Statistical Analysis Plan	
Study Code	D9480C00002
Edition Number	2.0
Date	15 March 2018

A phase 3 multicenter, prospective, randomised, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (sodium zirconium cyclosilicate), in patients with hyperkalemia-HARMONIZE Global

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Chiltern Study Statistician

PPD

Chiltern International Ltd.

19 MARCH 2018

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AstraZeneca Study Statistician PPD

19 MAR 2018
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AstraZeneca Gothenburg, Sweden

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Global Product Statistician PPD

19 Mar 2018
Date

AstraZeneca Gothenburg, Sweden

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AZ	AstraZeneca
BUN	Blood Urea Nitrogen
CHF	Congestive heart failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CTCAE	Common Terminology Criteria for Adverse Event
DM	Diabetes mellitus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
FAS-OLP	Full Analysis Set for the 48-hours Open Label Initial Phase
FAS-RTP	Full Analysis Set for the double blind Randomised Treatment Phase
GFR	Glomerular Filtration Rate
ITT	Intent-to-Treat
IPD	Important protocol deviation
HCG	Human chorionic gonadotropin
HF	Heart Failure
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
OLP	the 48-hours Open Label Initial Phase
P-Renin	Plasma-Renin
qd	Once Daily
qod	Every other day
RAAS	Renin-angiotensin-aldosterone system
RTP	Double-blind 28 Day Randomised Treatment Phase
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
SAF	Safety Analysis Set
SAF-OLP	Safety Analysis Set for the 48-hours Open Label Initial Phase
SAF-RTP	Safety Analysis Set for the double blind Randomised Treatment Phase
S-HCO3	Serum bicarbonate
S-K	Serum potassium
S-Mg	Serum magnesium
S-Na	Serum sodium
S-PO4	Serum phosphate
Tid	three times a day
VS	Vital signs
WHO	World Health Organization
ZS	Sodium zirconium cyclosilicate

AMENDMENT HISTORY

Date	Brief description of change
23 November 2017	The SAP was updated to better reflect AZ standards on the presentation of safety variables. Additionally, sensitivity analyses and subgroup analyses were updated. Evaluations of endpoints where updated to be analysed using only one method per endpoint. Various minor typos corrected. Harmonization in the use of RTP. See below for further details on the updates. List of abbreviations: Clarified that the RTP refers to the 28-day randomized treatment phase. WHO added to the list. Section 2.1.1: ”Enrolled” changed to ”entered” in the definition of the SAF-OLP. Section 2.2.1: Clarified that the number of patients with IPDs will be presented by study phase. Section 4.1.7.1: Following section was removed: ”If a patient’s Day 29 S-K assessment is made more than one day after the last dose, it will be treated as missing in data analysis and handled as defined above.” Section 4.2.2: The following hypotheses added to the list of secondary hypotheses to be tested: The mean change in P-Renin in the ZS 10g treatment group; The mean change in P-Renin in the ZS 5g treatment group. Section 4.3.2: “All screened patients” changed into “all enrolled patients” in the description of the patient disposition summary. ”Number of OLP registered patients” changed into ”Number of patients entered in OLP”. Section 4.3.4: ”AstraZeneca Drug Dictionary” replaced by ”WHO Drug Dictionary”. Section 4.3.5: Description of presentation of ”Expected exponential rate of change” removed from this section. Clarified that the nominal and percent changes referenced should be for the S-K values.

Date	Brief description of change
	Section 4.3.5.1: Formula for Expected exponential rate of change is removed. Clarified that the time estimate from the linear mixed model will be presented. ”Expected” is removed from this and other section referencing this endpoint. Section 4.3.5.3: Clarified that the Clopper-Pearson method for exact confidence interval for proportion will be used. Section 4.3.6.1: Removed text describing that that LSMEANs will be provided for each study visit. Added that results will also be provided back-transformed to the original scale. Section 4.3.6.2.1: Removed Fisher’s Exact Test for proportion of patients remaining normokalemic at Day 29/Exit. ”Day 29/EOS” changed to ”Day 29/Exit” to be in line with title. Text added to clarify that proportion of patients remaining normokalemic will be presented by study visit. Section 4.3.6.2.2: Clarified that LSMEANs will be provided for the number of normokalemic days. Section 4.3.6.2.3: Log-rank test for time to hyperkalemia removed. Section 4.3.7.1: Following two sensitivity analyses was removed: i) Including patients discontinuing before day 8 having a Day 8 measurement imputed using an interpolation based on an EM algorithm. ii) Repeating the primary analysis model on non-logged K values. Section renumbered to 4.3.7 Section 4.3.7.2: Sensitivity analysis for the secondary endpoint of number of normokalemic patients was removed. Section removed.

Date	Brief description of change
	Section 4.3.9.2: Section re-phrased to clarify that only AEs considered as treatment emergent will be included in summaries. Definition of treatment-emergent added. Clarified how to present AEs using the date of onset. Text not referring to the analysis or presentation removed. General updates to section 4.3.9.2 and subsections: TEAE replaced by AE. "Overall" removed from descriptions of presentations. Section 4.3.9.2.1: Added the following two bullets to the categories in the overall AE summary: • Number and percentage of patients experiencing AEs with outcome of death • Number and percentage of patients experiencing AEs leading to treatment withdrawal The following two bullets were removed: • the number and percentage of patients experiencing a TEAE by strongest relationship to study medication the number and percentage of patients experiencing a TEAE by greatest intensity Text referring to presentation of AEs leading to permanent discontinuation moved to 4.3.9.2.2. Section 4.3.9.2.2: Repetitions removed from the text. Section 4.3.9.2.3: SOC removed from description of presentation. Removed text describing that separate presentations will be provided for AEs classified as related and non-related by investigator. Section 4.3.9.2.4: SOC removed from description of presentation. Section 4.3.9.2.5: "Other SAEs" removed from title. Added description that AEs with outcome of death will be tabulated by SOC and PT.

Date	Brief description of change
	Section 8.1 Appendix A: Clarified that imputation of incomplete or missing onset date of an AE will be set to the day of the first dose of study medication only if the end date is on or after the first dose of study medication. Imputation rules for incomplete AE end dates removed as it has no impact on presentation of adverse events. Section 4.3.10: The presentation of subgroup analyses for CKD, CHF, DM and RAASi use has been modified. An interaction effect for treatment by subgroup was included.
29 November 2017	IPD added to list of abbreviations. Section 2.2: Corrected cross-reference to section 2.2.1. Section 3.4: Repeating information removed. Section 4.1: Clarified that Eq. 2 for eGFR will be used for Japan specific analyses alone. Section 4.1.5: Section regarding visit windows is moved to section 3.4.6. Section 4.1: Added description that p-values from tests not included in the closed testing procedures are considered exploratory and not called significant. Section 4.1.6.1: Removed paragraph describing imputation of Day 8 S-K values. This related to a now removed sensitivity analysis. Section 4.3.2: Added clarification for enrolled and entered into the OLP. Section 4.3.6.2.4: Clarified that t-tests will be performed for mean change from baseline for S-Aldo and P-Renin. Section 4.3.9.2: Study treatment exposure added. Section 4.3.10: Clarified that output for Japanese subgroup will be included in Japan specific CSR.
16 February 2018	Secondary efficacy variable of Exponential rate of change updated. Mention of 24-hour and 48-hour removed from Sections 3.2.1 and 4.2.2.

Date	Brief description of change
	Section 3.2.2: Clarified that change in S-K levels is computed as compared to OLP and RTP baselines. Section 3.4.5: New paragraph describing a change to the potassium assay calibration. Section 4.1.6.1: Imputation method modified to, in addition to the visit number, take into account the calibration method for the potassium assay at the central laboratory. Section 4.1.7: New section describing the definition of subgroups of patients with heart failure, chronic kidney disease and diabetes mellitus. Section 4.2.2: Hypotheses for mean change or percent change in S-K levels during RTP removed. Section 4.3.2: Language updated so that definition of entered patients does not contradict the definition given in section 2.1.1. Section 4.3.3: Removed paragraph describing a listing for prior and current medical history. Section 4.3.4: Analysis set for prior and concomitant medication changed to FAS. Section 4.3.5: Language updated to include all pre-planned time points in summary of S-K levels during OLP. Section 4.3.7: New subsection 4.3.7.2 describing sensitivity analyses to assess impact of a change to the calibration method of the potassium assay the central laboratory. Section 4.3.9.1: Sorting criteria for listing removed. Section 8.3: New Appendix added for definition of subgroups. Section 8.4: New Appendix added for details regarding the change to the potassium assay.
15 March 2018	Section 2.1.1: Clarified that patients that were entered and received study medication in OLP without meeting eligibility criteria will be included in the full Analysis Set for OLP. Section 4.3.5.1: Rephrased section to clarify the fixed and random effects used in the model.

Date	Brief description of change
	Section 4.3.9.2: Clarified that AEs occurring on OLP Day 3 (day of randomisation) should be summarised for OLP since it would not be possible to distinguish whether AE occurred before or after intake of randomised study medication. Sections 4.3.6.2.1-3: Clarified that effects for visit and visit-by-treatment interaction are not included in modelling.

1 STUDY DETAILS

HARMONIZE Global is a Phase 3 multicentre, prospective, randomised, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS in patients with hyperkalemia. It is intended to be included in applications for marketing authorisation in the countries where the study is performed. For details on study background and rationale, please refer to the Clinical study protocol for HARMONIZE Global (CSP, D9480C00002, Version 2.0 (07 Dec 2016)).

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study. This SAP, which will be finalised prior to database lock (DBL), should be read in conjunction with the HARMONIZE Global CSP.

1.1 Study objectives

Primary Objective:	**Outcome Measure:**
To evaluate the efficacy of two different doses (5 and 10 g) of ZS orally administered once daily (qd) for 28 days in maintaining normokalemia (serum potassium [S-K] between 3.5-5.0 mmol/L, inclusive) in normokalemic patients, following treatment in the 48h open-label phase, for hyperkalemic patients (two consecutive i-STAT potassium values ≥ 5.1 mmol/L, taken 60 minutes apart) at baseline	Comparison between placebo and each ZS treatment group (high to low) with regard to the mean S-K level during the 28-day randomised treatment study phase Days 8-29

Secondary Objectives:	**Outcome Measures:**
48-hour open-label initial phase: • To evaluate the proportion of patients who achieve normokalemia after 48 hours of open-label initial phase treatment	48-hour open-label initial phase efficacy endpoints: • Proportion of patients who achieve normokalemia during the initial phase at 24 and 48 hours • Exponential rate of change in S-K levels (blood) during the 48-hour open-label initial phase • Change (absolute and percent change) from baseline in S-K levels (blood) at all measured time intervals (See Table 1) post dose in 48-hour open-label initial phase • Time to normalisation in S-K levels (normalisation defined as S-K levels between 3.5-5.0 mmol/l, inclusive) in 48-hour open-label initial phase
28-day randomised treatment study phase: • To evaluate the efficacy of ZS in patients with hyperkalemia for the following subgroups*: - chronic kidney disease (CKD) - diabetes mellitus (DM) - heart failure (HF) - those on renin-angiotensin-aldosterone system (RAAS) inhibitors	28-day randomised treatment study phase efficacy endpoints: • The proportion of patients who remain normokalemic (as defined by S-K between 3.5 - 5.0 mmol/l, inclusive) at the end of the 28-day randomised treatment study phase and during the 28-day randomised treatment study phase • The number of days patients remain normokalemic during the 28-day randomised treatment study phase • The mean change and mean percent change in S-K levels evaluated relative to both baselines • The time to hyperkalemia (defined as S-K ≥ 5.1mmol/l)
• To evaluate the effect of ZS on serum-Aldosterone (S-Aldo) and plasma-Renin (P-Renin) levels	• The mean changes in S-Aldo and P-Renin levels
Patient reported outcomes: • To evaluate the health state in the study population using EQ-5D	Patient reported outcomes: • EQ-5D questionnaire

Safety Objectives:	Outcome Measures:
• To evaluate the effect of ZS on other serum electrolytes in both 48-hour open-label initial phase and 28-day randomised treatment study phase	• Serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]
• To evaluate the safety and tolerability profiles of ZS in both 48-hour open-label initial phase and 28-day randomised treatment study phase	• Adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations • ECG • Clinical laboratory evaluations, including assessment of hypokalemia

* Primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/l, inclusive) at the end of the 28-day randomised treatment study phase will be evaluated in patients with hyperkalemia for the subgroups.

1.2 Study design

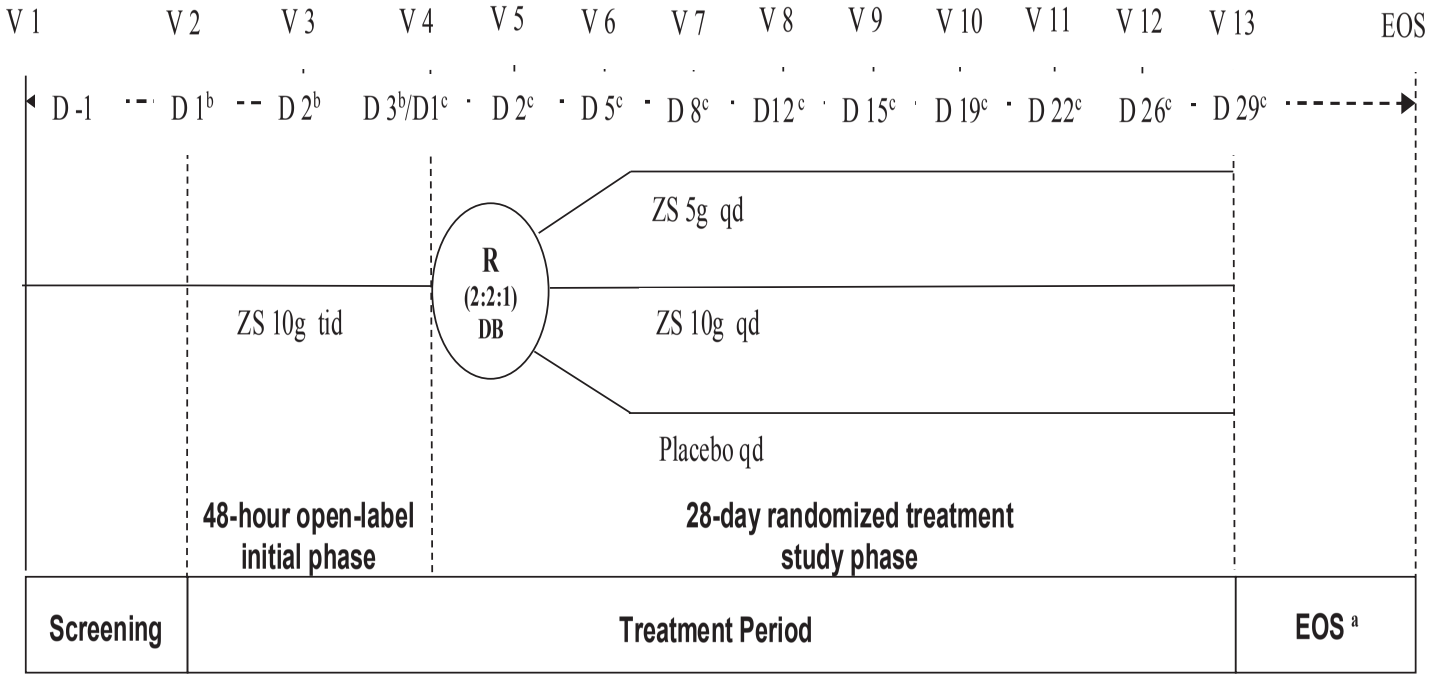
This is a 2-phase, prospective, randomised, double-blind, placebo-controlled, Phase 3 study to determine the safety and efficacy of ZS in patients with hyperkalemia.

This study consists of a screening period (1 day), 48-hour open-label initial phase (OLP), 28-day randomised treatment study phase (RTP), and follow-up period (7±1 days after the last administration of study medication). Screening procedures will be performed to determine patient eligibility during the screening period, and all baseline parameters should be measured/collected up to 1 day prior to administration of the first dose of study drug in the OLP.

During the OLP all patients will receive ZS per os (PO) at a dose of 10g three times a day (tid) for a maximum of 6 doses. If a patient develops confirmed i-STAT (as measured by a portable blood analyser) potassium values between 3.0 mmol/L and 3.4 mmol/L inclusive during the OLP, the patient will be directed to not take any more ZS during the rest of the day and return the next day to continue in the study. For patients who do not enter the RTP, the end of study (EOS) follow-up visit will be 7±1 days after the last administration of study medication in the 48-hour open-label initial phase.

Patients who achieve normokalemia (i-STAT potassium values between 3.5 to 5.0 mmol/l, inclusive) on the morning of Day 3 will then be randomised 2:2:1 into the double-blind 28-day randomised treatment study phase to receive ZS 5g, 10g or placebo, PO qd for the following 28 days. If the potassium level remains low (e.g., if a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4mmol/L, inclusive as confirmed by taking a second potassium measurement after a 10 ± 2 minute interval), dosing during the RTP will be reduced from qd to every other day. Patients will then be required to complete the study Day 29 visit, and the EOS visit which is 7±1 days after the last administration of study medication.

Figure 1. Study flow diagram



R=Randomization; DB=Double-blind; EOS=End of study; V=Visit; D=Day; tid=three times a day; qd=once daily

[a] EOS occurs 7±1 day after the last administration of study medication (same applies if patients leave the study during 48-hour open-label initial phase)

[b] Study Day for 48-hour open-label initial phase

[c] Study Day for 28-day randomized treatment study phase; Day 3 of the 48-hour open-label initial phase is the same day as Day 1 for 28-day randomized treatment study phase

1.2.1 Schedule of Visits

The study will be conducted according to the study flow diagram (Figure 1) and the Study Plan (Table 1 and Table 2). The study plan tables provide an overview of the procedures performed at each visit during the treatment period, and further details are provided in the protocol (CSP, D9480C00002, Version 2.0 (07 Dec 2016)).

Table 1 Study Plan detailing the procedures: 48-hour open-label initial phase

Study Visit	Visit 1	Visit 2	Visit 3	Visit 4[6]	EOS[8]
Initial Phase Day	**Screen**	**Day 1[12]**	**Day 2[12]**	**Day 3[12]**	**Day 9[12]**
Written informed consent	X				
Eligibility criteria		X[9]			
Demographics	X				
Medical History		X[9]			
EQ-5D questionnaire		X			
Physical exam including weight		X[9, 13]		X[13]	X[13]
Access IVRS/IWRS	X	X		X[10]	
Study drug (IP) dispensation		X			
Study drug (IP) administration		X	X		
ECG		X[9]		X	X
Vital signs		X[9]		X	X
Concomitant medications		X[9]	X	X	X
Adverse events		X[14]	X	X	X
Potassium[4, 11]		X[2]	X[3]	X[7]	X[7]
Clinical Chemistry[1,4]		X[9]		X	X
Hematology[1,4]		X[9]		X	X
Urinalysis[1,4]		X[9]		X	X
Urine HCG		X[5,9]			X[5]
IP Reconciliation					X

1. Parameters to be measured are detailed in Table 3 Laboratory Safety Variables.
2. Potassium will be measured twice 60 (±10) minutes apart within 1 day prior to any dose administration, and on initial phase Day 1 at 1, 2 and 4 hours (±15 min) after administration of the first dose of ZS. Potassium will be measured again at 90 minutes (±15 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) and 1 hour (±15 min) after the first dose on initial phase Day 2 (Visit 3)
4. Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting (nothing by mouth except water only for a minimum of 8 hours prior to collection). On initial phase Day 1(Visit 2), the

Central Laboratory clinical chemistry and hematology samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample;

5. For women of childbearing potential, urine-HCG will be measured at clinic, using the tube provided by Central Laboratory
6. Visit 4 (Day 3 for 48-hour open-label initial phase) is the same visit of Day 1 in 28-day randomised treatment study phase; i-STAT and S-K for all patients, remaining procedures only for patients with i-STAT potassium values >5.0 mmol/L as measured fasting
7. Central laboratory S-K sample collected as part of the serum clinical chemistry
8. EOS in initial phase only for patients NOT entering the 28-day randomised treatment study phase, and occurs 7±1 day after the last administration of IP
9. Baseline parameters should be measured/collected up to 1 day prior to administration of the 1st dose of study drug on initial phase Day 1(Visit 2)
10. Access IVRS/IWRS on initial phase Day 3 (Visit 4) or if patient permanently discontinues dosing before the end of initial phase dosing period
11. All potassium samples are analysed by i-STAT and by the Central Laboratories on all occasions. Haemolysed samples should not be sent to the Central Lab for potassium, the sample should be re-drawn to obtain a sample showing no haemolysis. For diabetic patients all potassium samples should be collected prior to insulin administration whenever possible.
12. Study Day in Table 1 is for 48-hour open-label initial phase
13. A complete physical examination should be performed within 1 day prior to administration the first dose of study drug on initial phase Day 1, and targeted physical examination will be conducted on initial phase Day 3 and 9 for patients not entering the 28-day randomised treatment study phase.
14. 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

Table 2 Study Plan detailing the procedures: 28-day randomised treatment study phase

Study Visit	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**(EOS)[8]**
28-day randomised treatment study phase Day[7]	**Day 1[10]**	**Day 2[10]**	**Day 5[10]**	**Day 8[10]**	**Day 12[10]**	**Day 15[10]**	**Day 19[10]**	**Day 22[10]**	**Day 26[10]**	**Day 29[10]**	**Day 35[10]**
Eligibility criteria	X										
EQ-5D										X	
Physical exam including weight[3, 11]	X					X				X	X
Access IVRS/IWRS[9]	X			X		X		X			
Study drug (IP) dispensation	X			X		X		X			
Study drug (IP) administration[4]	X	X	X	X	X	X	X	X	X		
ECG[3]	X			X		X		X		X	X
Vital signs[3]	X					X				X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Potassium[6]	X[2]	X	X	X	X	X[2]	X	X	X	X[2]	X[2]
Clinical chemistry[1,3]	X					X				X	X
Hematology[1,3]	X					X				X	X
Urinalysis[1,3]	X					X				X	X
Urine HCG											X[5]
IP Reconciliation										X	

1. Parameters to be measured are detailed in Table 3 Laboratory Safety Variables..
2. Potassium will be measured fasting prior to the 1st daily dose as part of the clinical chemistry panel on Day 1, 15, 29, 35 in the 28-day randomised treatment study phase.

3. Physical Exam, ECG, Vital signs, weight, urinalysis, clinical chemistry including S-Aldo and P-Renin, and hematology parameters will be measured fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic); On 28-day randomised treatment study phase Days 1,15, 29, and 35(EOS), blood sample which including S-Aldo and P-Renin test need to be collected prior to 10am after at the patient has been upright for at least 2 hours and before the ECG
4. IP administration may not happen during some scheduled visits in patients for which the dose was reduced to EOD dosing.
5. For women of Childbearing potential, urine-HCG will be measured at clinic, using the tube provided by Central Laboratory
6. All potassium samples are analysed by i-STAT and by the Central Laboratories on all occasions. Haemolysed samples should not be sent to the Central Lab for potassium, the sample should be re-drawn to obtain a sample showing no haemolysis. For diabetic patients all potassium samples should be collected prior to insulin administration whenever possible
7. If a scheduled clinic visit falls on a weekend or National holiday during the 28-day randomised treatment study phase, the scheduled visit may take place either 1 day early or 1 day late (i.e. within±24 hours of the scheduled day) for 28-day randomised treatment study phase Days 5, 8, 12, 15, 19, 22, 26 and 35, up to 2 days late for 28-day randomised treatment study phase Day 2 or 2 days early for Day 29. If the Day 29 visit is conducted early, the patient must take IP through Day 28 per protocol
8. EOS occurs 7±1 day after the last administration of IP
9. Access IVRS/IWRS on visit indicated or if patient permanently discontinues dosing before the end of 28-day randomised treatment study phase
10. Study Day in Table 2 is for 28-day randomised treatment study phase
11. Targeted physical examination will be conducted on Days 1, 15, 29, and Day 35 (EOS) during the 28-day randomised treatment study phase.

1.2.1.1 Enrolment/screening period (Visit 1)

Procedures will be performed according to the Study Plan in Table 1. At screening, consenting patients are assessed to ensure that they meet the study eligibility criteria. Patients who do not meet these criteria must not be entered in the study.

Patients can be re-screened once during the clinical trial period and will remain associated with the same enrolment number throughout the entire study.

1.2.1.2 48-hour open-label initial phase Days 1-3 (Visit 2-4)

On Day 1, patients will arrive in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). Patients who meet all inclusion and none of the exclusion criteria will be entered into the trial and treated with ZS 10g for 48-hour.

1.2.1.3 28-day randomised treatment study phase Days 1-29 (Visit 4-13)

Patients whose i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/L, inclusive) at Day 3 of the OLP will be randomised into the double-blind RTP to one of three treatment arms (i.e. ZS 5g, ZS 10g or placebo) and treated for 28 days. Note that the OLP Day 3 is also the RTP Day 1 (Visit 4).

a) Treatment Assignment and Randomisation Procedure

The randomisation codes will be computer generated using the AZ global randomisation system (AZRand) and loaded into the IVRS/IWRS database. Randomisation codes will be generated in blocks to ensure approximate balance (2:2:1) between the three treatment arms (ZS 5g, ZS 10g or placebo). Randomisation will be stratified by country.

No member of the study team at AZ, or representative, personnel at study centres or any clinical research organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AZ personnel generating the randomisation scheme as well as AZ Supply Chain, and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labeling of study medication. This documentation will be kept in a secure location until the end of the study.

b) Blinding

The RTP will have a double blind design. In order to ensure a double-blind randomised study, patients and Investigators will remain blinded to treatment assignment throughout the entire study. Personnel involved with the analysis and conduct of the study will remain blinded until protocol deviators have been identified and the database in locked.

To ensure blinding of the treatments, the actives and placebo will be identical in appearance and identical packaging and labeling will be used. Patients will take by mouth the entire contents of a single sachet per day containing either ZS 5g, ZS 10g or placebo. The exterior appearance of the sachets are identical, but the volume of study drug will differ depending upon the randomised treatment group. Individual sachets are enclosed in a carton with a tamper evident seal intended to be broken exclusively by patients just before taking the study drug.

c) Un-blinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient in the 28-day randomised treatment study phase, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS in case of an un-blinding situation. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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

AstraZeneca retains the right to break the code for Serious Adverse Events (SAEs) that are unexpected and are suspected to be causally related to the investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

1.2.1.4 Follow-up period (EOS)

A follow up visit will be performed at Day 9 in the OLP, and Day 35 in the RTP; or, 7 ±1 days following the last study medication administration for patients who are withdrawn from the study medication.

1.3 Number of patients

This study will be conducted in approximately 50 centres in several different countries. Before patients are randomised to the double-blind study phase, they will receive open-label ZS 10g for 48 hours during the initial phase. It is expected that approximately 443 patients will need to be enrolled, to have approximately 269 patients entered into the OLP, resulting in approximately 255 patients being randomised in the RTP. Enrolment will be stopped when approximately 255 patients have been initiated with the 28-day randomised treatment study phase.

1.3.1 Sample size estimate

The sample size is determined to detect a clinically meaningful difference in the primary endpoint of the mean S-K during 28-day randomised treatment study phase (Study Days 8-29) between each active dose (high to low) vs. placebo control. Assuming an inter-patient standard deviation of 0.50, a total of approximately 255 patients, or 102 patients per each active dose treatment arm and 51 patients for placebo control arm, will provide >90% power to detect a 0.30 mean 28-day randomised treatment study phase Day 8-29 S-K difference, comparing each active dose (high to low) vs. placebo control for a two-sided t-test at a significance level of 5%. Assuming 95% of patients will be normokalemic after treatment with at least 1 dose of ZS 10g (See CSP, Version 2.0 (Date: 07 Dec2016) Section 7.2), approximately 269 patients will be needed to enter 48-hour open-label initial phase.

The power and sample size is determine based on the number of patients required to evaluate the primary hypothesis of the study. However, in the testing sequence presented in Table 6, the 48-hour open-label phase mean change from baseline of S-K 48 hours after first dose of ZS 10g will be evaluated first. A sample size of 225 patients will provide >99% power to detect 1.05 absolute reduction (0.5 standard deviation of the change) in mean change from baseline of S-K 48 hours after the first dose of ZS 10g during the open label initial phase.

2 ANALYSIS SETS

2.1 Definition of analysis sets

The study will have prospectively defined analyses sets including separate evaluability rules for the OLP and RTP. The analyses sets defined below will be used for all data analyses in this study.

2.1.1 Full analysis sets

All efficacy analyses, unless otherwise specified, will be performed using the full analysis set (FAS), which is based on the Intention-to-Treat (ITT) principle. That is, patients allocated to a treatment group will be followed up, assessed, and analysed as members of that group irrespective of their compliance with the planned course of treatment.

FAS-OLP: for the OLP, the full analysis set will include all patients entered in the initial study phase (i.e. patients entered into the trial after meeting the eligibility criteria for the study), regardless of whether they took study medication or not. Patients who did not meet eligibility criteria but entered the OLP and received study medication will be included in FAS-OLP and will be identified as a protocol deviation

FAS-RTP: for the RTP, the full analysis set will include all patients who are randomised to the 28-day randomised treatment phase, regardless of whether they took study medication or not. In this set, patients will be analysed according to their randomised treatment assignment.

2.1.2 Safety analysis sets

All safety analyses will be performed using the safety analysis set (SAF). Safety analyses will be performed for each study phase, OLP and RTP.

SAF-OLP: For the OLP, the safety analysis set will include all patients in the FAS-OLP who receive at least 1 dose of study medication. Patients will be assigned on an as-treated basis for safety analyses.

SAF-RTP: For the subsequent RTP, the safety analysis set will include all patients in the FAS-RTP who receive at least 1 dose of study medication. Patients will be assigned on an as-treated basis for safety analyses. If a patient receives more than one treatment during the RTP, they will be analysed according to the highest dose of study medication received during the phase.

2.2 Violations and deviations

There is no defined Per Protocol population for this study and all efficacy analyses will be based on the FAS. Therefore, protocol deviations will not imply exclusion from analyses.

A protocol deviation occurs when a patient fails to adhere to pre-specified protocol eligibility criteria, and/or compliance during the course of the trial. It is anticipated that most of the deviations will be able to be determined programmatically from the data.

Protocol deviations relating to patient-level as well as patient-visit-level events will be reviewed by appropriate medical, clinical, data management, and statistical personnel and documented prior to un-blinding the study. All deviations considered as important (including, but not limited to, those defined in Section 2.2.1) will be tabulated and listed in the CSR.

2.2.1 Important protocol deviations

The following deviations are considered as important protocol deviations (IPDs):

- Study drug compliance < 80% or > 120%.
- Administration of wrong type of study drug (i.e. the one not randomised to) cumulatively for more than 1 week.
- Patients randomised who fail to receive treatment.
- Administration of prohibited concomitant medication or non-drug therapy.
- Eligibility criteria not fulfilled but patient still randomised and subsequently discovered to have failed the eligibility criteria, and where the failure to meet the eligibility criteria may have a negative impact on the analysis of the study.

The number and percentage of patients with any of these IPDs will be summarised for both study phases (OLP and RTP, respectively). The summary will display the number of patients with an important protocol deviation in each study phase.

2.2.2 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be entered into the study. These patients should be withdrawn from the study prior to receiving open label treatment. These patients should have the reason for study withdrawal recorded as 'Eligibility criteria not fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures.

Note that screen failure patients can be re-screened once during the clinical trial period and will remain associated with the same enrolment number throughout the entire study.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Primary efficacy variable

The primary efficacy parameter in this study will be the model-based least squares means (LSMEAN) of all S-K values during the RTP, Study Days 8-29.

3.2 Secondary efficacy variables

3.2.1 48-hour open-label initial phase

For the OLP, 24-hour assessments are those made on OLP Study Day 2; 48-hour assessments are those made on OLP Study Day 3. The following secondary efficacy endpoints will be included in the analysis:

- Exponential rate of change in S-K levels from baseline.
- Nominal and percent change from baseline in S-K levels at all measured time intervals post-dose
- Proportion of patients who achieve normokalemia during the OLP at 24 and 48 hours
- Time to normalisation in S-K levels (normalisation defined as S-K levels between 3.5-5.0 mmol/l, inclusive)

3.2.2 28-day randomised treatment phase

For the subsequent 28-day randomised treatment study phase, the following secondary efficacy endpoints will be included in the analysis.

- The proportion of patients who remain normokalemic (as defined by S-K levels between 3.5-5.0 mmol/l, inclusive) at the end of the RTP and during the RTP

- The number of days patients remain normokalemic during the 28-day randomised treatment study phase

- The mean change and mean percent change from baseline in S-K levels evaluated relative to both 48-hour open-label initial phase and 28-day randomised treatment study phase baselines.

- The time to hyperkalemia (defined as S-K ≥5.1 mmol/l)

- The mean changes in S-Aldo and P-Renin levels

3.3 Other variables

The health state of the study population will be assessed at Visit 2 and Visit 13 using the EQ-5D questionnaire. The EQ-5D comprises five questions about mobility, self-care, usual activities, pain/discomfort and anxiety/depression with five possible answers for each item (see appendix 3 in the protocol - CSP, D9480C00002, Version 2.0 (07 Dec 2016)). In addition, there is a visual analogue scale (VAS) to indicate the general health status with 100 indicating the best health status and 0 the worst.

3.4 Safety Variables

The following safety data will be collected: adverse events (AEs), vital signs, physical examinations, ECGs, clinical laboratory evaluations, and other electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

3.4.1 Adverse Events (AEs)

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

Events will be defined as treatment emergent if they onset, or worsen (by investigator report of a change in intensity), during the treatment period (by summarising based on date of onset). If partial dates of onset occur, a conservative approach will be followed and events will be assumed to be treatment emergent unless there is convincing evidence to the contrary.

A serious adverse event (SAE) is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

3.4.1.1 Recording of adverse events

AEs (including SAEs) will be collected from the time of informed consent, throughout the treatment period, including the EOS visit.

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

3.4.1.2 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Max intensity (mild, moderate or severe)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action take with regard to investigational product
- Outcome

The following variables will be collected for each SAE:

- Date AE met criteria for serous AE
- Date Investigator became aware of serious AE
- AE is serous due to

- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedures(s)
- Description of AE

3.4.2 Vital Signs

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed at Visits 2, 4, 9, 13 and the EOS visit using non-invasive equipment. Three (3) readings separated by 2 minutes will be averaged and the averaged result will be recorded in the eCRF.

3.4.3 Physical Examination

A complete physical examination will be performed within 1 day of administration of the first dose of study drug on initial phase Day 1 (Baseline: all patients), and targeted physical examination will be conducted on OLP Day 3 for all patients and on Day 9 for patients not entering the 28-day randomised treatment study phase. During the RTP targeted physical examination will be conducted on Days 1, 15, 29, and Day 35 (EOS).

The complete physical examination includes the following: general appearance including skin, height and weight, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular including assessment of signs of heart failure, lungs, abdomen, and neurological systems.

The targeted physical examination includes the following: weight (weighed on the same scale in the same state of dress), skin, extremities, cardiovascular including assessment of signs of heart failure, lungs, and abdomen.

3.4.4 Electrocardiogram ECG)

A 12-lead ECG will be performed at the times indicated in the Study Plan in Table 1 and Table 2. Heart rate, P and QRS durations, PR and QT intervals will be recorded from standard lead of the computerised quantitative 12-lead ECG.

ECGs will be recorded at OLP Days 1, 3 and 9 (EOS) for patients NOT entering the double-blinded RTP, and on RTP Days 1, 8, 15, 22, 29 and 35 (EOS) for those entering the RTP. For patients who have i-STAT potassium levels ≥ 6.1 mmol/L at the 1 hour post first dose time point in the 48h OLP Day 1, an additional ECG will be recorded 1.5 hours post second dose.

3.4.5 Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken during the OLP at Visits 2, 4 and the EOS visit for patients not entering the double-blind 28-day randomised treatment study phase and at Visits 4, 9, 13 and EOS visit for the RTP phase. The clinical chemistry, hematology and urinalysis will be performed at a central laboratory. Laboratory safety variables are described in Table 3.

Table 3 Laboratory Safety Variables

Haematology	**Clinical Chemistry (serum/plasma)**
B-Haemoglobin (Hb)	S-Total Protein
B-Haematocrit	S-Albumin
B-Erythocyte count (RBC)	S-Bicarbonate
B-Total leukocyte count (WBC)	S-Blood Urea Nitrogen
B-Leukocyte differential count (absolute count)	S-Creatinine
B-Platelet count	S-Bilirubin, total
	S-Alkaline phosphatise (ALP)
Urinalysis	S-Glucose
U-PH	S-Sodium
U-Specific gravity	S-Potassium[1]
U-Glucose	S-Inorganic phosphate
U-Ketones	S-Calcium, total
U-Bilirubin	S-Magnesium
U-Urobilinogen	S-Gamma-glutamyl transferase (GGT)
U-Blood	S-Aspartate transaminase (AST)
U- Human chorionic gonadotropin (HCG) (only for females of childbearing potential)[2]	S-Alanine transaminase (ALT)
	S-Aldosterone
	P-Renin

1. Potassium will be tested by i-STAT and Central Laboratory
2. Urine-HCG will be measured at clinic, used the tube provided by Central Laboratory

The calibration of the S-K assay was changed during the course of the study. Measurements analysed using the new calibration method are on average higher than when analysed by the old calibration method. Covance, the central laboratory provider, have performed analysis of the correlation and relationship between the old and new calibration methods and have

concluded that the bias is small enough to be within the variability of the assay and also small enough to leave the reference ranges unchanged. See Section 8.4, Appendix D for details on the change to the calibration of the potassium assay.

3.4.6 Visit windows

In the absence of nominal visits, the visits windows will apply. Measurements will be assigned to exhaustive visit windows based on study day such that measurements taken at any time point can be accounted for and used in summaries and/or analyses. In the event that both a scheduled and an unscheduled visit occurred in the same window, then the measurement from the scheduled visit will be used in the analysis. If there are multiple unscheduled visits in the same visit window, then the visit closest to the scheduled visit day will be used. If there are multiple records on the same day the last measurement will be used.

Table 5 Time windows for allocation of data to visits for statistical analysis

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Open-Label Phase			
Visit 1 (Screening)	-1	---	-1
Visit 2 (OLP-Day 1)	1	1	1
Visit 3 (OLP-Day 2)	1	2	2
Visit 4 (OLP-Day 3)	1	3	3
End of Study Visit (OLP-Day 9)[1]	9	4	16
Randomised Treatment Phase			
Visit 4 (RTP-Day 1)	1	1	1
Visit 5 (RTP-Day 2)	1	2	2
Visit 6 (RTP-Day 5)	3	3	6
Visit 7 (RTP-Day 8)	3	7	9
Visit 8 (RTP-Day 12)	4	10	13
Visit 9 (RTP-Day 15)	3	14	17
Visit 10 (RTP-Day 19)	4	18	20
Visit 11 (RTP-Day 22)	3	21	24
Visit 12 (RTP-Day 26)	4	25	27
Visit 13 (RTP-Day 29)	3	28	31
End of Study Visit (RTP-Day 35)[2]	9	32	43

1. **Note**: End of Study Visit (OLP-Day 9) in initial phase only for patients NOT entering the 28-day randomised treatment study phase, and occurs 7±1 day after the last administration of IP.
2. **Note**: End of Study Visit (RTP-Day 35) occurs 7±1 day after last administration of IP in RTP.

The pre-dose S-K measurements at Visit 3 and Visit 4 will be used to calculate the proportion of patients who achieve normokalemia during the 48-hour open-label initial phase at 24 and 48 hours, respectively. If there are multiple S-K measurements at the same time-point, the first measurement will be used.

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. Analysis of data from the OLP and the RTP will be performed after all patients have completed or discontinued from the study. In addition, all relevant data queries must be answered and the database must be locked and un-blinded for the 28-day randomised treatment study phase prior to the analysis.

Unless otherwise specified, all efficacy analyses will be carried out on the FAS-OLP or FAS-RTP, respectively. Safety analyses will be based on the SAF-OLP or SAF-RTP, respectively.

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

Individual patient data will be presented in patient listings. Unless otherwise specified, data listings will at least include patient ID, age, gender and race, and will be presented sorted by treatment group, centre/site, patient ID, and date/time of observations, by visit, where appropriate. Patient characteristics (e.g. demographics and baseline characteristics) and study medication information will be listed for all enrolled patients and flagged by analysis population (FAS-OLP or FAS-RTP) and treatment group in each phase, if appropriate.

The number and percentage of patients in each analysis set will be presented in summary tables, with the total number of patients in each study phase serving as the denominator for the respective summaries.

The number and percentages of patients within each important protocol deviation type will be summarised by study phase, OLP and RTP, respectively. In the RTP, summaries will be presented overall and by treatment group. All individual patients with important protocol deviations will be listed as well for OLP and RTP, respectively.

Continuous variables will be summarised by descriptive statistics, including number of non-missing observations (n), mean, standard deviation, median, minimum, and maximum. The means and medians will be presented to one further degree of precision than the raw data. Standard deviations will be reported to one further degree of precision than the means, and medians. Minimums and maximums will be displayed with the same number of decimal places as the collected data.

Categorical variables will be summarised by frequency counts and percentages. Percentages will be presented to 2 decimal places, unless most percentages in a particular table are small

(i.e. < 5%). All percentages within a table will be consistent. Any data presentation that includes percentages should clearly indicate the denominator used for the calculation of each percentage (e.g., in the footnote). The denominator will normally be the total number of patients with non-missing data (e.g., number entered in the OLP or in a treatment group for the RTP), unless otherwise stated.

Results of all statistical analyses will be presented using a 95% confidence interval (CI) and two-sided p-value, unless otherwise stated. All p-values will be rounded to 3 decimal places. If the fourth digit of the p-value is less than or equal to 4, the p-value will be rounded down. If the fourth digit of the p-value is greater than or equal to 5, the p-value will be rounded up. All p-values rounded to 0.000 will be presented as '< 0.001' and p-values that are rounded to 1.000 will be presented as '> 0.999'. A sequential closed testing procedure is used to adjust for multiplicity. P-values for tests not included in the sequential closed testing procedure are not adjusted for multiplicity and will not be called significant and are considered exploratory.

The eGFR will be calculated as in Equation 1 for all patients:

1. eGFR = 175 x (0.011312 x Creatinine umol/L)**(-1.154) x (age in years) **(-0.203) x 1.212 (if patient is black) x 0.742 (if female).

Additionally, for the Japan specific analyses alone, the eGFR will be calculated using both Equations 1 and 2 for the Japanese subpopulation to reflect muscle volume in Japanese patients (and potentially in East Asian) and also to facilitate comparison with Japan stand-alone studies:

2. eGFR = 194 x (0.011312 x Creatinine umol/L)**(−1.094)× (age in years) **(−0.287) x 0.739 (if female).

4.1.1 Definition of Baseline and Post Baseline

For the OLP, the baseline S-K will be established on initial phase Study Day 1 (pre-treatment) by taking the mean of 2 different S-K values, recorded 60 ± 10 minutes apart (time 0 and time 60 minutes). Post baseline for the OLP will be all S-K measurements taken after first dose.

For the subsequent RTP, the baseline S-K will be established on the morning of OLP Study Day 3 as the first S-K measurement performed on Study Day 3, which establishes patient eligibility into the 28-day randomised treatment study phase. Post baseline for the RTP will be all S-K measurements taken after patient randomisation in the randomised treatment phase.

The baseline for all other parameters will be the fasting parameter value measured within 1 day before the first study drug administration in the OLP.

4.1.2 Definition of change from baseline

The change from baseline will be calculated as follows:

$$\Delta_{Baseline} = Post\ baseline\ value - Baseline\ value$$

4.1.3 Definition of percent change from baseline

$$\%\Delta = \frac{Post\ baseline\ value - Baseline\ value}{Baseline\ value} * 100\%$$

4.1.4 Mixed Model: Terms and Estimation

The form of the mixed effects model employed in the analyses in this study is as follows:

$$\ln(SK\ level)_{ij} = X_{ij}\beta + Z_i b_i + \varepsilon_{ij},$$

where $ln(\text{SK Level})_{ij}$ is the S-K level in the natural log scale for the jth measurement for the ith patient, X_{ij} is the matrix of fixed effects covariates, β is a vector containing the fixed-effects regression coefficients, Z_i represents the random effects covariates, b_i is a normally distributed random effect parameter, and ε_{ij} is a normally distributed random error term.

Unless otherwise stated, all mixed effects models used in the evaluation of the study objectives will use the covariates in Table 4 in estimating the model parameters:

Table 4 Fixed and Random Effects

Fixed Effects	Random Effects
• visit (treated as a categorical variable) • treatment groups (ZS 10g qd, ZS 5g qd and placebo) • visit-by-treatment interaction • both baseline S-K values (48-hour open-label initial phase and double-blind randomised phase) • baseline eGFR (during 48-hour open-label initial phase) • age category (<55, 55-64, ≥65 years) • country • baseline binary indicators for RAAS inhibitors • baseline chronic kidney disease status (CKD) • baseline congestive heart failure status (CHF) • baseline diabetes mellitus status (DM)	• Patient

Variance components will be estimated using a restricted maximum likelihood method (REML) and an unstructured covariance structure will be assumed. Should the specified model fail to converge, the final covariance structure will be determined by Akaike's information criterion: Toeplitz, first-order autoregressive and compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

4.1.5 Log-transformation of S-K values

For the purpose of statistical modeling, a natural log transformation will be applied to the S-K level since historical data shows that S-K measurements follows a log-normal distribution, and will then stabilise the variance.

4.1.6 Handling of missing data

4.1.6.1 S-K efficacy endpoint

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 and with the same calibration method for the potassium assay. For details on the change to the potassium assay calibration assay, see Section 3.4.5 or Section 8.4, Appendix D.

If a patient is missing both the central laboratory and i-STAT values for the last visit on treatment, the EOS value will be used if it is within 1 day of a target study day and the last dose date.

No other data will be imputed or inferred for either missing baseline or on-study data for any other efficacy endpoint.

4.1.6.2 Missing start and stop dates – AEs and concomitant medications

AE and concomitant medication missing start/stop dates will appear as missing in the patient data listings, but will be imputed to permit the proper tabulation of AE data. The imputation of missing AE and concomitant medication onset/start and end/stop dates will be used to determine the status of each AE and the previous/concomitant status of each medication. Please refer to Section 8.1, Appendix A, for the method of imputation of missing AE onset/start and end/stop dates and Section 8.2, Appendix B, for the method of imputation of missing concomitant medication onset/start and end/stop dates.

4.1.7 Definition of subgroups

The definition of the subgroup of patients with heart failure, chronic kidney disease and diabetes mellitus will be coded from medical history using the narrow MedDRA SMQs. The full list of Preferred Terms is found in Section 8.3, Appendix C.

4.2 Hypotheses

4.2.1 Primary hypotheses

The null hypothesis is that there is no treatment difference in the mean S-K levels (Days 8-29) compared to placebo as follows (two null hypotheses):

$$H_0 : \mu_{sk}(ZS\_10g) = \mu_{sk}(Placebo) \text{ vs. } H_A : \mu_{sk}(ZS\_10g) \neq \mu_{sk}(Placebo)$$

$$H_0 : \mu_{sk}(ZS\_5g) = \mu_{sk}(Placebo) \text{ vs. } H_A : \mu_{sk}(ZS\_5g) \neq \mu_{sk}(Placebo)$$

4.2.2 Secondary hypotheses

For the 48-hour open-label initial phase, the following null hypotheses will be tested versus two-sided alternative:

Exponential rate of change in S-K levels =0;
Mean S-K change from baseline at 24hours of first dose = 0
Mean S-K change from baseline at 48 hours of first dose=0;
Mean S-K percent change from baseline at 24 hours = 0
Mean S-K percent change from baseline at 48 hours=0;

For the subsequent 28-day randomised treatment study phase, the following null hypotheses will be tested versus two-sided alternative relative to placebo:

The proportion of patients in the ZS 10g treatment group who remain normokalemic;

The proportion of patients in the ZS 5g treatment group who remain normokalemic;

The mean number of days patients in the ZS 10g treatment group remain normokalemic;

The mean number of days patients in the ZS 5g treatment group remain normokalemic;

The median time (days) to hyperkalemia in the ZS 10 g patients;

The median time (days) to hyperkalemia in the ZS 5 g patients;

The mean change in S-Aldo in the ZS 10g treatment group;

The mean change in S-Aldo in the ZS 5g treatment group.

The mean change in P-Renin in the ZS 10g treatment group.

The mean change in P-Renin in the ZS 5g treatment group.

4.2.3 Multiple testing strategy

An overall Type I error rate of 5% accounting for efficacy analyses, in both phases of the study, will be maintained using a sequential closed testing procedure.

The analyses for the 28-day randomised treatment study phase will focus on randomised withdrawals. Treatment testing will proceed from high dose (ZS 10g) to low dose (ZS 5g) relative to placebo, with statistical significance (two-sided p-value ≤ 0.05) required for the high dose vs. placebo control in order to proceed to the low dose vs. placebo control.

Specifically, the following fixed hierarchical sequence will be employed; progression to the next test in the sequence will continue until a 2-sided p-value >0.05 is encountered, at which point further testing will cease. Explicitly, Table 6 will be implemented.

Table 6 Confirmatory Testing Sequence

Seq	Study phase	Efficacy variable	Comparison
1	Acute[i]	48-hour open label phase mean change from baseline of S-K 48 hours after first dose of ZS 10g	
2	Maintenance[ii]	28-day randomised treatment study phase Days 8-29 mean S-K	ZS 10g QD vs. Placebo
3	Maintenance	28-day randomised treatment study phase Days 8-29 mean S-K	ZS 5g QD vs. Placebo
4	Maintenance	Proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomised treatment study phase at Study Day 29/Exit[iii]	ZS 10g QD vs. Placebo
5	Maintenance	Proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomised treatment study phase at Study Day 29/Exit[iii]	ZS 5g QD vs. Placebo
6	Maintenance	Number of days patients remain normokalemic during the 28-day randomised treatment study phase	ZS 10g QD vs. Placebo
7	Maintenance	Number of days patients remain normokalemic during the 28-day randomised treatment study phase	ZS 5g QD vs. Placebo
8	Maintenance	Time to hyperkalemia (defined as S-K $\geq$ 5.1 mmol/L during the 28-day randomised treatment study phase)	ZS 10g QD vs. Placebo
9	Maintenance	Time to hyperkalemia (defined as S-K $\geq$ 5.1 mmol/L during the 28-day randomised treatment study phase)	ZS 5g QD vs. Placebo

i Acute Study Phase refers to the 48-hour Open Label Initial Phase.
ii Maintenance Study Phase refers to the 28-day randomised treatment Study Phase.
iii Study Day 29/Exit refer to day of last dose of study treatment

4.3 Analysis methods

4.3.1 Demographics and baseline characteristics

Demographic and baseline characteristics of age (at screening), age categories (<55, 55-64, ≥65 years), country, sex, race, ethnicity, weight, height, BMI will be summarised by study phase using their respective full analysis sets. For the RTP, the baseline will be summarised by treatment groups as well as overall.

The number and percent of patients with the following baseline disease characteristics will also be summarised:

- chronic kidney disease (CKD)
- diabetes mellitus (DM)
- heart failure (HF)
- use of renin-angiotensin-aldosterone system (RAAS) inhibitors.

4.3.2 Patient disposition and study population

All enrolled patients will be included in summaries of patient disposition and patient availability for analysis populations by treatment group. Patients signing the ICF are considered enrolled. Patient accounting will be provided for the following parameters:

- Number of patients entered in the OLP and OLP completers. A completer is defined as a patient who were treated with study drug during the OLP and have both OLP baseline and 48-hour S-K assessments. Those who do not enter the randomised phase and have completed the EOS visit will be defined as OLP completers;
- Number of RTP-eligible patients defined as an OLP completer with S-K levels between 3.5 and 5.0 mmol/L, inclusive, at the OLP 48-hour time point;
- Number of RTP randomised patients, completion status, and reasons for discontinuations, where a completer is defined as patients who were randomised and completed Day 29 and EOS procedures.

Also, patient exclusions from analysis populations will be tabulated.

4.3.3 Medical History

Prior medical conditions/diseases are those medical conditions/diseases that are taken within 7 days before start of study medication while current medical conditions/diseases are those medical conditions/diseases that are still present when receiving first treatment of ZS or after first treatment.

The number of patients with any past and current medical conditions/diseases will be tabulated by MedDRA SOC and PT for OLP and RTP respectively. A patient will only be counted once within a particular SOC (or PT) even if he/she has multiple conditions/diseases in the same SOC (or PT). For RTP, the summary statistics will be displayed by treatment groups as well as overall.

4.3.4 Prior and/or Concomitant Medication

Prior medications are defined as medications taken with a start date that falls before the first dose of study medication (ZS). 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 data sets (FAS-OLP or FAS-RTP). For the RTP, the summary statistics will be displayed overall as well as by treatment groups.

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. A summary table for disallowed (and allowed) concomitant medication taken during the study will also be provided.

4.3.5 48-hour open-label initial phase efficacy analyses

Descriptive statistics will be presented for S-K level at baseline, Day 1 (1, 2 and 4 hours post first dose) and Day 2 (pre-dose and 1 hour post the first dose in the day), including the nominal and percent changes from baseline.

4.3.5.1 Exponential rate of change

The exponential rate of change in S-K levels will be derived from a mixed effects model (SAS PROC MIXED) of serial, log-transformed S-K levels during the OLP. In addition to the fixed effects in table 4 (with the exception of the visit and treatment effects) time will be included as a fixed effect. A random intercept and slope (for time) will be used in the model. The time effect estimate will be presented with corresponding standard errors and p-values.

4.3.5.2 Mean change from baseline and mean percent change from baseline

For changes from baseline and percent changes from baseline in S-K levels at Visit 3 (24 hours) and Visit 4 (48 hours), one sample, two-sided t-tests will be applied to test the null hypotheses that the means equal zero. The p-value for the change from baseline at Visit 4 will be used in the sequential closed testing procedure (the first test in the sequential closed testing procedure).

4.3.5.3 Proportion of normokalemic patients

The observed proportions of patients achieving normokalemia at Visit 3 (24 hours) and Visit 4 (48 hours) will be provided along with 95% two-sided Clopper-Pearson exact confidence intervals.

4.3.5.4 Time to normalisation in S-K values

The time to normalisation in S-K levels will be summarised using Kaplan-Meier life table curves and associated 95% CI points will be provided in the figure. All S-K assessments

during OLP (e.g., not just those at 24 and 48 hours) will be used. Patients who fail to achieve normalisation will be censored at last measurement (the last measurement before the first dose of 28-day randomised treatment study phase). Patients who discontinued due to high S-K levels (i-STAT potassium levels > 6.2 mmol/l at the 90-minute post dose 2 blood draw) will be treated the same as the patients who fail to achieve normalisation and will be censored at 48 hours. Other discontinued patients will be censored at the last S-K evaluation.

4.3.6 28-day randomised treatment study phase (RTP) efficacy analyses

4.3.6.1 Primary efficacy analysis

The primary endpoint in this study will be the model-based LSMEAN of available S-K values during the 28-day randomised treatment study phase for Study Days 8-29. The longitudinal model specified in Section 4.1.4 (SAS PROC MIXED) will be used to estimate the least squares means for Days 8-29 and compare each active dose (ZS 10g and ZS 5g) versus the placebo. The response variables will be S-K values (natural log scale) during Days 8-29. Fixed and random treatment effects are those in Table 4.

The p-value from two sample t-tests (two-sided) will be provided to compare the overall mean difference in S-K values between each active treatment (ZS 10g and ZS 5g) and placebo (the second and third tests in the sequential closed testing procedure).

The estimated mean difference in S-K values between each of the active treatment groups (ZS 10g and ZS 5 g) relative to the placebo treatment group will be provided along with accompanying 95% confidence intervals.

The results from the above analysis will be presented both as modelled and back-transformed to their original scale.

Descriptive statistics will be presented for S-K values at the OLP baseline, RTP baseline and Visit 5 (Day 1) through Visit 13 (Day 29), and the EOS visit. Nominal changes and percent changes from each baseline (OLP and RTP) will be summarised by treatment groups (ZS 5g, ZS 10g and placebo).

4.3.6.2 Secondary efficacy analysis

4.3.6.2.1 Number of patients who remain normokalemic at Study Day 29/Exit

For the Day 29/Exit time point, the percentage of normokalemic patients at RTP Day 29/Exit will be compared using a logistic regression model containing the same baseline covariates, with the exception of visit and visit-by-treatment interaction, as for the primary efficacy endpoint (See Section 4.1.4). The p-value at the Day 29/Exit time point will be used in the sequential closed testing procedure (fourth and fifth tests in the sequential closed testing

procedure). Additionally, the proportion of patients who remain normokalemic will be presented by study visit.

4.3.6.2.2 Number of days patients remain normokalemic

The number of normokalemic days during the RTP, inclusive of Days 8-29, 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 assessment time point is missing, the time interval will be extended until the next non-missing time point.

The number of normokalemic days will be analysed using a linear regression model with the same covariates, with the exception of visit and visit-by-treatment interaction, as for the primary efficacy endpoint analysis (See Section 4.1.4). The p-value (two-sided) will be provided to compare the LSMEANs of the normokalemic days between each active treatment versus placebo (sixth and seventh tests in the sequential closed testing procedure).

Descriptive statistics for the number of normokalemic days will be provided for each treatment group.

4.3.6.2.3 Time to hyperkalemia

Kaplan-Meier curves of the time to hyperkalemia will be displayed for each treatment group.

A proportional hazards model (SAS PROC PHREG) will be assessed with the same covariates, with the exception of visit and visit-by-treatment interaction, as for the primary efficacy endpoint analysis (See Section 4.1.4). The hazard ratio between each active treatment versus placebo will be reported along with a 95% confidence interval.

4.3.6.2.4 S-Aldo and P-Renin levels

Descriptive statistics will be presented for nominal values, change from baseline and percent change from baseline in S-Aldo and P-Renin levels during 28-day randomised treatment study phase at Visits 4, 9, 13 and EOS for each treatment group.

Treatment group differences (each active treatment vs. placebo) for the mean change from baseline will be assessed by two-sided, two sample t-test at each visit for both S-Aldo and P-Renin.

4.3.7 Sensitivity analyses of primary and selected secondary efficacy variable

4.3.7.1 Sensitivity analysis replacing central laboratory S-K with i-STAT

A sensitivity analysis will be conducted to assess the robustness of the results of the primary efficacy analysis. This will be performed by using the same longitudinal model on patients Day 8 to Day 29 i-STAT measurements.

4.3.7.2 Sensitivity analysis to assess impact of change to potassium assay

Sensitivity analyses will be conducted to assess the impact of the change to the calibration method for the potassium assay. The calibration method for the potassium assay at the central laboratory was changed during the study, and the new calibration method is on average 0.208 mmol/L larger compared to the old calibration method. Details are provided in Section 3.4.5 and Section 8.4, Appendix D. Because the change to the calibration was done late in the study, the majority of potassium measurements will be analysed by the old calibration.

In order to assess the impact of this change, sensitivity analyses will be conducted for the primary analysis of mean S-K during RTP Days 8-29 and for the secondary efficacy analyses included in the sequential closed testing procedures:

- Proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomised treatment study phase at Study Day 29/Exit
- Number of days patients remain normokalemic during the 28-day randomised treatment study phase
- Time to hyperkalaemia (defined as S-K $\geq$ 5.1 mmol/L during the 28-day randomised treatment study phase)

Sensitivity analyses will be performed by subtracting the average bias between the old and the new calibrations from all the S-K measurements analysed by the new assay. By doing this, results will reflect what could have been observed had the assay not been changed. Analyses will be repeated on this new data containing all original S-K measurements analysed by the old calibration method and the adjusted measurements analysed by the new method calibration.

4.3.8 Other secondary analysis

The health state of the study population will be assessed at Visit 2 and Visit 13 using the EQ-5D questionnaire. EQ-5D will be summarised separately using their respective full analysis sets at their respective study phases.

The five subscores of EQ-5D on mobility, self-care, usual activities, pain/discomfort and anxiety/depression at Visit 2 and Visit 13 will be summarised by presenting the number of patients and percentage for each category. Visual analogue scale (VAS) at Visit 2 and Visit 13 will be summarised by presenting the number of non-missing observations, mean, standard deviation, median, inter-quartile range, minimum and maximum.

4.3.9 Safety analyses

Separate safety analyses will be performed for the OLP and the RTP presented by treatment. Safety endpoints will include adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations, ECGs, clinical laboratory evaluations, and other electrolytes

(specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

The respective safety analyses will be undertaken on the safety analysis sets, separately for the initial phase (SAF-OLP) and for the 28-day randomised treatment study phase (SAF-RTP).

4.3.9.1 Treatment Duration, Treatment Compliance, and Exposure

Summary statistics (number of non-missing observations, mean, median, standard deviation, minimum and maximum values) will be presented for the total duration of exposure, study treatment exposure and compliance for the actual dose received in the OLP and for each of the randomised treatment groups (ZS 5g, ZS 10g and placebo) in the RTP

Total duration of exposure in each study phase will be calculated as:

$$[date\ of\ last\ dose\ of\ study\ drug - date\ of\ first\ dose\ of\ study\ drug + 1\ day].$$

Study treatment exposure in each study phase is the total duration of exposure minus the sum of days where the drug was not taken due to interruption.

Compliance will be calculated as:

$$Compliance\ (\%) = \frac{Total\ number\ of\ sachets\ taken}{Expected\ number\ of\ sachets\ taken} \times 100\%\,,$$

where the expected number of sachets is calculated over the patient's actual duration in the trial and not the planned duration.

A patient listing which describes dose regimen (the planned dose, the actual dose, the unit, frequency) and exposure will be provided.

A listing of patients with dose adjustments during the RTP will be provided. This listing will include the days when such change happened and the confirmed i-STAT potassium values that resulted in the dose adjustment.

4.3.9.2 Adverse Events (AEs)

Adverse Events will be presented separately for the OLP and the RTP. Only AEs considered treatment-emergent will be presented in summary tables. Treatment-emergence is defined as AEs occurring during treatment. That is, with an onset date on or after the day of first dose of study medication and no later than the day of last dose of study medication + 1 day. AE summaries will display the number of patients experiencing the event and not the total number of events. Adverse events will be classified into system organ class (SOC) and preferred term (PT) using the latest version of MedDRA. All AEs, including those not considered treatment-emergent, will be included in safety listings.

The onset date of the AE determines the phase in which the AE will be summarised. AEs with an onset date prior to administration of the first randomised study medication in the RTP will be included in the summary for the OLP. If a patient has an AE with an onset date that occurs after administration of the first dose of randomised study medication in the RTP, the AE will be included in the summary for the RTP. In order to have a consistent "worst case" allocation of AEs, any AE with an onset on OLP Day 3 (day of randomisation) will be summarized for the OLP, because it will not be able to distinguish AEs occurring before or after the actual intake of randomised IP.

Narratives will be written for every AE classified as serious or leading to withdrawal of IP.

All AEs will be presented in individual listings. The listing will contain the following information: phase, treatment group, verbatim term, PT, intensity, relationship to study medication, day of onset and duration of AE, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

4.3.9.2.1 Overall Summary of Adverse Events

AEs will be summarised by treatment group for the OLP phase and the RTP and will include the following:

- the number and percentage of patients experiencing an AE
- the number and percentage of patients experiencing an AE with an outcome of death
- the number and percentage of patients experiencing an SAE
- the number and percentage of patients experiencing an AE leading to treatment withdrawal

4.3.9.2.2 AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number and percentage of patients with AEs will be summarised by SOC and PT, by treatment group.

A patient with more than one type of AE in a particular SOC will be counted only once in the total of patients experiencing AEs in that particular SOC. Since a patient could have more than one type of AE within a particular SOC, the sum of patients experiencing different AEs within the SOC could be larger than the total number of patients experiencing AEs in that SOC. Similarly, a patient who has experienced an AE in more than one SOC will be counted only once in the total number of patients experiencing AEs in all SOCs.

The number of AEs and the number and percentage of patients with AEs that led to permanent discontinuation of study drug will be summarised by SOC and PT, by treatment group.

4.3.9.2.3 AEs and SAEs by PT, and Relationship

The number and percentage of patients with AEs will be summarised by PT, relationship to study drug, and treatment group.

4.3.9.2.4 AEs by PT, and Severity

The number and percentage of patients with AEs will be summarised by PT, intensity (mild, moderate, or severe), and treatment group.

4.3.9.2.5 Deaths

The number and percentage of patients with AEs with outcome of death will be summarised by SOC, PT, and treatment group.

Patient listings of all deaths and their causes will be provided by phase and treatment group.

4.3.9.3 Analyses for Laboratory Tests

Descriptive statistics by time of assessment will be presented for each laboratory parameter described in Table 3 separately for the initial phase (SAF-OLP) and for the 28-day randomised treatment study phase (SAF-RTP). Changes from baseline for continuous variables as well as shift tables for categorical variables will be presented, separately for the initial phase (SAF-OLP) and for the 28-day randomised treatment study phase (SAF-RTP). All laboratory values will be classified as low, normal, or high based on normal ranges supplied by the central laboratory. For purposes of analyses, laboratory results based upon standardised units will be used.

For each summary of continuous variables, the number of non-missing observations, mean, median, standard deviation, minimum, and maximum values will be presented by phase and by treatment group.

Bivariate plots for AST and ALT vs. Total Bilirubin will be provided.

4.3.9.4 Vital Signs

Vital sign measurements will be summarised at selected visits. For each summary, the number of non-missing observations, mean, median, standard deviation, minimum, and maximum will be presented by treatment group for each study phase (OLP or RTP).

4.3.9.5 Physical Examination

Physical examination is stated as a safety endpoint in the CSP. However, no separate analyses will be provided. Physical examinations are performed by the investigator according to the schedule of assessments (Table 1 and Table 2). If there are new or aggravated findings, as compared with baseline, these are to be reported as AEs.

4.3.9.6 Pregnancy Test

A by-patient listing of all pregnancy tests will be provided by phase as well as by treatment group.

4.3.10 Subgroup analyses

To facilitate a benefit-risk assessment for the purpose of regulatory submission in Japan, the subgroup of patients from Japan will be analysed separately, with respect to efficacy and safety variables for both phases of the study and presented in a Japanese specific Clinical Study Report.

For all summary tables, descriptive statistics will be generated for Japan patients. The selected models described in Section 4.2 will be separately applied to Japanese patients. The country-related covariates will be excluded when fitting the analysis models. For example, in the longitudinal models (SAS PROC MIXED), a term for country will be excluded from the models.

In addition, analyses will be performed for the primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/l, inclusive) at the end of the 28-day randomised treatment study phase in order to explore the variation of the treatment effect in the following subgroups:

- baseline chronic kidney disease status
- baseline diabetes mellitus status
- baseline heart failure status
- Those on RAAS inhibitors

Separate models will be fitted for each subgroup with a treatment by subgroup interaction term in addition to the covariates in the original analysis. Estimates of the treatment by subgroup interaction will be provided with corresponding p-values and confidence intervals. Additionally, for the analysis of the primary endpoint on the subgroups, LSMEANs for the combinations of treatment by subgroup levels will be presented with corresponding confidence intervals.

5 INTERIM ANALYSES

No applicable.

6 CHANGES OF ANALYSIS FROM PROTOCOL

In table 6 of the protocol, the sixth and seventh tests in the sequence were number of days patients remaining normokalemic during the 28-day randomised treatment study phase Days 8 to 29, inclusive. In SAP, the number of days patients remaining normakalemic will be calculated from day 1 to day 29 in RTP. It was revised in the table 6 of SAP.

7 REFERENCES

No applicable.

8 APPENDIX

8.1 Appendix A: Partial date conventions for AE

Missing type	Action
If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose of study medication	If AE's ending date is before the date of the first dose, the first day of the month will be used to complete the onset date of the AE. If AE's end date is on or after the first dose of study medication, the date of first dose of study medication will be used as the onset date of the AE.
If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study medication	If AE's end date is on or after the first dose of study medication, the date of the first dose of study medication will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE.
If the AE onset date is completely missing	If the end date is on or after the first dose of study medication,the date of the first dose of study medication will be used as the onset date of the AE.

8.2 Appendix B: Algorithm for prior/concomitant medications:

START	STOP	ACTION
Known	Known	If stop date < study med start date, assign as prior; If stop date ≥ study med start date and start date ≤ study med last date + 30 days, assign as concomitant; If stop date > study med start date and start date > study med last date + 30 days, assign as post study.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥study med start date and start date ≤ study med last date + 30 days, assign as concomitant If stop date > study med start date and start date > study med last date + 30 days, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ study med last date + 30 days, assign as concomitant If start date > study med last date + 30 days, assign as post treatment
	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date≥ study med start date and start date ≤ study med last date + 30 days, assign as concomitant If stop date > study med start date and start date > study med last date + 30 days, assign as post treatment

Partial	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date ≤ study med last date + 30 days, assign as concomitant If stop date > study med start date and start date > study med last date + 30 days, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ study med last date + 30 days, assign as concomitant If start date > study med last date + 30 days, assign as post treatment

8.3 Appendix C: Definition of subgroups

The narrow SMQs for cardiac failure, CKD and diabetes, found in Table 5, Table 6 and Table 7, respectively, will be used for the definition of the subgroups for heart failure, chronic kidney disease and diabetes mellitus.

Table 5 Definition of Heart Failure

Preferred term
Acute left ventricular failure
Acute pulmonary oedema
Acute right ventricular failure
Cardiac asthma
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiogenic shock
Cardiopulmonary failure
Cardiorenal syndrome
Chronic left ventricular failure
Chronic right ventricular failure
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Ejection fraction decreased
Hepatic congestion
Hepatojugular reflux
Left ventricular failure
Low cardiac output syndrome
Neonatal cardiac failure
Obstructive shock
Pulmonary oedema
Pulmonary oedema neonatal
Radiation associated cardiac failure
Right ventricular ejection fraction decreased
Right ventricular failure
Ventricular failure

Table 6 Definition of Chronic Kidney Disease

Preferred term
Artificial kidney device user
Azotaemia
Chronic kidney disease
Chronic kidney disease-mineral and bone disorder
Coma uraemic
Diabetic end stage renal disease
Dialysis
Dialysis device insertion
End stage renal disease
Glomerulonephritis chronic
Haemodialysis
Haemofiltration
Hepatorenal failure
High turnover osteopathy
Hyperparathyroidism secondary
Kidney fibrosis
Low turnover osteopathy
Nephrogenic anaemia
Nephrogenic systemic fibrosis
Nephrosclerosis
Oedema due to renal disease
Pericarditis uraemic
Peritoneal dialysis
Renal and liver transplant
Renal and pancreas transplant
Renal failure
Renal replacement therapy
Renal rickets
Renal transplant
Uraemia odour
Uraemic acidosis
Uraemic encephalopathy
Uraemic gastropathy
Uraemic myopathy
Uraemic neuropathy
Uraemic pruritus
Uridrosis

Table 7 Definition of Diabetes Mellitus

Preferred Term
Acquired lipoatrophic diabetes
Blood 1,5-anhydroglucitol decreased
Blood glucose increased
Diabetes complicating pregnancy
Diabetes mellitus
Diabetes mellitus inadequate control
Diabetes with hyperosmolarity
Diabetic arteritis
Diabetic coma
Diabetic hepatopathy
Diabetic hyperglycaemic coma
Diabetic hyperosmolar coma
Diabetic ketoacidosis
Diabetic ketoacidotic hyperglycaemic coma
Diabetic ketosis
Diabetic metabolic decompensation
Euglycaemic diabetic ketoacidosis
Fructosamine increased
Fulminant type 1 diabetes mellitus
Gestational diabetes
Glucose tolerance impaired
Glucose tolerance impaired in pregnancy
Glucose urine present
Glycosuria
Glycosuria during pregnancy
Glycosylated haemoglobin increased
Hyperglycaemia
Hyperglycaemic hyperosmolar nonketotic syndrome
Hyperglycaemic seizure
Hyperglycaemic unconsciousness
Impaired fasting glucose
Insulin resistance
Insulin resistance syndrome
Insulin resistant diabetes
Insulin-requiring type 2 diabetes mellitus
Ketoacidosis

Ketonuria
Ketosis
Ketosis-prone diabetes mellitus
Latent autoimmune diabetes in adults
Metabolic syndrome
Monogenic diabetes
Neonatal diabetes mellitus
Pancreatogenous diabetes
Type 1 diabetes mellitus
Type 2 diabetes mellitus
Type 3 diabetes mellitus
Urine ketone body present

8.4 Appendix D: Change in calibration of the potassium assay

Attached to this Appendix is communication from central laboratory provider Covance regarding the change to the calibration of the potassium assay. It contains the results from an analysis of the correlation and relationship between the old and new calibration methods performed by Covance.

COVANCE

Covance Inc.
Central Laboratory Services
8211 SciCor Drive
Indianapolis, Indiana
46214-2985
PPD

30 November 2017

RE: Chemistry – Measurement of Electrolytes (Sodium, Potassium and Chloride)

Dear Client:

Covance is completing its conversion from the Roche Modular to the Roche cobas testing platform. This is accomplished in Indianapolis, Geneva, Singapore and Japan. The last conversion is in Shanghai and is on schedule to complete in early December.

With this conversion, Covance is making a change in its calibration protocol for electrolytes (sodium, potassium and chloride). Both the current methods and the new methods are the same (ion-selective electrodes or ISE's). Only the calibration is different. This change results in a small increase in the final reported values: for sodium (2.35 mmol/L), and potassium (0.208 mmol/L). Chloride remains largely unchanged (0.08 mmol/L). The new calibration protocol is in accordance with recommendations provided by Roche Diagnostics.

The following statistics are taken from the correlation studies performed by Covance CLS as part of our assessment and validation of the new calibration protocol. The studies examined the current calibration protocol compared to the new calibration protocol. With this change, the reference ranges remain unchanged. The final reported results are within the acceptability of the assays' performance.

Thank you.

PPD

Covance Clinical Laboratory Services

COVANCE

Correlation Statistics for ISE Calibration: Current Compared to New

Sodium

Slope: 0.997 (0.989 to 1.005)*
Intercept: 2.76 (1.66 to 3.87)*
Correlation Coefficient: 0.9992
Bias: 2.37 or 1.67%
Xmean – current method: 139.79 ± 26.28; range = 91.4 – 177.7
Ymean – new method: 142.14 ± 26.20: range = 93.1 – 179.3
Number of observations: 112
Units of measure: mmol/L

* 95% Confidence Interval

Potassium

Slope: 1.003 (0.997 to 1.009)*
Intercept: 0.194 (0.167 to 0.221)*
Correlation Coefficient: 0.9996
Bias: 0.208 or 4.545%
Xmean – current method: 4.474 ± 1.460; range = 2.19 – 7.65
Ymean – new method: 4.682 ± 1.465; range = 2.40 – 7.92
Number of observations: 109
Units of measure: mmol/L

* 95% Confidence Interval

Chloride

Slope: 1.003 (0.995 to 1.010)*
Intercept: - 0.20 (- 0.98 to 0.58)*
Correlation Coefficient: 0.9992
Bias: 0.08 or 0.08%
Xmean – current method: 101.21 ± 20.71
Ymean – new method: 101.29 ± 20.77
Number of observations: 114
Units of measure: mmol/L

* 95% Confidence Interval