted both as a prior medication and as a concomitant medication. All prior medication and concomitant medications will be coded with the WHO Drug Dictionary, and summarized by treatment group by safety set. The number and percentage of patients with prior and concomitant medications will be tabulated by Anatomic Therapeutic Chemical classification system (ATC) Term and Drug Preferred Name.

4.2.2.3 Measurements of Treatment Compliance

Percent treatment compliance is calculated. For each type of medication, percent compliance is defined as the number of sachets actually taken divided by the number of sachets that should have been taken. A subject is considered compliant if percent compliance is $\geq$ 80% and $\leq$ 120%.

4.2.3 Efficacy

4.2.3.1 Primary efficacy variable

The primary efficacy variable in exponential rate of change in S-K through to 48 hours post dose.

The primary efficacy analysis will be carried out for Full Analysis Set.

The primary efficacy analysis for the exponential rate of change in S-K through to 48 hours post dose will be based on the random coefficient model including all the serial S-K measurement from baseline to 48 hours as response variable and time and time x treatment interaction as fixed continuous effect. In addition, subject-level random effects for intercept and time will be included (section 4.1.5).

The estimates of treatment difference in slopes (coefficients for the time by treatment interaction for each dose) with its 95%CI as well as two-sided p-values for pairwise comparison to placebo will be presented for both ZS 10g TID and ZS 5g TID groups. The confirmatory testing will proceed with a sequential manner (ZS 10g TID first, then ZS 5g TID) as specified in section 4.1.1.

Sensitivity analysis of primary efficacy analysis

Missing mechanism

The primary efficacy model would provide inference based on direct likelihood, which implicitly assumes Missing At Random (MAR) for missing mechanisms.

The discontinuation rate is expected to be minimal due to the short treatment duration of the treatment period. Hence the following analyses would be carried out only if the early discontinuation of treatment period exceeded 10% in any treatment group (in any ZS treatment group for the latter one). Depending on the volume of missing data as well as on the discontinuation reasons, further sensitivity analyses may be performed.

- Completer case analysis, where only subjects who completed Day 3 assessment will be included.
- Multiple imputation with Jump to Reference (Placebo) assumption for ZS treatment groups.

Analysis with S-K adjusted for assay change bias

Assay for S-K in [redacted] 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.

Analysis with iSTAT values

- The same analysis as primary efficacy analysis using iSTAT potassium values instead of S-K measured by Central lab [redacted]

Different set of covariates

- The same analysis as primary efficacy analysis model using different set of baseline covariates. Following fixed effects will be added to the primary model.
  : Age category (<55, 55-64, >= 65 years), baseline eGFR (as continuous), binary indicators for DM, CKD, HF and RAASi usage. This is the same model as used in the study ZS-003.

Subgroup analysis of primary efficacy variable

The primary efficacy analysis model will be repeated with the following subgroups.

- Patients with or without Heart Failure (HF)
- Patients with or without Diabetes Mellitus (DM)
- Patients with or without Chronic Kidney Disease (CKD)
- Patients treated or not treated by RAAS inhibitors

4.2.3.2 Key secondary efficacy variables

Proportion of normokalemic patients at 48 hours post initial dose will be analyzed by logistic regression model. The model will include treatment as a factor and baseline S-K as a covariate. In this analysis, a subject who did not have S-K measurement at 48 hours are treated as a non-responder (not normokalemic).

The estimated odds ratio and its 95%CI as well as nominal two-sided p-values for pairwise comparisons for ZS 10g TID vs. Placebo and ZS 5g TID vs. Placebo will be provided from the above logistic model.

Further, the same logistic regression analysis for key secondary variable will be repeated (1) with S-K values adjusted for assay change bias as well as (2) with iSTAT potassium measurements.

Subgroup analysis of key secondary variable

The logistic regression model will be repeated with the following subgroups.

- Patients with or without Heart Failure (HF)
- Patients with or without Diabetes Mellitus (DM)
- Patients with or without Chronic Kidney Disease (CKD)

- Patients treated or not treated by RAAS inhibitors

4.2.3.3 Other secondary efficacy variables

- Exponential rate of change in S-K values during the initial 24 hours of study drug treatment

The primary model used for primary efficacy analysis (section 4.1.5) will be repeated for the serum Potassium measurements from baseline to 24 hours post dose. Only data up-to 24 hours post dose will be included in this analysis.

- Proportion of patients who achieved normokalemia at 24 hours after start of dosing

The logistic regression model used for key secondary variable (section 4.1.6) will be repeated using the patients with normokalemia at 24 hours as a response variable. Patients with missing S-K at 24 hours will be handled as non-responder (not normokalemic).

- Proportion of patients who achieved normokalemia at each scheduled potassium assessment time-point after start of dosing

Number (%) of subjects who achieved normokalemia at each scheduled time point and EOS visit will be provided by treatment group.

The same descriptive summary will be provided by baseline by baseline eGFR category (<15, 15-<30, 30-<60, >= 60 mL/min/1.73m^2), by baseline S-K (< 5.3, 5.3-5.5, > 5.5 mmol/L), and by subjects with or without each of comorbidities/mediation use (CKD, HF, DM, RAASi use)

- Mean change and mean percent change from baseline in S-K values at all measured time intervals post dose

Descriptive summary will be provided by time for the values measured at each time point and EOS visit, change from baseline as well as percent change from baseline will be displayed.

The same descriptive summary will be provided by baseline by baseline eGFR category (<15, 15-<30, 30-<60, >= 60 mL/min/1.73m^2), by baseline S-K (< 5.3, 5.3-5.5, > 5.5 mmol/L), and by subjects with or without each of comorbidities/mediation use (CKD, HF, DM, RAASi use)

- Time to normalization in S-K values (normalization defined as S-K values between 3.5 and 5.0 mmol/L, inclusive).

Kaplan-Meier plot for cumulative percentage who achieved normokalemia will be provided. The subjects who did not achieve normokalemia until Hour 48 will be censored at the time point when the last available S-K measurement was obtained at or before Hour 48. Median time to normalization (hours) will be produced. Treatment comparison for each ZS dose vs. Placebo is carried out with log rank test and nominal two-sided p-values will be presented.

- Time to a decrease in S-K levels of 0.5 mmol/l

Kaplan-Meier plot for cumulative percentage who achieved S-K decrease by 0.5 mmol/l will be provided. Median time to S-K decrease by 0.5 mmol/L (hours) will be produced. Treatment comparison for each ZS dose vs. Placebo is carried out with log rank test and nominal two-sided p-values will be presented.

4.2.4 Safety

The Safety set will be used for all safety analyses. Safety data will be presented with descriptive summary by treatment group.

4.2.4.1 Adverse events

Adverse Events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs with an onset date on or after first dose of IP but on or before the Day 3 will be considered as treatment-emergent AEs (TEAEs). TEAEs will be analysed and evaluated. AEs starting before Day 1 will only be listed. Off-treatment AEs (AEs starting on or after Day 4) will be separately summarized as necessary.

All Adverse events (including SAEs)

Summary of following TEAEs will be presented by SOC and PT. Number and proportion of subjects with these events will be provided.

- Any AEs
- Adverse events by preferred term and treatment group
- Deaths
- Serious AEs (SAEs)
- AEs leading to drug discontinuation (DAEs)
- AEs by maximal intensity
- AEs related to study drug

Off -treatment AEs (AEs starting on or after Day 4) will be analysed by SOC and PT.

- Any AEs
- AEs related to study drug

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.

4.2.4.2 Safety laboratory parameters

Change from baseline over time

For continuous variables, observed values and changes from baseline to Day 3 and Day 9 (EOS) will be summarized by descriptive statistics.

For categorical variables, shift table from baseline to Day 3 and Day 9 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 with a lowest S-K assessment (regardless of scheduled or unscheduled, during Day 1-3 and during Day 4-EOS) <3.5 mmol/L and will be repeated for a more severe definition of < 3.0 mmol/L.

Other potentially clinically significant laboratory abnormalities will also be identified based on the most extreme (lowest and/or highest) post-baseline values (during Day 1-3 and during Day 4-EOS) and tabulated with number and proportion of subjects meeting each criterion.

Table 6 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

Variable	Unit	Low	High
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

4.2.4.3 Vital signs

Summary statistics for changes from baseline to Day 3 and Day 9 (EOS) for each parameter (SBP, DBP, HR and body weight) by treatment group will be provided.

In addition, potentially clinically significant abnormal changes at any time post-baseline (during Day 1-3 and during Day 4-EOS) will be summarized with number of subjects and proportions.

Table 7 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

4.2.4.4 ECGs

Number of subjects with clinically significant abnormality (as assessed by investigator) will be summarized for baseline and post-baseline visits (Day 3 and Day 9 (EOS)).

Summary statistics for changes from baseline to Day 3 and Day 9 (EOS) for each parameter (heart rate (HR), P, PR, QRS, QT and QTcB and QTcF) will be provided. Here QTcB and QTcF will be derived by below formula.

$$QTcB = \frac{QT}{(60/\mathrm{HR})^{1/2}}, QTcF = \frac{QT}{(60/\mathrm{HR})^{1/3}}$$

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

Abnormal prolongation of QTc (QTcB and QTcF) will be summarized based on criteria specified in the table below. The most extreme (highest) value for a subject during treatment (during Day 1-3 and during Day 4-EOS) will be used in this summary.

Table 8 Categorical evaluation of QTc prolongation

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

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

Additional efficacy variable of "Time to a decrease in S-K levels of 0.5 mmol/l" is added as one for the other secondary efficacy variables.

Baseline eGFR category is taken out from the primary and key secondary analysis models, since it was anticipated that extremely small number of subjects would be available in eGFR > 60 mL/min/1.73 m^2 stratum.

7. REFERENCES (NOT APPLICABLE)

8. APPENDIX (NOT APPLICABLE)