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

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VERSION HISTORY

Version 5.0, 13 September 2018 **Changes to Clinical Study Protocol version 4.0 [28 March 2018] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
2.3 Exploratory objectives	"To explore change in doses and reasonings of the change of RAAS inhibitors during the treatment period" was added.	To add a new Exploratory objective
3.9 Discontinuation of investigational product	Discription about IP discontinuation critera related to potassium value was ammended	Clarification
3.9 Discontinuation of investigational product	Paragraph indent was ajusted	Clarification
3.9 Discontinuation of investigational product	Explanation that visit5 or visit 23 procedure is required for patients discontinuing IP was added.	To collect the end of treatment data
3.11 Interruption of investigational product	The section was added	To make it possible to interrupt IP when necessary
4. STUDY PLAN AND TIMING OF PROCEDURES	Annotation text #9 in Table 2 was removed. Pationt questionnaire at EOS visit was removed	To align with the change in section 3.9 (visit5 or visit 23 procedure for patients discontinuing IP)
4.2.1 Correction Phase Day 1 (Visit 2)	Explanation that hematology and clinical chemistry samples can be collected at the same time as iSTAT sample collection was added	To reduce patioents' burden associated with frequent needlepick.
4.2.7 Maintenance Phase Day 5 (Visit 8) 4.2.8 Maintenance Phase Day 12 (Visit 9) 4.2.9 Maintenance Phase Day 19 (Visit 10) 4.2.10 Maintenance Phase Day 26- Day 334 (Visit 11- Visit 22)	IP doses in sentences which describe situations requiring a second potassium measurement were corrected	Correction of error

Version 5.0, 13 September 2018 **Changes to Clinical Study Protocol version 4.0 [28 March 2018] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
4.3 Follow-up period (EOS)	Paragraph about patient questionnaire was removed	To align with the change in section 3.9 (visit5 or visit 23 procedure for patients discontinuing IP)
7.2 Dose and treatment regimens 7.7 Concomitant and other treatments	Allowed visit window for an extra visit has been changed from "±1" to "±2".	To increase flexibility
7.2 Dose and treatment regimens 7.7 Concomitant and other treatments	Restrictions that patients should follow for an extra visit has been added.	To obtain appropriate investigational results
7.7 Concomitant and other treatments	Additional data collected related to concomitant medication was described.	To align with newly added Exploratory objectives

Version 4.0, 28 March 2018 **Changes to Clinical Study Protocol version 3.0 [26 September 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
3.2 Exclusion criteria	"Washout of SPS and CPS for 7 days (or longer) prior to the first dose of ZS is allowed, if termination of CPS or SPS is judged to be clinically acceptable by the investigator. Documented informed consent has to be obtained prior to the washout." was added to exclusion criteria #4.	To clarify that SPS/CPS can be discontinued before study participation and IC has to be obtained before the discontinuation.
4.1 Screening/Enrolment period (Visit 1)	"The following rule will be applied for the patient who will be ineligible due to the deviation of inclusion criteria No. 3. If the patient is expected to meet the eligibility criteria based on the patient's disease condition, the patient can be re-enrolled (including one re-screening) only once after 30 days	To allow inclusion of patients showing fluctuation of blood K+ concentration. One re-enrollment is not considered to

Version 4.0, 28 March 2018 **Changes to Clinical Study Protocol version 3.0 [26 September 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
	or later from the screening failure. In this case, new enrolment number will be allocated to the patient" was added.	be a risk to the patient's opportunity for other treatment or the purpose of the study.

Version 3.0, 26 September 2017 **Changes to Clinical Study Protocol version 2.0 [11 May 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
CLINICAL STUDY PROTOCOL SYNOPSIS Objectives 2.3 Exploratory objectives 4 STUDY PLAN AND TIMING OF PROCEDURES 4.2.11 Maintenance Phase Day 362 (Visit 23) 4.3 Follow-up period (EOS) Appendix D	Exploratory objective, the adherence questionnaire was added.	Exploratory objective was added.
3.2 Exclusion criteria	"Non peritoneal dialysis (PD) patients only" was added.	To clarify the study procedure.
4 STUDY PLAN AND TIMING OF PROCEDURES	Table 2 Footnote 5 was amended.	Visit allowance was expanded to provide flexibility.
4.2.2 Correction Phase Day 2 (Visit 3)	"1 hour (± 15 min) after first serum potassium measurement a potassium sample (i-STAT and Central Laboratory) will be collected. " was added if	To align with Figure 4.

Version 3.0, 26 September 2017 **Changes to Clinical Study Protocol version 2.0 [11 May 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
	the i-STAT potassium value is between 3.0 and 3.4 mmol/L inclusive.	
4.2.6 Maintenance Phase Day 2 (Visit 7) ~ 4.2.11 Maintenance Phase Day 362 (Visit 23)	'The time' was changed to 'when' from phrase "examine the returned investigational product sachets and make note of the time the doses were taken and any unused investigational products on the eCRF and source documents."	Correction of error. The Dosing time will not be collected.
4.2.6 Maintenance Phase Day 2 (Visit 7) 4.2.7 Maintenance Phase Day 5 (Visit 8) 4.2.9 Maintenance Phase Day 19 (Visit 10)	boxes was deleted from "examine the returned investigational product boxes."	Correction of error
5.2.3.1 Resting 12-lead ECG	or <4.0 mmol/L was added.	To align with Figure 4.
7.7.1 Oral medications with gastric pH-dependent bioavailability	This section was included.	Updated information was added.

Version 2.0, 11 May 2017 **Changes to Clinical Study Protocol version 1.0 [09 March 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
4 STUDY PLAN AND TIMING OF PROCEDURES	Table 2 Added the assessment of serum chemistry on Visit 6 and footnote 8.	To clarify the study procedure.
4.2.1 Correction Phase Day 1 (Visit 2)	Order of SF-36 v2 questionnaire was changed and added sentence.	To clarify the study procedure.
4.2.5 Maintenance Phase Day 1 (Visit 6) 5.2.1 Laboratory	Added Clinical chemistry.	To align with Table 2 changes

Version 2.0, 11 May 2017 **Changes to Clinical Study Protocol version 1.0 [09 March 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
safety assessments		
4.2.11 Maintenance Phase Day 362 (Visit 23)	Order of SF-36 v2 questionnaire was changed and added sentence.	To clarify the study procedure.
5.10 Volume of blood	Table 5 Number of Samples and Maximum blood volume Total (mL) were updated. Added Visit 6 in footnote 1.	To align with Table 2 changes

Version 1.0, 9 March 2017
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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CLINICAL STUDY PROTOCOL SYNOPSIS

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

Principal Investigator(s)

See Addendum.

Study site(s) and number of patients planned

This study will be conducted in approximately 30 centers in Japan. The primary objective of this Japanese study is to assess the safety and tolerability of long-term treatment of ZS flexible dose regimen (initial dose 5g once daily [QD] then up- or down- titrated based on the potassium level) for 12 months. In total 150 subjects will be entered into the Correction Phase to have approximately 100 subjects treated for 1 year, assuming a drop-out rate of around 35%.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2017	Phase III
Estimated date of last patient completed	Q3 2019	

Study design

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

Correction Phase: If the subject is normokalemic (i-STAT [A portable blood analyser] potassium between 3.5 and 5.0 mmol/L, inclusive) on the morning of Correction Phase Study Day 2 after 3 doses of ZS 10 g, they will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID treatment (6 total doses). If the subject's i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, on the morning of Correction Phase Study Day 3, the subject will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID treatment (9 total doses). If the subject's i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, on the morning of Correction Phase Study Day 4, the subject will enter the Maintenance Phase. If the i-STAT potassium value is still < 3.5 mmol/L or ≥ 5.1 mmol/L on the morning of Correction Phase Study Day 4, after 72 hours of TID treatment, the subject will be withdrawn from the study and referred to their normal health care provider for standard of care treatment. Subjects withdrawn from the Correction Phase of the study will return to the clinic 7 (± 1) days after their last dose of ZS for an End of Study (EOS) visit.

Maintenance Phase: Patients will initially be dosed with ZS at a starting dose of 5g QD. Potassium (i-STAT and central laboratory) will be measured as indicated in the study schedule (Table 2). During the Maintenance Phase, the ZS dose may be increased up to 15 g QD or decreased down to 5g QOD (or 2.5 g QD) based on i-STAT potassium measurements as outlined in Section 7.2.

Throughout all phases of the study, most potassium values will be measured at fasting before taking ZS. Nothing should be taken by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications, for a minimum of 8 hours prior to the blood collection. Potassium level should be determined by both i-STAT and the Central Laboratory on all occasions. Treatment decisions (eg, dose titration, stopping rules) will be made based on i-STAT potassium values, as these provide clinical sites with a real-time measurement, according to dose modification rules as described in Section 7.2. Statistical analyses on the study data will in principle be based on S-K values as measured by the Central Laboratory.

Safety and tolerability will be assessed on an ongoing basis. Standard study assessments including blood potassium, clinical chemistry (including calcium, magnesium, sodium, phosphate, creatinine, bicarbonate, and blood urea nitrogen [BUN]), aldosterone, renin and hematology parameters, urinalysis, vital signs, physical examinations, and electrocardiograms (ECGs) will be assessed during the study at the time points specified in Table 1 and Table 2. All women of childbearing potential will have a urine pregnancy test prior to enrollment and at their End of Study (EOS) visit.

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

Objectives

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

Secondary Objectives:	Outcome Measures:
Maintenance Phase	
• To evaluate the proportion of ZS-treated subjects in whom normokalemia can be maintained over prolonged periods of time, using an individually titrated dose (5 g every other day [or 2.5 g once daily], 5 g once daily, 10 g once daily or 15 g once daily)	• Proportion of patients who can maintain normokalemia (defined as S-K level of ≥ 3.5 and ≤ 5.0 mmol/L, inclusive) on ZS at each Maintenance Phase study visit • Proportion of patients with average S-K ≤ 5.1 mmol/L • Proportion of patients with average S-K ≤ 5.5 mmol/L • Proportions of patients who were normokalemic (S-K ≥ 3.5 and ≤ 5.0 mmol/L), hypokalemic (< 3.5 mmol/L), or hyperkalemic (> 5.0 mmol/L) at each Maintenance Phase visit. • Subject-level average S-K over certain period of time • Observed values at visit and change from baseline in S-K over time • Number of normokalemic days during Maintenance Phase • Change in S-K level from the last on-treatment Maintenance Phase visit to the End of Study (EOS)
• To explore the time course of S-Aldosterone and S-Bicarbonate	• Change from baseline in S-Aldosterone over time • Proportion of patients with normal S-Aldosterone • Change from baseline in S-Bicarbonate • Proportion of patients with normal S-Bicarbonate
• To evaluate the health state in the study population using SF-36 v2.	• SF-36 v2 questionnaire
Correction Phase To assess efficacy, safety and tolerability of 10 g TID ZS in Japanese patients with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L).	• Observed values and change from Correction Phase baseline in S-K • Proportion of patients who achieved normokalemia at 24, 48 and 72 hours after start of dosing • Safety and tolerability as measured by adverse events reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements during Correction Phase

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

Target patient population

The target patient population consists of male and female patients aged ≥ 18 years with hyperkalemia, defined as two consecutive i-STAT potassium values, measured 60-minutes (± 15 minutes) apart, both ≥ 5.1 mmol/L within 1 day before the first dose of ZS on Correction Phase Study Day 1.

Duration of treatment

The study will start with the screening period, and all baseline parameters should be measured/collected up to 1 day prior to administration of first dose of study drug on Correction Phase Day 1. Subjects with 2 consecutive i-STAT potassium values ≥ 5.1 mmol/L will enter the Correction Phase and receive ZS 10 g TID for up to 72 hours, depending on potassium values. Once normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) is restored (whether after 24, 48 or 72 hours), subjects will be entered into the Maintenance Phase to be dosed with ZS at a starting dose of 5 g QD. Potassium (i-STAT and Central Laboratory) will be measured Days 1, 2, 5, 12, 19 and 26 throughout the first month of study and every 4 weeks thereafter until Day 362 (Visit 23) then patients will be required to complete the EOS visit which is 7±1 days after the last administration of study medication. For patients who do not enter the Maintenance Phase the last visit will be 7±1 day after the last treatment dose in the Correction Phase. The total expected study duration for an individual patient is approximately 53-54 weeks.

Investigational product, dosage and mode of administration

Sodium Zirconium Cyclosilicate (ZS) should be administered orally as a suspension in water.

Correction Phase: ZS 10g TID for 24, 48 or 72 hours (3, 6 or 9 doses). Patients will enter the Maintenance phase after 24, 48 or 72h if the morning i-STAT potassium is between 3.5 and 5.0 mmol/L, inclusive.

If a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval) during the Correction Phase the subject will be directed to not take any more study drug for the remainder of the day and return the next day to continue in the study.

Patients with i-STAT potassium <3.0 mmol/L (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval) should discontinue from therapy.

Maintenance Phase: The starting dose is ZS 5 g QD. The ZS dose may be increased in increments of 5 g up to a maximum of 15 g QD or decreased to a minimum of 5 g QOD (or 2.5 g QD) dependent upon i-STAT potassium measurements (see Dose modification rules in Table 6).

Statistical methods

Separate efficacy and safety analyses will be performed for the correction phase and maintenance phase. Separate analysis sets will be defined for each phase.

For the correction phase, patients will be considered evaluable if 1) they receive the correction dose and 2) they have any post-baseline S-K levels after receiving the ZS during the correction phase. Then, the full analysis set will include all patients that receive the ZS, and have any post-baseline S-K levels. The safety analysis set will include all patients as treated with at least one dose of correction phase ZS among those treated and with any post-baseline correction phase safety data.

For the subsequent maintenance phase, patients will be considered evaluable if 1) they receive the ZS and 2) they have any post-baseline maintenance phase S-K levels after receiving the ZS. Then, the full analysis set will include all patients who receive any ZS and have any post-baseline maintenance phase S-K levels. The safety analysis set will include all patients as treated with at least one dose of ZS among those dosed with any post-baseline maintenance phase safety data.

All safety and efficacy analyses will be carried out in a descriptive manner. If deemed necessary, 95% confidence intervals will also be presented.

Safety endpoints will include adverse events (including incidence of oedema-related events), vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters. Kidney function will be evaluated by assessments of creatinine, estimated Glomerular Filtration Rate (eGFR), urine protein-to-creatinine ratio (UPCR) and urine albumin-to-creatinine ratio (UACR) over time. Liver function will be evaluated by assessing bilirubin, AST and ALT.

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APD	Automated Peritoneal Dialysis
AST	Aspartate aminotransferase
AZ	AstraZeneca
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAPD	Continuous Ambulatory Peritoneal Dialysis
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPS	Calcium Polystyrene Sulfonate
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
i-STAT	A portable blood analyser
ITT	Intent-to-Treat
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HD	Hemodialysis
HF	Heart Failure
IB	Investigator's Brochure
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PD	Peritoneal Dialysis
PI	Principal Investigator
QD	once daily
QOD	every other day
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin angiotensin aldosterone system inhibitors
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S-K	Serum potassium
SPS	Sodium Polystyrene Sulfonate
TEAE	Treatment Emergent Adverse Event
TID	three times daily
UACR	Urine Albumin-to-Creatinine Ratio
UPCR	Urine Protein-to-Creatinine Ratio
WBC	White Blood Cell
WBDC	Web Based Data Capture
ZS	Sodium Zirconium Cyclosilicate

1. INTRODUCTION

1.1 Background and rationale for conducting this study

[redacted]

[redacted]

[redacted]

1.2 Rationale for study design, doses and control groups

[redacted]

1.3 Benefit/risk and ethical assessment

[redacted]

[redacted]

[redacted]

1.4 Study Design

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

Correction Phase: If the subject is normokalemic (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) on the morning of Correction Phase Study Day 2 after 3 doses of ZS 10 g, they will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID treatment (6 total doses). If the subject's i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, on the morning of Correction Phase Study Day 3, the subject will enter the Maintenance Phase. If the subject is not normokalemic, they will receive an additional 24 hours of ZS 10 g TID treatment (9 total

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

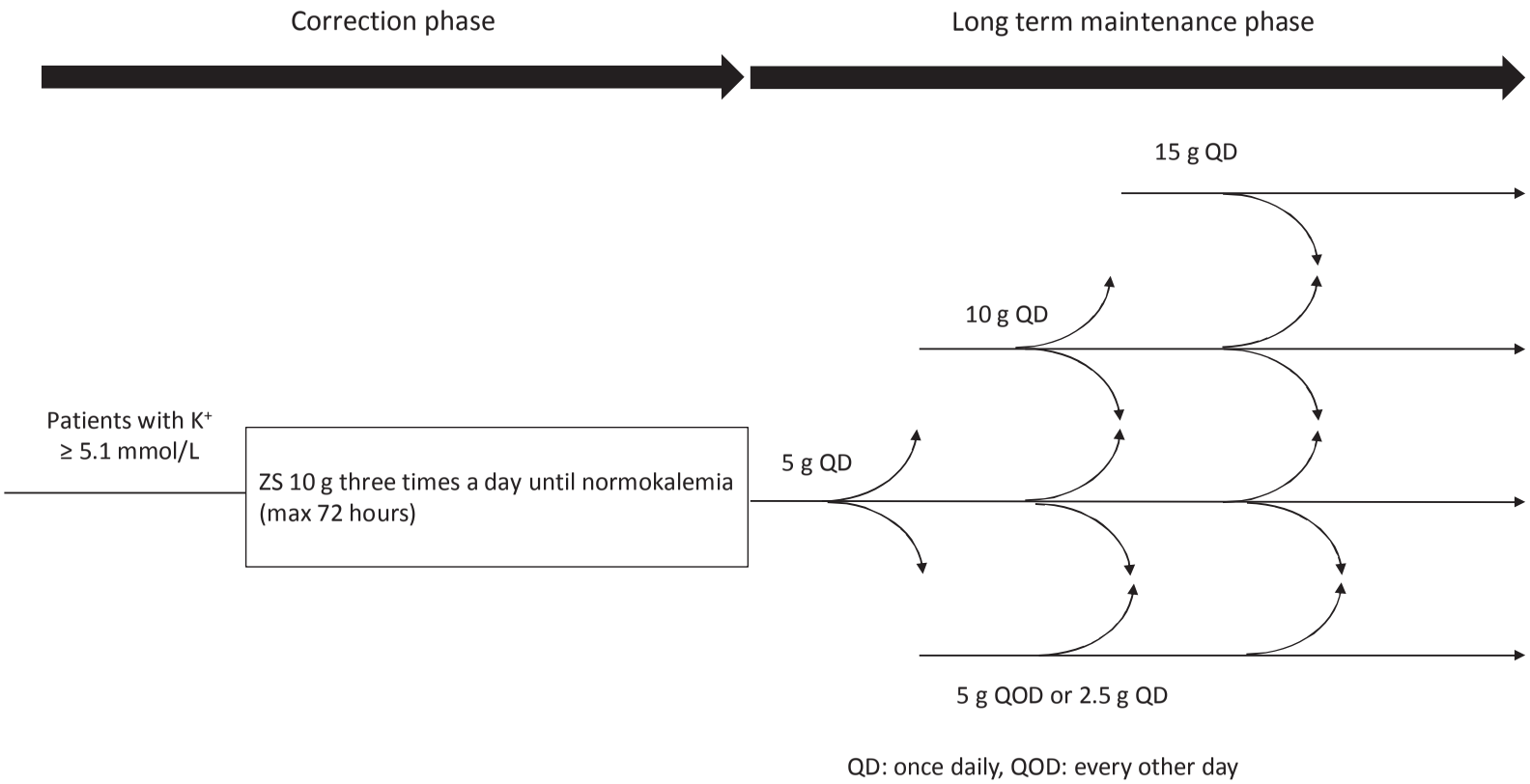
Maintenance Phase: Patients will initially be dosed with ZS at a starting dose of 5g QD. Potassium (i-STAT and central laboratory) will be measured as indicated in the study schedule (Table 2). During the Maintenance Phase, the ZS dose may be increased up to 15 g QD or decreased down to 5g QOD (or 2.5 g QD) based on i-STAT potassium measurements as outlined in Section 7.2.

Throughout all phases of the study, most potassium values will be measured at fasting before taking ZS. Nothing should be taken by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications, for a minimum of 8 hours prior to the blood collection. Potassium level should be determined by both i-STAT and the Central Laboratory on all occasions. Treatment decisions (eg, dose titration, stopping rules) will be made based on i-STAT potassium values, as these provide clinical sites with a real-time measurement, according to dose modification rules as described in Section 7.2. Statistical analyses on the study data will in principle be based on S-K values as measured by the Central Laboratory.

Safety and tolerability will be assessed on an ongoing basis. Standard study assessments including blood potassium, clinical chemistry (including calcium, magnesium, sodium, phosphate, creatinine, bicarbonate, and blood urea nitrogen [BUN]), aldosterone, renin and hematology parameters, urinalysis, vital signs, physical examinations, and electrocardiograms (ECGs) will be assessed during the study at the time points specified in Table 1 and Table 2. All women of childbearing potential will have a urine pregnancy test prior to enrollment and at their End of Study (EOS) visit.

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

Figure 3 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

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

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

2.3 Exploratory objectives

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

3. PATIENT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Patients aged ≥18. For patients aged <20 years, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

3. Two consecutive i-STAT potassium values, measured 60-minutes (± 15 minutes) apart, both ≥ 5.1 mmol/L and measured within 1 day before the first dose of ZS on Correction Phase Study Day 1.

4. Patients who are on peritoneal dialysis (PD) can be enrolled if their SK level is ≥5.5 and ≤ 6.5 mmol/L in two consecutive i-STAT potassium evaluation at least 24 hours apart before Day 1 (in each evaluation, two i-STAT potassium measurements at least 1 hour apart are required). i-STAT potassium measurement should be performed in the morning before breakfast and in the evening before dinner in PD patients on continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), respectively.

5. Ability to have repeated blood draws or effective venous catheterization.

6. Women of childbearing potential must be using 2 forms of medically acceptable contraception (at least 1 barrier method) and have a negative pregnancy test within 1 day prior to the first dose of ZS on Correction Phase Study Day 1. Women who are surgically sterile or those who are postmenopausal for at least 1 year are not considered to be of childbearing potential.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Cause or symptoms of pseudohyperkalemia, such as

   1) hemolyzed blood specimen due to excessive fist clenching to make veins prominent

   2) hemolyzed blood specimen due to difficult or traumatic venepuncture

   3) history of severe leukocytosis or thrombocytosis

3. Patients treated with lactulose, rifaxan (rifaximin), or other non-absorbed antibiotics for hyperammonemia within 7 days prior to first dose of ZS.

4. Patients treated with resins (such as sevelamer hydrochloride, sodium polystyrene sulfonate [SPS; e.g. Kayexalate®] or calcium polystyrene sulfonate [CPS]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug. Washout of SPS and CPS for 7 days (or longer) prior to the first dose of ZS is allowed, if termination of CPS or SPS is judged to be clinically acceptable by the investigator. Documented informed consent has to be obtained prior to the washout.

5. Patients with a life expectancy of less than 12 months

6. Patients who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the patients' tasks associated with the protocol

7. Female patients who are pregnant, lactating, or planning to become pregnant

8. Patients who have an active or history of diabetic ketoacidosis

9. Presence of any condition which, in the opinion of the investigator, places the patient at undue risk or potentially jeopardizes the quality of the data to be generated

10. Known hypersensitivity or previous anaphylaxis to ZS or to components thereof

11. Treatment with a drug or device within the last 30 days that has not received regulatory approval at the time of study entry.

12. Patients with cardiac arrhythmias that require immediate treatment

13. Hemodialysis patients (including those who are on both PD and hemodialysis [HD])

14. Patients who have been on PD less than 6 months or more than 6 months with a history of hypokalemia within 6 months before Correction Phase Day 1

15. Documented Glomerular Filtration Rate (GFR) < 15 mL/min within 90 days prior to study entry (Non peritoneal dialysis (PD) patients only)

16. If patients joined ZS study in the past, the patients cannot join this study within the last 30 days of the last study drug administration day.

For procedures for withdrawal of incorrectly enrolled patients, see Section 3.4.

3.3 Patient enrolment

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form (ICF).

2. Assign potential patient a unique enrolment number via Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS), beginning with 'E#'.

3. Patients will remain associated with the same enrolment number throughout the entire study, and patients should NOT receive any new E-code if re-screened. If a patient signs the ICF but does not meet the inclusion/exclusion criteria the patient will be marked as a screen failure on the Screening and Enrolment Log provided by the Sponsor and will be entered in the Web Based Data Capture (WBDC) as a screen failure. Patients can be re-screened once. A new ICF does not need to be signed before re-screening if the original ICF was signed within 30 days and the ICF has not been revised.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused.

3.4 Procedures for handling incorrectly enrolled

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not start treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups (Not Applicable)

3.6 Methods for ensuring blinding (Not Applicable)

3.7 Methods for unblinding (Not Applicable)

3.8 Restrictions

For concomitant medications which are restricted during the study, please see Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Risk to patient as judged by investigator
- Pregnancy
- Require treatment with medications prohibited or contraindicated for use due to safety concerns with ZS
- Patient develops potassium values which meet the IP discontinuation criteria described in Table 6 (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). Patients discontinuing due to this criterion must immediately receive appropriate medical treatment to manage their hypo- or hyperkalemia.

Patient develops clinically significant cardiac condition (see below). The patient should immediately receive appropriate medical treatment and be discontinued from study drug.

- Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])
- Acute heart failure
- Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block) or widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block). If an ECG shows peaked T-wave, the serum potassium must be checked immediately and decide whether to continue the IP based on the criteria described in Section 3.9.
- An absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec. All patients meeting the QTc>500ms criterion should immediately have potassium assessed by i-STAT and central lab, if not already done within 1 hour of the collection of the ECG

Patients who discontinue from study medication during the Correction Phase conduct Visit5 procedure soon after the discontinuation and conduct EOS Visit one week after last IP.

Patients who discontinue from study medication during the Maintainance Phase conduct Visit23 procedure soon after the discontinuation and conduct EOS Visit one week after last IP.

At the time of IP discontinuation, procedures will be performed in accordance with the required order whenever possible, see Section 4.2.4 and 4.2.11.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up; and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

The term withdrawal from the study refers to discontinuation from both study medication and study assessments.

Specific reasons for withdrawal from study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment (see Section 3.10.2)
- Severe non-compliance to protocol as judged by the Investigator and/or Sponsor
- Lost of patient to follow-up
- Death

Any patient who is withdrawn from the study medication prior to study completion will return to the clinic 7 (± 1) days after the last IP administration for an EOS visit. Dosing schedule cards and all study drugs should be returned by the patient.

The date and reason for patient withdrawal must be recorded on the appropriate electronic Case Report Form (eCRF). Every attempt should be made to contact any patient considered lost to follow-up.

It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

3.10.1 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, i.e. patients that are withdrawn 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.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events. The Investigator will follow up AEs outside of the clinical study.

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

3.11 Interruption of investigational product

Investigational product (IP) may be interrupted in situations such as an adverse event, laboratory abnormality other than potassium abnormality (only during Maintainance Phase) at the investigator's discretion.

During an interruption of IP, the patient will return to the site at least every 7 (± 2) days as an extra visit for a potassium measurement and recording of any adverse events and concomitant medications (Patient will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.). In case it is unlikely to re-start IP, patient should be discontinued from the IP. On each extra visit, investigator and sponsor should discuss the study continuation. When the patient re-start IP, dose should the same as the last dose before interrutption. If the IP was interrupted due to an AE, the causality of the AE must be judged by investigator to be not related to IP upon resuming the IP.

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that are assessed as causally related to study drug and are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan for the Correction Phase

Study Visit	**Visit 1**	**Visit 2[7]**	**Visit 3[5]**	**Visit 4[5]**	**Visit 5[5]**	**EOS[6]**
Correction Phase Day	**Screening**	**Day 1[7]**	**Day 2[5]**	**Day 3[5]**	**Day 4[5]**	**Day 10[6]**
Written informed consent	X					
Eligibility criteria		X				
Demographics	X					
Medical History		X				
SF-36 v2 questionnaire		X				
Physical exam including weight		X[8]				X[8]
Access IVRS/IWRS	X	X	X[9]	X[9]	X[9]	
Study drug (IP) dispensation		X	X[9]	X[9]		
Study drug (IP) administration		X	X[9]	X[9]		
ECG		X	X[9]	X[9]	X[9]	X
Vital signs		X		X[9]	X[9]	X
Concomitant medications		X	X	X	X	X
Adverse events		X[10]	X	X	X	X
Potassium[1]		X[2]	X[3,11]	X[11]	X[12]	X[12]
Serum Chemistry[1]		X			X[9]	X
Hematology[1]		X			X[9]	X
Aldosterone and renin[1]		X				
Urinalysis[1]		X			X[9]	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 ZS. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible.
2. Blood potassium will be measured twice 60 (±15) minutes apart within 1 day of first dose administration on Correction Phase Day 1(Visit 2) and at 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. The Central Laboratory serum chemistry, hematology, aldosterone and renin samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample, but will be analysed only in confirmed hyperkalemic subjects.

3. Potassium will be measured predose (0 hour) and 1 hour (±15 min) after the first dose on Correction Phase 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. Visit 3, 4 and 5 (Day 2, 3 and 4 for the Correction Phase) are the same as visit 6 Day 1 in the Maintenance Phase for patients achieving normokalemia in the morning the day of the visit. Patients not achieving normokalemia at Visit 4 will be dosed with ZS 10g TID for an additional 24h and then return to the site for Visit 5.
6. EOS in Correction Phase only for patients NOT entering the Maintenance Phase, and occurs 7±1 day after the last administration of IP.
7. 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.
8. A complete physical examination should be performed within 1 day of administration of the first dose of study drug on Correction Phase Day 1, and targeted physical examination will be conducted on EOS.
9. If subject does not qualify for the Maintenance Phase on/before Correction Phase Day 4.
10. 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.
11. Blood potassium will be measured upon return to the clinic to determine if the subject is eligible to enter the Maintenance Phase or if the subject should receive an additional 24 hours of dosing.
12. Central laboratory potassium sample collected as part of the serum chemistry panel.

Table 2 Study Plan for the Maintenance Phase

Study Visit (Visit)	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**EOS**
Maintenance Phase Day[5] (Day)	**1**	**2**	**5**	**12**	**19**	**26**	**54**	**82**	**110**	**138**	**166**	**194**	**222**	**250**	**278**	**306**	**334**	**362**	**One week after last IP[6]**
Targeted physical exam including weight	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36 v2 questionnaire																		X	
Access IVRS/IWRS[7]	X			X		X	X	X	X	X	X	X	X	X	X	X	X		
Study drug (IP) dispensation	X			X		X	X	X	X	X	X	X	X	X	X	X	X		
Study drug (IP) administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG	X	X	X	X	X	X	X	X			X			X			X	X	X
Vital signs	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Potassium[1,2]	X[2,3,8]	X[2]	X[2,8]	X[2,8]	X[2,8]	X[2,8]	X[2]	X[2,8]	X[2]	X[2]	X[2,8]	X[2]	X[2]	X[2,8]	X[2]	X[2]	X[2,8]	X[2,8]	X[2,8]
Serum chemistry[1]	X		X	X	X	X		X			X			X			X	X	X
Hematology[1]			X	X	X	X		X			X			X			X	X	X

Table 2 Study Plan for the Maintenance Phase

Study Visit (Visit)	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**EOS**
Maintenance Phase Day[5] (Day)	**1**	**2**	**5**	**12**	**19**	**26**	**54**	**82**	**110**	**138**	**166**	**194**	**222**	**250**	**278**	**306**	**334**	**362**	**One week after last IP**[6]
Aldosterone and renin											X							X	
Urinalysis[1]						X		X			X			X			X	X	X
Urine HCG																			X[4]
IP Reconciliation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient questionnaire																		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 ZS. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible.
2. Please see Table 6 for details on how to adjust the dose based on the measured potassium values.
3. Maintenance Phase Study Day 1 sample will be the same sample as obtained on the last day of the Correction Phase.
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. Pregnancies are instead reported on the dedicated Case Report Form (CRF) page.
5. During the 12 months Maintenance Phase, the scheduled visit may take place either up to 2 days early or late by Visit 10 and up to 3 days early or late from Visit 11.
6. EOS occurs 7±1 day after the last administration of IP
7. Access IVRS/IWRS on visit indicated or if patient permanently discontinues dosing before the end of Maintenance phase.
8. Central laboratory potassium sample collected as part of the serum chemistry panel.

4.1 Screening/Enrolment 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 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. The following rule will be applied for the patient who will be ineligible due to the deviation of inclusion criteria No. 3. If the patient is expected to meet the eligibility criteria based on the patient‘s disease condition, the patient can be re-enrolled (including one re-screening) only once after 30 days or later from the screening failure. In this case, new enrolment number will be allocated to the patient.A new ICF does not need to be signed before re-screening if the original ICF was signed within 30 days and has not been revised.

After a patient has signed ICF at Visit 1, the site investigator will use the IVRS/IWRS to obtain a unique patient enrolment number after collecting the demographic parameters from the patient (including sex, date of birth, race, ethnic group).

4.2 Treatment period

Table 1 and Table 2 provide an overview of the procedures performed at each visit during the treatment period, and further details are provided below. Changing the order of the procedures at a visit, e.g. for logistical reasons, would not constitute a protocol violation if agreed in advance and in writing between the site and the sponsor study physician.

4.2.1 Correction Phase Day 1 (Visit 2)

Patients will arrive in the morning, fasting (except water, coffee or tea, with or without milk and/or sugar, and essential medications) for a minimum of 8 hours prior to potassium sample collection at the clinic. Between 1 and 7 hours may be needed for the visit, during which the following assessments will be performed:

- Administer the SF-36 v2 questionnaire. (The SF-36 v2 needs to be completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures.)
- Review and confirm the patient eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- Collect blood samples for assessment of potassium 60 minutes apart (± 15 min). Potassium will be analyzed using i-STAT, and samples will be prepared for potential shipment to the Central Laboratory for each time-point.
- If either i-STAT potassium value is < 5.1 mmol/L the patient will be declared a screen failure and discontinue from the study.
- If both i-STAT values are ≥ 5.1 mmol/L the following assessments will be performed:

  - Collect blood samples for assessment of hematology and clinical chemistry. (This sample can be collected at the same time as iSTAT sample collection. The patient should be informed that samples can be disposed of in case i-STAT potassium level <5.1 mmol/L and this process should be recorded before the sample collection)

  - Collect urine samples for assessment of urinalysis parameters, including a pregnancy test if the patient is a woman of childbearing potential.

  - Aldosterone and renin collected prior to 10 am (1000) after the subject has been in an upright position for at least 2 hours and before recording the ECG and physical examination.

- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- Patient medical and surgical history including co-morbidities will be obtained with the review of selection criteria.
- Perform 12-lead Electrocardiogram (ECG).
- Perform a complete physical examination including weight, see Section 5.2.2.
- Review and record the concomitant medications and AEs/SAEs.

Note: The above procedures should be performed within 1 day of the first administration of study drug and before any IP administration.

Patients who meet all inclusion/exclusion criteria will be entered into the trial and the following procedures will take place:

- The site will access the IVRS/IWRS and the system will assign the patient a Correction Phase IP kit.
- The first doses of study IP will be administered as a suspension in water. The patient will be shown/instructed on how to mix and administer the IP, following which the patient is allowed to break the fast.
- 4 hours (± 15 min) after dose administration a potassium sample (i-STAT and Central Laboratory) will be collected.
- Patients with i-STAT potassium levels < 6.1 and ≥4.0 mmol/L at the 4 hour (± 15 minutes) post Dose 1 blood draw will be sent home with instructions on how to take the IP. They will be requested to fill out a dosing schedule card indicating when they took the IP. The patient will return to the clinic the following morning of the Correction Phase Day 2 (Visit 3).
- Patients with i-STAT potassium ≥ 6.1 or <4.0 mmol/L at the 4 hour post Dose 1 blood draw will stay in the clinic and take the second dose of study drug approximately 4-hours after the first dose. They will then remain in the clinic an extra 90 minutes (±15 minutes) after taking the second dose when another blood

sample for potassium determination (i-STAT and Central Laboratory) will be collected and an ECG will be recorded.

  - If the potassium level is > 6.5 mmol/L as determined by the i-STAT at the 90-minute post Dose 2 blood draw, the patient will be discontinued from the study. Patient will return to the clinic 7 (±1) days later for an EOS visit.

  - If the potassium level is ≤6.5 mmol/L as determined by i-STAT, and the ECG does not exhibit any of the ECG withdrawal criteria, the patient will be sent home with the 3rd dose of study drug and the dosing card and return to the clinic in the morning of Correction phase Day 2 (Visit 3).

- See section 7.2 regarding how to handle patients with potassium < 3.5 mmol/L.

4.2.2 Correction Phase Day 2 (Visit 3)

Subjects will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.

- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the investigational product dosing boxes and sachets and make note of the time the doses were taken and any unused investigational products on the eCRF and source documents.
- Potassium values will be evaluated by i-STAT and the Central Laboratory.
- If the i-STAT potassium value is between 3.0 and 3.4 mmol/L inclusive, the subject should not take a study IP doses that day and return the next day to assess potassium.

  - 1 hour (± 15 min) after first serum potassium measurement a potassium sample (i-STAT and Central Laboratory) will be collected.
- If the i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, the subject will enter the Maintenance Phase and complete the procedures detailed in Section 4.2.5.
- If the i-STAT potassium value is ≥ 5.1 mmol/L, the subject will receive an additional 24 hours of ZS 10 g TID and the following procedures will be performed:

  - The site will access the IVRS/IWRS and provide the 7-digit subject identification number. The system will assign the subject an investigational product kit.

  - An ECG will be performed (Section 5.2.3).

  - The morning dose of ZS will be administered in the clinic as a suspension in water.

- 1 hour (± 15 min) after dose administration a potassium sample (i-STAT and Central Laboratory) will be collected.

- Patients with i-STAT potassium levels ≤ 6.5 and ≥3.5 mmol/L at the 1 hour (± 15 minutes) post Dose 1 blood draw will be sent home with 2 doses of study drug and instructions on how to take ZS. They will be requested to fill out a dosing schedule card indicating when they took the IP. The patient will return to the clinic the following morning of the Correction Phase Day 3 (Visit 4).

- If the potassium level is > 6.5 mmol/L as determined by the i-STAT at the 1 hour (± 15 minutes) post Dose 1 blood draw, the patient will be discontinued from the study. Patient will return to the clinic 7 (±1) days later for an EOS visit.

- See section 7.2 regarding how to handle patients with potassium < 3.5 mmol/L.

4.2.3 Correction Phase Day 3 (Visit 4)

Subjects will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.

- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the investigational product dosing boxes and sachets and make note of the time the doses were taken and any unused investigational products on the eCRF and source documents.
- Potassium values will be evaluated by i-STAT and the Central Laboratory.
- If the i-STAT potassium value is between 3.0 and 3.4 mmol/L inclusive, the subject should not take a study IP doses that day and return the next day to assess potassium.
- If the i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, the subject will enter the Maintenance Phase and complete the procedures detailed in Section 4.2.5.
- If the i-STAT potassium value is ≥ 5.1 mmol/L, the subject will receive an additional 24 hours of ZS 10 g TID and the following procedures will be performed:
  - The site will access the IVRS/IWRS and provide the 7-digit subject identification number. The system will assign the subject an investigational product kit.
  - Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
  - An ECG will be performed (Section 5.2.3).

  - The morning dose of ZS will be administered in the clinic as a suspension in water.

  - Subjects will then be sent home with 2 doses of study drug and instructions on how to take ZS. They will be requested to fill out a dosing schedule card indicating when they took ZS.

  - Subjects will return to the clinic the following morning and bring the used investigational product boxes and sachets and dosing schedule card with them.

- See section 7.2 regarding how to handle patients with potassium < 3.5 mmol/L.

4.2.4 Correction Phase Day 4 (Visit 5) (Visit 5 is only for patients who needed 72 hour correction phase.)

Subjects will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.

- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the investigational product dosing boxes and sachets and make note of the time the doses were taken and any unused investigational products on the eCRF and source documents.
- Potassium values will be evaluated by i-STAT and the Central Laboratory.
- If the i-STAT potassium value is between 3.5 and 5.0 mmol/L, inclusive, the subject will enter the Maintenance Phase and complete the procedures detailed in Section 4.2.5.
- If the i-STAT potassium value is < 3.5 or ≥ 5.1 mmol/L following 72 hours of dosing with ZS 10 g TID, the following procedures will be performed:
  - Collect blood samples for assessment of hematology and clinical chemistry.

  - Collect urine samples for assessment of urinalysis parameters.

  - Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).

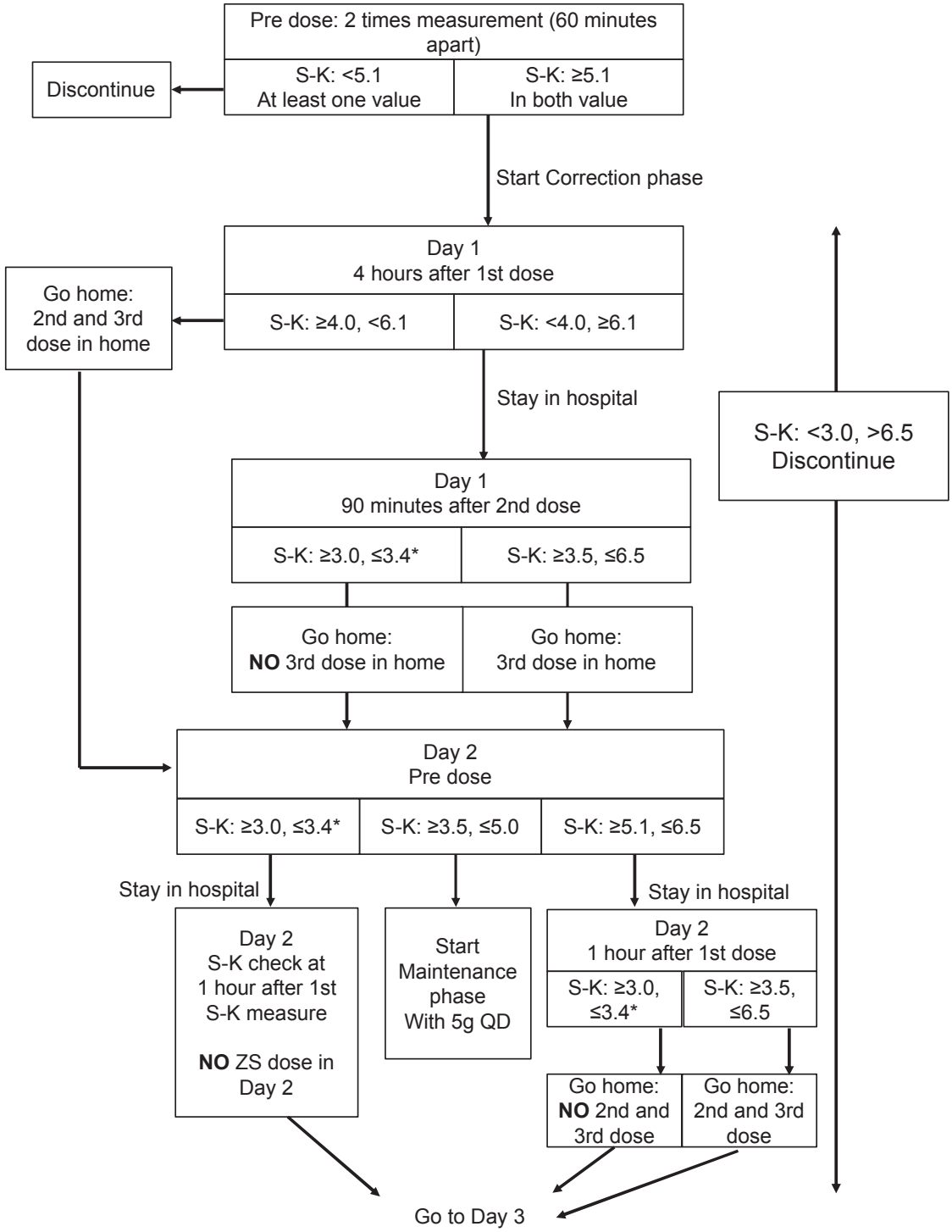
  - An ECG will be performed (Section 5.2.3).

  - The site will access the IVRS/IWRS, provide the 7-digit subject identification number, and document that the subject did not qualify for the Maintenance Phase.

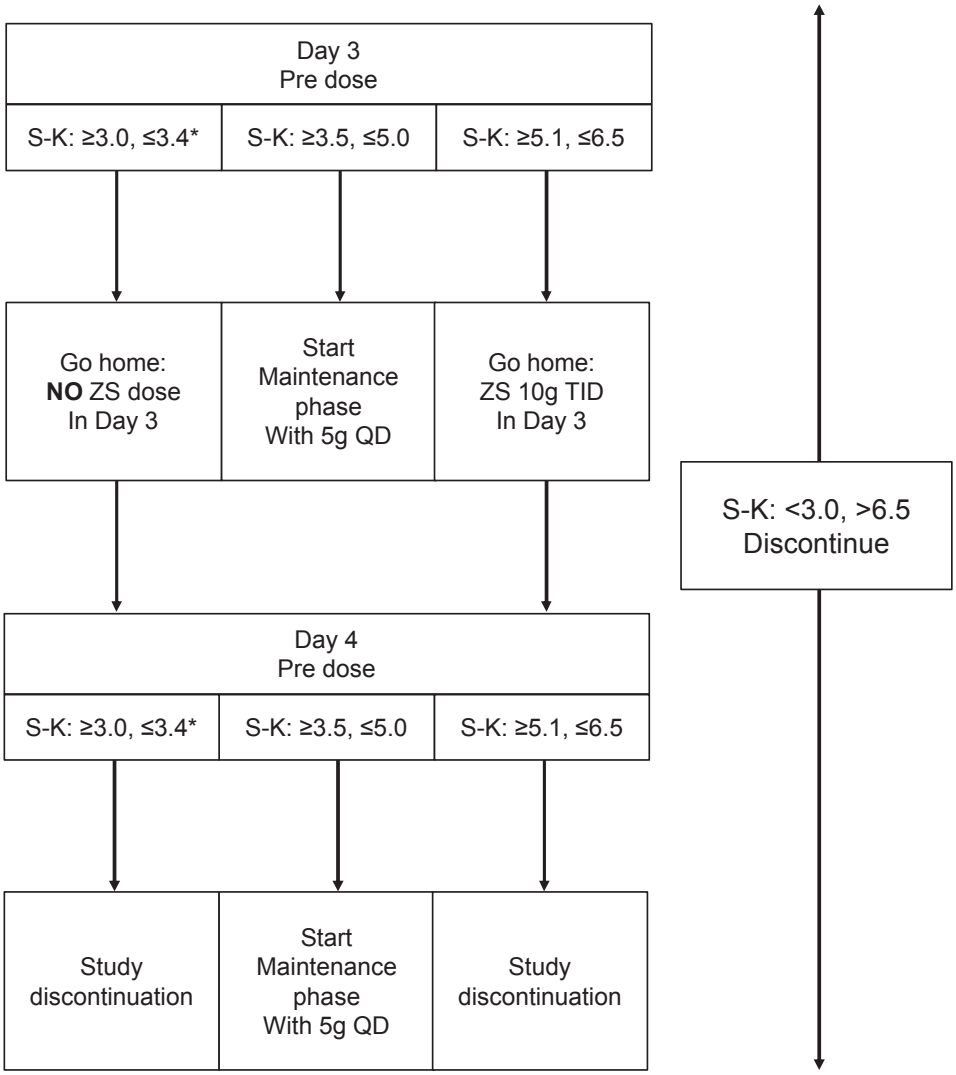
  - Subjects will then DISCONTINUE from the study, and receive standard of care at the discretion and the direction of his/her own physician. However, the subject will need to return to the clinic in the morning, fasting for at least 8

hours prior to potassium sample collection, 7 (± 1) days later after the last administration of IP for an End of Study visit.

Figure 4 Flow chart based on the S-K level: Correction Phase



S-K: Serum potassium, QD: Once daily, TID: Three times daily
*: Confirmation by an additional measurement after 10 minutes is required.



S-K: Serum potassium, QD: Once daily, TID: Three times daily
*: Confirmation by an additional measurement after 10 minutes is required.

4.2.5 Maintenance Phase Day 1 (Visit 6)

The Maintenance Phase Day 1 will take place on the day the subject achieves an i-STAT potassium value between 3.5 and 5.0 mmol/L, inclusive, after 24 (Visit 3), 48 (Visit 4), or 72 hours (Visit 5) of ZS 10 g TID treatment during the Correction Phase and procedures listed below should take place immediately after procedures of visit 3, 4 or 5, as applicable.

The following assessments will be performed:

- Clinical chemistry will be performed (Sample will be the same sample as obtained on the last day of the Correction Phase).
- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- A targeted physical examination including weight (Section 5.2.2).
- The clinic staff access the IVRS/IWRS to record that the subject entered the Maintenance Phase. The system will assign the subject a new Maintenance Phase investigational product kit containing an additional supply of ZS.
- The first dose of ZS during the Maintenance Phase will be administered in the clinic as a suspension in water. The clinic staff will solicit any adverse events.
- Subjects will be sent home. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic on Maintenance Phase Day 2 and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.6 Maintenance Phase Day 2 (Visit 7)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection. Subjects need to bring kit previously dispensed at Maintenance Phase Day 1.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- An ECG will be performed (Section 5.2.3).
- Prior to ZS administration, potassium samples (i-STAT and Central Laboratory) will be collected. If the i-STAT value is > 5.0 mmol/L or between 3.0 and 3.4 mmol/L while receiving 5 g QD, a second potassium measurement (i-STAT and Central Laboratory) will be obtained 10 (± 2) minutes later. If both i-STAT values are as stated above, the dose will be adjusted in accordance with Section 7.2, Table 6.
- The ZS dose will be administered in the clinic as a suspension in water.
- Subjects will be sent home. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic for the next scheduled visit and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.7 Maintenance Phase Day 5 (Visit 8)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection. Subjects need to bring kit previously dispensed at Maintenance Phase Day 1.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- An ECG will be performed (Section 5.2.3).
- Blood samples for the assessment of hematology will be collected.
- Prior to ZS administration, blood samples for i-STAT potassium and assessment of clinical chemistry including S-K will be collected. If the i-STAT value is > 5.0 mmol/L while receiving 5 g QD, 5 g QOD (or 2.5 g QD), 10 g QD or 15 g QD or between 3.0 and 3.4 mmol/L, inclusive, a second potassium measurement (i-STAT and Central Laboratory) will be obtained 10 (± 2) minutes later. If both i-STAT values are as stated above, the dose will be adjusted in accordance with Section 7.2, Table 6.
- The ZS dose will be administered in the clinic as a suspension in water.
- Subjects will be sent home. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic for the next scheduled visit and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.8 Maintenance Phase Day 12 (Visit 9)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product boxes and sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- A targeted physical examination including weight (Section 5.2.2).
- Blood samples for the assessment of hematology will be collected.
- Prior to ZS administration, blood samples for i-STAT potassium and assessment of clinical chemistry including S-K will be collected. If the i-STAT value is > 5.0 mmol/L while receiving 5 g QD, 5 g QOD (or 2.5 g QD), 10 g QD or 15 g QD or

between 3.0 and 3.4 mmol/L, inclusive, a second potassium measurement (i-STAT and Central Laboratory) will be obtained 10 (± 2) minutes later. If both i-STAT values are as stated above, the dose will be adjusted in accordance with Section 7.2, Table 6.

- The clinic staff will access the IVRS/IWRS and provide the 7-digit subject identification number and the i-STAT potassium value. The system will assign the subject a new Maintenance Phase investigational product kit containing an additional supply of ZS.
- The ZS dose will be administered in the clinic as a suspension in water.
- Subjects will be sent home with the investigational product kit and instructions on how to take ZS. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic for the next scheduled visit and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.9 Maintenance Phase Day 19 (Visit 10)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection. Subjects need to bring kit previously dispensed at Maintenance Phase Day 12.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- Blood samples for the assessment of hematology will be collected.
- Prior to ZS administration, blood samples for i-STAT potassium and assessment of clinical chemistry including S-K will be collected. If the i-STAT value is > 5.0 mmol/L while receiving 5 g QD, 5 g QOD (or 2.5 g QD), 10 g QD or 15 g QD or between 3.0 and 3.4 mmol/L, inclusive, a second potassium measurement (i-STAT and Central Laboratory) will be obtained 10 (± 2) minutes later. If both i-STAT values are as stated above, the dose will be adjusted in accordance with Section 7.2, Table 6.
- The ZS dose will be administered in the clinic as a suspension in water.
- Subjects will be sent home. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic for the next scheduled visit and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.10 Maintenance Phase Day 26- Day 334 (Visit 11- Visit 22)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product boxes and sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- Prior to ZS administration, potassium samples (i-STAT and Central Laboratory) will be collected. S-K will be evaluated as part of the clinical chemistry sample on Visits 11, 13, 16, 19 and 22. If the i-STAT value is > 5.0 mmol/L while receiving 5 g QD, 5 g QOD (or 2.5 g QD), 10 g QD or 15 g QD or between 3.0 and 3.4 mmol/L, inclusive, a second potassium measurement (i-STAT and Central Laboratory) will be obtained 10 (± 2) minutes later. If both i-STAT values are as stated above, the dose will be adjusted in accordance with Section 7.2, Table 6.
- Samples will be collected prior to any IP administration.
  - Blood samples for assessment of hematology and clinical chemistry including S-K (Visits 11, 13, 16, 19 and 22).
  - Aldosterone and renin collected prior to 10 am (1000) after the subject has been in an upright position for at least 2 hours and before recording the ECG and physical examination (Visits 16).
  - Urine for urinalysis parameters (Visits 11, 13, 16, 19 and 22).
- An ECG will be performed (Section 5.2.3) (Visits 11, 12, 13, 16, 19 and 22).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- A targeted physical examination including weight (Section 5.2.2).
- The site will access the IVRS/IWRS and provide the 7-digit subject identification number and the i-STAT potassium value. The system will assign the subject a new Maintenance Phase investigational product kit containing an additional supply of ZS.
- The ZS dose will be administered in the clinic as a suspension in water.
- Subjects will be sent home with the investigational product kit and instructions on how to take ZS. They will be requested to fill out a dosing schedule card indicating when they took ZS. Subjects will return to the clinic for the next scheduled visit and bring the used investigational product boxes and sachets and dosing schedule card with them.

4.2.11 Maintenance Phase Day 362 (Visit 23)

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection.
- Administer the SF-36 v2 questionnaire. The patient should complete the questionnaire prior to any other study procedures.
- Enter the patient questionnaire in patients who were prescribed ZS 5 g QOD.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, note if the subject has visited a doctor or emergency room since the last visit, examine the returned investigational product boxes and sachets and make note of when the doses were taken and any unused investigational products on the eCRF and source documents.
- Blood samples for i-STAT potassium and assessment of hematology and clinical chemistry including S-K will be collected.
- Aldosterone and renin collected prior to 10 am (1000) after the subject has been in an upright position for at least 2 hours and before recording the ECG and physical examination.
- Assessment of urinalysis parameters.
- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- A targeted physical examination including weight (Section 5.2.2).
- Subjects will be instructed to return in 7 (± 1) days after the last administration of IP for the End of Study visit.

4.3 Follow-up period (EOS)

Follow up visit will be performed at Day 10 for Correction Phase, and 7 ±1 days following the last study IP administration in Maintenance Phase, or 7 ±1 days following the last study IP administration for patients who are withdrawn from the study medication.

- Subjects will arrive at the clinic in the morning, fasting for at least 8 hours prior to potassium sample collection.
- The clinic staff will solicit any adverse events, note any changes in concomitant medications, and if the subject has visited a doctor or emergency room since the last visit. A final accounting of all ZS dosing supplies will be performed.
- Blood samples for i-STAT potassium and assessment of hematology and clinical chemistry including S-K will be collected.
- Assessment of urinalysis parameters.
- A urine pregnancy test will be performed if the subject is a woman of childbearing potential.

- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4).
- A targeted physical examination including weight (Section 5.2.2).

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Potassium

Blood samples for determination of potassium will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). 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.

5.1.2 Aldosterone and Renin Samples

Aldosterone and renin samples will be collected as summarized in Table 1 and Table 2. Samples will be collected prior to 10 am (1000) after the subject has been upright (sitting or standing) for at least 2 hours and prior to any ECG/physical examination assessments.

Aldosterone samples should be collected into serum separator tubes and renin samples should be collected into EDTA tubes. All samples must be processed to serum (aldosterone) or plasma (renin) according to the central laboratory manual, and immediately frozen (~ –20°C). All serum and plasma samples should be examined and any hemolyzed samples MUST be redrawn.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). Additional

safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded in the appropriate eCRF module.

The clinical chemistry, hematology and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 3 Laboratory Safety Variables

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

1. Blood 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 Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at

center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Blood chemistry and hematology parameters will be evaluated fasting, by the Central Laboratory, on Correction Phase Visit 2, 5 and EOS visit for patients NOT entering the Maintenance Phase, and on Maintenance Phase Visits 6 (blood chemistry), 8, 9, 10, 11, 13, 16, 19, 22, 23 and EOS.

The Correction Phase Visit 2 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration, Correction Phase EOS visit for patients NOT entering the Maintenance Phase and at Maintenance Phase EOS visit.

Urinalysis, will be performed by the Central Laboratory at Correction Phase Visit 2, 5 and EOS visit for patients NOT entering the Maintenance Phase, and on Maintenance Phase Visits 11, 13, 16, 19, 22, 23 and EOS.

Note: Whenever possible, all blood draws collected prior to meals should be collected prior to insulin/insulin analog treatment.

5.2.2 Physical examination

A complete physical examination should be performed no earlier than 1 day before administration of the first dose of study drug on Correction Phase Visit 2, and targeted physical examination will be conducted during the Correction Phase EOS visit for patients not entering the Maintenance Phase. During the Maintenance Phase targeted physical examinations will be performed at Visits 6, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 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.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

A 12-lead ECG will be performed after the patient has been lying down for 5 minutes 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 computerized quantitative 12-lead ECG.

ECGs will be recorded at Correction Phase Visits 2, 3, 4, 5, EOS visit for patients NOT entering the Maintenance Phase, and on Maintenance Phase Visits 6, 7, 8, 9, 10, 11, 12, 13,

16, 19, 22, 23 and EOS. When applicable ECGs will be performed after the aldosterone and renin samples are drawn and before the first daily dose of IP. In addition, for patients who have i-STAT potassium levels ≥ 6.1 mmol/L or <4.0 mmol/L at the 4 hours post 1st dose time point on the Correction Phase Day 1(Visit 2), an additional ECG will be recorded 90 minutes post 2nd dose.

5.2.4 Vital signs

5.2.4.1 Pulse rate and blood pressure

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed using non-invasive equipment by an adequately trained health care professional. Measurements with a calibrated sphygmomanometer are preferred. If not available, another device calibrated carefully in proportion to a mercury sphygmomanometer is preferred. Use of aneroid manometers should be avoided. Appropriate cuff size must be used to ensure accurate measurement.

The disappearance of sound (Korotkov phase V) should be used for the diastolic reading. Three (3) readings separated by 2 minutes should be averaged, and the average result will be recorded in the eCRF. If the first two readings of SBP differ by more than 5 mmHg, additional readings should be obtained.

Blood pressure should be checked in both arms at the first visit. Subsequent blood pressure measurements should be recorded in the arm with the higher pressure. Blood pressure should be measured in either supine or sitting position. No shift from one position to another should be made during the study. Supine or sitting posture should be adopted for at least 5 minutes before measurement. The patient should be relaxed and with the arm outstretched and supported. Blood pressure should be measured under standardized conditions, as nearly as possible at the same time each visit, on the same arm, by the same personnel, and with the same apparatus.

5.3 Other assessments

The SF-36 v2 questionnaire will be administered in Japanese. The results will be recorded in the eCRF.

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Genetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

5.8 Storage, re-use and destruction of biological samples

After the analyses are complete the samples will be either completely consumed during the analytical process or disposed of after the analysis.

5.9 Labeling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

5.10 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 4 and Table 5 as below. The collection of additional samples is performed locally at the discretion of the investigator and recorded in the eCRF as appropriate, thus requiring additional sample volumes.

Table 4 Volume of blood to be withdrawn from each patient: Correction Phase

Assessment	Sample Volume (mL)	Number of Samples					Maximum blood volume Total (mL)
		V 2 (D 1)	V 3 (D 2)	V 4 (D 3)	V 5 (D 4)	EOS (D 10)	
Hematology	2	1[2]			0-1[4]	1	6
Clinical Chemistry	2.5	1[2]			0-1[4]	1	7.5
Aldosterone and renin	6	1[2]					6
Potassium (i-STAT and Central Lab S-K)	4.5	3-4[1,5]	2[3]	1	1[5]	1[5]	40.5
Maximum blood volume Total (mL)		**28.5**	**9**	**4.5**	**9**	**9**	**60**

V= Visit; D=Day

1. Potassium will be measured twice 60 (±15) minutes apart within 1 day of first dose administration on Correction Phase Day 1(Visit 2) and 4 hours (±15 min) after administration of the first dose of ZS; An extra potassium will be measured at 90 minutes (±15 minutes) after taking the second dose for patients with i-STAT potassium ≥ 6.1 or <4.0 mmol/L at the 4 hour post Dose 1
2. On Correction Phase Day 1(Visit 2), the Central Laboratory clinical chemistry, hematology, aldosterone and renin samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample, but will be analysed only in confirmed hyperkalemic subjects.
3. Potassium will be measured predose (0 hour) and 1 hour (±15 min) post 1st dose on Correction Phase Day 2 (Visit 3)
4. Clinical chemistry and hematology samples only for patients with i-STAT potassium values < 3.5 or ≥ 5.1 mmol/L as measured fasting on Correction Phase Day 4 (Visit 5)

5. Central laboratory S-K sample collected as part of the clinical chemistry

Table 5 Volume of blood to be withdrawn from each patient: Maintenance Phase

Assessment	Sample Volume (mL)	Number of Samples																			Maximum blood volume Total (mL)
		V6 D1	V7 D2	V8 D5	V9 D12	V10 D19	V11 D26	V12 D54	V13 D82	V14 D110	V15 D138	V16 D166	V17 D194	V18 D222	V19 D250	V20 D278	V21 D306	V22 D334	V23 D362	EOS	
Hematology	2			1	1	1	1		1			1			1			1	1	1	**20**
Clinical Chemistry	2.5	1		1	1	1	1		1			1			1			1	1	1	**27.5**
Aldosterone and renin	6											1							1		**12**
Potassium (i-STAT and Central Lab S-K[1])	4.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**85.5**
Maximum blood volume Total (mL)		**7**	**4.5**	**9**	**9**	**9**	**9**	**4.5**	**9**	**4.5**	**4.5**	**15**	**4.5**	**4.5**	**9**	**4.5**	**4.5**	**9**	**15**	**9**	**145**

V=Visit; D=Day

1. Potassium will be measured fasting prior to the daily dose. Central laboratory S-K sample collected as part of the serum clinical chemistry at Visit 6, 8, 9, 10, 11, 13, 16, 19, 22, 23 and EOS.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (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.

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

6.2 Definitions of serious adverse event

A serious adverse event 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 hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

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

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment (EOS) 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.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of AE.

Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the Case Report Form (CRF).

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

6.5 Overdose

ZS has been given to patients at doses of up to 30 g per day for 1 to 3 days and up to 15 g per day for 11 months. For the purpose of this study, an overdose is defined as more than 30 g per day.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on ZS occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

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

- If the pregnancy is discovered before the study subject has received any study drug

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

6.6.2 Paternal exposure

Nonclinical data with ZS based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development did not reveal special hazard effect on libido, fertility, or embryofetal and postnatal development (see Investigator's Brochure [IB] for further details). Therefore there is no restriction on fathering children or donating sperm during the study.

In case of pregnancy of the patient's partners, an ICF FOR PREGNANT PARTNERS OF STUDY PATIENTS the partner's pregnancy will be sent to the partner to obtain her consent for collection of pregnancy information. Such pregnancy report will follow the same timeframe and routing as described for any participant's pregnancy. These pregnancies will be also followed up, and the

outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be obtained and documented if possible.

6.7 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If an medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product and strength	Dosage form	Manufacturer
Sodium Zirconium Cyclosilicate (ZS) 2.5 g	Powder for Oral Suspension in a sachet	AstraZeneca
Sodium Zirconium Cyclosilicate (ZS) 5 g	Powder for Oral Suspension in a sachet	AstraZeneca
Sodium Zirconium Cyclosilicate (ZS) 10 g	Powder for Oral Suspension in a sachet	AstraZeneca

7.2 Dose and treatment regimens

Sodium Zirconium Cyclosilicate (ZS) should be administered orally as a suspension in water.

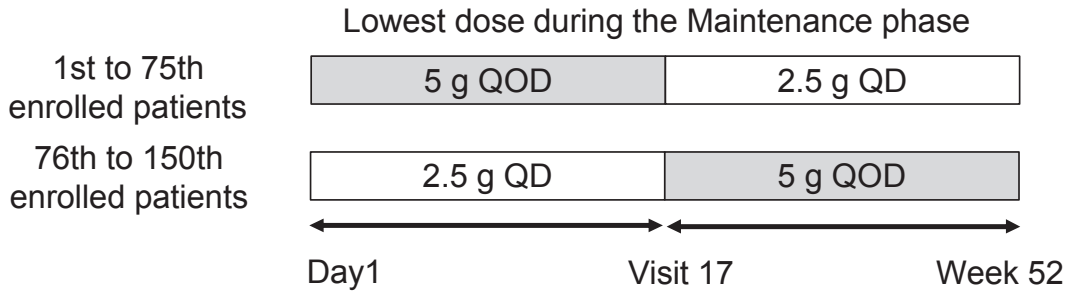
Correction Phase: ZS 10g TID for 24, 48 or 72 hours (3, 6 or 9 doses). Patients will enter the Maintenance phase after 24, 48 or 72h if the morning i-STAT potassium is between 3.5 and 5.0 mmol/L, inclusive.

Maintenance Phase: The starting dose is ZS 5 g QD. The ZS dose may be increased in increments of 5 g up to a maximum of 15 g QD or decreased to a minimum of 5 g QOD (or 2.5 g QD) dependent upon i-STAT potassium measurements (see Dose modification rules in Table 6).

Table 6 Dose modification rules:

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

For subjects who require a lower dose than 5 g QD, the first 75 subjects will have their dose reduced to 5 g QOD if this their potassium values indicate that they need this lower dose at any time during the first 6 months of the maintenance phase, and then be switched to 2.5 g QD for the final Month 6 (Visit 17) to Week 52 (end of treatment), if their potassium values are still such that this lower dose is required. The remaining 75 subjects will receive the reduced dose of 2.5 g QD for the first 6 months (up to Visit 17) of the maintenance phase, and then be switched to 5 g QOD for the final Month 6 (Visit 17) to Week 52 (end of treatment), if a their potassium values confirm that a lower dose is still required.



Any time the ZS dose is adjusted, the subject will return to the site 7 (± 2) days later as an extra visit for a potassium measurement and recording of any adverse events and concomitant medications(Subjects will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.). There is no limit to the number of dose titrations allowed. Subjects will receive up to 12 months of treatment with open-label ZS.

If a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval) during the Correction Phase the subject will be directed to not take any more study drug for the remainder of the day and return the next day to continue in the study. E.g. Patients with potassium values between 3.0 mmol/L and 3.4mmol/L on Day 2 will not take the drug the rest of the doses on Day 2, and will return fasting to have their potassium tested again on Day 3 and continue their therapy. If the potassium has normalized, the patients will start Maintenance Phase from the day. If patients with potassium values between 3.0 mmol/L and 3.4 mmol/L on Day 3, the patients will not take the drug the rest of the doses on Day 3, and will return fasting to be assessed for entering into the Maintenance Phase on Day 4.

Patients with i-STAT potassium <3.0 mmol/L (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval) should discontinue from therapy.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drug should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

IP kits will have the unique number identifiers and will be assigned through the Correction Phase and subsequent the Maintenance Phase. On receipt of IP supplies the Investigator/designee will check the supplies against the shipment manifest and will confirm receipt of IP shipments via the IVRS/IWRS. The system will then issue an acknowledgement

receipt. Sites are required to place all shipment manifests and acknowledgement receipts in the site regulatory binder.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

7.7 Concomitant and other treatments

All concomitant medications taken by the patient from 7 days prior to the Correction Phase Day 1 until Maintenance Phase EOS visit, or the end of the study (7 ± 1 days after the last dose of IP) for patients, will be recorded (including the reasons for increase/decrease/initiation/discontinuation of RAASi doses after Correction Phase Day 1).

It is expected that patients with diabetes will be enrolled. Use of insulin/insulin analog is not restricted however whenever possible, all blood draws collected for the study evaluation prior to meals during the study treatment period should be collected prior to any insulin/insulin analog treatment.

During the study, the patient must not receive alternative treatment for hyperkalemia (including medication). If dosing with IP is discontinued or the patient has completed dosing, the patient may receive alternative treatment for hyperkalemia if clinically indicated prior to completing the EOS visit scheduled 7 days after the last dose. Any alternative treatment administered during the above period must be recorded in eCRF.

In addition to therapies for hyperkalemia also other drugs with World Health Organization Anatomic Therapeutic Chemical classification code V03AE, i.e. potassium or ion binders such as sevelamer, calcium acetate, and lanthanum carbonate, are prohibited to be taken while receiving IP, as the effects of potassium binding drugs may effect safety laboratory assessments.

Any time a RAAS inhibitor or diuretic dose is adjusted or initiated during the Maintenance Phase, the subject will return to the site 7 (± 2) days later for a potassium measurement and recording of adverse events and concomitant medications (Subjects will arrive at the clinic in the morning after fasting for at least 8 hours prior to potassium sample collection.). If required the dose of ZS will adjusted or stopped based on the rules in this protocol.

7.7.1 Oral medications with gastric pH-dependent bioavailability

When co-administered with ZS, some oral medications with gastric pH-dependent bioavailability may exhibit a clinically meaningful increase or decrease in their bioavailability. Therefore, these drugs should be administered at least 2 hours before or 2 hours after ZS to mitigate the risk of drug interactions.

Drugs that should be taken 2 hours before or after ZS to avoid a possible raised gastric pH drug interaction are listed below:

Class of Drug	Drugs
Azole antifungals	Ketoconazole, Itraconazole, Posaconazole, Voriconazole
Anti-HIV drugs	Atazanavir, Nelfinavir, Indinavir, Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine
Tyrosine kinase inhibitors	Erlotinib, Dasatinib, Nilotinib

7.8 Post Study Access to Study Treatment (Not Applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient dosed and any subsequent amendments will be documented, with final amendments completed prior to database lock.

8.2 Sample size estimate

The sample size is estimated so that sufficient safety data of at least 100 Japanese subjects treated by ZS for at least one year can be generated, as required by ICH E1 guideline. Assuming approximately 35% drop out rate, approximately 150 subjects would be enrolled to this open-label study.

8.3 Definitions of analysis sets

Analysis sets will be defined for each of correction phase and maintenance treatment phase.

8.3.1 Full analysis sets

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

For the correction phase, the full analysis set will include all patients that receive the correction phase ZS dose and have any post-baseline correction phase S-K values.

For the subsequent long-term maintenance phase, the full analysis set will include all patients who receive ZS dose during maintenance phase and have any post-baseline maintenance phase S-K values.

8.3.2 Safety analysis sets

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

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

8.4 Outcome measures for analyses

8.4.1 Efficacy variables (Secondary)

Maintenance phase

- Proportion of patients who can maintain normokalemia (defined as S-K level of ≥ 3.5 and ≤ 5.0 mmol/L, inclusive) on ZS at each Maintenance Phase study visit
- Proportion of patients with average S-K ≤ 5.1 mmol/L
- Proportion of patients with average S-K ≤ 5.5 mmol/L
- Proportions of patients who were normokalemic (S-K ≥ 3.5 and ≤ 5.0 mmol/L), hypokalemic (< 3.5 mmol/L), or hyperkalemic (> 5.0 mmol/L) at each Maintenance Phase visit.
- Subject-level average S-K over certain period of time
- Observed values at visit and change from baseline in S-K over time
- Number of normokalemic days during Maintenance Phase
- Change in S-K level from the last on-treatment Maintenance Phase visit to the End of Study
- Change from baseline in S-Aldosterone over time
- Proportion of patients with normal S-Aldosterone
- Change from baseline in S-Bicarbonate
- Proportion of patients with normal S-Bicarbonate
- SF-36 v2 questionnaire

Correction phase

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

- Proportion of patients who achieved normokalemia at 24, 48 and 72 hours after start of dosing
- Safety and tolerability as measured by adverse events reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements during Correction Phase

8.4.2 Efficacy variables (Exploratory)

- Patient questionnaire on preference for low intensity ZS dosing(QOD or QD)
- Proportion of subjects increased RAASi doses
- Proportion of subjects who decrease or discontinued RAASi doses
- Proportion of subjects who increased at least once RAASi due to each reason
- Proportion of subjects who decreased/discontinued at least once RAASi due to each reason
- Time to first reduction/discontinuation of RAASi

8.4.3 Safety Variables

In this study, the following safety data will be collected: adverse events reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements.

8.5 Methods for statistical analyses

8.5.1 Analyses of efficacy variables

Efficacy analyses will be performed separately for the correction phase and maintenance phase.

For continuous variables, the values at visit and change from baseline (and percent change from baseline, if appropriate) will be summarized by descriptive statistics. For categorical variables frequency and percentage will be summarized. Model-based point estimates and 95% CIs will also be presented if appropriate. Time to event (such as RAASi reduction) will be displayed with Kaplan-Meier plot. No formal statistical testing will be performed in this study.

8.5.2 Analysis of Safety data

Safety analyses will be performed separately for the correction phase and maintenance phase. Safety endpoints will include adverse events (including incidence of Oedema related events, defined as Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral and Peripheral swelling), vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters. Kidney function will be evaluated by assessments of creatinine, eGFR, urine protein-to-creatinine ratio (UPCR) and urine albumin-to-creatinine ratio (UACR) over time. Liver function will be evaluated by assessing bilirubin, AST and ALT.

Treatment emergent AEs (TEAE) will be mainly analyzed. Adverse events will be classified by the Medical Dictionary for Regulatory Activities (MedDRA) to be consistent with other ZS studies. Safety data will be collected and analyzed while on study phases and reported until treatment-emergent adverse events are resolved. Unresolved adverse event outcomes at the end of treatment will be followed for an additional 7 days or until resolution, whichever occurs earlier. The type, incidence, timing (onset, duration), relationship, and severity of adverse events will be reported for treatment-emergent and serious adverse events. Reasons for withdrawal due to adverse events will also be reported. Narratives will be written for every adverse event classified as serious or associated with death.

Vital signs, ECGs and laboratory measurements will also be summarized descriptively.

8.5.3 Interim analysis

An interim analysis may be performed when all enrolled subjects completed at least 6-month visit, for the purpose of regulatory submission.

An interim analysis is planned in this study. The data of interim analysis will be cut off when the last subject goes through Visit 17. An interim analysis will include all patients' data available until data cut-off even if patients withdraw prior to Visit 17 including analysis at the correction phase endpoints as well as safety evaluation up to Visit 17.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q2 2017 and to end by Q3 2019.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ZS.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Center staff or other party, according to the Data Management Plan.

Data will be entered into the WBDC system at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then undergo quality control and be validated as described in the Data Management Plan.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AZ Drug Dictionary or WHODRUG. Classification coding will be performed by the Medical Coding Team at the AZ Data Management Center or other party.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study is completed.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) external to AstraZeneca.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will assure that the data collection tools for IVRS are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the Clinical Study Protocol re-approval.

Before enrolment of any subject into the study, the final Clinical Study Protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the Clinical Study Protocol to be amended, the new version of the Clinical Study Protocol should be submitted to the Head of the Study Site. If the changes are of an administrative nature, it is submitted to the IRB. If the changes have a significant impact on the safety of the subjects, the scientific value of the study, the conduct and management of the study, and the quality of any investigational product used in the study, it should be approved by the IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a Clinical Study Protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory

requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

Kosiborod M et al 2014
Kosiborod M, Rasmussen HS, Lavin PT, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA 2014;312:2223-33

Luo J et al 2016
Luo J, Brunelli SM, Jensen DE, et al. Association between serum potassium and outcomes in patients with reduced kidney function. Clin J Am Soc Nephrol 2016;11:90-100.

Packham DK et al 2015
Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372:222-31.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C SF-36 v2

Study Number: D9482C00001		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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Study Number: D9482C00001		Site Number:
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4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Study Number: D9482C00001		Site Number:
Subject Number:	Visit Number:	Assessment Date:

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Study Number: D9482C00001		Site Number:
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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Study Number: D9482C00001		Site Number:
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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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Appendix D Patient questionnaire English ver. (for Visit 23 or EOS visit)

Study Number: D9482C00001		**Site Number:**
Subject Number:	**Visit Number:**	**Assessment Date:**

Q1. In the study you are participating in, two dosages of once daily and once in every other day are tested. Since you have experienced both dosages, please answer what you felt about these dosages when you compare both.

□ 1. I prefer once daily intake
□ 2. I somewhat prefer once daily intake
□ 3. Either is okay to me
□ 4. I somewhat prefer once in every other day intake
□ 5. I prefer once in every other day intake

Q2. If you felt anything else about the study drug intake, please comment.

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