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

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VERSION HISTORY

Version 3.0, 26 Sep 2017 **Changes to Clinical Study Protocol version 2.0 [14 June 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
CLINICAL STUDY PROTOCOL SYNOPSIS Study period 9.3 Study timetable and end of study	Estimated date of last patient completed was updated.	Changed by study progress.
7.7.1 Oral medications with gastric pH-dependent bioavailability	This section was included.	Updated information was added.
9.4 Data management by AstraZeneca or delegate	"The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator." was deleted.	This procedure is not applicable in Japan. Correction of error.

Version 2.0, 14 June 2017 **Changes to Clinical Study Protocol version 1.0 [13 February 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
4 STUDY PLAN AND TIMING OF PROCEDURES 4.1 Screening/Enrolment period (Visit 1)	It was added that "If eGFR assessments are performed within 1 month prior to Visit 1, the latest one can be used for Visit 1 data."	To decrease burden for patients.
4.2.1 Day 1 (Visit 2) 4.2.2 Day 2 (Visit	"from 11:00 pm (2300) on the previous day" was corrected to "for a minimum of 8 hours"	Correction of error

Version 2.0, 14 June 2017 **Changes to Clinical Study Protocol version 1.0 [13 February 2017] are summarised below.**		
Section, Heading	**Revision Summary**	**Reason for Revision**
3) 4.2.3 Day 3 (Visit 4) 4.3 Follow-up period (EOS)		

Version 1.0, 13 February 2017
Initial creation

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

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CLINICAL STUDY PROTOCOL SYNOPSIS

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

Principal Investigator(s)

See Addendum.

Study site(s) and number of patients planned

A total of approximately 102 subjects with mild to moderate hyperkalemia at screening (potassium values of ≥ 5.1 mmol/L and ≤ 6.5 mmol/L) will be randomized in the study at approximately 20 investigational sites in Japan.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2017	Phase II/III
Estimated date of last patient completed	Q1 2018	

Study design

Patients not receiving any therapy for hyperkalemia and with 2 consecutive i-STAT (A portable blood analyser) potassium values of ≥ 5.1 mmol/L and ≤ 6.5 mmol/L will be enrolled and randomized 1:1:1 to receive ZS 5 g, ZS 10 g, or placebo TID for 48 hours.

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

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

Stopping rules will be implemented to ensure subjects discontinue the study treatment and receive alternative therapy in case of significant hyperkalemia, hypokalemia, or significant cardiac arrhythmias.

Objectives

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

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

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

Target patient population

The target patient population consists of male and female patients aged ≥ 18 years with hyperkalemia, defined as two consecutive i-STAT potassium values, measured 60-minutes apart, both ≥ 5.1 mmol/L and ≤ 6.5 mmol/L within 1 day before the first dose of study drug on Study Day 1.

Duration of treatment

The treatment duration is 48 hours per subject post-randomization with a subsequent final follow up visit 7 days later after the last study treatment administration for all subjects.

Investigational product, dosage and mode of administration

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

Subjects were randomized to receive either ZS 5 g, 10 g or placebo, administered TID for 48 hours (total 6 doses).

If i-STAT potassium levels are > 6.5 mmol/L as determined by the i-STAT, the patient will be discontinued from the study.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive at any time point on the Day 1 the subject will be directed to not take any more study drug for the remainder of the day and return the next day to evaluate whether to continue dosing in Day 2.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive at any timepoint on the Day 2, the subject will be directed to not take any more study drug for the remainder of the day and return the next day for evaluation.

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

Statistical methods

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, and patients will be analyzed according to their randomized treatment assignment. Patients without any post randomization data will not be used in any of the inferential analyses, but will be accounted for in summary statistics tables.

Primary analysis for primary efficacy variable of exponential rate of change in S-K will be based on a random slope model. All available S-K measurements from baseline through to 48-hr post initial dose (Day 3, 0-hour) will be included as the response variables after log-transformation. The model will include time and time x treatment interaction as fixed continuous effects and intercept and time as patient-level random effect with unstructured covariance matrix. In addition, baseline estimated glomerular filtration rate (eGFR) category (<60, ≥ 60 mL/min/1.73m^2) will be included as a factor in the model.

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

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

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

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

Proportion of normokalemic patients at 48 hours post initial dose will be analyzed by logistic regression model. The model will include treatment and stratification factor of baseline estimated glomerular filtration rate (eGFR) category (<60, ≥ 60 mL/min/1.73m^2) as factors and baseline S-K value as a covariate.

Safety endpoints will include adverse events (including incidence of oedema-related events), vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters. All safety analyses will be conducted for Safety analysis set, which will include all patients who took at at least one dose of investigational product (IP) during the study. Safety variables will be summarized by treatment group and descriptively evaluated.

Sample size

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

Sample size for the exponential rate of change during the study is calculated based on a random slope model, with parameters estimates based on the ZS-003 data, and here it is assumed that K measurement schedule is same as that in study 003 correction phase, i.e. K is measured at Baseline(0),1,2,4,24,25,28 and 48 hours post first dose. [redacted] respectively.

[redacted] Here it was assumed that proportion of normokalemic patients

[redacted], respectively.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZ	AstraZeneca
AZRand	AZ global Randomization System
BP	Blood pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPS	Calcium Polystyrene Sulfonate
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GGT	Gamma-glutamyl transferase

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
i-STAT	A portable blood analyser
ITT	Intent-to-Treat
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HF	Heart Failure
IB	Investigators Brochure
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
qd	once daily
qod	every other day
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin angiotensin aldosterone system inhibitors
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S-Ca	Serum calcium
S-HCO3	Serum bicarbonate
S-K	Serum potassium
S-Mg	Serum magnesium
S-Na	Serum sodium
S-PO4	Serum phosphate
SPS	Sodium Polystyrene Sulfonate
TEAE	Treatment Emergent Adverse Event
tid	three times daily
WBC	White Blood Cell

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture
ZS	sodium zirconium cyclosilicate

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 normal potassium values in serum are between 3.5 and 5.0 mmol/L, with the kidney being the main regulator of potassium values.

Hyperkalemia develops when there is excessive intake or insufficient elimination of potassium. Insufficient elimination can be hormonal, pharmacologic or due to reduced kidney function. Increased extracellular potassium leads to impairment of the neuromuscular, cardiac, and gastrointestinal organ systems. Impairment of cardiac conduction can lead to fatal cardiac arrhythmias. Severe hyperkalemia must therefore be immediately corrected.

There is a close correlation between the degree of kidney failure and serum potassium (S-K) values. In addition, a number of different commonly used drugs can cause hyperkalemia, as can advanced degrees of heart failure (HF), massive injuries, burns, intravascular hemolysis, or 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.

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. Potassium lowering therapies used in the emergency setting include intravenous, calcium, insulin, glucose, inhaled beta receptor agonists and dialysis.

The only pharmacologic therapies increasing elimination of potassium from the body are the potassium binding resins sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). Due to constipation, SPS and CPS cannot be administered on a chronic basis in many patients. Hence there is a significant medical need for new and better treatment for acute and chronic treatment of hyperkalemia.

Sodium zirconium cyclosilicate (ZS) has a crystal geometry conferring a high and selective exchange capacity for potassium and ammonium ions, and is being developed for the treatment of hyperkalemia.

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 represents 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%. Toxicology studies have shown ZS to be well tolerated. ZS is not systemically absorbed, but exerts its effects locally in the gastrointestinal tract, significantly reducing the risk of systemic toxicity.

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

In addition 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

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. The studies are described in detail in the Investigator Brochure, and have been published. (Packham DK et al 2015, Luo J et al 2016, Kosiborod M et al 2014).

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)

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. 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 the previous studies, the reductions of S-K by ZS 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.

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. A total of 751 patients have been included in the Acute Phase, of whom 746 patients entered Extended Dosing.

In the Acute Phase of the study, 99.3% of patients achieved normokalemia. Of the 746 patients who entered Extended Dosing, 526 have completed ≥ 3 months of therapy, 364 have completed ≥ 6 months, 247 have completed ≥ 9 months, and 145 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 4.6 mmol/L. Safety data were consistent with other ZS studies.

Two double-blind phase 3 studies (HARMONIZE Asia, D9480C00001 and HARMONIZE Global, D9480C00002) are currently under set up. Both studies are multicenter, prospective, randomized, placebo-controlled, double-blind, dose-ranging maintenance studies to investigate the safety and efficacy of ZS in patients with hyperkalemia (i-STAT potassium values ≥ 5.1 mmol/L).

1.2 Rationale for study design, doses and control groups

The dosage and administration to be evaluated in the Japan dose response study was decided referring to the Study ZS-003 data.

In Study ZS-003, the primary efficacy outcome variable of the proportion of patients who achieve normokalemia after 48 hours of initial treatment showed statistical significance in all the groups of ZS 10 g TID, 5 g TID and 2.5 g TID as compared with placebo group, and numerically, the proportion of patients with normokalemia increased dose-dependently, with 86.4% patients in 10 g TID group achieving normokalemia after 48 hours. Regarding safety, in the 2 days treatment at doses between ZS 10 g TID and 1.25 g TID, ZS was safe and well tolerated with no dose-dependent increase of adverse events. Based on this result, the dosage and administration of 10 g TID was recommended for the correction phase in foreign countries.

During the correction phase of Study ZS-004, patients received ZS 10 g TID for 2 days. Based on Kaplan-Meier estimates, 84.28% of subjects had normalized S-K values at 24 hours after the first dose ZS, and 97.62% of subjects had normalized S-K values at 48 hours after the first dose ZS. The treatment was safe and well tolerated.

Because it is necessary to normalize serum potassium within 48 hours of dosing in as many patients as possible, the most beneficial regimen for Japanese patients with hyperkalemia was considered to be 10 g TID for 2 days which achieved normokalemia in approximately 86-88% of non-Japanese patients. In Study ZS-003, clear dose response was observed in the 4 groups of 1.25 g TID, 2.5 g TID, 5 g TID and 10 g TID. Although a certain level of efficacy is expected with 2.5 g TID, it was judged that comparison of the 2 doses of ZS 5 g TID and ZS 10 g TID with placebo is sufficient to evaluate dose response.

Specific exclusion criteria ensure that appropriate patients, who are not at excess risk from treatment with ZS or placebo, will be enrolled. The multicenter design enhance the external validity, reproducibility, and generalizability of the results observed.

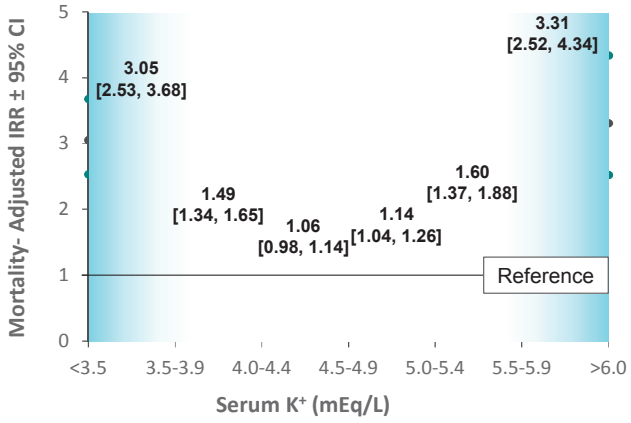
The patient selection criteria allows for the assessment of both efficacy and safety of ZS in a relevant population of patients with hyperkalemia. Since hyperkalemia affects both men and women, the inclusion criteria allows equal access to the protocol for both sexes. Exclusion criteria are developed 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 (Luo 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).

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). This physiologic effect 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 interactions (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. Only 1 of 7 patients developed K^+ <3.0 mmol/L. In ZS-004, one case of hypokalemia (3.4 mmol per liter in a patient receiving the 10-g dose) was reported in the 48 hours initial phase. This case was transient and resolved without potassium repletion.

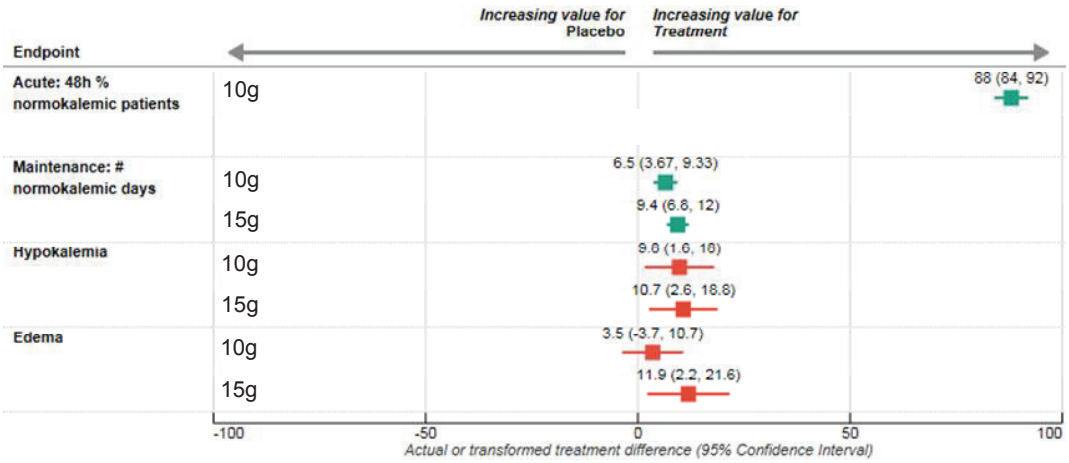
Edema: Among subjects randomized to placebo, ZS 5, 10 or 15g QD, edema was reported by 1.7, 0.9, 4.4 and 14.3%, respectively (ZS-003 & -004). Edema was untreated in 47% (7/15) of ZS-treated subjects and managed with diuretic initiation or dose adjustment and/or discontinuation of calcium channel blocker 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

Based on available oversea data, 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 mortality; potassium lowering reduces this risk even if normokalemia is not achieved (Figure 1). 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 oversea 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

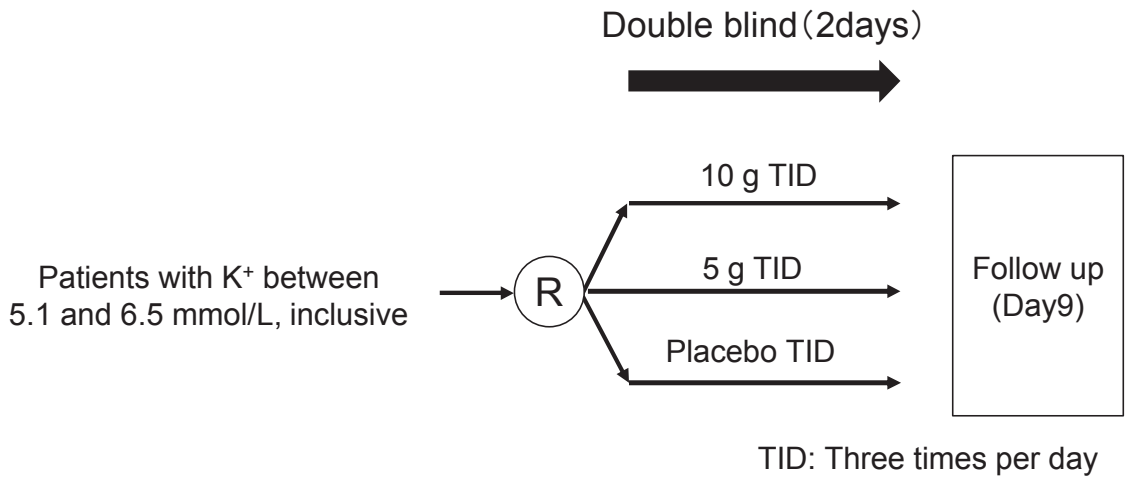
Patients not receiving any therapy for hyperkalemia and with 2 consecutive i-STAT potassium values of ≥ 5.1 mmol/L and ≤ 6.5 mmol/L will be enrolled and randomized 1:1:1 to receive ZS 5 g, ZS 10 g, or placebo TID for 48 hours.

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

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

Stopping rules will be implemented to ensure subjects discontinue the study treatment and receive alternative therapy in case of significant hyperkalemia, hypokalemia, or significant cardiac arrhythmias.

Figure 3 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

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

2.3 Safety objectives

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

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

3. Two consecutive i-STAT potassium values, measured 60 (± 10) minutes apart, both values should be ≥ 5.1 mmol/L and ≤ 6.5 mmol/L and measured within 1 day before the first dose of study drug on Study 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. Cause or symptoms of pseudohyperkalemia, such as

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

   2) hemolyzed blood specimen due to difficult or traumatic venepuncture

3) history of severe leukocytosis or thrombocytosis

3. Patients treated with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within 7 days prior to first dose of study drug on Study Day 1.

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

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

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

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

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

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

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

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

12. Patients with cardiac arrhythmias that require immediate treatment.

13. Patients on dialysis.

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

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

If a patient withdraws from participation in the study, then his/her enrolment/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 (1:1:1) between the three treatment arms (ZS 5g or ZS 10g or placebo three times per day). Randomization will be stratified by eGFR (<60, >= 60 mL/min/1.73m^2) measured at each study centre during the screening period, so that proportion of subjects with eGFR >=60 mL/min/1.73m^2 will not exceed 25% of the entire randomized subjects.

3.6 Methods for ensuring blinding

This study will have a double blind design. Patients will take by mouth the entire contents of a single sachet containing either ZS 5g, ZS 10g or placebo three times per day. 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 investigational product (IP). 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, 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 representatives who are independent to the study evaluation at the Patient Safety Department 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

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's decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol

- Risk to patient as judged by investigator
- Pregnancy
- Require treatment with medications prohibited or contraindicated for use due to safety concerns with ZS
- Patient unblinded due to emergency
- Patient develops potassium values > 6.5 mmol/L or <3.0 mmol/L (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). Patients discontinuing due to this criterion must immediately receive appropriate medical treatment to manage their hypo- or hyperkalemia.
- Patient develops clinically significant cardiac condition (see below). The patient should immediately receive appropriate medical treatment and be discontinued from study drug.
  - Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])
  - Acute heart failure
  - Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block) or widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block). If an ECG shows peaked T-wave, the serum potassium must be checked immediately and decide whether to continue the IP based on the criteria described in Section 3.9.
  - An absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec. All patients meeting the QTc>500ms criterion should immediately have potassium assessed by i-STAT and central lab, if not already done within 1 hour of the collection of the ECG

Patients who discontinue from study medication 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
- Lost of patient to follow-up
- Death

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

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

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

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as ‘Screen failure’(the potential subject who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomized patients).

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

Study Visit	**Visit 1**	**Visit 2[6]**	**Visit 3**	**Visit 4**	**EOS[5]**
Study Day	**Screening**	**Day 1[6]**	**Day 2**	**Day 3**	**Day 9[5]**
Written informed consent	X				
Eligibility criteria		X			
Demographics	X				
Medical History		X			
Physical exam including weight		X			X
Randomization		X			
Access IVRS/IWRS	X	X			
Study drug (IP) dispensation		X			
Study drug (IP) administration		X	X		
ECG		X		X	X
Vital signs		X		X	X
Concomitant medications		X	X	X	X
Adverse events		X[7]	X	X	X
eGFR[8]	X				
Potassium[1]		X[2]	X[3]	X	X
Serum Chemistry[1]		X		X	X
Hematology[1]		X		X	X
Urinalysis[1]		X		X	X
Urine HCG		X[4]			X[4]
IP Reconciliation				X	

1. All blood potassium samples are analyzed by i-STAT and by the Central Laboratories on all occasions. Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting and before administration of study drug. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible
2. Potassium will be measured twice 60 (±10) minutes apart within 1 day prior to first dose administration, and prior to, 1, 2 and 4 hours (±15 min) after administration of the first dose of study drug on Day 1. Potassium will be measured again at 90 minutes after taking the second dose for patients with i-STAT potassium ≥6.1 mmol/L or <4.0 mmol/L 4 hours after the first dose
3. Potassium will be measured predose (0 hour), 1 and 4 hour (±15 min) after the first dose on Day 2 (Visit 3)
4. U-HCG will be performed exclusively for women of childbearing potential. Samples will be analysed locally, and the data will not need to be collected in the database. Pregnant women are excluded from the study.
5. The End of Study (EOS) visit will occur 7±2 day after the last administration of IP.

6. Baseline parameters should be measured/collected no earlier than 1 day prior to administration of the 1st dose of study drug on Day 1 (Visit 2). Visits 1 and 2 may be combined into a single visit on the same day.
7. AEs will be collected after the patient has signed informed consent, so during the Day 1 (Visit 2), investigator need to check if any AE happened since from inform consent
8. If eGFR assessments are performed within 1 month prior to Visit 1, the latest one can be used for Visit 1 data.

4.1 Screening/Enrolment period (Visit 1)

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

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be entered in the study.

Patients can be re-screened once during the clinical trial period. 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).

S-creatinine (local laboratory) will be measured for stratification (based on eGFR value) prior to randomization. If eGFR assessments are performed within 1 month prior to Visit 1, the latest one can be used for Visit 1 data.

The GFR was estimated using the following equation generated by the Japanese Society of Nephrology: GFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (× 0.739 if female) (Matsuo S et al 2009).

4.2 Treatment period

An overview of the procedures for this period are included in the Study Plan (see Table 1). The specific procedure(s) to be performed at each visit are detailed below.

4.2.1 Day 1 (Visit 2)

Subject will arrive fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only prior to the blood collection for a minimum of 8 hours) at or before 8:00 am (0800 ± 120 minutes). Then, the following steps will be taken:

- All eligibility criteria will be assessed. This includes 2 consecutive S-K measurements at 60 (± 10) - minute intervals by using both i-STAT and the Central Laboratory. If both i-STAT values are ≥ 5.1 mmol/L and ≤ 6.5 mmol/L the following samples will be collected: a standard assessment of clinical chemistry, hematology and urinalysis, a pregnancy test if the subject is a woman of

childbearing potential, vital signs, an ECG and a full physical including weight, performed by the Principal Investigator (PI)/sub PI. The standard clinical chemistry and hematology assessments are analyzed by the central laboratory. Patient medical and surgical history including co-morbidities will be obtained with the review of selection criteria. 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.

- S-K samples (i-STAT and central laboratory) will be taken prior to administration of Dose 1 and at 1, 2 and 4 hours (± 15 min) post Dose 1 (prior to administration of Dose 2).
- The first two (2) doses of study IP will be administered at the clinic at as a suspension in water.
- The first doses of study IP will be administered at ~ 9.00 am (0900 ± 120 minutes) followed by a light breakfast. At dose administrations the subject will be 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.
- The second dose (Dose 2) will be administered 4 hours after Dose 1, after the 4 hour post Dose 1 blood sample will be drawn, before lunch.
- 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 after the second dose with instructions on how to take the IP. They will be requested to fill out a dosing schedule card indicating when they took the IP; The patient will return to the clinic the following morning of Day 2 (Visit3).
- Patients with i-STAT potassium ≥ 6.1 or <4.0 mmol/L at the 4 hour post Dose 1 blood draw will stay in the clinic and take the second dose of study drug approximately 4-hours after the first dose. They will then remain in the clinic an extra 90 minutes (±15 minutes) after taking the second dose when another blood sample for potassium determination (i-STAT and Central Laboratory will be collected and an ECG will be recorded).
  - If i-STAT potassium levels are > 6.5 mmol/L as determined by the i-STAT at the 90-minute post Dose 2 blood draw, the patient will be discontinued from the study. Patients will return to the clinic 7 (±1) days later for an EOS visit.
  - If i-STAT potassium levels are ≤ 6.5 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 Day 2 (Visit 3).
- All other activities will take place as outlined in the Study Plan (see Table 1).

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

4.2.2 Day 2 (Visit 3)

Subjects will arrive at the clinic at or before 8:00 am (0800 ± 120 minutes) with any remaining IP and empty sachets and IP boxes from the previous day and completed dosing schedule card. Subjects will arrive fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only prior to the blood collection for a minimum of 8 hours).

- The clinic staff will solicit any AEs, and will note any unused IP on the eCRF and source documents.
- Potassium levels will be evaluated prior to administration of the first daily dose (Dose 1; 0 hour) and then at 1 and 4 hour (± 15min) post Dose 1. Samples will be evaluated by i-STAT and the central laboratory.
- If the predose potassium level is > 6.5 mmol/L as determined by i-STAT, subjects will be considered treatment failures and will be withdrawn from the study and will receive standard of care. Subjects will return to the clinic on Study Day 9 for an EOS visit.
- The first two doses of IP on day 2 will be administered in the clinic. Dose 1 will be administered as a suspension in water before breakfast. The second dose (Dose 2) will be administered ~ 4 hours after Dose 1, and after the 4 hour post Dose 1 blood draw.
- If the 4-hour post Dose 1 potassium level is > 6.5 mmol/L as determined by i-STAT, subjects will be considered treatment failures and will be withdrawn from the study and will receive standard of care. Subjects will return to the clinic on Day 9 for an EOS visit.
- After receiving the second dose subjects will be sent home with instructions on how to take the IP at dinnertime. They will be requested to fill out a dosing schedule card indicating when they took the IP.
- See section 7.2 regarding how to handle patients with potassium < 3.5 mmol/L.

4.2.3 Day 3 (Visit 4)

Subjects will arrive at the clinic at or before 8:00 am (0800 ± 120 minutes) with any remaining IP and empty sachets and IP boxes from the previous day and completed dosing schedule card. Subjects will arrive fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only prior to the blood collection for a minimum of 8 hours).

The clinic staff will solicit any AEs, and will note any unused IP on the eCRF and source documents.

A standard assessment of blood chemistry, hematology and urinalysis assessment, an ECG and vital signs will be performed. In addition S-K will also be determined by i-STAT.

4.3 Follow-up period (EOS)

Subjects will arrive at the clinic at 8:00 am (0800 ± 120 minutes). Subjects will arrive at the clinic fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only prior to the blood collection for a minimum of 8 hours).

- The clinic staff will solicit any adverse events, note any changes in concomitant medications, and if the subject has visited a doctor or emergency room since the last visit. A final accounting of all study drug dosing supplies will be performed.
- Blood samples for i-STAT potassium and assessment of hematology and clinical chemistry including S-K will be collected.
- Assessment of urinalysis parameters.
- A urine pregnancy test will be performed if the subject is a woman of childbearing potential.
- An ECG will be performed (Section 5.2.3).
- Obtain vital signs (pulse rate and blood pressure) (Section 5.2.4)
- Perform a complete physical examination including weight, see Section 5.2.2
- A full clinical supply inventory for each subject will be conducted and reconciled.

5. STUDY ASSESSMENTS

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

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

5.1 Efficacy assessments

5.1.1 Potassium

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

Table 2 Summary of Serum Potassium Collection Times

Study Day	Time	Central Laboratory	i-STAT
-1 ~ 1	1st assessment to confirm qualification (within 1 day of the first administration of study drug)	X	X
	1 hour post 1st assessment	X[1]	X
1	0 hour (pre-dose)	X	X
	1 hour post Dose 1	X	X
	2 hours post Dose 1	X	X
	4 hours post Dose 1	X	X
	90 minutes post Dose 2	X[2]	X[2]
2	0 hour (pre-dose)	X	X
	1 hour post Dose 1	X	X
	4 hours post Dose 1	X	X
3	0 hour	X[1]	X
EOS	0 hour	X[1]	X

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

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). 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.

Table 3 Laboratory Safety Variables

Haematology	**Clinical Chemistry (serum)**
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-Platelet count	S-Creatinine (including eGFR assessment[1])
	S-Bilirubin, total
Urinalysis	S-Alkaline phosphatise (ALP)
U-PH	S-Glucose
U-Specific gravity	S-Sodium
U-Glucose	S-Potassium[2]
U-Ketones	S-Inorganic phosphate
U-Bilirubin	S-Calcium, total
U-Urobilinogen	S-Magnesium
U-Blood	S-Gamma-glutamyl transferase (GGT)
U-Albumin	S-Aspartate aminotransferase (AST)
U-Creatinine	S-Alanine aminotransferase (ALT)
U- Human chorionic gonadotropin (HCG) (only for females of childbearing potential) [3]	

1. eGFR will be measured at each study site during at Visit 1 only.
2. Blood potassium will be tested by i-STAT and Central Laboratory
3. Urine-HCG will be measured at clinic, using 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, at Visit 2, 4 and EOS.

The Visit 2 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration and at EOS visit.

Urinalysis, will be performed by the Central Laboratory at Visit 2, 4 and EOS.

Note: Whenever possible, all blood draws collected prior to meals should be collected prior to

insulin/insulin analog treatment.

5.2.2 Physical examination

A complete physical examination should be performed no earlier than 1 day before administration of the first dose of study drug on Visit 2 and EOS visit.

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.

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. 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 Visits 2, 4 and EOS. In addition, for patients who have i-STAT potassium levels ≥ 6.1 mmol/L at the 4 hour post 1st dose time point on the Day 1(Visit 2), an additional ECG will be recorded 90 minutes post 2nd dose.

5.2.4 Vital signs

5.2.4.1 Pulse rate and blood pressure

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

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

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

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Genetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

5.8 Storage, re-use and destruction of biological samples

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

5.9 Labeling and shipment of biological samples

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

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

5.10 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 4 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

Assessment	Sample Volume (mL)	Number of Samples					Maximum blood volume Total (mL)
		V 1 (Screening)	V 2 (D 1)	V 3 (D 2)	V 4 (D 3)	EOS (D 9)	
eGFR	2.5[1]	1					2.5
Hematology	2		1[3]		1	1	6
Clinical Chemistry	2.5		1[3]		1	1	7.5
Potassium (i-STAT and Central Lab S-K)	4.5		6-7[2,5]	3[4]	1[5]	1[5]	54

Table 4 Volume of blood to be withdrawn from each patient

Assessment	Sample Volume (mL)	Number of Samples					Maximum blood volume Total (mL)
		V 1 (Screening)	V 2 (D 1)	V 3 (D 2)	V 4 (D 3)	EOS (D 9)	
Maximum blood volume Total (mL)		**2.5**	**36**	**13.5**	**9**	**9**	**70**

V= Visit; D=Day

1 Actual blood volumes in each study centre may be a little different.

2 Potassium will be measured twice 60 (±10) minutes apart within 1 day of first dose administration on Day 1(Visit 2) and pre dose and at 1, 2 and 4 hours (±15 min) after administration of the first dose of study drug; An extra potassium will be measured 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 at the 4 hour post Dose 1

3 On 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

4 Potassium will be measured predose (0 hour), 1 and 4 hour (±15 min) post 1st dose on Day 2 (Visit 3)

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

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

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

The following variables will be collect for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of AE.

Intensity rating scale:

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

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

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

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

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

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

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

6.4 Reporting of serious adverse events

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

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

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

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

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

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

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

6.5 Overdose

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

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

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

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

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

6.6 Pregnancy

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

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

6.6.1 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

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

6.6.2 Paternal exposure

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

In case of pregnancy of the patient's partners, an ICF FOR PREGNANT PARTNERS OF STUDY PATIENTS the partner's pregnancy will be sent to the partner to obtain her consent for collection of pregnancy information. Such pregnancy report will follow the same timeframe and routing as described for any participant's pregnancy. These pregnancies will be also followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be obtained and documented if possible.

6.7 Medication Error

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

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

Medication error includes situations where an error.

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

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

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

- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

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

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

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

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

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product and strength	Dosage form	Manufacturer
Sodium Zirconium Cyclosilicate (ZS) 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

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

Subjects were randomized to receive either ZS 5 g, 10 g or placebo, administered TID for 48 hours (total 6 doses).

If i-STAT potassium levels are > 6.5 mmol/L as determined by the i-STAT, the patient will be discontinued from the study.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive at any time point on the Day 1 the subject will be directed to not take any more study drug for the remainder of the day and return the next day to evaluate whether to continue dosing in Day 2.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive at any timepoint on the Day 2, the subject will be directed to not take any more study drug for the remainder of the day and return the next day for evaluation.

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

7.3 Labelling

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

7.4 Storage

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

7.5 Compliance

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

7.6 Accountability

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

IP kits will have the unique number identifiers and will be assigned through the study. On receipt of IP supplies the Investigator/designee will check the supplies against the shipment manifest and will confirm receipt of IP shipments via the IVRS/IWRS. The system will then issue an acknowledgement receipt. Sites are required to place all shipment manifests and acknowledgement receipts in the site regulatory binder.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The designated individual (e.g. pharmacist) is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents ‘Procedures for drug accountability’ and ‘Procedures for drug storage’ which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

7.7 Concomitant and other treatments

All concomitant medications taken by the patient from 7 days prior to Day 1 until EOS visit, or the end of the study (7 ± 1 days after the last dose of IP) for patients, will be recorded.

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

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

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

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, Voriconazole
Anti-HIV drugs	Atazanavir, Nelfinavir, Indinavir, Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine
Tyrosine kinase inhibitors	Erlotinib, Dasatinib, Nilotinib

7.8 Post Study Access to Study Treatment (Not Applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Analyses will be performed by AstraZeneca or its representatives.

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

8.2 Sample size estimate

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

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

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

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.

8.3.1 Full analysis set

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

8.3.2 Safety analysis set

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

8.4 Outcome measures for analyses

8.4.1 Efficacy variables (Primary)

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

8.4.2 Efficacy variables (Key Secondary)

Key secondary efficacy variable is the proportion of patients who achieved normokalemia at 48 hours after start of dosing.

8.4.3 Efficacy variables (Secondary)

Also, secondary efficacy variables include the followings:

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

8.4.4 Safety Variables

In this study, the following safety data will be collected: adverse events (AEs), vital signs, ECGs, physical examinations, clinical laboratory evaluations, and other electrolytes (specifically, serum potassium [S-K], 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

8.5.1 Analyses of efficacy variables

8.5.1.1 Analysis of Primary efficacy variable

Primary analysis for primary efficacy variable of exponential rate of change in S-K will be based on a random slope model. All available S-K measurements from baseline through to 48-hr post initial dose (Day 3, 0-hour) will be included as the response variables after log-transformation. The model will include time and time x treatment interaction as fixed

continuous effects and intercept and time as patient-level random effect with unstructured covariance matrix. In addition, baseline eGFR category (<60, ≥ 60 mL/min/1.73m^2) will be included as a factor in the model.

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

8.5.1.2 Confirmatory testing strategy

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

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

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

8.5.1.3 Analysis of Key secondary efficacy variable

Proportion of normokalemic patients at 48 hours post initial dose will be analyzed by logistic regression model. The model will include treatment and baseline eGFR category (<60, ≥ 60 mL/min/1.73m^2)as factors and baseline S-K as a covariate.

8.5.2 Analysis of Safety data

Safety endpoints will include adverse events (including incidence of Oedema related events, defined as Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral and Peripheral swelling), vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters.

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

8.5.3 Interim analysis

NOT APPLICABLE.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

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

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

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

9.2 Monitoring of the study

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

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

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

9.2.1 Source data

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

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any

inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

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

The study is expected to start in Q2 2017 and to end by 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 [redacted] according to the Data Management Plan.

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

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

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

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

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify

the roles and responsibilities of the various functions and personnel involved in the data management process.

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

Serious Adverse Event (SAE) Reconciliation

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

Data associated with human biological samples

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

Management of external data

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

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

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

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

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

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

10.6 Audits and inspections

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

11. LIST OF REFERENCES

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

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

Matsuo S et al 2009
Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-92

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

Appendix A Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

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

Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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