1 Title Page

ZS-005

Clinical Study Report

A Phase 3 Multicenter, Multi-dose, Open-label Maintenance Study to Investigate the Long-term Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects With Hyperkalemia

Indication studied:	Treatment of Hyperkalemia
Developmental phase of study:	3
First subject enrolled:	23 June 2014
Last subject completed:	04 November 2016
Document ID:	CSR-ZS-005
Sponsor:	ZS Pharma, Inc (a member of the AstraZeneca Group) PPD San Mateo, CA 94403
Responsible Medical Officer/Signatory:	PPD PPD ZS AstraZeneca Research & Development PPD Gaithersburg, MD 20878 Phone: PPD e-mail: PPD
Report Status:	Final
Date:	01 August 2017

This trial was conducted in accordance with the ethical principles of Good Clinical Practices (GCP), according to the International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) Harmonised Tripartite Guideline.

2 Synopsis

Name of Sponsor/Company: ZS Pharma	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: ZS (sodium zirconium cyclosilicate, United States Adopted Name)		
Name of Active Ingredient: sodium zirconium cyclosilicate		

Title of Study: A Phase 3 Multicenter, Multi-dose, Open-label Maintenance Study to Investigate the Long-term Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects with Hyperkalemia

Investigators:

A complete list of investigators is presented in Appendix 16.1.4.

Study center(s):

Multicenter: 56 sites in United States (US), Australia, Germany, the United Kingdom, the Netherlands, and South Africa. Site information is presented in Appendix 16.1.4.

Publication (reference):

None

Studied period (years):	**Phase of development:**
First subject enrolled: 23 June 2014 Last subject completed: 04 November 2016	3

Objectives:

Primary Objective

The primary objective was to generate open-label, long-term (up to 12 months) safety and tolerability data for ZS in subjects with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L).

Secondary Objectives

The secondary objectives were to evaluate:

- the proportion of ZS-treated subjects in whom normokalemia was maintained over prolonged periods of time, using a dose range from 5 g every other day (QOD) to 15 g once daily (QD)
- the effect of ZS on various renal and bone biomarkers over prolonged periods of time, using doses from 5 g QOD to 15 g QD
- the safety and tolerability of investigational product consumed in ~40 mL of water with no mandatory rinses and in ~180 mL of water with two ~30 mL rinses

Methodology:

This was an open-label, multicenter, multi-dose, prospective maintenance study to investigate the long-term safety and efficacy of ZS in subjects with hyperkalemia. Baseline potassium was determined prior to taking the first dose of ZS by collecting 2 consecutive potassium measurements (i-STAT and central laboratory) at 0 and 60 (± 15) minutes. Subjects with 2 consecutive i-STAT potassium values ≥ 5.1 mmol/L entered the Acute Phase and received ZS 10 g TID for 24 to 72 hours, depending on potassium values. Once normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) was restored (whether after 24, 48, or 72 hours) in the Acute Phase, subjects were enrolled in the Extended Dosing Phase to receive ZS at a starting dose of 5 g QD. Potassium (i-STAT and central laboratory) was measured weekly throughout the first month of study and every 4 weeks thereafter through Month 12.

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Methodology (continued): During the Extended Dosing Phase, the ZS dose may have been increased or decreased in increments/decrements of 5 g QD up to a maximum of 15 g QD or a minimum of 5 g QOD based on i-STAT potassium measurements as outlined below:

- > 5.0 mmol/L while receiving 5 g QD or 5 g QOD or > 5.5 mmol/L while receiving 10 g QD: ZS dose increased in 5 g QD increments to a maximum dose of 15 g QD.
- Between 3.0 and 3.4 mmol/L, inclusive: ZS dose decreased in 5 g QD decrements to a minimum dose of 5 g QOD; if a subject's i-STAT potassium value remained between 3.0 and 3.4 mmol/L, inclusive, on the ZS 5 g QOD dose, the subject was withdrawn from the study and received standard of care treatment.

Any time the ZS dose was adjusted or a renin-angiotensin-aldosterone system (RAAS) inhibitor or diuretic dose was adjusted or initiated during the Extended Dosing Phase, the subject returned to the site 7 (± 1) days later for a potassium measurement and recording of adverse events and concomitant medications. There was no limit to the number of dose titrations allowed.

Safety stopping rules were specified for this study and were administered by the ZS Pharma Medical Monitor. Any subject who was withdrawn from the study prior to study completion returned to the clinic 7 (± 1) days after the last dose of study drug for an End of Study visit.

Efficacy evaluation consisted of S-K and i-STAT measurements collected at regular intervals during the study. Additional evaluations consisted of measurements of sodium, calcium, magnesium, bicarbonate, phosphorus, blood urea nitrogen, and estimated glomerular filtration rate (eGFR). Assessments performed only at sites in North America included whole blood and urine samples for serum aldosterone, plasma renin, serum galectin-3, plasma brain natriuretic peptide, plasma parathyroid hormone, serum insulin, glycated hemoglobin, and urine chemistry including albumin, sodium, potassium, creatinine, and protein. In addition, blood zirconium levels were determined for subjects at selected study sites in North America. Safety evaluations included physical examinations, weight, vital signs, 12-lead electrocardiograms (ECGs), and standard laboratory parameters (hematology, serum chemistry, and urinalysis). Adverse events and use of concomitant medications were collected throughout the study.

Health care utilization data (incidence of hospitalizations, emergency room visits, and non-protocol required doctor's office visits) were also collected.

Number of subjects (planned and analyzed):

Planned:	750 subjects
Enrolled:	
ZS-005:	751 subjects
Acute Phase:	751 subjects treated with ZS 10 g TID
Extended Dosing Phase:	746 subjects treated with ZS initiated at 5 g QD

Diagnosis and main criteria for inclusion:

Subjects were male or female, > 18 years of age with 2 consecutive i-STAT potassium values ≥ 5.1 mmol/L; an upper limit on the i-STAT potassium value at study entry was specified for subjects enrolled at sites in Germany (≤ 6.5 mmol/L).

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Test product, dose and mode of administration, batch number:

Sodium zirconium cyclosilicate (ZS, particle size ≥ 3 μm) administered orally as a slurry/suspension in water.

Subjects at selected sites in the US who enrolled in the study on Acute Phase Day 1 under Amendment 5 or later, if applicable, consumed study drug suspended in ~40 mL of water with no mandatory rinses. Subjects at all other sites consumed study drug suspended in ~180 mL of water followed by two ~30 mL rinses.

Acute Phase: Subjects were to receive ZS 10 g TID before breakfast, lunch, and dinner for at least 24 hours and up to 72 hours (3 to 9 total doses).

Extended Dosing Phase: The starting dose was ZS 5 g QD, prior to breakfast. Thereafter, the dose was adjusted based on i-STAT potassium values.

The ZS lot numbers used during the study were ZS130008, ZS140005, ZS140006, ZS140007, ZS140008, ZS140009, ZS140010, ZS140011, ZS140017, ZS140018, ZS140019A, ZS140020A, ZS140021A, ZS140022A, ZS140023A, ZS140024A, ZS140025A, ZS140026A, ZS140027A, ZS140028A, ZS140029A, ZS140030A, ZS140034A, ZS140035A, ZS140037A, ZS140038A, ZS140039A, ZS140040A, ZS140041A, ZS140042A, ZS140043A, ZS140044A, ZS140045A, ZS140046A, ZS140048A, ZS140049A, ZS140050A, ZS140051A, ZS140052A, ZS140053A, ZS140054A, ZSB14001A, ZSB14002A, ZSB14004A, ZSB15005A, ZSB15015A, ZSB15022A, ZSB14001B, ZSB14002B, ZSB14004B, ZSB15001C, ZSB15002C, and ZSB15004C.

Duration of treatment:

Treatment duration was up to 72 hours in the Acute Phase and up to 12 months in the Extended Dosing Phase.

Reference therapy, dose and mode of administration, batch number:

None

Criteria for evaluation:

The primary efficacy endpoint for the Acute Phase was the restoration of normal S-K values (3.5 to 5.0 mmol/L, inclusive; 3.5 to 5.5 mmol/L, inclusive, was also presented). For the Extended Dosing Phase, the primary efficacy endpoint was the maintenance of normokalemia (as defined by proportion of subjects with mean S-K < 5.1 mmol/L from Month 3 to 12 [Extended Dosing Phase Days 85, 113, 141, 176, 211, 239, 267, 295, 330, 365, and End of Study] for subjects in the Extended Dosing Phase intent-to-treat (ITT) Population; mean S-K < 5.5 mmol/L from Month 3 to 12 was also presented.

Secondary efficacy endpoints included: proportion of subjects with mean S-K between 3.5 and 5.5 mmol/L, inclusive, Months 3 to 12 (Extended Dosing Phase Days 85, 113, 141, 176, 211, 239, 267, 295, 330, 365, and End of Study) for subjects in the Extended Dosing Phase ITT Population; mean S-K values Months 3 to 12 (Extended Dosing Phase Days 85, 113, 141, 176, 211, 239, 267, 295, 330, 365, and End of Study), Months 6 to 9, and Months 9 to 12 for subjects in the Extended Dosing Phase ITT Population; change (absolute and percent [%]) baseline (Acute Phase baseline) in S-K levels at each Extended Dosing Phase Day 8-365/End of Study for subjects in the Extended Dosing Phase ITT Population; nominal and % change from Acute Phase Baseline in bicarbonate at Extended Dosing Phase Days 8, 15, 22, 29, 57, 85, 176, 267, 365, and End of Study for subjects in the Extended Dosing Phase Safety Population; proportion of subjects with normal bicarbonate values at Acute Phase Day 1 and Extended Dosing Phase Days 1, 8, 15, 22, 29, 57, 85, 176, 267, 365, and End of Study for subjects in the Extended Dosing Phase Safety Population.

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Criteria for evaluation (continued):

In addition, the primary safety endpoint was safety and tolerability as measured by adverse event reporting, vital signs, ECGs, physical examinations, and safety laboratory measurements.

Statistical methods:

Study populations were prospectively defined based on separate evaluability rules for the Acute Phase and Extended Dosing Phase. Safety Populations included subjects who received at least 1 dose of ZS and the ITT Populations included subjects who received at least 1 dose of ZS with at least 1 S-K assessment after administration of ZS.

Efficacy: Separate analyses were performed for the Acute and Extended Dosing Phases. All analyses of S-K were based on S-K values analyzed by the central laboratory. When means, proportions, nominal changes or percent changes were presented, 95% confidence intervals (CIs) and t-tests (paired from baseline or independent 2-group) with 2-sided p-values were presented where appropriate. Selected efficacy endpoints were summarized within clinically important baseline subpopulations (CKD, heart failure, diabetes mellitus, use of RAAS inhibitor medication, Acute Phase baseline eGFR < 60 mL/min, Acute Phase baseline S-K < 5.5, 5.5 to < 6.0 mmol/L, and ≥ 6.0 mmol/L and ages < 55 years, 55 to 64 years, and ≥ 65 years).

Safety: Separate analyses were performed for the Acute and Extended Dosing Phases. Treatment-emergent adverse events (TEAEs) were defined as any event that started during the study phase and was not present at baseline of that study phase or one that represented an exacerbation of a condition present at baseline of that study phase. The Medical Dictionary for Regulatory Activities, Version 17.0, was used for coding adverse events. The number and percentage of subjects experiencing each TEAE as well as the number of events recorded, classified by system organ class and preferred term, were tabulated. Similar tabulations were presented for TEAEs considered related to study drug by the investigator, that were serious, and that led to discontinuation from the study. All and related TEAEs were also summarized by severity (mild, moderate, or severe; missing determinations were assumed to be severe), in which a subject's most severe event within a category (eg, system organ class, preferred term) was counted.

Change and percent change from baseline for clinical laboratory analytes were summarized for each study phase. Laboratory analytes were cross-classified relative to reference ranges for baseline versus maximum and minimum follow-up assessments for Acute Phase and Extended Dosing Phase separately. This analysis was repeated using potentially clinically significant criteria prespecified by the Sponsor for select analytes.

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

Change and percent change from baseline for vital signs and quantitative ECG measures were summarized for each study phase. The proportions of subjects meeting prespecified ECG and vital signs criteria were tabulated.

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Summary – Conclusions

Of the 751 subjects enrolled in the Acute Phase of the study, 746 (99.3%) completed and continued into Extended Dosing based on i-STAT potassium values within the normal range (3.5 to 5.0 mmol/L, inclusive). A total of 466 (62.5%) subjects completed the Extended Dosing Phase; the most common reasons leading to premature termination were withdrawal of consent (10.9%), adverse event (6.8%), expected progression of CKD requiring dialysis, transplant, or other treatment (5.4%), lost to follow-up (4.2%), and subject compliance (2.3%).

At baseline, age ranged from PPD to PPD years, with a mean age of 63.6 years. The majority of the subjects were male (59.7%), White (83.1%), and not of Hispanic origin (57.4%). Comorbid conditions included CKD (based on eGFR < 60 mL/min, 73.5%), diabetes mellitus (62.7%), and heart failure (37.9%). The majority of the subjects had a history of hypertension (82.8%). Diuretic use was reported by 51.0% of subjects and use of RAAS inhibitor medication was reported by 70.2% of subjects.

Efficacy Results:

Results of this study showed rapid correction of hyperkalemia during the Acute Phase, similar to results of the previous placebo-controlled studies that demonstrated rapid correction of hyperkalemia with ZS dosing. In addition, normokalemia can be maintained during long-term administration.

Subjects achieved normokalemia (S-K values between 3.5 and 5.0 mmol/L, inclusive) during the Acute Phase with ZS 10 g TID (77.9%; 583/748), with 66.0% of them responding within 24 hours. Among the 583 subjects who achieved normokalemia during the Acute Phase, 84.7% (494/583) did so within 24 hours and 98.7% were between 3.5 and 5.5 mmol/L, inclusive, at the end of Acute Phase dosing.

Results were consistent across subpopulations defined by age, baseline eGFR, RAAS inhibitor use, and comorbid conditions of diabetes mellitus, heart failure, and CKD. Subjects with lower S-K values at baseline had greater proportions achieving normokalemia compared to those with higher baseline S-K values (< 5.5 mmol/L: 87.4%; ≥ 5.5 to < 6.0 mmol/L: 77.4%; ≥ 6.0 mmol/L: 57.9%).

Overall, the mean reduction in S-K values at the end of Acute Phase dosing was -0.85 mmol/L, representing a mean percent decrease of 14.81%. When subjects were summarized by time point (24, 48 or 72 hours) at which they completed Acute Phase dosing (based on i-STAT values), mean baseline S-K values were higher (5.55, 5.77, and 5.93 mmol/L, respectively) and the mean reductions were greater for subjects who required more than 24 hours to respond (-0.81, -1.02, and -1.10 mmol/L, respectively). This pattern was also observed for subjects with baseline S-K values ≥ 6.0 mmol/L, with mean baseline S-K values of 6.22, 6.33, and 6.56 mmol/L and mean reductions of -1.30, -1.43, and -1.73 mmol/L for subjects who completed Acute Phase dosing at the 24-, 48-, and 72-hour time points, respectively. Although subjects with baseline S-K ≥ 6.0 mmol/L had a lower proportion of subjects achieving normokalemia (57.9%), irrespective of the day they completed Acute Phase dosing, 98.4% had S-K values between 3.5 and 5.5 mmol/L, inclusive, and demonstrated a greater reduction from baseline (-1.35 mmol/L) compared to those with lower baseline S-K values (S-K ≥ 5.5 to < 6.0: -0.81 mmol/L; S-K < 5.5: -0.51 mmol/L).

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Efficacy Results (continued):

Differences were observed in the evaluation of efficacy data between potassium values measured by i-STAT versus S-K values measured by the central laboratory. The proportions of subjects who achieved normokalemia during the Acute Phase based on i-STAT was 99.5% compared to the 77.9% observed for S-K. However, i-STAT (99.9%; 747/748) and S-K (98.7%, 738/748) values yielded similar results for the proportions of subjects with potassium values between 3.5 and 5.5 mmol/L following Acute Phase dosing.

Across Extended Dosing Phase Days 85 to 365, 88.4% of subjects had mean S-K values ≤ 5.1 mmol/L and 98.8% had mean S-K values ≤ 5.5 mmol/L. Efficacy findings were similar across the Extended Dosing Phase time points; for subjects who completed 12 months of treatment (N = 439), the proportion whose mean serum potassium was ≤ 5.1 mmol/L and ≤ 5.5 mmol/L was 87.2% and 96.1%, respectively.

These results were consistent across the analyses of subpopulations defined by age, baseline eGFR, RAAS inhibitor use, and comorbid conditions of diabetes mellitus, heart failure, and CKD. Greater proportions of subjects with baseline S-K values < 5.5 mmol/L achieved mean S-K values ≤ 5.1 mmol/L (94.8%) as compared to subjects with baseline S-K values ≥ 6.0 mmol/L (75.5%).

At each time point during Extended Dosing, mean decreases from Acute Phase baseline in S-K were observed, ranging from -0.78 to -1.00 mmol/L. Changes observed relative to the Extended Dosing baseline were much smaller (increases ≤ 0.07 mmol/L and decreases ≤ 0.15 mmol/L), which is consistent with subjects maintaining normokalemia with the S-K values they achieved at the time they entered Extended Dosing. Mean S-K values were maintained within the normal range throughout the Extended Dosing Phase time points; however, approximately 1 week following discontinuation of ZS dosing, the mean S-K value increased by 0.35 mmol/L.

Early in the course of treatment, mean increases from Acute Phase baseline were observed in bicarbonate values among the overall population as well as in subjects with metabolic acidosis (defined as baseline bicarbonate value of < 22 mmol/L). Across Extended Dosing time points, mean increases in bicarbonate values ranging from 0.76 to 1.22 mmol/L were observed for the overall population and from 1.70 to 2.82 mmol/L for subjects with metabolic acidosis.

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Safety Results:

The safety profile observed in this study was consistent with results from previous controlled and uncontrolled studies of ZS in which similar patient populations with similar comorbidities (including CKD, hypertension, heart failure, and diabetes mellitus) were enrolled.

While the majority of subjects completed the 12-month study, the overall rate of premature discontinuation of study drug during the Extended Dosing Phase was 37.5%. The most common reasons leading to discontinuation from study were withdrawal of consent (81 subjects, 10.9%), adverse event (51 subjects, 6.8%), expected progression of CKD requiring dialysis, transplant, or other treatment (40 subjects, 5.4%), lost to follow-up (31 subjects, 4.2%), and subject compliance (17 subjects, 2.3%). Among the reasons leading to discontinuation, the incidence of those possibly associated with decreased tolerability (ie, adverse event, met hypokalemia/ hyperkalemia stopping criteria, met ECG withdrawal criteria, and death) was 10.7% (80/746).

Duration of treatment in the Extended Dosing Phase ranged from 1 to 371 days, with a mean and median duration of 286.2 and 364.0 days, respectively. The majority of subjects (87.0%) received a mean dose of 5 to < 10 g during the Extended Dosing Phase. More than half (55.9%) of the subjects required at least 1 dose modification, most of which were up-titrations to the 10 g QD dose. At least 2 dose modifications were observed in 16.5% of subjects with < 4% requiring at least 3 dose modifications.

Commonly reported TEAEs during Acute Phase dosing were associated with gastrointestinal disorders including nausea (0.5%), diarrhea (0.3%), and constipation (0.3%). During the 12-month Extended Dosing Phase, the overall incidence of TEAEs was 65.5%, the most common (≥ 5.0%) of which were hypertension (11.0%), edema peripheral (9.7%), urinary tract infection (7.9%), nausea (7.5%), constipation (6.4%), anemia (5.9%), and upper respiratory tract infection (5.0%).

A total of 8 (1.1%) subjects died during the Extended Dosing Phase, none of which was considered related to study drug by the investigator. Serious TEAEs occurred in 0.1% of subjects in the Acute Phase and 21.6% of subjects in the Extended Dosing Phase. The most commonly reported serious TEAEs during Extended Dosing included pneumonia (1.9%), cardiac failure congestive (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and renal failure acute (1.1%). Two subjects experienced serious TEAEs during the Extended Dosing Phase that were considered related to study drug by the investigator (pulmonary edema in 1 subject and cardiac failure congestive in 1 subject); both subjects had a medical history of the condition. Discontinuations due to TEAEs occurred in 0.3% of subjects in the Acute Phase and 13.7% of subjects in Extended Dosing Phase. The most common events that led to premature discontinuation during Extended Dosing were cardiac failure congestive (1.5%) and renal failure acute (1.2%). No trend was apparent for the types of serious events reported or among those that led to premature discontinuation from study drug.

The incidence of TEAEs in the haemodynamic oedema, effusions, and fluid overload Standardised Medical Dictionary for Regulatory Activities Query (SMQ), the cardiac failure SMQ, and the hypertension SMQ that were reported during the Extended Dosing Phase was 15.1%, 15.8%, and 11.4%, respectively. Among subjects with TEAEs associated with fluid overload, most had a history of CKD (92.9%) and over half had a history of heart failure (53.1%). Among the 36 subjects with cardiac failure-type TEAEs (after exclusion of TEAEs associated with oedema peripheral, oedema, and pulmonary oedema), most had a history of CKD (86.1%) and/or heart failure (80.6%). Among subjects with TEAEs in the hypertension SMQ, 91.8% had a history of hypertension and/or CKD; none of the hypertension events reported led to premature discontinuation from study drug.

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Safety Results (continued):
The incidence of hypokalemia (S-K < 3.5 mmol/L) was 0.1% in the Acute Phase and 5.8% in the Extended Dosing Phase. All of the events were mild or moderate hypokalemia, with S-K ranging from 2.6 to 3.3 mmol/L. The incidence of hyperkalemia (S-K value ≥ 5.0 mmol/L) was 72.8% in the Extended Dosing Phase; maximum S-K values observed were > 5.0 to ≤ 5.5 mmol/L for 277 (37.1%) subjects, > 5.5 to ≤ 6.0 for 194 (26.0%) subjects, and > 6.0 mmol/L for 72 (9.7%) subjects. During Extended Dosing, the incidence of premature discontinuation from study due to meeting potassium-related stopping criteria was 1.2% for hypokalemia (i-STAT < 3.0 mmol/L) and 0.7% for hyperkalemia (i-STAT > 6.5 mmol/L).

Throughout the study, changes observed in laboratory parameters or vital signs were generally consistent with the underlying comorbidities of the study population. The incidences of potentially clinically significant low magnesium, phosphorus, or calcium values as well as high calcium or sodium values was < 1%. No clinically significant mean changes from Acute Phase baseline in PR interval, QRS duration, and heart rate were observed during the Extended Dosing Phase. Small mean increases in QTc interval were observed throughout the Extended Dosing time points relative to Acute Phase baseline; however, these increases in QTc interval are to be expected with correction of potassium into the normokalemic range.

Conclusions:

This long-term, open-label study showed:

- Rapid reduction of S-K into the normokalemic range within 24 to 72 hours after initiating ZS 10 g TID;
- Maintenance of normokalemia over 12 months and S-K increased after dosing with ZS was stopped, confirming continued need for S-K control;
- Consistent results across subgroups defined by age, baseline eGFR, RAAS inhibitor use, and presence of diabetes mellitus, heart failure, and CKD;
- Although a lower proportion of subjects with higher baseline S-K values achieved and maintained normokalemia during the Acute and Extended Dosing Phases, these subjects had the largest reductions in S-K;
- Consistent safety profile with previous studies of ZS, with no new safety findings identified.

Date of report: 01 August 2017

[redacted]

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

The original protocol, dated 23 April 2014, had 6 amendments. Full details of the Clinical Protocol and the amendments are provided in Appendix 16.1.1. Among the 751 subjects enrolled in the Acute Phase, 2 were enrolled under the original protocol, 142 were enrolled under Amendment 1, 167 were enrolled under Amendment 2, 80 were enrolled under Amendment 3, 114 were enrolled under Amendment 4, 7 were enrolled under Amendment 4A, and 239 were enrolled under Amendment 5.

A summary of the clinically important changes included in each amendment is provided as follows:

Amendment No. 1 (27 June 2014):

- Changed the description of ZS to sodium zirconium cyclosilicate to be consistent with the US adopted name.
- Increased the number of subjects in the randomized withdrawal study from 120 to 200 subjects due to a US FDA request for a less sensitive power analysis which necessitated a larger sample size to maintain statistical power.
- Removed the testing for fasting plasma glucose since fasting serum glucose was collected at the same time points.

- Modified the dose stopping rule to include the Acute Phase and changed the upper limit of the i-STAT potassium value that required discontinuation of study drug from 6.4 to 7.0 mmol/L to mirror the upper limit that was used in the recently completed Phase 3 study, ZS-003.

- Added details regarding the analysis of data from the randomized withdrawal study.

Amendment No. 2 (16 October 2014):

- Reduced the i-STAT potassium value requiring a dose increase of ZS to 5 g QD or 10 g QD from 5.6 to 7.0 mmol/L to 5.1 to 7.0 mmol/L.

- Reduced the i-STAT potassium value that required discontinuation of study drug in the randomized withdrawal study from > 7.0 mmol/L to > 6.2 mmol/L, which was consistent with the completed study, ZS-004, which had a placebo arm.

- Limited participation in the randomized withdrawal study to selected sites in North America rather than all study sites.

- Clarified that the site was to contact the Medical Monitor for dosing directions in the rare case that the i-STAT potassium value was between 3.0 to 3.4 mmol/L during the Acute Phase.

- Updated animal toxicity data from a 9-month oral toxicity study in dogs to support dosing in man beyond 9 months.

- Removed the requirement that a person who was reading a consent form to a vision-impaired non-English speaking subject be a member of the research team who was fluent in the language of the subject since it was not always possible to have members of the research team fluent in multiple languages. In most cases, study sites had access to individuals who were not members of the study team who could read the consent to the subject in the subject's primary language and translate information between the subject and the investigator.

- Clarified that only sexually active women of childbearing potential were to use 2 forms of medically acceptable contraception with at least 1 being a barrier method.

- Removed the lower limit for room temperature storage of study drug based on ongoing stability data.

Amendment No. 3 (22 December 2014):

- Reduced the i-STAT potassium value that required a subject to stop dosing in the Extended Dosing Phase from > 7.0 mmol/L to > 6.5 mmol/L for increased safety during long-term dosing.
- Required subjects to return to the site 7 (± 1) days later if a RAAS inhibitor or diuretic dose was adjusted or initiated during the Extended Dosing Phase or randomized withdrawal study to measure potassium since changes in either of these medications may have altered the level of blood potassium. The i-STAT potassium value was to be evaluated, and the dose of ZS was adjusted or stopped based on the rules in the protocol.
- Clarified that all Extended Dosing Phase visits from Day 8 onwards may have taken place either 1 day early or 1 day late to provide greater flexibility with scheduling.
- Removed the requirement for the randomized withdrawal study to start when the first subject on Extended Dosing Phase Day 176 met the criteria for entry in the randomized withdrawal study.
- Changed the lower limit of age of an eligible subject from 19 to 18 years of age.
- Added the collection of blood samples for analysis of zirconium at baseline and on the morning of Acute Phase Day 2 as recommended by the US FDA at selected study sites in North America.
- Added additional sampling time points for the collection of blood for aldosterone and renin on Extended Dosing Phase Days 29 and 267.
- Modified secondary and exploratory endpoints and a secondary objective.
- Removed information from nonclinical studies that was available in the Investigator's Brochure.
- Deleted the collection of urine for p-cresol and indole at all time points and deleted the collection of blood for BNP and galectin-3 at all time points except baseline (Acute Phase Day 1).

Amendment No. 4 (18 February 2015):

- Increased the enrollment in the Extended Dosing Phase from 500 to 750 subjects to allow sites in Europe sufficient opportunity to enroll subjects in the study.

- Allowed the Medical Monitor to request a dose adjustment based on the central laboratory potassium value and not the i-STAT value if there was a significant discrepancy between the values. This was to be determined on a case-by-case basis by the Medical Monitor. Dose escalation was still only requested if central laboratory S-K value was > 5.0 mmol/L (increase from 5 g QOD to 5 g QD or increase from 5 to 10 g QD) or > 5.5 mmol/L (increase from 10 to 15 g QD).

- Defined medically acceptable contraception as requested by the Clinical Trials Facilitation Group in the European Union as part of the Voluntary Harmonization Procedure assessment.

Amendment No. 4A (11 March 2015):

- Added clarification of medically acceptable contraception methods to Inclusion Criterion 5.

Amendment No. 5 (29 April 2015):

- Incorporated the use of a lower volume of water (40 mL with no mandatory rinses) to deliver the study drug for subjects who enrolled in the trial under this amendment at selected sites in the US. All other subjects were to continue to use 180 mL plus 2 mandatory rinses of 30 mL each to deliver the study drug. This allowed for the collection of safety and tolerability data of the study drug using a lower volume of water.

  Subjects who enrolled in the study under this amendment at selected sites in the US received a dosing card that provided detailed written directions for proper preparation of study drug doses.

  If a subject who should have consumed ZS using 40 mL of water with no mandatory rinses mistakenly used 180 mL of water followed by two 30 mL rinses, this was to be recorded on the subject's dosing card and in EDC as a deviation and accounted for during data analysis.

- Added 2 new secondary endpoints and modified an exploratory endpoint.
- Incorporated all country-specific wording, thereby eliminating the need for any country-specific amendments.
- Specified that expected progression of CKD requiring dialysis, transplant or other treatment resulting in study discontinuation was not to be reported as an adverse event in this trial. The event was to be reported on the End of Study eCRF in EDC.
- Removed the requirement that the independent Data Monitoring Committee (iDMC). review data on an ongoing basis for this study. The ZS Pharma Medical Monitor continued to monitor safety data throughout the study.

Amendment No. 6 (2 February 2016):

- Removed the randomized withdrawal study from the trial. Emerging data from ZS-005 consistently showed that once treatment was stopped (on Day 365), S-K values returned into the hyperkalemic range. In addition, interim data from Study ZS-005 very clearly demonstrated that ZS maintained normokalemia in 90 to 100% of the subjects with a mean S-K value of 4.6 mmol/L.
- Changed the title of the protocol due to removal of the randomized withdrawal study from the trial.
- Clarified that subjects who had a history of heart failure were classified according to the New York Heart Association functional classification system.
- Clarified that adverse events were collected for 7 (± 1) days after the last dose of study drug which corresponded with the acceptable time frame of the End of Study visit.
- Clarified that expected progression of CKD requiring dialysis, transplant, or other treatment resulting in study discontinuation not related to ZS was not to be reported as an adverse event or serious adverse event.

[redacted]

Sodium zirconium cyclosilicate Study ZS-005

COMPLETE NAME OF THE TEST INVESTIGATIONAL MEDICINAL PRODUCT / VOLLSTÄNDIGER HANDELSNAME DES TESTPRÜFPRÄPARATS

Das Testprüfpräparat ”Sodium zirconium cyclosilicate“ ist der wirksame Bestandteil Natriumzirconium-Hydrogencyclohexasilicat des Arzneimittels „Lokelma® 5 g Pulver zur Herstellung einer Suspension zum Einnehmen bzw. Lokelma® 10 g Pulver zur Herstellung einer Suspension zum Einnehmen“

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