Clinical Study Protocol	
Drug Substance	Sodium Zirconium Cyclosilicate (ZS)
Study Code	D9480C00005
Version	2.0
Date	13 June 2018

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ENERGIZE)

Sponsor: ***AstraZeneca AB, 151-85 Södertälje, Sweden***

Regulatory Agency Identifying Number(s):

EudraCT number 2017-003955-50

VERSION HISTORY

Version 2.0 dated 13 June 2018
- Time 0h redefined as time of first administration of ZS/placebo - Inclusion criterion 4 changed to allow enrolment of patients with S-K≥5.8 mmol/L - Exclusion criterion 5 re-worded to clarify requirements on co-existing conditions - Exclusion criterion 6 wording adjusted to only exclude patients with a high likelihood of dialysis within 4h - Exclusion criterion 8 changed to enable sites to enrol selected patients treated with insulin and glucose - Changes in the CSP body to match above-mentioned changes in eligibility criteria - Changes in statistical considerations to reflect changes in eligibility criteria - IP preparation instruction changed – required volume of water is 45 mL (Table 4) - Concomitant medication requirements updated (list of pH-dependent bioavailability drugs in Table 6) - Minor changes in procedure descriptions to eliminate ambiguity - Typographical errors corrected - Statistical considerations (section 9) updated – statistical hypotheses, sample size determination and efficacy analyses revised - Synopsis statistical methods updated to align with the revised section 9
Version 1.0 dated 29 Sep 2017
Initial creation

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study Assessments

Visit						1					2	
Day						1					8[c]	
Assessment/Task	Screening	0h[a]	1h +/- 15 min	2h +/- 15 min	4h +/- 15 min	6h +/- 15 min	8h[b] +/- 30 min	10h[b] +/- 30 min	12h[b] +/- 30 min	24h[b] +/- 2h (EOT)	+/- 2 days	Details in CSP section or Appendix
Informed consent	X[d]											Appendix A, Section A 3
Inclusion /exclusion criteria	X											Section 5.1 and 5.2
Clinical procedures												
Demography	X											Section 8.10
Physical examination	X									X		Section 8.2.3
Medical history and comorbid conditions	X											Section 8.10
Vital signs	X				X			X		X		Section 8.2.4
Height[e]	X[e]											Section 8.2.4
Weight	X											Section 8.2.4
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Safety measurements												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
ECG	X				X					X		Section 8.2.5
Pregnancy test (serum or urine)	X											Section 5.1
Safety laboratory assessments (clinical chemistry, haematology)	X									X		Section 8.2.1
Efficacy measurements												

Potassium and glucose by i-STAT and Central lab	X	X	X	X	X	X	X	X	X	X	
Study treatment administration											
Randomisation	X										Section 6.3
Study treatment administered		X[a]			X			X			Section 6.1
Administration of insulin and glucose		X[a]									Section 6.5.1

a) Time 0h is defined as the time at which ZS/placebo is first administered. For patients consented before insulin administration, insulin and glucose should be administered as soon as logistically possible after the start of screening. For all patients, ZS/placebo should be administered as close in time to the administration of insulin and glucose as logistically possible, but not more than 30 min after. Once patients are randomized, ZS/placebo must be administered even if outside of the 30 minutes time window.

b) If medically appropriate patients may leave the study site between the 12h and 24h assessments, as long as they return for the 24h assessment. Patients treated with dialysis during Visit 1 should have the 24h / EoT assessment performed before initiation of dialysis, and will not undergo any further assessments during Visit 1. Patients unwilling to participate in all assessments should have the 24h / End of Treatment assessment performed before leaving the site.

c) The Day 8 Visit can be performed as a phone call.

d) Informed consent can be signed after administration of insulin (see Exclusion 8 and Section 6.5.1 for details), but must always be signed before any study specific procedures that are not part of standard care.

e) Height can be assessed at any time during Visit 1, and only needs to be assessed once.

Synopsis

International co-ordinating investigator

[redacted]

Protocol Title:

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ENERGIZE)

Rationale:

Elevated serum potassium (S-K) is potentially life threatening, and is frequently seen in emergency departments. Insulin and glucose is the standard of care among patients with S-K ≥6.0 due to a rapid onset of action. As insulin is a temporizing agent with a short duration of effect, additional clinical benefits may be achieved when ZS is added to insulin and glucose. ZS rapidly binds and eventually displaces potassium from the body, while insulin merely shifts S-K to the intracellular space. The purpose of this phase 2 study is to compare the effect of ZS 10g administered up to three times over 10 hours versus placebo added to insulin and glucose in the emergency department setting.

Table 2 Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the reduction of potassium at 4 hours after start of dosing	Mean absolute change in S-K from baseline until 4h after start of dosing with ZS/placebo
Secondary objectives:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the response to therapy	Fraction of patients responding to therapy with responders to therapy defined as • S-K <6.0mmol/L between 1 and 4h and S-K <5.0mmol/L at 4h AND • No additional therapy administered for hyperkalaemia from 0 to 4h with exception of the initial insulin treatment administered
To assess the effect of ZS vs placebo when added to insulin and glucose on the change in serum potassium at 1h and 2h after start of dosing	Mean absolute change in S-K from baseline to 1 and 2h after start of dosing with ZS/placebo

To assess the effect of ZS vs placebo when added to insulin and glucose on achieving normokalaemia	The fraction of patients achieving normokalaemia 1, 2 and 4h after start of dosing with ZS/placebo
To assess the effect of ZS vs placebo when added to insulin and glucose on achieving S-K <5.5mmol/l and <6.0mmol/l	The fraction of patients achieving S-K <5.5mmol/l and <6.0mmol/l 1, 2, and 4h after start of dosing with ZS/placebo
To assess the need for additional therapies for hyperkalaemia between ZS and placebo when added to insulin and glucose	The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 0 to 4h. The considered therapies are: • 2nd dose of insulin • Beta-agonists • Diuretics • Dialysis • Sodium bicarbonate • Potassium binders
Safety objective:	**Endpoint/variable:**
To characterize the safety of ZS when added to insulin and glucose	Adverse events (AEs) and serious AEs (SAEs) Changes in vital signs (VS), physical examinations, and ECGs Changes in clinical laboratory parameters, including assessment of hypokalaemia using S-K measurements and of hypoglycaemia using P-glucose measurements
Exploratory objectives:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the change in S-K over time	Mean absolute change in S-K from baseline to 6, 8, 10, 12, and 24h after start of dosing with ZS/placebo
To assess the effect of ZS vs. placebo when added to insulin and glucose on achieving normokalaemia	The fraction of patients achieving normokalaemia 6, 8, 10, 12 and 24h after start of dosing with ZS/placebo
To assess the effect of ZS vs. placebo when added to insulin and glucose on achieving S-K <5.0mmol/l, <5.5mmol/l and <6.0mmol/l	The fraction of patients achieving S-K <5.0 mmol/L; <5.5mmol/l and <6.0mmol/l 6, 8, 10, 12 and 24h after start of dosing with ZS/placebo

To assess the need for additional therapies due to hyperkalaemia between ZS and placebo when added to insulin and glucose	The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 4 to 24h. The considered therapies are: • 2nd dose of insulin • Beta-agonists • Diuretics • Dialysis • Sodium bicarbonate • Potassium binders
To assess the time and disposition of patients when leaving the treating department between ZS and placebo when added to insulin and glucose	Time from randomization until leaving the treating department, and disposition after leaving the treating department
To compare the effect between ZS and placebo when added to insulin and glucose on duration of hospitalization	Time from randomization until discharge

Overall design:

The study is designed to determine if ZS 10g administered up to three times over 10h added to insulin and glucose in patients presenting with hyperkalaemia will prove tolerable and efficacious by performing a multicentre, international, randomized, double-blind, placebo-controlled, prospective, parallel-group study.

Study Period:

Estimated date of first patient enrolled Q4 2017.

Estimated date of last patient completed Q4 2018.

Number of Subjects: approximately 132.

Treatments and treatment duration: All patients will be treated with insulin and glucose. In addition, each patient will be treated with ZS or placebo for up to 10 hours.

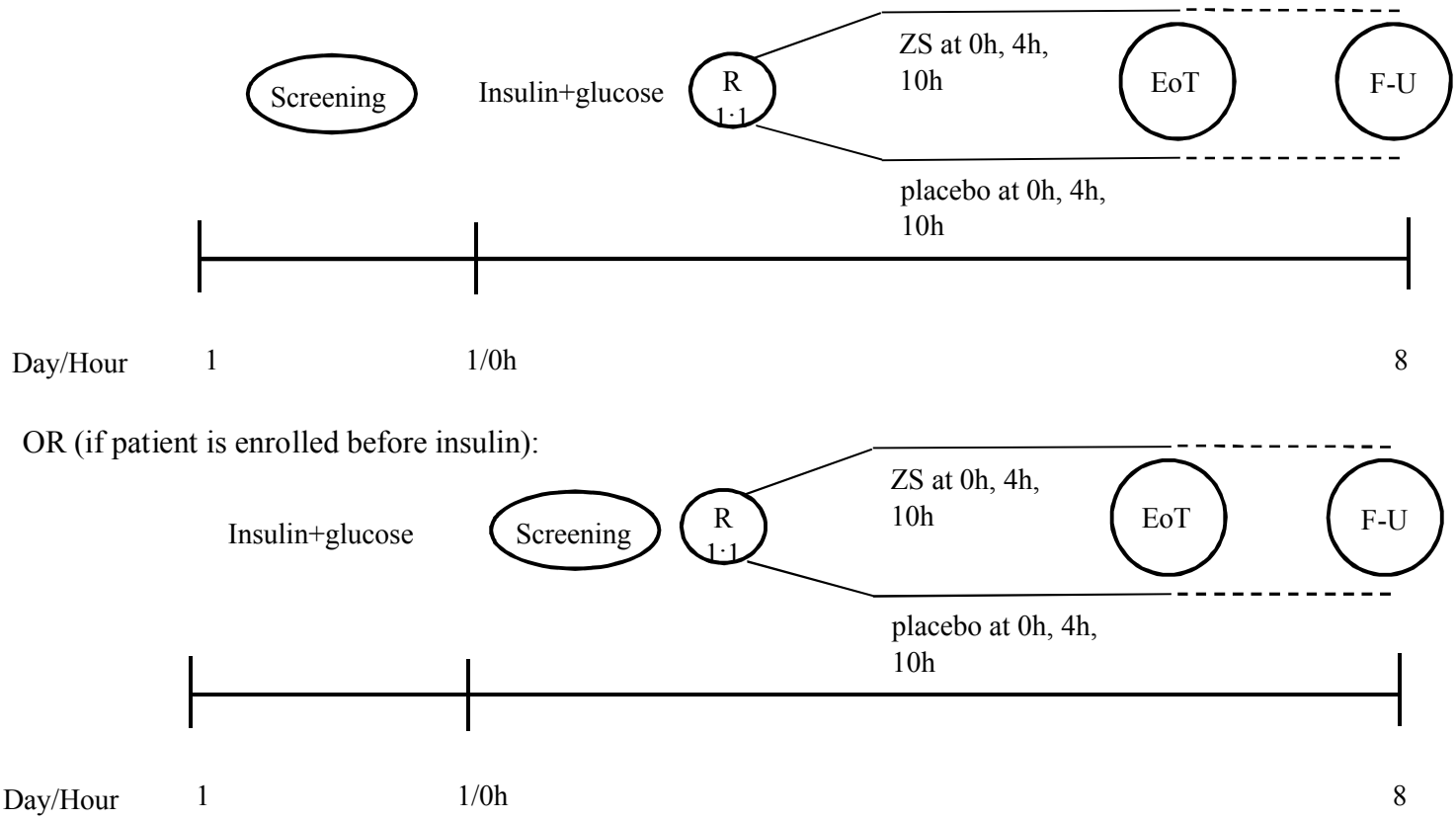
Statistical methods

The study will employ a 1:1 randomization scheme. Based on ZS-004 and patients treated with medications only in ZS-007, the standard deviation for S-K change from baseline at 4 hours is assumed to be 0.7 mmol/L. With 66 patients per group a two-sided 95% confidence interval for the mean difference in S-K change will extend 0.239 mmol/L from the observed difference in means.

1.2 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



2. INTRODUCTION

2.1 Study rationale

This study is a first step in the development of ZS as a treatment to manage hyperkalaemia in the emergency department setting, where achievement of normokalaemia in a relatively short period is of particular importance. Insulin and glucose is the standard of care among patients with S-K ≥6.0 due to a rapid onset of action. As insulin is a temporizing agent with a short duration of effect additional clinical benefits may be achieved when ZS is added to insulin and glucose. ZS rapidly binds and eventually displaces potassium from the body, while insulin merely shifts S-K to the intracellular space. The purpose of this phase 2 study is to compare the effect of ZS 10 g administered up to three times over 10h versus placebo added to insulin and glucose.

Hyperkalaemia is defined as an abnormally high serum potassium (S-K) concentration, usually greater than 5.0 mmol/L. The prevalence has been reported to 3-4% in hospitalized patients, and the risk is considerably increased in persons with advanced chronic kidney disease, heart failure, diabetes and/or treatment with renin angiotensin-aldosterone inhibitors (Einhorn et al 2009, Fleet et al 2012, Kovesdy 2015). Hyperkalaemia 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 even with mild elevations of S-K (S-K > 5.0 mmol/L), but a causal relationship remains to be established (Einhorn 2009, Collins 2014, Nakhoul 2015).

Current management of hyperkalaemia with S-K above 6.0 mmol/L at the emergency department has not been well studied previously (Rossignol 2016), but frequently includes administration of insulin and glucose to shift extracellular potassium to the intracellular space. The effect is rapid and substantial, but only lasts for 4 to 6 hours, and therefore further therapies are required, e.g. hemodialysis or potassium binding drugs. The use of insulin and glucose as the mainstay of therapy is recommended by clinical guidelines such as the American Heart Association guidelines from 2005, and in recent literature (Rossignol 2016, Kovesty 2015, Li and Vijayan 2014).

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, potassium is removed from the blood stream, decreasing the serum potassium concentration and then removing the potassium from the body through faecal excretion. A global clinical programme including more than 1800 patients with hyperkalaemia demonstrated the efficacy of ZS compared with placebo for correction of hyperkalaemia, with 88% of patients reaching normal S-K after 48 hours of treatment with ZS 10 g three times a day (TID). A detailed description of the chemistry, pharmacology, efficacy, and safety of ZS are given in the Investigators' Brochure.

The onset of action of ZS is slower than for insulin and glucose, but statistically significant lowering of S-K has been demonstrated at 1 hour. The efficacy of ZS, measured as change in S-K, appears to increase with higher baseline S-K. Combining insulin and glucose with ZS may

therefore provide enhanced short term as well as longer term lowering of S-K in the emergency department setting.

2.2 Benefit/risk assessment

Hyperkalaemia with S-K≥6.0 mmol/L is a potentially life-threatening condition. The primary potential benefit for patients randomized to ZS, insulin and glucose is a more pronounced and prolonged decrease of S-K compared with patients randomized to placebo, insulin and glucose. For patients with hyperkalaemia requiring emergency therapy this may significantly decrease the need for additional treatment for hyperkalaemia (including but not limited to additional insulin and glucose, beta-agonists, or potassium binding resins).

All randomized patients will receive standard of care treatment for hyperkalaemia and may benefit from close medical monitoring. Additional therapies will be administered whenever clinically warranted.

Patients with S-K ≥6.0 mmol/L may require rapid therapy to minimize the risk of arrhythmias. The study is therefore designed to allow rapid assessment, randomization and standard of care treatment of patients to minimize arrhythmia risk. Furthermore, intravenous calcium may be administered at the discretion of the treating physician to minimize the risk of dangerous arrhythmias.

Insulin and glucose therapy has been reported to be associated with a significant rate of hypoglycaemia. The weight based dosing of insulin together with the monitoring schedule was selected in order to minimize the risk of hypoglycaemia, and to detect and correct any hypoglycaemia if it were to occur.

Hypokalaemia has been reported at a low rate in prior studies with ZS. In this study, subjects will receive also insulin and glucose, which could increase the risk of hypokalaemia. However this study recruits patients with higher S-K (≥5.8 mmol/L) compared with earlier ZS studies (generally >5.0mmol/L), which decreases the risk of hypokalaemia. Furthermore, the peak effect of insulin and glucose is expected to wear off after 4-6 hours, by which time the effect of ZS is still limited to a fraction of the full ZS effect. Hence, the risk for hypokalaemia is limited.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of ZS may be found in the ZS Investigator's Brochure.

The management of hyperkalaemia is poorly researched with few prospective randomized trials performed previously (Rossignol et al 2016). ZS may represent a helpful addition to insulin and glucose to manage emergent hyperkalaemia. This study therefore has potential to improve the scientific basis for the clinical management of hyperkalaemia irrespective of outcome by properly documenting the effects of the insulin and glucose regimen used, and to improve the clinical management of hyperkalaemia if successful. Hence, the limited risk the recruited patients will be exposed to is deemed acceptable considering the expected benefits of performing the trial.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the reduction of potassium at 4 hours after start of dosing	Mean absolute change in S-K from baseline until 4h after start of dosing with ZS/placebo
Secondary objectives:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the response to therapy	Fraction of patients responding to therapy with responders to therapy defined as • S-K <6.0mmol/L between 1 and 4h and S-K <5.0mmol/L at 4h AND • No additional therapy administered for hyperkalaemia from 0 to 4h with exception of the initial insulin treatment administered
To assess the effect of ZS vs placebo when added to insulin and glucose on the change in serum potassium at 1h and 2h after start of dosing	Mean absolute change in S-K from baseline to 1h and 2h after start of dosing with ZS/placebo
To assess the effect of ZS vs placebo when added to insulin and glucose on achieving normokalaemia	The fraction of patients achieving normokalaemia 1, 2 and 4h after start of dosing with ZS/placebo
To assess the effect of ZS vs placebo when added to insulin and glucose on achieving S-K <5.5mmol/l and <6.0mmol/l	The fraction of patients achieving S-K <5.5mmol/l and <6.0mmol/l 1, 2, and 4h after start of dosing with ZS/placebo
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Safety objective:	**Endpoint/variable:**
To characterize the safety of ZS when added to insulin and glucose	Adverse events (AEs) and serious AEs (SAEs) Changes in vital signs (VS), physical examinations, and ECGs Changes in clinical laboratory parameters, including assessment of hypokalaemia using S-K measurements and of hypoglycaemia using P-glucose measurements
Exploratory objectives:	**Endpoint/variable:**
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To assess the effect between ZS and placebo when added to insulin and glucose on achieving normokalaemia	The fraction of patients achieving normokalaemia 6, 8, 10, 12 and 24h after start of dosing with ZS/placebo
To compare the effect between ZS and placebo when added to insulin and glucose on achieving S-K <5.0mmol/l, <5.5mmol/l and <6.0mmol/l	The fraction of patients achieving S-K <5.0 mmol/L, <5.5mmol/l and <6.0mmol/l 6, 8, 10, 12 and 24h after start of dosing with ZS/placebo
To assess the need for additional therapies due to hyperkalaemia between ZS and placebo when added to insulin and glucose	The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 4 to 24h. The considered therapies are: • 2nd dose of insulin • Beta-agonists • Diuretics • Dialysis • Sodium bicarbonate • Potassium binders
To assess the time and disposition of patients when leaving the treating department between ZS and placebo when added to insulin and glucose	Time from randomization until leaving the treating department, and disposition after leaving the treating department
To compare the effect between ZS and placebo when added to insulin and glucose on duration of hospitalization	Time from randomization until discharge

4. STUDY DESIGN

4.1 Overall design

The study is designed to determine if ZS 10g administered up to three times over 10h added to insulin and glucose in patients presenting with hyperkalaemia will prove tolerable and efficacious by performing a multicentre, international, randomized, double-blind, placebo-controlled, prospective, parallel-group study.

The study will recruit patients with S-K ≥5.8 mmol/L. Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1 ratio to ZS or placebo.

The study includes a single treatment visit no longer than 24h followed by a single follow up contact 7 days later.

For a graphical overview of the study design see Figure 1, Section 1.2.

4.2 Scientific rationale for study design

A prospective, randomized, double-blind, placebo-controlled, prospective, parallel arm design remains the gold standard to minimize potential biases. The use of multiple study sites increases the chances of recruiting a broad and representative patient population.

The inclusion and exclusion criteria were set to be as broad as possible without jeopardizing the safety of recruited subjects, and ensuring only patients for which insulin and glucose is the currently best standard of care therapy would be recruited.

Insulin and glucose were chosen as background therapy based on guidelines (eg. the American Heart Association guidelines from 2005) and current practice in most US and European emergency departments.

The study design (adding ZS or placebo to insulin and glucose) is consistent with recent publications describing the acute treatment of hyperkalaemia in the emergency department (Rossignol et al 2016).

The primary endpoint (S-K at 4h) was selected as lowering S-K is of paramount interest in hyperkalaemic patients, and as the vast majority of patients receiving placebo on top of insulin and glucose is not expected to require additional therapy to maintain S-K in an acceptable range for the first 4 hours following the initial therapy. A key concern is the risk that any benefit in terms of S-K of ZS is erased if the control arm were to be administered significantly more additional therapies to manage hyperkalaemia. Sites will therefore be instructed to minimize the additional hyperkalaemia therapies for the first 4h without sacrificing patient safety.

Additional therapies are increasingly more likely to be administered to the control arm at time-points beyond 4h, and any imbalance in the administration of additional therapies would be expected to increase beyond 4h, as the ZS effect is expected to become more pronounced over time. Hence, all measurements beyond the 4h time-point may be biased and are considered

exploratory in nature. Furthermore, not all data beyond the 4h time-point is likely to be collected, as subjects are increasingly likely to receive dialysis therapy or leave the emergency department over time.

4.3 Justification for doses

All randomized patients will be treated with insulin and glucose. The insulin and glucose therapy administered in the trial will consist of 0.1 units/kg of insulin administered IV as a bolus or for up to 30 minutes together with 25g of glucose administered just before (<15 minutes) the insulin. Glucose will be withheld for patients with plasma glucose > 400mg/dl. Additional glucose may be administered at the discretion of the treating physician, and as medically appropriate.

The insulin and glucose treatment regimen is based on the American Heart Association (AHA) guidelines from 2005 and the UK Renal Association guidelines from 2014, but with modifications based on more recently published treatment protocols. In particular the use of 0.1 units/kg of insulin rather than administering 10 units to all patients is intended to minimize the risk of hypoglycaemia and to minimize variability in post treatment S-K measurements (Li and Vijayan 2014), thereby improving patient safety and the precision of S-K based endpoints in the trial.

The dose of ZS used in the study (10g administered at 0, 4 and 10h) is based on the results of prior dose-finding studies, and has been used in the Correction Phase of all phase III studies performed with ZS to date. ZS 10g three times per day (TID) is the expected dose to be recommended for the Correction Phase once ZS is approved by healthcare authorities globally. See the ZS Investigator's Brochure for details on the dose of ZS explored in all prior studies and the associated safety and efficacy results.

4.4 End of study definition

The end of study is defined as the last expected visit or telephone contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed Visit 2.

5. STUDY POPULATION

The target study subject population consists of patients with S-K ≥5.8 mmol/L for whom treatment with insulin and glucose to manage hyperkalaemia has been determined medically appropriate by the Investigator.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to section 5.4.

In this protocol, “enrolled” subjects are defined as those who sign informed consent. “Randomized” subjects are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3

Age

3. ≥ 18 years of age at the time of signing the informed consent form.

Type of subject and disease characteristics

4. S-K ≥5.8 mmol/L, as determined using an i-STAT device. Patients with S-K 5.8 or 5.9 mmol/L can be included only if treatment of the patient with insulin and glucose is in accordance with the local standard of care. S-K measured by a local laboratory prior to insulin administration may replace S-K measured by i-STAT for assessment against this inclusion criterion for patients having received insulin before signing the informed consent form.

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

5.2 Exclusion criteria

Medical conditions

1. Possible pseudohyperkalaemia as assessed by the investigator, e.g. secondary to hemolyzed blood specimen. See section 7.1.1 for details on how to handle suspected hemolyzed samples.

2. Hyperkalaemia caused by any condition for which a therapy directed against the underlying cause of hyperkalaemia would be a better treatment option than treatment with insulin and glucose. This includes, but is not limited to, hyperkalaemia reasonably likely to be caused by physical injury, intoxication, pre-renal kidney failure, substance abuse, diabetic ketoacidosis, and rhabdomyolysis.

3. Life-threatening cardiac arrhythmias requiring immediate treatment before an informed consent can be collected.

4. Any condition representing a contra-indication to treatment with the rapid acting insulin to be used, e.g. allergy to any of the constituents of the insulin product to be used, or hypoglycaemia at study entry.

5. Presence of any other acute or chronic medical condition which, in the opinion of the investigator, places the patient at undue risk due to the severity of illness or potentially jeopardizes patients' ability to follow study procedures due to required interventions, investigations or procedure in the acute setting. Patients having any acute or chronic medical condition other than hyperkalaemia that would alone require immediate treatment in the hospital setting at Visit 1 are not eligible for the study

6. Dialysis session expected within 4h after randomization.

Prior/concomitant therapy

7. Treated with sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa) within the past 24h.

8. Treated with any therapy intended to lower S-K between arriving at the hospital and randomization during Visit 1, with exception of patients meeting the following criteria:

   - Treated with no more than one course of insulin since arriving at the hospital
   - S-K measured by i-STAT device or local laboratory prior to administration of insulin. S-K must have met Inclusion criterion 4.
   - Reasonably likely to randomize, have screening and 0h assessments done, and dose the patient with ZS/placebo within 30 minutes of the start of administration of insulin.

Prior/concurrent clinical study experience

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

Reproduction

10. Known pregnancy or actively attempting to become pregnant. A pregnancy test (urine or serum, analysed by a local laboratory) will be collected during screening for female subjects of childbearing potential, but randomization can take place before the result is available. If the pregnancy test is positive the patient will discontinue therapy (see sections 7.1and 8.4.2).

Other exclusions

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

12. Judgment by the investigator that the subject should not participate in the study as the subject is unlikely to comply with study procedures, restrictions or requirements.

13. Previous randomisation in the present study.

5.3 Lifestyle restrictions

Not applicable.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to Study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes the reason for failing screening, demography, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned the same subject number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. During rescreening all assessments are to be performed again.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to Sodium Zirconium Cyclosilicate (ZS), placebo, insulin and glucose. Investigational Products (IPs) in this study refers to ZS and placebo. Insulin and glucose are considered background therapy, and thus are non-IPs (NIPs).

6.1 Treatments administered

Table 4 Investigational products

Study Treatments

	Treatment 1	Treatment 2
Study treatment name:	Sodium Zirconium Cyclosilicate (ZS) 5g	Placebo
Dosage formulation:	Powder for oral suspension in a sachet	Powder for oral suspension in a sachet
Route of administration:	Oral use	Oral use
Dosing instructions:	Single dose contains two sachets that should be suspended in 45 mL of water by patient.	Single dose contains two sachets that should be suspended in 45 mL of water by patient.
Packaging and labelling:	Study treatment will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider:	AstraZeneca	AstraZeneca

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

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.

Further guidance and information for the final disposition of unused study treatment will depend on local regulations in a given study country.

6.3 Measures to minimise bias: randomisation and blinding

All subjects will be centrally assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site. Randomization will be stratified by country.

If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

The IVRS/IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit.

Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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.

The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the subject's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual subject have been made and documented.

6.4 Treatment compliance

Any change from the dosing schedule, such as dose discontinuations, should be recorded in patient's medical notes and eCRF.

The Investigator or designee is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Table 5 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Potassium lowering drugs (e.g. potassium binders, beta agonists)	See section 6.5.3
Potassium substitution (e.g. KCl)	All treatments for hypokalaemia to be withheld from enrolment to Visit 1 discharge
Antidiabetics	See section 6.5.2
Drugs with pH dependent absorption (see section 6.5.4 for details)	Drugs with pH-dependent absorption should be administered at least 2 hours before or 2 hours after ZS to mitigate the risk of drug interactions.

6.5.1 Background medication

All randomized patients will be treated with insulin and glucose. The insulin and glucose therapy administered in the trial will consist of 0.1 units/kg of insulin administered IV as a bolus or for up to 30 minutes together with 25g of glucose administered just before (<15 minutes) the insulin.

At the discretion of the treating physician additional glucose may be administered, e.g. as a slow infusion, if medically appropriate.

Glucose will be withheld for patients with plasma glucose > 400mg/dl or if any contraindication for treatment with glucose exists in the opinion of the investigator.

Insulin and glucose are NIPs, and will not be provided by AstraZeneca. The brand of insulin to be used is up to each study site, but the insulin brand used must belong to the "rapid acting" class of insulins including among others insulin lispro, insulin aspart and insulin glulisine.

The brand of glucose to be used and how to prepare it for administration is determined by each study site.

Both insulin and glucose can be administered as a bolus or as a rapid infusion, as long as glucose administration is completed within 15 minutes before the insulin therapy is started, and as long as the administration of both insulin and glucose takes no longer than 30 minutes.

For patients consented before insulin administration, insulin and glucose should be administered as soon as logistically possible after the start of screening. For all patients, ZS/placebo should be administered as close in time to the administration of insulin and glucose as logistically possible, but not more than 30 min after. Once patients are randomized, ZS/placebo must be administered even if outside of the 30 minutes time window.

Each site must complete a worksheet detailing their procedure for administering insulin and glucose with regards to the brand of insulin and glucose to use, how the insulin and glucose will be prepared for administration, and at what speed the insulin and glucose will be administered. The worksheet should also describe when ZS is to be administered, which should occur as closely as logistically possible to when the insulin therapy is started. The completed worksheet must be available to site staff when subjects are randomized to minimize variations in how the background therapy is administered at each site.

The flexibility provided in this section is intended to allow as many sites as possible to administer insulin and glucose as per their current standard of care for hyperkalaemia.

6.5.2 Other concomitant treatment

Medication other than described above, but considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF, including start and stop time.

Calcium salts may be administered (intravenously) to patients with ECG changes or as deemed appropriate by the treating physician.

Administration of sodium bicarbonate may be considered for patients with blood pH < 7.2 or critically low plasma bicarbonate.

Investigators will monitor patients with diabetes mellitus as per the local standard of care. Antidiabetic therapies may be administered to patients at the discretion of the treating physician. Concomitant medications administered to maintain metabolic control will not be considered additional treatment for hyperkalaemia.

6.5.3 Additional treatment for hyperkalaemia

The study site will administer additional therapies to lower potassium if required for the safety of the patient. Additional potassium lowering therapies will not be provided by AstraZeneca.

Although the use of additional potassium lowering therapies is allowed, the use of such therapies should be delayed, if at all possible without jeopardizing the safety of the patient, until after the 4h S-K samples have been collected for analysis of the primary endpoint in the trial.

The date and time of additional potassium lowering therapy administration as well as the name and dosage regimen of the therapy must be recorded, as for any other concomitant medications.

Examples of when additional potassium lowering therapy may be administered, also before 4h after ZS/placebo administration, are when:

Whole blood potassium measured with i-STAT is found to be higher than at baseline at any time >1h after the administration of insulin

Whole blood potassium measured with i-STAT is >6.5mmol/L at any time >1h after the administration of insulin

ECG changes likely to be related to hyperkalaemia develop or worsen significantly.

If additional potassium lowering therapy needs to be administered the first choice should be to administer an additional course of insulin and glucose therapy, assuming it would be medically appropriate to do so.

For patients receiving routine renal replacement therapy with either hemo- or peritoneal dialysis the preferred additional therapy will be a dialysis session, if available. Before dialysis is initiated all assessments planned for the end of treatment (24h time-point in the Schedule of Assessments) must be performed. Following the initiation of dialysis no further study assessments or procedures should be performed with the exception of the Day 8 follow up.

6.5.4 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 treatment to mitigate the risk of drug interactions.

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

Table 6 Drugs with pH-dependent absorption

Class of Drug	Drugs
Azole antifungals	Ketoconazole, itraconazole, posaconazole, voriconazole
Anti-HIV drugs	Amprenavir, atazanavir, delaviridine, fosamprenavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine
Antibiotics	Cefditoren, clarithromycin
Antiepileptics	Gabapentin. phenytoin
Bisphosphonates	Risedronic acid
Cardiac glycosides	Digoxin
Immunosupressants	Methotrexate, mycophenolate mophetil, mycophenolic acid, tacrolimus
Intestinal anti-inflammatory agents	Mesalazine
Iron preparations	Iron salts
Tyrosine kinase inhibitors	Erlotinib, dasatinib, nilotinib

6.6 Dose modification

Not applicable.

6.7 Treatment after the end of Visit 1

After the 24h time-point, the initiation of dialysis, or discontinuation of study assessments, patients should be administered standard of care therapy as needed, at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product (IP) in the following situations.

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse Event precluding further dosing in the opinion of the investigator or sponsor
- A subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at the time of screening
- Severe non-compliance with the Clinical Study Protocol
- Pregnancy (see section 8.4.2)
- Dialysis administered (see section 6.5.3)
- Whole blood potassium <3.5mmol/L as measured with i-STAT before the administration of ZS at 10h.

7.1.1 Procedures for discontinuation of study treatment

A subject who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date and time of last intake of study treatment should be documented in the eCRF. Subjects discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator (see section 6.7).

Discontinuation of study treatment, for any reason, does not impact on the subject´s participation in the study. Data collection should continue according to the study protocol, with the exception of patients discontinuing due to dialysis (see section 6.5.3). If the subject does not agree to continue assessments as scheduled, a modified follow-up can be arranged to maximize the collection of endpoints and safety information. This could be a telephone contact with the subject, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Any subject leaving the study site before the 24h assessment should always have the 24h / End of Treatment assessment performed before departing if at all possible and acceptable to the patient.

Alternatively, the patient can return to the study site at 24h to have the assessments performed. It will not constitute a protocol deviation if a patient leaves the study site after the 12h assessment during Visit 1, as long as the patient returns in time to have the 24h assessment performed as per the protocol.

The time and date that the patient leaves the treating department (the department or ward administering insulin, glucose and ZS or placebo) will be recorded, as well as the disposition of patients from the treating department.

The first time and date that the patient is discharged (i.e. told to leave) from the hospital after randomization will be recorded. If the patient decides to leave the hospital before being discharged, the time and date that the patient leaves the hospital will be recorded.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record
- Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study.

7.3 Withdrawal from the study

A subject may withdraw from the study (eg, withdraw consent), at any time at his/her own request, without prejudice to further treatment.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AEs). The Investigator will follow up subjects as medically indicated.

A subject who withdraws consent during Visit 1 will be asked if they would agree to undergo minimal follow up, e.g. all or part of the 24h / EoT assessment (see Table 1 for details) before leaving the site during Visit 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the Table 1.

The investigator will ensure that data are recorded on the eCRF. The Web Based Data Capture (WBDC) system Rave will be used for data collection and query handling.

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 eCRF. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Table 1, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Table 1.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 60 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

All efficacy endpoints are entirely or partially based on S-K measurements, and whole blood potassium measured by i-STAT is the main safety parameter to monitor in recruited patients. The proper collection and analysis of S-K and whole blood potassium is therefore of exceptional importance for the successful assessment of efficacy in the study, and for keeping recruited patients safe.

8.1.1 Potassium Assessments

Blood samples for determination of potassium and glucose will be taken at the times indicated in the Schedule of Assessments (see Table 1). Whole blood samples will be analyzed locally using i-STAT devices for the purposes of study inclusion and monitoring. Samples drawn at the same time-points will be prepared and shipped to the Central Laboratory for analysis of S-K.

All blood 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 blood samples must be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF.

See the laboratory manual for details on drawing, preparation and analysis of blood samples.

Blood glucose will be assessed simultaneously with the potassium assessments. See section 8.2.2

8.2 Safety assessments

Planned time-points for all required safety assessments are provided in Table 1.

8.2.1 Clinical safety laboratory assessments

See Table 7 for the list of clinical safety laboratory tests to be performed and see Table 1 for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the Table 1.

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 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator, and will then be analysed at a local laboratory on or near the study site if required for the appropriate monitoring and medical management of the patient.

Analysis of clinical chemistry and haematology will be performed at a central laboratory.

Table 7 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S-Creatinine
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count, %)	S-Alkaline phosphatise (ALP)
B-Platelet count	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
	S-Albumin
	S-Potassium
	S-Calcium, total
	S-Sodium
	S-C-reactive protein (CRP)
	S-Bicarbonate
	S-Phosphorous
	S-Blood Urea Nitrogen (BUN)
	S-Magnesium
	S-Lactate dehydrogenase
	S-Creatine kinase (CK)

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.2 Glucose assessments

Blood glucose will be assessed at each time-point when potassium is assessed using the i-STAT device, as indicate in Table 1. The i-STAT device will report both potassium and glucose at the same time using the same whole blood sample for both analyses. See section 8.1.1.

8.2.3 Physical examinations

A physical examination will be performed at screening and end of treatment/24h, and include an assessment of the following: general appearance, respiratory, cardiovascular (including signs of volume overload), and abdomen.

Investigators should pay special attention to clinical signs related to previous or concurrent serious illnesses. New or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

8.2.4 Vital signs, height and weight

Temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure and weight will ideally be assessed before blood collection for laboratory tests. Height may be measured at any

time during Visit 1. Patient reported dry weight should be used for patients receiving regular hemodialysis whenever available. Patient reported weight is acceptable also for non-dialysis patients, but measured weight is preferred.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.5 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.6 Other safety assessments

Patients may present at an emergency department with hyperkalaemia due to a diverse range of causes. Additional safety assessments should be added as appropriate based on the suspected underlying cause of hyperkalaemia. Participation in the study will not replace or prevent any such additional assessment or investigation to diagnose, monitor or manage the underlying cause of hyperkalaemia or any concurrent conditions. Any diagnoses made and any additional signs, symptoms or laboratory results from such assessments or investigations will be reported on the AE eCRF page if appropriate.

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events (including SAEs) will be collected from time of signature of informed consent form throughout the treatment period and including the follow-up period (Visit 2 or last contact).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AE, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

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

8.3.4 Adverse event data collection

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time (time required for Day 1 only) when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused subject'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 hospitalisation
- 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.

8.3.5 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 B to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject 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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.8 Hy's law

Cases where subject 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 D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

8.4 Safety reporting and medical management

8.4.1 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 eCRF.

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 eCRF, an automated email alert is sent to the designated AstraZeneca representative.

If the eCRF 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.

Investigators or other site personnel send relevant eCRF modules by fax to the designated AstraZeneca representative.

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca unless the pregnancy is discovered before the study subject has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy. Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.3 Overdose

For this study, any dose of ZS greater than 30g within 1 day will be considered an overdose.

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

An overdose without associated symptoms is only reported on the Overdose eCRF 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 8.4.1). For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a 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 (Initial Fatal/Life-Threatening or follow up Fatal/Life-

Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

Not applicable.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 Demography and medical history

Demographic parameters to be collected from patients include sex, date of birth, race, and ethnic group.

Medical history parameters to be included include relevant medical and surgical history.
In addition information about prior dialysis therapy will be collected.

9. STATISTICAL CONSIDERATIONS

9.1 Sample size determination

The study will employ a 1:1 randomization scheme. Based on ZS-004 and patients treated with medications only in ZS-007, the standard deviation for S-K change from baseline at 4 hours is assumed to be 0.7 mmol/L. With 66 patients per group a two-sided 95% confidence interval for the mean difference in S-K change will extend 0.239 mmol/L from the observed difference in means.

9.2 Populations for analyses

For purposes of analysis, the following populations are defined:

The full analysis set will be used for all efficacy analyses. Patients will be analysed according to their randomised study medication.

The safety analysis set will be used for all safety analyses. Erroneously treated patients (eg, those randomised to ZS but actually given placebo or vice versa) will be accounted for in the actual treatment group. A patient who in error has received both ZS and placebo will be accounted for in the randomised treatment group.

Population	Description
Enrolled	All subjects who sign the ICF.
Full analysis set	All randomised subjects.
Safety analysis set	All subjects randomly assigned to Study treatment and who take at least 1 dose of IMP.

9.3 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

Demographics and patient characteristics, relevant medical history, prior medications and patient disposition will be summarised by treatment group using frequency and percentages (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median, and maximum (for continuous variables) using the full analysis set.

Exposure will be summarised by treatment group using frequency and percentage of patients receiving 1, 2 and 3 doses using the safety analysis set.

9.3.1 Efficacy analyses

For all analyses of potassium with the exception of sensitivity analyses, the central laboratory S-K will be used. If central laboratory data is missing, i-STAT will be used instead, adding the average difference between the central lab S-K and i-STAT in those subjects with both values available at the relevant time point.

The primary and secondary variables of mean absolute change from baseline (the measurement at 0h) in S-K to different time points will be analysed using a linear model including treatment group, baseline S-K, time from the start of dosing insulin to the start of dosing ZS/placebo and the dose (units/kg) of the first course of insulin as covariates. The difference in least square means between treatment groups with associated 95% confidence intervals will be presented in addition to the mean absolute changes and standard deviations. For subjects with both S-K and i-STAT missing, data will be imputed using last observation carried forward. If both S-K and i-

STAT is missing at baseline the measurement at screening will be used as baseline. Sensitivity analyses, to be further defined in the SAP, will be performed using different assumptions for subjects with missing data for the primary variable as well as using i-STAT instead of S-K.

Secondary variables of fraction of patients will be analysed using logistic regression models including the same covariates as the primary analysis. Odds ratios and 95% confidence intervals will be presented in addition to frequency and percentages.

For the first secondary objective patients with any missing potassium value from 1h to 4h inclusive will be treated as non-responders.

9.3.2 Safety analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be coded using the MedDRA dictionary. Number of subjects with events and percentages will be tabulated by preferred term and system organ class. Adverse events will also be summarised by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Serious AEs, AEs leading to discontinuation will be summarised in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to study discontinuation will be summarised for each treatment group as applicable. AEs occurring between 0h to 24 h and AEs occurring after 24 h will be summarised separately.

Laboratory data will be summarised by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable lab abnormalities will be summarised.

Vital sign data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarised.

ECG intervals will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable ECG abnormalities will be summarised.

9.3.3 Other analyses

Exploratory objectives will be presented using summary statistics. Further details will be described in the SAP.

9.3.4 Methods for multiplicity control

There will be no adjustment for multiplicity, except for the primary analysis, p-values will be considered exploratory and confidence intervals used as a measure of precision.

9.4 Interim analyses

There are no planned interim analyses in this study.

9.4.1 Data monitoring committee (DMC)

No data monitoring committee will be utilized for this study, as the study does not meet any of the criteria proposed by the FDA to be used to identify studies requiring a DMC in the guidance document "The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors".

10. REFERENCES

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

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

Li, T., and Vijayan, A. (2014) "Insulin for the treatment of hyperkalemia: a double-edged sword?" Clin Kidney J. 7(3):239-41.

Rossignol, P, et al (2016) "Emergency management of severe hyperkalemia: Guideline for bestpractice and opportunities for the future" Pharmacol Res. 113(Pt A):585-591.

FDA Guidance for Clinical Trial Sponsors "Establishment and Operation of Clinical Trial Data Monitoring Committees"

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of S AEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date and time the written consent was obtained. Both subject and authorised person obtaining the informed consent must sign and date the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subjects who are rescreened are required to sign a new ICF.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on clinicaltrails.gov as will the summary of the study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification and source data review to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed and dated ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

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

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

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

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

Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment.

Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.

Intensive treatment in an emergency room or at home for allergic bronchospasm.

Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation.

Development of drug dependency or drug abuse.

B 6 Intensity rating scale:

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

Is this a recognized feature of overdose of the drug?

Is there a known mechanism?

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

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

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

B 8 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 participant or has the potential to cause harm to the participant.

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 participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant 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 participant
- 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 participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (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
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant 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.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 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
(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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

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

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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
(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)

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 D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 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 subject 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 AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN 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 ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

D 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 subject who meets any of the following identification criteria in isolation or in combination:

ALT ≥ 3 × ULN

AST ≥ 3 × ULN

TBL ≥ 2 × ULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the 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 subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

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

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

D 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)
- 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 subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. For studies using a central laboratory add: 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.

D 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 subject 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.

D 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to subjects who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met.

If there is no significant change, no action is required.

If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5.

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease),

If **No**: Follow the process described in Appendix D 4.1.

If **Yes**: Determine if there has been a significant[#] change in the subject's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix D 4.

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix E Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
CONSORT	Consolidated Standards of Reporting Trials
eCRF	electronic case report form
CSA	clinical study agreement
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	discontinuation of investigational product due to adverse event
DNA	deoxyribonucleic acid
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
EOT	End of treatment
EOS	End of study
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HL	Hy's law
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IV	Intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LSLV	last subject last visit
LIMS	laboratory information management system
MedDRA	Medical Dictionary for Regulatory Activities
NIP	Non-Investigational procduct
OAE	other significant adverse event
PHL	Potential Hy's law
PI	principal investigator
SAE	serious adverse event

Abbreviation or special term	Explanation
SAP	statistical analysis plan
SoA	Schedule of Activities
S-K	Serum potassium
WBDC	web based data capture

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Document Name: d9480c00005-csp-v2		
Document Title:	D9480C00005 Clinical Study Protocol version 2	
Document ID:	Doc ID-003614013	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
14-Jun-2018 13:54 UTC	[redacted]	Content Approval
14-Jun-2018 11:47 UTC	[redacted]	Author Approval
14-Jun-2018 11:56 UTC	[redacted]	Content Approval
14-Jun-2018 11:55 UTC	[redacted]	Content Approval

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