AstraZeneca

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 3.0, 22 Sep 2016
The main reason for the protocol amendment was to clarify guidance with respect to concomitant use of ZS and drugs with gastric pH-dependent bioavailability. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized as below.
Section 3.9 (Discontinuation of investigational product): The discontinuation criteria for significant increase in PR interval was updated to better reflect that "new onset peak T-wave".
Section 4.2.3 (48-hour open-label initial phase Day 3 (Visit 4)): The section was updated to reflect that relevant assessments also to be performed if the i-STAT potassium value is < 3.5 mmol/L during the Visit 4.
Section 6.3.1 (Time period for collection of adverse events): The section was further updated to specify the follow up for adverse events.
Section 7.7.1 (Oral medications with gastric pH-dependent bioavailability): The section was added to clarify guidance with respect to concomitant use of ZS and drugs with gastric pH-dependent bioavailability. For a specific list of drugs the recommendation is to administer those at least 2 hours before or 2 hours after study drug to mitigate the risk of drug interactions.
Section 8.5.1 (Analysis of the primary variable): Minor typographical error was updated in this section.
Section 8.5.3 (Safety analysis): Minor typographical errors and formatting was updated in this section.

Version 2.0, 07 Dec 2016 The main reasons for the protocol amendment were to clarify how patients developing hypokalemia during the 48h initial open label treatment phase are to be monitored and handled, and to update the Benefit Risk section with additional information. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized below.
Study Synopsis: The synopsis was updated to align with the amendments made in the body of the CSP.
Section 1.1 (Background and rationale for conducting this study): This section was updated to better reflect how hyperkalemia is treated. Minor typographical errors and formatting was updated. Section 1.2 (Rationale for study design, doses and control groups): This section was updated to better reflect the rationale for the study design and the doses selected. Minor typographical errors and formatting was updated in this section. Section 1.3 (Benefit/risk and ethical assessment): This section was updated to better reflect the benefits, risks, and benefit-risk balance of the study.
Section 2 (Study objective): Minor typographical errors and formatting was updated in this section, In particular, physical examination was added to "Outcome Measures" under the "Safety Objective" to ensure all collected data relevant to patient safety are thoroughly analyzed.
Section 3.2 (Exclusion criteria): The wording in exclusion criterion 3 was improved Section 3.6 (Methods for ensuring blinding): This section was updated to provide additional details on blinding during the 28-day randomized treatment study phase. Section 3.9 (Discontinuation of investigational product): This section was updated to emphasize that patients will discontinue when i-STAT potassium values are <3.0 mmol/L at any time during the study or > 6.2 mmol/L during the 28-day randomized treatment study phase, and that discontinued patients must immediately receive appropriate medical treatment to manage their hypo- or hyperkalemia. In addition the discontinuation criteria for QTc prolongation were re-worded to align better with when QT prolongation begins to represent a medical risk.

Section 4 (Table 1): The study plan and timing of procedures for the 48h open label initial phase (Table 1) was updated as demographics will be collected and the IVRS/IWRS accessed on visit 1, and to reflect that AE collection will begin after the patient has signed informed consent.

Throughout section 4, minor typographical errors and formatting was updated to improve the wording.

Section 4.2 (Treatment period): This section was updated in line with the updates in Table1 and Table 2, and to clarify that sites may change the order of the procedures at a visitif agreed in advance with the sponsor study physician.

Section 4.2.1 (48-hour open-label initial phase Day 1): This section was updated to clarify how to handle patients with i-STAT potassium <4.0 mmol/L at the 4 hour post Dose 1 blood draw.

Section 4.2.3 (48-hour open-label initial phase Day 3): Vital signs were added to the study procedures in this section to align with Tables 1 and 2.

Section 4.2.9 (28-day randomized treatment study phase Day 15): Vital signs were added to the study procedures in this section to align with Table 2.

Section 4.2.13 (28-day randomized treatment study phase Day 29): Vital signs were added to the study procedures in this section to align with Table 2.

Section 4.3 (Follow-up period): Vital signs were added to the study procedures in this section to align with Table 2.

Section5.1 .1(Efficacy assessments-Potassium): This section was updated to better reflect the assessment for potassium throughout the study.

Section 5.2.1 (Laboratory safety assessments): This section was updated to clarify that urine samples will be collected at the EOS visit.

Section 5.2.2 (Physical examination): This section was updated to add targeted physical examination to the initial phase Day 3 procedures.

Section 5.2.4.1 (Pulse Rate and blood pressure): More details were added to the description of how pulse rate and blood pressure will be assessed.

Section 5.3 (Other assessments): This section was updated to modify the timepoint when the EQ-5D questionnaire will be completed.

Section 5.10 (Table 4): The footnote was updated to add an extra potassium assessment 90 minutes after taking the second dose of ZS for patients with i-STAT potassium ≥ 6.1 or < 4.0 mmol/L 4 hours after the first ZS Dose.
Section 6.3.1 (Time period for collection of adverse events): This section was updated to specify that Adverse Events (including SAEs) will be collected from the signing of the informed consent until the EOS visit.
Section 7.1 (Identity of investigational product): This section was updated to align with a change in drug packaging. Section 7.2 (Dose and treatment regimens): This section was updated to provide guidance on how to handle patients developing hypokalemia while receiving ZS. Section 7.7 (Concomitant and other treatments): This section was updated with more details on prohibited medications.
Section 8.3 (Definitions of analysis sets): The definition of the Full Analysis Set (FAS) and the Safety Analysis Set (SAF) were revised to align with the ICH E9- and CRGI Statistical Guidance. Section 8.4.3 (Safety Variables): This section was updated to include the physical examinations and ECGs as the safety variables. Section 8.5 (Methods of statistical analyses): This section was revised to remove repetitive statements and to explicitly define the fixed hierarchical testing sequence of the study. Section 8.5.2 (Analysis of the secondary and additional variables): This section was updated to clarify the health state of the study population will be assessed on initial phase Day 1, and on 28-day randomized treatment study phase Day 29 using the EQ-5D questionnaire. Section 8.5.3 (Safety analysis): This section was updated to include the physical examinations and ECGs as the safety analysis. Section 8.5.4 (Subgroup analysis): This section was revised to clarify that subgroup analysis, for the purpose of regulatory submission, will only be performed in Japanese patients.

Version 1.0, 17 June 2016
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.

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

Dr. Faiez Zannad, Professor of therapeutics and cardiology, director of the Clinical Investigation Centre at the Institut National de la Santé et de la Recherche Médicale, INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France

Study site(s) and number of patients planned

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

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2017	Phase 3
Estimated date of last patient completed	Q1 2018	

Study design

This is a prospective, randomized, double-blind, placebo-controlled, phase 3 study to determine the safety and efficacy of ZS in patients with hyperkalemia. This study consists of screening period (1 day), 48-hour open-label initial phase, 28-day randomized treatment study phase, and follow-up period (7±1 days after the last administration of study medication).

Screening procedures will be performed to determine patient eligibility during the screening period, and all baseline parameters should be measured/collected up to 1 day prior to administration of first dose of study drug on 48-hour open-label initial phase. In the initial phase, patients will receive open-label ZS at a dose of 10g per os (PO) three times a day (tid) for 48 hours. Patients who achieve normokalemia (i-STAT [A portable blood analyser] potassium values between 3.5 to 5.0 mmol/L, inclusive) by the morning of Day 3 will then be randomized in the ratio of 2:2:1 into the double-blind 28-day randomized treatment study phase to receive ZS 5g every day (qd), 10g qd, or placebo qd for the following 28 days.

Treatment will end on the study Day 29 visit, which will be followed by the end of study (EOS) visit taking place 7±1 days after the last administration of study medication.

For patients who do not enter the 28-day randomized treatment study phase, the last visit will be 7±1 days after the last treatment dose in the 48-hour open-label initial phase.

Objectives

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

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

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

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

Target patient population

The target patient population consists of male and female patients aged ≥ 18 to ≤ 90 years with hyperkalemia, defined as two consecutive i-STAT potassium values, measured 60-minutes apart, both ≥ 5.1 mmol/L within 1 day of the first ZS dose.

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 initial phase Day 1. During the 48-hour open-label initial phase patients will receive ZS per os (PO) at a dose of 10g three times a day (tid) for 48 hours. Patients who achieve normokalemia (i-STAT potassium values between 3.5 to 5.0 mmol/L, inclusive), by the morning of Day 3 will then, be randomized in a ratio of 2:2:1 to the double-blind 28-day randomized treatment study phase to receive ZS 5g, 10g or placebo, PO qd for the following 28 days. Patients in the double-blind treatment phase will be required to complete the Day 29 visit and the EOS visit which is 7±1 days after the last administration of study medication. For patients who do not enter the 28-day randomized treatment study phase the last visit will be 7±1 day after the last treatment dose in the initial phase. The total expected study duration for each individual patient is approximately 5-6 weeks.

Investigational product, dosage and mode of administration

48-hour open-label initial phase:

- ZS 10g will be administered orally three times a day (tid) for 48 hours as an oral suspension

28-day randomized treatment study phase:

- ZS 5g will be administered orally once daily (qd) for 28 days as an oral suspension

- ZS 10g will be administered orally once daily (qd) for 28 days as an oral suspension

- Matching Placebo for ZS will be administered orally once daily (qd) for 28 days as an oral suspension

Please note: 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), dosing during the 28-day randomized treatment study phase will be reduced from qd to once every other day (qod).

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive during the 48h initial open label treatment phase the subject will be directed to not take any more ZS for the remainder of the day and return the next day to continue in the study, if the potassium is then between 3.5 and 5.0 mmol/L.

Patients with confirmed i-STAT potassium <3.0 mmol/L should discontinue from therapy.

Statistical methods

Separate efficacy and safety analyses will be performed for the 48-hour open-label initial phase and 28-day randomized treatment study phase. All patient analysis sets will be confirmed and documented in a Statistical Analysis Plan (SAP) prior to database lock. The study will have prospectively defined patient analysis sets including separate evaluability rules for the 48-hour open-label initial phase and 28-day randomized treatment study phase.

For the initial phase, the full analysis set will include all patients registered in the 48 hours open label initial phase. The safety analysis set, for the initial phase, will include all patients with at least one dose of IP during this treatment phase, and will be analysed on an as-treated basis.

For the subsequent 28-day randomized treatment study phase, the full analysis set will include all randomized patients. The safety analysis set, for the 28-day randomized treatment study phase, will include all patients with at least one dose of 28-day randomized treatment study phase IP among those randomized, and will be analysed on an as-treated basis.

Unless otherwise specified, all efficacy analyses will be carried out on the full analysis sets and all safety analyses will be based on the safety analysis sets.

The null hypothesis for the study is that there is no difference between each ZS dose (high to low) versus placebo control. The alternative hypothesis is that ZS is more effective than the placebo control in maintaining mean 28-day randomized treatment study phase Day 8-29 serum potassium levels (3.5-5.0 mmol/L, inclusive) among hyperkalemic patients in whom normokalemia is established during the 48-hour open-label initial phase.

All efficacy analyses will be based on the S-K values obtained from the Central Laboratory. If Central Laboratory data are missing, they will be replaced by i-STAT values adjusted to

reflect the mean difference between i-STAT and S-K values from all available paired lab samples. More details on how to handle dropouts and missing data will be provided in the SAP.

The primary endpoint in the study will be the model-based least squares means of all available S-K values during 28-day randomized treatment study phase Days 8-29. A log transformation will be applied to the S-K levels, since historical data shows that S-K measurements follows a log-normal distribution, and also to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (high to low) versus placebo control for the 28-day randomized treatment study phase to estimate the least squares mean Day 8-29 values stratified by country; the model will include all S-K data collected at the scheduled visits between Day 8-29 as response variables, and baseline covariates for initial phase eGFR and initial phase and 28-day randomized treatment study phase S-K values as well as age (<55, 55-64, ≥65 years), country and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus. In addition, the primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated for the subgroups (i.e. CKD, DM, HF and those on RAAS inhibitors) . More details will be described in the SAP.

Secondary efficacy endpoints will include:

- The proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during 28-day randomized treatment study phase
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase
- The mean change and mean percent change in S-K levels evaluated relative to both baselines
- The time to hyperkalemia (defined as S-K ≥ 5.1 mmol/L)
- The mean change in S-Aldo and P-Renin levels

EQ-5D will be used to assess the health state of the patient population.

Safety endpoints will include adverse events, serious AEs (SAEs), vital signs, clinical laboratory evaluations, physical examinations, ECGs, and other serum electrolytes (specifically, calcium [S-Ca], magnesium [S-Mg], serum sodium [S-Na], phosphate [S-PO4], bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

The confirmed i-STAT potassium value on Study Day 3 of the 48-hour open-label initial phase will be used to establish the patient's eligibility into the 28-day randomized treatment

study phase, however central laboratory S-K values will be used for all analyses. The baseline S-K for the 28-day randomized treatment study phase will use the first S-K measurement taken the morning of 48-hour open-label initial phase on Study Day 3. Baseline for all other parameters will be the fasting parameter value measured within 1 day of the first study drug administration in the initial phase.

There is no planned interim analysis in this study.

A sample size of approximately 255 patients (i.e. 102 patients for each active treatment arm and 51 patients for placebo control arm) will provide >90% power to detect a 0.30 mean 28-day randomized treatment study phase Day 8-29 S-K difference, assuming a 0.5 intra-subject standard deviation, comparing each active dose (high to low) vs. placebo control using a two-sided t-test at significance level of 5%. Assuming 95% of enrolled patients will be normokalemic after treatment with at least 1 dose of ZS 10g (see Section 7.2), approximately 269 patients will be needed to enter 48-hour open-label initial phase.

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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
ACE	Angiotensin-converting-enzyme
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARBs	Angiotensin-receptor blockers
AST	Aspartate aminotransferase
AZ	AstraZeneca
AZRand	AZ global Randomization System
BP	Blood pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
FAS-OLP	Full Analysis Set for the 48-hours Open Label Initial Phase
FAS-RTP	Full Analysis Set for the double blind Randomized Treatment Phase
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HF	Heart Failure
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PGx	Pharmacogenetic research
PI	Principal Investigator
PO	Per Os
PP	Per Protocol
P-Renin	Plasma-Renin
qd	once daily
qod	every other day
RAAS	Renin-angiotensin-aldosterone system
RBC	Red Blood Cell
S-Aldo	Serum-Aldosterone
SAE	Serious adverse event
SAF	Safety Analysis Set
SAF-OLP	Safety Analysis Set for the 48-hours Open Label Phase
SAF-RTP	Safety Analysis Set for the double blind Randomized Treatment Phase
SAP	Statistical Analysis Plan
SARs	Suspected Adverse Reactions
S-Ca	Serum calcium
S-HCO3	Serum bicarbonate
S-K	Serum potassium
S-Mg	Serum magnesium

Abbreviation or special term	Explanation
S-Na	Serum sodium
S-PO4	Serum phosphate
SPS	Sodium Polystyrene Sulfonate
SST	Serum Separator Tube
tid	three times a day
VS	Vital Sign
WBC	White Blood Cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Potassium is a ubiquitous ion, involved in numerous processes in the human body. It is the most abundant intracellular cation and is critically important for numerous physiological processes, including maintenance of cellular membrane potential, homeostasis of cell volume, and transmission of action potentials. The main dietary sources are vegetables (tomatoes and potatoes), fruit (oranges, bananas) and meat. The normal potassium values in serum (S-K) are between 3.5 and 5.0 mmol/L, with the kidney being the main regulator of potassium values. The renal elimination of potassium is passive (through the glomeruli) with active reabsorption in the proximal tubule and the ascending limb of the loop of Henle. There is active excretion of potassium in the distal tubules and the collecting duct, both of which processes are controlled by aldosterone.

Hyperkalemia develops when there is excessive production (oral intake, tissue breakdown) or insufficient elimination of potassium. Insufficient elimination, which is the most common cause of hyperkalemia, can be hormonal (as in aldosterone deficiency), pharmacologic (treatment with angiotensin-converting-enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARBs]) or, most commonly, due to reduced kidney function. Increased extracellular potassium values result in depolarization of the membrane potential of cells. This depolarization opens some voltage-gated sodium channels, but not enough to generate an action potential. After a short period of time, the open sodium channels inactivate and become refractory, increasing the threshold to generate an action potential. This leads to impairment of the neuromuscular, cardiac, and gastrointestinal organ systems, and is responsible for the symptoms seen with hyperkalemia. Of greatest concern is the effect on the cardiac system, where impairment of cardiac conduction can lead to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. Because of the potential for fatal cardiac arrhythmias, hyperkalemia represents an acute metabolic emergency that must be immediately corrected.

The most common cause of hyperkalemia is renal insufficiency, and there is a close correlation between the degree of kidney failure and S-K values. In addition, a number of different commonly used drugs can cause hyperkalemia, such as ACE inhibitors, ARBs, potassium-sparing diuretics (eg, amiloride, spironolactone), nonsteroidal anti-inflammatory drugs (eg, ibuprofen, naproxen, celecoxib), heparin, and certain cytotoxic and antibiotic drugs (eg, cyclosporin and trimethoprim). Finally, beta-receptor blocking agents, digoxin or succinylcholine are other well-known causes of hyperkalemia. In addition, advanced degrees of heart failure (HF), massive injuries, burns, or intravascular hemolysis cause hyperkalemia as can metabolic acidosis, most often as part of diabetic ketoacidosis.

Symptoms of hyperkalemia are non-specific and include malaise and muscle weakness or signs of cardiac arrhythmias, such as palpitations, bradycardia, or tachycardia. Often, however, the hyperkalemia is detected during routine screening blood tests for a medical disorder, or after complications have developed, such as cardiac arrhythmias or sudden death.

Diagnosis is established by S-K or plasma potassium measurements. Serum potassium values are most commonly used for diagnosis and to evaluate treatment response.

Treatment of hyperkalemia depends on the S-K values. In mild to moderate hyperkalemia acute treatment with a potassium-binding resin, combined with dietary advice (low potassium diet) and possibly modification of drug treatment (if treated with drugs causing hyperkalemia) will be standard of care. In severe hyperkalemia, or if arrhythmias are present, emergency lowering of potassium and close monitoring in a hospital setting are mandated..

- Sodium polystyrene sulfonate (sodium polystyrene sulfonate [SPS]; eg, Kayexalate) is a resin that binds potassium in the intestine and increases fecal excretion, thereby reducing S-K values. However, as SPS has been shown to cause intestinal obstruction and potential rupture, diarrhea needs to be simultaneously induced, significantly reducing the palatability of the treatment. Even without the induction of diarrhea, a substantial proportion of patients complain of gastrointestinal symptoms, such as constipation, abdominal pain, cramping, distension, nausea, and vomiting. In addition, SPS is non-specific and also binds calcium and magnesium, thereby increasing the risk of inducing hypocalcemia and/or hypomagnesemia.

- Intravenous insulin (administered with or without glucose to prevent hypoglycemia) to shift potassium into the cells and away from the blood.

- Intravenous calcium gluconate or chloride decreases myocardial excitability and stabilizes the myocardium, reducing the risk for cardiac arrhythmias, but does not affect S-K.

- Severe cases not responding to other medical therapy may require dialysis.

Thus, the only pharmacologic therapy that increases elimination of potassium from the body is SPS. However, due to the need to induce diarrhea, SPS cannot be administered on a chronic basis. Even in the acute setting, the need to induce diarrhea, combined with inconsistent efficacy and a foul smell and taste, reduces the usefulness of SPS. Hence, there is a significant medical need for new and better treatment modalities for the acute as well as chronic treatment of hyperkalemia.

ZS-9 is a microporous zirconium silicate with a specific crystal geometry that confers a high, selective exchange capacity for potassium and ammonium ions. Sodium zirconium cyclosilicate (ZS) is a partially protonated form of ZS-9 that is being developed for the treatment of hyperkalemia.

ZS has been shown to bind potassium in the intestine of animals in exchange for hydrogen and sodium. The potassium-binding capacity of ZS has been shown *in vitro* to be approximately 10 times that of SPS in the presence of calcium and magnesium cations, which would represent a significant therapeutic advantage over SPS. *In vivo* studies in dogs and rats demonstrated significant dose-related reductions in the fractional excretion of urinary potassium up to 95% without any change in serum magnesium or calcium levels. Toxicology

studies have shown ZS to be well tolerated at doses up to ~2.3-fold higher than the maximum three times a day ZS dose planned for registration or ~14-fold higher than the recommended starting once daily dose of 5 g per day. In addition, animal studies have demonstrated that ZS is not systemically absorbed, but exerts its effects locally in the gastrointestinal tract, significantly reducing the risk of any systemic toxicity.

Four clinical studies of ZS have been completed (ZS-002, ZS-003, ZS-004, and ZS-004E) in patients with hyperkalemia.

As ZS is not systemically absorbed, traditional phase 1 studies of the pharmacokinetics of ZS in healthy patients were not conducted. However, a phase 1 pharmacodynamic study (Study ZS-006) was conducted to characterize the potential effect of ZS on sodium and potassium excretion.

Completed Phase 2 and 3 Studies

Four clinical phase 2 and 3 studies (ZS-002, ZS-003, ZS-004, and ZS-004E) of ZS in patients with hyperkalemia have been completed. ZS-002 was a proof-of-concept phase 2 study to assess the safety and efficacy of acute dosing in patients with chronic kidney disease (CKD) and hyperkalemia. ZS-003 and ZS-004 were phase 3 studies to assess the safety and efficacy of acute and extended dosing with ZS in patients with hyperkalemia. ZS-004E was an open-label, long-term extension (11 months) of Study ZS-004.

Study ZS-002 was a multicenter, prospective, randomized, placebo-controlled, double-blind, dose-escalating phase 2 study to investigate the safety, tolerability, and pharmacodynamics of ZS in patients with CKD (defined by an estimated glomerular filtration rate [GFR, eGFR] between 30 and 60 mL/min) and hyperkalemia (defined by S-K values between 5.0 and 6.0 mmol/L, inclusive). A total of 90 patients were enrolled and, in a dose-escalating fashion, received ZS doses of 0.3, 3.0 or 10.0 g tid or placebo for a minimum of 48 hours or a maximum of 96 hours. Of the 90 randomized patients, a total of 30 patients were randomized to placebo, 12 to ZS 0.3 g tid, and 24 each to ZS 3 g tid and ZS 10 g tid.

Study ZS-003(Packham DK et al 2015, Luo J et al 2016) was a phase 3, multicenter, prospective, randomized, placebo-controlled, double-blind, dose-ranging study to investigate the safety and efficacy of ZS in patients with hyperkalemia (i-STAT potassium values at entry between 5.0 and 6.5 mmol/L, inclusive). Patients were randomized to receive 1 of 4 doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo, administered tid with meals for the initial 48 hours (Acute Phase), followed by a randomized dose of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered qd in the morning for 12 days (Subacute Phase). There was a one-time randomization to assign the Acute Phase and the Subacute Phase (in the event that normalized S-K was achieved after completion of the Acute Phase) treatments. The Subacute Phase randomized normokalemic patients to 1 of the 4 active doses in a 1:1 ratio between the same Acute Phase dose administered qd and placebo administered qd, whereas patients who received placebo in the Acute Phase were randomized to receive either 1.25 g or 2.5 g of ZS administered qd in the Subacute Phase. A total of 753 patients were randomized and treated in the Acute Phase of the study (158 placebo, 154 ZS 1.25 g tid, 141 ZS 2.5 g tid, 157 ZS 5 g tid,

and 143 ZS 10 g tid). Of the 579 ZS-treated patients who completed the Acute Phase, 447 continued into the Subacute Phase and were randomized to continue on the same ZS dose they received in the Acute Phase but administered qd or placebo (49 ZS 1.25 g qd and 41 placebo; 54 ZS 2.5 g qd and 46 placebo; 65 ZS 5 g qd and 68 placebo; and 63 ZS 10 g qd and 61 placebo).

ZS-004(Kosiborod M et al 2014) was a phase 3, multicenter, prospective, randomized, placebo-controlled, double-blind, dose-ranging maintenance study to investigate the safety and efficacy of ZS in patients with hyperkalemia (i-STAT potassium values ≥ 5.1 mmol/L). Patients were enrolled in the Open-label Acute Phase (Acute Phase) and treated with ZS 10 g tid for the initial 48 hours (6 doses). Patients who achieved normokalemia during the Acute Phase were randomized in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of ZS (5 g, 10 g, or 15 g) or placebo administered qd for a further 28 days (Maintenance Phase). A total of 258 patients were enrolled in the Acute Phase of the study and were treated with ZS 10 g tid. Of the 251 patients who completed ZS 10 g tid dosing during the Acute Phase, 237 continued into the Maintenance Phase and were randomized to either placebo (85 patients) or ZS (5 g [45 patients], 10 g [51 patients], or 15 g [56 patients] qd).

ZS at doses of 3 g and 10 g tid in Study ZS-002, 2.5 g, 5 g, and 10 g tid in Study ZS-003, and 10 g tid in Study ZS-004 demonstrated highly statistically significant and clinically meaningful dose-dependent decreases in S-K within 48 hours of treatment. Following S-K normalization via acute tid administration, extended dosing maintained normokalemia for up to 12 days with ZS qd doses of 5 g and 10 g in Study ZS-003, and for up to 28 days with ZS qd doses of 5 g, 10 g, and 15 g in Study ZS-004. The effectiveness of acute and extended dosing with ZS was evident across all predefined subpopulations (diabetes mellitus, heart failure [HF], CKD, and concurrent use of renin-angiotensin-aldosterone system [RAAS] inhibitor medication). Importantly, there was a close correlation between starting S-K and effect so that the higher starting S-K, the greater the effect. For example, in Study ZS-003, patients with a starting S-K > 5.5 mmol/L demonstrated a mean reduction in S-K of -1.1 mmol/L at 48 hours versus a reduction of -0.57 mmol/L at 48 hours in patients with a starting S-K ≤ 5.3 mmol/L. This effect was also observed in Study ZS-004 with the mean reductions in S-K at 48 hours increasing with higher baseline S-K values (S-K ≥ 6.0: -1.49 mmol/L; S-K ≥ 5.5 to < 6.0: -1.19 mmol/L; S-K < 5.5: -0.78 mmol/L). (Kosiborod M et al 2014, Packham DK et al 2015, Luo J et al 2016)

Study ZS-004E was a long-term (up to an additional 11 months), open-label extension to Study ZS-004. Patients who completed extended dosing in Study ZS-004 or who discontinued due to hypo- or hyperkalemia, and had a mean i-STAT potassium value between 3.5 and 6.2 mmol/L, inclusive, were eligible to participate. If the i-STAT potassium value was between 3.5 and 5.5 mmol/L, inclusive, at the end of Study ZS-004, the patient entered the Extended Dosing Phase and started open-label ZS at a dose of 10 g qd. If the i-STAT potassium value was > 5.5 mmol/L at the end of Study ZS-004, the patient entered an Acute Phase, where they received ZS 10 g tid for 24 (3 doses) or 48 hours (6 doses), depending on their daily i-STAT potassium measurement. Patients who attained normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) after either 24 or 48 hours of treatment entered the Extended

Dosing Phase. The starting dose of ZS was 10 g qd, which could be titrated according to a patient's i-STAT potassium value from a maximum dose of 15 g qd to a minimum dose of ZS 5 g every other day (qod). Not all patients who completed Study ZS-004 and who were eligible for Study ZS-004E per protocol criteria continued in Study ZS-004E as drug product was not available for 77 patients who completed Study ZS-004. Hence, only 123 patients were enrolled and treated in Study ZS-004E.

In Study ZS-004E, extended dosing with ZS for up to 11 months was effective in maintaining normokalemia. Across Study Days 8 to 337, 88.3% (95% Confidence Interval [CI]: 81.2%, 93.5%) of patients had average S-K values ≤ 5.1 mmol/L, which is statistically significantly higher than the 50% null hypothesis. The least squares mean from a logistic regression analysis, which adjusted for baseline covariates, was 92.8% (95% CI: 84.7%, 96.8%). Results were consistent across subgroups defined by age and baseline presence of CKD, HF, diabetes mellitus, and RAAS inhibitor use. In addition, the proportions of patients with S-K values ≤ 5.1 mmol/L were relatively constant among the extended dosing time points, ranging from 77.1% to 87.5%. The effectiveness of ZS in maintaining normokalemia was also demonstrated by the proportion of patients with average S-K values ≤ 5.5 mmol/L during Study Days 8 to 337, as 100% (95% CI: 97.0%, 100.0%) of patients had average S-K values ≤ 5.5 mmol/L, which is statistically significantly higher than the 60% null hypothesis. The proportions of patients with S-K values ≤ 5.5 mmol/L were relatively constant across the extended dosing time points, ranging from 91.4% to 98.5%.

Given the potency of ZS in reducing S-K levels, the reductions were not associated with events of significant hypokalemia or other clinically significant changes in electrolytes. Dose-related increases in bicarbonate and reductions in blood urea nitrogen (BUN) were consistently observed in ZS-treated patients. There were no clinically important changes in other clinical laboratory tests, including no dose-related changes in serum magnesium, sodium, or calcium.

ZS treatment was well tolerated at all dose levels administered in Studies ZS-002, ZS-003, ZS-004, as well as the long-term Study ZS-004E. In these studies, commonly reported treatment-emergent adverse events among patients who received ZS or placebo were gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and dyspepsia). The majority of the treatment-emergent adverse events reported were mild or moderate in severity and most were considered unrelated to study drug. In Study ZS-004, an increased incidence of events associated with peripheral edema was reported with the ZS 15 g qd dose during extended dosing; however, this might be explained by more severe disease at baseline in the ZS 15 g group as compared to placebo (greater proportions of patients with HF [45% versus 31%]). Edema was also monitored in long-term Study ZS-004E and the exposure-corrected edema rate (taken into consideration total exposure days) was comparable to the placebo rate in Study ZS-004. Furthermore, peripheral edema did not increase with duration of treatment with ZS, indicating that edema is unlikely to be related to ZS. No dose-response relationship has been observed for the occurrence of any other specific treatment-emergent adverse event.

No clinically significant dose-related changes in vital signs have been observed in ZS-treated patients. Consistent with the decrease in S-K, a small dose-related increase in QTc interval has been observed in patients during treatment with ZS. The level of increase in QTc is considered clinically insignificant and no increase in cardiac arrhythmias has been observed.

Completed Phase 1 Study

ZS is not systemically absorbed, as was confirmed from blood and urine samples collected as part of Study ZS-004. Thus, traditional phase 1 studies of the pharmacokinetics of ZS in healthy patients were not conducted. However, a phase 1 pharmacodynamic study (Study ZS-006) was conducted to characterize the potential effect of ZS on sodium and potassium excretion in 30 healthy patients on a fixed, low-sodium and high-potassium diet. A total of 30 patients received 4 days of dosing with ZS during this trial; 15 patients were dosed with 5 g qd and 15 were dosed with 10 g qd. Overall, the small dose-dependent reduction in urine sodium excretion (5 g: -0.93 mmol/24 hours; 10 g: -5.47 mmol/24 hours) observed in this study suggests that ZS does not increase urinary sodium output in this patient population and study conditions. The decreases in urinary potassium with concomitant increases in fecal potassium are consistent with the mechanism of action of ZS. The decreases in urinary potassium of ~379 and ~829 mg correspond to an *in vivo* KEC of 9.7 and 21.2 mEq potassium for the 5 g and 10 g doses of ZS, respectively.

Ongoing Clinical Studies

One open-label phase 3 study (ZS-005) is currently ongoing, evaluating the long-term (up to 1 year) safety and efficacy of ZS in maintaining normokalemia. The study contains an Acute Phase, in which patients are dosed with ZS 10 g tid for 24 to 72 hours, followed by a long-term Extended Dosing period in which patients are dosed with ZS starting at 5 g qd, which may be increased or decreased in increments/decrements of 5 g qd up to a maximum of 15 g qd or a minimum of 5 g qod based on i-STAT potassium measurements. As of 7 December 2015, a total of 751 patients had been included in the Acute Phase, of whom 746 patients entered Extended Dosing.

In the Acute Phase of the study, 99% of patients achieved normokalemia. Of the 746 patients who entered Extended Dosing, 488 have completed ≥ 3 months of therapy, 436 have completed ≥ 6 months, 287 have completed ≥ 9 months, and 155 have completed 12 months. The vast majority of patients maintained normal serum potassium on ZS, with 87.9% and 98.8% of patients reporting mean serum potassium ≤5.1 and ≤5.5 mmol/L throughout months 3-12. Similar results were observed in pre-specified subgroups of patients with CKD, HF, diabetes mellitus, and those receiving RAAS inhibitor therapy. Mean S-K levels were maintained at 4.7 mmol/L. Safety data were consistent with other ZS studies.

1.2 Rationale for study design, doses and control groups

This phase 3 study is intended to be included in applications for marketing authorization in the countries where the study is performed.

A double-blind, placebo-controlled, randomized study represents the optimal design for obtaining unbiased estimates of treatment group differences for a new drug under development. Recognizing that all patients will receive active treatment during the open-label 48-hour open-label initial phase, combined with the fact that all patients will be monitored in the clinic for at least 4 hours after the initial dose of ZS, the level of hyperkalemia that could be included is not limited.

The randomized portion of the study (28-day randomized treatment study phase) is designed to assess whether extended administration of ZS maintains control of S-K values and to demonstrate that hyperkalemia recurs once ZS is withdrawn. Such design represents state-of-the-art in demonstrating the need for ongoing longer-term treatment of a new drug under development. A 28-day, double-blind treatment phase is selected as a compromise between ensuring a sufficiently long treatment period to demonstrate that ZS can maintain normokalemia over extended time, while not exposing patients with a potentially life-threatening condition to extended treatment with placebo. Eligibility for the 48-hour open-label initial phase, eligibility for the 28-day randomized treatment study phase, and potassium-related stopping criteria are based on i-STAT measurements as these decisions need to be made in 'real-time' due to the risk of potentially life-threatening cardiac arrhythmias associated with severe hyperkalemia or hypokalemia. However, all endpoint analyses will be based on standardized S-K measurements analyzed at a central laboratory. For treatment decisions (ie, S-K values on i-STAT <3.5 mmol/L), a second i-STAT sample will be taken 10 minutes after the initial abnormal sample to ensure that treatment is only changed once hypokalemia is confirmed. For a treatment decision to be made, both samples, taken 10 minutes apart, need to be below 3.5 mmol/L.

The design of this study is similar to the global ZS-004 study. In study ZS-004(Kosiborod M et al 2014), ZS was highly effective in reducing S-K in patients with hyperkalemia, demonstrating statistically significant improvement from baseline in S-K with ZS 10 g TID over the first 48 hours of dosing. Patients who achieved normokalemia after receiving ZS 10 g TID in the Acute Phase were randomized to 28 days of placebo, ZS 5 g QD, ZS 10 g QD, or ZS 15 g QD dosing during the Maintenance Phase. ZS was effective in maintaining normokalemia (S-K between 3.5 mmol/L and 5.0 mmol/L, inclusive), meeting the predefined primary efficacy endpoint of mean S-K value during Maintenance Phase Study Days 8 to 29 at all 3 doses of ZS. Treatment with ZS was well tolerated in the patients recruited in ZS-004. The doses studied in this study were selected considering both efficacy and tolerability of the doses studied in ZS-004.Specific exclusion criteria ensure that appropriate patients, who are not at excess risk from treatment, will be enrolled. The multicenter design enhance the external validity, reproducibility, and generalizability of the results observed.

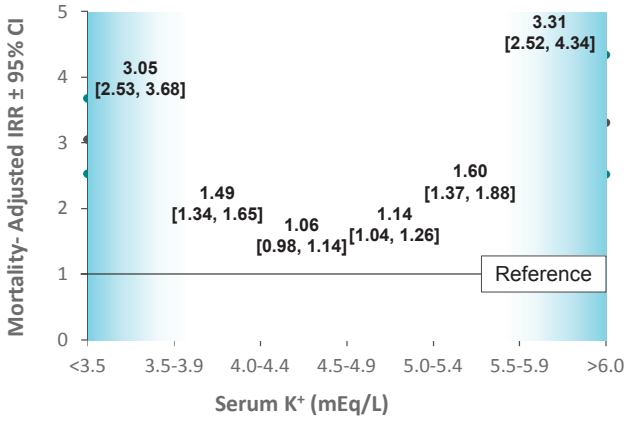
The patient selection criteria allows for the assessment of both efficacy and safety of ZS in a relevant population of patients with hyperkalemia. Since hyperkalemia affects both men and women, the inclusion criteria allows equal access to the protocol for both sexes. Exclusion criteria are developed based on consideration of safety concerns and to prevent enrollment of patients who are unsuitable for the study. In order to ensure the study population reflect 'real life', the exclusion criteria are not extensive, as the Sponsor want to ensure that the patient

population enrolled is representative of the patient population receiving the drug post-approval. Hence, a large number of concomitant diseases and concomitant treatments are allowed, recognizing that many patients with hyperkalemia would also suffer from a range of concomitant diseases. This approach was further justified by the favorable safety and tolerability profile observed in Study ZS-003 and Study ZS-004, combined with the fact that ZS is not systemically absorbed.

1.3 Benefit/risk and ethical assessment

Hyperkalemia is common in patients with chronic kidney disease or heart failure, particularly when treated with renin angiotensin aldosterone system inhibitors (RAASi). Mortality risk with hyperkalemia parallels the magnitude of potassium elevation.

Figure 1. Multivariable-adjusted mortality by serum potassium level in a cohort of 55,266 patients with eGFR <60 ml/min per 1.73 m^2 during median follow up 2.76 years (Lou J et al 2016)



For acute treatment, intravenous glucose/insulin and inhaled beta-adrenergic agonists drive potassium into cells. Potassium can be removed from the body by dialysis or with non-absorbed polymers which non-selectively bind potassium and are excreted. Polymers do not lower potassium rapidly and cause significant gastrointestinal (GI) side effects (colonic necrosis, bowel obstruction, GI bleeding, ischemic colitis, perforation), bind to many oral medications and to other cations, lowering magnesium and calcium levels. Thus, an unmet need remains for safe, rapid, and an effective treatment for hyperkalemia.

Sodium zirconium cyclosilicate (ZS) is a non-absorbed, inorganic crystal that selectively exchanges hydrogen and sodium cations for potassium in a dynamic process throughout the upper and lower gastrointestinal tract. Bound potassium ions are excreted from the body. ZS is a white, insoluble, powder provided in 5g and 10g sachets to be suspended in water for oral administration.

1.3.1 Clinical benefits

In randomized, double-blind, placebo-controlled trials, ZS rapidly corrected potassium levels and maintained normokalemia in patients with hyperkalemia including those with chronic kidney disease, heart failure, diabetes mellitus and RAASi use. ZS was effective regardless of the underlying cause of hyperkalemia, age, sex, race or baseline potassium level.

ZS acts rapidly, statistically significantly reducing potassium within one hour (study ZS-003). With ZS10g TID, 77% of patients achieved normokalemia within 24 hours and 86% within 48 hours. Median time to normokalaemia was 2.2 hours (ZS-004).

ZS is self-equilibrating. Potassium fell 0.8, 1.2 and 1.5 mmol/L at 48 hours among patients with baseline potassium <5.5, 5.5-5.9 and ≥6.0 mmol/L, respectively (ZS-004). Self-equilibration reduces the risk of hypokalemia and reflects the mechanism of action; as potassium levels normalize, less potassium is excreted into the GI tract and fewer cations are exchanged.

ZS maintains normokalemia. Patients who achieved normokalemia with TID dosing were randomized to maintenance therapy with once daily ZS or placebo for 12 days (ZS-003) or 28 days (ZS-004). ZS-003 met predefined efficacy endpoints at the 5 and 10g doses when compared with placebo. In ZS-004, ZS 5, 10 or 15g increased the number of normokalemic days ($p \leq 0.0001$ for each dose vs placebo) and maintained potassium at lower levels than placebo ($p \leq 0.0001$ for all doses). ZS maintained normokalemia for up to 12 months in the open label extension; when ZS was stopped, potassium rose to near baseline levels (ZS-004E).

Co-administration of ZS with clopidogrel, dabigatran, glipizide, losartan, furosemide, atorvastatin, amlodipine, warfarin, and levothyroxine identified no clinically meaningful drug-drug interaction (ZS-009).

1.3.2 Clinical risks

In double-blind, placebo-controlled trials 1009 patients received ZS. Subjects were 22 to 93 years of age, 42% female, 86% white, 12% black and nearly all had chronic kidney disease, heart failure and/or diabetes mellitus.

Hypokalemia: During treatment up to 12 months at doses titrated to maintain normokalemia, hypokalemia was identified in 5.7% (7/123) of subjects in ZS-004E and 2.5% (17/684) in ZS-005. Only 1 patient developed K^+<3.0 mmol/L.

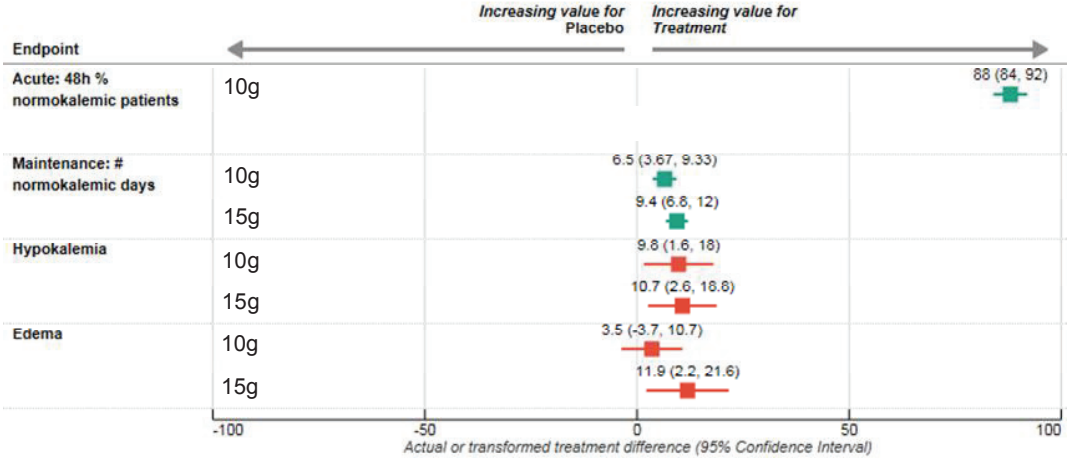
Edema: Among subjects randomized to placebo, ZS 5, 10 or 15g QD, edema was reported by 1.7, 0.9, 4.4 and 14.3%, respectively (ZS-003 & -004). Edema was untreated in 47% (7/15) of ZS-treated subjects and managed with diuretic initiation or dose adjustment and/or discontinuation of calcium channel blocker in the remainder. Although ZS exchanges protons and sodium for potassium, ZS did not increase urine sodium excretion in study ZS-002, -004 or -006 indicating no increase in sodium absorption; the mechanism underlying edema remains uncertain.

1.3.3 Clinical benefit-risk balance

For correction of hyperkalemia, ZS 10g TID is recommended for up to 3 days until normokalemia is achieved. Thereafter, maintenance therapy is initiated with 5g QD and dose adjusted from 10g daily to 5g every other day to maintain normokalemia.

Benefits and risks for ZS are summarized below:

Figure 2 Forest plot of benefits (green) and risks (red) for ZS 10g and 15g



Hyperkalemia increases the risk of arrhythmic death; potassium lowering reduces this risk even if normokalemia is not achieved. Benefits of ZS over placebo in patients with hyperkalemia include rapidly reducing serum potassium to achieve normokalemia and maintenance of normokalemia. Advantages over currently available therapies include rapidity of potassium lowering, no clinically meaningful drug-drug interactions, no increase in gastrointestinal adverse events or hypomagnesemia.

No serious safety risks have so far been identified. Serum potassium should be periodically monitored.

1.3.4 Conclusions

Based on available data, the benefit-risk assessment for sodium zirconium cyclosilicate is favourable for correction of hyperkalemia (10g TID for up to 3 days) and for maintenance treatment of patients with hyperkalemia across the dose range 15g daily to 5g every other day.

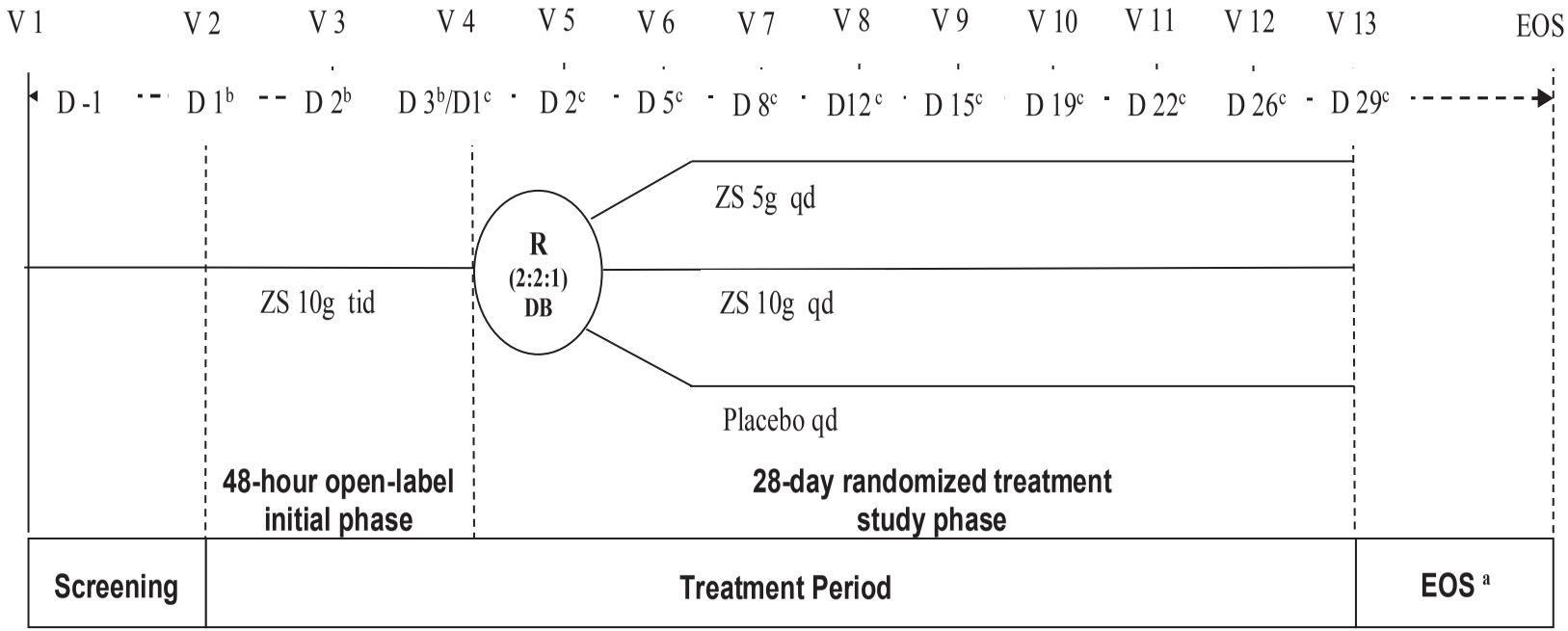
1.4 Study Design

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

This study consists of screening period (1 day), 48-hour open-label initial phase, 28-day randomized treatment study phase and EOS visit which is 7±1 days after the last administration of study medication. For patients who do not enter the 28-day randomized treatment study phase the last visit will be 7±1 day after the last treatment dose in the 48-hour open-label initial phase.

The study comprises 14 visits: enrolment visit (Visit 1), entering visit to 48-hour open-label initial phase (Visit 2), treatment visit in initial phase (Visit 3), randomization visit to 28-day randomized treatment study phase (Visit 4), treatment visit in 28-day randomized treatment study phase (Visit 5-12), safety visit in 28-day randomized treatment study phase (Visit 13), and end of study (EOS) visit. For details on timing of visits, see Figure below:

Figure 3 Study flow chart



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

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

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

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

2. STUDY OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

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

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

2.3 Safety objectives

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

2.4 Exploratory objectives

Not applicable.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, 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. Female and male patients aged ≥18 and ≤ 90 years

3. Two consecutive i-STAT potassium values, measured 60-minutes (± 10 minutes) apart, both ≥ 5.1 mmol/L and measured within 1 day of the first ZS dose on 48-hour open-label initial phase Day 1

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

5. Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of ZS/matching placebo to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used

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. Participation in another clinical study with an investigational product during the last 3 months

3. Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis.

4. Patients treated with lactulose, xifaxan (rifaximin) or other non-absorbed antibiotics for hyperammonemia within 7 days prior to the first dose of study drug

5. Patients treated with resins (such as sevelamer acetate or sodium polystyrene sulfonate [SPS; e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug

6. Patients with a life expectancy of less than 3 months

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

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

9. Patients with diabetic ketoacidosis

10. 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

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

12. Patients with cardiac arrhythmias that require immediate treatment

13. Patients on dialysis

14. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of ZS

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomization

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 patients a unique enrolment number via IVRS/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 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/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized patients

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 be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or 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

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

3.6 Methods for ensuring blinding

The 28-day randomized treatment phase will have a double blind design. Patients will take by mouth the entire contents of a single sachet per day containing either ZS 5g, ZS 10g or placebo. The exterior appearance of the sachets are identical, but the volume of study drug will differ depending upon the randomized treatment group. Individual sachets are enclosed in a carton with a tamper evident seal intended to be broken exclusively by patients just before taking the study drug.

A designated individual (e.g. pharmacist) at each study site will be responsible for performing study drug accountability and if required, this person will answer questions from patients related to the IP administered during the 28-day randomized treatment phase. The designated individual will not participate in patient management or patient assessments.

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

3.7 Methods for unblinding

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

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

AstraZeneca retains the right to break the code for Serious Adverse Event (SAE) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.8 Restrictions

Patients on RAAS inhibitors and/or diuretics are not allowed to titrate or discontinue or switch RAAS inhibitor and/or diuretic therapy during the study, in addition, patients are not allowed to start dialysis while in the study. 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 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
- Start dialysis while in the study
- Patient unblinded due to emergency
- Patients who change or switch RAAS inhibitor and/or diuretic dose during the study
- Patient develops severe hypokalemia (i-STAT potassium values <3.0 mmol/L) at any time during the study or > 6.2 mmol/L during the 28-day randomized treatment study phase (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 has a clinically significant cardiac arrhythmia (see below) at any time in the 28-day randomized treatment study phase, the patient should immediately receive appropriate medical treatment and be discontinued from study drug. Any of the following cardiac events will result in immediate discontinuation from the study drug (independent of whether it is in the 48-hour open-label initial phase or 28-day randomized treatment study phase):
  - 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), widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block) or new onset peaked T-wave

- 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 but agree to remain in the study should continue to follow protocol-specified procedures and assessments except for dispensing of study medication for the study.

Note: Discontinuation of investigational product does not necessarily imply discontinuation of follow-up or termination of all study participation.

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
- Patient lost 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 recieving open label treament. 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/randomisation code cannot be reused. Withdrawn patients will not be replaced.

3.11 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 detailing the procedures: 48-hour open-label initial phase

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

1. Parameters to be measured are detailed in Table 3.
2. Potassium will be measured twice 60 (±10) minutes apart within 1 day prior to any dose administration, and on initial phase Day 1 at 1, 2 and 4 hours (±15 min) after administration of the first dose of ZS. Potassium will be measured again at 90 minutes (±15 minutes) after taking the second dose for patients with i-STAT potassium ≥6.1 mmol/L or <4.0 mmol/L 4 hours after the first dose
3. Potassium will be measured predose (0 hour) and 1 hour (±15 min) after the first dose on initial phase Day 2 (Visit 3)
4. Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting (nothing by mouth except water only for a minimum of 8 hours prior to collection). On initial phase Day 1(Visit 2), the Central Laboratory clinical chemistry and hematology samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample;
5. For women of childbearing potential, urine-HCG will be measured at clinic, using the tube provided by Central Laboratory

6. Visit 4 (Day 3 for 48-hour open-label initial phase) is the same visit of Day 1 in 28-day randomized treatment study phase; i-STAT and S-K for all patients, remaining procedures only for patients with i-STAT potassium values >5.0 mmol/L as measured fasting
7. Central laboratory S-K sample collected as part of the serum clinical chemistry
8. EOS in initial phase only for patients NOT entering the 28-day randomized treatment study phase, and occurs 7±1 day after the last administration of IP
9. Baseline parameters should be measured/collected up to 1 day prior to administration of the 1st dose of study drug on initial phase Day 1(Visit 2)
10. Access IVRS/IWRS on initial phase Day 3 (Visit 4) or if patient permanently discontinuous dosing before the end of initial phase dosing period
11. All potassium samples are analyzed by i-STAT and by the Central Laboratories on all occasions. And haemolysed samples should not be sent to the Central Lab for potassium, the sample should be re-drawn to obtain a sample showing no haemolysis. For diabetic patients all potassium samples should be collected prior to insulin administration whenever possible.
12. Study Day in Table 1 is for 48-hour open-label initial phase
13. A complete physical examination should be performed within 1 day prior to administration the first dose of study drug on initial phase Day 1, and targeted physical examination will be conducted on initial phase Day 3 and 9 for patients not entering the 28-day randomized treatment study phase. Please refer to section 5.2.2
14. AEs will be collected after the patient has signed informed consent, so during the Day 1 (Visit 2), investigator need to check if any AE happened since from inform consent

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

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

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

3. Physical Exam, ECG, Vital signs, weight, urinalysis, clinical chemistry including S-Aldo and P-Renin, and hematology parameters will be measured fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic); On 28-day randomized treatment study phase Days 1,15, 29, and 35(EOS), blood sample which including S-Aldo and P-Renin test need to be collected prior to 10am after at the patient has been upright for at least 2 hours and before the ECG
4. IP administration may not happen during some scheduled visits in patients for which the dose was reduced to EOD dosing.
5. For women of Childbearing potential, urine-HCG will be measured at clinic, using the tube provided by Central Laboratory
6. All potassium samples are analyzed by i-STAT and by the Central Laboratories on all occasions. And haemolysed samples should not be sent to the Central Lab for potassium, the sample should be re-drawn to obtain a sample showing no haemolysis. For diabetic patients all potassium samples should be collected prior to insulin administration whenever possible
7. If a scheduled clinic visit falls on a weekend or National holiday during the 28-day randomized treatment study phase, the scheduled visit may take place either 1 day early or 1 day late (i.e. within±24 hours of the scheduled day) for 28-day randomized treatment study phase Days 5, 8, 12, 15, 19, 22, 26 and 35, up to 2 days late for 28-day randomized treatment study phase Day 2 or 2 days early for Day 29. If the Day 29 visit is conducted early, the patient must take IP through Day 28 per protocol
8. EOS occurs 7±1 day after the last administration of IP
9. Access IVRS/IWRS on visit indicated or if patient permanently discontinues dosing before the end of 28-day randomized treatment study phase
10. Study Day in Table 2 is for 28-day randomized treatment study phase
11. Targeted physical examination will be conducted on Days 1, 15, 29, and Day 35 (EOS) during the 28-day randomized treatment study phase, please refer to 5.2.2

4.1 Enrolment/screening period (Visit 1)

Procedures will be performed according to the Study Plan in Table 1.

At screening, consenting patients are assessed to ensure that they meet 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. 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 the 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 48-hour open-label initial phase Day 1 (Visit 2)

Patients will arrive in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic).

The following assessments will be performed:

- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- Two potassium samples for assessment using both i-STAT and the Central Laboratory will be collected 60 minutes (+/-10 min) apart.
- 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 samples will be collected:
  - A blood sample for standard assessment of hematology and clinical chemistry
  - Urine for standard assessment of urinalysis parameters including a pregnancy test if the patient is a woman of childbearing potential
- Obtain vital signs (pulse rate and blood pressure)
- Administer the EQ-5D questionnaire

- 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 an initial phase IP kit
- The first doses of study IP will be administered as a slurry/suspension in water. The patient will be shown/instructed on how to mix and administer the IP
- 1 hour (± 15 min) after dose administration a potassium sample (i-STAT and Central Laboratory) will be collected, following which the patient is allowed to break the fast
- Two additional potassium samples (i-STAT and Central Laboratory) will then be taken at 2 and 4 hours (±15 min) after dose administration.
- 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 for the initial 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 approxtimately 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 i-STAT potassium levels are > 6.2 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. Patients will return to the clinic 7 (±1) days later for an EOS visit.
- If i-STAT potassium levels are ≤6.2 mmol/L as determined by i-STAT, and the ECG does not show 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 initial phase Day 2 (Visit 3).
- See section 7.2 regarding how to handle patients with potassium < 3.5 mmol/L.

4.2.2 48-hour open-label initial phase Day 2 (Visit 3)

Patients will arrive fasting at the clinic in the morning (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium levels will be evaluated by i-STAT and the Central Laboratory.
- Following completion of the above procedures, the first daily dose of IP will be administered in the clinic as a slurry/suspension in water, followed by the 1 hour post Dose 1 blood draw, after which the patient is allowed to break the fast.
- Patients will then be sent home with study drug and instructions on how to take the IP. They will be requested to fill out a dosing schedule card indicating when they took the IP.
- Patients will return to the clinic the following morning and bring the used IP and dosing schedule card with them.

4.2.3 48-hour open-label initial phase Day 3 (Visit 4)

Please note, the initial phase Day 3 is also the same day as the 28-day randomized treatment study phase Day 1 (Visit 4).

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- Potassium levels will be evaluated by i-STAT and the Central Laboratory. If the i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/L, inclusive) the patient will be randomized into the 28-day randomized treatment study phase and complete the procedures detailed in Section 4.2.4). However if the i-STAT potassium value is > 5.0 mmol/L or <3.5 mmol/L the below assessments will be performed:

- Samples will be collected: Blood samples for the standard assessment of clinical chemistry; blood sample for standard assessment of heamatology; Urine for standard assessment of urinalysis parameters
- An ECG will be performed (Section 5.2.3)
- Perform target physical examination including weight (Section 5.2.2)
- Withdraw the patient from the 48-hour open-label initial phase
- Patients will then DISCONTINUE from the study medication, and receive standard of care at the discretion and the direction of his/her own physician. However, the patient will need to return to the clinic 7 (± 1) days later for an EOS visit in the morning, fasting, nothing by mouth except water

4.2.4 28-day randomized treatment study phase Day 1 (Visit 4)

The Day 1 of 28-day randomized treatment study phase is the same day as the Day 3 of 48-hour open-label initial phase. Patients whose i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/L, inclusive) at Day 3 of 48-hour open-label initial phase, will be randomized into the double-blind 28-day randomized treatment study phase.

The following assessments will be performed:

- Samples will be collected prior to any IP administration:
  - Blood samples for standard assessment of hematology and clinical chemistry including S-K.
  - Urine for standard assessment of urinalysis parameters
- An ECG will be performed (Section 5.2.3).
- A targeted physical examination including weight (Section 5.2.2).
- Site investigator access the IVRS/IWRS and randomize the patient. The system will assign the patient a study IP kit (Week 1) containing a 7-day supply of IP.
- If the 28-day randomized treatment study phase Day 2 visit falls on a national holiday or weekend, the patient should be informed when next to return to the clinic . They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day and to bring the used IP and dosing schedule card with them when they return to the clinic.

4.2.5 28-day randomized treatment study phase Day 2 (Visit 5)

If the scheduled 28-day randomized treatment study phase Day 2 clinic visit falls on a weekend or National holiday the Day 2 visit (Visit 5) may occur up to 2 days late.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (28-day randomized treatment study phase Day 5) and bring the used IP and dosing schedule card with them.

4.2.6 28-day randomized treatment study phase Day 5 (Visit 6)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (28-day randomized treatment study phase Day 8) and bring the used IP and dosing schedule card with them.

4.2.7 28-day randomized treatment study phase Day 8 (Visit 7)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Prior to IP administration, potassium samples (i-STAT and Central Laboratory) will be collected and an ECG will be performed (Section 5.2.3).

- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit (Week 2) containing an additional 7-day supply of IP.
- Patients will return to the clinic, in the morning, four (4) days later (28-day randomized treatment study phase Day 12) and bring the used IP and dosing schedule card with them.

4.2.8 28-day randomized treatment study phase Day 12 (Visit 8)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (28-day randomized treatment study phase Day 15) and bring the used IP and dosing schedule card with them.

4.2.9 28-day randomized treatment study phase Day 15 (Visit 9)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests will be performed before any IP administration
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including S-K
  - Blood for a standard assessment of hematology parameters
  - Urinalysis parameters

- An ECG will be performed (Section 5.2.3)
- A targeted physical examination will be performed (Section 5.2.2)
- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit for use in Week 3 containing an additional 7-day supply of IP.
- Patients will return to the clinic, in the morning, four (4) days later (28-day randomized treatment study phase Day 19 and bring the used IP and dosing schedule card with them.

4.2.10 28-day randomized treatment study phase Day 19 (Visit 10)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (28-day randomized treatment study phase Day 22) and bring the used IP and dosing schedule card with them.

4.2.11 28-day randomized treatment study phase Day 22 (Visit 11)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Blood samples for measurement of potassium (i-STAT and Central Laboratory) will be collected.
- An ECG will be performed (Section 5.2.3)
- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit (Week 4) containing an additional 7-day supply of IP.

- Patients will return to the clinic, in the morning, four (4) days later (28-day randomized treatment study phase Day 26) and bring the used IP and dosing schedule card with them

4.2.12 28-day randomized treatment study phase Day 26 (Visit 12)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Blood samples for measurement of potassium (i-STAT and Central Laboratory) will be collected.
- Patients will return to the clinic, in the morning, three (3) days later (Day 29), fasting, nothing by mouth except water and bring the used IP and dosing schedule card with them.

4.2.13 28-day randomized treatment study phase Day 29 (Visit 13)

Please note: If the Day 29 visit is conducted early, the patient must take IP through 28-day randomized treatment study phase Day 28 per protocol. In this instance IP will be administered after all of the Day 29 procedures have been conducted.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests will be performed:
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including S-K
  - Blood for a standard assessment of hematology parameters
  - Urinalysis parameters

- An ECG will be performed (Section 5.2.3)
- A targeted physical examination will be performed (Section 5.2.2)
- The EQ-5D questionnaire will be administered
- Patients will be instructed to return to the clinic, in the morning, 7 ±1 days following the last study IP administration (28-day randomized treatment study phase Day 35) for an EOS visit.

4.3 Follow-up period (EOS)

Follow up visit will be performed at Day 9 for 48-hour open-label initial phase, and Day 35 for 28-day randomized treatment study phase, or 7 ±1 days following the last study IP administration for patients who are withdrawn from the study medication.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic).

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests/procedures will be performed:
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including, S-K
  - Blood for a standard assessment of hematology parameters
  - Urine for standard urinalysis parameters
  - A pregnancy test if the patient is a woman of childbearing potential
  - An ECG will be performed (Section 5.2.3)
  - A targeted physical examination will be performed (Section 5.2.2)

Note: If the EOS for the 48-hour open-label initial phase or 28-day randomized treatment study phase falls on a weekend, the EOS visit can be performed either on the preceding Friday or the following Monday.

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 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.

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

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

The 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 initial phase Days 1, 3 and 9 (EOS visit) for patients NOT entering the double-blind 28-day randomized treatment study phase and on 28-day randomized treatment study phase Days 1, 15, 29 and 35 (EOS).

S-K will be evaluated as part of the clinical chemistry sample on initial phase Day 1 (60 minute baseline sample), initial phase Days 3 and 9 (EOS) for patients not entering the 28-day

randomized treatment study phase, and on 28-day randomized treatment study phase Days 1,15, 29 and 35 (EOS)

Urine samples will also be collected during the study. The 48-hour open-label initial phase Day 1 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration and is repeated at the last visit of the study, either on 48-hour open-label initial phase Day 9, or on28-day randomized treatment study phase Day 35.

Urinalysis will be performed by the Central Laboratory at 48-hour open-label initial phase Day 1 for all patients and on initial phase Days 3 and 9 for patients NOT entering the 28-day randomized treatment study phase, and on 28-day randomized treatment study phase Days 1, 15, 29 and Day 35 (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 within 1 day of administing the first dose of study drug on initial phase Day 1 (Baseline: all patients), and targeted physical examination will be conducted on initial phase Day 3 for all patients and on Day 9 for patients not entering the 28-day randomized treatment study phase. During the 28-day randomized treatment study phase, targeted physical examination will be conducted on Days 1, 15, 29, and 35 (EOS).

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

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

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 initial phase Day 1, initial phase Day 3 and Day 9 (EOS) for patients NOT entering the double-blind 28-day randomized treatment study phase, and on 28-day randomized treatment study phase Days 1, 8, 15, 22, 29, and 35 (EOS). When applicable ECGs will be performed after the S-Aldo and P-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 at

the 1 hour post 1st dose time point on 48-hour open-label initial phase Day 1, an additional ECG will be recorded 1.5 hours 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 EQ-5D questionnaire in the local language will be administered on initial phase Day 1, and on 28-day randomized treatment study phase Day 29. The results will be recorded in the eCRF. See Appendix C.

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics (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: 48-hour open-label initial phase

Assessment	Sample Volume (mL)	Number of Samples				Maximum blood volume Total (mL)
		V 2 (D 1[6])	V 3 (D 2[6])	V 4 (D 3[6])	EOS (D 9[6])	
Hematology	2	1[2]		0-1[4]	1	6
Clinical Chemistry	8.5	1[2]		0-1[4]	1	25.5
Potassium (i-STAT and Central Lab S-K)	4.5	5-6[1,5]	2[3]	1[5]	1[5]	45
Maximum blood volume Total (mL)		**37.5**	**9**	**15**	**15**	**76.5**

V= Visit; D=Day

1. Potassium will be measured twice 60 (±10) minutes apart within 1 day of first dose administration on initial phase Day 1(Visit 2) and at 1,2 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 initial phase Day 1(Visit 2), the Central Laboratory clinical chemistry and hematology samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample
3. Potassium will be measured predose (0 hour) and 1 hour (±15 min) post 1st dose on initial phase Day 2 (Visit 3)
4. Clinical chemistry and hematology samples only for patients with i-STAT potassium values >5.0 mmol/L as measured fasting on initial phase Day 3 (Visit 4)
5. Central laboratory S-K sample collected as part of the clinical chemistry
6. Study Day in Table 4 is day for 48-hour open-label initial phase

Table 5 Volume of blood to be withdrawn from each patient: 28-day randomized treatment study phase

Assessment	Sample Volume (mL)	Number of Samples											Maximum blood volume Total (mL)
		V4 D1[2]	V5 D2[2]	V6 D5[2]	V7 D8[2]	V8 D12[2]	V9 D15[2]	V10 D19[2]	V11 D22[2]	V12 D26[2]	V13 D29[2]	EOS D35[2]	
Hematology	2	1					1				1	1	**8**
Clinical Chemistry	8.5	1					1				1	1	**34**
Potassium (i-STAT and Central Lab S-K[1])	4.5	1	1	1	1	1	1	1	1	1	1	1	**49.5**
Maximum blood volume Total (mL)		**15**	**4.5**	**4.5**	**4.5**	**4.5**	**15**	**4.5**	**4.5**	**4.5**	**15**	**15**	**91.5**

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 Day 1, 15, 29, and 35.
2. Study Day in Table 5 is day for 28-day randomized treatment study phase

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 an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may 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, and followed up to resolution of the Adverse Event.

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)
- Description of AE.

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 personnel: '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 protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. 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 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 personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel 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 30g 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.

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-9 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 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.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product and strength	Dosage form	Manufacturer
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

Placebo	Powder for Oral Suspension in a sachet	AstraZeneca

7.2 Dose and treatment regimens

During the 48-hour open-label initial phase all patients will receive ZS per os (PO) at a dose of 10g three times a day (tid) for a maximum of 6 doses, study drug will be administered orally before breakfast on initial phase Days 1 and 2, but for other dose during the initial phase, study drug will be administrated orally with or without food. The individual kit will be assigned through IVRS/IWRS. For patients with i-STAT potassium values within the normokalemic range (3.5 to 5.0 mmol/L, inclusive) on the morning of 48-hour open-label initial phase Day 3, the site will contact IVRS/IWRS to determine which on-site kit to use for the 28-day randomized treatment study phase. Thereafter the 28-day randomized treatment study phase kits will be assigned weekly through IVRS/IWRS and be dispensed by designated and trained site pharmacy staff. Study drug will be taken orally in the morning during the 28-day randomized treatment study phase, with or without food.

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), dosing during the 28-day randomized treatment study phase will be reduced from qd to every other day.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive during the 48h initial open label treatment phase the subject will be directed to not take any more ZS during the rest of the day and return the next day to continue in the study. E.g. patients with potassium values between 3.0 mmol/L and 3.4 mmol/L on Day 2 will not take the rest of the doses on Day 2, and will return fasting to be assessed for randomization into the 28-day randomized treatment study phase on Day 3. Patients with potassium values between 3.0 mmol/L and 3.4mmol/L already on Day 1 will not take the rest of the doses on Day 1, and will return fasting to have their potassium tested again on Day 2 and continue their therapy as per the study schedule if the potassium has is then between 3.5 and 5.0 mmol/L. If the potassium remains low (≤3.4 mmol/L but not <3.0 mmol/L) on Day 2, the Day 2 doses should not be taken and the patient will return fasting to be assessed for randomization into the 28-day randomized treatment study phase on Day 3, and only normokalemic patients (potassium between 3.5 - 5.0 mmol/L, inclusive) will be randomized.

Patients with confirmed potassium <3.0 mmol/L should discontinue from therapy as per section 3.9.

For doses administered in the clinic during the 48-hour open label initial phase each dose will be individually dispensed by designated, trained site staff.

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 study protocol.

The designated individual (e.g. pharmacist) will account for all study drugs dispensed to and returned from the patient.

IP kits will be uniquely coded and assigned through the randomization and subsequent visits via the IVRS/IWRS. 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.

The designated individual (e.g. pharmacist) is also responsible for maintaining accurate records accounting for the receipt, dispensing and final disposition of all investigational products using the appropriate IP logs provided by AstraZeneca.

7.7 Concomitant and other treatments

All concomitant medications taken by the patient from 7 days prior to 48-hour open-label initial phase Day 1 until 28-day randomized treatment study phase Day 35(EOS), or the end of the study (7 ± 1 days after the last dose of IP) for patients, will be recorded.

Whenever possible, all blood draws collected prior to meals should be collected prior to any insulin/insulin analog treatment. From 48-hour open-label initial phase Day 1 through 28-day randomized treatment study phase Day 28, the time of dosing with insulin/insulin analogs must be recorded when IP is administered in the clinic.

During the study, the patient cannot receive alternative treatment for hyperkalemia while taking IP. 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. Any alternative treatment administered after the end of IP administration and prior to the EOS visit must be recorded in the concomitant medication eCRF page (and as AE if applicable).

In addition to therapies for hyperkalemia also other drugs with World Health Organization Anatomic Therapeutic Chemical classification code V03AE, i.e. potassium 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.

Changes to RAAS inhibitor and/or diuretics (including adding a new, changing the dose or discontinuation or switching of RAAS inhibitor and/or diuretics) during the study are prohibited. If clinically indicated to change the RAAS inhibitor and/or diuretics, the patients should discontinue study medication.

Other medication other than that described above, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

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 study drug, to mitigate the risk of drug interactions.

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

Class of Drug	**Drugs**
Azole antifungals	Ketoconazole, Itraconazole, Posaconazole or 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

All personnel involved with the analysis and conduct of the study will remain blinded until protocol violators have been identified, and database is locked. Analyses will be performed by AstraZeneca or its representatives.

A detailed Statistical Analysis Plan (SAP) will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

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

The assumptions used in the above sample size estimations are taken from the ZS-004 study.

8.3 Definitions of analysis sets

All efficacy analyses will be performed using the full analysis set (FAS) based on the Intent-to-Treat (ITT) principle. The FAS includes all randomized patients. The main analysis will be analysed according to their randomized treatment assignment. Patients without any post randomization data will not be used in any of the analyses, but will be accounted for in summary statistics tables. Explicit definitions are presented in Section 8.3.1 below.

This study will have prospectively defined analysis sets including separate evaluability rules for the 48-hour open-label initial phase and 28-day randomized treatment study phase.

8.3.1 Full analysis sets (FAS)

FAS-OLP: For the 48-hour open-label initial phase, the full analysis set will include all patients registered in the 48h open-label initial phase.

FAS-RTP: For the 28-day randomized treatment study phase, the full analysis set will include all patients who are randomized to the 28-day randomized treatment study phase.

Unless otherwise specified, all efficacy analyses will be carried out on the FAS.

8.3.2 Safety analysis sets (SAF)

SAF-OLP: For the 48-hour open-label initial phase, the safety analysis set will include all patients as treated with at least one dose of IP in the 48h open label initial phase.

SAF-RTP: For the subsequent 28-day randomized treatment study phase, the safety analysis set will include all patients as treated with at least one dose of 28-day randomized treatment study phase IP among those randomized.

All safety analyses will be based on the SAF sets.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

The primary efficacy endpoint in this study will be the model-based least squares means (LSMEAN) of all S-K value during the 28-day randomized treatment study phase Study Days 8-29.

8.4.2 Secondary efficacy variables

For the 48-hour open-label initial phase, the secondary efficacy endpoints will include the following parameters:

- Exponential rate of change in S-K levels (blood)
- Change (absolute and percent (%) change) from baseline in S-K levels at all measured time intervals post dose (See Table 1)
- Proportion of patients who achieve normokalemia during the 48-hour open-label initial phase at 24 and 48 hours
- Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/L, inclusive)

For the subsequent 28-day randomized treatment study phase, the secondary efficacy endpoints will include the following parameters:

- The proportion of patients who remain normokalemic (as defined by S-K levels between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during 28-day randomized treatment study phase
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase
- The mean change and mean percent change in S-K levels evaluated relative to both 48-hour open-lable initial phase and 28-day randomized treatment study phase baselines
- The time to hyperkalemia (defined as S-K ≥5.1 mmol/L)
- The mean changes in S-Aldo and P- Renin levels

8.4.3 Safety Variables

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

8.5 Methods for statistical analyses

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

All efficacy analyses will be performed separately for the 48-hour open-label initial phase and 28-day randomized treatment study phase using their respective full analysis sets. Safety data will be separately summarized in a descriptive manner on the safety analysis sets for the initial phase and 28-day randomized treatment study phase, respectively.

All efficacy and safety data will be listed by patient. Descriptive statistics will consist of the number of patients (n), mean, standard deviation, median, minimum, and maximum for continuous variables and counts and percentage for categorical variables. Within-treatment group changes will be analysed using paired t-tests, and comparisons between each active dose treatment group vs. placebo control group will be performed using a 2-sample t-tests.

Results of all statistical analysis will be presented with a 95% confidence interval (CI) and two-sided p-value, unless otherwise stated.

For the initial phase, the baseline S-K will be established on initial phase Study Day 1 (pre-treatment) by taking the mean of 2 different S-K values, recorded 60 ± 10 minutes apart.

For the subsequent 28-day randomized treatment study phase, the baseline S-K will be established in the morning of initial phase Study Day 3 and will use the first S-K measurement performed on Study Day 3, that establishes patient eligibility into the 28-day randomized treatment study phase.

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

Multiple testing strategy

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

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

Specifically, the following fixed hierarchical sequence (see Table 6; progressing to the next test in the sequence till a 2-sided p-value of > 0.05 is encountered. At which point further testing will cease. Explicitly, Table 6 will be implemented:

Table 6 Confirmatory Testing Sequence

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

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

8.5.1 Analysis of the primary variable

The primary endpoint in this study will be the model-based LSMEAN of all available S-K values during the 28-day randomized treatment study phase Study Days 8-29. A log transformation will be applied to the S-K level since historical data shows that S-K measurements follows a log-normal distribution, and also to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (high to low dose) versus placebo control for the 28-day study treatment period to estimate the least squares mean Day 8-29 values stratified by country; the model will include

all S-K data collected at the schedule visits between Day 8-29 as response variables, and baseline covariates for initial phase eGFR and open label and double-blind randomized phase baseline S-K values as well as age (<55, 55-64, ≥65 years), country and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus. In addition, the primary efficacy endpoint will be evaluated in patients with hyperkalemia for the subgroups defined in Section 8.5.4. More details will be described in the SAP.

The S-K levels used for this analysis will be based on the Central Laboratory outcome. If Central Laboratory data are missing, they will be replaced by i-STAT values adjusted to reflect the mean difference between i-STAT and S-K values from all available paired lab samples collected in this study. More details on how to handle dropouts and missing data will be provided in the SAP.

8.5.2 Analysis of the secondary and additional variables

For the initial phase, the mean and relative reduction in the secondary efficacy endpoints will be evaluated for all enrolled patients. The change from baseline will be assessed using a paired t-test, and a two-sided p-value ≤ 0.05 will be considered statistically significant.

For the 28-day randomized treatment study phase, the same modelling strategy (as described in Section 8.5.1) will be applied to the secondary efficacy endpoint to compare each active dose (high to low) vs. placebo control.

Secondary efficacy endpoints will include:

- The proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during 28-day randomized treatment study phase
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase
- The mean change and mean percent change in S-K levels evaluated relative to both baselines
- The time to hyperkalemia (defined as S-K ≥5.1 mmol/L)
- The mean change in S-Aldo and P-Renin levels

The health state of the study population will be assessed on initial phase Day 1, and on 28-day randomized treatment study phase Day 29 using the EQ-5D questionnaire.

In addition, the secondary efficacy endpoint at the end of the 28-day randomized treatment study phase will be evaulated in patients with hyperkalemia for the subgroups defined in Section 8.5.4. More details will be specified in the SAP.

8.5.3 Safety analysis

Separate safety analyses will be performed for the initial phase and 28-day randomized treatment study phase. Safety endpoints will include adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations, ECGs, clinical laboratory evaluations, and other electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

The respective safety analysis will be undertaken on the safety analysis sets, separately for the initial phase and for the 28-day randomized treatment study phase. Safety and tolerability data will be presented by treatment arm. More details will be described in the SAP. Only AE with date of onset during the respective observation period will be presented. Laboratory data and other investigations will be presented descriptively. More information will be provided in the SAP.

Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA [latest version]). For each study treatment, safety data will be collected and analysed while on initial phase or 28-day randomized treatment study phase treatment, and follow up until adverse events are resolved. The type, incidence, timing (onset, duration), relationship, and severity of AEs will be reported for treatment-emergent and SARs. Reasons for withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or leading to withdrawal of IP. Safety results will be displayed separately for each of these phases.

The time frames of interest will be from 28-day randomized treatment study phase Study Day 1 through the end of 28-day randomized treatment study phase Day 28. Unresolved adverse event outcomes at the end of 28-day randomized treatment study phase will be followed for an additional seven days or until resolution, whichever occurs earlier.

8.5.4 Subgroup analysis

To facilitate a benefit-risk assessment for the purpose of regulatory submission in Japan, subgroup of patients from Japan will be analyzed separately, with respect to all efficacy and safety variables for both phases of the study. More details will be presented in the SAP.

In addition, the primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated for the following subgroups:

- chronic kidney disease (CKD)
- diabetes mellitus (DM)
- Heart failure (HF)

- those on RAAS inhibitors

More details will be described in the SAP.

8.5.5 Interim analysis

No interim analyses are planned.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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 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).

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site.

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 Q1 2017 and to end by Q1 2018.

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.

The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator.

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 Ethics Committee should approve the final 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 Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee 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.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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 Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principle Investigator (PI) and AZ or AZ delegate.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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 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

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.

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.

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 (eg, 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 (eg, 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 (eg, 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 eg, 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 eg, 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 EQ-5D Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

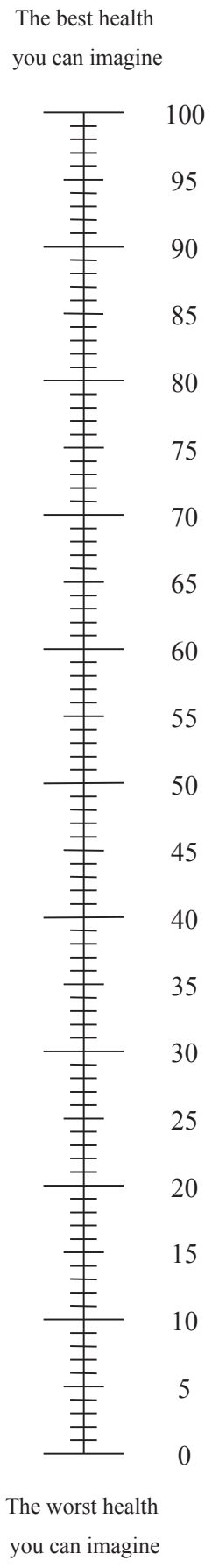
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.