Clinical Study Protocol	
Drug Substance	Sodium Zirconium Cyclosilicate (ZS)
Study Code	D9480C00006
Version	4.0
Date	05 February 2018

A phase 3b, multicenter, prospective, randomized, double blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalemia with Sodium Zirconium Cyclosilicate (DIALIZE)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

(Japan) AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku Osaka 530-0011, Japan

[redacted]

EudraCT number 2017-003029-14

VERSION HISTORY

Version 4.0, 05 February 2018
- Visit schedule updated (additional potassium sampling visits after Short Inter-Dialytic Interval) - EOT/EOS requirements updated for premature treatment discontinuation - Contraception and pregnancy restrictions updated to reflect EU guidelines - Outcome measure for primary objective updated - IDMC related wording added - Eligibility criteria updated (EC #2 removed; IC #9 added; IC #7 and EC #6 clarified) - Patient dietary counseling and compliance with diet restrictions added - Dialysis adequacy and Interdialytic Weight Gain assessment clarified - Dosing instruction for Investigational Product updated - The list of pH-dependent drugs updated - EOS visit window updated - Study requirements for safety assessments and rescue treatment clarified - Minor typos/errors corrected
Version 3.0, 11 September 2017
- Cardiac monitoring/arrhythmia endpoint and related wording removed - Visit schedule updated (Visit 14 and 16 removed) - Medications restrictions updated to reflect new information
Version 2.0, 28 July 2017
Stratification changed from site to country (section 3.5).
Version 1.0, 19 July 2017
Initial creation

CLINICAL STUDY PROTOCOL SYNOPSIS

A phase 3b, multicenter, prospective, randomized, double blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalemia with Sodium Zirconium Cyclosilicate (DIALIZE)

International Co-ordinating Investigator

Steven Fishbane, MD

Study site(s) and number of patients planned

180 patients at approximately 70 sites

Phase of development **3b**

Study design

This is a randomized, double-blind, placebo-controlled study to determine the safety and efficacy of ZS in patients with hyperkalemia and on stable hemodialysis. This study consists of a screening period, an 8 week randomized treatment period, and a follow-up period. Stable hemodialysis patients with persistent pre-dialysis hyperkalemia will be enrolled in the study across research sites in US, EU and Japan

Objectives

Primary Objective:	**Outcome Measure:**
Evaluate the efficacy of ZS in the treatment of hyperkalemia in patients on hemodialysis	Proportion of patients who maintain a pre-dialysis serum K between 4.0-5.0 mmol/L on 3 out of 4 dialysis treatments following the long interdialytic interval during the evaluation period (last 4 weeks) and who do not receive rescue therapy during the evaluation period

Secondary Objective:	**Outcome Measure:**
Evaluate the need for rescue therapy	Frequency and proportion of patients requiring any urgent intervention consistent with local practice patterns to reduce serum K including insulin/glucose, beta adrenergic agonists, sodium bicarbonate, K binders or any form of renal replacement therapy

Evaluate safety of ZS in hemodialysis	Adverse events (AEs), changes in laboratory values, physical examination, vital signs, ECG

Exploratory Objective:	**Outcome Measure:**
Evaluate if treatment of hyperkalemia with ZS in hemodialysis patients allows for an increase in the dialysate K concentration prescription	Proportion of patients who are able to increase dialysate K concentration

Target patient population

Approximately 180 patients with ESRD receiving maintenance hemodialysis treatments 3 times per week with an indication for treatment of hyperkalemia. Patients must have hemodialysis access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter which is expected to remain in place for the entire duration of the study.

Duration of treatment

1-week screening period, 8-week treatment period, 2-week follow-up

Study period

The study is expected to start in 4Q 2017 and to end by 4Q 2018.

For Japan: the study is expected to start in1Q 2018 and to end by 4Q 2018.

Investigational product, dosage and mode of administration

Sodium zirconium cyclosilicate (ZS), powder for oral suspension, starting dose 5 g on non-dialysis days, adjusted during the study

Statistical methods

The primary efficacy endpoint will be analysed using Fisher's exact test applied to the Full Analysis Set to assess the proportion difference between ZS and Placebo. Sensitivity analysis for the primary efficacy endpoint will be carried out to account for the influence of missing data.

Safety endpoints will be analysed using the Safety Analysis Set.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ADR	Adverse Drug Reaction
AE	Adverse Event
AV	Arterio-vascular
BUN	Blood urea nitrogen
c-lab	Central laboratory
CKD	Chronic Kidney Disease
CPS	Calcium polystyrene sulfonate
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DMP	Data Monitoring Plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EOS	End of study
EOT	End of treatment
ESRD	End-Stage Renal Disease
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).
GMP	Good Manufacturing Practice
HF	Heart failure
IB	Investigators' Brochure
ICF	Informed Consent Form

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
ICI	International Co-ordinating Investigator
IDMC	Independent Data Monitoring Committee
IDWG	Interdialytic Weight Gain
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LSLV	Last Subject Last Visit
LIDI	Long Inter-Dialytic Interval
LIMS	Laboratory Information Management System
MWF	Monday-Wednesday-Friday (dialysis scheme)
PI	Principal Investigator
Qb	Blood flow (dialysis)
Qd	Dialysate flow rate
PTDV	Premature Treatment Discontinuation Visit
RAASi	Renin-Angiotensin-Aldosterone inhibitors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCD	Sudden Cardiac Death
SIDI	Short Inter-Dialytic Interval
SPS	sodium polystyrene sulfonate
S-K	Serum potassium
TTS	Tuesday-Thursday-Saturday (dialysis scheme)
URR	Urea Reduction Ratio
USRDS	United States Renal Data System
WBDC	Web Based Data Capture
WOCBP	Woman of childbearing potential
ZS	Sodium Zirconium Cyclosilicate

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Serum potassium (K) is tightly regulated, typically between 3.5 and 5.0 mmol/L. Homeostatic maintenance of serum potassium is important for many physiologic processes, such as cardiac conduction and inotropy, smooth muscle tone, and neuronal signaling.

Hyperkalemia is defined as an abnormally high serum potassium (S-K) concentration, usually greater than 5.0 mmol/L, and with an incidence of up to 10% of hospitalized patients, and 2-3% in the general population (Mahoney 2005, Kovesdy 2014). Potassium homeostasis is essential for maintaining the cellular membrane potential and proper neuromuscular functioning, and hyperkalemia impairs neuromuscular, cardiac, and gastrointestinal function. Hyperkalemia often presents without symptoms or with non-specific symptoms including malaise, confusion, muscle weakness or signs of cardiac arrhythmias (Henneman 2016). The risk of fatal cardiac arrhythmias is increased, especially at S-K levels above 6.0 mmol/L, and the mortality risk is increased also with modest elevations of S-K (Collins 2014, Nakhoul 2015).

Potassium homeostasis is essential for maintaining the cellular membrane potential and hyperkalemia causes electrophysiological disturbance which impairs neuromuscular, cardiac and gastrointestinal function. The most common underlying cause of hyperkalemia is decreased urinary potassium excretion due to reduced kidney function, as in patients with chronic kidney disease (CKD) and heart failure (HF), or due to pharmacologic treatments, such as renin angiotensin-aldosterone inhibitors (RAASi) (Einhorn et al 2009, Fleet et al 2012, Kovesdy 2015). As the underlying causes of hyperkalemia are often chronic conditions that worsen over time, there is a need for treatments not only for the correction of hyperkalemia into the normal range (S-K 3.5-5.0 mmol/L) but also for chronic treatment to maintain S-K within the normal range.

Sodium zirconium cyclosilicate (ZS) is a non-absorbed, inorganic crystalline compound that selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract after oral administration. Thereby, excess potassium is removed from the body through faecal excretion and serum potassium is decreased. A global clinical programme including more than 1800 patients with hyperkalemia demonstrated effective correction of hyperkalemia with ZS compared with placebo, where 88% of patients reached normal S-K after 48 hours of treatment with ZS 10 g three times a day [TID]). Maintenance of normokalemia was also demonstrated, with lower mean S-K and increased number of normokalemic days with ZS 5 g or 10 g once daily (QD) compared with placebo, and a lasting maintenance effect for up to 12 months. [redacted]

The kidney plays a major role in eliminating potassium. Patients with end-stage renal disease (ESRD) have reduced renal potassium excretion ability which frequently leads to hyperkalemia (K > 5.1 mmol/L). These patients depend on the administration of renal replacement therapies (e.g. hemodialysis including low K dialysates as necessary), dietary

potassium restriction, and occasionally the use of oral potassium binding resins to maintain serum potassium levels in a physiologic range (Luo 2016, Kovesdy 2007).

High serum potassium can lead to ventricular arrhythmias and cardiac death. Recent studies have shown that among patients with ESRD on hemodialysis therapy, serum K > 5.6 mmol/L is associated with increased mortality, both all-cause and cardiovascular, compared to a referent category of K levels between 4.6 to 4.99 mmol/L (Kovesdy 2007, Yusuf 2016). In addition, sudden cardiac death (SCD) is the leading cause of death in hemodialysis patients. In the United States Renal Data System (USRDS) database, 26.9% of all-cause mortalities in prevalent dialysis patients between 2009 and 2011 were attributed to cardiac arrest or arrhythmias. The incidence of SCD in hemodialysis patients was 49.2 per 1000 patient-years in 2011, which is much higher than that of the general population (Huang 2015). Hyperkalemia is considered an important risk factor for arrhythmias and SCD. This condition is also independently associated with greater short-term risk of hospitalization and emergency department visits, and with greater hospital costs (Brunelli 2017). Hence prevention and treatment of hyperkalemia in hemodialysis patients are of paramount importance.

Previous studies with ZS have demonstrated efficacy and safety in the treatment of hyperkalemia, but hemodialysis patients were excluded. The study is designed to evaluate the efficacy and safety of ZS in hyperkalemic ESRD patients on hemodialysis and to determine the appropriate ZS dosing regimen in this patient population.

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design and control group

Currently the only universally accepted option for the treatment of hyperkalemia in patients with ESRD is dialysis including low K dialysates as necessary (hemo- or peritoneal dialysis, and hemodiafiltration). Despite dialysis the prevalence of hyperkalemia remains high in this population with a prevalence as high as 62.9 per 100 patient-months at the end of the long interdialytic interval (Yusuf 2016 AJN). In this latter study hyperkalemia was defined as a pre-dialysis serum potassium greater than 5.5 mmol/L and its presence was associated with increased all-cause mortality. Although potassium-binding resins are used in some instances to treat hyperkalemia in dialysis patients, these agents have not been systematically studied, are not universally used, and have no specific indications in this population.

The study is designed to provide efficacy data for the ZS clinical development program and provide information relevant to the efficacy of ZS in the treatment of hyperkalemia in hemodialysis patients. The study is a randomized, double-blind study with two treatment groups, ZS or placebo, and includes hemodialysis patients that have been on dialysis for a minimum of 3 months and receive treatment 3 times a week. No clinically justified therapy for severe acute hyperkalemia will be withheld in study patients. Rescue therapy will be available according to local practice patterns. Thus, placebo is deemed to be the appropriate comparator in this study.

1.2.2 Rationale for doses

Initial (hyperkalemia correction) and maintenance doses of ZS were studied extensively in the Phase 2 and Phase 3 programs. The doses to be used in this study are consistent with those found to be effective for maintenance of normokalemia in the non-dialysis population. Dose adjustments were allowed in these studies according to pre-specified rules in order to normalize serum potassium levels and minimize hypokalemia. Dose adjustment rules are also adopted in this study with appropriate modifications.

The starting dose of ZS will be 5g once daily on non-dialysis day and may be adjusted to a maximum of 15g per non-dialysis day to maintain a pre-dialysis serum K between 4-5 mmol/L. ZS or placebo will be administered orally on non-dialysis days for a treatment period of eight weeks.

1.3 Benefit/risk and ethical assessment

The primary benefit for patients randomized to ZS is expected to be the maintenance of normokalemia during the long interdialytic interval, potentially including the relief of associated signs and symptoms and an improved quality of life. ZS is expected to be at least as safe as it has been shown to be in the non-dialysis population.

Patients treated with placebo may not obtain any benefit in terms of hyperkalemia correction, but may benefit from the closer follow-up and will receive alternative therapies whenever clinically indicated.

An established dose adjustment algorithm will be used during the study to titrate ZS doses to enable patients to achieve and maintain pre-dialysis normokalemia after the Long Inter-Dialytic Interval (LIDI), while evaluating any changes in prescribed dialysate potassium concentrations, and the rate of reduction of serum potassium during dialysis based on the difference between pre- and post-dialysis potassium levels.

ZS doses may be reduced in the event that pre-dialysis serum potassium levels after the LIDI fall below 4 mmol/L and no further adjustment on prescribed dialysate potassium concentration is feasible.

Five clinical studies including a long-term safety study (ZS-002, ZS-003, ZS-004, ZS-004E and ZS-005) have been completed with ZS in subjects with hyperkalemia. Despite the potency of ZS in reducing S-K levels, the reductions have not been associated with adverse events of severe hypokalemia or other clinically significant changes in electrolytes, including serum calcium and magnesium. Dose related increases in bicarbonate and reductions in BUN have been observed in ZS treated subjects. There were no clinically important changes in other clinical laboratory tests. ZS treatment was well tolerated at all dose levels administered.

The most commonly reported ADRs were edema-related events, which were reported in 5.7% of ZS-treated subjects; 1.7%, 2.7%, 5.2%, and 14.3% of subjects randomized to placebo, ZS 5g, 10g or 15g QD for up to 1 month, respectively. Fifty-three percent of edema-related events

were managed by initiating a diuretic or adjusting the diuretic dose; the remainder did not require treatment.

In clinical studies, 2.3% of subjects developed hypokalemia with S-K value of <3.5 mmol/L, which was resolved with dose adjustment or discontinuation of ZS. One subject reported an S-K value <2.8 mmol/L. No cases of hypokalemia were reported as serious.

No potential risks based on mechanism of action, nonclinical or clinical data have been identified for ZS.

1.4 Study design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ZS in the treatment of hyperkalemia in patients with ESRD on stable hemodialysis. Approximately 180 patients with ESRD receiving maintenance hemodialysis treatments 3 times per week will be enrolled in the study across research sites in the US, Europe and Japan.

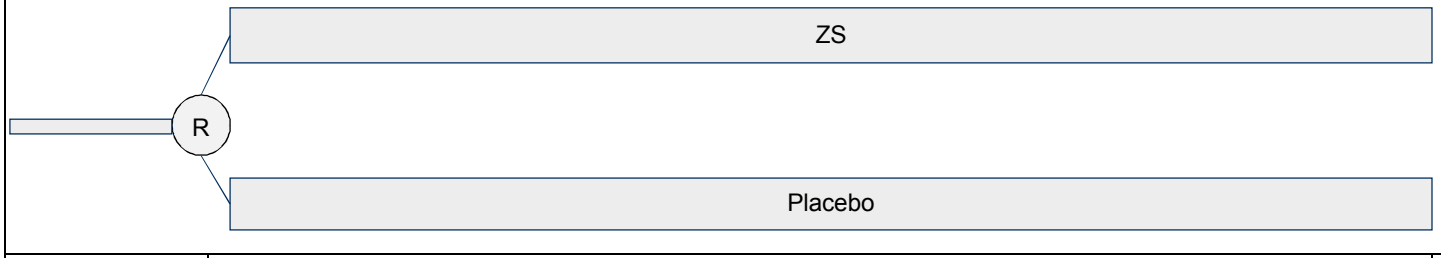
1.4.1 Treatment duration and dosing

The study will consist of three study periods as follows:

- Screening Period: one week
- Treatment Period: Patients will be randomized (1:1) to double-blind treatment with either ZS or placebo, started at 5g once daily on non-dialysis days, and titrated during a period of 4 weeks to achieve and maintain a pre-dialysis serum potassium between 4 and 5 mmol/L after the LIDI. Maximum ZS dose is 15g once daily on non-dialysis days. Treatment will be continued unchanged for an additional 4 week evaluation period to complete a total of 8 weeks.
- Post-Treatment Follow-Up Period: 2 weeks (14 +/- 3 days to match dialysis schedule)

Figure 1 Study flowchart

Visit	1	2	3	4	5	6	7	7.5	8	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	16
Week	-1			1			2			3		4		5		6		7		8		9	11
Day	-7	-5	-3	1	3	5	8	10	12	15	17	22	24	29	31	36	38	43	45	50	52	57	71 +/- 3



Screening	Treatment period	Follow-up

1.5 Study governance and oversight

An Independent Data Monitoring Committee will be appointed in the study (See section 6.8).

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
Evaluate the efficacy of ZS in the treatment of hyperkalemia in patients on hemodialysis	Proportion of patients who maintain a pre-dialysis serum K between 4.0-5.0 mmol/L on 3 out of 4 dialysis treatments following the long interdialytic interval during the evaluation period (last 4 weeks) and who do not receive rescue therapy during the evaluation period

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
Evaluate the need for rescue therapy	Frequency and proportion of patients requiring any urgent intervention consistent with local practice patterns to reduce serum K including insulin/glucose, beta adrenergic agonists, sodium bicarbonate, K binders or any form of renal replacement therapy
Evaluate safety of ZS in hemodialysis	Adverse events (AEs), changes in laboratory values, physical examination, vital signs, ECG

2.3 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
Evaluate if treatment of hyperkalemia with ZS in hemodialysis patients allows for an increase in the dialysate K concentration prescription	Proportion of patients who are able to increase dialysate K concentration

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

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

3.1 Inclusion criteria

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

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

2. Female or male aged ≥ 18 years at screening Visit 1. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

3. Receiving hemodialysis (or hemodiafiltration) 3 times a week for treatment of end-stage renal disease (ESRD) for at least 3 months before randomization.

4. Patients must have hemodialysis access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter which is expected to remain in place for the entire duration of the study.

5. Pre-dialysis serum K >5.4 mmol/L after long inter-dialytic interval and >5.0 mmol/L after one short inter-dialytic interval during screening (as assessed by central lab).

6. Prescribed dialysate K concentration ≤ 3 mmol/L during screening

7. Sustained Qb ≥200 ml/min and spKt/V ≥1.2 (or URR ≥ 63) on stable hemodialysis/hemodiafltration prescription during screening with prescription (time, dialyzer, blood flow [Qb], dialysate flow rate [Qd] and bicarbonate concentration) expected to remain unchanged during study

8. Heparin dose (if used) must be stable during screening and expected to be stable during the study

9. Subjects must be receiving dietary counseling appropriate for ESRD patients treated with hemodialysis/hemodiafiltration as per local guidelines, which includes dietary potassium restriction

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, including ZS Pharma staff and/or staff at the study site)

2. Hemoglobin <9 g/dL on screening (as assessed on Visit 1)

3. Lack of compliance with hemodialysis prescription (both number and duration of treatments) during the two-week period preceding screening (100% compliance required)

4. Patients treated with sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa) within 7 days before screening or anticipated in requiring any of these agents during the study

5. Myocardial infarction, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism, but excluding vascular access thrombosis) within 12 weeks prior to randomization

6. Laboratory diagnosis of hypokalemia (K < 3.5 mmol/L), hypocalcemia (Ca < 8.2 mg/d; for Japan hypocalcemia is defined as albumin-corrected Ca < 8.0 mg/dL), hypomagnesemia (Mg < 1.7 mg/dL) or severe acidosis (serum bicarbonate 16 mEq/L or less) in the 4 weeks preceding randomization

7. Pseudohyperkalemia secondary to hemolyzed blood specimen (this situation is not considered screening failure, sampling or full screening can be postponed to a later time as applicable)

8. Severe leukocytosis (>20× 10^9/L) or thrombocytosis (≥450 × 10^9/L) during screening

9. Polycythemia (Hb >14 g/dL) during screening

10. Diagnosis of rhabdomyolysis during the 4 weeks preceding randomization

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

12. Patients unable to take oral ZS drug mix

13. Scheduled date for living donor kidney transplant

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

15. Female patients who are pregnant or breastfeeding

16. Females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence (see Section 3.8)

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

18. Participation in another clinical study with an investigational product during the last 1 month before screening

19. Any medical condition, including active, clinically significant infection, that in the opinion of the investigator or Sponsor may pose a safety risk to a patient in this study, which may confound safety or efficacy assessment and jeopardize the quality of the data, or may interfere with study participation

20. Presence of cardiac arrhythmias or conduction defects that require immediate treatment

21. History of alcohol or drug abuse within 2 years prior to randomization

22. Previous randomization in the present study

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 before any study specific procedures are performed.

2. Assign the potential patient a unique enrolment number, beginning with 'E#', via IWRS/IVRS.

3. Determine patient eligibility. See Section 3.1 and 3.2.

4. Assign eligible patient unique randomization code via IWRS/IVRS

Screening should begin on a hemodialysis day following the long interdialytic interval (D -7) and be completed by the third hemodialysis session of the same week (D -3).

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

Patients will remain associated with the same enrolment number throughout the entire study, and patients should NOT receive any new E-code if re-screened. If a patient signs the ICF but does not meet the inclusion/exclusion criteria the patient will be marked as a screen failure on the Screening and Enrolment Log provided by the Sponsor and will be entered in WBDC as a screen failure.

A screen-fail patient may be re-screened if deemed appropriate by the investigator. A maximum of one re-screening period is allowed (for a total of two screenings) and these screening periods should be performed within 60 days.

A new ICF does not need to be signed before re-screening if the original ICF was signed within 60 days and the ICF has not been revised.

Randomization codes will be assigned strictly sequentially within each centre as patients become eligible for randomization. Randomization of qualified patients must take place on Visit 4 (Day 1), which corresponds to the hemodialysis day that follows the long interdialytic interval immediately after completion of screening. The randomization visit should be scheduled at a time that ensures that study drug has arrived to the study site.

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.

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 AstraZeneca global randomization system (AZRand) and loaded into the IVRS/IWRS database. Randomization codes will be generated in blocks to ensure approximate balance (1:1) between the 2 treatment arms. Randomization will be stratified by country.

3.6 Methods for ensuring blinding

The randomized treatment phase will have a double blind design. Patients will take by mouth assigned dose from the sachet(s) containing either ZS or placebo. 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.

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 randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs 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

The following restrictions apply in the study:

Women of childbearing potential must have a negative pregnancy test during screening (before first dose of IP).

Sexually active women of childbearing potential must be using a highly effective medically acceptable contraception method such as:

- Combined hormonal contraception associated with inhibition of ovulation
- Progesterone only hormonal contraception, associated with inhibition of ovulation
- IUD (intrauterine device)
- IUS (intrauterine hormone-releasing system)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (true abstinence in line with the subjects preferred and usual lifestyle. Subjects practicing abstinence will agree to have a documented second acceptable method of birth control such as a combination of the following: (1) oral contraceptive, depo progesterone or intrauterine device; and (2) a barrier method (condom or diaphragm),

should they become sexually active during the course of study participation).

Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential.

Contraceptive methods must be practiced upon being randomized to the study and through 12 weeks after the last dose of study treatment. If a patient discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (see Section 6.6).

The following must remain unchanged during the study:

- Hemodialysis prescription including treatment time and frequency (3/week MWF or TTS), dialyzer size and type, blood flow (Qb) ≥200 ml/min and dialysate bicarbonate concentration (dialysate potassium concentration can be modified as specified in the protocol)
- Heparin dose (if used)
- Hemodialysis access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter
- Patient compliance with hemodialysis prescription (both number and duration of treatments)
- Patient dietary counseling and compliance with diet: Dialysis clinics included in the study should provide patients dietary advice compiled from clinical sources and local Nephrology societies' recommendations that are consistent with the KDOQI (US) and KDIGO (global) guidelines. Patients should be instructed on avoidance of high potassium foods as well as selection of low potassium foods in order to restrict daily dietary potassium intake to between 2 and 2.5g or as described by local guidelines.

  Although details may vary across countries and sites (from general advice to detailed instructions), the overall approach should be to give patients dietary advice targeted to maintain low potassium intake (limited amount of high-potassium food, restrictions on raw vegetables) while maintaining adequate nutrition in terms of protein and caloric intake. The use of print educational materials to educate patients is encouraged.

The study physician should be informed if the investigator deems that changes in any of these parameters is necessary or patient is noncompliant with hemodialysis prescription. Any changes should be recorded in the eCRF.

3.9 Discontinuation of investigational product

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Incorrectly randomized patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
- Adverse Event for which the investigator judges continued treatment may put the patient at undue risk
- Severe non-compliance with the Clinical Study Protocol
- Pregnancy
- Renal transplant
- Development of any study specific criteria for discontinuation:
    - Severe hypokalemia - if a patient develops severe hypokalemia (as defined by potassium values <2.7 mmol/l, confirmed by a second potassium measurement after a 10 ± 2- minute interval) on non-dialysis days or pre-dialysis the patient should immediately receive appropriate medical intervention and be discontinued from the study. Post-dialysis hypokalemia should be managed as per established dialysis clinic protocols and if severe and persistent beyond the immediate post-dialysis period (2 hours) should also lead to study discontinuation. Patients considered for discontinuation from study due to post-dialysis hypokalemia should be discussed with the study physician
    - QT prolongation - if an absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec is reached the patient should immediately receive appropriate medical intervention and be discontinued from the study treatment. The QTcF algorithm is recommended. 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

3.9.1 Procedures for discontinuation of a patient 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.

Discontinuation from study medication is **not** the same as complete withdrawal from the study (withdrawal of consent), which has a direct impact on the potential validity of all study data, and should be avoided wherever possible. It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. All discontinued patients will be followed up during entire visit schedule.

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), and a Premature Treatment Discontinuation Visit (PTDV) should be performed at the earliest possible dialysis visit after last dose of ZS. The reason for permanent discontinuation of treatment with the study medication and the date of the last intake of the study medication must also be documented in the eCRF. The PTDV includes the same assessments as the EOT visit in addition to any other assessments scheduled for that day, if any. Any patient who is withdrawn from the study medication prior to study completion will have 3 options:

- Option 1: this is the preferred option, the patient continues to undergo all scheduled visits and assessments until EOS
- Option 2: applies if a patient rejects Option 1. In this case the patient will at a minimum return to the clinic for an EOS visit 2 weeks (14 +/- 3 days to match dialysis schedule) after a PTDV. All assessments stipulated for EOS visit will be collected and recorded at this time
- Option 3: applies if the patient refuses Options 1 and 2. In this case PTDV and EOS visits will occur simultaneously at the earliest possible dialysis visit after last dose of ZS, and all assessments stipulated for these visits will be collected and recorded.

Any study related materials and all study drugs should be returned by the patient. Adverse events will be followed up (See Section 6).

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

3.10 Criteria for withdrawal

Patients are at any time free to withdraw from the study (i.e., discontinue study medication permanently and withdraw from visit assessments), without prejudice to further treatment (withdrawal of consent).

Withdrawal of consent from the study must be ascertained and documented by the investigator and recorded in the appropriate electronic Case Report Form (eCRF). Such patients will always be asked about the reason(s) and the presence of any AEs. The date and reason for patient withdrawal must be recorded in the eCRF. Every attempt should be made to contact any patient considered lost to follow-up.

To ensure validity of study data, it is very important to collect as much data as possible throughout the scheduled study visits.

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.

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

Specific reasons for withdrawal from study are:

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

3.10.1 Screen failures

Screening failures are patients who are enrolled in the study but do not fulfil the eligibility criteria for randomization in the study, and therefore must not be randomized (see Section 3.2, Exclusion criteria #8 for special case). These patients should have the reason for study withdrawal recorded as ‘Screen failure’ (the potential patient 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). ‘Failure to meet randomization criteria’ should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomized group.In the case of a hemolyzed sample yielding an invalid serum K value, a repeat sample can be obtained during the screening period, or if this is not possible, the screening process can be repeated at a later time without a need to re-consent the patient.

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 (AE). The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment and 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,
- 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 the study must be recorded in the eCRF.

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

4.1 Screening period

Table 1 Schedule of assessments - screening

Visit	**1**	**2**	**3**	**For details see Section**
Day	**-7**	**-5**	**-3**	
Day of the week	**M/T**	**W/Th**	**F/S**	
Informed consent	X			4.3
Inclusion /exclusion criteria	X	X	X	3.1, 3.2
Demographics	X			4.3
Medical/surgical history	X			
Physical examination	X			5.2.2
Vital signs and BP[a]	X			5.2.4
Weight[b]	X	X	X	
Height	X			
Safety lab assessments	X			5.2.1
Serum hCG pregnancy test[c]	X			
12-lead ECG	X			5.2.3
Serum K[d]	X	X	X	5.1.1
Concomitant medication	X	X	X	
Dialysate K prescription	X	X	X	5.1.2
Dialysis prescription[e]	X			5.3.1
Dialysis adequacy[f]	X			5.3.2
Interdialytic weight gain[g]	X	X	X	5.3.3
AE review	X	X	X	6

a: BP should be measured prior to the hemodialysis procedure. HR and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min
b: Dry weight and pre-dialysis weight on Visit 1; pre-dialysis weight on all other visits
c: Collect from female patients of childbearing potential only
d: Serum K sampling: pre-dialysis c-Lab during screening
e: Blood flow (Qb, ml/min), time on dialysis (minutes)
f: spKt/V and/or urea reduction ratio (URR); record the most recent value but this should be no older than 5 weeks
g: Interdialytic weight gain: current pre-dialysis weight minus previous post-dialysis weight in Kg

4.2 Treatment and follow-up

Table 2 Schedule of assessments – treatment and follow-up phase

Visit description	**Randomization**																		**EOT**	**EOS**	**For details see Section**
Visit	**4**	**5**	**6**	**7**	**7.5**	**8**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**16**	
Day	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**22**	**24**	**29**	**31**	**36**	**38**	**43**	**45**	**50**	**52**	**57**	**71**	
Day of the week	**M/T**	**W/Th**	**F/S**	**M/T**	**W/Th**	**F/S**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**+/- 3**	
Physical exam	X			X[i]			X[i]		X[i]								X[i]			X	5.2.2
Vital signs and BP[a]	X			X			X		X		X		X		X		X			X	5.2.4
Weight[b]	X			X			X		X		X		X		X		X			X	
Safety lab assessments	X			X			X		X								X		X	X	5.2.1
Serum hCG pregnancy test[c]	X										X						X				
12-lead ECG				X							X									X	5.2.3
Serum K[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.1
Inclusion/Exclusion criteria	X																				3.1 ; 3.2
Randomization	X																				3.3
Dialysate K prescription	X	X	X	X		X	X		X		X		X		X		X		X	X	5.1.2
Dialysis prescription[e]	X										X								X		5.3.1
Dialysis adequacy[f]											X								X		5.3.2
Interdialytic weight gain[g]	X										X								X		5.3.3

Visit description	Randomization																		EOT	EOS	For details see Section
Visit	**4**	**5**	**6**	**7**	**7.5**	**8**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**16**	
Day	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**22**	**24**	**29**	**31**	**36**	**38**	**43**	**45**	**50**	**52**	**57**	**71**	
Day of the week	**M/T**	**W/Th**	**F/S**	**M/T**	**W/Th**	**F/S**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**W/Th**	**M/T**	**+/- 3**	
Drug dispensation/Drug accountability	X[j]			X			X		X		X		X		X		X		X[k]		7.2
Dose adjustment review[h]				X			X		X												
Concomitant medication	X	X	X	X		X	X		X		X		X		X		X		X	X	7.7
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6

a: BP should be measured prior to the hemodialysis procedure. HR and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min
b: Dry weight and pre-dialysis weight on Visit 1; pre-dialysis weight on all other visits
c: Collect from female patients of childbearing potential only
d: Serum K sampling: pre- and post-dialysis c-Lab is measured after LIDI (M/T) throughout the study; pre-dialysis i-STAT is measured during treatment phase after LIDI (M/T) on V4 and subsequent dose review visits; only pre-dialysis c-Lab is measured after SIDI (W/Th or F/S) throughout the study on visits as indicated in the table
e: Blood flow (Qb, ml/min), time on dialysis (minutes)
f: spKt/V and/or urea reduction ratio (URR); record the most recent value but this should be no older than 5 weeks
g: Interdialytic weight gain: current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the study visit) in Kg
h: Dose adjustment review will be done weekly during the first 4 weeks of the treatment period based on the pre-dialysis iStat serum K level measured following the long interdialytic interval
i: Targeted physical examination only
j: Drug accountability will not be assessed on Visit 4, only dispensation will take place
k: No drug dispensation will take place on the End of Treatment Visit, only drug accountability will be assessed

4.3 Screening/Enrolment period

Procedures will be performed according to the Study Plan (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 enrolled 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 60 days and has not been revised.

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

4.4 Treatment period and follow-up

Table 2 provide an overview of the procedures performed at each visit during the treatment period, and further details are provided below. In general, order of the procedures during the visit should match site's practice of handling dialysis patients, for specific requirements please refer to the Table 2 and paragraphs below. AZ Study Physician should be contacted if for any reason site needs to deviate from the requirements.

4.4.1 Description of visits (order of assessments etc.)

Procedures will be performed according to the Study Plan (Table 1 and Table 2).

Pre-dialysis c-lab serum K samples will be obtained during the screening phase and will determine eligibility of patients to enter the study.

During the treatment phase i-STAT serum K samples will be obtained to determine the need for adjustments in ZS dose or in dialysate K concentration. In addition, both pre- and post-dialysis c-lab samples will be obtained during the treatment phase for final analysis. All adjustments in study drug dose and dialysate K concentration prescription will be based on pre-dialysis i-STAT serum K values.

After the treatment period (ending with the EOT visit), patients will proceed to the 2-week post-treatment follow up period (ending with EOS visit). Pre- and post-dialysis c-Lab serum K samples will be obtained during follow up.

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 eCRF. An electronic copy of the completed eCRF will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Serum potassium measurements

Serum potassium levels (Serum K) will be measured using i-STAT device (Point-Of-Care analyser) and central laboratory (c-Lab).

Blood samples for determination of potassium will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). Potassium samples will be analysed locally using i-STAT devices for the purpose of dose titration and treatment control. At the same time serum samples will be prepared and shipped to the Central Laboratory. Results obtained from Central Laboratory will be used for statistical analyses of the study. All serum samples should be examined and any hemolyzed samples MUST be redrawn. In the event that hemolysis or other artefacts are suspected based on the reported i-STAT result the sample may be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF.

5.1.2 Dialysate potassium concentration prescription and potassium levels

The dialysate K concentration prescription should be recorded at the times indicated in the Study Plan (see Table 1 and Table 2).

For pre-dialysis serum potassium concentrations <4 mmol/L, subsequent adjustments will be made in accordance to locally accepted clinical practice patterns and guided by the investigator's clinical judgment.

For centers that adopt the clinical practice of modifying the prescribed dialysate potassium concentration when the pre-dialysis serum potassium concentration decreases, if pre-dialysis serum K is below 4 mmol/L the dialysate K concentration should be increased by 0.5 or 1 mmol/L according to standard of care, e.g. increase dialysate K from 1K to 1.5 or 2K, from 2K to 2.5 or 3K, or from 3K to 3.5 or 4K.

5.2 Safety assessments

Safety will be assessed throughout the study. During the course of the study, vital signs, physical examinations and laboratory tests will be performed at regular intervals. Particular emphasis should be placed on identifying signs and symptoms of worsening volume retention

such as increases in IDWG, rising blood pressure, uncontrolled hypertension, and excessive edema.

Adverse events (AE), serious adverse events (SAEs) and ongoing concomitant medication usage will be monitored and recorded throughout the study. SAE reports will be evaluated individually to assess for the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. SAEs and AEs will be followed until resolved, stable, or until the patient's EOS visit. See Section 6 for details on AE and SAE reporting.

Safety will be assessed through:

- Adverse events
- Laboratory parameters
- Vital signs (blood pressure, heart rate, ECG)
- Physical Examination

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the times indicated in the Study Plan (see Section 4).

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 on the appropriate eCRF.

The clinical chemistry and haematology will be performed at a central laboratory contracted by AstraZeneca. Sites will be provided with ready-to-use laboratory kits, as well as appropriate instructions/manuals. Procedures for collection, processing and sending samples to the central laboratory will be provided in above-mentioned manuals.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
	S/P-Gamma-glutamyl transferase (GGT)
	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Chloride
	S/P-Creatine kinase (CK)
	S/P-Bicarbonate
	S/P-Phosphorus
	S/P-Glucose
	S/P-Blood urea nitrogen
	S/P-Magnesium
	S/P-Lactate dehydrogenase
	S/P-Total protein
	S/P Pregnancy test (serum hCG)

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

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.2 Physical examination

A physical examination will be performed as specified in Study Plan and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. Particular attention must be given to any signs and symptoms of worsening volume retention such as increases in IDWG, rising blood pressure, uncontrolled hypertension and excessive edema.

A complete physical examination should be performed on Day -7, Day 1 and Day 71, and targeted physical examination will be conducted as specified in the Study Plan.

The complete physical examination includes the following: general appearance, skin, height (Day -7 only) and weight, head and neck, lymph nodes, thyroid, musculoskeletal (including spine and extremities), respiratory, cardiovascular including assessment of signs of heart failure, abdomen, and neurological systems.

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

5.2.3 ECG

ECG will be performed as safety measurement pre-dialysis at timepoints as per schedule of assessments. ECG will be assessed by Investigators according to local practice.

5.2.3.1 Resting 12-lead ECG

Standard 12-lead ECGs will be performed on all patients at specific time points as described in the Study Plan, Table 1 and Table 2, as to local routines. A single ECG will be taken after the patient has been resting in the supine position for 5 minutes. Any abnormalities must be evaluated in clinical context (based on patient's medical history and concomitant medication) and the investigator should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE.

Only the visit, ECG date, heart rate (HR), P and QRS durations and PR and QT intervals (if available), overall interpretation and relevant comments will be recorded in the eCRF. ECG recordings will be kept as source documents.

5.2.4 Vital signs and blood pressure

Vital signs will be assessed at visits as specified in schedule of assessments. Any clinically significant changes in vital signs should be investigated and reported as AEs (see section 6.3.6). Particular attention must be given to evidence of worsening volume retention as reflected by rising blood pressure or uncontrolled hypertension.

On specific visits indicated in Table 1 and Table 2, HR and BP will be measured in triplicate after the patient has been comfortably at rest in either supine or seated position for at least 5

min. The position of the patient should be comfortable with the arm where the blood pressure is recorded to be within the level of heart (the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The patient will be instructed to relax as much as possible and to not talk during the measurement procedure. Preferably measurement will be done with an electronic automated oscillometric device. The same device should preferably be used for the patient during the course of the study and in the same arm. Blood pressure will be measured in triplicate with at least one minute intervals between measurements. In HD patients BP and HR will be assessed prior to initiation of the dialysis procedures. All the three readings will be reported in the eCRF.

The heart rate will be assessed by pulse palpation of radial artery for 30 s immediately after each recording of the blood pressure. It could be also performed with an oscillometric device if this is used for blood pressure measurement. The triplicate heart rate assessments will be recorded in the eCRF.

Blood pressure measurements are to be obtained prior to initiation of each dialysis procedure

5.3 Other assessments

5.3.1 Dialysis prescription

Dialysis prescription parameters including blood flow (Qb, ml/min) and time on dialysis (minutes) should be recorded at the times specified in Tables 1 and 2.

5.3.2 Dialysis adequacy

Dialysis adequacy indices including spKt/V and/or urea reduction ratio (URR) should be recorded at the times specified in Tables 1 and 2. Investigators should record the most recent values but these should be no older than 5 weeks. If no values within 5 weeks are available a new assessment of spKt/V and/or URR should be performed on the next weekly visit. Sites should consistently use either spKt/V or URR in determining dialysis adequacy. A combination of both is not acceptable.

5.3.3 Interdialytic weight gain

Interdialytic weight gain (IDWG) will be calculated as the difference between current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the visit) in kilograms. In order to obtain all required measurements of IDWG the investigators must make sure that a post-dialysis weight is available for the immediate dialysis session (as per usual schedule) prior to the visit.

5.4 Pharmacokinetics

Pharmacokinetic samples will not be taken during the study

5.5 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study

5.6 Genetics

Genetic samples will not be taken during the study

5.7 Biomarker analysis

Biomarker samples will not be taken or analysed during the study

5.8 Storage, re-use and destruction of biological samples

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

5.9 Labelling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labelled and shipped in accordance with the Laboratory Manual and appropriate IATA regulations (see Appendix B)

5.10 Volume of blood

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

Table 4 Volume of blood to be drawn from patient during study

Assessment	Sample volume (mL)	Number of samples taken	Total volume: (mL)
Hematology	2	8	16
Clinical chemistry	2.5	8	20
Serum potassium (central lab)[a]	2.5	25	62.5
Serum potassium (I-Stat)	1	8	8
Serum potassium (i-Stat) - Japan	2	8	16
Total	**-**	**-**	**106.5**
Total - Japan			**114.5**

a: only on timepoints when no clinical chemistry sample is taken. If taken, clinical chemistry panel includes serum potassium measurement
b: WOCBP only

Note: if any of above mentioned samples need to be repeated (eg. due to sample hemolysis), total blood volume may exceed the total volume provided in Table 4.

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 jeopardise the patient 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 will be collected from time of randomization throughout the treatment period and including the follow-up period (until Visit 16 or the last patient visit in the study)

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. 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 collected 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/no) no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- 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.

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 (if applicable) or reported in response to the open question from the study site staff: *('Have you had any health problems since the previous visit/you were last asked?')* or revealed by observation will be collected and recorded in the CRF. 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 CSR. Deterioration as compared to baseline in protocol-mandated assessments 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

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4 Reporting of serious adverse events

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

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

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

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

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

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

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

[redacted]

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 12 months. An overdose is defined as more than 30g per day.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug 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 patient 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.

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

6.7 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 recognized 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 e.g. kept in the fridge when it should be at room temperature
- 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.

6.8 Independent Data Monitoring Committee

The IDMC will be responsible for monitoring the safety of the study participants, ensuring that the study is being conducted with the highest scientific and ethical standards and making appropriate recommendations based on the available data. The IDMC will review safety and efficacy data. The IDMC will function independently of all other individuals associated with the conduct of the studies, including AstraZeneca. The committee will operate in accordance with an Independent Data Monitoring Committee Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form	Dosing instructions	Manufacturer
Sodium Zirconium Cyclosilicate (ZS) 5g	Powder for oral suspension in a sachet	Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days	AstraZeneca
Placebo	Powder for oral suspension in a sachet	Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days	AstraZeneca

7.2 Dose and treatment regimens

ZS or placebo will be suspended in 45 ml of water and administered orally on non-dialysis days for a treatment period of eight weeks. The initial ZS dose will be 5g once daily and may be adjusted to a maximum of 15g per non-dialysis day to maintain a pre-dialysis serum K between 4-5 mmol/L.

All dose adjustments will be based on pre-dialysis serum K values measured by i-STAT. Management of dialysis prescription will be according to local clinical pattern practices.

During the first 4 weeks of the treatment period, the ZS dose should be adjusted if the pre-dialysis potassium value after the long inter-dialytic interval is > 5.0 mmol/L (one weekly dose adjustment). For patients taking 5 g on non-dialysis days, the dose should be increased to 10 g on non-dialysis days. For patients taking 10 g, the dose should be increased to 15 g on non-dialysis days.

During the first 4 weeks of the treatment period, both pre- and post-dialysis serum potassium concentrations should be evaluated.

For pre-dialysis serum potassium concentrations < 4 mmol/L, subsequent adjustments will be made in accordance to locally accepted clinical practice patterns and guided by the investigator's clinical judgment.

For sites that adopt the clinical practice of modifying the prescribed dialysate potassium concentration when the pre-dialysis serum potassium concentration decreases, if pre-dialysis serum K is below 4 mmol/L the dialysate K concentration should be increased by 0.5 or 1

mmol/L according to standard of care, e.g. increase dialysate K from 1K to 1.5 or 2K, from 2K to 2.5 or 3K, or from 3K to 3.5 or 4K. If dialysate K concentration cannot be increased further (e.g. patient already using 4K dialysate bath), the dose of ZS can be decreased by 5g or held if the patient is already taking the minimum dose (5g).

For sites where local clinical practice does not include increasing the dialysate K concentration when pre-dialysis serum K falls, the dose of ZS can be decreased by 5g or held if the patient is already taking the minimum dose (5g).

If during the treatment phase (initial 4 weeks) the dose of ZS has been reduced or held and the pre-dialysis potassium value after the next long interdialytic interval is above 5.0 mmol/L, every effort should be made to increase the dose by 5g or restart ZS 5g if it was held.

After the first 4 weeks, no additional adjustments of ZS dose or dialysate potassium concentration should be made unless in the judgement of the principal investigator there is a compelling medical need to treat an abnormal serum potassium concentration, i.e. severe hyperkalemia or hypokalemia with clinical manifestations. If such an event were to occur the appropriate ZS dose adjustment (increase or reduction) can be made with documentation of the event. In the case of hyperkalemia with clinical manifestations deemed to require urgent treatment, rescue therapy defined as any intervention consistent with local practice patterns to reduce serum K can be administered followed by the appropriate ZS dose adjustment and proper documentation of the event. During the last 4 weeks of the treatment period, both pre- and post-dialysis serum potassium concentrations will continue to be evaluated.

It is recommended that the dietary regimen is maintained unchanged during the duration of the study.

7.2.1 Rescue therapy

Rescue therapy is defined as any therapeutic intervention considered necessary in accordance to local practice patterns to reduce serum K in the setting of severe hyperkalemia (>6 mmol/L). Treatments considered rescue include the potassium binders: sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) and patiromer (Veltassa), as well as beta-adrenergic agonists, sodium bicarbonate, insulin/glucose and any additional dialysis or other forms of renal replacement treatments when used specifically for the treatment of severe hyperkalemia. In addition, any reduction in the dialysate K concentration that is prescribed for the treatment of severe hyperkalemia during the study is also considered rescue therapy. Rescue therapy should be followed by the appropriate ZS dose adjustment if appropriate and proper documentation of the event.

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.

For Japan: Labels will be prepared in accordance with GCP Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products

7.4 Storage

All study drugs 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.

The study site staff will account for all study drugs dispensed to and returned from the patient.

Study site staff or the AZ monitor (as applicable*)* will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

For Japan: 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 patient has returned all unused study drug.

7.7 Concomitant and other treatments

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies", used by a patient while participating in this clinical study.
For all concomitant medications, an indication for its use should be provided. If the stated indication is a non-specific condition, eg. "rash", documentation of the condition, as specific as possible, should be maintained in the patient's clinical study records as source documentation.

Restricted Medication/Class of drug:	Usage:
Sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa)	Patients taking these drugs within the past 7 days before screening or anticipated to require them during the study should be excluded. These drugs should be avoided during the study and can only be used as rescue therapy.
Heparin (if used)	Patients taking heparin should be on stable dose from screening throughout study
Diuretics	Changes to diuretics (including adding a new, changing the dose or discontinuation or switching of diuretics) during the study are prohibited. If clinically indicated to change the diuretics, the patients should discontinue study medication

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:

Table 5 Gastric pH-dependent bioavailability drugs

Class of drug	Drugs
Azole antifungals	Ketoconazole, Itraconazole, Posaconazole or Voriconazole
Anti-HIV drugs	Amprenavir, Atazanavir, Delavirdine, Fosamprenavir, Nelfinavir, Indinavir, Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine,
Antibiotics	Cefditoren, Clarithromycin
Antiepileptics	Gabapentin, Phenytoin
Bisphophonates	Risedronic acid
Cardiac glycosides	Digoxin
Immunosuppressants	Methotrexate, mycophenolate mofetil, mycophenolic acid, tacrolimus
Intestinal anti-inflammatory agents	Mesalazine
Iron preparations	Iron salts
Tyrosine kinase inhibitors	Acalabrutinib, Gefitinib, Pazopanib, Erlotinib, Dasatinib, Nilotinib

7.7.2 Other concomitant treatment

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

7.8 Post Study Access to Study Treatment

Not applicable

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- A comprehensive Statistical Analysis Plan (SAP) will be prepared and signed off before enrollment of the first patient

8.2 Sample size estimate

For the primary efficacy endpoint, 90 patients per treatment group (180 patients in total) will yield power at least 90%, assuming a placebo proportion of at most 0.3, a difference in proportions (ZS – placebo) of 0.25, using a 2-sided Fisher's exact test at significance level 5%.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

The full analysis set (FAS) will be the primary analysis set for the efficacy analysis and will include all randomized patients. Patients will be analysed according to their randomised investigational product.

8.3.2 Safety analysis set

The safety analysis set (SAS) will comprise all randomized patients who took at least one dose of study drug. Patients will be analysed according to the treatment actually received.

8.3.3 PK analysis set

Not applicable

8.3.4 Other analysis sets

Not applicable

8.4 Outcome measures for analyses

The primary efficacy outcome measure is the proportion of patients with 3 out of 4 pre-dialysis K measurements following the LIDI within 4.0-5.0 during the last 4 weeks of the treatment period and that do not receive rescue therapy during the evaluation period.

The safety outcome measures are frequencies of AEs, serious adverse events (SAEs), physical examination findings and vital signs, descriptive measures for laboratory values.

The first exploratory efficacy outcome measure is the proportion of patients who are able to increase dialysate K concentration at the end of the study compared to baseline.

The secondary outcome measure is the frequency and proportion of patients requiring any urgent intervention consistent with local practice patterns to reduce serum K.

Further details will be provided in the SAP.

8.5 Methods for statistical analyses

Descriptive statistics will be used to summarize all reported laboratory values, vital signs, and ECGs for the changes from baseline to each subsequent visit. Selected shift tables will be created to compare baseline classification to follow up classification. Additionally, individuals with abnormal serum laboratory values, vital signs, ECGs, and physical examinations will also be summarized and listed.

Demographic and baseline characteristics will be summarized and listed.

Duration of exposure to ZS and compliance rate will be summarized. Duration of exposure will be summarized overall, by study phase, and by treatment.

8.5.1 Analysis of the primary variable (s)

The primary efficacy endpoint of proportion of patients with maintained K 4.0-5.0 on at least 3 out of 4 pre-dialysis days following the LIDI and that do not receive rescue therapy during the evaluation period will be analysed using Fisher's exact test at the significance level 5% (2-sided). This analysis will be based on the FAS.

All randomized patients will be classified as either a responder or a non-responder regardless of premature discontinuation of IP, premature discontinuation of study or recieving treatments other than rescue. Patients with more than one missing K measurement during the evaluation period will be classified as a non-responder.

8.5.2 Analysis of the secondary variable(s)

The secondary endpoints will be presented using a frequency table based on the FAS.

8.5.3 Analysis of the safety variables

For safety analyses, adverse events will be listed. Frequency of patients with any adverse events will be summarized by SOC and preferred term for the following categories: all adverse events, adverse events by intensity, and adverse events by causality as assessed by the Investigator. All adverse events will be summarized by decreasing frequency for all patients within SOC. Treatment discontinuations due to any adverse event will be summarized. The number of days from the initial study administration date to adverse event onset date will be computed. Serious adverse events or deaths will be listed and summarized.

Safety analyses will be based on the SAF.

8.5.4 Subgroup analysis (if applicable)

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

8.5.5 Interim analysis

N/A

8.5.6 Sensitivity analysis (if applicable)

For the primary efficacy endpoint, sensitivity analysis will be performed to evaluate the impact of missing data, again using the Fisher's exact test. Details will be presented in the SAP.

8.5.7 Exploratory analysis (if applicable)

The exploratory endpoint of proportion of patients who are able to increase dialysate K concentration will be analysed using Fisher's exact test at the significance level 5% (2-sided). This analysis will be based on the FAS. There will be no adjustments for multiplicity and hence the p-value from the analysis is descriptive.

8.5.8 Handling of Missing Data

Patients with at least 3 pre-dialysis K measurements within 4.0-5.0 mmol/L and who do not receive rescue therapy during the evaluation period will be defined as responders and all other patients will be defined as non-responders. The impact of patients being classified as non-responders due to missing potassium data will be assessed through sensitivity analyses to be presented in the SAP.

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 system(s) utilised, including, but not limited to, Rave WBDC.

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 both face to face and remote 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 and review (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patient s. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

Source data composition and location will be described in detail in Clinical Study Agreement for each site.

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 patient s and in all other respects, not relating to study conduct or treatment of patient s, 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 patient s 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 patient undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to 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 Sodium Zirconium Cyclosilicate (ZS)

For Japan: The study is expected to start in 1Q 2018 and to end by 4Q 2018.

9.4 Data management by AstraZeneca

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

Data will be entered into the eCRF 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 eCRF 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 DMP.

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 WHODRUG. Classification coding will be performed by the Medical Coding Team at the AZ Data Management Center.

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 as defined in the DMP. All entries to the study database will be available in an audit trail.

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

For Japan: The PI is responsible for eCRF signature, and it can not be delegated.

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 DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Any treatment revealing data in the data base will be inaccessible for all individuals before data base lock. With the exception of those who need this information for data cleaning and/or patient safety reasons. A person with access to any treatment revealing data must not take part in any decisions made regarding the analysis sets or patient populations.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be released and the final database will be locked. An electronic 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 Management of genotype data

Not Applicable

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or 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 DMP.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

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

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

The Ethics Committee should approve all advertising used to recruit patients for the study.

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

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

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

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

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

For countries where it is applicable, each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

For Japan: 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 patients. 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 patient should into the study.

The IRB should approve all advertising used to recruit patients 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 patient 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 patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

For Japan: 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 and be approved by its 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 Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-

related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (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

Brunelli et al 2017

Brunelli SM, MSCE, Du Mond C, Oestreicher N, Rakov V, MD, Spiegel DM. Serum Potassium and Short-term Clinical Outcomes Among Hemodialysis Patients: Impact of the Long Interdialytic Interval. Am J Kidney Dis 70:21-29 2017

Huang et al 2015

Huang CW, Lee MJ, Lee PT, Hsu CY, Huang WC, Chen CL, Chou KJ, Fang HC. Low Potassium Dialysate as a Protective Factor of Sudden Cardiac Death in Hemodialysis Patients with Hyperkalemia. PLoS One. 2015 Oct 6;10(10): e0139886. doi:10.1371/journal.pone.0139886.

Kovesdy et al 2007

Kovesdy CP, Regidor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Serum and Dialysate Potassium Concentrations and Survival in Hemodialysis Patients. Clin J Am Soc Nephrol 2: 999-1007, 2007

Luo et al 2016

Luo J, Brunelli SM, Jensen, DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. Clin J Am Soc Nephrol 11: 90–100, 2016

Yusuf et al 2016

Yusuf AA, Hu Y, Singh B, Menoyo JA,Wetmore JB. Serum Potassium Levels and Mortality in Hemodialysis Patients: A Retrospective Cohort Study. Am J Nephrol 44:179–186, 2016

Einhorn et al 2009

Einhorn, L. M., et al. (2009). "The frequency of hyperkalemia and its significance in chronic kidney disease." Arch Intern Med 169(12): 1156-1162.

Fleet et al 2012

Fleet JL, Shariff SZ, Gandhi S, et al. Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. BMJ Open 2012;2: e002011

Nakhoul et al 2015

Nakhoul, G. N., et al. (2015). "Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease." Am J Nephrol 41(6): 456-463.

Henneman et al 2016

Henneman, A., et al. (2016). "Emerging therapies for the management of chronic hyperkalemia in the ambulatory care setting." Am J Health Syst Pharm 73(2): 33-44.

Kovesdy 2015

Kovesdy, C. P. (2015). "Management of Hyperkalemia: An Update for the Internist." Am J Med 128(12): 1281-1287.

Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient 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 patient'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).

Hospitalization

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 patient 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, hospitalization, disability or incapacity but may jeopardize the patient 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 hospitalization

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 patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

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

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

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

Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together **with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. Follow-up

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'