Clinical Protocol ZS-004

A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS (Microporous, Fractionated, Protonated Zirconium Silicate), an Oral Sorbent, in Subjects with Hyperkalemia.

IND 108951

SPONSOR
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508 Wrangler Drive, Suite 100
Coppell TX 75019

Original Protocol: 8 July 2013
Amendment 1: 23 December 2013
Amendment 2: 24 February 2014
Amendment 3: 14 April 2014

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1 STUDY TITLE

A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS (Microporous, Fractionated, Protonated Zirconium Silicate), an Oral Sorbent, in Subjects with Hyperkalemia.

2 SPONSOR INFORMATION

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 Chief Medical and Chief Scientific Officer
 ZS Pharma, Inc.

4-14-2014
Date
3 LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event (s)</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>am</td>
<td>Ante Meridian (before noon)</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Co-Variance</td>
</tr>
<tr>
<td>AP</td>
<td>Acute Phase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BNP</td>
<td>Brain Natriuretic Peptide</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CLM</td>
<td>Central laboratory Manual</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CRTC</td>
<td>Controlled Room Temperature Conditions</td>
</tr>
<tr>
<td>DB</td>
<td>Double-blind</td>
</tr>
<tr>
<td>DMP</td>
<td>Data Management Plan</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene-diamine-tetra-acetic acid</td>
</tr>
<tr>
<td>EOS</td>
<td>End of the Study</td>
</tr>
<tr>
<td>ER</td>
<td>Emergency Room</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Hemoglobin A1c (glycated hemoglobin)</td>
</tr>
<tr>
<td>HCG</td>
<td>Human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>HDPE</td>
<td>High Density Polyethylene</td>
</tr>
<tr>
<td>iDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>hpf</td>
<td>High power field</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
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### Abbreviation | Definition
--- | ---
IVRS | Interactive voice response system
IWRS | Interactive web response system
KIM-1 | Kidney Injury Molecule -1
LDH | Lactate Dehydrogenase
MedDRA | Medical Dictionary for Regulatory Activities (Version 15.1E)
ml | Milliliter
ml/min | Milliliter/Minute
min | Minute
mmol/l | Milli-moles/liter
msec | Milliseconds
Na | Sodium
NF | National Formulary
NSAID | Nonsteroidal Anti-Inflammatory Drugs
NAG | N-Acetyl-β-D glucosaminidase
NGAL | Neutrophil Gelatinase-Associated Lipocalin
PE | Physical Evaluation
PK | Pharmacokinetics
POC | Proof-of-Concept
P-BNP | Plasma Brain Natriuretic Peptide
PP | Per Protocol
pm | Post Meridian (after noon)
P-PTH | Plasma Parathyroid Hormone
P-Renin | Plasma Renin
qd | Once a day
RAAS | Renin angiotensin aldosterone system
RBC | Red Blood Cell
SAE | Serious Adverse Event(s)
S-Aldo | Serum Aldosterone
SAP | Statistical Analysis Plan
SAR | Suspected Adverse Reaction(s)
SID | Subject Identification Number
S-Ca | Serum Calcium [Ca+2]
S-Cr | Serum Creatinine
S-HCO3 | Serum Bicarbonate [HCO3-]
S-Insulin | Serum Insulin
S-K | Serum Potassium [K+]
S-Mg | Serum Magnesium [Mg+2]
SPS | Sodium Polystyrene Sulfonate
S-Na | Serum Sodium [Na+]
S-PO4 | Serum Phosphate
**Abbreviation**       **Definition**
SOP(s)                  Standard Operating Procedure(s)
SUSAR                   Serious Unexpected Suspected Adverse Reaction
tid                     Three times a day
U-Alb                   Urinary Albumin
UACR                    Urine albumin/urinary creatinine ratio
U-Cr                    Urinary Creatinine
U-hCG                   Urine Human Chorionic Gonadotropin
U-K                     Urine Potassium [K+]
U-Na                    Urine sodium (Na+)
UPCR                    Urinary protein/urinary creatinine ratio
UTI                     Urinary Tract Infection(s)
VS                      Vital Signs
WBC                     White Blood Cell
Zr                      Zirconium
ZS                      Microporous, Zirconium Silicate (protonated)
ZS-9                    Microporous Zirconium Silicate (unprotonated)
ZS Pharma               ZS Pharma, Inc.
4 STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>ZS Pharma, Inc.</th>
<th>Protocol No. ZS-004</th>
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<tr>
<td>Name of Drug: ZS</td>
<td>Phase of Development: 3</td>
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<tr>
<td>Name of Active Ingredient: Microporous, Fractionated, Protonated Zirconium Silicate</td>
<td>Date of Study Synopsis 14 April 2014</td>
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</tbody>
</table>

Protocol Title
A Phase 3 Multicenter, Multi-phase, Multi-dose Prospective, Randomized Double-blind, Placebo-controlled, Maintenance Study to Investigate the Safety and Efficacy of ZS (Microporous, Fractionated, Protonated Zirconium Silicate) an Oral Sorbent, in Subjects with Hyperkalemia

Investigational sites:
This will be a multi-site study involving up to 75 global sites.

Study Objectives:
Primary objective
To evaluate the safety and efficacy of three (3) different doses of ZS administered once daily (qd) for 28 days in maintaining normokalemia (serum potassium (S-K) between 3.5 – 5.0 mmol/l, inclusive) in subjects achieving normokalemia following two days of acute therapy for subjects with hyperkalemia (two consecutive i-STAT potassium values ≥ 5.1 mmol/l, taken 60 minutes apart) at baseline.

Secondary objectives:
- To evaluate the proportion of subjects who convert to normokalemia after 48 hours of open-label run-in treatment with 10g ZS three times a day (tid)
- To evaluate the safety and efficacy of ZS in subjects with hyperkalemia for the following pre-defined subgroups:
  - chronic kidney disease (CKD)
  - diabetes mellitus (DM)
  - congestive heart failure (CHF)
  - those on RAAS inhibitors
- To evaluate the effect of three (3) different doses of ZS administered qd on kidney function in subjects with hyperkalemia
- To evaluate the effect of three (3) different doses of ZS administered qd on serum-Aldosterone (S-Aldo) and plasma-Renin (P-Renin) levels
- To evaluate the effect of ZS on other electrolytes

No. Subjects to be enrolled:
Approximately 275 subjects with hyperkalemia (two consecutive i-STAT potassium levels ≥ 5.1 mmol/l, taken 60 minutes apart at baseline) will be enrolled in the Open-label Acute Phase to provide 232 subjects in the DB Randomized Maintenance Phase.
Enrollment into the Acute Phase will stop once 232 subjects have begun treatment in the Randomized Maintenance Phase.

**Study Design:**

Initially all subjects will receive open-label ZS at a dose of 10g three times a day (tid) for 48 hours (AP). Subjects who achieve normokalemia (i-STAT potassium values between 3.5 to 5.0 mmol/l, inclusive on the morning of Study Day 3 (after 6 doses of 10g ZS) will then, in a double-blind fashion, be randomized 4:4:4:7 to receive one of three doses of ZS (5g, 10g or 15g) or placebo control, qd for the following 28 days (DBRMP).

Safety and tolerability will be assessed on an ongoing basis by an Independent Data Monitoring Committee (iDMC). Each active dose group in the DBRMP will consist of 49 subjects and the placebo control group will consist of 85 subjects for a total of 232 subjects to detect a 0.6 effect size difference between each ZS dose (from highest to lowest) and placebo control; the 4:4:4:7 allocation optimizes the multiple comparisons to the placebo control for the DBRMP. Subjects who enter the DBRMP and complete the DBRMP Day 29 study visit or who discontinue due to hypo- or hyperkalemia may, depending on drug availability, be offered participation in a 2-month open label extension study (ZS-004E) contingent upon availability of investigational product

**Endpoints:**

**Primary:**

The primary efficacy endpoints will be a comparison between placebo and each ZS treatment group (highest to lowest) with regard to the mean S-K level during DBRMP Days 8-29.

**Secondary:**

Secondary AP efficacy endpoints will include the following parameters:

- Exponential rate of change in S-K levels (blood)
- Change (absolute and percent change) from baseline in S-K levels (blood) at all measured time intervals post dose
- Proportion of subjects who achieve normokalemia during the AP at 24 and 48 hours
- Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/l, inclusive)

Secondary DBRMP efficacy endpoints will include comparisons of the below parameters between placebo and each active treatment group (highest to lowest), using a hierarchical testing strategy:

- The number of days subjects remain normokalemic during the 28-day DBRMP
- The proportion of subjects who remain normokalemic during DBRMP at the end of the 28-day DBRMP (as defined by S-K between 3.5-5.0 mmol/l, inclusive)
- The mean intra-subject S-K standard deviation during the 28-day DBRMP
- The time to first day of hyperkalemia during DBRMP
- The mean changes in S-Aldo and P-Renin levels
Safety and tolerability.

Exploratory Endpoints:
- Surrogate markers for a possible kidney preserving effect (eGFR, protein and albumin in the urine) as measured by urinary protein: creatinine ratio (UPCR) and urinary albumin: creatinine ratio (UACR)
- Surrogate markers for a possible liver preserving effect (bilirubin, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels)
- Other electrolytes (serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN])
- Surrogate markers of cardiac function (serum Galectin-3 [S-Galectin-3], plasma Brain Natriuretic Peptide [P-BNP]) and intestinal health (urinary p-Cresol and indole)
- Surrogate markers for possible effects on bone metabolism (parathyroid hormone [P-PTH], S-Ca, S-PO4)
- Surrogate markers for possible effects on glucose metabolism (serum insulin [S-Insulin] and HbA1c)
- Hospitalization and emergency room (ER) visits
- Non-protocol specified doctor visits

AP Measurements:
All potassium values will be measured by both i-STAT and by the Central Laboratory on all occasions throughout both phases of the study. All baseline parameters (AP Study Day 1) may be measured/collected up to 1 day prior to administration of the first dose of AP study drug.

Potassium levels will be evaluated fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection), two (2) times at 0 and 60 minutes (± 10 minutes) on AP Study Day 1. If both i-STAT values are ≥ 5.1 mmol/l the subject will be enrolled into the AP and receive 10g ZS tid for a total of 6 doses. Women of childbearing potential will have a urine HCG test prior to enrollment. Subjects who screen fail may be rescreened up to two (2) more times during the study.

Potassium levels will be measured 1, 2 and 4 hours (±15 min) after the first dose on AP Study Day 1, and prior to (0h) and 1 hour (± 15 min) after the first daily dose on AP Study Day 2. Subjects who are normokalemic (i-STAT potassium between 3.5 to 5.0 mmol/l, inclusive) in the morning of AP Study Day 3 (after 6 doses of 10g ZS) will be randomized into the DBRMP. If i-STAT potassium levels are still elevated (≥ 5.1 mmol/l) or less than 3.5 mmol/l in the morning of AP Study Day 3 subjects will NOT enter the DBRMP and instead the subject will be referred to his/her own physician to receive standard of care.

Vital signs (VS), physical exams (PE) including weight, 12-lead (or 10-lead if a 12-lead is not available) electrocardiogram (ECG), standard hematology and serum chemistry assessments including other electrolytes (S-Ca, S-Mg, S-Na, S-PO4, S-Cr,
S-HCO3, BUN), as well as urine for culture and urinalysis including sediment will be assessed predose (0h) on AP Study Days 1 (baseline), and AP Study Day 3 (except urine culture) and at the end of study (EOS) visit for those subjects not entering the DBRMP. A urine pregnancy test will also be performed at the AP-EOS visit for women of childbearing potential.

**North American Sites only:**
S-Galectin-3, S-Insulin, S-Aldo, P-BNP, P-PTH, P-Renin, HbA1c and urine chemistry (including urinary Sodium [U-Na], potassium [U-K], UPCR, UACR, p-Cresol and indole will be determined fasting on AP Study Day 1 (baseline).

Whole blood and urine for the baseline analysis of Zr (selected USA sites only) will be collected predose on AP Study Day 1.

**DBRMP Measurements:**
For subjects who continue into the DBRMP, potassium values will be measured predose (0h), on DBRMP Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29 (and 35/EOS for subjects who do not enter the ZS-004E extension study). If, at the end of the DBRMP, i-STAT potassium levels are still elevated (≥5.1 mmol/l), and the subject does not enter the ZS-004E extension study, the subject will be referred to his/her own physician for standard of care treatment. The Central Laboratory S-K sample will be collected as part of the serum chemistry panel on DBRMP Study Days 1, 15, 29 and 35/EOS for subjects not entering the ZS-004E extension study.

If a subject develops i-STAT potassium values <3.0 mmol/l at any time during the study or > 6.2 mmol/l during the DBRMP or a clinically significant cardiac arrhythmia (see below) at any time in the DBRMP, the subject will be withdrawn from the study and referred to their own physician for standard of care treatment. If a subject develops i-STAT potassium values between 3.0 mmol/l and 3.4 mmol/l, inclusive, dosing during the DBRMP will be reduced from qd to every other day for the remainder of the study. All i-STAT potassium measurements meeting a study drug stopping rule or dose adjustment criteria will be confirmed by taking a second potassium measurement after a 10 ± 2-minute interval. Discontinuation of study drug or dose adjustment will require that both i-STAT values meet the study drug stopping rule or dose adjustment criteria.

VS, PEs, ECGs, standard hematology and serum chemistry, including S-Ca, S-Mg, S-Na, S-HCO3, S-PO4, S-Cr, BUN, bilirubin, AST, ALT and urine for urinalysis including sediment, will be evaluated fasting on DBRMP Study Days 1, 15, 29 and 35 (EOS). Urine culture, and a urine pregnancy test for women of childbearing potential, will be performed at DBRMP Study 29 for subjects entering the ZS-004E extension study or DBRMP Study Day 35 (EOS).

**North American Sites Only**
S-Aldo and P-Renin will be measured pre-dose (before 10am [1000]) on DBRMP Study Day 29.
S-Galectin-3, S-Insulin, P-BNP, P-PTH, HbA1c, urine chemistry including U-Na, U-K, UACR, UPCR, p-Cresol and Indole will also be determined on DBRMP Study Day 29 (end of treatment).
Whole blood and urine for zirconium determination (selected USA sites) will be evaluated before the morning dose on DBRMP Study Days 15 and 29 (end of treatment).

**Inclusion criteria:**

1. Provision of written informed consent.
2. Over 18 years of age.
3. Two consecutive i-STAT potassium values, measured 60-minutes apart, both $\geq 5.1$ mmol/l and measured within 1 day of the first ZS dose on AP Study Day 1.
4. Ability to have repeated blood draws or effective venous catheterization.
5. Women of childbearing potential must be using two forms of medically acceptable contraception (at least one barrier method) and have a negative pregnancy test at AP Study Day 1. Women who are surgically sterile or those who are post-menopausal for at least 2 years are not considered to be of childbearing potential.

**Note:** Controlled diabetic subjects can be enrolled. Whenever possible, all blood draws collected prior to meals should be collected prior to insulin/insulin analog treatment.

**Exclusion criteria:**

1. Pseudohyperkalemia signs and symptoms, such as excessive fist clenching hemolyzed blood specimen, history of severe leukocytosis or thrombocytosis.
2. Subjects treated with lactulose, Xifaxan or other non-absorbed antibiotics for hyperammonemia within 7 days prior to the first dose of study drug.
3. Subjects treated with resins (such as sevelamer acetate or sodium polystyrene sulfonate [SPS; e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug.
4. Subjects with a life expectancy of less than 3 months.
5. Subjects who are severely physically or mentally incapacitated and who in the opinion of the investigator are unable to perform the subjects’ tasks associated with the protocol.
6. Women who are pregnant, lactating, or planning to become pregnant.
7. Subjects with diabetic ketoacidosis.
8. Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
9. Known hypersensitivity or previous anaphylaxis to ZS or to components thereof.
10. Randomization into the previous ZS-002 or ZS-003 studies.
11. Treatment with a drug or device within the last 30 days that has not received regulatory approval at the time of study entry.
12. Subjects with cardiac arrhythmias that require immediate treatment.
13. Subjects on dialysis.

**Drug, dose and mode of administration:**
Microporous, Fractionated, Protonated Zirconium Silicate (ZS, particle size ≥ 3 μm) administered orally as a slurry/suspension in water.

**AP:** 10g ZS will be administered tid in conjunction with meals for 48 hours (6 doses)

**DBRMP:** ZS (5g, 10g or 15g) or matching placebo will be administered qd, in conjunction with breakfast, on DBRMP Study Days 1-28, inclusive.

**Study Duration:**
The treatment duration is 2 days in the AP, followed by 28 days per subject post-randomization into the DBRMP with a subsequent final follow up visit 7± 1 day after the last study drug administration unless subjects continue into the open label extension study ZS-004E; the study will be performed entirely on an outpatient basis. For subjects who do not enter the DBRMP the last visit will be 7±1 day after the last treatment dose in the AP.

**Reference therapy and mode of administration:**
Oral placebo powder (silicified microcrystalline cellulose, NF) with the exact same appearance, taste, odor, and mode of administration as ZS.

**Criteria for evaluation:**

**Efficacy**
- S-K at regular intervals

**Pharmacodynamic/safety parameters**
- Serum-creatinine (S-Cr) and BUN at regular intervals
- Other electrolytes (S-Na, S-Ca, S-Mg, S-HCO3 and S-PO4)
- S-Aldo and P-Renin
- Surrogate markers (eGFR, UPCR and UACR) for possible kidney preserving effect.
- Surrogate markers for a possible liver preserving effect (serum bilirubin, AST and ALT levels)
- Surrogate markers of cardiac function (serum Galectin-3 (S-Galectin-3), plasma Brain Natriuretic Peptide [P-BNP])
- Possible effect on bone metabolism (P-PTH, S-Ca, S-PO4)
- Possible effect on glucose metabolism (serum insulin (S-Insulin), fasting blood glucose (FBG) and HbA1c)
- Adverse Events (AEs), Serious Adverse Events (SAEs) Suspected Adverse Reactions (SARs) and Serious Unexpected Suspected Adverse Reactions (SUSARs)
- Incidence of clinically significant cardiac arrhythmias
- Laboratory safety data, vital signs, temperature, at regular intervals
- Whole blood and urine samples for analysis of Zr (selected sites only)
- Health utilization data (ER visits, hospital admission, doctor’s visits other than those specified by the protocol etc.)

**Stopping Rules:**

If a subject develops i-STAT potassium values <3.0 mmol/l any time during the study or > 6.2 mmol/l during the DBRMP, or a clinically significant cardiac arrhythmia (see below) at any time, the subject should immediately receive appropriate medical treatment and be discontinued from study drug. All i-STAT potassium measurements meeting a study drug stopping rule will be confirmed by taking a second potassium measurement after a 10 ± 2-minute interval. The study drug should be discontinued only if both i-STAT values meet the stopping criteria.

Any of the following cardiac events will result in immediate discontinuation from the study (independent of whether it is in the AP or DBRMP):

- Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, paroxysmal supraventricular tachycardia [other than sinus tachycardia], 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])
- Acute congestive heart failure
- Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block), or widening of the QRS complex (> 140msec in the absence of pre-existing bundle branch block) or peaked T-wave or an increase in QTc interval > 25msec to more than 500msec or > 25msec in somebody with a baseline QTc of >500msec

**Dose Modification Rules**

If a subject develops i-STAT potassium values between 3.0 mmol/l and 3.4 mmol/l, inclusive, dosing during the DBRMP will be reduced from qd to every other day for the remainder of the study. All i-STAT potassium measurements meeting dose adjustment criteria will be confirmed by taking a second potassium measurement after a 10 ± 2-minute interval. The dose should be adjusted only if both i-STAT values meet the dose adjustment criteria.

**Study Hypothesis:**

It is hypothesized that the alternative hypothesis that ZS is more effective than placebo control in maintaining mean DBRMP Day 8-29 serum potassium levels (3.5 – 5.0 mmol/l, inclusive) among hyperkalemic subjects in whom normokalemia was established during the open-label acute phase versus the null hypothesis of no difference between each ZS dose (highest to lowest) versus placebo control (null hypothesis).

**Statistical Considerations**

All analyses will be based on the S-K values generated by the Central Laboratory. If Central Laboratory data are missing, they will be replaced by i-STAT values adjusted
to reflect the mean difference between i-STAT and S-K values from all available paired lab samples.

The primary endpoint in the study will be the mean S-K during DBRMP Study Days 8-29. A log transformation will be applied to the S-K level to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (highest to lowest dose) versus placebo control for the 28-day DBRMP to estimate the mean Day 8-29 values; the model will include all S-K data collected at the scheduled visits in addition to baseline covariates for AP eGFR and AP and DBRMP S-K as well as age (<55, 55-64, ≥65 years) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, congestive heart failure, and diabetes mellitus. Labeling claims will be sought for these four pre-defined subgroups.

Secondary efficacy endpoints will be evaluated as follows:

1. The cumulative DBRMP days normokalemic in the three dose (3) groups will be compared to the placebo-treated subjects using a linear regression model to control for the same covariates as for the primary efficacy endpoint in comparing maintenance doses (highest to lowest) versus placebo control
2. The percent normokalemic at DBRMP Day 29 will be compared using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint
3. The mean S-K levels at other time points evaluated relative to baseline using paired t-tests to compare doses (highest to lowest) vs. placebo control using unpaired t-tests
4. The time to hyperkalemia (defined as S-K ≥ 5.1 mmol/l) computed using a Kaplan-Meier life table and using a log rank test and a proportional hazard model containing the same baseline covariates as for the primary efficacy endpoint
5. The time to relapse (defined as return to original AP baseline S-K level) computed using a Kaplan-Meier life table and using a log rank test and a proportional hazard model (SAS PROC PHREG) containing the same baseline covariates as for the primary efficacy endpoint
6. The mean intra-subject standard deviation using a linear regression model containing the same baseline covariates as for the primary efficacy endpoint
7. The proportion of subjects who remain normokalemic at 8, 15, 22 and 29 days compared using a two-sided Fisher Exact test and a SAS PROC GENMOD longitudinal model containing the same baseline covariates as for the primary efficacy endpoint

Kidney function will be evaluated by assessments of S-Cr, eGFR (MDRD equation), UPCR and UACR over time. Liver function will be evaluated by assessing bilirubin, AST and ALT. S-Aldo and P-renin will also be evaluated to assess the possible impact of ZS on the RAAS system. S-Galectin-3, S-Insulin, HbA1c, P-PTH, P-BNP, urinary p-cresol and indole will be assessed to determine possible effects on cardiac health, bone and glucose metabolism, and intestinal health. Safety endpoints will include adverse events, vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters.
Baseline S-K for the AP will be established on AP Study Day 1 (pre-treatment) by taking the mean of 2 different S-K values, recorded 60 ± 10 minutes apart (time 0 and 60 minutes).

The baseline S-K for the DBRMP will be established in the morning of AP Study Day 3 and will use the first S-K measurement performed on Study Day 3 after 48 hours of tid treatment that establishes subject eligibility into the DBRMP. Baseline for all other parameters will be the fasting parameter value measured within 1 day of the first study drug administration in the AP.

As shown below, a sample size of 49 subjects per active dose group and 85 placebo controls will have 90% power to detect a 0.30 mean DBRMP Day 8-29 S-K difference assuming a 0.5 intra-subject standard deviation, comparing each active dose vs. placebo control for a two-sided t-test with 5.0% Type I error; the same pre-defined dose order will be applied (highest to lowest dose) in comparing the doses vs. placebo control.

Unpaired T-test: Equal DBRMP Study Day 8-29 S-K Means (unequal n's)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test significance level, a</td>
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</tr>
<tr>
<td>1 or 2 sided test?</td>
<td>2</td>
</tr>
<tr>
<td>Mean difference, m₁ - m₂</td>
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</tr>
<tr>
<td>Common standard deviation, s</td>
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</tr>
<tr>
<td>Effect size, d =</td>
<td>m₁ - m₂</td>
</tr>
<tr>
<td>Power ( % )</td>
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</tr>
<tr>
<td>Placebo, n₁</td>
<td>85</td>
</tr>
<tr>
<td>ZS Dose, n₂</td>
<td>49</td>
</tr>
<tr>
<td>Ratio: n₂ / n₁</td>
<td>1.735</td>
</tr>
<tr>
<td>N = n₁ + 3n₂</td>
<td>232</td>
</tr>
</tbody>
</table>

An unpaired t-test will be employed for other continuous endpoints to compare each maintenance treatment (highest to lowest dose) vs. placebo control.

Monitoring:

Baseline parameters (e.g. ECG, VS, PE, medical history, eligibility criteria, hematology, clinical chemistry including S-Aldo and P-Renin, urinalysis including chemistry) will be collected up to 1 day prior to the first AP dose. All potassium measurements will be performed both by the Central Laboratory (S-K) and using an i-STAT. Missing or hemolyzed Central Lab S-K measurements will be replaced by i-STAT values adjusted to reflect the mean difference between i-STAT and S-K values from all available paired lab samples as applicable.

Potassium will be measured fasting, 2 times at a 60-minute interval on AP Study Day 1 (time 0 and 60 ± 10 minutes) for establishment of a baseline, at 1, 2 and 4 hours post the 1st dose on AP Study Day 1, pre-dose (0h) and 1 hour after the first daily dose on AP Study Day 2 and on AP Study Days 3 and 9 for subjects NOT entering the DBRMP. During the DBRMP potassium will be measured pre-dose on DBRMP Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29 and 35 (EOS visit for subjects not continuing into the open label ZS-004E extension study).
North American Sites Only
S-Aldo and P-Renin will be measured before 10 am (1000) on AP Study Day 1 (baseline) and on DBRMP Study Days 1 and 29. S-Galectin-3, P-BNP, P-PTH, S-Insulin, HbA1c, and urine chemistry including p-Cresol and Indole will also be determined predose on AP Study Day 1 (baseline) and on DBRMP Study Day 29.

Safety Assessments:
ECGs will be assessed pre-dose on AP Study Day 1 (baseline) for all subjects, and AP Study Days 3 and 9 (EOS) for subjects not entering the DBRMP and on DBRMP Study Days 1, 8, 15, 22, 29 and 35 (EOS for subjects not continuing into the open label ZS-004E extension study) VS, PEs, serum chemistry, urine analysis (including sediment, and hematology will be performed on AP Study Day 1 (baseline), and also on AP Study Days 3 and 9 (EOS) for subjects NOT entering the DBRMP, and on DBRMP Study Days 1, 15, 29, and 35 (EOS for subjects not continuing into the open label ZS-004E extension study). A pregnancy test will be performed for women of childbearing potential on AP Study Days 1 (baseline), DBRMP Study Day 29 for subjects continuing into the open label ZS-004E extension study and at the EOS visit (both phases) for subjects who do not continue into the open label ZS-004E extension study. Urine will be cultured on AP Study Day 1 (baseline), DBRMP Study Day 29 for subjects continuing into the open label ZS-004E extension study and at the EOS visit (both phases) for subjects who do not continue into the open label ZS-004E extension study. Adverse events and SARs will be solicited throughout the study duration following administration of the first dose.

PK endpoints: At selected USA sites only whole blood and urine samples for measurement of Zr content will be collected on AP Study Day 1 (baseline) and in the morning on DBRMP Study Days 15 and 29 (end of treatment).
5 Events Schedule: Phase 3 Dose-ranging Efficacy and Safety Study Against Placebo

5.1 Open-Label Acute Phase (AP) – All Sites

<table>
<thead>
<tr>
<th>AP Study Day Parameter</th>
<th>SCRN&lt;sup&gt;10&lt;/sup&gt;</th>
<th>1</th>
<th>2</th>
<th>3&lt;sup&gt;7&lt;/sup&gt;</th>
<th>9 (EOS)&lt;sup&gt;9&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SCRN&lt;sup&gt;10&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Access IVRS/IWRS</td>
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<td></td>
</tr>
<tr>
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<td></td>
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<tr>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Concomitant medications</td>
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<td>X</td>
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<tr>
<td>Adverse events and non-protocol Physician/ER visits</td>
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<td></td>
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<tr>
<td>Potassium&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine HCG</td>
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<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>IP Reconciliation</td>
<td></td>
<td>X</td>
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</tr>
</tbody>
</table>

1 Parameters to be measured are detailed in Appendix 1. All blood potassium samples are analyzed by i-STAT and by the Central Laboratories on all occasions.
2 Blood potassium will be measured at time 0 and 60 (± 10) minutes within 1 day of any dose administration and on AP Study Day 1 at 1, 2 and 4 hours (± 15 min) after administration of the first dose of ZS.
3 Potassium values will be measured predose (0 hour) and 1 hour (± 15 min) post 1<sup>st</sup> dose on AP Study Day 2.
4 Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection). On AP Study Day 1, the Central Laboratory serum chemistry and hematology samples will be collected at the same time as the 60 minute i-STAT screening potassium sample.
5 Study drug will be administered orally before breakfast, lunch and dinner on AP Days 1 and 2.
6 For women of childbearing potential using kits supplied by the Central Laboratory.
7 i-STAT and S-K for all subjects, remaining procedures only for subjects with i-STAT potassium values > 5.0 mmol/l as measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection).
8 Central laboratory S-K sample collected as part of the serum clinical chemistry.
9 EOS occurs 7 ± 1 day after the last administration of IP.
10 Baseline parameters may be measured/collected up to 1 day prior to administration of the first dose of study drug on AP Study Day 1.
11 Access IVRS/IWRS on AP Study Day 3 or if subject permanently discontinues dosing before the end of the AP dosing period.
5.1.1 Open-Label Acute Phase (AP)- North American Sites ONLY

<table>
<thead>
<tr>
<th>AP Study Day Parameter</th>
<th>1,10</th>
<th>2</th>
<th>3</th>
<th>9 (EOS)(^{11}) for subjects NOT entering the DBRMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zr whole blood &amp; urine(^7)</td>
<td>X</td>
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</tr>
<tr>
<td>S-Aldo &amp; P-Renin(^8)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP(^3)</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Galectin-3(^1,4)</td>
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<td></td>
</tr>
<tr>
<td>PTH(^2)</td>
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<tr>
<td>Insulin(^1)</td>
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</tr>
<tr>
<td>HbA1c(^{12})</td>
<td>X</td>
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<tr>
<td>Urine Chemistry(^{13})</td>
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<tr>
<td>Indole(^7)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Cresol(^6)</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1. Collected into serum separator tubes, separate and freeze within 2 hours of collection
2. Minimum volume 0.5 ml serum
3. Collected into EDTA, separate and freeze plasma within 2 hours of collection
4. Requires minimum 1.0 ml
5. Requires 3 ml of well mixed urine
6. Requires 2 X 4 ml well mixed urine
7. Requires 2x 3 ml whole blood and 2 X 3 ml urine samples-selected sites only.
8. S-Aldo is collected into serum separator tubes; P-Renin is collected into EDTA tubes at selected sites only. Both samples are collected prior to 10am after subject is in upright position at least 2 hours and prior to ECG/PE measurements. Samples are to be aliquoted immediately after processing and frozen until sent for analysis. At least 1ml of the processed sample is required
9. Whole blood for Zr analysis, S-Aldo, P-Renin, S-Insulin, HbA1c, and urine chemistry will be measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection). On AP Study Day 1, these samples will be collected at the same time as the 60 minute i-STAT screening potassium sample.
10. Baseline parameters may be measured/collection up to 1 day prior to administration of the first dose of study drug on AP Study Day 1
11. EOS occurs 7 ± 1 day after the last administration of IP.
12. Whole blood collected into K2EDTA, frozen and shipped within 2 days of collection
13. Requires 15 ml urine
14. All parameters will be measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection).
### 5.2 DB Randomized Maintenance Phase (DBRMP)- All Sites

<table>
<thead>
<tr>
<th><strong>DBRMP Study Day</strong>&lt;sup&gt;7&lt;/sup&gt;</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>8</th>
<th>12</th>
<th>15</th>
<th>19</th>
<th>22</th>
<th>26</th>
<th>29</th>
<th>35 (EOS)&lt;sup&gt;8&lt;/sup&gt;</th>
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<td><strong>Eligibility criteria</strong></td>
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</tr>
<tr>
<td><strong>Physical exam including weight</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<td>X</td>
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<tr>
<td><strong>Access IVRS/IWRS</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>X</td>
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<tr>
<td><strong>Study drug (IP) administration</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td><strong>ECG</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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</tr>
<tr>
<td><strong>Vital signs</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td><strong>Adverse events and non-protocol Physician/ER visits</strong></td>
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<tr>
<td><strong>Serum chemistry</strong>&lt;sup&gt;1, 3&lt;/sup&gt;</td>
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1. Parameters to be measured are detailed in Appendix 1. All blood potassium samples are analyzed by i-STAT and by the Central Laboratories.

2. Potassium will be measured fasting, prior to the 1<sup>st</sup> daily dose as part of the serum chemistry panel. Samples will be analyzed by i-STAT and the Central Laboratory.

3. Physical Exam, ECG, Vital signs, weight, urinalysis, urine chemistry, whole blood and urine for Zr determination, serum clinical chemistry including S-Aldo and P-Renin, and hematology parameters will be measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours potassium sample collection at the clinic).

4. Study drug will be administered orally just before breakfast on DBRMP Study Days 1-28. Study drug is administered in the clinic on DBRMP Days 1, 2, 5, 8, 12, 15, 19, 22 and 26.

5. For women of childbearing potential using kits supplied by the Central Laboratory.

6. i-STAT and Central Laboratory.

7. If a scheduled clinic visit falls on a weekend or National holiday during the DBRMP, the scheduled visit may take place either 1 day early or 1 day late (i.e. within ± 24 hours of the scheduled day) for DBRMP Study Days 5, 8, 12, 15, 19, 22, 26 and 35, up to 2 days late for DBRMP Study Day 2 or 2 days early for DBRMP Day 29. If the Day 29 visit is conducted early, the subject must take IP through Day 28 per protocol.

8. EOS occurs 7 ± 1 day after the last administration of IP. Subjects entering the extension study, ZS-004E, will not have an EOS visit as part of the ZS-004 protocol.

9. Access IVRS/IWRS on days indicated or if subject permanently discontinues dosing before the end of the DBRMP dosing period.

10. Perform only if subject enters the extension study, ZS-004E.
5.2.1 DB Randomized Maintenance Phase (DBRMP) - North American Sites ONLY

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1 Collected into serum separator tubes, separate and freeze within 2 hours of collection
2 Minimum volume 0.5 ml serum
3 Collected into EDTA, separate and freeze plasma within 2 hours of collection
4 Requires minimum 1.0 ml
5 Requires 3 ml of well mixed urine
6 Requires 2 X 4 ml well mixed urine
7 Requires 2 x 3 ml whole blood and 2 X 3 ml urine samples-selected sites only.
8 S-Aldo is collected into serum separator tubes; P-Renin is collected into EDTA tubes at selected sites only. Both samples are collected prior to 10am after at least 2 hours in the upright position and prior to ECG/PE measurements. Samples are to be aliquoted immediately after processing and frozen until sent for analysis. At least 1ml of the processed sample is required
9 Whole blood for Zr analysis, S-Aldo and P-Renin will be measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection).
10 EOS occurs 7 ± 1 day after the last administration of IP
11 Whole blood collected into K2EDTA, frozen and shipped within 2 days of collection
6 INTRODUCTION

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

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

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

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

Treatment depends on the S-K levels. In milder cases (S-K between 5-6.5 mmol/l), acute treatment with a potassium binding resin (Kayexalate®), combined with dietary advice (low potassium diet) and possibly modification of drug treatment (if treated with drugs
causing hyperkalemia) will be standard of care; if S-K is above 6.2 mmol/l or if arrhythmias are present, emergency lowering of potassium and close monitoring in a hospital setting is mandated. The following treatments would typically be used:

- Sodium Polystyrene Sulfonate (SPS; e.g. Kayexalate®) is a resin that binds potassium in the intestine and hence increases fecal excretion, thereby reducing S-K levels. However, as SPS has been shown to cause intestinal obstruction and potential rupture, diarrhea needs to be simultaneously induced, reducing the palatability of the treatment.
- Insulin IV (+ glucose to prevent hypoglycemia) to shift potassium into the cells and away from the blood.
- Calcium supplementation. Calcium does not lower S-K, but it decreases myocardial excitability and hence stabilizes the myocardium, reducing the risk for cardiac arrhythmias.
- Bicarbonate. The bicarbonate ion will stimulate an exchange of K for Na, thus leading to stimulation of the sodium-potassium ATPase.
- Severe cases might require dialysis.

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

7 BACKGROUND

ZS-9/ZS (microporous, fractionated, protonated, zirconium silicate) is a potent inorganic oral sorbent that has been shown to bind potassium in the intestine of animals in exchange for sodium; its potassium-binding capacity has been shown in-vitro to be approximately 10 times that of SPS in the presence of calcium and magnesium cations, which, if that translates into humans, would represent a significant therapeutic advantage over Kayexalate®.

The current protocol is the third human study to be conducted with ZS (microporous, fractionated, protonated, zirconium silicate) and serves as an important dose-finding study for registration.

Two clinical studies, ZS-002 and ZS-003, have been completed to date:

**ZS-002**

ZS-002 was a single multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating Phase 2 study to investigate the safety, tolerability and pharmacodynamics of ZS in subjects with chronic kidney disease and mild to moderate hyperkalemia. Nine (9) clinical sites with overnight facilities within the United States participated in the study.
Protocol Number ZS-004 (Amendment 3)
Date: 14 April 2014

Ninety (90) subjects with moderate CKD (defined as GFR between 30 - 60ml/min) and mild hyperkalemia (S-K between 5-6 mmol/l) were enrolled in the study where they, in a double-blind dose-escalating fashion (three separate cohorts), were to be randomized to receive escalating doses of ZS (0.3g, 3g and 10g) or placebo, administered tid daily with meals. The first cohort (0.3g/dose) was to enroll 18 subjects (12 active: 6 placebo) while both of the second (3g/dose) and third (10g/dose) cohorts were to enroll 36 subjects each (24 active: 12 placebo). Baseline parameters were measured on Study Days -1 (S-K) and 0 (GFR); subjects then returned to the clinic on the morning of Study Day 1. ZS or placebo were to be administered for at least 48 hours (or up to 96 hours for subjects whose S-K had not normalized [3.5 – 5.0 mmol/l]) but did not exceed 6.5 mmol/l, after 48 h of treatment). If S-K levels were still elevated (S-K ≥ 5.0 mmol/l) after 48 hours, subjects were to receive another 24 hours of study drug treatment and then be re-assessed at 72 hours. If S-K levels were normal (3.5 – 5.0 mmol/l), the subject was to be discharged from the clinic without further study drug treatment; if levels were still elevated (≥5.0 mmol/l), subjects was to receive a final 24 hours of study drug treatment (for a total of 96 hours). If, at the end of 96 hours of study drug treatment, S-K was still elevated (≥5.0 mmol/l), the subject was to be referred to his/her own physician for standard of care treatment. The standard in-clinic diet was provided for the inpatient portion of the study. S-K measurements were taken at 0, 30, 60 and 120 minutes post dose on Study Day 1, every 4h post dose on Study Days 1 and 2 (and Study Days 3/4 for subjects whose S-K had not normalized), at 4 am on Study Day 3 (and Study Days 4 and 5 for subjects whose S-K had not normalized), and then daily until Study Day 7 (168 hours). Serum chemistry hematology, physical exams, electrocardiograms (ECG), urinalysis (including urinary sodium (U-Na), potassium (U-K) and urea nitrogen (UUN)) vital signs (VS), adverse events (AEs) and concomitant medications were determined daily from Study Days 1-7. Urine cultures were performed on Study Days -1 (screening) and 7. Whole blood samples for measurement of zirconium (Zr) were collected at 8 am on Study Days 0-2 and 4 hours post the third dose on Study Days 1 and 2, and urine samples for Zr determination were collected from 24-hour urine samples collected on Study Days 0-2. Urine pregnancy tests were performed on subjects of childbearing potential on Study Days -1 and 7. 24-hour urine samples were collected on Study Days 0-2 (and 3/4 for those subjects whose S-K had not normalized after 48 or 72 hours of treatment) and analyzed for the renal injury biomarkers Kidney Injury Molecule -1 (KIM-1) and Neutrophil Gelatinase Associate Lipocalin (NGAL).

A total of 90 subjects (38 females, 52 males) with a mean age of 72 years (range 42-96 years) and mild to moderate CKD (mean GFR = 55.9 ml/min, range 30 – 60ml/min) and mild to moderate hyperkalemia (mean screening S-K = 5.3 mmol/l; range 4.9 – 6.1 mmol/l/l, and mean baseline S-K = 5.1 mmol/l; range 4.3 – 6.1 mmol/l) were enrolled. Eighty-eight (88) out of 90 subjects were white. All 90 subjects received all doses per protocol and all subjects had S-K measurements performed at screening (Study Day 0), at baseline (pre-dose on Study Day 1) and at the time of the primary endpoint at 48 hours; hence, all subjects were included in all analyses according to the intention-to-treat (ITT) principle. All subjects completed all 7 days of study assessments and there were no premature study discontinuations. Seventy-six (76) subjects received 2 days of study drug treatment, fourteen (14) subjects (9/30 on placebo, 5/60 on ZS) received 3 days of
study drug treatment, and four (4) subjects (3 on placebo, 1 on ZS) received 4 days of study drug treatment.

ZS resulted in significant dose-dependent reductions in S-K in subjects with mild to moderate hyperkalemia and met the predefined primary endpoint of exponential decrease in S-K from baseline to 48 hours at the 10g tid dose (p<0.0001) as well as the 3g tid dose (p=0.048). ZS at the 3g tid dose and 10g tid dose resulted in mean maximal reductions of 0.42 mmol/l and 0.92 mmol/l, respectively. The within-dose group effect started immediately with statistically significant reductions 1 hour after the first 10g tid dose (p=0.022). During Study Day 2 (from 28 to 48 hours post first study dose), all S-K levels were significantly reduced at all time points measured as compared to baseline (p < 0.001) at the 10g tid dose. The effect on S-K lasted for >4 days after last study drug administration with S-K levels still lower on the morning of Study Days 4 (p < 0.001), 5 (p = 0.001) and 6 (p = 0.016) at the 10g tid dose. There was no effect on S-K beyond Study Day 2 at the 3g tid dose. There was no statistically significant effect on S-K levels at the 0.3g tid dose of ZS or placebo.

Other S-K assessments (such as time to a decrease in S-K of ≥ 0.5 mmol/l or time to normalization of S-K [p=0.04]) also demonstrated dose-dependent responses. In general, there was a clear dose-response relationship with respect to time to first S-K decrease of 0.5 mmol/l, with the greatest reduction at the 10g tid dose of ZS, a medium reduction at the 3g tid dose of ZS and no effect at the 0.3g tid dose of ZS or placebo. No subjects at the 10g tid dose received more than the initial 48 hours of treatment, demonstrating that S-K levels had normalized in 24/24 subjects after 48 hours of treatment. In contrast, 9/30 (30%) subjects in the placebo group received study drug treatment beyond the initial 2 days (p<0.05). There was no statistically significant reduction in S-K at any time point at the 0.3g tid dose of ZS or placebo. The reduction in S-K levels was accompanied by a similar reduction in urinary potassium excretion with a 23% reduction in urinary potassium excretion observed from baseline to Study Day 2 at the 10g tid dose (p<0.002). There were no statistically significant reductions in urinary potassium excretion at the two lower doses of ZS or placebo.

Despite the potent lowering of S-K, there were no significant cases of hypokalemia (defined as S-K ≤ 3.0 mmol/l).

There was a dose-related statistically significant reduction in BUN from Study Day 2 to Study Day 7, mirroring that of S-K (p-values between 0.035 [Study Day 2] and <0.001 [Study Days 5-7]), which was attributed to the ammonium binding capacity of the crystal. There was a statistically significant decrease in S-Ca that remained within the normal range (from 9.5 mg/dl to 9.05 mg/dl) at the 10g tid dose of ZS (p-values from 0.047 to 0.001 on Study Days 2-6), but no subjects developed hypocalcemia; there were no significant changes in S-Mg, S-Na, S-HCO3 or any other electrolytes at any dose level of ZS. There was a trend towards a reduction in S-Cr that reached statistical significance on Study Day 6 (p=0.048). There were no dose-related changes in any other evaluated kidney parameters, including urinary sediment, creatinine clearance or the renal biomarkers NGAL and KIM-1.

ZS was very well tolerated. There were a total of 23 adverse events: 5 events in 3 subjects on placebo, 2 events in 1 subject at 0.3g tid, 4 events in 3 subjects at 3.0g tid and 12
events in 8 subjects at the 10g tid dose. Only 3 AE were judged by the investigator as being possibly, probably, or definitely related to study drug, 2 cases on placebo (nausea and vomiting) and 1 case at the 3g tid dose of ZS (constipation). All AEs were either mild (18/23) or moderate (5/23), and all were transient and disappeared during the 7-day study period. Most of the AEs were gastrointestinal (nausea, vomiting, abdominal pain or discomfort). There were 4 cases of urinary tract infection, 1 at the 3g tid dose, and 3 at the 10g tid dose of ZS. Only 3 UTI’s at the 10g tid dose were reported as AE’s; the remaining UTI was discovered incidentally. However, all 4 cases were pre-existing and present at baseline before any study drug administration, and hence were not considered to be related to ZS treatment.

There were no clinically or statistically significant changes in vital signs or ECG parameters during the study and no subject developed any new, clinically significant cardiac arrhythmias. Some abnormal laboratory safety tests were noted but none were described as AEs and there were no significant increases in any other laboratory safety test values (such as liver enzymes or renal parameters).

**ZS-003**

The ZS-003 study was a Phase 3 multicenter, two-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS in subjects with mild to moderate hyperkalemia (i-STAT potassium levels at entry between 5.0-6.5mmol/l, inclusive). Sixty five (65) clinical sites in the US, Australia and South Africa participated in the study. A total of 753 subjects (448 males and 305 females) with a mean age of 65.6 years (range 22 to 93 years) and mild to moderate hyperkalemia (mean screening S-K = 5.39 mmol/l and mean baseline S-K = 5.32 mmol/l) were randomized to one of four doses of ZS (1.25g, 2.5g, 5g or 10g of ZS tid) or placebo for two days (Acute Phase Study Days 1 and 2), followed by a Subacute Phase of 12 days of treatment with 1.25, 2.5, 5 or 10g ZS qd in subjects who were normokalemic at the end of the Acute Phase.

The predefined primary endpoint was the mean difference in S-K between placebo and each of the four (4) ZS treatment groups over 48 hours in the Acute Phase and over the 12 days in the Subacute Phase. The primary endpoint was met at the three (3) top doses (2.5g, 5g and 10g tid) of ZS in the Acute Phase and at the two top doses (5g and 10g qd) in the Subacute Phase in a dose related fashion. The effect on S-K started immediately and was statistically significantly different from placebo 1h post-first dose at the10g tid dose level (p=0.011), two hours post-first dose at the 5g tid dose level (p=0.033) and at 4 hours post-dose at the 2.5g tid dose level (p=0.011). The mean change from baseline to 48 hours was -0.73mmol/l, -0.54mmol/l, -0.47mmol/l and 0.31mmol/l at the 10g, 5g, 2.5g and 1.25g tid dose levels, respectively. Similarly, during the 12-day Subacute Phase, normokalemia was maintained compared to placebo at both the 10g (p<0.05) and 5g qd (p<0.05) dose levels. The effect of ZS was consistent in subgroups of patients with chronic kidney disease (CKD; ~61% of all subjects enrolled), congestive heart failure (CHF; ~40% of all subjects enrolled), diabetes mellitus (DM; ~60% of all subjects enrolled) and patients being treated with Renin-Angiotensin-Aldosterone System (RAAS) inhibitors (~65% of all subjects enrolled).
Overall, ZS was well tolerated at all dose levels with a safety and tolerability profile comparable to placebo. There were a total of 16 serious adverse events (SAE), one in the Acute Phase (on placebo) and 15 in the Subacute Phase (5 on placebo, 3 on the 1.25g dose, 4 on the 2.5g dose, 3 on the 5g dose, and 0 on the 10g dose). All except one SAEs were reported as being “not related” to study drug; the one SAE that was described as “possibly related to study drug” was gastroenteritis and occurred in a subject on placebo. There was a slightly higher incidence of urinary tract infections (UTIs) reported in the ZS groups compared to placebo but there was no dose-response relationship.

Initial non-clinical pharmacology and toxicology studies have been conducted with both ZS-9 and ZS and are detailed in the Investigator’s Brochure. The in vivo data is summarized below.

In vivo the administration of ZS-9 in food decreased the urinary excretion of potassium (U-K) and urea nitrogen (U-NH) and increased fecal excretion of potassium and urea nitrogen in a dose-dependent manner when administered to rats at doses of up to 6 g/kg/day. Urinary excretion of sodium (U-Na) was increased while fecal sodium excretion decreased. There was no effect on urinary or fecal calcium and magnesium excretion or on S-K, S-Na, BUN S-Ca, or S-Mg.

Due to the insolubility of ZS-9/ZS in vehicles compatible with in vitro assessments of cardiac function such as the hERG assay to assess effects on QT interval, no in vitro cardiac assessments have been performed. However, the effect of ZS-9 on cardiovascular function in vivo was assessed as part of a GLP toxicity study in Beagle dogs administered ZS-9 at doses of up to 1,300 mg/kg/dose (anhydrous weight), with food, three times a day (tid) at 6 h intervals over a 12-hour period for 14 consecutive days. ZS-9 had no adverse effect on respiration and heart rate, or on PR, QRS or QT duration.

In a non-GLP mass balance study in rats there was no evidence of systemic absorption following a single dose of 2000 mg ZS-9/kg when administered in food. Ninety nine percent of the administered dose was recovered in feces with less than 0.3% found in urine. The latter was considered to be due to contamination of the urine during the collection process.

In both non-GLP and GLP oral toxicity studies ZS-9 was well tolerated when administered by oral gavage as single or once daily repeat doses of up to 2000 mg/kg to rats and dogs. In these studies clinical signs were limited to the finding of white granules in stool from dogs at doses of 500 mg/kg and above and a slight increase in prothrombin time in rats at 2000 mg/kg. When administered to rats in food at doses of up to 6 g/day for 5 days soft to very soft stool was observed at doses of 4 g/kg and above. Since ZS-9 does not appear to be absorbed systemically following oral consumption in rats the finding of white granules in the stool of dogs is attributed to excretion of test article.

ZS-9 is also well tolerated in rats and dogs when administered three times a day (tid) at 6-hour intervals over a 12-hour period for up to 14 days. In rats ZS-9 was administered by gavage as an oral suspension in 0.5% methylcellulose at a dose volume of 10 ml/kg. ZS-9 treatment resulted in an increase in urinary pH in all dose groups and dose related decreases in urinary potassium and urea nitrogen concentrations and increases in urinary sodium concentrations. The changes in urinary sodium, potassium and ammonium concentrations were attributed to the pharmacological action of ZS-9 and not considered
toxicologically adverse. Test article related microscopic findings were limited to the urinary bladder and included minimal to mild mononuclear cell infiltration, mucosal hyperplasia and acute inflammation sometimes associated with minimal hemorrhage, edema and/or mineralization in individual animals at terminal necropsy. These changes were not observed following the 10-day recovery period indicating that they were reversible. The presence of mucosal hyperplasia with accompanying inflammatory cell infiltrates is likely a consequence of irritation of the urinary bladder mucosa, possibly due to the increased urinary pH, and the presence of acute inflammation and mononuclear cell infiltration likely represents a continuum of change involving irritation of the urinary bladder.

Based on the finding in the urinary bladder the no observed adverse effect level (NOAEL) of ZS-9 is considered to be 400 mg/kg/dose in males and 800 mg/kg/dose (following correction for water content) in females, equivalent to a single human dose of ~4.8 or 9.6g, respectively based on a 65 kg body weight.

In dogs administered 0, 325, 650 or 1,300 mg ZS-9/kg/dose in food, tid at 6-hour intervals over a 12-hour period for 14-days clinical signs were limited to the observation of white material, presumed to be test article, in the feces of some dogs at the 325 mg/kg/dose and in all animals receiving ≥650 mg/kg/dose during the second week of treatment. There were no adverse effects on body weight, body weight change, food consumption or ophthalmoscopic and ECG evaluations. Several clinical chemistry parameters showed statistically significant changes compared to Control at Day 13. At 325 mg/kg/dose BUN was increased and chloride was decreased in males; at 650 mg/kg/dose lactate dehydrogenase (LDH) was increased and triglyceride was decreased in females, and cholesterol was increased in males. At ≥650 mg/kg/dose creatinine and magnesium were increased and glucose and chloride were decreased in females and phosphorus and the albumin/globulin ratio were decreased in males and at 1300 mg/kg/dose AST was increased and potassium was decreased in females and sodium, globulin, LDH and AST were increased in males. A dose-related decrease in serum potassium was observed in males but failed to reach significance. All changes were minor, with individual animal values well within the normal range observed pretest and not considered clinically adverse. With the possible exception of the decrease in serum potassium observed in both sexes and with no consistent group-related patterns/trends to suggest a relationship for these variations to the administration of ZS-9, all changes were considered incidental and not related to test article.

Treatment with ZS-9 was associated with increased urinary pH and dose-dependent decreases in mean urinary potassium (up to 80-90%) and urea nitrogen (up to 40-50%) concentrations and increases in mean urinary sodium concentration in both sexes that was attributed to the pharmacological effect of ZS-9.

There were no macroscopic findings associated with administration of ZS-9. Microscopically minimal to mild focal and/or multifocal inflammation was observed in the kidneys of treated animals but not in Control animals. The lesions had similar incidence and severity at 650 and 1300 mg/kg and were less frequent and severe at 325 mg/kg. In some dogs the inflammation was unilateral rather than bilateral, and in some cases was associated with inflammation in the urinary bladder and origin of the ureter. Taken together these observations suggest that alterations in urine composition of ZS-9
treated dogs may have resulted in increased susceptibility to subclinical urinary tract infections, even though no microorganisms were observed in these tissues. In recovery animals the inflammation was completely resolved in females and partly resolved in males indicating that whatever the cause of the inflammation it was reversible following cessation of dosing.

In order to elucidate the possible cause of the inflammation seen in the urinary tract a second non-GLP study was conducted to examine the effects of urine alkalinity, potassium supplementation and ZS-9 particle size and protonation on the urinary tract of female beagle dogs following repeat oral administration. Nine groups of experimentally naive female Beagle dogs (3/group) were administered ZS-9 at 600 or 100 mg/kg/dose, potassium supplemented ZS-9 (ZS-9 + K) at 600 mg ZS-9 and 117 potassium chloride/kg/dose, fractionated ZS-9 (ZS-9: particle size >5 µm) at 600 or 100 mg/kg/dose, fractionated and protonated microporous zirconium silicate (ZS) at 600 or 100 mg/kg/dose, or 50 mg/kg/dose of sodium bicarbonate (NaHCO3). An additional group, dosed with the vehicle (wet dog food), served as the control (0 mg/kg/dose).

ZS-9/ZS administration had no effect on mortality, body weight, body weight gain, organ weights, clinical chemistry, urinary Neutrophil gelatinase-associated lipocalin (NGAL) and N-Acetyl-β-D glucosaminidase (NAG) or blood gas parameters. Test article related findings included increases in the fractional excretion of sodium and urinary pH (~2 units) in animals receiving fractionated or unfractonated ZS-9 with or without potassium supplementation at 600 mg/kg/dose; and deceases in the fractional excretion of potassium and the urinary urea nitrogen/creatinine ratio in animals dosed at 600 mg/kg/dose ZS-9, fractionated ZS-9 or ZS. The changes in fractional excretion were attributed to the test article and were not considered toxicologically adverse. The absence of urine alkalization in animals treated with 600 mg/kg/dose of ZS suggests that in animals treated with non-protonated material, hydrogen is exchanged for sodium as the non-protonated ZS-9 passes through the gastrointestinal (GI) tract causing an increase in blood pH which in turn causes the kidney tubules to respond by increasing acid absorption and actively transporting bases into the urine, thereby raising the pH of the urine.

Test article related microscopic findings observed at the 600 mg/kg/dose included minimal to mild mixed leukocyte infiltrates and minimal to mild renal tubular regeneration in the kidney and minimal to mild mixed leukocyte infiltrates in the urethra and/or ureters, minimal renal tubular degeneration/necrosis and minimal pyelitis in some animals treated with ZS-9 and fractionated ZS-9. The significant reduction in the incidence and severity of the findings in animals treated with ZS and ZS-9 supplemented with potassium suggest the observed lesions are a function of the urinary composition and pH that affect the antibacterial efficiency and/or urinary solute profile and solubility, thereby increasing susceptibility to the background insult from bacteria and urinary crystal formation.

The no-observable-effect-level (NOEL) established for female Beagle Dogs in this study was 100 mg/kg/dose ZS-9 with or without fractionation at 5 µm or ZS, and the no-observable-adverse-effect-level (NOAEL) for ZS or ZS-9 supplemented with potassium was 600 mg/kg/dose. These doses correspond to single human equivalent doses of ~3.5 and 23g, respectively, given three times daily, assuming a body mass of 65 kg.
ZS, the protonated form of ZS-9 is also well tolerated in rats and dogs when administered either once a day or tid at 6-hour intervals over a 12-hour period for up to 28 days.

ZS was administered tid at 6-hour intervals over a 12-hour period, by gavage, to male and female Sprague Dawley rats for 28 consecutive days followed by a 14-day post-dose observation period. In the Main Study ZS was administered as a suspension in 0.5% MC, at a dose volume of 10 ml/kg, to groups of 10 rats/sex/dose at dose levels of 0, 300, 1000, or 2000 mg/kg tid or 2000 mg/kg qd. An additional two groups of 5 rats/sex were dosed concurrently with the Main Study with 0 or 2000 mg/kg tid and then retained off treatment for 14 days to determine recovery. Accuracy of the dose formulations was confirmed using a validated method.

No clinical signs of systemic toxicity were noted although light colored feces were noted in animals receiving total daily doses of 3000 or 6000 mg/kg, and were attributed to the presence of test article. Body weight, body weight change, food consumption, hematology, coagulation, clinical chemistry, ophthalmoscopy and organ weights were all unaffected by treatment with ZS.

Consistent with the expected pharmacological action of ZS, urinary sodium was higher and potassium and chloride, with or without correction for creatinine concentration, were lower in ZS treated animals, compared with controls. These changes were dose-related and more pronounced in males than in females. A full recovery was noted by the end of the 14-day recovery period.

There was no evidence of any macroscopic or microscopic findings that were considered to be related to ZS-treatment.

Based on these results, the NOAEL in male and female rats given oral doses of ZS three times a day for 28 consecutive days was considered to be 2000 mg/kg/dose (6000 mg/kg/day), the highest dose level tested. For ZS administered once a day for 28 consecutive days, the NOAEL was considered to be 2000 mg/kg/day, the highest dose level tested. These dosages correspond to a single HED of 62.4g/day. A 6-month GLP compliant, oral toxicity study with an interim kill at 3 months is being conducted in rats to evaluate the potential subchronic toxicity of ZS.

Forty (40) animals/sex were assigned to each of 4 dose groups that received ZS at dosages of 0 (vehicle), 1000, 3000 or 60000 mg/kg/day. ZS was administered in aqueous 0.5% methyl cellulose (w/v: vehicle) at a dose volume of 10 ml/kg/dose three times a day (tid) at 6-hour intervals over a 12-hour period. Dose formulation accuracy was confirmed using a validated method.

Observations for morbidity and mortality were conducted twice daily, food consumption was measured weekly and detailed clinical observations were conducted once a week. Body weights were measured and recorded once pretreatment, weekly for the first 4 weeks of the study and twice a week thereafter. Ophthalmoscopic examinations were conducted pretreatment and before the scheduled interim necropsy. Blood for clinical pathology evaluations was collected from interim kill animals during Week 4 and from all animals during Week 13. Urine samples for urinalysis and urine chemistry evaluations were collected from all animals during Weeks 12 and 13. At the end of the
interim period (Day 90), necropsy examinations were performed on 10 animals/sex/group.

There were 4 unscheduled deaths during the first 3 months of the study, none of which were considered to be related to ZS treatment. No clinical signs of systemic toxicity were noted. During the treatment period light colored feces were noted in animals dosed at 6000 mg/kg/day and were attributed to the presence of test article. Treatment with ZS had no effect on body weight and body weight change, food consumption, hematology, coagulation or the eye.

ZS-related changes in clinical pathology parameters, when compared with controls, included:

- Lower mean plasma potassium concentration in males receiving 6000 mg/kg/day and females receiving ≥ 3000mg/kg/day and lower urea in females treated with ≥ 3000 mg/kg/day
- Higher mean urinary sodium and chloride concentrations, with and without correction for creatinine, in both sexes at ≥ 1000 mg/kg/day
- Dose-related lower mean urinary potassium concentration, with and without correction for creatinine, in both sexes at ≥ 1000 mg/kg/day
- Lower mean urinary magnesium concentration in females at ≥3000 mg/kg/day and in males at 6000 mg/kg/day.

No macroscopic or microscopic treatment-related findings were noted at any dose level.

Overall Sprague-Dawley rats tolerated the daily oral administration of ZS for 13 weeks at up to 6000 mg/kg, given as three daily doses of 2000 mg/kg approximately 6 hours apart, without any adverse effects. The only findings noted were expected disturbances in electrolyte concentrations due to the pharmacological effect of the compound. Based on these results, the 13-week NOAEL was considered to be 2000 mg/kg/dose (= 6000 mg/kg/day), the highest dosage tested, which is equivalent to a single HED of 62.4g/day.

In the 28-day dog study there were no ZS-related effects on survival, clinical observations, body weights, body weight gain, food consumption, ophthalmology, hematology, fecal occult blood, macroscopic pathology, or organ weights.

ZS had no effect on qualitative ECG parameters such as heart rate, RR or PR intervals or QRS duration. However, a slight increase in the QTc interval, that was not considered clinically meaningful, was observed in females at the1000 mg/kg tid dose when compared to controls and was considered secondary to the ZS-induced hypokalemia in these animals.

Dose-related changes in mean clinical chemistry parameters included decreases in serum potassium, phosphorous, and aldosterone, a mild to moderate increase in mean urine volume with associated decreases in specific gravity and osmolality, a dose-related reduction in the mean fractional excretion of urinary potassium (FE: K) and a slight increase in mean urine pH. There was a tendency for mean serum bicarbonate to be minimally increased in both sexes receiving 1000 mg/kg tid that corresponded to a mild increase in mean serum pH relative to controls. In most treatment groups, there was a
mild to moderate increase in the mean fractional excretion of sodium (FE: Na), relative to control groups but these were not associated with meaningful changes in mean serum sodium. All changes were reversible following a 21-day recovery period. Mild increases in FE: K and fractional excretion of chloride (FE: Cl) were noted in both sexes receiving potassium supplemented ZS (1000 mg/kg + KCl; tid) relative to controls and were considered secondary to KCl supplementation.

The decrease in FE: K with the correlating decrease in serum potassium was attributed to the pharmacological action of ZS which in turn was considered responsible for the decrease in aldosterone production and the increase in urine volume and decreases in urine osmolality and specific gravity. None of these changes were considered toxicologically adverse except in the case of three females at the 1000 mg/kg tid dose where serum potassium was decreased by up to 1.8 mmol/l over the dosing period resulting in hypokalemia. These same animals also had increased alanine aminotransferase (ALT) and aspartate transaminase (AST) values at Weeks 2 and/or 4. One animal had a single small area of hepatocyte loss and subacute inflammation that was unlikely to be responsible for increased serum chemistry values, another had no microscopic changes indicative of hepatocellular injury but had sinusoidal leukocytosis that is of unknown significance and the third animal, which was assigned to the recovery group, had normal ALT/AST and no abnormal microscopic findings after the recovery period. The relationship of these minor microscopic findings to the elevated ALT and AST levels and to ZS is therefore unclear. No elevations in ALT/AST were observed in high dose animals that remained within the normokalemic range or in high dose animals supplemented with potassium suggesting that the elevations may have been a secondary response to the hypokalemia.

ZS-related microscopic findings present in the adrenal glands included increased intracytoplasmic lipid vacuolation in cells of the zona glomerulosa in all groups of ZS-treated animals given daily ZS doses ≥ 900 mg (300, 1000 + KCl, and 1000 mg/kg/dose tid, and 1000 mg/kg qd) and an increased incidence of cystic degeneration in the zona glomerulosa in males and females given 1000 mg/kg tid. These changes were attributed to the decrease in aldosterone production. Kidneys from animals given 1000 mg/kg tid had multifocal areas in the medulla and cortex with a spectrum of tubular and interstitial degenerative and inflammatory changes that included vacuolation/degeneration of tubules or vacuolation/degeneration of tubules with concomitant expansion of the interstitium by inflammatory cells (primarily lymphocytes, macrophages, and/or fibroblasts). Some animals had dilation of tubules with attenuation of tubular epithelium and one hypokalemic female animal in this group also had hemorrhage, hyperplasia of transitional epithelium lining the renal pelvis, and increased neutrophils in addition to the other inflammatory cells in the interstitium. These renal findings are consistent with changes described in the kidneys of animals with prolonged decreased body potassium, and were prevented by potassium chloride supplementation.

Based on these results the NOAEL for ZS alone was 300 mg/kg tid or 1000 mg/kg qd and 1000 mg/kg tid when supplemented with potassium, these dosages correspond to single human equivalent doses of ~10.5g and 35g tid, respectively, and 35g qd assuming a body weight of 65 kg.
A 9-month oral toxicity study in dogs to evaluate the potential subchronic toxicity of ZS is currently in progress. Five groups of experimentally naïve male and female beagle are being dosed at 0 mg/kg/day (10/sex), 300 mg/kg/day (7/sex), 1000 mg/kg/day (7/sex), 2000 mg/kg/day (10/sex) or 2000 mg/kg/day + potassium chloride (KCl) (7/sex) once a day via dietary consumption in Hill’s® Science Diet Gourmet Chicken Entrée dog food. After the first 3 months of administration 3 animals/sex/group were submitted to necropsy for interim evaluations. Observations for morbidity, mortality, injury, and the availability of food and water were conducted on all study animals three times daily. Clinical observations were conducted once weekly. Body weights were measured and recorded on Day -1 and once weekly (on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84). Wet (vehicle) and dry food consumption was measured and recorded daily. Ophthalmoscopic examinations were conducted pretest and prior to the scheduled interim necropsy. A pretest physical examination was performed on each animal. Electrocardiographic examinations were conducted twice pretest and once during Week 13. Blood for clinical pathology evaluations and blood gas analysis was collected from all animals pretest and during Weeks 2, 4 (serum potassium only), 6, and 13. Blood samples for aldosterone analysis were collected from all animals pretest and during Weeks 6 and 13. Urine samples for urinalysis and urine chemistry evaluations were collected pretest and during Weeks 2, 6, and 13. At the end of the interim period (Day 90), necropsy examinations were performed on 3 animals/sex/group, organ weights were recorded, and tissues microscopically examined. Following 13 weeks of dosing, there were no ZS related clinical findings, no effect on survival, and no effects on body weights, food consumption, ophthalmology, hematology, ECG parameters, macroscopic pathology, or organ weights.

Alterations in clinical pathology parameters included minimal and transient increases in tCO2, that correlated with minimal, transient increases in bicarbonate in animals at 2000 mg/kg/day with and without potassium supplementation and minimal decreases in serum potassium and decreased aldosterone in animals receiving 2000 mg/kg/day without KCl. Dose related increases in urine pH were observed in animals receiving ≥ 1000 mg/kg/day with and without potassium supplementation, and minimal increases in urine volume occurred in animals at 2000 mg/kg/day with and without potassium supplementation. The minimal changes in tCO2 that correlated with minimal, transient increases in bicarbonate at the higher dosages may have been due to binding of ammonia by ZS. Pronounced decreases in renal potassium excretion occurred in animals receiving ≥ 300 mg/kg/day, and mild increases in renal sodium excretion occurred in males administered ≥ 1000 mg/kg/day, females at ≥ 300 mg/kg/day, and 2000 + KCl mg/kg/day in both sexes. While these findings were considered related to ZS administration, none were considered to be adverse.

Test article-related microscopic findings were confined to the adrenal glands and kidneys of males given 2000 mg/kg/day and were the same as those seen in the 28-day study at total daily doses of 3g/kg. The findings included mild intracytoplasmic lipid vacuolation in cells of the zona glomerulosa and multifocal areas in the renal medulla and cortex with a spectrum of tubular and interstitial degenerative and inflammatory changes (inflammation, tubulointerstitial). The increased lipid vacuolation in the zona glomerulosa was likely due to altered steroidogenesis (aldosterone biosynthesis) and cholesterol/cholesterol ester accumulation and the microscopic findings in the kidneys.
are consistent with the changes described in the kidneys of animals with prolonged decreased body potassium. Neither of these findings was observed following potassium supplementation.

Based on the results of this interim analysis after 13 consecutive weeks of administration, the NOAEL for ZS alone was 1000 mg/kg/day in male animals, 2000 mg/kg/day in females, and 2000 mg/kg/day in male and female animals when supplemented with potassium. These doses correspond to single human equivalent doses of 35g and 70g, respectively.

ZS-9 tested negative for mutagenicity and clastogenicity when tested in GLP compliant in vitro Ames and chromosomal aberration studies and ZS tested negative for micronuclei formation when administered for 28 consecutive days at a dose of 6g/kg/day.

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8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective is to evaluate the safety and efficacy of three (3) different doses of ZS administered once a day (qd) for 28 days in maintaining normokalemia (S-K between 3.5 – 5.0 mmol/l, inclusive) in subjects with hyperkalemia (2 consecutive i-STAT potassium measurements, measured at a 60-minute interval, both ≥ 5.1 mmol/l) at baseline. All subjects will be treated with 10g ZS, tid for 48 hours (6 doses). Subjects who achieve normokalemia within this initial open label treatment period (AP) will then be randomized 4:4:4:7, in a double blind manner, to one of three (3) doses of ZS (5g, 10g or 15g) or placebo control, to be administered qd for a further 28-days (DBRMP). The AP dose of 10g tid was selected based on efficacy data obtained from the ZS-003 Phase 3 study in which ZS dosages of 5g and 10g tid significantly decreased S-K in subjects with mild to moderate hyperkalemia within 48 hours of treatment in a dose-dependent manner and with significant reductions noted within 1-hour of the first 10g ZS dose. The doses to be tested in the DBRMP (5g, 10g or 15g qd for 28 days) were selected based on results from the Subacute Phase of the ZS-003 Phase 3 study to ensure optimal control of S-K levels throughout the 28-day Maintenance Phase. Based on data from ZS-003, combined with modeling, it is estimated that the two top doses of ZS (10g and 15g qd) will be able to maintain the majority of subjects within the normokalemic range throughout the 28-day period. The 5g qd dose is included to try to establish a minimum effective dose.

8.2 Additional Objectives

The secondary objectives are to evaluate:

1. The proportion of subjects who convert to normokalemia after 48 hours of open-label run-in treatment with 10g ZS three a day (tid)

2. To evaluate the safety and efficacy of ZS in subjects with hyperkalemia for the following pre-defined subgroups:
3. The effect of three (3) different doses of ZS administered qd on kidney function in subjects with hyperkalemia
4. The effect of three (3) different doses of ZS administered qd on serum-Aldosterone (S-Aldo) and plasma-Renin (P-Renin) levels
5. Possible effects on other electrolytes (S-Ca, S-Mg, S-Na, S-Cr, S-PO4, HCO3, BUN)
6. Hospitalization and emergency room (ER) visits
7. Non-protocol specified doctor’s visits
8. Possible effects on plasma BNP (P-BNP), S-Galectin-3, S-Insulin, P-PTH, HbA1c and urinary p-cresol and indole

9  INFORMED CONSENT

The investigator or designee will be responsible for obtaining a signed, written informed consent form (ICF) and providing a copy to each subject, legally authorized guardian, or a person with legal responsibility for the subject’s health care decisions prior to the performance of any clinical activities or procedures pursuant to this protocol. Subjects who are vision impaired may have the ICF read to them and their witnessed consent documented. Only the consent form approved by the IRB will be used. If English is NOT the subject’s primary language, the subject will be consented using an IRB-approved informed consent form in the requisite language. This consent will be conducted by a member of the research team who is fluent in the language and thus able to answer any scientific or procedural questions raised by a non-English speaking subject.

10  STUDY POPULATION

10.1 Inclusion Criteria
1. Provision of written informed consent.
2. Over 18 years of age.
3. Two consecutive i-STAT potassium values, measured 60-minutes apart, both ≥5.1 mmol/l and measured within 1 day of the first ZS dose on AP Study Day 1.
4. Ability to have repeated blood draws or effective venous catheterization.
5. Women of childbearing potential must be using two forms of medically acceptable contraception (at least one barrier method) and have a negative pregnancy test at AP Study Day 1.
Women who are surgically sterile or those who are post-menopausal for at least 2 years are not considered to be of child bearing potential.

Note: Diabetic Subjects can be enrolled. Whenever possible, all blood draws collected before meals should be collected prior to insulin/insulin analog treatment.

10.2 Exclusion Criteria

1. Pseudohyperkalemia signs and symptoms, such as excessive fist clinching, hemolyzed blood specimen, history of severe leukocytosis or thrombocytosis.

2. Subjects treated with lactulose, Xifaxan or other non-absorbed antibiotics for hyperammonemia within 7 days prior to first dose of IP.

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

4. Subjects with a life expectancy of less than 3 months.

5. Subjects who are severely physically or mentally incapacitated and who in the opinion of investigator are unable to perform the subjects’ tasks associated with the protocol.

6. Women who are pregnant, lactating, or planning to become pregnant.

7. Subjects with diabetic ketoacidosis.

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

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

10. Randomization into the previous ZS-002 or ZS-003 studies.

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

12. Subjects with cardiac arrhythmias that require immediate treatment.

13. Subjects on dialysis.

Note: Subjects who do meet the criteria for entering the AP may be rescreened two (2) more times during the study.

10.3 Design

This is a Phase 3 multicenter, prospective, randomized, placebo-controlled, double-blind, dose ranging maintenance study to investigate the safety and efficacy of ZS, an oral sorbent, in subjects with hyperkalemia.

The study will be conducted on an outpatient basis at up to 75 global sites.

Approximately 275 subjects with hyperkalemia (i-STAT potassium value ≥ 5.1 mmol/l) will be enrolled in the Open-label Acute Phase (AP) to provide 232 subjects in the Double blind Randomized Maintenance Phase (DBRMP). Enrollment into the AP will
stop once 232 subjects have entered into the DBRM. Initially all subjects will be treated with 10g ZS, three times a day (tid) for 48 hours (6 doses). Subjects who achieve normokalemia within this initial open label treatment phase will then be randomized 4:4:4:7, in a double blind manner, to one of 3 doses of ZS (5g, 10g or 15g) or placebo control, to be administered qd for a further 28 days. DBRMP subjects who complete the DBRMP Study Day 29 visit or who discontinue due to hypo- or hyperkalemia may, depending on drug availability, be offered participation in a 2-month open label extension study (ZS-004E) designed to evaluate the longer term safety and efficacy of ZS in maintaining normokalemia.

Safety stopping rules are specified for this study and will be administered by the ZS Pharma Medical Monitor and an independent Data Monitoring Committee (iDMC).

**Table 1 Dose Group Summary**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Regimen</th>
<th>ZS 5g</th>
<th>ZS 10g</th>
<th>ZS 15g</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>tid</td>
<td>–</td>
<td>~275</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DBRMP*</td>
<td>qd</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>85</td>
</tr>
</tbody>
</table>

* Assuming all subjects that enter the Acute Phase are randomized into the Maintenance Phase

All potassium values will be measured by both i-STAT and by the Central Laboratory on all occasions throughout both phases of the study. Treatment decisions will be based on the potassium i-STAT values as these provide clinical sites with a real-time measurement.

Baseline potassium levels will be recorded fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection), two (2) times at 0 and 60 minutes (±10 min) within 1 day of administration of any study drug. If both i-STAT measurements are ≥ 5.1 mmol/l, the subject will be enrolled in the AP. Women of childbearing potential will have a urine HCG test prior to enrollment.

If either screening i-STAT potassium value is < 5.1 mmol/l at baseline, the subject will not be randomized to study treatment but declared a screen failure, removed from being considered for study participation, and returned to the standard of care. Such subjects may be rescreened up to two (2) more times during study. Subjects re-screened within 30 days of initial screening will not need to sign new ICF providing there have been no changes to the ICF. It should be noted that based on data collected from subjects enrolled in ZS-003, an i-STAT blood potassium value is on average 0.15 mmol/l lower than the corresponding S-K value.

During the AP all randomized subjects will take study drug 3 times a day for two (2) days for a total of 6 doses. Subjects who attain normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/l, inclusive) after 48 hours of treatment will be randomized into the DBRMP. Any subject whose i-STAT potassium level is not within the normal range (i-STAT potassium between 3.5 to 5.0 mmol/l, inclusive) by the morning of AP Study Day 3 will be exited from the study and will NOT progress into the DBRMP. These subjects
will discontinue from the study, and receive standard of care treatment at the discretion and the direction of their own physician but will return to the clinic for an End of Study (EOS) visit 7 ± 1 day later on AP Study Day 9.

During the AP the first daily dose will be administered at the clinic and the second and third doses will be taken at home just before lunch and the evening meal, respectively. Potassium will be measured fasting, nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to collection, two (2) times at 0 and 60 minutes (±10 min) for establishment of a baseline, at 1, 2 and 4 hours (±15 min) post the 1st dose on AP Study Day 1, before (0h) and 1 hour (±15 min) after the first daily dose on AP Study Day 2.

Subjects who are normokalemic (i-STAT potassium values 3.5 - 5.0 mmol/l, inclusive) on the morning of AP Study Day 3 will be randomized into the DBRMP (qd dosing). Subjects will take the first dose of the DBRMP study drug in the clinic (DBRMP Study Day 1) and thereafter will take the study drug at home, in the morning just before breakfast, except on days with scheduled clinic visits, when study drug will be taken in the clinic. Subjects will return to the clinic on DBRMP Study Days 2, 5, 8, 12, 15, 19, 22, 26, 29 and 35 (EOS), fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to collection of blood potassium sample) for a measurement of their blood potassium. All study subjects who do not enter the extension study will be followed for a total of 7 (±1) days after the last study treatment administration (AP Study Day 9 for subjects NOT enrolled in the DBRMP, and DBRMP Study Day 35 for subjects enrolled in the DBRMP). Breakfast will be provided by the clinic on AP Study Days 1 and 2, and on DBRMP Study Day 1.

If a subject develops an i-STAT potassium value <3.0 mmol/l at any time during the study or >6.2 mmol/l during the DBRMP, and/or a clinically significant cardiac arrhythmia at any time, the subject will immediately receive appropriate medical treatment and care in accordance with the clinic standard procedures for any necessary emergency treatment and study drug will be discontinued. The study Principal Investigator (PI) will be notified and will in turn notify ZS Pharma, Inc. within 24 hours of becoming aware of the event. If a subject develops i-STAT potassium values between 3.0 mmol/l and 3.4 mmol/l, inclusive, during the DBRMP, IP administration will be reduced from qd to every second day for the remainder of the study.

**North American Sites Only:**
- S-Insulin, HbA1c, S-Aldo, P-BNP, P-PTH, P-Renin, urine chemistry (including Urinary sodium [U-N], potassium [U-K], creatinine [U-Cr], albumin and protein will be measured on AP Study Day 1 (baseline, within 24 hours of administration of study drug) and on DBRMP Study Day 29. S-Aldo and P-Renin samples must be collected prior to 10am (1000) after the subject has been upright for at least 2 hours and prior to any ECG/Physical Exam (PE) assessments). Additionally whole blood and urine for Zr determination will be collected at selected sites only on AP Study Day 1 (Baseline) and on DBRMP Study Days 15 and 29.

All subjects who are withdrawn from the study prior to study completion will return to the clinic 7 (±1) days after the last IP administration for an EOS visit. However, subjects in the DBRMP who discontinue due to hypo- or hyperkalemia may participate in the
open-label ZS-004 extension study. Such subjects will start dosing in ZS-004E study within 2 days of the last administration of IP in the DBRMP and the EOS visit will not occur until 7 ± 1 days after the last IP administration in the ZS-004E study.

All analyses will be based on the S-K values generated by the Central Laboratory. If Central Laboratory data are missing, they will be replaced by i-STAT values adjusted to reflect the mean difference between i-STAT and S-K values from all available paired lab samples.

For in-clinic evaluation purposes, normokalemic control will be defined as i-STAT between 3.5 – 5.0 mmol/l, inclusive.

Time to the first episode of hyperkalemia will be defined as S-K >5.0 mmol/l.

Kidney function over time will be evaluated by assessments of S-Cr, estimated glomerular filtration rate (eGFR; MDRD equation), urinary protein:creatinine ratio [UPCR] and urinary albumin:creatinine ratio [UACR]. Liver function will be evaluated by assessments of bilirubin, AST and ALT levels over time. Possible effects on bone metabolism (P-PTH, S-Ca, S-PO4) and glucose metabolism (S-Insulin and HbA1c) over time will also be evaluated.

S-Aldo and P-renin will also be evaluated to assess the possible impact of ZS on the RAAS system.

Safety endpoints will include incidence of hospitalization and ER visits, incidence of non-protocol required Doctor’s visits, incidence, timing, severity, relationship, and resolution of all treatment-emergent adverse events, vital signs, and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, urinalysis parameters and health utilization data.

**10.3.1 Stopping Rules**

If a subject develops excessive hypokalemia (i-STAT potassium values <3.0 mmol/l) at any time during the study or >6.2 mmol/l during the DBRMP, or a clinically significant cardiac arrhythmia (see below) at any time in the DBRMP, the subject should immediately receive appropriate medical treatment and be discontinued from study drug.

Any of the following cardiac events will result in immediate discontinuation from the study (independent of whether it is in the AP or DBRMP):

- Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])

- Acute congestive heart failure

- Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block), widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block) or peaked T-wave or an increase in QTc interval > 25msec to more than 500msec or > 25msec in somebody with a baseline QTc of >500msec
Any subject who is withdrawn from the study prior to study completion will return to the clinic 7 (± 1) days after the last IP administration for an EOS visit.

10.3.2 Dose Adjustment

If a subject develops i-STAT potassium values between 3.0 mmol/l and 3.4 mmol/l, inclusive, dosing during the DBRMP will be reduced from qd to every other day for the remainder of the study. All i-STAT potassium measurements meeting dose adjustment criteria will be confirmed by taking a second potassium measurement after a 10 ± 2-minute interval. The dose should be adjusted only if both i-STAT values meet the dose adjustment criteria.

10.4 Recordkeeping and Monitoring

All subject data will be reported in the electronic data capture (EDC) with the exception of the Central Laboratory reports, which will be uploaded by electronic transfer by the Central Laboratory. All EDC data should be filled out in a timely manner. All original source documents should be available for periodic monitoring and/or retrieval by a Sponsor representative designee. The investigator is responsible for the accuracy of all data entered in the eCRFs and for the timely completion of the eCRFs. The supporting documentation will be maintained at the site for a minimum of either:

1. Two (2) years following the approval of the study drug for this indication by the FDA

Or

2. Two (2) years following notification by ZS Pharma, Inc. to the FDA of the termination of the entire investigation.

The Sponsor must be contacted and give written authorization prior to any study records being destroyed at investigative sites.

This study will be conducted in compliance with Good Clinical Practice (GCP), which includes the Sponsor and Independent Review board (IRB)/Independent Ethics Committee (IEC) approved protocol and Informed Consent Form (ICF) and the FDA and ICH regulatory guidelines and requirements. No changes will be made without prior approval unless it is imperative for subject’s safety. Any such departures from the protocol will be reported immediately to the Sponsor and relevant IRB/IEC.

All subject’s medical records and study-related documents will be made available to the Sponsor for regular monitoring and audits as well as to the IRB/IEC and FDA or other governmental agency with oversight or compliance responsibilities for assuring subject rights and welfare.

10.5 Investigational Supplies

10.5.1 Study Drug Description

The active investigational product is microporous, fractionated, protonated zirconium silicate (ZS) with a particle size ≥3 μm, a free flowing, odorless, tasteless white crystalline powder.
The placebo is silicified microcrystalline cellulose, NF, a white powder with same appearance, taste, odor and mode of administration as ZS.

Note: Henceforth, active investigational product (ZS) and placebo will be referred to as “investigational product” (IP).

10.5.2 Packaging

The IP will be packaged and labeled in sachets at Sharp Clinical Packaging.

Each individual dose will consist of 2 sachets in the AP and 3 sachets in the DBRMP and will be packaged in single use boxes.

**AP:**

The IP will be packaged in kits containing six (6) individual boxes (1 box/dose). Each box will contain 10g ZS (2 sachets of 5g each/box). Each kit (and all boxes and all sachets within that kit) will have the same unique code. Kits will be assigned through an Interactive Voice/Web Response System (IVRS/IWRS).

**DBRMP:**

The IP will be packaged in weekly kits consisting of 8 boxes (3 sachets/box)/kit. Each kit (and all boxes and sachets within that kit) will have the same unique code. Kits will be assigned on a weekly basis through IVRS/IWRS. Each kit contains one (1) extra dose as a contingency.

Following receipt of Form FDA 1572 and Institutional Review Board (IRB)/IEC approval for a given site, IP will be sent to the study site. Initial shipments will consist of at least one Open-label kit and several double blind Maintenance Phase kits. The actual number supplied will depend on the expected enrollment. Sites will also be sent standardized dosing vessels equipped with lids, that can be sent home with the subjects.

10.5.3 Investigational Product (IP) Dispensing

During the AP all subjects will receive three (3) daily doses of 10 g ZS for a maximum of 6 doses. The individual kit will be assigned through IVRS/IWRS. For subjects with i-STAT potassium values within the normokalemic range (3.5 to 5.0 mmol/l, inclusive) on the morning of AP Study Day 3, the site will contact IVRS/IWRS to determine which on-site kit to use for the DBRMP. Thereafter DBRMP kits will be assigned weekly through IVRS/IWRS and be dispensed by designated and trained site pharmacy staff. Once a kit has been assigned to a subject, the pharmacist/designee will enter the dose/kit number on the IP dispensing log and relevant source documents. The subject identification number (SID) will serve as the subject’s randomization number throughout the study.

10.5.4 Dosage Preparation and Administration

For doses administered in the clinic each dose will be individually dispensed by designated, trained site staff. The site staff will empty either two (AP) or three (DBRMP) sachets from 1 box from the assigned kit into a ZS-supplied standardized dosing vessel, fill the vessel with water up to the calibration line (~180 ml), cap the dosing vessel and shake for at least 30 seconds to form a slurry/suspension immediately prior to administration. The dosing vessel will then be sequentially rinsed twice (2 x ~30 ml water) and each rinse will also be consumed by the subject. Clinic staff will use the
in-clinic dose preparation procedure to instruct the subject on how to make up the dose at home.

10.5.5 Storage Requirements

The IP should be stored under Controlled Room Temperature Conditions (CRT defined as 20 – 25°C/68 - 77°F with excursions of less than 24 consecutive hours permitted between 15 – 30 °C/59° to 86° F).

10.5.6 Investigational Product Accountability

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

The Investigator or designee is also responsible for maintaining accurate records accounting for the receipt, dispensing and final disposition of all investigational products using the appropriate IP logs provided by ZS Pharma, Inc.

10.5.7 Retrieval and Destruction

Periodically throughout the study sites will perform IP reconciliation on a per subject basis. The ZS site monitor will review the log and once any discrepancies have been resolved, authorize destruction/disposition of the supplies associated with a given subject by signing the reconciliation log and will witness the destruction/disposition.

10.6 Randomization and Blinding

Each subject will be assigned a SID by the site after the subject provides written informed consent.

The SID will consist of a seven (7) digit number:

- The first four (4) digits will designate the site number as assigned by ZS Pharma, Inc.
- The last three (3) digits will designate the order of the subject at that site

The first subject who signs the ICF at the site is assigned the subject number 001, the second subject who signs the ICF is assigned 002, the third is assigned 003, etc.

Example:

For the first subject who signs consent at Site 4075 the SID will be 4075-001, the second who signs consent is 4075-002, the third 4075-003 etc.

The subject will maintain the same SID number throughout the entire study except if the subject fails the first screening. If a subject signs the ICF but does not meet the inclusion/exclusion criteria the subject will be marked as a screen fail on the Screening and Enrollment Log provided by the Sponsor and will be entered in EDC as a screen failure. The subject can be re-screened up to two (2) additional times during the clinical trial period. However, if this occurs the site will assign the subject a new SID at each
subsequent screening. If the ICF has been signed within 30 days and there are no new revisions, a new ICF is not necessary.

If the subject qualifies for the AP after screening, the site staff will access the IVRS/IWRS and the system will assign the subject an open label treatment kit that will be used for AP Study Days 1 and 2. All subjects will receive open-label ZS (10g tid) for a total of six (6) doses.

On the morning of AP Study Day 3, the subject’s i-STAT potassium will be assessed. If the i-STAT potassium is < 3.5 mmol/l or >5.0 mmol/l, the subject will discontinue the study, and this will be recorded in the IVRS/IWRS. For subjects who are normokalemic (i-STAT potassium between 3.5 mmol/l to 5.0 mmol/l, inclusive) on the morning of the AP Study Day 3, the site will contact IVRS/IWRS to obtain the DBRMP kit assignment (Week 1). A new kit number will be assigned weekly during the DBRMP via the IVRS/IWRS.

The assignment of unique numeric codes to active product or placebo will be securely retained until such time as designated by the Statistical Analysis Plan (Section 12).

On each dosing day, the investigator/designee will confirm the matching of the investigational product assignment to the subject identification number. The IP assignment should be confirmed and documented by a second party prior to administering. Each kit (both AP and DBRMP) will contain a 2-part label, one of which will be affixed to the appropriate source document and retained in the site study file.

10.7 Study Visits

10.7.1 General Information

- All treatment is on an outpatient basis
- All recorded clock times should utilize a 24-hour clock
- Unless stated otherwise samples should be collected within ±15 minutes of the scheduled time in the AP
- All baseline parameters may be collected up to 1 day prior to the first administration of study drug on AP Study Day 1
- End of study visits occur 7 ± 1 day after the last administration of study drug except for subjects in the DBRMP who continue into the open-label extension study ZS-004E
- For all study visits subjects must arrive at the clinic in the morning fasting, as defined by nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection
- All S-Aldo and P-renin samples must be collected prior to 10am (1000) after at the subject has been upright for at least 2 hours and before the ECG and/or the physical exam (PE)
- All measurements involving determination of blood potassium will be performed by both i-STAT and the Central Laboratory on all occasions
For diabetic subjects all blood potassium samples should be collected prior to insulin administration whenever possible

Whole blood and urine samples for Zr analysis will only be collected at designated sites in the USA

Serum Galectin-3, P-BNP, S-Insulin, P-PTH, HbA1c, and urine chemistry including p-cresol and indole will be measured at sites in North America ONLY

For the AP, the in-clinic breakfast should be given after collection of the 1-hour post Dose 1 potassium sample

During the period a subject is treated with IP, the site must access the IVRS/IWRS:

- On AP Study Day 1 prior to the first dose of the AP to obtain the subject’s AP kit number.
- On AP Study Day 3 to record that the subject will not advance to the DBRMP or prior to first dose of the DBRMP to obtain the subject’s DBRMP kit number.
- Every 7 days during the DBRMP to obtain the subject’s DBRMP weekly kit number. The subject will be assigned the same IP treatment throughout the DBRMP although the IP kit numbers will vary.
- If the subject withdraws from the study any time during the dosing period.

The following procedures will take place on the days indicated in the events schedule (Section 5) with the following exceptions:

1. Baseline AP measurements/procedures including the two (2) consecutive baseline potassium measurements may be performed within 1 day of the initial administration of study drug on AP Study Day 1

2. If a scheduled clinic visit falls on a weekend or National holiday during the DBRMP, the scheduled visit may take place either 1 day early or 1 day late (i.e. within ± 24 hours of the scheduled day) for DBRMP Study Days 5, 8, 12, 15, 19, 22, 26 and 35 and up to 2 days late for DBRMP Study Day 2 or 2 days early for DBRMP Day 29. If the Day 29 visit is conducted early, the subject must take IP through Day 28 per protocol. The IP will be taken after all of the Day 29 procedures have been conducted. The number of doses to be sent home with a subject at each visit may need to be increased or decreased as appropriate to avoid national holiday or weekend visits.

DBRMP Study Day 1 must take place on the day the subject achieves normokalemia after 48 hours of tid treatment. All subjects will continue on whatever concomitant treatments they were on upon admission into the study. Subjects will be identified at the clinic during routine or acute visits, when potassium levels ≥ 5.1 mmol/l are detected. The initial visit will take place once the potential subject has been diagnosed with potassium levels ≥ 5.1 mmol/l and after the subject has provided written informed consent. It should be noted that based on data collected in Clinical Study ZS-003, an i-STAT blood potassium value is on average 0.15mmol/l lower than the S-K value.
In accordance with the clinical site SOPs, an intravenous catheter or a butterfly needle (of a sufficient gauge to avoid sample hemolysis) may be inserted for the purpose of collection of blood samples. The venous access lock solution MUST NOT contain potassium. Alternatively, the site preference may be to use direct venipuncture for the purpose of collection of blood samples. Either method is acceptable.

If any subject is withdrawn from the study prior to study completion, the subject will return to the clinic 7 (± 1) days after the last IP administration for an EOS visit.

There are no dietary restrictions in this study. Subjects should continue to eat their normal diet. Breakfast is administered in the clinic on AP Study Day 1 after collection of the 1 h post Dose 1 potassium blood sample and on DBRMP Study Day 1.

10.7.2 AP Study Day 1

Subjects will arrive in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). Then, the following baseline parameters will be collected:

1. All eligibility criteria will be assessed

Two (2) consecutive potassium samples, determined by both i-STAT and the Central Laboratory, will be measured at 0 and 60 minutes (± 10 min)

If either i-STAT potassium value is <5.1 mmol/l the subject will be declared a screen failure, exited from the study and all blood samples discarded. Subjects whose i-STAT potassium values do not meet the inclusion criteria may be re-screened two more times during the trial. If the ICF has been signed within 30 days and there are no new revisions, a new ICF is not necessary. If a subject is re-screened, the subject will be given a new screening number in the eCRF system and source documents.

If both i-STAT values are ≥5.1 mmol/l the following samples will be collected:

- Two (2) Whole Blood samples for Zr determination (2 x 3 ml collected into K2EDTA) – designated USA sites only
- S-Aldo and P-Renin collected prior to 10am (1000) after subject has been in an upright position for at least 2 hours and before recording the ECG and Physical exam (PE) (Appendix 1) – All North American Sites only
- Blood samples for measurement of, S-Galectin-3, S-Insulin, P-PTH, P-BNP,HbA1c. All North American Sites only
- A blood sample for standard assessment of hematology (Appendix 1)
- Urine for
  - Standard assessment of urinalysis parameters including sediment and culture (Appendix 1; 10 ml for urinalysis and 10 ml for urine culture)
  - Assessment of urinary creatinine (U-CR), urinary albumin (U-Alb), urinary protein (U-Prot), urinary sodium (U-Na) and urinary potassium (U-K); 15 ml – All North American Sites only
  - A pregnancy test if the subject is a woman of childbearing potential
  - Zr determination (U-Zr; 2 x 3 ml) – designated USA sites only
3. An ECG will be performed (Section 10.9.1)

4. A full physical including weight and vital signs, to be performed by the PI/sub PI or designee whose license permits the performing of physical examinations

5. Medical history, demographics and concomitant medication information will be collected

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

6. Subjects who meet all inclusion/exclusion criteria will be enrolled into the trial and the following procedures will take place:

   - The site will access the IVRS/IWRS and provide the 7-digit Subject ID number, initials and date of birth. The system will assign the subject an Acute Phase IP kit
   - The first doses of study IP will be administered as a slurry/suspension in water. The subject will be shown/instructed on how to mix and administer the IP
   - 1 hour (± 15 min) after dose administration a blood potassium sample (i-STAT and Central Laboratory) will be collected followed by a light breakfast
   - Two additional blood potassium samples (i-STAT and Central Laboratory) will then be taken at 2 and 4 hours (±15 min) after dose administration.
   - Subjects with i-STAT potassium levels < 6.1 mmol/l at the 4 hour (± 15 minutes) post Dose 1 blood draw will be sent home before lunch with two (2) doses of study drug, and instructions on how to take the IP just before eating lunch and dinner. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate lunch and dinner
   - Subjects with i-STAT potassium levels ≥ 6.1 mmol/l at the 4 hour post Dose 1 blood draw will stay in the clinic and take the second dose of study drug ~ 4-hours after the first dose. They will then remain in the clinic an extra 90 minutes after taking the second dose when another blood sample for potassium determination (i-STAT and Central Laboratory will be collected and an ECG will be recorded).
   - If i-STAT potassium levels are > 6.2 mmol/l as determined by the i-STAT at the 90-minute post Dose 2 blood draw, the subject will be discontinued from the study and standard of care will be instituted. Subjects will return to the clinic 7 (±1) days later for an EOS visit.
   - If i-STAT potassium levels are ≤6.2 mmol/l as determined by i-STAT, and the ECG does not show any of the ECG withdrawal criteria, the subject
will be sent home with the 3rd dose of study drug and the dosing card and return to the clinic in the morning of AP Study Day 2.

10.7.3 AP Study Day 2

1. Subjects will arrive at the clinic in the morning (fasting, nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used boxes and sachets and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the IP dosing boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. Potassium levels will be evaluated by i-STAT and the Central Laboratory.

4. Following completion of the above procedures, the first daily dose of IP will be administered in the clinic as a slurry/suspension in water followed by a light breakfast ~1 hour later, at home, after the 1 hour post Dose 1 blood draw.

5. Subjects will then be sent home with two (2) doses of study drug and instructions on how to take the IP just before eating lunch and dinner. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate lunch and dinner.

6. Subjects will return to the clinic the following morning and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.4 AP Study Day 3

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used boxes and sachets and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the IP dosing boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. Potassium levels will be evaluated by i-STAT and the Central Laboratory.

- If the i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/l, inclusive) the subject will be randomized into the DBRMP and complete the procedures detailed in Section 10.7.5).

- If the i-STAT potassium value is > 5.0 mmol/l the following samples will be collected:
  - Blood samples for the standard assessment of clinical chemistry (Appendix 1)
- A blood sample for standard assessment of hematology (Appendix 1)
- Urine for
  - Standard assessment of urinalysis parameters including sediment (Appendix 1; 10 ml)
- An ECG will be performed (Section 10.9.1)
- A full physical including weight and VS, to be performed by the PI/sub PI or designee whose license permits the performing of physical examinations
- The site will access the IVRS/IWRS and provide the 7-digit Subject ID number, and withdraw the subject from the AP
- Subjects will then DISCONTINUE from the study, and receive standard of care at the discretion and the direction of his/her own physician. However, the subject will need to return to the clinic in the morning, fasting, nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection, 7 (± 1) days later for an EOS visit.

10.7.5 DBRMP Study Day 1

Note: This is the same day as AP-Study Day 3.

Following completion of the above AP activities the following procedures will occur for subjects entering the DBRMP.

1. The following procedures/samples will be performed/collected prior to any IP administration
   - Blood samples for standard assessment of hematology and clinical chemistry including S-K (Appendix 1)
   - Urine for
     - Standard assessment of urinalysis parameters including sediment (Appendix 1; 10 ml)

2. An ECG will be performed (Section 10.9.1).

3. A full physical including weight and VS, to be performed by the PI/sub PI or designee whose license permits the performing of physical examinations.

4. The site will access the IVRS/IWRS and provide the 7-digit Subject ID number and randomize the subject. The system will assign the subject a DBRMP IP kit (Week 1) containing a 7-day supply of IP.

5. Following completion of the above procedures, the first qd dose of IP will be administered in the clinic as a slurry/suspension in water and the subjects sent home. If the DBRMP Study Day 2 visit falls on a national holiday or weekend the subject should be informed when next to return to the clinic and will be sent home with the 1 or 2 doses to cover the period until the next scheduled visit.
They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day and to bring the used IP boxes and sachets and dosing schedule card with them when they return to the clinic.

10.7.6 DBRMP Study Day 2

Note: If the scheduled DBRMP Study Day 2 clinic visit falls on a weekend or National holiday the DBRMP Study Day 2 visit may occur up to 2 days late (DBRMP Study Day 3 or 4).

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection).

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. A blood potassium samples (i-STAT and Central Laboratory) will be collected.

4. IP will be administered in the clinic as a slurry/suspension in water and the subject sent home with 5 IP boxes and instructed to take the IP just before breakfast for the next 5 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

5. Subjects will return to the clinic, in the morning, six (6) days later (DBRMP Study Day 8) and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.7 DBRMP Study Day 5

1. Subjects will arrive at the clinic, in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. Blood potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.

4. Following collection of the above samples study IP will be administered in the clinic as a slurry/suspension in water and subjects sent home with 2 IP boxes and instructed to take the IP just before breakfast the next day. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast.

5. Subjects will return to the clinic, in the morning, three (3) days later (DBRMP Study Day 8) and bring the used IP boxes and sachets and dosing schedule card with them.
10.7.8 DBRMP Study Day 8

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. Prior to IP administration blood potassium samples (i-STAT and Central Laboratory) will be collected and an ECG will be performed (Section 10.9.1).

4. The site will access the IVRS/IWRS and provide the 7-digit Subject ID number. The system will assign the subject a new DBRMP IP kit (Week 2) containing an additional 7-day supply of IP.

5. IP will be administered in the clinic as a slurry/suspension in water and the subject sent home with 3 IP boxes and instructed to take the IP just before breakfast for the next 3 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

6. Subjects will return to the clinic, in the morning, four (4) days later (DBRMP Study Day 12) and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.9 DBRMP Study Day 12

6. Subjects will arrive at the clinic, in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

7. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

8. Blood potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.

9. Following collection of the above samples study IP will be administered in the clinic as a slurry/suspension in water and subjects sent home with 2 IP boxes and instructed to take the IP just before breakfast for the next 2 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

10. Subjects will return to the clinic, in the morning, three (3) days later (DBRMP Study Day 15) and bring the used IP boxes and sachets and dosing schedule card with them.
10.7.10 DBRMP Study Day 15

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the empty IP boxes and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. The following tests will be performed before any IP administration
   - i-STAT and Central Laboratory blood potassium assessment
   - Blood for a standard assessment of hematology parameters (Appendix 1)
   - WHOLE blood for Zr determination (2 x 3 ml collected into K2EDTA tubes) – designated North American sites only
   - Urine for:
     - Zr determination (2 x 3 ml) – designated USA sites only
     - Urinalysis parameters including sediment (Appendix 1; 10 ml)

1. An ECG (Section 10.9.1) and full physical exam including weight and VS will be performed.

2. The site will access the IVRS/IWRS and provide the 7-digit Subject ID number. The system will assign the subject a new DBRMP IP kit for use in Week 3 containing an additional 7-day supply of IP.

3. Following completion of the above procedures IP will be administered in the clinic as a slurry/suspension in water and the subjects sent home with three (3) IP boxes and instructed to take the IP just before breakfast for the next three (3) days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.
   a. Subjects will return to the clinic, in the morning, four (4) days later (DBRMP Study Day 19 and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.11 DBRMP Study Day 19

1) Subjects will arrive at the clinic, in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

2) The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
3) Blood potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.

4) Following collection of the above blood samples study IP will be administered in the clinic as a slurry/suspension in water and the subject sent home with 2 IP boxes and instructed to take the IP just before breakfast for the next 2 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

5) Subjects will return to the clinic, in the morning, three (3) days later (DBRMP Study Day 22) and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.12 DBRMP Study Day 22

1) Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

2) The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3) Blood samples for measurement of potassium (i-STAT and Central Laboratory) will be collected.

4) An ECG (Section 10.9.1) will be performed.

5) The system will assign the subject a new DBRMP IP kit (Week 4) containing an additional 7-day supply of IP.

6) Following collection of the above samples study IP will be administered in the clinic as a slurry/suspension in water and the subject sent home with 3 IP boxes and instructed to take the IP just before breakfast for the next 3 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

Subjects will return to the clinic, in the morning, four (4) days later (DBRMP Study Day 26) and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.13 DBRMP Study Day 26

1. Subjects will arrive at the clinic, in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the empty IP boxes and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit,
examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. Blood samples for measurement of potassium (i-STAT and Central Laboratory), will be collected.

4. After collection of the above samples study IP will be administered in the clinic as a slurry/suspension in water and the subject sent home with 2 IP boxes and instructed to take the IP just before breakfast for the next 2 days. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day.

5. Subjects will return to the clinic, in the morning, three (3) days later (DBRMP Study Day 29), fasting, nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection and bring the used IP boxes and sachets and dosing schedule card with them.

10.7.14 DBRMP Study Day 29

Note: If the Day 29 visit is conducted early, the subject must take IP through DBRMP Study Day 28 per protocol. In this instance IP will be administered after all of the Day 29 procedures have been conducted.

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection). They will bring the used IP boxes and sachets and completed dosing schedule card with them.

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, note if the subject has visited a doctor or ER since the last visit, examine the returned IP boxes and sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.

3. The following tests will be performed
   - i-STAT blood potassium assessment
   - Blood samples for a standard assessment of clinical chemistry including, S-K
   - Blood samples for determination of S-Aldo and P-Renin collected prior to 10 am (1000) after subject has been in an upright position for at least 2 hours and prior to recording the ECG (Appendix 1) – North American Sites ONLY
   - Blood samples for measurement of S-Galectin-3, S-Insulin, HbA1c, P-PTH, P-BNP, North American sites ONLY
   - Blood for a standard assessment of hematology parameters (Appendix 1)
   - WHOLE blood for Zr determination (2 x 3 ml collected into K2EDTA tubes) – designated USA sites only
   - Urine for:
- Determination of U-Na, U-K, U-Cr, U-Alb and U-Prot (10 ml) – North American sites ONLY
- Urinalysis parameters including sediment (Appendix 1; 10 ml)
- Zr determination (2 x 3 ml) – designated USA sites only
- p-Cresol (3 ml) and Indole (2 x 4 ml well mixed urine) – North American sites ONLY
- Urine culture if the subject is continuing into the open label extension study
- A pregnancy test if the subject is a woman of childbearing potential who is continuing into the open label extension study

4. An ECG (Section 10.9.1) and full physical exam including weight and VS will be performed

5. Subjects who do not enter the open-label extension study will be instructed to return to the clinic, in the morning, 7 ±1 days following the last study IP administration (DBRMP Study Day 35) for an EOS visit.

10.7.15 End of Study Visit
(AP Study Day 9; DBRMP Study Day 35 or 7 ±1 days following the last study IP administration for subjects who are withdrawn from the study and do not enter the open-label ZS-004E extension study)

1. Subjects will arrive at the clinic in the morning, fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for at least 8 hours prior to potassium sample collection).

2. The clinic staff will solicit any AEs, note any changes in concomitant medications, and if the subject has visited a doctor or ER since the last visit on the eCRF and source documents.

3. The following tests/procedures will be performed:
   - i-STAT blood potassium assessment
   - Blood samples for a standard assessment of clinical chemistry including, S-K
   - Blood for a standard assessment of hematology parameters (Appendix 1)
   - Urine for:
     - Standard urinalysis parameters including sediment and culture (Appendix 1; 10 ml for urinalysis and 10 ml for culture)
     - A pregnancy test if the subject is a woman of childbearing potential

4. An ECG (Section 10.9.1) and full physical exam including weight and VS

Note: If the EOS for the AP or DBRMP falls on a weekend, the EOS visit can be performed either on the preceding Friday or the following Monday.
10.8 Clinical Laboratory Evaluations

10.8.1 Blood chemistry and hematology

Details of the parameters to be evaluated are presented in Appendix 1. Detailed instructions on sample collection and processing are provided in the Central laboratory Manual and collection times are summarized in Table 2, and the Events Schedule (Section 5 and Section 10.7).

Blood potassium will be analyzed while the subject is fasting, by i-STAT as well as by the Central Laboratory on all occasions. All serum samples should be examined and any hemolyzed samples MUST be redrawn.

Blood potassium (i-STAT and Central Laboratory) only will be measured fasting, in the morning before (0h), 1, 2 and 4 hours (±15 min) post the first daily dose on AP Study Day 1, before (0h) and 1 hour post the first daily dose on AP Study Day 2 and before (0h) the first daily dose on DBRMP Study Days 1, 2, 5, 8, 12, 19, 22 and 26.

Blood chemistry and hematology parameters will be evaluated fasting, by the Central Laboratory, on AP Study Days 1, 3 and 9 (EOS visit) for subjects NOT entering the DBRMP and on DBRMP Study Days 1, 15, 29 and 35 (EOS).

- Clinical chemistry and S-K samples will be collected into Serum Separator Tubes (SST)
- i-STAT samples will be collected into “green top” lithium heparin tubes
- S-K will be evaluated as part of the clinical chemistry sample on AP Study Day 1 (60 minute baseline sample), AP study Days 3 and 9 (EOS) for subjects not entering the DBRMP, and on DBRMP Days 1, 15, 29 and 35 (EOS)

10.8.2 WHOLE Blood for Zr determination-designated USA sites only

Whole blood samples for the analysis of Zr will be collected into K2EDTA tubes prior to the first daily dose on AP Study Days 1 and on DBRMP Study Days 15 and 29, as summarized in Table 2.

Blood samples will consist of approximately 2 x 3 ml venous blood. The tubes will be labeled with the study protocol number, the subject identification number (SID), the target collection time and date of collection, and stored frozen at ~ ≤−20 °C until sent to the Central Laboratory for storage as directed by the Sponsor.

Following receipt of the last set of frozen samples from the last subject and resolution of any sample discrepancies the Central Laboratory will ship the samples on dry ice, in insulated boxes in accordance with the shipping details provided by the Sponsor. Samples will be shipped to the address below from the Central Laboratory via overnight carrier for measurement of Zr concentration using validated methods.
10.8.3 Aldosterone determination – North American Sites ONLY
S-Aldo levels will be measured fasting on AP Study Day 1 and on DBRMP Study Day 29. Samples will be collected prior to 10 am (1000) after at least 2 hours in the upright position. Samples are collected in an EDTA tube (lavender top) processed to plasma according to the CLM, and immediately frozen. All plasma samples should be examined and any hemolyzed samples MUST be redrawn. The minimum sample size for renin determination is 1ml plasma.

10.8.4 Renin sample processing – North American Sites ONLY
P-renin levels will be measured fasting on AP Study Day 1 and on DBRMP Study Day 29. Samples will be collected prior to 10 am (1000) after at least 2 hours in the upright position. Samples are collected in an EDTA tube (lavender top) processed to plasma according to the CLM, and immediately frozen. All plasma samples should be examined and any hemolyzed samples MUST be redrawn. The minimum sample size for renin determination is 1ml plasma.

Both aldosterone and renin samples must be shipped frozen to the Central Laboratory within 18 days of collection.

10.8.5 S-Galectin-3, S-Insulin, P-BNP, P-PTH and HbA1c sample processing– North American Sites ONLY
All samples are collected fasting, on AP Study Day 1 and at the end of treatment in the DBRMP (DBRMP Study Day 29).

P-BNP and P-PTH samples are collected into K2EDTA tubes (lavender top).
S-Galectin-3 and S-Insulin samples are collected into SST.

All samples must be processed to serum (S-Galectin-3, S-Insulin) or plasma (P-BNP and P-PTH) within 2 hours of collection and immediately frozen (~ –20°C). Any hemolyzed samples must be redrawn.
HbA1c is collected into K2EDTA tubes and frozen. The sample should be shipped within 2 days of collection.

10.8.6 Urine collections
Urinalysis and urine chemistry parameters for evaluation are detailed in Appendix 1 and are performed by the Central laboratory. Detailed instructions on sample collection and
processing are provided in the Central laboratory Manual. The sample approximate volumes required for each analysis are:

- **Urinalysis:** 10 ml
- **Urine Culture:** 10 ml

### All North American Sites ONLY

- **Urine Chemistry:** 15 ml
- **p-Cresol:** 3 ml
- **Indole:** 2 X 4 ml

The AP Day 1 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration using the pregnancy kit supplied by the Central Laboratory and at DBRMP Study Day 29 (for subjects entering the open label extension study) or DBRMP Study Day 35 (EOS) for subjects not entering the open-label extension study.
Table 2

Summary of Blood Potassium, Zr, S-Galectin-3, S-Insulin, P-BNP, P-PTH, HbA1c, Aldosterone and Renin samples to be collected and analyzed

<table>
<thead>
<tr>
<th>AP Study Day</th>
<th>Time</th>
<th>Zr5</th>
<th>S-Galectin-3, S-Insulin, S-Aldo, P-Renin, P-BNP, P-PTH, HbA1c (North American Sites Only)</th>
<th>S-K</th>
<th>i-STAT</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>✓</td>
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<tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
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<td>✓</td>
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</tr>
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<td>✓</td>
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</tr>
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<td>✓</td>
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</tr>
<tr>
<td>26</td>
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<td>✓</td>
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<tr>
<td>29</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>35 (EOS)</td>
<td>0 h</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

1 S-K analyzed as part of the serum chemistry assessment
2 Sample only collected IF subject is still hyperkalemic (i-STAT potassium >5.0 mmol/l) at the am blood draw
3 Sample only collected IF i-STAT potassium value at the 4-hour post Dose 1 timepoint is ≥ 6.1 mmol/l
4 WHOLE blood collected into K2 EDTA tubes – designated USA sites only
5 2 x 3 ml WHOLE blood collected into K2 EDTA tubes

10.8.7 Urine for Zr determination-designated USA sites only

Urine for Zr determination will be collected fasting, prior to any dose administration on AP Study Days 1 and on DBRMP Study Days 15 and end of treatment (DBRMP Study Day 29).
Two (2) x 3 ml samples will be collected wherever possible. The tubes will be labeled with the study protocol number, SID, target collection time and date of collection, and stored frozen (≤ −20 °C) until sent to the Central Laboratory for storage as directed by the Sponsor.

Following receipt of the last set of frozen samples from the last subject and resolution of any sample discrepancies the Central Laboratory will ship the samples on dry ice, in insulated boxes in accordance with the shipping details provided by the Sponsor. Samples will be shipped to the address below from the Central Laboratory via overnight carrier for measurement of Zr concentration using validated methods.

Attn: Sample Team
QPS Netherlands B.V.
Petrus Campersingel 123
9713 GA Groningen
The Netherlands
+31 50 368 1048
+31 50 304 8001
sampleteam@qps.com

10.8.8 Urine for sediment and Culture

Urine for culture will be collected within 1 day of the first AP Study Day 1 dose administration, at DBRMP Study Day 29 for subjects entering into the open-label ZS-004E extension study and at the EOS visit in either Phase. Where a positive culture is identified the name of the organism and any prescribed treatment will be entered onto the eCRF.

Urinalysis, including assessment of sediment, will be performed by the Central Laboratory at AP Study Day 1 for all subjects and on AP Study Days 3 and 9 for subjects NOT entering the DBRMP, and on DBRMP Study Days 1, 15, 29 and DBRMP Study Day 35 (EOS) for subjects not entering the into the open-label ZS-004E extension study.

10.8.9 Urine Chemistry – All North American Sites ONLY

Urine chemistry will be assessed by the Central Laboratory at AP Study Day 1 and on DBRMP Study Day 29 (end of treatment).

Urine sample collection times and analyses are summarized in Table 3.
Table 3  Summary of urine samples to be collected and analyzed

<table>
<thead>
<tr>
<th>AP Study Day</th>
<th>Time</th>
<th>U-HCG</th>
<th>Zr¹</th>
<th>Central Laboratory²</th>
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</thead>
<tbody>
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<td></td>
<td>Urinalysis²</td>
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<td></td>
<td></td>
<td>including Sediment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chemistry³,⁷</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Urine Culture⁴</td>
</tr>
<tr>
<td>1</td>
<td>0 h</td>
<td>✓</td>
<td>✓</td>
<td>✓,³</td>
</tr>
<tr>
<td>2</td>
<td>0 h</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>0 h</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>9 (EOS)</td>
<td>0 h</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</table>

**DB Randomized Maintenance Phase**

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<td></td>
<td></td>
<td></td>
<td>Urinalysis²</td>
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<td>including Sediment</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chemistry³,⁷</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Urine Culture⁴</td>
</tr>
<tr>
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<td>0 h</td>
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</tr>
</tbody>
</table>

¹ 2 x 3 ml only collected by designated sites
² Parameters listed in Appendix 1
³ 15 ml for analysis of urine chemistry, 3 ml for p-cresol-3 ml and 2 x 4 ml for indole
⁴ Additional 10 ml for culture
⁵ Only for women of childbearing potential
⁶ Only if i-STAT potassium is >5.0 mmol at the morning blood draw
⁷ North American sites only
⁸ Conduct only if subject enters the extension study, ZS-004E

10.9 Clinical Procedures and Observations

Each research clinic will follow its own standard operating procedures for the daily ongoing monitoring of subjects while subjects are in the clinic, e.g., Pulse/0-2 saturation. Subjects will be monitored for any adverse events occurring at any time throughout the study.

10.9.1 ECG

ECGs will utilize a 12-lead recording; however a 10-lead ECG is acceptable in the absence of a 12 lead capability. ECG results will be assessed by PI/Sub-PI.

ECGs will be recorded at AP Study Day 1 and 2 and AP Study Days 3 and 9 (EOS) for subjects NOT entering the DB Randomized Maintenance Phase, and on DBRMP Study Days 1, 8, 15, 22, 29, and 35 (EOS) for subjects not entering the open-label ZS-004E extension study. When applicable ECGs will be performed after the S-Aldo and P-Renin samples are drawn and before the first daily dose of IP. In addition, for subjects who have i-STAT potassium levels ≥ 6.1 mmol/l at the 1 hour post 1st dose time point on AP Study Day 1, an additional ECG will be recorded 1.5 hours post 2nd dose.

10.9.2 Concomitant Medications

All concomitant medications taken by the subject from 30 days prior to AP Study Day 1 until DBRMP Study Day 29 for subjects entering the open-label ZS-004E extension...
study or the end of the study (7 ± 1 days after the last dose of IP) for subjects that do not continue into ZS-004E, will be recorded.

Whenever possible, all blood draws collected prior to meals should be collected prior to any insulin/insulin analog treatment. From AP Study Day 1 through DBRMP Study Day 28, the time of dosing with insulin/insulin analogs must be recorded when IP is administered in the clinic.

During the study, the subject cannot receive alternative treatment for hyperkalemia while taking IP. If dosing with IP is discontinued or the subject has completed dosing, the subject may receive alternative treatment for hyperkalemia if clinically indicated prior to completing the EOS visit. Any alternative treatment administered after the end of IP administration and prior to the EOS visit must be recorded in the concomitant medication CRF (and as AE if applicable).

10.9.3 Physical Examination

A full physical exam, including weight (weighed on the same scale in the same state of dress), and assessment of signs of heart failure, will be conducted within 1 day of administration of the first dose of study drug on AP Study Day 1 (Baseline: all subjects) and AP Study Day 9 for subjects not entering the DBRMP and on DBRMP Study Days 1, 15, 29 and for subjects not entering the open-label ZS-004E extension trial on DBRMP Study Day 35 (EOS) for subjects entering the 28-day DBRMP.

When applicable, the physical examination will be performed after the S-Aldo and P-Renin samples are drawn and before the first dose of IP for the day.

10.9.4 Urine Pregnancy Test

A urine pregnancy test will be conducted within 1 day of administration of the first dose of study drug on AP Study Day 1 and at the EOS visit (AP Study Day 9 for subjects NOT entering the DBRMP; or DBRMP Study Day 29 for subjects entering the open-label ZS-004E extension; or DBRMP Study Day 35 for subjects not entering the open-label ZS-004E extension) for all women of childbearing potential (defined as not surgically sterile for two years or post-menopausal). Tests will be performed on site, using the kits supplied by the Central Laboratory.

10.9.5 Meals and Dose Administration

In the AP the first daily dose of IP will be taken in the clinic ~1 hour before breakfast and the second and third daily doses will be taken at home just before lunch and dinner. During the DBRMP study drug will be taken once a day for 28 consecutive days, just before breakfast. On DBRMP Study Days 1, 5, 8, 12, 15, 19, 22 and 26, study drug will be taken in the clinic. On all other days it will be taken at home, just before breakfast. When study drug is administered in the clinic breakfast should be eaten after the collection of any 1-hour post Dose 1 blood collections and within ~1 h of dose administration.
11 ADVERSE EVENT REPORTING

All adverse events (AEs) will be recorded on the designated study CRF for each subject beginning with the first administration of study drug and ending with the date of the end of study treatment follow-up. Any unresolved AEs will be followed by the investigator until event resolution, the subject is lost to follow-up, the AE is otherwise explained or not considered clinically significant by the investigator.

11.1 Investigator Reporting Requirements

The investigator must immediately report (within 24 hours by telephone and followed by a written report sent by fax or e-mail) all serious adverse events to ZS Pharma, Inc. regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure. (See Definitions below)

These serious adverse events must be reported to:

Henrik Rasmussen, MD, PhD
Chief Medical and Chief Scientific Officer
ZS Pharma, Inc.
508 Wrangler Drive, Suite 100
Coppell TX 75019
Tel: 817-885-8143
Cell: 443-699-5230
Fax 888-389-4759
E-mail: sae@zspharma.com

Because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject’s response to the drug, is aware of the subject’s clinical state and thus may be sensitive to distinctions between events due to an underlying disease process versus events that may be drug-related, and may have observed the event, the investigator must include an assessment of causality (i.e., whether there is a reasonable possibility that the drug caused the event) in the report to ZS Pharma, Inc. Copies of each report to ZS Pharma, Inc. will be kept in the investigator’s study file.

The investigator is responsible for complying with their IRB/IEC’s requirements for reporting serious adverse events. Any IND Safety Report received from ZS Pharma, Inc. should be submitted to the IRB/IEC. Copies of each report and documentation of IRB/IEC notification will be kept in the investigator’s study file.

The investigator must record non-serious adverse events in the eCRF and report them to Sponsor according to the timetable for reporting (e.g., end of study). The investigator’s assessment of causality is not required for non-serious adverse events.

11.2 Definitions

Adverse Event: Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be
any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or
disease temporally associated with the use of a drug, without any judgment about
causality.

Adverse Reaction: Adverse reaction (AR) means any AE definitely caused by the drug.

Suspected Adverse Reaction: Suspected adverse reaction (SAR) means any adverse event
for which there is a “reasonable possibility” (i.e., evidence indefinite but suggests a
causal relationship between the drug and the AE) that the drug caused the AE.

Examples that would suggest a causal relationship:

A single occurrence of an event that is uncommon and known to be strongly associated
with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

One or more occurrences of an event that is not commonly associated with drug
exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon
rupture)

An aggregate analysis of specific events observed in a clinical trial (e.g., known
consequences of the underlying disease or condition under investigation or other events
that commonly occur in the study population independent of drug therapy) that indicates
those events occur more frequently in the drug treatment group than in a concurrent of
historical control group.

Unexpected Adverse Event or Unexpected Adverse Reaction: An AE or AR is
considered “unexpected” if it is not listed in the investigator brochure or is not listed at
the specificity or severity that has been observed.

AEs or ARs that are mentioned as occurring with a class of drugs or as anticipated from
the pharmacological properties of the drug will be considered “unexpected” if they are
not specifically mentioned as occurring with the particular drug under investigation.

Until the investigator brochure is updated to include a new serious SAR, subsequent
occurrences of similar serious SARs must be submitted expeditiously to FDA in IND
Safety Reports.

Serious Adverse Event or Serious Adverse Reaction: An AE or AR is considered
“serious” if, in the view of either the investigator or Sponsor, it results in any of the
following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to
  conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require
hospitalization may be considered serious when, based upon appropriate medical
judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the investigator or Sponsor believes that the event is serious, it must be evaluated by the Sponsor for expedited reporting to FDA.

Life-Threatening Adverse Event or Life-Threatening Adverse Reaction: An AE or SAR is considered “life-threatening” if, in the view of either the investigator or ZS Pharma, its occurrence places the subject at immediate risk of death.

Serious Unexpected Suspected Adverse Reaction (SUSAR): An adverse event for which there is a reasonable possibility that the drug caused the adverse event, and it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed, and it results in any of the serious outcomes listed above. This criterion is consistent with the concepts of FDA 21 CFR 312 and the ICH E2A Guideline.

IND Safety Report: The Sponsor must notify FDA and all participating investigators in an “IND Safety Report” of potentially serious risks from clinical trials or any other source (i.e., a serious unexpected SAR or SUSAR), as soon as possible, but no later than 15 calendar days after ZS Pharma, Inc. receives the safety information and determines that the information qualifies for reporting.

During the course of drug development, the Sponsor may become aware of new safety information from a variety of sources and will decide if an individual case of a serious and unexpected adverse event meets the criteria for reporting to FDA.

If the adverse event does not meet all criteria (i.e., reasonable possibility of causality, serious and unexpected), it should not be submitted as an expedited IND Safety Report.

Any unexpected fatal or life-threatening SAR must be reported to FDA no later than 7 calendar days after ZS Pharma, Inc. receives the safety information.

11.3 Breaking the Blind

Breaking the blind in a clinical trial on an emergency basis by the site should only occur when knowledge of the treatment to which a subject was allocated would have implications for the medical management of the subject in case of a SAR. However, as there is no specific antidote to ZS, treatment of a SAR would be purely symptomatic and the breaking of the blind would have no implication for treatment. Therefore, emergency unblinding by the site will not be allowed and consequently no mechanisms have been put in place to secure emergency unblinding.

The iDMC can request a code break, either for an individual subject or on a group basis as described in the iDMC charter. The iDMC may request to break the blind if:

- There is an imbalance in safety parameters between groups
- If stopping criteria are met

and/or

- In case of single or multiple significant AEs/SARs that might be drug-related.

In such a case, the chair of the iDMC would request unblinding from the Sponsor’s Chief Medical Officer (CMO), either of an individual subject or on a group basis, and the,
CMO would then request unblinding from the third party keeper of the randomization codes.

12 STATISTICAL CONSIDERATIONS

The study analyses will be conducted in a GCP environment (ICH E6). All analyses will be pre-specified in a Statistical Analysis (SAP) prior to beginning patient enrollment.

12.1 Study Populations

The study will have prospectively defined study populations including separate evaluability rules for the AP and DBRMP.

For the AP, subjects will be considered evaluable if:

1) they receive the acute dose

2) they have any post-baseline S-K levels after receiving the investigational product during the first 48 hours

The Intent-to-Treat (ITT) population will include all subjects that received the investigational product, and had any post-baseline S-K levels. The Safety Population will include all subjects as treated with Acute Phase IP (even if they only received one dose of IP) among those treated and with any post-baseline AP safety data.

For the subsequent DBRMP, subjects will be considered evaluable for the primary endpoint if: 1) they receive the randomized investigational product, and 2) they have any post-baseline DBRMP S-K levels after receiving the investigational product. The ITT population will include all subjects who were randomized, received any investigational product, and had any post-baseline DBRMP S-K levels; the ITT population will be used for the primary analyses. If >5% are to be excluded from the ITT population, then a per protocol (PP) analysis will also be performed, including all subjects who were eligible, treated as randomized, had any post-baseline DBRM S-K levels, and did not have any major protocol violations (major defined as protocol violations that potentially interfered with the ability to evaluate the efficacy and/or safety of ZS). The Safety Population will include all subjects as treated with DBRMP IP (even if they only received one dose of IP) among those randomized and with any post-baseline DBRMP safety data.

12.2 Primary S-K Hypothesis

The primary study hypothesis (alternative hypothesis) is that ZS maintains a lower mean S-K level than placebo control over DBRMP Days 8-29 in hyperkalemic subjects in whom normokalemia was established during the AP versus the null hypothesis of no mean difference between the ZS dose (highest to lowest) and placebo control (null hypothesis).

12.3 Primary S-K Endpoint

The primary endpoint in the study will be the mean S-K value for DBRMP Days 8-29. A log transformation will be applied to the S-K level to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (highest to lowest dose) versus placebo control for the 28-day DBRMP
to estimate the mean Day 8-29 values; the model will include all S-K data collected at the scheduled visits in addition to baseline covariates for AP eGFR and AP and DRMP S-K as well as age (<55, 55-64, ≥65 years) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, congestive heart failure, and diabetes mellitus. Labeling claims will be sought for these four pre-defined subgroups.

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

12.4 Additional S-K Endpoints

The following endpoints will be included in the analyses for the Acute Phase:

- Exponential rate of change in S-K levels (blood)
- Change (absolute and percent (%) change) from baseline in S-K levels at all measured time intervals post dose
- Proportion of subjects who achieve normokalemia during the AP at 24 and 48 hours
- Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/l, inclusive)

The following endpoints will be included in the secondary analyses for the DBRMP:

- The mean cumulative DBRMP days normokalemic
- The percent normokalemic at DBRMP Day 29
- The mean S-K levels at other time points evaluated relative to both AP and DBRMP baselines (absolute and percent change)
- The mean time to hyperkalemia (defined as S-K ≥ 5.1mmol/l, inclusive)
- The mean intra-subject standard deviation
- The proportion of subjects who remain normokalemic at DBRMP Study Days 8, 15, 22 and 29 days

12.5 Additional Endpoints

The following additional endpoints will be recorded and analyzed for both study phases:

- S-Mg, S-Ca, S-Na, BUN, HCO3, S-PO4, Bilirubin, AST, ALT, S-Aldo, P-Renin, as well as UPCR and UACR
- S-Galectin-3, S-Insulin, P--BNP, P-PTH, HbA1c and urinary p-cresol and indole
- Incidence of doctor’s visits other than those specified by protocol
- Incidence of hospitalization and ER visits
12.6 Sample Size Calculations

The sample size is based on the mean S-K during DBRMP Study Days 8-29. To optimize the comparison of three active doses vs. placebo control, the placebo group will have 1.6 x the number of subjects per active dose. A 4:4:4:7 allocation best approximates the optimum Dunnett’s allocation.

A sample size of 232 DBRMP subjects (49 per active dose and 85 placebo controls) will have 90% power and 5% Type 1 error for a two-sided hypothesis test to detect a mean 0.3 mmol/l advantage for DBRMP Study Days 8-29 for any active dose vs. placebo control using a pre-specified closed testing order (highest to lowest dose); a mean 0.3 mmol/l decrease represents a meaningful advantage between any dose and placebo for a pooled 0.5 standard deviation. The sample size also has 90% power and 5% Type I error to detect a mean 4-day increase in days normokalemic between any dose and placebo over the 28 day DBRMP for a pooled 6 day standard deviation. The power calculation for the mean S-K during DBRMP Days 8-29 is displayed in Column 1 while the mean days normokalemic is displayed in Column 2 for that sample size (Table 4). To control the Type I error for multiple testing, the same pre-defined dose order will be applied (highest to lowest dose) in comparing the doses vs. placebo control.

Table 4   Sample Size Requirements:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean S-K DBRMP Days 8-29</th>
<th>DBRMP Days Normokalemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test significance level, alpha</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>1 or 2 sided test?</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean Difference, m1 - m2</td>
<td>0.3 mmol/l</td>
<td>3.6 days</td>
</tr>
<tr>
<td>Pooled SD, s</td>
<td>0.5 mmol/l</td>
<td>6 days</td>
</tr>
<tr>
<td>Effect size, d =</td>
<td>m2 – m1</td>
<td>/ s</td>
</tr>
<tr>
<td>Power (%)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Active Dose Group, n2</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Placebo Controls, n1</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Total N=n1 + 3n2</td>
<td>232</td>
<td>232</td>
</tr>
</tbody>
</table>

12.7 Overall Type I Error Control

The overall Type I error is to remain two-sided 5% accounting for the sample size re-estimation and for testing DBRMP efficacy after testing AP efficacy. Type I error control will be maintained by requiring the mean change from AP baseline in S-K to be statistically significant (two-sided p<0.05) in order to test the mean change from baseline during the subsequent DBRMP for registration purposes for the primary efficacy endpoint. Treatment testing will proceed from highest to lowest dose relative to placebo with statistical significance required for the highest dose vs. placebo control to proceed to the test for the next highest dose relative to placebo control and lastly to the test for the lowest dose relative to placebo control. After testing for significance for each dose for
the primary efficacy endpoint, then a hierarchical testing plan is in place to control Type I error to extend labeling claims in a pre-defined testing order where statistical significance (two-sided \( p<0.05 \)) is required at each step.

### 12.8 Efficacy Analysis Approach

Separate analyses will be performed for the AP and DBRMP. All calculations will be performed using SAS statistical software, version 9.1 or later, and StatXact, version 10 or later. All analyses will be pre-specified in the SAP approved prior to study launch.

**AP:** The mean and relative reduction will be performed for all enrolled subjects. The change from baseline will be assessed using a paired t-test; a two-sided \( p \)-value \( \leq 0.05 \) will be considered statistically significant.

**DBRMP:**

The analyses for the DBRMP will focus on randomized withdrawal so there will be three active dose groups to be compared to the placebo control group. These analyses will be performed according to a closed testing procedure (highest to lowest dose) to preserve the Type I error; specifically, the dose comparisons versus placebo will be performed in a sequential manner as follows: (1) the highest dose comparison first and proceeding if significant to, (2) the middle dose comparison next and proceeding if significant to (3) the lowest dose. This strategy will be used for the primary efficacy endpoint and for the secondary efficacy endpoints. In addition, the Type I error to extend registration labeling for five of the seven secondary efficacy endpoints will be achieved using a hierarchical testing procedure to pre-define the specific testing order.

Baseline will be established by averaging the mean of two different screening S-K values, recorded 60 minutes apart (time 0 and 60 ± 10 minutes) with the Day 1 S-K value taken just before the first dose.

For establishing efficacy, a mean 0.3 S-K advantage is deemed to be a minimal clinically significant difference between treatment and placebo control over the 28 days.

**Primary Efficacy Endpoint:**

The primary endpoint in the study will be the mean S-K on DBRMP Study Days 8-29. A log transformation will be applied to the S-K level to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (highest to lowest dose) versus placebo control for the 28-day DBRMP to estimate the mean Day 8-29 values; the model will include all S-K data collected at the scheduled visits in addition to baseline covariates for AP eGFR and S-K as well as age (<55, 55-64, ≥65 years) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, congestive heart failure, and diabetes mellitus. The model will simultaneously compare each active dose (highest to lowest dose) vs. placebo control.

**Extended Labeling:**

As described above, the primary efficacy endpoint will be evaluated while controlling for RAAS inhibitors, chronic kidney disease, congestive heart failure, and diabetes mellitus. To establish extended labeling claims for these pre-defined subgroups, the model described above will be expanded to include dose-time-subgroup interaction terms to simultaneously evaluate dose effects in each subgroup relative to the control.
Secondary Efficacy Endpoints:
The same modeling strategy will be applied for the secondary efficacy endpoints while controlling for the same baseline covariates and simultaneously comparing each active dose (highest to lowest) vs. placebo control.

Secondary efficacy endpoints will be analyzed as follows:

- The cumulative DBRMP days normokalemic in the three dose (3) groups will be compared to the placebo-treated subjects using a linear regression model to control for the same covariates as for the primary efficacy endpoint in comparing maintenance doses (highest to lowest) versus placebo.
- The percent normokalemic at DBRMP Day 29 will be compared using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint.
- The mean S-K levels at other time points evaluated relative to baseline using paired t-tests to compare doses (highest to lowest) vs. placebo using unpaired t-tests.
- The time to hyperkalemia (defined as S-K $\geq$ 5.1 mmol/l) computed using a Kaplan-Meier life table and using a log rank test and a proportional hazard model (SAS PROC PHREG) containing the same baseline covariates as for the primary efficacy endpoint.
- The time to relapse (defined as return to original AP baseline S-K level) computed using a Kaplan-Meier life table and using a log rank test and a proportional hazard model (SAS PROC PHREG) containing the same baseline covariates as for the primary efficacy endpoint.
- The mean intra-subject standard deviation using a linear regression model containing the same baseline covariates as for the primary efficacy endpoint.
- The proportion of subjects who remain normokalemic at 8, 15, 22 and 29 days compared using a Fisher Exact test and a SAS PROC GENMOD longitudinal model containing the same baseline covariates as for the primary efficacy endpoint.

Additional Endpoints:

Kidney function will be evaluated by assessments of S-Cr, eGFR (MDRD equation), UPCR and UACR over time. Liver function will be evaluated by assessing bilirubin, AST and ALT. S-Aldo and P-renin will also be evaluated to assess the possible impact of ZS on the RAAS system. S-Galectin-3 and P-BNP will be evaluated for possible effects on myocardial function. P-PTH, S-Ca, S-PO4 will be evaluated for possible effects on bone metabolism and S-Insulin and HbA1c will be evaluated for possible effects on glucose metabolism. For the continuous lab measures, the mean changes from AP baseline to Study Day 29 will be displayed for S-Na, S-Mg, S-Ca, S-PO4 and BUN, bilirubin, AST, ALT, S-Aldo, P-Renin, as well as UPCR and UACR; an unpaired t-test will be used to compare each active dose (highest to lowest dose) vs. placebo; in addition, a paired t-test will be performed for the change from baseline for each study treatment group.
The number of ER visits and doctor visits will be evaluated using a Wilcoxon Rank Sum test to compare each active dose (highest to lowest) with placebo.

Hierarchical Testing:
The following five of the seven secondary efficacy endpoints for the DBRMP will be tested in the following order for making labeling claims per dose group until no longer significant (two-sided \( p \leq 0.05 \)):

- Cumulative DBRMP days normokalemic (S-K levels between 3.5-5.0 mmol/l, inclusive) in each treatment group
- Time to hyperkalemia (defined as S-K \( \geq 5.1 \) mmol/l)
- Time to relapse (return to original S-K baseline level) in S-K levels in each treatment group
- Percent within each treatment group who retain normal S-K levels (defined as S-K levels between 3.5-5.0 mmol/l, inclusive) at Day 29
- Mean intra-subject standard deviation.

12.9 Safety Analysis
Separate safety analyses will be performed for the AP and DBRMP. Safety endpoints will include adverse events (AE), vital signs (VS), and other relevant clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters.

The respective safety analysis will be undertaken on all subjects randomized who have received any amount of IP, separately for the AP and for the DBRMP. The principle of treatment emergence will be employed for the analysis of AE data. Treatment emergence is defined to be any event that occurred during the observation period and was not present at baseline, or one which represents an exacerbation of a condition present at baseline.

Events emerging during AP will be counted during the DBRMP if not resolved by the start of DBRMP treatment initiation.

Adverse events will be classified by MedDRA (Version 15.1E). For each study treatment, safety data will be collected and analyzed while on AP or DBRMP treatment or until treatment-emergent adverse events are resolved. The type, incidence, timing (onset, duration), relationship, and severity of AEs will be reported for treatment-emergent and SARs. Reasons for withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or associated with death. Safety results will be displayed separately for each of these phases.

Safety and tolerability will be assessed using a two-sided Fisher Exact test compare each active dose (highest to lowest) vs. placebo; mean changes from AP baseline as well as from DBRMP baseline to Study Day 29 will be displayed for S-Na, S-Mg, S-Ca, S-PO4, BUN, bilirubin, AST, and ALT; an unpaired t-test will be used to compare each active dose (highest to lowest dose) vs. placebo; in addition, a paired t-test will be performed for the change from baseline for each study treatment group.
**DBRMP:**

Analyses will be performed using two-sided Fisher Exact test for binary outcomes or an unpaired t-test for continuous outcomes to compare each active dose (highest to lowest) vs. placebo control. Continuous outcomes will be assessed using unpaired t-tests to compare each active dose vs. the respective placebo control while paired t-tests will be used to compare changes from baseline for each study group. Binary outcomes, e.g. incidence, will be assessed using a two-sided Fisher Exact test to compare each active dose vs. placebo control.

**AP Safety Analyses:**

Changes from baseline for each of S-Na, S-Mg, S-Ca, BUN, S-Cr, S-PO4 and HCO3 once daily, will be analyzed using a paired t-test for the change from baseline.

**DBRMP Safety Analyses:**

The same analyses are planned for the four DBRMP treatment groups. The time frames of interest will be from DBRMP Study Day 1 through the end of DBRMP Study Day 28. Unresolved adverse event outcomes at the end of DBRMP will be followed for an additional seven days or until resolution, whichever occurs earlier.

**12.10 Interim Analysis**

No interim analysis is planned.

**13 WITHDRAWAL FROM STUDY**

Subjects who develop i-STAT potassium values <3.0 at any time during the study or > 6.2 mmol/l, during the DBRMP will be considered treatment failures and will be withdrawn from the study. Subjects who have i-STAT potassium values > 6.2 mmol/l, 90-minutes after the 1st dose of IP on Open Label Acute Phase Study Day 1 will be withdrawn from the study. Similarly, subjects who develop cardiac arrhythmias as described under the stopping criteria (Section 10.3.1) will also be withdrawn from the study. Such subjects will receive standard of care and will be entered into the IVRS/IWRS as “withdrawn”.

Every reasonable effort should be made to maintain protocol compliance and participation in the study. Should a subject withdraw or be prematurely terminated from the study for any reason, the reason for early study withdrawal will be recorded. If withdrawal is the result of a serious AR the subject will be followed until the condition has resolved, as determined by the investigator.

The investigator or Sponsor may withdraw any subject at any time for medical reasons or for administrative reasons (i.e., subjects unable or unwilling to comply with the protocol). If so, the subject will be censored at time of withdrawal and if possible a final evaluation (EOS procedures) will be made. All treated subjects (those who have received at least one dose of investigational product) will be included in the ITT and Safety analyses.

In the unlikely event the Sponsor or FDA should determine it is appropriate to terminate the study early, every effort will be made for transitioning subjects with minimal disruption to the subject and investigator. The IRB will be notified of termination, and
reason(s) and procedures for follow-up of research subjects will be developed by the study physician in consultation with the Sponsor and IRB/IEC.

14 DATA MANAGEMENT

The standard procedures for handling and processing records will be followed as per GCP and the data management CRO’s Standard Operating Procedures (SOPs). A comprehensive Data Management Plan (DMP) will be developed and approved by a representative of the Data Management CRO and the Sponsor.


The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All data are entered in the database
- All adverse events are coded to the satisfaction of the Chief Medical Officer
- All data queries have been resolved to the satisfaction of the Lead Biostatistician
- All decisions have been made regarding all protocol violators and ITT population exclusions
- Written authorizations to lock the database are obtained from ZS Pharma Clinical Data Management and Chief Scientific Officer. The randomization code for this study, generated and held by the Lead Biostatistician, will not be revealed until the previous preconditions are fulfilled.

15 ETHICAL CONSIDERATIONS

15.1 Ethical Conduct of the Study

The study will be conducted in accordance with US Title 21 Code of Federal Regulations and the ICH E6 (R1) Guidelines of Good Clinical Practice. The Declaration of Helsinki and its most recent updates (Seoul, 2008) will be observed.

The investigator will provide the Sponsor/designee, with documentation of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and the sample informed consent document before the study may begin at the investigative site. The IRB/IEC will review the protocol as required.

The investigator will supply the following to the IRB/IEC:

The current Investigator’s Brochure and updates

- Study protocol and amendments
- Informed consent and assent document and updates
- Relevant curricula vitae
- Safety Alerts
• Serious AR Reports
The investigator must provide the following documentation to the Sponsor or designee:
  • The IRB/IEC original approval of the protocol and the informed consent, and re-
    approval of the study (annual or semi-annual, per IRB guidelines)
  • The IRB/IEC approvals of any revisions to the informed consent document or
    amendments to the protocol
  • All other documents that are required by local regulatory authorities

15.2 Regulatory Considerations
After reading the protocol, each PI/sub PI will sign a protocol signature page and return a
copy of the signed page to the Sponsor/designee, while maintaining the original at the
site.

15.3 Protocol Amendments and Study Termination
The IRB/IEC must be informed and give approval for any amendments likely to affect
the safety of the subjects or the conduct of the study.

The IRB must be advised in writing of the study’s completion or early termination and a
copy of the notification must be provided to the Sponsor.

15.4 Safety Monitoring
The Sponsor’s Medical Monitor and an iDMC will monitor safety data throughout the
course of the study. ZS Pharma Drug Safety, or their designee, will expedite to the
regulatory authorities only the SARs that are product-related and unexpected in
accordance with FDA 21 CFR 312, FDA draft guidance (Sept 2010) on Safety Reporting
Requirements for INDs, and the ICH E2A guideline.

15.5 Quality Control and Quality Assurance
By signing this protocol, the Sponsor agrees to be responsible for implementing and
maintaining quality control and quality assurance systems with written standard operating
procedures to ensure that the study is conducted and data are generated, documented, and
reported in compliance with the protocol, accepted standards of GCPs, and all applicable
federal, state, and local laws, rules and regulations relating to the conduct of the clinical
study.

By signing this protocol, the investigator agrees to conduct the study in an efficient and
diligent manner and in conformance with this protocol, generally accepted standards of
GCP, and all applicable federal, state, and local laws, rules and regulations relating to the
conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, IRB review and regulatory
agency inspection of study-related documents and procedures and provide for direct
access to all study-related source data and documents. Investigators will be given notice
before a quality assurance audit occurs.

The investigator shall prepare and maintain complete and accurate study documentation
in compliance with GCP standards and applicable federal, state, and local laws, rules and
regulations, and promptly submit to the Sponsor all forms and reports required by this protocol following completion or termination of the clinical study or as otherwise required due to any agreement with the Sponsor

16 GENERAL CONSIDERATIONS

16.1 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study or investigator’s participation in this study for safety or administrative reasons at any time.
17 AGREEMENT WITH PROTOCOL

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with ZS Pharma, Inc. and its appointed Clinical Research Organization (CRO) during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), revised Declaration of Helsinki (2008) and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

Principal Investigator:

Printed Name: 

Signature: 

Date:

Protocol ZS-004

A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS (Microporous, Fractionated, Protonated Zirconium Silicate), an Oral Sorbent, in Subjects with Hyperkalemia.

Original Protocol: 8 July 2013
Amendment 1: 23 December 2013
Amendment 2: 24 February 2014
Amendment 3: 14 April 2014
Appendix 1  Safety Hematology, Clinical Chemistry and Urinalysis Tests
Performed by the Central laboratory at Screening, During the Study and at Follow-up (EOS)

<table>
<thead>
<tr>
<th>Clinical Chemistry</th>
<th>Hematology²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Concentrations of:</td>
<td></td>
</tr>
<tr>
<td>Total protein¹</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Albumin¹</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>Bicarbonate¹</td>
<td>Erythrocyte count (RBC)</td>
</tr>
<tr>
<td>Blood Urea Nitrogen¹</td>
<td>Differential leukocytes</td>
</tr>
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<td>Creatinine¹</td>
<td>Total leukocytes (WBC)</td>
</tr>
<tr>
<td>Total bilirubin¹</td>
<td>Platelets</td>
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<td>Alkaline phosphatase¹</td>
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<td>Glucose¹</td>
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<td>Potassium¹</td>
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<td>Calcium (total)¹</td>
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</tr>
<tr>
<td>Magnesium¹</td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (GGT)¹</td>
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</tr>
<tr>
<td>Alanine Amino Transferase (ALT)¹</td>
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</tr>
<tr>
<td>Aspartate aminotransferase (AST)¹</td>
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<tr>
<td><strong>North American Sites ONLY</strong></td>
<td></td>
</tr>
<tr>
<td>Aldosterone¹,²,⁴</td>
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</tr>
<tr>
<td>Renin²,⁴</td>
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<tr>
<td>Insulin¹</td>
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<td>BNP²</td>
<td></td>
</tr>
<tr>
<td>PTH²</td>
<td></td>
</tr>
<tr>
<td>Galectin-3¹</td>
<td></td>
</tr>
<tr>
<td>HbA1c⁵</td>
<td></td>
</tr>
</tbody>
</table>

| Urinalysis                                               |             |
| pH                                                      |             |
| Specific gravity                                        |             |
| Glucose                                                 |             |
| Ketones                                                 |             |
| Bilirubin                                               |             |
| Urobilinogen                                            |             |
| Blood                                                   |             |
| Urine Sediment                                          |             |
| Urine Culture                                           |             |
| Urine pregnancy test ³                                  |             |

**North American Sites ONLY**

| Albumin                                                 |             |
| Sodium                                                  |             |
| Potassium                                               |             |
| Insulin                                                 |             |
| BNP                                                     |             |
| PTH                                                     |             |
| Galectin-3                                               |             |
| p-Cresol                                                |             |
| Indole                                                  |             |

1 Collected into SST tubes
2 Collected into EDTA tubes
3 Urine dipstick: all women of childbearing potential at AP Study Day 1 and EOS. Performed on site using the pregnancy kit supplied by the Central Laboratory
4 Samples are collected prior to 10am after subject has been upright for at least 2 hours. Samples are to be aliquoted immediately after processing and frozen until sent for analysis. At least 1ml of the processed sample is required
5 Collected into EDTA tubes and frozen
Clinical Protocol ZS-004

Statistical Analysis Plan

A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects with Hyperkalemia

IND 108951

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A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects with Hyperkalemia.

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Version Date: 15Jul2014

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## 1. Abbreviations

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<th>Definition</th>
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<tr>
<td>AP</td>
<td>Acute Phase</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event(s)</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Class</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EOS</td>
<td>End of the Study</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>iDMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mITT</td>
<td>modified Intent-to-Treat</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>ml/min</td>
<td>Milliliter/Minute</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>mmol/l</td>
<td>Milli-moles/liter</td>
</tr>
<tr>
<td>MP</td>
<td>Maintenance Phase</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>PCS</td>
<td>potentially clinically significant</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>QD</td>
<td>Once a day</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin Angiotensin-Aldosterone System</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cell</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event(s)</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>S-Ca</td>
<td>Serum Calcium [Ca+2]</td>
</tr>
<tr>
<td>S-Cr</td>
<td>Serum Creatinine</td>
</tr>
</tbody>
</table>
2. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

2.1. Statistical and Analytical Plans

2.1.1. Definitions and General Considerations for Data Analysis

1. All calculations will be performed using SAS statistical software, version 9.1 or later, and StatXact, version 10 or later.

2. This Statistical Analysis Plan (SAP) is based on ZS-004 Protocol Amendment 3, dated 24 February 2014 containing the study background, justification, design, and objectives.

3. **Acute Phase (AP):** Single-arm, two day, three times daily (TID) treatment phase

4. **Maintenance Phase (MP):** Randomized withdrawal, double-blind, placebo-controlled, 26-day once daily (QD) treatment phase; in conjunction with the AP, this yields a total of 28 treatment days. An additional week of safety follow-up after the last dose day extends the study to a total of 35 days.

5. **AP Baseline:** AP Study Day 1

6. **MP Baseline:** AP Study Day 3 / MP Study Day 1

7. **Normokalemia:** Serum potassium (S-K) levels between 3.5 and 5.0 mmol/L, inclusive

8. A log transformation will be applied to the S-K level to stabilize the variance.

9. Study days will be determined as indicated in the cleaned and locked database. No attempt will be made to re-assign study days except for subjects terminating treatment early for whom their last assessments will be assigned the study day on
or before last dose date that corresponds to a scheduled assessment time and is no more than 2 calendar days prior to the actual date of assessment (this allows the use of an End of Study [EOS] assessment not directly linked to a follow-up study day that is close enough to a scheduled visit to be expected to reasonably represent the subject’s S-K level on that study day).

10. The eGFR will be calculated as follows:

\[
eGFR = 175 \times (0.011312 \times \text{Creatinine \, umol/L})^{**-1.154} \times (\text{age \, in \, years})^{**-0.203} \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}.
\]

2.1.2. Analysis Populations

2.1.2.1. Acute Phase Safety (AP-S) Population

A subject will be included in the AP-S population if they receive at least one AP dose administration. This analysis population will be used for description of AP safety. Subjects will be analyzed for safety outcomes as treated.

2.1.2.2. Acute Phase Intent-to-treat (AP-ITT) Population

A subject will be included in the AP-ITT population if they:

1) are included in the AP-S population;
2) have any post-baseline S-K levels after receiving the investigational product during the first 48 hours

This analysis population will be used for description of AP efficacy. Subjects will be analyzed as treated.

2.1.2.3. Maintenance Phase Safety (MP-S) Population

A subject will be included in the MP-S population if they receive at least one MP dose administration. This analysis population will be used for description of MP safety. Subjects will be analyzed for safety outcomes as treated regardless of their randomized treatment assignment.

2.1.2.4. Maintenance Phase Intent-to-treat (MP-ITT) Population

A subject will be included in the MP-ITT population if they:

1) are included in the MP-S population;
2) have at least one observed S-K assessment on or after Day 8.

This analysis population will be used for the primary assessment of efficacy. Subjects will be analyzed according to randomized treatment assignments.

2.1.2.5. Maintenance Phase Modified Intent-to-treat (MP-mITT) Population

A subject will be included in the MP-mITT population if they:

1) are included in the MP-ITT population;
2) have no significant protocol deviations that may be expected to bias the subject’s S-K assessments.

Analyses for the MP-mITT population will only be executed if at least 5% of the MP-ITT population requires exclusion and will only be used for assessment of efficacy. Subjects will be analyzed according to randomized treatment assignments.

2.1.3. Disposition of Subjects

All screened subjects will be included in summaries of subject disposition and subject evaluability for analysis populations by treatment group. Subject accounting will be provided for the following parameters:

1. Number of AP-treated subjects and AP completers defined as subjects who were treated with study drug during the AP and have both AP baseline and 48-hour S-K assessments;
2. Number of MP-eligible subjects defined as an AP completer with S-K levels between 3.5 and 5.0 mmol/L, inclusive, at the AP 48-hour time point;
3. Number of MP-randomized subjects, completion status, and reasons for discontinuation.

Also, subject exclusions from analysis populations will be tabulated.

2.1.4. Major Deviations and Protocol Violations

Major deviations and protocol violations relating to subject-level and subject-visit level events will be reviewed by appropriate medical, clinical, data management, and statistical personnel and documented prior to unblinding the study.

2.1.5. Demographic and Other Baseline Characteristics

Age, gender, race, and ethnicity will be summarized for the AP-S and MP-S Populations. In addition, the incidence of insulin use one day prior to AP Study Day 1 and insulin use on the day of a clinical visit and before a blood draw will be tabulated. Similarly, the use of RAAS inhibitors (RAASi) will be tabulated as will the incidence of congestive heart failure (CHF), chronic kidney disease (CKD), and diabetes mellitus (DM). The proportion of patients with baseline eGFR<60 and =>60 and AP baseline S-K <5.5, 5.5-<6.0, and >=6.0 will be tabulated.

2.1.6. Prior and Concomitant Medications

Prior medications include medications and therapies started prior to the first day of a study phase. Concomitant medications include medications that (1) started prior to, but continued after the first day of a study phase, or (2) medication changes (including newly initiated medications) during a study phase. All prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version will be designated in the clinical study report). The number and percentage of subjects exposed to each medication will be tabulated. These concomitant medication data for each study phase will be summarized by Anatomical Therapeutic Chemical (ATC) class and
preferred name within ATC, and by treatment group and overall, for the corresponding phase’s Safety Population.

2.1.7. **Analysis of Efficacy**

2.1.7.1. **Efficacy Parameters**

2.1.7.1.1. **Primary Efficacy Parameter**

The primary efficacy parameter will be the model-based least squares mean (LSMEAN) of all available S-K values inclusive of MP Days 8-29.

2.1.7.1.2. **Secondary Efficacy Parameters**

For the MP:

- Number of normokalemic days during the MP inclusive of Days 8-29. This parameter will be calculated assuming that the time interval between assessments is normokalemic only if both the beginning and end assessments for that time interval display normal S-K values. If an intermediate assessment time point is missing, the time interval will be extended until the next non-missing time point.

- Nominal and percent change from AP Baseline to each MP assessment time point (MP Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29, 35)

- Nominal and percent change from MP Baseline to each MP follow-up time point (MP Study Days 2, 5, 8, 12, 15, 19, 22, 26, 29, 35)

- The mean and median time to hyperkalemia (defined as S-K ≥ 5.1 mmol/L, inclusive)

- The Kaplan-Meier lifetable and the mean and median time to relapse (defined as return to original AP baseline S-K level)

- The mean S-K intra-subject standard deviation calculated among subjects with at least 2 values on or after MP Study Day 8.

- The proportion of subjects who remain normokalemic at MP Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29, and 35.

For the AP (note: 24-hour assessments are those made on AP Study Day 2; 48-hour assessments are those made on AP Study Day 3):

- Exponential rate of change in S-K levels (as of the 48-hour time point) derived from a mixed effect model of serial S-K levels during the AP (log-transformed) on time, treatment-by-time interaction, baseline eGFR, CKD status, CHF status, RAASi use (yes, no), diabetes status, and age as:

\[
\text{exp}[\ln((\text{mean baseline S-K}) + \text{time}(\beta_{\text{time}} + \beta_{\text{time*treatment}})/(\text{mean baseline S-K})) - 1 ]
\]

- Nominal and percent change from baseline in S-K levels at 24 hours

- Nominal and percent change from baseline in S-K levels at 48 hours
• Proportion of subjects who achieve normokalemia at 24 hours
• Proportion of subjects who achieve normokalemia at 48 hours
• Time to normalization in S-K levels.

2.1.7.1.3. Additional Outcomes

• S-Mg, S-Ca, S-Na, BUN, HCO3, S-PO4, Bilirubin, AST, ALT, S-Aldo, P-Renin, as well as urinary protein:creatinine ratio (UPCR) and urinary albumin:creatinine ratio (UACR).
• S-Galectin-3, S-Insulin, P-BNP, P-PTH, HbA1c and urinary p-cresol and indole
• Incidence of doctor’s visits other than those specified by protocol
• Incidence of hospitalization and emergency room visits
• Percent change in urinary protein over time.
• For MP Days 8-29:
  • Proportion of patients with mean S-K <5.1 (based on simple average of available S-K assessments between MP Days 8-29)
  • Proportion of patients with mean S-K <5.6 (based on simple average of available S-K assessments between MP Days 8-29)
  • Percent of S-K measurements <5.1 per patient
  • Percent of S-K measurements <5.6 per patient
  • Intra-patient range (based on difference between the max and min values during MP Days 8-29)
  • Percent attainment of goal S-K (S-K<=5.1) from each subject’s AP baseline at Days 15 and 29 (truncate at 100%)
• Proportion of subjects with >=70% attainment of goal S-K at Days 15 and 29
• For the AP:
  • Percent of patients with >=1.0 drop in S-K at Day 2/hr 0 and Day 3/hr 0
  • Percent of patients with >=0.5 drop in S-K at Day 2/hr 0 and Day 3/hr 0
  • Percent of patients with baseline S-K >=6.0 dropping by >=0.5 by Day 1/hr 2 and Day 1/hr 4
  • Percent of patients with baseline S-K >=6.0 dropping by >=1.0 by Day 2/hr 0 and Day 3/hr 0

2.1.7.2. Statistical Methodology

Acute Phase (AP)

Descriptive statistics at baseline, 24 hours, and 48 hours will be calculated for the nominal and percent changes from baseline and the exponential rate of change. One-sample, two-sided t-tests for each of these parameters will assess the null hypotheses that the means equal zero. A p-value ≤0.05 will be considered statistically significant.
The proportions of subjects achieving normokalemia at 24 hours and 48 hours and corresponding 95% two-sided confidence intervals for differences will be calculated and a two-sided Fisher Exact test will assess the null hypotheses of no difference. A p-value ≤0.05 will be considered statistically significant.

The time-to-normalization of S-K will be summarized using Kaplan-Meier life table curves. All AP assessments (e.g., not just those at 24 and 48 hours) will be used.

Maintenance Phase (MP)

The primary efficacy parameter will be the mean of the Day 8-29 S-K values derived from a longitudinal model (SAS PROC MIXED) to simultaneously compare each active dose (highest to lowest dose) versus placebo control as follows:

- Dependent variable: S-K data at scheduled visits inclusive of Days 8-29
- Unstructured variance covariance matrix
- Random effect: subject
- Fixed effects: MP treatment group; AP baseline eGFR; AP and MP baseline S-K; age (<55, 55-64, ≥65 years); binary indicators for RAASi use, CKD, CHF, and DM.
- Least squares means (LSMEANS) of the treatment effect with the observed margins (OM option) will be used to estimate the primary efficacy parameter

Two supportive analyses of the primary efficacy parameter will be executed.

- First, the above model will be repeated adding in subjects that discontinued study treatment before obtaining a Day 8 S-K level. An expectation-maximization (EM) algorithm (defined in Section 2.1.7.2.2 Handling of Dropouts or Missing Data) will be used to interpolate data for these subjects.
- Second, the above model will be repeated with two modifications: 1) each subject’s day 8 through 29 S-K assessments will be rescaled by subtracting the MP baseline and 2) the MP baseline factor will be dropped from the model.

The nominal and percent changes in S-K from AP and MP baselines to MP follow-up time points will be summarized by time point and analyzed using a mixed effect regression model with the same covariates delineated above for the primary efficacy parameter. Additionally, within treatment group changes will be assessed using one-sample, two-sided t-tests and comparisons between treatment groups will be assessed using two-sample, two-sided t-tests.

The number of normokalemic days will be analyzed using a linear regression model with the same covariates delineated above for the primary efficacy parameter.

The proportion of subjects who remain normokalemic at each MP follow-up time point will be compared for each active dose (highest to lowest) versus placebo control using a two-sided Fisher Exact test. Additionally for the Day 29/EOS time point, the percentage of normokalemic subjects at MP Day 29/EOS will be compared using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint.
The time to hyperkalemia and the time to relapse will be summarized using a Kaplan-Meier life table with corresponding log rank tests comparing each active dose (highest to lowest dose) versus placebo control. A proportional hazard model (SAS PROC PHREG) will be assessed with the same covariates delineated above for the primary efficacy parameter.

The intra-subject standard deviation will be calculated as the square root of the back-transformed mean square error from a one-way analysis of variance (PROC GLM) by treatment group of the natural-log-transformed S-K assessments for Days 8-29, inclusive, with a factor for subject.

**Additional Endpoints**

The additional endpoints will be analyzed among the AP and MP ITT Populations for their respective study phases.

All continuous-scaled parameters will be summarized by time point and for their nominal and percent changes from AP baseline, for AP follow-up time points, for both the AP and MP baseline, and for MP follow-up time points. For continuous parameters, within treatment group changes from baseline will be assessed using one-sample, two-sided t-tests and, for the MP, comparisons between treatment groups for the change from baseline will be assessed using two-sample, two-sided t-tests.

Nominal-scaled parameters (e.g., number of unscheduled doctor visits, hospitalizations, and emergency room visits) will be summarized for the AP and MP. For the AP and MP, these parameters will be assessed for within treatment group statistical significance using one-sample, two-sided t-tests or a binomial test (if percent is more appropriate to the number of events being at most one).

For the MP, comparisons between treatment groups will be assessed using two-sample, two-sided t-tests or a two-sided Fisher Exact test, as appropriate.

**2.1.7.2.1. Adjustments for Covariates**

Regression models will control for baseline AP eGFR; baseline AP and MP S-K; age (<55, 55-64, >65 years); binary indicators for RAASi use, CKD, CHF, and DM, as described in Statistical Methodology, Section 2.1.7.2.

**2.1.7.2.2. Handling of Dropouts or Missing Data**

Aberrant S-K data, defined as S-K change >=2.0 mmol/L over 24 hours or >=1.6 mmol/L over 4 hours, will be reviewed by data management, medical, and statistical personnel to determine if the data should be considered invalid and thus considered missing for the data analysis. All such changes will be made before the database is unblinded and will be documented by the ZS-004 Project Manager and approved by the Chief Scientific Officer and Chief Biostatistician.

In the event of missing S-K data from the central laboratory, the i-STAT data will be used to replace missing data by adjusting for the average paired difference between the central and i-STAT levels collected at the same visit. As illustration of the change methodology, if the mean difference between central laboratory and i-STAT assessments for subjects / visits with both is 0.12 mmol/L higher for the
central laboratory assessment, then 0.12 mmol/L will be added to the i-STAT level to impute the missing central laboratory assessment.

If both the central laboratory and i-STAT values are missing, the EOS value will be used if it is within 1 day of a target study day and the last dose date.

If a subject’s Day 29 S-K assessment is made more than one day after the last dose, it will be treated as missing in data analysis and handled as defined above.

If a subject discontinues the MP before Day 8, a Day 8 S-K will be interpolated based on an EM algorithm in which the Day 8 average from subjects with Day 8 data in the same treatment group will be used. These data will only be used in a confirmatory analysis of the primary efficacy assessment.

No other data will be computed or inferred for either missing baseline or on-study data for any other efficacy or safety endpoint.

2.1.7.2.3. Interim Analyses and Data Monitoring

No interim analyses are planned for this study. An independent data monitoring committee (iDMC) will monitor safety data during the study as directed by an approved iDMC charter. ZS Pharma Pharmacovigilance, or their designee, will expedite to the regulatory authorities only the serious adverse reactions that are product-related and unexpected in accordance with FDA 21 CFR 312 and 320 and the ICH E2A guideline.

2.1.7.2.4. Multiple Comparisons / Multiplicity

An overall Type I error rate of 5% will be maintained using a sequential closed testing procedure in which the following sequence of tests will each be assessed at a 5% type I error rate, recognizing that the first lack of significance of a test precludes significance claims for subsequent tests:

- AP S-K exponential rate of change from baseline through 48 hours (Null hypothesis: exponential rate of change from baseline equals 0)
- MP Day 8-29 mean S-K (Null hypothesis: 15 g = placebo)
- MP Day 8-29 mean S-K (Null hypothesis: 10 g = placebo)
- MP Day 8-29 mean S-K (Null hypothesis: 5 g = placebo)
- MP Total number of days normokalemic (Null hypothesis: 15 g = placebo)
- MP Total number days normokalemic (Null hypothesis: 10 g = placebo)
- MP Total number days normokalemic (Null hypothesis: 5 g = placebo)
- MP Day 29 (or day of last dose) proportion of subjects normokalemic (Null hypothesis: 15 g = placebo)
- MP Day 29 (or day of last dose) proportion of subjects normokalemic (Null hypothesis: 10 g = placebo)
- MP Day 29 (or day of last dose) proportion of subjects normokalemic (Null hypothesis: 5 g = placebo)
• MP mean S-K intra-subject standard deviation (Null hypothesis: 15 g = placebo)
• MP mean S-K intra-subject standard deviation (Null hypothesis: 10 g = placebo)
• MP mean S-K intra-subject standard deviation (Null hypothesis: 5 g = placebo)

For evaluation of efficacy in key clinical subgroups (e.g., RAASi, CKD, CHF, or DM), comparisons will be made with no adjustment for multiple comparisons.

2.1.7.2.5. Examination of Subgroups

To prospectively assess efficacy claims within clinically important subgroups (separate subpopulations using RAASi, or having CKD, CHF, or DM], the model described in Section 2.1.7.2 will be separately applied to each subgroup; in addition, descriptive statistics will be generated for each subgroup. In addition, the same model will be expanded to include treatment-by-subgroup interaction terms to simultaneously evaluate dose effects in each subgroup relative to the placebo control; all subjects (i.e., with and without the condition) will be included in these models.

Additionally, AP and MP mean, change and percent changes over time will be summarized in the following subgroups: baseline eGFR<60 and AP baseline S-K <5.5, 5.5-<6.0, and >=6.0.

2.1.8. Safety Evaluation

Analyses for all safety assessments, including adverse events (AE), vital signs, electrocardiograms (ECGs), and clinical chemistry (specifically, the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis parameters, will be conducted separately for the AP and MP using their respective safety analysis populations.

2.1.8.1. Extent of Exposure

Summary tables on exposure to the study treatment will be generated for the AP-SPopulation and the MP-SPopulation for their respective study phases. Descriptive statistics will be presented for the following parameters:

1. Length of study treatment: number of days between the first and the last dose of study treatment plus one.
2. Number of administrations of study medication
3. Compliance as measured by the percentage of prescribed study treatments administered; this includes the percentage and timing of dose reductions for S-K levels <-3.5 mmol/L.

2.1.8.2. Adverse Events

Adverse events will be classified by MedDRA (Version 15.1E or later; the final version used for the study will be designated in the clinical study report). Treatment emergent AEs (TEAEs) for a particular study phase (AP vs. MP) are defined as any event that started during the study phase and was not present at baseline of that study phase or one that represents an exacerbation of a condition present at baseline of that study phase. The MP includes safety follow-up beyond the last dose of study drug as defined in the clinical
trial protocol. No attempt will be made to integrate AEs captured during the extension study (Protocol ZS-004E). If the start date of an AE is partially or completely missing and the end (stop) date does not indicate that it occurred prior to first dose, then the determination of treatment emergence status will be based on the following:

- If the start year does not overlap with the treatment period (combined AP and MP), then the AE is not considered treatment-emergent.
- If the start year overlaps with the treatment period:
  - and the start month is missing, then the AE will be considered treatment-emergent for both the AP and MP;
  - and the start month is present and overlaps with either or both of the treatment phases, then the AE will be considered treatment-emergent for the corresponding phase(s).
- If the start date is completely missing, then the AE will be considered treatment-emergent for both the AP and MP.

Related AEs are defined as those that the investigator designated as possible, probable, or definitely related to the study medication or those with missing relationship.

The number and percentage of subjects experiencing each TEAE as well as the number of events recorded, classified by System Organ Class (SOC) and Preferred Term (PT), will be tabulated. The following subpopulations of TEAEs will be similarly tabulated: related, serious, and those leading to study treatment discontinuation. All and related TEAEs will also be summarized by severity (mild, moderate, or severe; missing determinations will be assumed to be severe), in which a subject’s most severe event within a category (e.g., SOC, PT) will be counted. Listings will be provided for all SAEs and AEs leading to treatment discontinuation.

MP TEAEs (all and the related subpopulation) will be assessed using two-sided Fisher Exact tests to compare each active dose to placebo.

2.1.8.3. Clinical Laboratory Evaluation

Summary statistics for continuous-scaled analytes below will be calculated at baseline and follow-up time points as well as the nominal and percent changes from baseline for each study phase. The MP tabulations will also include changes relative to the AP baseline. If multiple values are recorded for the same analyte during a visit window, the assessment closest to the target study day will be used. The changes within treatment groups will be assessed using paired t-tests. In addition, for the MP, differences in changes between each active dose and placebo will be assessed using two-sample t-tests.

Categorical-scaled analytes will be summarized as number and percent for each observed category at each study time point.

**Laboratory Tests Performed: Screening, During Study, and at Follow-up**

<table>
<thead>
<tr>
<th>Clinical Chemistry</th>
<th>Hematology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Concentrations of:</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Total protein</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>Albumin</td>
<td>Erythrocyte count (RBC)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Differential leukocytes</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>Total leukocytes (WBC)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Platelets</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>pH</td>
</tr>
<tr>
<td>Glucose</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Sodium</td>
<td>Glucose</td>
</tr>
<tr>
<td>Potassium</td>
<td>Ketones</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Calcium (total)</td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Blood</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (GGT)</td>
<td>Urine Sediment</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Urine Culture</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Urine pregnancy test</td>
</tr>
</tbody>
</table>

**North American Sites ONLY**

<table>
<thead>
<tr>
<th>Aldosterone</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Sodium</td>
</tr>
<tr>
<td>Insulin</td>
<td>Potassium</td>
</tr>
<tr>
<td>BNP</td>
<td>Creatinine</td>
</tr>
<tr>
<td>PTH</td>
<td>Protein</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>p-Cresol</td>
</tr>
<tr>
<td>HbA1c5</td>
<td>Indole</td>
</tr>
</tbody>
</table>

The incidence of hypokalemia will be evaluated by tabulating the proportion of subjects in each study phase (e.g., AP and MP separately) with a minimum S-K follow-up assessment < 3.5 mmol/L and will be repeated for a more severe definition of < 3.0 mmol/L. The degree of hypokalemia is defined as follows: mild (3.0-3.4 mmol/L), moderate (2.5-2.9 mmol/L), and severe (< 2.5 mmol/L).

Laboratory analytes will be cross-classified relative to reference ranges for baseline versus maximum and minimum follow-up assessments for AP and MP separately. This analysis will be repeated using potentially clinically significant (PCS) criteria for select analytes (see Appendix 1).

### 2.1.8.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

**Vital Signs**

Vital signs will include weight, body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure for all time points. Summary statistics will be calculated at baseline and follow-up time points as well as the nominal and percent changes from baseline for each study phase. The MP tabulations will also include changes relative to the AP baseline. The changes within treatment groups will be assessed using paired t-tests. In addition, for the MP, differences in changes between each active dose and placebo will be assessed using two-sample t-tests.
Heart rate and systolic and diastolic blood pressure will be cross-classified relative to PCS criteria (see Appendix 1) for baseline versus maximum and minimum follow-up assessments for AP and MP separately.

Physical Findings

Adverse physical examination changes are captured as adverse events and will be listed.

Electrocardiogram

The following measurements are taken in 12-lead ECG during the AP (Days 1, 3, and 9/EOS) and MP (Days 1, 8, 15, 22, 29, and 35/EOS):

- PR interval
- QRS duration
- QT/QTc (note: QTc will be based on Bazett’s correction)
- Overall evaluation (normal; abnormal-clinically significant; abnormal-not clinically significant).

For the continuous variables above, summary statistics will be calculated at baseline and follow-up time points as well as the nominal and percent changes from baseline to each follow-up time point for each study phase. The MP tabulations will also include changes relative to the AP baseline. The changes within treatment groups will be assessed using paired t-tests. In addition, for the MP, differences in changes between each active dose and placebo will be assessed using two-sample t-tests.

Additionally, for AP and MP separately, the incidence of the following findings will be tabulated:

- Each subject’s maximum absolute QTc interval prolongation across their post-baseline ECG assessments within the study phase > 500
- Each subject’s maximum increase from QTc baseline across their post-baseline ECG assessments within the study phase:
  - >30
  - >60
- Each subject’s maximum absolute QTc interval prolongation across their post-baseline ECG assessments within the study phase > 500 AND maximum increase from QTc baseline across their post-baseline ECG assessments within the study phase:
  - >30
  - >60

For overall evaluation, the number and percentage of subjects in each category will be tabulated over time and the proportion shifting from normal at baseline to abnormal-clinically significant at any subsequent time point will be tabulated for AP and MP separately.

2.2. Determination of Sample Size

The sample size is based on the mean S-K during MP Study Days 8-29. To optimize the comparison of three active doses vs. placebo control, the placebo group will have 1.73 x the
number of subjects per active dose. A 4:4:4:7 allocation best approximates the optimum Dunnett’s allocation.

A sample size of 232 MP subjects (49 per active dose and 85 placebo controls) will have 90% power and 5% Type 1 error for a two-sided hypothesis test to detect a mean 0.3 mmol/L advantage for MP Study Days 8-29 for any active dose vs. placebo control using a pre-specified closed testing order (highest to lowest dose); a mean 0.3 mmol/L decrease represents a meaningful advantage between any dose and placebo for a pooled 0.5 standard deviation. The sample size also has 90% power and 5% Type I error to detect a mean 4-day increase in days normokalemic between any dose and placebo over the 28-day MP for a pooled 6-day standard deviation. The power calculation for the mean S-K during MP Days 8-29 is displayed in Column 1 while the mean days normokalemic is displayed in Column 2 for that sample size.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean S-K DBRMP Days 8-29</th>
<th>DBRMP Days Normokalemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test significance level, alpha</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>1 or 2 sided test?</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean Difference, m1 - m2</td>
<td>0.3 mmol/L</td>
<td>3.6 days</td>
</tr>
<tr>
<td>Pooled SD, s</td>
<td>0.5 mmol/L</td>
<td>6 days</td>
</tr>
<tr>
<td>Effect size, d =</td>
<td>m2 – m1</td>
<td>/ s</td>
</tr>
<tr>
<td>Power (%)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Active Dose Group, n2</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Placebo Controls, n1</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Total N=n1 + 3n2</td>
<td>232</td>
<td>232</td>
</tr>
</tbody>
</table>

3. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The study protocol definition of a TEAE during the MP includes events emerging during the AP if not resolved by the start of MP treatment. This definition has been changed such that only events that started or worsened during the MP will be considered treatment emergent and was made possible by rigorous data collection on AE start dates and dates of severity changes. This change will allow more clear interpretation of safety signals arising during the randomized treatment phase.

Additional safety analyses have been planned including shift tables relative to laboratory reference ranges, shift tables for both laboratory and vital sign parameters relative to potentially clinically significant criteria, and a thorough assessment of clinically relevant ECG changes as defined in ICH Guidance E14 “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs”.

The sample size justification narrative was corrected to reflect that the placebo group will have 1.73x, rather than 1.6x, the number of subjects per active dose.
### 4. APPENDIX 1 – POTENTIALLY CLINICALLY SIGNIFICANT CRITERIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Significance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/dL</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>Inorganic Phosphorus</td>
<td>mg/dL</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/dL</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>mmol/L</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Sodium</td>
<td>mmol/L</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Total Protein</td>
<td>g/dL</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>mg/dL</td>
<td>&lt;0.9</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>IU/L</td>
<td>NA</td>
</tr>
<tr>
<td>GGT</td>
<td>IU/L</td>
<td>NA</td>
</tr>
<tr>
<td>AST</td>
<td>IU/L</td>
<td>NA</td>
</tr>
<tr>
<td>ALT</td>
<td>IU/L</td>
<td>NA</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>%</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>× 10⁹/L</td>
<td>&lt;50</td>
</tr>
<tr>
<td>WBC</td>
<td>× 10⁹/L</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Vital Sign</td>
<td>Direction</td>
<td>Criterion</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Low</td>
<td>Value $\leq 90$ mmHg and decreased $\geq 20$ mmHg from initial value</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Value $\geq 180$ mmHg and increased $\geq 20$ mmHg from initial value</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Low</td>
<td>Value $\leq 50$ mmHg and decreased $\geq 15$ mmHg from initial value</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Value $\geq 105$ mmHg and increased $\geq 15$ mmHg from initial value</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Low</td>
<td>Value $\leq 50$ bpm and decreased $\geq 15$ bpm from initial value</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Value $\geq 120$ bpm and increased $\geq 15$ bpm from initial value</td>
</tr>
</tbody>
</table>