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APPLICATION NUMBER:

207078Orig1s000

MEDICAL REVIEW(S)

Clinical Review
{ Shen Xiao, M.D., Ph.D }
{NDA 207-078 supplement; SN-042}
{ LOKELMA™, sodium zirconium cyclosilicate}

CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	207-078
Priority or Standard	Standard
Submit Date(s)	November 22, 2017
Received Date(s)	November 22, 2017
PDUFA Goal Date	May 22, 2018
Division/Office	DCRP/ODEI/OND
Reviewer Name(s)	Shen Xiao M.D, PhD
Review Completion Date	May 16, 2018
Established Name	Sodium zirconium cyclosilicate (ZS)
(Proposed) Trade Name	Lokelma™
Applicant	AstraZeneca Pharmaceuticals LP
Formulation(s)	Power for Oral Suspension
Dosing Regimen	10g three time a day (b) (4)
Proposed Indication(s)	Treatment of Hyperkalemia
Intended Population(s)	Adult patients with hyperkalemia
Recommendation on Regulatory Action	Approval

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1. Executive Summary and conclusion

The applicant initially submitted an NDA (NDA 207078) for the treatment of hyperkalemia on May 26, 2015. The original submission included a phase 2 dose-range finding study (Study ZS002) and two phase 3 studies (Study ZS003 and Study ZS004/ZS004E). From a clinical perspective, the data from these studies provided substantial evidence efficacy and adequate data to support safety. However, two complete response letters were issued. The first CR letter cited deficiencies related to CMC issues (facility inspection findings and impurity levels), clinical pharmacology issues (drug-drug interaction liability), and outstanding labeling issues. The second CR letter cited facility inspection findings.

The current submission includes the results of Study ZS-005, which was designed to generate additional open-label, long-term (up to 12 months) safety and efficacy data in subjects with hyperkalemia. As in previous studies, the product was effective in lowering serum potassium (S-K) to the normal range, with the majority of the subjects responding within 24 hours. The majority of subjects maintained normal S-K on daily ZS administration during extended dosing. There were no clear differences in response based on the underlying etiology of hyperkalemia including heart failure, chronic kidney disease (CKD), hypertension, and diabetes. Subjects were not under any specific dietary restrictions and concomitant RAAS inhibitor use was not restricted. Thus, the population evaluated in this long-term study is likely representative of patients who would receive the drug in clinical practice.

Potential risks based on findings in previous studies, the mechanism of action of the drug, and/or its sodium counterion include hypokalemia, edema and heart failure, and GI tolerability. Safety findings in this study were consistent with results from previous controlled and uncontrolled studies of ZS in which similar patient populations were enrolled. No new safety signals were identified.

Interpretation of the safety and efficacy findings in this study is limited by the lack of a control group. The relatively high dropout rate observed in this study (37.5%) also limits interpretation of the efficacy findings. However, the data, both from this study and other studies, support adding a statement to Section 14 of the label indicating that the “treatment effect on serum potassium was maintained during continued therapy” in this study.

2. Background

Sodium zirconium cyclosilicate (ZS) is a powder for oral suspension, its active ingredient is a microporous zirconium silicate with a specific crystal geometry that provides selective exchange capacity for potassium and ammonium ions. ZS is developed for the treatment of hyperkalemia.

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This is the third review cycle for the application. The first CR letter, which was issued on May 27, 2016, cited deficiencies related to CMC issues (facility inspection findings and impurity levels), clinical pharmacology issues (drug-drug interaction liability), and outstanding labeling issues. The second CR letter, issued on March 16, 2017, cited facility inspection findings.

The current study (Study ZS-005) was designed to generate additional open-label, long-term (up to 12 months) safety and efficacy data in subjects with hyperkalemia.

3. Clinical Review

Study ZS-005 was a phase 3, single-arm, open-label, multicenter, prospective maintenance study to investigate the long-term (12 months) safety and efficacy of ZS in subjects with hyperkalemia.

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). The secondary objectives were to evaluate: 1) 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); 2) 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

3.1. Trial Design

Reviewer's Note: Some text in this section was taken verbatim from the Applicant's submission.

The study was conducted on an outpatient basis at 56 global sites. Approximately 750 subjects with hyperkalemia (i-STAT potassium value ≥ 5.1 mmol/L) were to be enrolled in the study and treated with ZS during the open-label Acute and Extended Dosing Phases. 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.

During the Acute Phase, the first daily dose was administered at the clinic, approximately 1 hour before breakfast, and the second and third doses were taken at home just before lunch

and the evening meal, respectively. In the extended phase, Subjects took the first dose of the Extended Dosing Phase study drug in the clinic (Extended Dosing Phase Day 1) and thereafter took the study drug at home, in the morning just before breakfast, except on days with scheduled clinic visits, when study drug was taken in the clinic. Subjects received up to 12 months (365 days) of treatment with open-label ZS and returned to the clinic on Extended Dosing Phase Days 8, 15, 22, 29, 57, 85, 113, 141, 176, 211, 239, 267, 295, 330, and 365 and 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.

Study Endpoints:
The primary efficacy parameter 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 Month 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).

The study included several secondary efficacy endpoints. For the most part, these endpoints also assessed treated effects on potassium.

Safety parameters detailed in the statistical analysis plan included adverse events, vital signs, ECGs, and other relevant clinical chemistry (specifically the incidence of hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), hematology, and urinalysis laboratory measurements.

Key inclusion criteria:
- Over 18 years of age

- Mean i-STAT potassium values between 5.0 – 6.5 mmol/l inclusive, at screening
- 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 screening.

Key exclusion criteria:

- Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis.
- Treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within 7 days prior to first dose of ZS on Acute Phase Day 1.
- Treatment with SPS or calcium polystyrene sulfonate within 3 days prior to first dose of ZS on Acute Phase Day 1.
- Life expectancy of less than 12 months.
- Severely physically or mentally incapacitated and, in the opinion of investigator, unable to perform the tasks associated with the protocol.
- Women who were pregnant, lactating, or planning to become pregnant.
- Diabetic ketoacidosis.
- Presence of any condition which, in the opinion of the investigator, placed the subject at undue risk or potentially jeopardized the quality of the data to be generated.
- Known hypersensitivity or previous anaphylaxis to ZS or to components thereof.
- Treatment with a drug or device within the last 30 days that had not received regulatory approval at the time of study entry.
- Cardiac arrhythmias that required immediate treatment.
- Receiving dialysis.
- Randomization/enrollment in the previous ZS-002, ZS-003, ZS-004, or ZS-004E studies.
- Documented glomerular filtration rate (GFR) < 15 mL/min within 90 days prior to study entry.
- For subjects in Germany: Subjects presenting with a heart-rate corrected QT (QTc) interval of 450 msec and additional risk factors for Torsade de pointes (eg, heart failure or family history of long QT-syndrome) and taking concomitant medications causing QT prolongation.

Dose modification and discontinuation:

Dose modification: 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.

Discontinuation: If a subject developed i-STAT potassium values < 3.0 mmol/L at any time during the study or > 6.5 mmol/L at any time during the Extended Dosing Phase, the subject was to immediately receive appropriate medical treatment and be discontinued from study drug. All i-STAT measurements that triggered the stopping rule were confirmed by taking a second measurement after a 10 (± 2)-minute interval. Both i-STAT potassium values must have met the stopping rule criterion to discontinue the subject. Any of the following cardiac events were to result in immediate discontinuation from the study (independent of whether it occurred during the Acute or Extended Dosing Phase):

- 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 atrioventricular block or significant bradycardia [heart rate < 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 > 30 msec to more than 500 msec, > 30 msec increase in QTc in a subject with a baseline QTc of > 500 msec, or an absolute increase in QTc > 60 msec

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.

Concurrent Medications: All concomitant medications, including reduction or discontinuation of RAAS inhibitors, taken by the subject from 30 days prior to Acute Phase Day 1 through the end of study (7[±1] days after the last dose of study drug), as well as the need to initiate new hyperkalemia- or hypokalemia-related treatments were recorded. Increases or decreases in concomitant medications were allowed, as dictated by clinical practice, including dose optimization of RAAS inhibitors as per relevant clinical guidelines. Whenever possible, all blood draws collected prior to meals were obtained prior to any insulin/insulin analog treatment. The time of dosing with insulin/insulin analogs was to be recorded when study drug was administered in the clinic.

During the study, the subject was not to receive alternative treatment for hyperkalemia while

taking study drug. If dosing with study drug was discontinued or the subject had completed dosing, the subject may have received alternative treatment for hyperkalemia if clinically indicated prior to completing the End of Study visit. Any alternative treatment administered after the end of study drug administration and prior to the End of Study visit was to be recorded in the concomitant medication eCRF (and as an adverse event, if applicable).

Statistical Analysis Plan: The statistical analysis plan was on finalized on December 10, 2016. The database was locked on 10 February 2017. The Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0, was used for coding adverse events and medical history data, and the World Health Organization Drug Dictionary (1 March 2014) was used to code prior and concomitant medications.

No prospective sample size calculations were performed for the study. There was no prespecified plan to control the type 1 error in testing efficacy endpoints.

Protocol Amendments: The original protocol, dated 23 April 2014, had 6 amendments. The most significant change was the removal of a planned randomized withdrawal phase from the trial. This change was made in Amendment No. 6 (2 February 2016). According to the sponsor, emerging data from ZS-005 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 indicated that ZS maintained normokalemia in 90 to 100% of the subjects during treatment.

3.2 Study Results

3.2.1. Patient Disposition

Overall, 1561 subjects were screened for entry into the study. Of these, 810 failed to meet the entry criteria, primarily due to i-STAT potassium values not within the acceptable range (788 subjects), and were not enrolled in the study.

Acute Phase: The 751 subjects enrolled in the Acute Phase of the study were treated with ZS 10 g TID. As shown in the table below, 746 (99.3%) subjects completed the Acute Phase of the study and continued into Extended Dosing based on i-STAT potassium values.

Table 1: Acute Phase: Subject Disposition – All Subjects

Disposition, n (%)	ZS 10 g TID
Enrolled in Acute Phase	751 (100.0)
Treated	751 (100.0)
Completed Acute Phase	746 (99.3)
Discontinued Acute Phase	5 (0.7)
Consent withdrawn	1 (0.1)
Participant's compliance	1 (0.1)
Investigator's decision	1 (0.1)
Protocol violation	1 (0.1)
Hyperkalemia	1 (0.1)[a]

a. Subject 5096-018 was prematurely discontinued from the Acute Phase due to hyperkalemia. The subject subsequently enrolled as Subject 5096-046 and was treated in the Acute and Extended Dosing Phases; this subject is counted as 2 separate exposures for the Acute Phase.

Source: CSR table 10-1, page 83

Extended Dosing Phase: All 746 subjects who completed the Acute Phase had i-STAT potassium values within the normal range (3.5 to 5.0 mmol/L, inclusive) and entered the Extended Dosing Phase. A total of 280 subjects (37.5%) were prematurely terminated from Extended Dosing. The most common reasons leading to discontinuation 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%). Nine subjects (1.2%) discontinued due to hypokalemia, with i-STAT potassium values indicated on the End of Study page of the eCRF as leading to withdrawal ranging from 2.5 to 2.9 mmol/L; final on-treatment S-K values for these subjects ranged from 2.6 to 3.3 mmol/L.

Table 2: Extended Dosing Phase: Subject Disposition – All Subjects

Disposition, n (%)	ZS
Treated	746 (100)
Completed Extended Dosing Phase	466 (62.5)
Discontinued Extended Dosing Phase	280 (37.5)
Adverse event	51 (6.8)
Consent withdrawn	81 (10.9)
Subject compliance	17 (2.3)
Investigator's decision	8 (1.1)
Sponsor's decision	5 (0.7)
Lost to follow-up	31 (4.2)
Protocol violation	2 (0.3)
Hypokalemia	9 (1.2)
Hyperkalemia	5 (0.7)
Expected progression of chronic kidney disease requiring dialysis, transplant, or other treatment	40 (5.4)
Death	8 (1.1)
Met electrocardiogram withdrawal criteria	7 (0.9)
Other[a]	16 (2.1)

a Did not return for study visit (4 subjects), subject incarcerated (3 subjects), subject relocation (3 subjects), did not take study drug (2 subjects), site error (1 subject), initiated potassium chloride (1 subject), time constraints (1 subject), and follow-up activities associated with post total knee replacement (1 subject).
Source: CSR table 10-2 page 85

Protocol Violations/Deviation: Thirty-two subjects had major protocol deviations during the study. A summary of major protocol deviations across the Acute Phase and Extended Dosing Phase of the study is summarized in the table below. These violations do not raise concern about the integrity of the trial or interpretability of the data.

Table 3: Major Protocol Deviations – All Enrolled Subjects

Major Deviation, n (%)	ZS 10 g TID (N = 751)
Dispensed incorrect study drug kits	11 (1.5)[a]
Receipt of incorrect doses of study drug due to dosing adjustment errors	8 (1.1)[a]
Previously participated in Study ZS-003	4 (0.5)
Met the ECG stopping rules, but continued dosing with study drug	3 (0.4)
Started hemodialysis while continuing to take study drug	2 (0.3)
Enrolled and treated but later confirmed to have CKD progression	2 (0.3)
Enrolled and treated twice	1 (0.1)
Not fasting for 0-hour central laboratory assessment on AP Day 2	1 (0.1)
Denied participation in another research study and was enrolled; however, after receiving study drug, admitted to participation in another research study	1 (0.1)
Total	32[a]

a Includes one subject (Subject 5041-021) with 2 major protocol deviations (dispensed incorrect study drug kits and receipt of incorrect dose of study drug due to dosing adjustment error).
Source: CSR table 10-3, page 86

3.2.2. Demographic Characteristics

Acute phase: Key demographic and other baseline characteristics are shown in the table below. Age ranged from 21 to 93 years, with a mean age of 63.6 years. The majority of subjects were male (59.7%) and White (83.1%), with 85.1% (639 subjects) enrolled from sites located in the United States. Baseline S-K values (per central laboratory) were < 5.5 mmol/L for 38.2% of subjects, ≥5.5 to < 6.0 mmol/L for 45.0% of subjects, and ≥ 6.0 mmol/L for 16.8% of subjects. Comorbid conditions included CKD (based on eGFR < 60 mL/min, 73.5%), diabetes mellitus (62.7%), and heart failure (37.9%). The majority of 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.

Table 4: Acute Phase: Demographic and Other Baseline Characteristics –Safety Population

Demographic Parameter Statistic	ZS 10 g TID (N = 751)
Age at screening (years)	
Mean (SD)	63.6 (13.03)
Median	64.0
Minimum, maximum	21, 93
Gender, n (%)	
Male	448 (59.7)
Female	303 (40.3)
Race, n (%)	
White	624 (83.1)
Black or African American	89 (11.9)
Asian	25 (3.3)
Native Hawaiian or other Pacific Islander	3 (0.4)
Other	10 (1.3)
Ethnicity, n (%)	
Hispanic	320 (42.6)
Not Hispanic	431 (57.4)
Acute Phase S-K baseline[a], n (%)	
< 5.5 mmol/L	287 (38.2)
5.5 - < 6.0 mmol/L	338 (45.0)
≥ 6.0 mmol/L	126 (16.8)
Acute Phase eGFR at baseline, n (%)	
< 60 mL/min	552 (73.5)
≥ 60 mL/min	190 (25.3)
Missing	9 (1.2)
Comorbid Conditions, n (%)	
Diabetes mellitus	471 (62.7)
Chronic kidney disease	513 (68.3)
Heart failure	285 (37.9)
Geographic Region, n (%)	
United States	639 (85.1)
Other Countries	112 (14.9)
Acute Phase Baseline Weight, n (%)	
< 85 kg	406 (54.1)
≥ 85 kg	342 (45.5)
Missing	3 (0.4)
RAAS Inhibitor Use, n (%)	527 (70.2)
Diuretic Use, n (%)	383 (51.0)
History of Hypertension, n (%)	622 (82.8)

a Acute Phase baseline S-K is the mean of 2 different pretreatment S-K values, recorded 60 (± 15 minutes) apart on Acute Phase Day 1.

Source: CSR table 11-3, page 90.

Extended Dosing Phase: As all but 5 subjects in the Acute Phase entered the Extended Dosing Phase, the demographic and other baseline characteristics of the Extended Dosing Phase Safety Population were nearly identical to those noted for the Acute Phase Safety Population.

The most common (> 50% of subjects) types of medications received during the Extended Dosing Phase were consistent with those received during the Acute Phase and included agents acting on the renin-angiotensin system (68.0%), lipid-modifying agents (63.3%), and drugs used in diabetes (57.4%).

3.2.3. Efficacy Results

Acute Phase: Overall, 77.9% (95% CI: 74.8%, 80.9%) of subjects achieved S-K values between 3.5 and 5.0 mmol/L, inclusive, with Acute Phase dosing. Data are summarized in the table below.

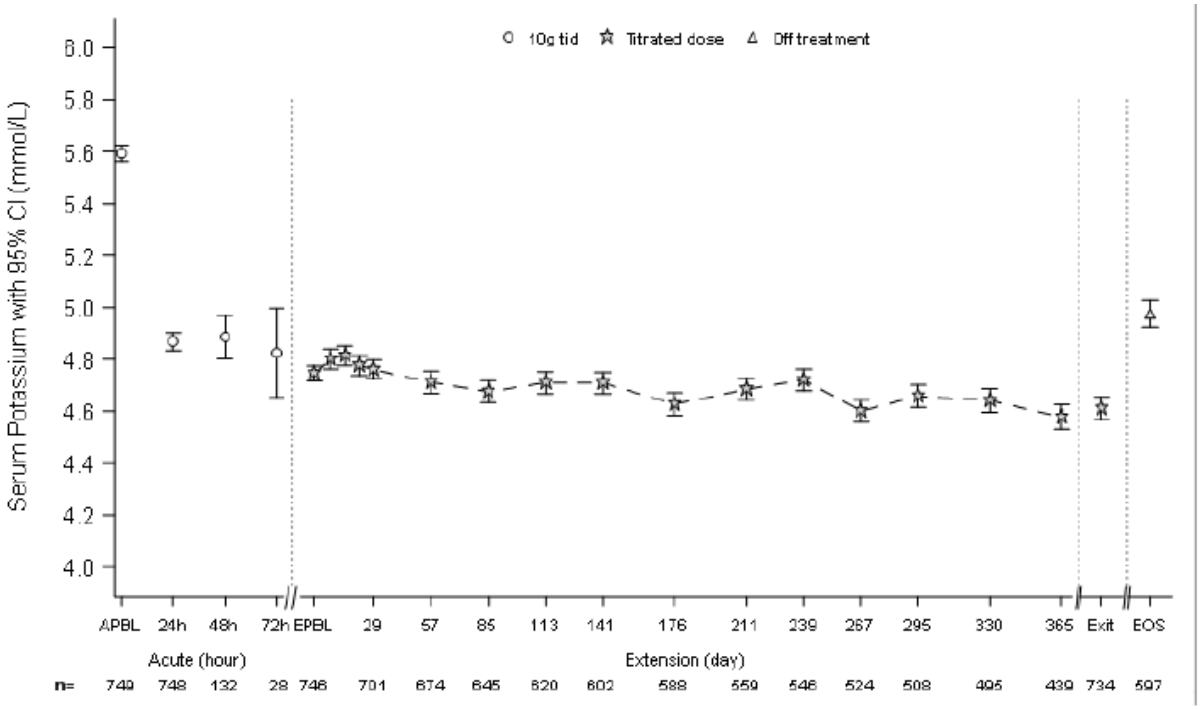
Table 5: Acute Phase: Proportion of Subjects With S-K Values Between 3.5 and 5.0 or Between 3.5 and 5.5 mmol/L Day - ITT Population

	ZS 10 g TID (N = 749)					
	S-K 3.5 to 5.0 mmol/L, inclusive			S-K 3.5 to 5.5 mmol/L, inclusive		
Acute Phase	**n/N**	**Proportion**	**95% CI**	**n/N**	**Proportion**	**95% CI**
AP at 24 hours	494/748	0.660	0.625, 0.694	692/748	0.925	0.904, 0.943
AP at 48 hours	563/748	0.753	0.720, 0.783	732/748	0.979	0.965, 0.988
AP at 72 hours/AP Last	583/748	0.779	0.748, 0.809	738/748	0.987	0.976, 0.994

Source: CSR table 11-6, page 94

Extended phase: Mean serum potassium levels over time are shown in the figure below. Efficacy in controlling potassium levels was maintained over time during continued dosing.

Figure 1: Extended Dosing Phase: Mean (95% CI) S-K (mmol/L) Over Time - ITT Population



Abbreviations: AP = Acute Phase; BL = baseline; EP = Extended phase; EOS = end of study. Exit is the last visit within 1 day of last dose. The EOS time point includes all subjects with data within 7 (±1) days of the last dose of study drug.
Source: CSR Figure 11-1, page 109

Subgroup Analysis: The efficacy of ZS was evaluated in different subgroups including ages (<55, 55-64 and ≥65), gender, original diseases (CKD eGFR< 60 ml/min, heart failure, diabetes), Use of RAAS inhibitors, and baseline of S-K. With the exception of the baseline S-K value, efficacy appeared similar across the examined subgroups. In the Acute Phase, subjects with lower baseline values (< 5.5 mmol/L) had greater proportions of subjects with S-K values between 3.5 and 5.0 mmol/L, inclusive (87.4%), whereas higher baseline values (≥ 6.0 mmol/L) were associated with lower proportions of subjects achieving the endpoint (57.9%). In the Extended Dosing Phase, subjects with lower baseline values at the start of Acute Phase (< 5.5 mmol/L) had greater proportions of subjects with mean S-K values ≤ 5.1 mmol/L (94.8%), whereas higher baseline values (≥ 6.0 mmol/L) were associated with lower proportions of subjects achieving the endpoint (75.5%).

Renin-Angiotensin-Aldosterone System Inhibitor Use: Among the 746 subjects in the Extended Dosing Phase Safety Population, 483 subjects (64.7%) were taking RAAS inhibitors and 263 subjects (35.3%) were not taking RAAS inhibitors at Acute Phase baseline.

Of the 263 subjects not taking RAAS inhibitors at Acute Phase baseline, 37 (14.1%) initiated RAAS inhibitor therapy during the Extended Dosing Phase.

Among the 483 subjects taking RAAS inhibitors at baseline, the majority continued the same dose (358 subjects; 74.1%). Increases in RAAS inhibitor dose occurred in 62 subjects (12.8%), decreases occurred in 69 subjects (14.3%), and 51 subjects (10.6%) discontinued RAAS inhibitor use altogether. Similar results were observed among subjects with diabetes, heart failure, and eGFR < 60 mL/min.

Efficacy Summary and Conclusion: The efficacy findings are consistent with previous placebo-controlled studies (i.e., relatively rapid correction of hyperkalemia and maintenance of efficacy during long-term administration).

3.2.4. Safety

Safety analyses focused on adverse events (AEs) and laboratory changes of interest based on the drug's mechanism of action and sodium counterion, as well as GI safety and tolerability. Because the trial lacked a control arm, interpretation of safety findings is limited. Many of the safety analyses presented in this review were conducted by Dr. Christine Garnett. See her memo for further discussion.

Overall Exposure:

A total of 751 subjects were treated with ZS 10 g TID for 24 to 72 hours during the Acute Phase. Study drug exposure during the Extended Dosing Phase is summarized in the table below. Of the 746 subjects who entered the Extended Dosing Phase, 466 (62.5%) completed the 12-month study. 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 mean and median dose received was 7.18 g and 5.74 g, respectively. Most subjects were maintained on doses between 5 to 10g QD, with 10% subjects taking 15g QD by end of treatment.

Table 6: Extent of Exposure and Distribution of Doses in Extended Dosing Phase

Days of Treatment	ZS-005 (N=746) 5 g QD Titration[1]
>30 d >90 d >180 d >270 d >360 d	689 (92%) 627 (84%) 576 (77%) 523 (70%) 470 (63%)
Distribution of doses at EoT 5 g QOD 5 g QD 10 g QD 15g QD	 23 (3%) 358 (48%) 291 (39%) 74 (10%)

[1]ZS dose was adjusted based on the i-STAT potassium values: K>5.0 mmol/L (5 g QD/QOD) or 5.5 mmol/L (10 mg QD), dose titrated by 5 g QD to maximum dose of 15 mg QD; K between 3 and 3.4 mmol/L, dose titrated by 5 g QD minimum dose of 5 mg QOD.
Source: Dr. Christine Garnett's memo

Deaths: No subject died during the Acute Phase. Eight subjects (1.1%) died during the Extended Dosing Phase. Each of the TEAEs leading to death was considered not related to study drug by the investigator. Data are summarized in the table below.

Table 7: Extended Dosing Phase: Subjects with TEAEs Leading to Death – Safety Population

Subject Number	Age/Sex/ Race	Dose Prior to Onset	Study Day Onset	Preferred Term	Relationship to Study Drug as Assessed by Investigator	Relevant Medical History
(b) (6)	83/M/W	ZS 10 g QD	ED 110	Myocardial infarction	Not related	CAD, hypertension, sleep apnea, hyperlipidemia, obesity, CABG, MI
	74/F/W	ZS 5 g QD	ED 154	Cystitis haemorrhagic	Not related	CKD
	80/M/B	ZS 5 g QD	ED 66	Dyspnoea	Not related	HPT, HF, hyperkalemia, hyponatremia, 1st degree AV block
				Electrocardiogram abnormal	Not related	
	60/F/W	ZS 10 g QD	ED 130	Cardiac arrest	Not related	Anxiety, HPT, chest pain, SOB, sleep apnea, HF
				Toxicity to various agents	Not related	
	67/F/W	ZS 10 g QD	ED 37	Interstitial lung disease	Not related	Hoarseness, hyperkalemia, HF
	83/M/W	ZS 10 g QD	ED 54	Heart injury	Not related	HPT, hyperlipidemia, CAD, mitral valve prolapse, cerebrovascular disease, ventricular hypertrophy, ischemic heart disease, MI, exertional dyspnea, peripheral edema
	57/M/B	ZS 10 g QD	ED 236	Renal failure chronic	Not related	Renal failure, renal anemia
	72/M/O	ZS 10 g QD	ED 90	Hypercapnia	Not related	HPT, congestive cardiac failure, dyslipidemia, non-STEMI (2x), tracheostomy, sleep apnea, ischemic heart disease
				Respiratory failure	Not related	

Abbreviations: B = Black or African American; CAD = coronary artery disease; CABG = coronary artery bypass graft; CKD = chronic kidney disease; ED = Extended Dosing; F = female; HF = heart failure; HPT = hypertension; M = male; MI = myocardial infarction; O = Other; QD = once daily; SOB = shortness of breath; STEMI = ST-elevation myocardial infarction; W = White.
Source: CSR page 147, table 12-11

Reviewer comments: Review of the provided narratives did not suggest a causal link (such as evidence of hypokalemia) with study drug in any of these cases. The reported events are not unexpected events in the study populations.

Serious Adverse Events: One serious TEAE (urinary tract infection) was reported during the Acute Phase of the study.

During the Extended Dosing Phase, 21.6% of subjects reported at least 1 serious TEAE. Serious adverse events were generally consistent with the severe underlying comorbidities of the subject population. The most commonly reported serious TEAEs included pneumonia (1.9%), cardiac failure congestive (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and renal failure acute (1.1%). Of the 161 subjects who experienced serious TEAEs in the Extended Dosing Phase, 2 had serious events that were considered related to study drug by the investigator.

Table 8: Extended Dosing Phase: Summary of Serious TEAEs Overall by System Organ Class and Preferred Term - Safety Population

	ZS QD
	Overall (N = 746)
Any Event, n (%)[a]	161 (21.6)
System Organ Class Preferred Term, n (%)	
Cardiac disorders	39 (5.2)
Acute myocardial infarction	6 (0.8)
Cardiac failure	4 (0.5)
Cardiac failure congestive	11 (1.5)
General Disorders and Administration Site Conditions	17 (2.3)
Chest pain	11 (1.5)
Infections and Infestations	55 (7.4)
Cellulitis	7 (0.9)
Osteomyelitis	8 (1.1)
Pneumonia	14 (1.9)
Urinary tract infection	4 (0.5)
Metabolism and Nutrition Disorders	16 (2.1)
Hyperkalaemia	4 (0.5)
Hypoglycaemia	4 (0.5)
Renal and Urinary Disorders	15 (2.0)
Renal failure acute	8 (1.1)
Renal failure chronic	4 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	21 (2.8)
Acute respiratory failure	5 (0.7)
Dyspnoea	5 (0.7)
Skin and Subcutaneous Tissue Disorders	7 (0.9)
Skin ulcer	4 (0.5)
Vascular Disorders	9 (1.2)
Hypertension	4 (0.5)

a Subjects reporting more than 1 event during the Extended Dosing Phase were counted only once in the total number of subjects reporting any event.

Source: CSR page 149, table 12-12

Reviewer comments: These SAEs are not unexpected events in this patient population. Because safety signals can be obscured by splitting similar preferred terms, with similar meanings, into multiple categories, additional analyses were conducted to evaluate safety topics of interest (see "Analysis of Submission-Specific Safety Issues" below).

Dropouts and/or Discontinuations Due to Adverse Effects: In the Acute Phase, two subjects were prematurely discontinued from the study due to TEAEs. One subject had 2 adverse events (abdominal pain upper and flatulence) that started in the Acute Phase; the subject continued into Extended Dosing and was treated for 13 days prior to stopping therapy. One subject had a serious TEAE (urinary tract infection) that led to premature discontinuation after 1 dose of ZS. This subject's pre-dose urine sample indicated that the infection was present prior to entering the study. None of the events that led to premature discontinuation were considered related to study drug.

During the Extended Dosing Phase, TEAEs led to premature discontinuation from study drug in 13.7% of subjects. Among the 102 subjects prematurely discontinued from study drug due to TEAEs, 12 had events that were considered related to study drug by the investigator including cardiac failure congestive (4 subjects), vomiting (2 subjects), rash (1 subject), nausea (1 subject), constipation (1 subject), hypokalemia (1 subject), diarrhea (1 subject), and white blood cell count decreased, eosinophil count increased, monocyte count increased, and neutrophil count decreased (1 subject). Data are summarized in the table below.

Table 9: Extended Dosing Phase: Summary of TEAEs Leading to Discontinuation Overall by System Organ Class and Preferred Term - Safety Population

	ZS QD
	Overall (N = 746)
Any Event, n (%)[a]	102 (13.7)
System Organ Class	
Preferred Term, n (%)	
Cardiac Disorders	32 (4.3)
Acute myocardial infarction	3 (0.4)
Atrial fibrillation	4 (0.5)
Cardiac failure	4 (0.5)
Cardiac failure congestive	11 (1.5)
Myocardial infarction	3 (0.4)
Ventricular tachycardia	2 (0.3)
Gastrointestinal Disorders	13 (1.7)
Constipation	2 (0.3)
Diarrhoea	2 (0.3)
Vomiting	2 (0.3)
General Disorders and Administration Site Conditions	4 (0.5)
Chest pain	3 (0.4)
Infections and Infestations	11 (1.5)
Osteomyelitis	4 (0.5)
Pneumonia	2 (0.3)
Investigations	6 (0.8)
Electrocardiogram abnormal	2 (0.3)
Metabolism and Nutrition Disorders	8 (1.1)
Fluid overload	2 (0.3)
Hyperkalaemia	3 (0.4)
Renal and Urinary Disorders	17 (2.3)
Renal failure acute	9 (1.2)
Renal failure chronic	6 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	9 (1.2)
Dyspnoea	5 (0.7)
Pulmonary mass	2 (0.3)

a Subjects reporting more than 1 event during the Extended Dosing Phase were counted only once in the total number of subjects reporting any event.
Source: CSR page 151,table 12-13

Overall Adverse events:

Acute phase: The overall incidence of TEAEs during the Acute Phase was 4.1%. The most common TEAEs reported during the Acute Phase were associated with the Gastrointestinal Disorders (1.3%) system organ class, including nausea (0.5%), diarrhea (0.3%), and constipation (0.3%).

Extended Dosing Phase: The overall incidence of TEAEs during the Extended Dosing Phase 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%).

Treatment-emergent adverse events considered related to study drug by the investigator occurred in 12.1% of subjects; constipation (3.1%), nausea (1.7%), and edema peripheral (1.7%) were the related events reported in ≥ 1.0% of subjects during the Extended Dosing Phase. Data are summarized in the table below.

Table 10: Extended Dosing Phase: Overall Summary of TEAEs– Safety Population

	ZS QD
Subjects With TEAEs, n (%)	Overall (N = 746)
Any event	489 (65.5)
Any event considered related to study drug by the investigator	90 (12.1)
Any severe event	125 (16.8)
Deaths	8 (1.1)
Any serious event	161 (21.6)
Any event leading to premature discontinuation from study drug	102 (13.7)

Data source: CSR page 140, table12-8

Table 11: Extended Dosing Phase: Summary of TEAEs Considered Related to Study Drug Overall by System Organ Class and Preferred Term - Safety Population

	ZS QD
	Overall (N = 746)
Any Event, n (%)[a]	90 (12.1)
System Organ Class Preferred Term, n (%)	
Gastrointestinal Disorders	43 (5.8)
Constipation	23 (3.1)
Nausea	13 (1.7)
General Disorders and Administration Site Conditions	17 (2.3)
Oedema peripheral	13 (1.7)

Source: CSR page 143, table 12-10

Laboratory Findings:
See Section 5.3 for information on low potassium values. The incidence of treatment-emergent potentially clinically significant values was < 1% for sodium, magnesium, and calcium.

Vital Signs: During the Extended Dosing Phase, no clinically significant mean changes from Acute Phase baseline in blood pressure, heart rate, weight, and temperature were observed.

Electrocardiograms (ECGs): During the Extended Dosing Phase, no clinically significant mean changes from Acute Phase baseline in PR interval, QRS duration, and heart rate were observed. Small mean increases in QTc interval were observed at each of the time points during Extended Dosing relative to Acute Phase baseline. These increases in QTc interval were attributed to correction of potassium into the normokalemic range.

Twenty-five subjects had ECG evaluations that were normal or not clinically significant abnormalities at Acute Phase baseline and shifted to clinically significant abnormalities during Extended Dosing. Twenty-one subjects with the ECG evaluation at the End of Study were normal or not clinically significant abnormal. The incidence of maximum QTc intervals > 500 msec was 1.7% during the Extended Dosing Phase, with a magnitude ranging from 501 to 565 msec. Five subjects (0.7%) experienced a maximum QTc interval > 500 msec and a > 30 msec increase from baseline. Three subjects (0.4%) had a > 60 msec increase from Acute Phase baseline in QTc interval to a maximum QTc interval > 500 msec. Each of the subjects with an increase in QTc of > 30 msec with a corresponding QTc interval > 500 msec who met the ECG withdrawal criteria had multiple comorbidities and was receiving numerous concomitant medications.

Reviewer comments: The ECG data and provided narratives do not raise a safety concern.

Analysis of Submission-Specific Safety Issues

Dr. Christine Garnett conducted analyses focusing on submission specific safety issues, including hypokalemia and potential risks related to sodium absorption from the product (e.g., edema, heart failure and worsening hypertension). This review focuses on cases of interest related to volume overload and/or edema and heart failure identified as part of her review.

Volume overload and/or edema: As shown in the table below, in the extended phase, 102 (14%) subjects reported edema-related AEs, 4 (<1%) reported SAEs and 3 (<1%) discontinued study medication.

Table 12: Edema and Fluid Retention AEs (population in extended phase)

MedDRA Preferred Term	ZS-005 N=746	
	n	%
Total	*102*	*13.7*
Oedema	15	2.0
Oedema peripheral	73[1]	9.8
Generalized oedema	4	<1
Fluid overload	12	1.6
Fluid retention	1	<1
Serious AEs	***4***	***<1***
AEs leading to discontinuation	***3***	***<1***

Source: Dr. Christine Garnett safety review memo

The narratives of all 4 cases of SAEs related to edema were reviewed. All patients had edema at baseline due to co-morbid diseases such as advanced kidney disease, diabetes, heart failure or/and hypertension. Such SAEs would not be unexpected in this population; however, given the sodium content of the drug, it is possible that the drug contributed to these events.

The 4 SAES included the 3 AEs leading to discontinuation.

Heart Failure: According to Dr. Garnett's review heart failure events (associated with the MedDRA Preferred Terms, cardiac failure, cardiac failure acute, chronic or congestive) and pulmonary edema were reported in 34/746 (4.6%) of subjects during the extended phase. As shown in the table, 19 (2.5%) subjects reported SAEs.

Table 13: Adverse Events Suggestive of Heart Failure (ED population)

MedDRA Preferred Term	**ZS-005 (N=746)**	
	n	**%**
Total	***34***	***4.6***
Cardiac failure	5	<1
Cardiac failure acute	1	<1
Cardiac failure chronic	1	<1
Cardiac failure congestive	24	3.2
Pulmonary edemas	3	<1
Serious AEs	***19***	***2.5***
AEs leading to discontinuation	***16***	***2.1***

Source: Source: Dr. Christine Garnett safety review memo

The narratives of the 19 SAEs were reviewed. According to the provided narratives, these patients had a history of cardiac failure and/or pulmonary edema. As such SAEs would not be unexpected in this population, it is difficult to determine whether the study drug played a role.

Hypertension: As discussed in Dr. Garnett's review, 6 (0.8%) subjects reported SAEs related to hypertension (i.e., preferred terms within the Hypertension SMQ); none of the SAEs led to discontinuation of treatment.

Narratives for the 6 subjects were reviewed. Based on the provided narratives, all of these patients had a history of hypertension. As such SAEs would not be unexpected in this population, it is difficult to determine whether the study drug played a role.

Integrated Assessment of Safety: This is a single arm, open label study. Given the lack of a control arm, the data from this trial are difficult to interpret. Overall, 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. No new safety signals or other significant safety concerns were identified in this long-term open-label study.

4. Labeling Recommendations

See the Executive Summary.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN XIAO
05/16/2018

ALIZA M THOMPSON
05/16/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 11, 2018

From: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

Subject: Complete Response Package for NDA 207078

Sponsor: ZS Pharma, Inc.

Name: LOKELMA (sodium zirconium cyclosilicate)

A New Drug Application (NDA) for sodium zirconium cyclosilicate (ZS) for the treatment of hyperkalemia was submitted to the FDA on 05/26/2015. The first Complete Response Letter was issued on 05/26/2016 citing deficiencies in facility inspections, clinical pharmacology studies, product quality and prescribing information. The Applicant submitted a complete response to the FDA's action letter on 9/16/2016. A second Complete Response Letter was issued on 03/16/2017 citing additional deficiencies related to the facility of the drug substance manufacturing. As part of the resubmission, the Applicant submitted a safety update and provided a final study report and supporting datasets for their open-label, long-term safety and efficacy study ZS-005.

Reviewer's Comments on the Applicant's Safety Update

There are no new safety findings with up to 12 months of treatment with ZS in Study ZS005.

REVIEW OF SUBMISSION

Approach to Safety Review

The safety review focused on adverse events (AEs) and laboratory values related to edema, heart failure, hypertension and hypokalemia in the open label, uncontrolled safety and efficacy study ZS-005 with dosing up to one year. The following materials were reviewed:

- Complete Response Letter (dated 03/16/2017)
- ZS-005 Clinical Study Report: \\CDSESUB1\evsprod\NDA207078\0042\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperkalemia\5352-stud-rep-uncontr\zs-005\ zs-005-clinical-study-report.pdf
- Integrated Summary of Safety: \\CDSESUB1\evsprod\NDA207078\0042\m5\53-clin-

stud-rep\535-rep-effic-safety-stud\hyperkalemia\5353-rep-analys-data-more-one-stud\iss\safety-update-2017.pdf

- Response to Information Request NDA 207078 Lokelma™ (sodium zirconium cyclosilicate) oral suspension (22 February 2018).

Standard MedDRA queries (SMQ) for fluid overload, cardiac failure and hypertension were based on MedDRA 18.1. Subgroup analysis of AEs focused on risk factors for edema including chronic kidney disease, chronic heart failure, diabetes and concomitant use of calcium channel blockers.

AEs were analyzed using SMQ in MAED and customized MedDRA queries in JMP/Excel[1].

Study ZS-005

ZS-005 is an open-label, phase 3, multicenter, multi-dose, prospective, maintenance study to investigate the long-term (up to 12 months) safety and efficacy of ZS in subjects with hyperkalemia. 751 subjects with hyperkalemia (i-STAT potassium value ≥ 5.1 mmol/L) were enrolled and treated with ZS during the open-label Acute and Extended Dosing phases. Subjects with 2 consecutive i-STAT potassium measurements at screening ≥ 5.1 mmol/L were entered the Acute phase and received ZS 10 g TID for at least 24 hours and up 72 hours. If the subject was normokalemic (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) on the morning of Acute Phase Day 2 after 3 doses of ZS 10 g, they entered the Extended Dosing phase.

In the Extended Dosing (ED) phase, subjects received a starting dose of 5 g QD. ZS doses were adjusted based on the i-STAT potassium values collected on study days Days 8, 15, 22, 29, 57, 85, 176, 267, 365 and the End of Study visit.

- K>5.0 mmol/L (5 g QD/QOD) or 5.5 mmol/L (10 mg QD), dose titrated by 5 g QD to maximum dose of 15 mg QD
- K between 3 and 3.4 mmol/L, dose titrated by 5 g QD minimum dose of 5 mg QOD.

The overall extent of exposure in the ED phase is shown in **Table 1**. Most subjects were maintained on doses between 5 to 10g QD, with 10% subjects taking 15g QD by end of treatment.

[1] A comparison between SMQ and customized MedDRA queries did not reveal any discrepancies between the two approaches.

Table 1. Extent of Exposure and Distribution of Doses in ED Phase

Days of Treatment	ZS-005 N=746 5 g QD Titration[1]
>30 d >90 d >180 d >270 d >360 d	689 (92%) 627 (84%) 576 (77%) 523 (70%) 470 (63%)
Distribution of doses at EoT 5 g QOD 5 g QD 10 g QD 15g QD	 23 (3%) 358 (48%) 291 (39%) 74 (10%)

[1]ZS dose was adjusted based on the i-STAT potassium values: K>5.0 mmol/L (5 g QD/QOD) or 5.5 mmol/L (10 mg QD), dose titrated by 5 g QD to maximum dose of 15 mg QD; K between 3 and 3.4 mmol/L, dose titrated by 5 g QD minimum dose of 5 mg QOD.
Source: Reviewer's analysis using adsl.xpt and adexvis.xpt
Cross-reference: Table 12-2 in ZS-005 Clinical Study Report and Table 6-2 in Integrated Summary of Safety
Abbreviations: QD, once daily; QOD, once every other day; EoT, end of treatment

Reviewer's comment: The results of the FDA analysis are different from those presented by the Applicant. The Applicant shows the distribution of average doses whereas the FDA analysis shows the dose the subject was taking at the end of treatment. Per the Applicant, "Dose titrations occurred according to the protocol-defined dose adjustment rules and, at some point during the study, 32 (4.3%) subjects were titrated to the 5 g QOD dose, 396 (53.1%) subjects were titrated to the 10 g QD dose, and 87 (11.7%) to the 15 g QD dose." The results of the FDA analysis are numerically different from the Applicant's in the overall number of subjects exposed to ZS, but the differences do not impact interpretation of findings.

Fluid Retention, Edema and Heart Failure AEs

The MedDRA higher level terms "Oedema NEC" and "Total fluid volume increased" were used to identify edema-related AEs. These AEs corresponded to the customized MedDRA query used within DCRP for Edema.

In the Acute phase, there was 1 AE of peripheral edema. ZS-005/5704-002 reported a mild case of peripheral edema on study day 2. The subject went on to complete the ED phase without reporting another edema-related AE.

In the ED phase, 102 (14%) subjects reported edema-related AEs (**Table 2**). Four subjects reported SAEs and 3 subjects discontinued study medication.

Table 2. Edema and Fluid Retention AEs (ED population)

MedDRA Preferred Term	ZS-005 N=746	
	n	%
Total	***102***	***13.7***
Oedema	15	2.0
Oedema peripheral	73[1]	9.8
Generalized oedema	4	<1
Fluid overload	12	1.6
Fluid retention	1	<1
Serious AEs	***4***	***<1***
AEs leading to discontinuation	***3***	***<1***

Source: Reviewer's analysis using datasets ae.xpt
Cross-reference: Table 12-14 in ZS-005 Clinical Study Report
[1]Includes the 1 subject who experienced peripheral edema in the acute phase.

Reviewer's comment: The 4 subjects with SAEs related to edema are listed. Dr Xiao has provided narratives for these subjects in his review.

USUBJID	PT	Severity	Start Day	End Day
(b) (6)	Fluid overload	Severe	267	270
	Fluid overload	Moderate	334	338
	Generalised oedema	Severe	24	31
	Fluid overload	Severe	130	133

Of the 102 subjects reporting edema-related events, most had a history of CKD (n=96) and over half had a history of heart failure (n=58) or diabetes (n=76).

Table 3. Edema-Related AEs by Subgroup (ED population)

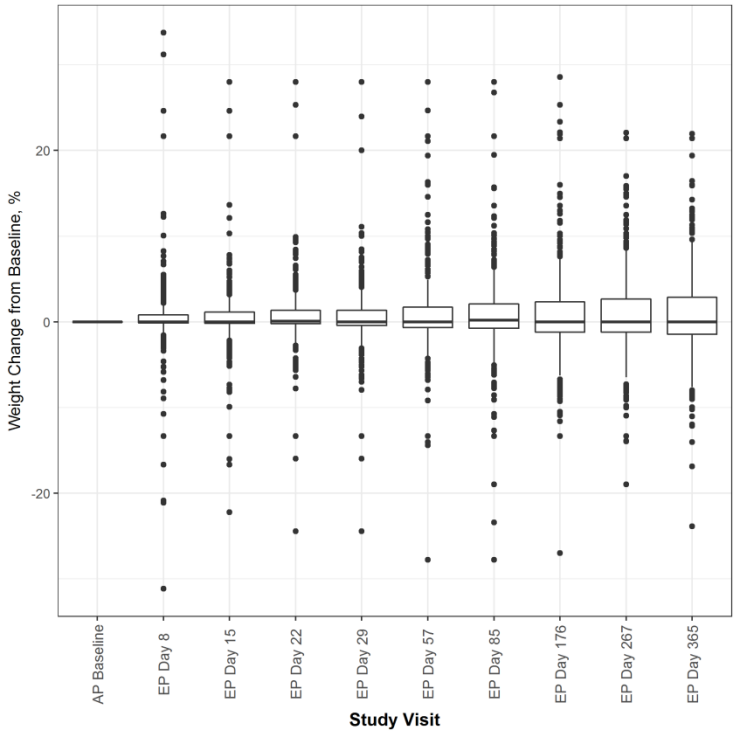
	Total Subjects	Subjects with Edema-Related AE (n=102)	
		n	%
Overall	746	102	14
Chronic Kidney Disease			
Yes	510	96	19
No	236	7	3
Renal Group (ml/min per 1.73m^2)			
<15	43	7	16
15- <30	243	46	19
30- <60	263	45	17
≥60	188	3	2
Missing	9	2	22
Diabetes			
Yes	468	76	16
No	278	27	10

Heart Disease			
Yes	283	58	20
No	463	45	10
Taking Calcium Channel Blockers			
Yes	296	69	23
No	450	33	7

Source: Reviewer's analysis using datasets dm.xpt, ae.xpt and cm.xpt
Cross-reference: Table 14.1.3 in ZS-005 Clinical Study Report

Overall, there were no changes in the distribution of body weight over the study duration (**Figure 1**).

Figure 1. Box Plots of Body Weight by Time



Source: Reviewer's analysis using advs.xpt. Box plot show the median (line within each box); 25th and 75th percentile (width of box); 1.5 interquartile range (whiskers); and outliers (filled circles). Abbreviations: AP, acute phase; EP, extended dosing phase.*
Note: Subject ZS-005/5040-004 was excluded from the plot because there appears to be erroneous body weight recordings, where the subject lost 100 kg (>50% of baseline weight) by EP Day 8.

Heart failure events (associated with the MedDRA Preferred Terms, cardiac failure, cardiac failure acute, chronic or congestive) and pulmonary edema were reported in 34/746 (4.6%) of subjects during the ED phase (**Table 4**). There were no heart failure or pulmonary edema events in the Acute dosing phase.

19 (2.5%) subjects reported SAEs: 16 (2.1%) subjects reported SAEs of heart failure/congestive heart failure and 3 (<1%) subjects reported SAEs of pulmonary edema. These SAEs led to

treatment discontinuation in 16 (2.1%) subjects. Of the 34 subjects with heart failure/pulmonary edema AEs, 26 had a history of heart disease at baseline.

Table 4. Adverse Events Suggestive of Heart Failure (ED population)

MedDRA Preferred Term	ZS-005 (N=746)	
	n	%
Total	***34***	***4.6***
Cardiac failure	5	<1
Cardiac failure acute	1	<1
Cardiac failure chronic	1	<1
Cardiac failure congestive	24	3.2
Pulmonary edemas	3	<1
Serious AEs	***19***	***2.5***
AEs leading to discontinuation	***16***	***2.1***

Source: Reviewer's analysis using datasets ae.xpt
Cross-reference: Tables 14.3.2.2.5 and 6 in ZS005 CSR
Abbreviations: HLT, high level term; PT, preferred term, NEC, not elsewhere classified

Reviewer's comment: The 19 subjects with SAEs related to heart failure/pulmonary edema are listed. Dr Xiao has provided narratives for these subjects in his review.

USUBJID	PT	Severity	Start Day	End Day
(b) (6)	Cardiac failure congestive	Severe	217	229
	Cardiac failure congestive	Severe	83	86
	Cardiac failure	Severe	7	15
	Pulmonary oedema	Mild	242	244
	Cardiac failure congestive	Severe	22	28
	Pulmonary oedema	Severe	196	198
	Cardiac failure congestive	Severe	89	99
	Pulmonary oedema	Severe	328	329
	Cardiac failure congestive	Moderate	174	176
	Cardiac failure congestive	Moderate	125	126
	Cardiac failure congestive	Severe	234	237
	Cardiac failure congestive	Moderate	84	91
	Cardiac failure	Mild	45	46
	Cardiac failure congestive	Mild	9	14
	Cardiac failure congestive	Moderate	8	15
	Cardiac failure acute	Severe	117	121
	Cardiac failure	Severe	7	22
	Cardiac failure congestive	Severe	238	253
	Cardiac failure	Severe	35	40
	Cardiac failure congestive	Severe	130	133

Hypertension AEs

AEs from the SMQ Hypertension were reported in 85 subjects (11%) during the ED phase. No AEs were reported in the Acute phase. Among the 85 subjects reporting these events, the majority had a history of hypertension and/or CKD (78 subjects each). 6 (<1%) subjects reported SAEs, but none of the SAEs led to discontinuation of treatment.

Table 5. Adverse Events Suggestive of Hypertension (ED population)

Preferred Terms	ZS-005 (N=746)	
	n	%
Total	***85***	***11***
Hypertension	83	11.13
Hypertensive crisis	3	<1
Malignant hypertension	1	<1
Blood pressure increased	1	<1
Blood pressure inadequately controlled	1	<1
Secondary hypertension	1	<1
Serious AEs	***6***	***0.8***
AEs leading to discontinuation	***0***	***0***

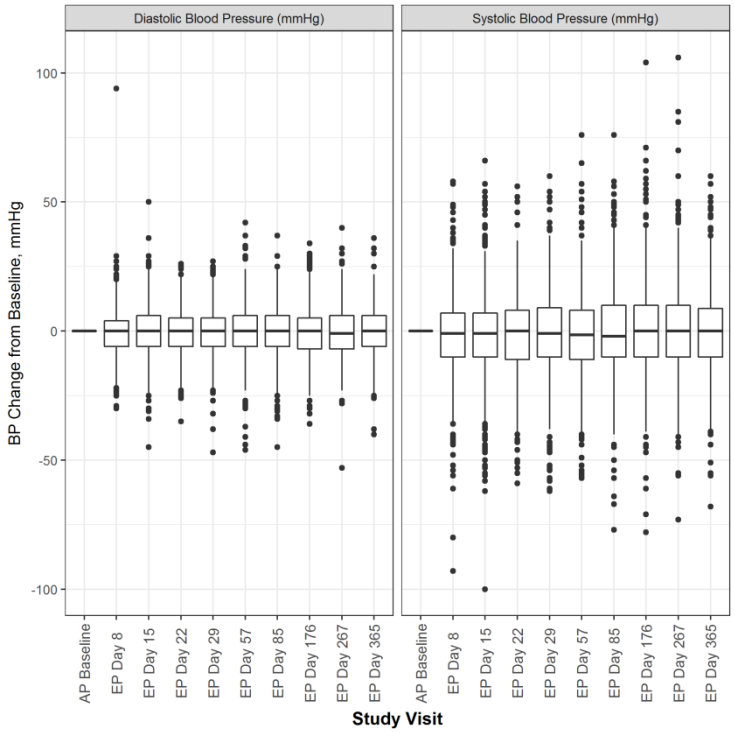
Source: Reviewer's analysis using datasets ae.xpt
Cross-reference: Tables 12-16 in ZS005 CSR

Reviewer's comment: The 6 subjects with SAEs related to hypertension are listed. Dr Xiao has provided narratives for these subjects in his review.

USUBJID	PT	Severity	Start Day	End Day
(b) (6)	Hypertension	Severe	37	40
	Malignant hypertension	Severe	126	128
	Hypertensive crisis	Severe	213	214
	Hypertension	Moderate	151	155
	Hypertension	Moderate	113	116
	Hypertension	Moderate	306	307

In the overall population, there was no changes in the distribution of blood pressure over the study duration (**Figure 2**).

Figure 2. Box Plot of Blood Pressure



Source: Reviewer's analysis using advs.xpt. Box plot show the median (line within each box); 25th and 75th percentile (width of box); 1.5 interquartile range (whiskers); and outliers (filled circles). Abbreviations: BP, blood pressure; AP, acute phase; EP, extended dosing phase.*

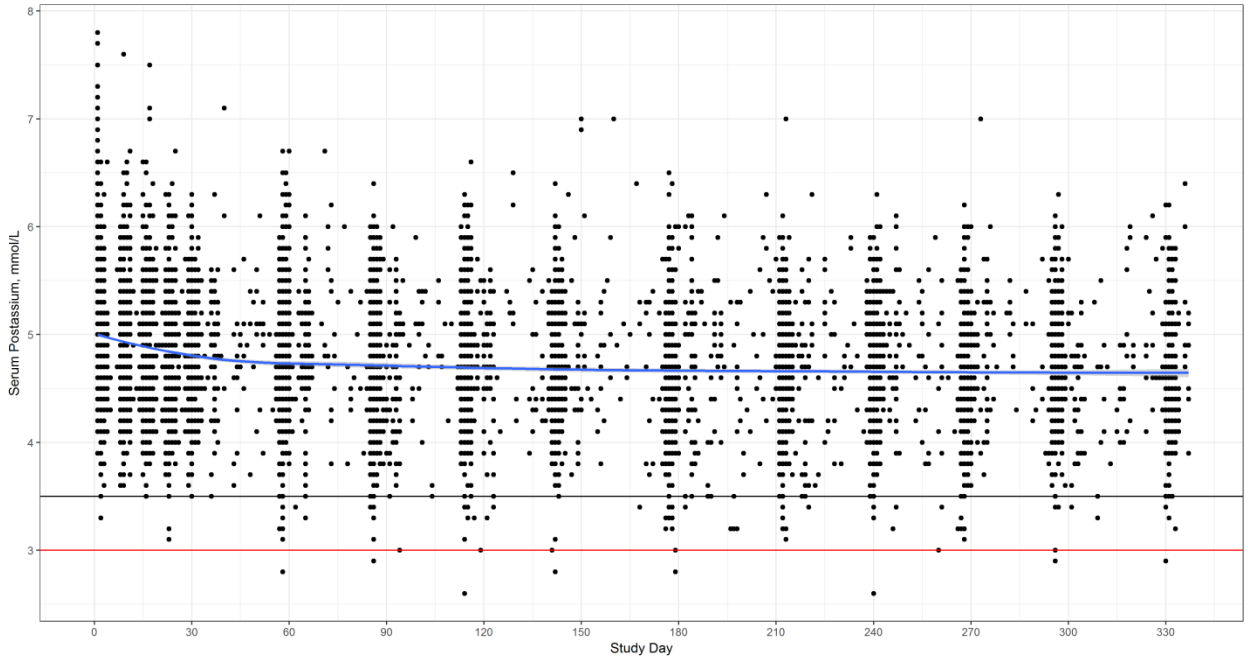
Hypokalemia AEs (Acute and ED phases)

11 (1.5%) subjects reported hypokalemia as an AE. There were no SAEs and 1 subject discontinued treatment.

A scatter plot of S-K levels by study visit is presented in Figure 1. There were 50 subjects with 1 S-K level <3.5mmol/L in the acute (n=1) or extended-dosing (n=49) phases and 9 subjects with 1 S-K level <3.0 mmol/L (all in extended dosing phase). None of the subjects had a S-K level below 2.5 mmol/L.

24 subjects with hypokalemia were prematurely discontinued from the Extended Dosing Phase. The most common reasons for discontinuation among these subjects were meeting hypokalemia stopping criteria (8 subjects), adverse event (3 subjects), consent withdrawn (4 subjects), investigator decision (2 subjects) and expected progression of CKD requiring dialysis, transplant, or other treatment (5 subjects).

Figure 3. S-K Levels by Time



Source: Reviewer's analysis using adsk.xpt

Reviewer's comments: In Table-12-17, the Applicant reported 43 subjects in ED phase who had a S-K level <3.5 mmol/L; however, the FDA analysis found 49 subjects. The subjects identified in the FDA analysis are shown in **Table 6**. *The 6 additional subjects identified by FDA had abnormal S-K levels at an unscheduled visit. In response to an Information Request, the Applicant proposes adding these 6 additional hypokalemia events for a total of 49 hypokalemia events from the ZS-005 study. The label was updated to incorporate this change and the percentage of patients with S-K <3.5mmol/L is reported as 4.1%.*

Table 6. Subjects with Hypokalemia (Lab Values) in Acute and ED Phases

USUBJID	VISIT	AVISIT	AVAL	Applicant Identified?
(b) (6)	Maintenance D211	EP Minimum	3.1	Y
	Maintenance D85	EP Minimum	3.4	Y
	Maintenance D295	EP Minimum	2.9	Y
	Maintenance D141	EP Minimum	2.8	Y
	Maintenance D57	EP Minimum	2.8	Y
	Maintenance D141	EP Minimum	3	Y
	Maintenance D176	EP Minimum	3.4	Y
	Maintenance D239	EP Minimum	3.3	Y
	Maintenance D239, Unscheduled 3	EP Minimum	3	No
	Maintenance D295	EP Minimum	3.4	Yes
	Maintenance D211	EP Minimum	3.3	Yes
	Maintenance D176	EP Minimum	2.8	Yes
	Maintenance D211, Unscheduled 1	EP Minimum	3.4	No

USUBJID	VISIT	AVISIT	AVAL	Applicant Identified?
(b) (6)	Maintenance D239, Unscheduled 1	EP Minimum	3.4	No
	Maintenance D330	EP Minimum	2.9	Yes
	Maintenance D113, Unscheduled 1	EP Minimum	3.4	No
	Maintenance D85	EP Minimum	2.9	Yes
	Maintenance D330	EP Minimum	3.3	Yes
	Maintenance D176	EP Minimum	3.4	Yes
	Maintenance D22	EP Minimum	3.1	Yes
	Maintenance D365	EP Minimum	3.2	Yes
	Maintenance D176, Unscheduled 1	EP Minimum	3.2	Yes
	Maintenance D141, Unscheduled 1	EP Minimum	3.4	No
	Maintenance D176	EP Minimum	3.2	Yes
	Maintenance D295	EP Minimum	2.9	Yes
	Maintenance D57	EP Minimum	3.1	Yes
	Maintenance D176	EP Minimum	3.3	Yes
	Maintenance D113	EP Minimum	2.6	Yes
	Maintenance D176	EP Minimum	3.3	Yes
	Maintenance D57	EP Minimum	3.3	Yes
	Maintenance D57	EP Minimum	3.2	Yes
	Maintenance D239	EP Minimum	3.4	Yes
	Maintenance D176, Unscheduled 1	EP Minimum	3.4	No
	Maintenance D295	EP Minimum	3.4	Yes
	Maintenance D267	EP Minimum	3.1	Yes
	Maintenance D267	EP Minimum	3.2	Yes
	Maintenance D85	EP Minimum	3.3	Yes
	Maintenance D239	EP Minimum	2.6	Yes
	Maintenance D1	AP Minimum	3.3	Yes
	Maintenance D113	EP Minimum	3.1	Yes
	Maintenance D176	EP Minimum	3.2	Yes
	Maintenance D267	EP Minimum	3.3	Yes
	Maintenance D113	EP Minimum	3.3	Yes
	Maintenance D267	EP Minimum	3.2	Yes
	Maintenance D113	EP Minimum	3.3	Yes
	Maintenance D239, Unscheduled 2	EP Minimum	3.2	Yes
	Maintenance D365	EP Minimum	3.4	Yes
	Maintenance D176	EP Minimum	3.4	Yes
	Maintenance D365	EP Minimum	3.1	Yes
	Maintenance D85	EP Minimum	3.1	Yes

Source: Reviewer's analysis using adsk.xpt
Cross-reference: Table 12-17 in ZS005 CSR

Conclusion

- In uncontrolled long term safety study, ZS005, most subjects were taking 5 to 10 g QD and 10% subjects required 15g QD. The incidence of edema (includes preferred terms of edema, peripheral edema and generalized edema) was 14%, which is similar to the incidence in the long-term safety extension study ZS004E (13%). The incidence for adverse events associated with the MedDRA HLT heart failure was 5%. The distinction between AEs related to either edema or heart failure may be arbitrary. Without a placebo control, the interpretation of these findings is limited.
- Hypokalemia AEs were reported in 11 subjects, but 49 subjects had a S-K lab values <3.5mmol/L at any time during the study.

Labeling

The applicant submitted the following labeling statements for sections 5 Warnings and Precautions and 6 Adverse Reactions as shown in the following text highlighted using grey shading.

> **5 WARNINGS AND PRECAUTIONS**
>
> **5.2 Edema**
>
> Each 5 g dose of LOKELMA contains approximately 400 mg of sodium. In clinical trials of LOKELMA, edema was generally mild to moderate in severity and was more commonly seen in (b) (4) treated with 15 g once daily. Monitor for signs of edema, particularly in (b) (4) who should restrict their sodium intake or are prone to fluid overload (e.g., heart failure or renal disease). Advise subjects to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed [see Adverse Reactions (6)].

Reviewer's comment: The proposed labeling reflects the results of the clinical trials. The Applicant has removed (b) (4) *from the title. I agree with this change.*

> **6 ADVERSE REACTIONS**
>
> 6.1 Clinical Studies Experience
>
> Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.
>
> The total exposure to LOKELMA in the safety and efficacy clinical trials of (b) (4) with hyperkalemia was 1,760 (b) (4) with 652 (b) (4) exposed to LOKELMA for at least 6 months and 507 (b) (4) exposed for at least one year.

Note from Applicant: Number of subjects exposed to ZS for 180 or 360 days or more counting from first day of dosing in the correction phase and last day of dosing in the extension phase in studies ZS-004e and ZS-005. For subjects in ZS-004e, the number of days of exposure is calculated by adding the number of days of exposure in ZS-004 and ZS-004e. Module 5.3.5.3 Integrated Summary of Safety- Safety Update Section 6: Table 6-1, Table 6-2.

> The population (n=1,009) in the placebo-controlled trials included subjects aged 22 to 96 years, females (n=454), Caucasians (n=859) and Blacks (n=130). Subjects had hyperkalemia

in association with comorbid diseases such as chronic kidney disease, heart failure and diabetes mellitus.

In placebo-controlled trials in which (b) (4) were treated with once daily doses of LOKELMA for up to 28 days, edema was reported in 4.4% of (b) (4) receiving 5 g, 5.9% of (b) (4) receiving 10 g, and 16.1% of (b) (4) receiving 15 g LOKELMA compared to 2.4% of (b) (4) receiving placebo. In longer-term uncontrolled trials in which most (b) (4) were maintained on doses < 15 g once daily, adverse reactions of edema (edema, generalized edema and peripheral edema) were reported in 8% to 11% of (b) (4)

Laboratory Abnormalities

In clinical trials, (b) (4)% of LOKELMA-treated (b) (4) developed hypokalemia with a serum potassium value less than 3.5 mEq/L, which resolved with dosage reduction or discontinuation of LOKELMA.

- *Table 6-2 in Integrated Summary of Safety shows a total of 658 subjects were treated for > 180 days and 469 subjects were treated for > 360 days with ZS. The Applicant responded to an Information Request by stating that the values presented in the proposed product label (and highlighted in yellow above) reflect the duration of exposure of subjects during the clinical program. These values account for all days of exposure to LOKELMA in both the correction and maintenance phases during the clinical studies. The values presented in Table 6-2 of the updated safety report only include exposure during the maintenance phase of the clinical studies and do not include exposure during the correction phase.*
  I agree with the Applicant's response.

Table 6-2 Extended Dosing: Extent of Exposure (Safety Population; Studies ZS-003 and ZS-004 Pooled, ZS-004E, and ZS-005)

Number of Days of Treatment, n	Placebo[a]	Starting Dose of ZS in Extended Dosing				Titration	Titration	Total ZS n (%)
		≤ 2.5 g QD	5 g QD	10 g QD	15 g QD	ZS-004E 10 g QD	ZS-005[b] 5 g QD	
≥ 1	301	199	110	114	56	123[c]	746[c]	1273 (100)
> 30						113	702	815 (64.0)
> 90						89	646	735 (57.7)
> 180						68	590	658 (51.7)
> 270						61	527	588 (46.2)
> 360						0	469	469 (36.8)

Source: ISS Statistical Table 3.2; Study ZS-004E CSR Appendix 16.2.5; and Study ZS-005 CSR Statistical Table 14.3.1.3

Abbreviations: QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate

[a] Following treatment with ZS TID during the Acute Phase.

[b] For Study ZS-005, numbers of subjects with dosing data on Extended Dosing Days 1, 29, 85, 176, 267, and 365 were used for the time points of 1, 30, 90, 180, 270, and 360 days, respectively.

[c] Of the 123 subjects in Study ZS-004E, 75 are already counted as part of the Extended Dosing active dose groups for Study ZS-004.

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/s/

CHRISTINE E GARNETT
05/11/2018

Office of Drug Evaluation-I: Decisional Memo

Date	March 16, 2017
From	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	207078
Applicant Name	ZS Pharma, Inc.
Date of Submission	September 16, 2016
PDUFA Goal Date	March 16, 2017
Proprietary Name	Lokelma
Established (USAN) Name	Sodium zirconium cyclosilicate powder for suspension
Dosage Forms/ Strengths	Powder for suspension, 5 gram and 10 gram packets
Proposed Indication	…is a potassium binder indicated for the treatment of hyperkalemia
Action:	*Complete Response*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Brian Proctor
Clinical Analyst	Christine Garnett
Clinical Pharmacology Review	Ju-Ping Lai; Lars Johannesen; Jeffry Florian; Sudharshan Hariharan
Office of Process and Facilities	Mohan Sapru; Thomas Wong; Raymond Frankewich; Vidya Pai; Dahlia Woody
Division of Medication Error Prevention and Analysis	Sarah Thomas; Chi-Ming (Alice) Tu
Office of Medication Error Prevention and Risk Management	Mona Patel; Leah Hart
Cross-Discipline Team Leader	Aliza Thompson
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge

1. Summary/Benefit-Risk Assessment

As noted by Dr. Stockbridge, the original *Complete Response* was primarily about CMC issues, and these issues remain unresolved. Pursuant to a re-inspection in January, a "withhold" recommendation remains for the site for drug substance manufacturing, release, and stability testing. (b) (4)

(b) (4) Given that more data will be needed to ensure that the specific activity issue is understood and mitigated, I agree with Dr. Stockbridge that issuing a second *Complete Response* action, rather than a clock extension, is appropriate.

None of the reviewers who filed reviews in this cycle favor approval at this time.

The overall benefit-risk assessment remains unchanged from my memorandum of May 26, 2016.

2. Background

See assessment in my memorandum of May 26, 2016.

3. Product Quality

Objectionable conditions were identified during the initial inspection of the drug substance manufacturing, release, and stability testing facility (ZS Pharma Inc., Coppell, TX). These conditions resulted in a 'Withhold" recommendation for the facility from the Office of Process and Facilities, and a *Complete Response* action from this Office.

When the NDA was originally submitted, the applicant attested that the facility in Coppell, TX was inspection-ready; however, this was not the case. The original pre-approval inspection, conducted March 17-29, 2016, revealed several deficiencies, leading to issuance of an FDA Form 483.

The firm's response was reviewed in detail. Although many problems were found to have been addressed satisfactorily, there were continued concerns with respect to: a) procedures in place for cleaning and maintaining process equipment; b) assessment of impact of adequate validation, control and monitoring of software used for manufacturing and quality control operations; and c) inadequate response to support validation of test methods used in manufacture.

Given that the ZS Pharma, Inc. Coppell, TX site was considered unacceptable, we issued a *Complete Response* on May 26, 2016 citing two chemistry, manufacturing, and controls (CMC) deficiencies:

1) Objectionable conditions identified during inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX). Because of the inspection findings, the Office of Process and Facilities issued a 'Withhold" recommendation for the facility.

2) Concern that potential daily exposures (b) (4) for each of these

elements at a maximum daily dose of 15 g (the maximum daily dose recommended by the FDA).

With the applicant's resubmission, the applicant stated that they had addressed the issues that were responsible for the *Complete Response*. FDA re-inspected the facility between January 18th and 30th, 2017, and another FDA Form 483 was issued because of observed violations of Section 501(a)(2)(B) of the Act.

Per Dr. Sapru:

> "From the chemistry, manufacturing and controls perspective, NDA 207078 is not recommended for approval because the Office of Process and Facilities has issued a 'Withold' recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX (FEI#3010199915). The unresolved FDA-483 issues concern firm's capabilities to meet the requirements of Section 501(a)(2)(B) of the Act for human drugs and commitments of the NDA. The application cannot be approved until all the inspectional observations cited in FDA Form 483 concerning this facility are satisfactorily resolved. Hence, the Office of Pharmaceutical Quality recommends issuing of Complete Response Letter to the applicant."

According to the Office of Process and Facilities, outstanding concerns include, but are not limited to, the following:

1. Failure to adequately qualify production equipment and validate production processes (b) (4)

2. Inadequate procedures for cleaning and maintaining processing equipment, (b) (4)

3. Inadequately controlled manufacturing process, (b) (4)

FDA received and reviewed ZS Pharma's response to FDA Form 483, dated February 10, 2017, and held a follow-up teleconference with the applicant on March 8, 2017. The Agency concluded that the applicant's responses concerning specific violations of Section 501(a)(2)(B) of the Act lack sufficient corrective actions, and hence remain unresolved.

I have considerable concerns with respect to the above deficiencies. In discussions with staff from the Office of Process and Facilities during recent team meetings, they have expressed the view that the applicant has not succeeded in identifying the root cause(s) of the above deficiencies. The (b) (4) is particularly troublesome and concerning.

4. Nonclinical Pharmacology/Toxicology

See assessment in my memorandum of May 26, 2016.

5. Clinical Pharmacology

Drug-Drug Interactions:

Our May 26, 2016, *Complete Response* letter noted our concern regarding the potential risk of drug-drug interactions. Of 39 drugs screened for interactions *in vitro*, 9 exhibited a significant decrease in concentration (30% to 99%) in one or more media, 7 exhibited a significant increase in concentration or binding capacity (40% to 560%), and 5 exhibited inconsistent findings over different pH ranges in different media.

Although many of these interactions appeared to be the result of pH changes caused by sodium zirconium cyclosilicate, some drugs showed concentration changes that could not be explained solely by pH changes.

The applicant conducted Study ZS-009 in healthy subjects, a phase 1, single-dose, open-label, single-sequence crossover study to assess the effects of sodium zirconium cyclosilicate on the pharmacokinetics of 9 different drugs: losartan, warfarin, atorvastatin, amlodipine, furosemide, levothyroxine, glipizide, clopidogrel and dabigatran. These drugs are weak acids, bases and drugs with a narrow therapeutic index, and they had shown increases, decreases, or inconsistent results in prior *in vitro* studies.

The results, conclusions, and plan for mitigation are discussed in the Clinical Pharmacology Review and the memoranda of the Cross-Discipline Team Leader (CDTL) and Division Director. Briefly, for drugs with pKa in the range of ~2 to 6, sodium zirconium cyclosilicate increased the solubility of acidic drugs and decreased the solubility of basic drugs, thereby affecting the bioavailability of both. Specifically, for the weakly acidic drugs – atorvastatin, furosemide, and warfarin – increases in peak concentration (C_{max}) of 69%, 66% and 38% were observed, respectively. For the weakly basic drugs, dabigatran and clopidogrel, decreases in both C_{max} and area under the curve (AUC) were observed in the range of 32 to 43%.

At this juncture, the applicant and the Office of Clinical Pharmacology agree that the mechanistic basis of these interactions is reasonably well established; however, the consequences of the interactions and the best approach for mitigation in labeling have been under active discussion with the applicant.

On the basis of the *in vivo* findings from Study ZS-009, the applicant had asserted that sodium zirconium cyclosilicate is free of clinically relevant drug-drug interaction liabilities, (b) (4) The Office of Clinical Pharmacology review team did not agree with the applicant's interpretation of the study results, arguing eloquently that these interactions could be clinically meaningful for furosemide, dabigatran, and other drugs. Based on a comparison of the acid neutralizing capacity of antacids with that of sodium zirconium

cyclosilicate, the Office of Clinical Pharmacology review proposed separation of dosing of drugs by 2 hours in order to mitigate drug-drug interactions.

In continuing discussions, the applicant continued to assert that the drug-drug interactions observed with the 9 drugs in Study ZS-009 are not clinically meaningful. The applicant identified a number of other drugs (atazanavir, nelfinavir, saquinavir, ketoconazole, digoxin, iron salts, erlotinib, and mycophenolate mofetil), based on experience with proton pump inhibitors, with potentially clinically meaningful interactions. (b) (4)

As summarized in the CDTL memorandum, the Clinical Pharmacology review team has expressed a number of concerns (b) (4) Dr. Thompson interpreted their concerns as follows:

- Even if one were to accept the premise that proton pump inhibitors represent a worst case scenario, the applicant's list of drugs that interact with proton pump inhibitors is not comprehensive (i.e., the review team has identified additional drugs with interactions with proton pump inhibitors that were not listed by the applicant).
- The review team also questions the premise that proton pump inhibitors represent a worst case scenario. The review team notes that CYP2C19 and CYP3A4 interactions might, in some settings, attenuate the proton pump inhibitor's effect on pH and its pH-mediated interactions.
- In essence, it would not be plausible to list *all* drugs with potentially important drug-drug interactions, and the list would change with time. Thus, Office of Clinical Pharmacology continues to believe a more pragmatic approach to labeling is needed (i.e., that labeling should recommend spacing of *all* orally administered medications with sodium zirconium cyclosilicate by 2 hours).

I agree with the views of the Office of Clinical Pharmacology, and Drs. Thompson and Stockbridge. Although it would be possible to identify many of the drugs with the potential for clinically significant drug-drug interactions, a more reliable strategy is to avoid taking most drugs at the same time as sodium zirconium cyclosilicate, except when one is sure it is safe to do so. Given that sodium zirconium cyclosilicate is to be administered only once a day after the initial TID regimen, the 2-hour separation will be reasonable and practicable.

Proposed Maximum Dose:

In our May 26, 2016, *Complete Response* letter, we indicated that, based on our review of the data, a maximum maintenance dose of 15 g once daily (b) (4) should be recommended in labeling. In response, the applicant provided analyses to support the concept that the recommended maintenance dose should be (b) (4) once daily, because the majority of patients with hyperkalemia were effectively treated with these doses.

The Office of Clinical Pharmacology continues to recommend a maximum maintenance dose of 15 g once daily based on individual response. They note that one of the analyses presented by the applicant shows that at least 10-13% of patients would require a 15-g once daily dose in order to achieve the target serum potassium level.

The Office of Clinical Pharmacology's recommendation was conveyed to the applicant in a January, 2017 advice letter and discussed during a teleconference with the applicant on February 9, 2017. In correspondence received from the applicant on February 16, 2017, they agreed that labeling will recommend a maximum maintenance dose of 15 g once daily. In order to make this possible, the applicant has revised the acceptance criteria for elemental impurities (b) (4) to be within ICH recommended limits.

6. Clinical/Statistical – Efficacy

See assessment in my memorandum of May 26, 2016.

7. Safety

See assessment in my memorandum of May 26, 2016.

8. Advisory Committee Meeting

See my memorandum of May 26, 2016.

9. Pediatrics

See my memorandum of May 26, 2016.

10. Other Relevant Regulatory Issues

None.

11. Postmarketing Recommendations

See my memorandum of May 26, 2016.

12. Recommended Comments to the Applicant

See the *Complete Response* letter, issued today.

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/s/

ELLIS F UNGER
03/16/2017

Cross-Discipline Team Leader Memo

Date	March 6, 2017
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Memo
NDA #	207078
Applicant	ZS Pharma Inc
Date of Submission	September 16, 2016
PDUFA Goal Date	March 16, 2017
Proprietary Name / Non-Proprietary Name	Lokelma / sodium zirconium cyclosilicate
Dosage form(s) / Strength(s)	Powder for Oral Suspension / 5 g and 10 g packets
Applicant Proposed Indication(s)/Population(s)	Treatment of hyperkalemia
Recommendation on Regulatory Action	*Complete Response unless the facility inspection issues can be resolved and agreement can be reached on labeling*

This secondary review is based on the following reviews:

Material Reviewed/Consulted	
Clinical Pharmacology Review (1/27/17)	Ju-Ping Lai, Lars Johannesen, Jeffry Florian, and Sudharshan Hariharan
Clinical Review (1/18/2017)	Christine Garnett
Division of Medication Error Prevention and Analysis Reviews (12/21 and 12/29/2016)	Sarah Thomas and Chi-Ming (Alice) Tu

At this time, the Quality Assessment and Division of Risk Management reviews are pending.

Background

On May 26, 2015, ZS Pharma Inc submitted NDA 207078 for sodium zirconium cyclosilicate (Lokelma) for the treatment of hyperkalemia. On May 27, 2016, FDA issued a Complete Response Letter citing deficiencies related to CMC issues (facility inspection findings and impurity levels), clinical pharmacology issues (drug-drug interaction liability), and outstanding labeling issues. On September 16, 2016, ZS Pharma resubmitted NDA 207078 for sodium zirconium cyclosilicate (Lokelma) oral suspension for the treatment at of hyperkalemia. At this time, it seems unlikely that the application will be approved during the current review cycle. As discussed below, GMP violations and other issues were identified during reinspection of the drug substance manufacturing, release and stability testing facility. There are also outstanding labeling issues that will need to be resolved prior to approval.

CMC

FDA's Complete Response (CR) Letter cited two chemistry, manufacturing, and controls (CMC) deficiencies:

1) Objectionable conditions identified during inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX). Because of the inspection findings, the Office of Process and Facilities issued a 'Withhold" recommendation for the facility.
2) Concern that potential daily exposures (b) (4) for each of these elements at a maximum daily dose of 15 g (the maximum daily dose recommended by the FDA).

With regard to the first issue, the applicant stated in their resubmission that they had addressed the issues identified during inspection of the drug substance manufacturing, release and stability testing facility. In late January 2017, the facility was reinspected by FDA. GMP violations and other issues were again identified and another FDA Form 483 was issued. At this time, the Dallas District Office and the facility review team are reviewing the applicant's responses to the latest 483 issues.

Reviewer's Comment: According to Dr. Sapru, CMC Lead, at the conclusion of the inspection, a form FDA-483 was issued to the API manufacturing site because of observed violations of Section 501(a)(2)(B) of the Act. The manufacturing facility's response to form FDA-483, dated February 10, 2017, has been reviewed. Outstanding concerns include, but are not limited to, the following:

1. *Failure to adequately qualify production equipment and validate production processes* (b) (4)
2. *Inadequate procedures for cleaning and maintaining processing equipment,* (b) (4)
3. *Inadequate drift correction practices* (b) (4)

4. *Inadequately controlled manufacturing process,* (b) (4)

In their response to the second issue, ZS Pharma stated that they were still proposing a maximum daily dose of (b) (4) g (not 15 g, as recommended by the Agency) and hence changes to the acceptance criteria for elemental impurities in the drug substance were not warranted. There is now agreement that the maximum recommended daily dose during continued treatment will be 15 g once daily, (b) (4) and the applicant has revised the acceptance criteria to comply with the ICH Q3D recommended PDE limits.

Clinical Pharmacology

The CR letter cited two clinical pharmacology issues, the first related to the assessment of sodium zirconium cyclosilicate's drug-drug interaction liability and the second related to the maximum maintenance dose that should be recommended in labeling. The applicant's resubmission included an *in vivo* drug interaction study report and the applicant's rationale for a maximum maintenance dose of (b) (4) g.

Drug-drug interaction liability

As discussed in the Office of Clinical Pharmacology (OCP) review and my prior CDTL memo, results of *in vitro* screening tests raised concern that sodium zirconium cyclosilicate might interact with other orally administered medications. The applicant conducted an *in vivo* drug-drug interaction study to evaluate this potential risk. The applicant's response to FDA's CR letter includes the final study report and data sets for this study, which evaluated nine drugs in healthy subjects.

The tested drugs (losartan, warfarin, atorvastatin, amlodipine, furosemide, levothyroxine, glipizide, clopidogrel and dabigatran) represent weak acids, bases and drugs with a narrow therapeutic index; these drugs also showed an increase, decrease or inconsistent result in the *in vitro* studies conducted with sodium zirconium cyclosilicate. According to the OCP review, "Systemic exposures for 5 of 9 compounds (atorvastatin, clopidogrel, dabigatran, furosemide, and warfarin) were altered when administered in the presence of sodium zirconium cyclosilicate. Among weakly acidic drugs, increase in peak concentration (C_{max}) by 69 %, 66% and 38% were observed for atorvastatin, furosemide and warfarin, respectively. Amongst weakly basic drugs, decrease in both C_{max} and area under the curve (AUC) by ~32-43% were observed for dabigatran and clopidogrel acid."

At this point, both the applicant and OCP agree that the mechanistic basis for the interaction is reasonably well understood. Specifically, sodium zirconium cyclosilicate can transiently increase gastric pH and thus affect the absorption of co-administered oral medications that exhibit pH-dependent solubility. Until recently, a key area of disagreement has been the clinical significance of the *in vivo* study results. In their response to the CR letter, the applicant asserted that the *in vivo* findings indicate that sodium zirconium cyclosilicate does not possess a clinically relevant drug interaction liability (b) (4) The Clinical Pharmacology team disagrees. The OCP review notes that although the

increase in peak concentration was transient for weakly acidic drugs such as atorvastatin and furosemide, the magnitude of change was large (increase in Cmax of ~65% for these drugs). The review also notes that while the increase in gastric pH following administration of sodium zirconium cyclosilicate is short-lived, a decrease in Cmax and also AUC of up to ~40% was observed for a weakly basic drug (dabigatran). The review goes on to discuss the potential clinical relevance of the changes in exposure seen in the *in vivo* study.

OCP's conclusion regarding the product's potential DDI liability and measures to mitigate risk were conveyed to the applicant via an advice letter in January 2017. With regard to the latter, OCP believes that labeling should recommend 2-hour spacing with all concomitant oral medications. For further discussion of the data supporting a 2-hour spacing window (as opposed to a longer or shorter time window), see the OCP review.

Since January 2017, there have been several back-and-forths with the applicant on the product's potential to interact with orally administered medications, including written correspondence from the applicant (received on February 1 and 16, 2017) and a teleconference between representative of the firm and FDA on February 9, 2017. At this point, there appears to be agreement that *some drugs* may exhibit clinically relevant interactions with sodium zirconium cyclosilicate, but not on *which drugs* or the best approach to mitigate this risk/address the risk in labeling.

In their latest submission, the applicant has identified the following drugs with potentially clinically meaningful interactions with sodium zirconium cyclosilicate based on the experience with proton pump inhibitors (PPIs): atazanavir, nelfinavir, saquinavir, ketoconazole, digoxin, iron salts, erlotinib, and mycophenolate mofetil. (b) (4) Of note, the applicant maintains that the results of *in vivo* interaction do not suggest a clinically relevant interaction with any of the drugs that were tested in those studies.

The Clinical Pharmacology review team has voiced a number of concerns (b) (4) I understand these concerns to be as follows:

- According to the Clinical Pharmacology review team, even if one were to accept the premise that PPIs represent a reasonable worst case scenario, the applicant's list of drugs that interact with PPIs is not comprehensive (i.e., in going through PPI drug labels, the team has identified additional drugs that were not identified by the applicant).
- The review team also questions the premise that PPIs necessarily reflect a worst case scenario. As relates to this issue, the review team notes that metabolic interactions (CPY2C19 and CYP 3A4) might, in some settings, offset a PPI's pH-mediated interaction. For this reason, the review team believes it may also be important to consider drugs that show a significant interaction with antacids. Based on such an approach (i.e., oral medications that exhibit clinically relevant interactions with PPIs or antacids), the review team has so far identified 25 drugs that should be included on the list, and notes that a more comprehensive search would likely identify additional drugs.

Based on the number of drugs identified to date, OCP continues to believe a more pragmatic approach to labeling is needed (i.e., that the label should recommend spacing of all orally administered medication with sodium zirconium cyclosilicate by 2 hours).

Reviewer's Comment: Based on the findings to date, I think that labeling should describe the basis for the interaction and recommend spacing with other oral medications unless the prescriber has ascertained that the coadministered medication does not exhibit pH-dependent solubility.

Proposed Maximum Dose

In its CR letter, the Agency indicated that, based on its review of the data, a maximum maintenance dose of 15 g once daily (b) (4) should be recommended in labeling. In their response to the CR letter, the applicant asserted that the recommended maintenance doses should be (b) (4) once daily since the majority of subjects with hyperkalemia were effectively treated with these doses. OCP continues to recommend that labeling permit a maximum maintenance dose of 15 g once daily based on individual response. In support of this conclusion, OCP cites the results of studies ZS004E and ZS005. In both of these studies, approximately 10% of subjects were titrated to 15 g once daily because of inadequate control of serum potassium.

OCP's recommendation was conveyed to the applicant in the Division's January 2017 advice letter and discussed during the teleconference with the applicant on February 9, 2017. In correspondence received from the applicant on February 16, 2017, the applicant agreed that labeling will recommend a maximum maintenance dose of 15 g once daily.

Reviewer's comment: (b) (4)

Clinical

In Study ZS-004, edema/fluid overload, presumably resulting from absorption of sodium from the product, was observed at a higher frequency in the sodium zirconium cyclosilicate groups compared to the placebo group, particularly at the highest dose evaluated for extended use (15 g once daily). As might be expected, certain subgroups, such as those with more severe renal impairment and those with heart failure, appeared to be more susceptible to this risk.

In its CR letter, the Agency indicated that a Warning and Precaution was warranted to address the risk of edema and fluid overload with sodium zirconium cyclosilicate. In its response to the Agency's CR letter, the applicant asserted that a Warning and Precaution was not warranted and cited the following reasons: edema is commonly observed in patients with the same underlying diseases as those enrolled in the study population; that the incidence of edema in the clinical program is similar to that observed in the patient population studied; and that

prescribers are well versed in treating edema and the edema observed in the clinical program was easily managed.

Dr. Garnett's review contains a comprehensive discussion of the findings in Study ZS-004 that speak to this issue. These analyses, such as the ones shown in the tables below, support the conclusion that sodium zirconium cyclosilicate can cause edema and fluid overload in susceptible patients, particularly at higher dose.

Table 1: Edema and Fluid Retention adverse events in Study ZS-004

MedDRA HLT and PT	Acute Phase Treatment 10 g ZS TID (2 days) / Maintenance Phase Treatment (28 days)									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	***2***	***4.4***	***3***	***5.9***	***9***	***16.1***	***14***	***9.2***	***2***	***2.4***
Oedema NEC	1	2.2	3	5.9	8	14.3	12	7.9	2	2.4
Generalised oedema	0	0	0	0	2	3.6	2	1.3	0	0
Oedema	1	2.2	0	0	1	1.8	2	1.3	0	0
Oedema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Total fluid volume increased	1	2.2	0	0	1	1.8	2	1.3	0	0
Fluid overload	1	2.2	0	0	0	0	1	0.7	0	0
Fluid retention	0	0	0	0	1	1.8	1	0.7	0	0
Joint related signs and symptoms	0	0	0	0	1	1.8	1	0.7	0	0
Joint swelling	0	0	0	0	1	1.8	1	0.7	0	0

Source: Dr. Garnett's Review, Table 2
Per Dr. Garnett (email dated March 3, 2017), all of the edema AEs reported in Study ZS-004 occurred during the maintenance phase, as opposed to the acute phase, of treatment.

Table 2: Fluid Retention Adverse Events by Subgroup in Study ZS-004

Subgroup	Acute Phase Treatment 10 g ZS TID (2 days)									
	Maintenance Phase Treatment (28 days)									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Number in subgroup (n)/Total (N)	*2/45*	*4.4*	*3/51*	*5.9*	*9/56*	*16.1*	*14/152*	*9.2*	*2/85*	*2.4*
Patients with CKD (N=152)	2/29	6.9	3/36	8.3	9/37	24.3	14/102	13.7	1/50	2.0
Subjects with No CKD (N=85)	0/16	0	0/15	0	0/19	0	0/50	0	1/35	2.9
Subjects with HF (N=87)	1/18	5.6	2/18	11.1	5/25	20	8/61	13.1	1/26	3.9
Subjects with No HF (N=150)	1/27	3.7	1/33	3.0	4/31	12.9	6/91	6.6	1/59	1.7
Subjects with DIAB (N=157)	2/26	7.7	3/38	7.9	7/39	17.9	12/103	11.7	0/54	0
Subjects with No DIAB (N=80)	0/19	0	0/13	0	2/17	11.8	2/49	4.1	2/31	6.5

Abbreviations: CKD, chronic kidney disease with glomerular filtration rate less than 60 ml/min; HF, heart failure as reported at baseline; DIAB, diabetes as reported at baseline.

Source Dr. Garnett's Review, Table 3

**This table corrects errors in Table 13 of my CDTL memo dated May 2016

Analyses conducted by Dr. Garnett and by the applicant indicate that the risk of edema/fluid retention is manageable over the short-term and during more extended treatment. Of the edema related AEs shown in Table 1, one of the AEs in the sodium zirconium cyclosilicate 15-g dose group (1/56, or ~2%) and none in the 5-g, 10-g and placebo groups was reported to be serious.[1] Safety data from longer-term studies (i.e., maintenance treatment for more than 28 days) are difficult to interpret because of the lack of a control arm and because events of edema would be expected due to other underlying conditions in the population (heart failure, chronic kidney disease). Bearing this in mind, the data from these longer-term studies, in which most patients were maintained on doses < 15 g once daily, seem, as a whole, reassuring. In these studies, AEs of edema (edema, generalized edema and peripheral) were reported in 8 to 11% of patients; serious AEs suggestive of heart failure were reported at a low incidence (~3% or 4/123 subjects in Study ZS-004E and ~2% or 15/746 subjects in Study ZS-005).[2]

The review team's conclusion regarding the need for a Warning and Precaution related to the risk of edema was conveyed to the applicant in the Division's January 2017 advice letter and discussed during the teleconference with the applicant on February 9, 2017. In correspondence

[1] Subject 4704-001 had a serious adverse event (SAE) of "generalized edema related to CKD" on day 13 of the maintenance phase that led to discontinuation of study treatment (correction to page 4 of Dr. Garnett's review, which states that none of the AEs was serious). In addition, according to Dr. Garnett's analysis of adverse events in the Cardiac Failure SMQ (see Table 5), one subject in the 5-g treatment group had an SAE of "cardiac failure congestive" that did not result in discontinuation of treatment.

[2] Analysis combines preferred terms (PTs) falling within the Cardiac Failure SMQ and AEs of pulmonary edema.

received from the applicant on February 16, 2017, the applicant proposed potential language for such a Warning and Precaution.

Current Status of Labeling

At this time, agreement had not been reached on labeling related to the potential risk of DDIs, and the wording of Warnings and Precautions related to (1) sodium absorption and edema and (2) use in patients with impaired GI motility.

DMEPA's review contains recommendations on how to further improve container labels, carton labeling, and prescribing information to promote the safe use of Lokelma. DMEPA's recommendations related to container labels, carton labeling, and professional sample have been conveyed to the applicant; DMEPA's recommendations on revisions to the prescribing information were incorporated into the draft label that is undergoing internal review.

The proposed proprietary name, Lokelma, has been deemed acceptable by the Office of Medication Error Prevention and Risk Management.

Recommendation on Regulatory Action

The application cannot be approved until the facility inspection and outstanding labeling issues have been resolved.

Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
At this time, product labeling is expected to be adequate to ensure that the product's benefits outweigh its risks in the postmarket setting.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
Upon approval for the treatment of hyperkalemia in adults, a PMR should be issued to conduct a two-part, safety and pharmacodynamic study in children 0 to (b) (4) years of age with hyperkalemia. (b) (4)

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/s/

ALIZA M THOMPSON
03/06/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 18, 2017

From: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

Subject: Complete Response Package for NDA 207078

Sponsor: ZS Pharma, Inc.

Name: LOKELMA (sodium zirconium cyclosilicate)

A New Drug Application (NDA) for sodium zirconium cyclosilicate for the treatment of hyperkalemia was submitted to the FDA on 05/26/2015. A Complete Response Letter was issued on 05/26/2016 citing deficiencies in the application. The sponsor submitted a complete response to the FDA's action letter on 9/16/2016.

Primary Reviewer's Comments on the Applicant's Responses to the Clinical Comments in the Complete Response Letter

Complete Response Issue 6

ZS Pharma Response: Warnings and Precautions are intended to identify and describe serious or clinically significant adverse drug reactions (ADR) that have implications for prescribing decisions or for additional patient management. Based on review of the mechanistic data as well as the clinical data, no special management is required and therefore a warning and precaution statement is not warranted.

Conclusions

- Urinary sodium excretion suggests that sodium exposure from ZS is minimal.
- Edema appeared more frequently at the highest dose tested in ZS004, 15 g.
- Edema occurs commonly in patients with hyperkalemia that have multiple comorbidities (Chronic kidney disease (CKD), heart failure, hypertension, diabetes) or are taking medications which cause edema (calcium channel blockers) and hence use of these agents and ongoing contribution to this event cannot be eliminated.
- Edema did not require treatment in 40-50% of ZS-treated patients and consisted mainly of mild or moderate peripheral edema. When treated, edema was treated as is customary for the patient population which commonly experiences edema. The incidence of treated edema was 5-6% in the long-term studies.

- The incidence and rates of edema in the long-term studies appear similar to other studies in similar populations and durations.
- Long-term use of ZS does not lead to increased rate of edema.

Reviewer's Comment: Because patients will be titrated to a maximum dose of 15 g QD, I recommend a Warnings and Precaution statement of fluid retention and edema when using ZS. This statement is supported by the clinical AE data presented in the placebo-controlled study ZS-004, and supported by the long term safety studies, ZS-004E and ZS-005.

Complete Response Issue 11

ZS Pharma Response: Safety data obtained from the original NDA submission, the 120-Day Safety Update, and from ongoing Study ZS-005 as of 7 December 2015 have been collectively analyzed to assess the tolerability of sodium zirconium cyclosilicate and is included in M5 5.3.5.3 Safety Update Report.

Reviewer's Comment: There are no new safety findings with up to 12 months of treatment with ZS in the Safety Update Report.

REVIEW OF SUBMISSION

Approach to Safety Review

The safety review focused on adverse events (AEs) and lab values related to sodium retention in study ZS004 because this study included a placebo control and subjects received fixed doses of sodium zirconium cyclosilicate (ZS) for 28 days in the extended dosing phase. Supportive safety data came from the open label, uncontrolled safety studies (ZS004E, ZS005) with dosing up to one year. Safety data from clinical studies were not pooled because of the differences in treatment duration and dosing during the extended dosing phases as described in **Table 1**. The following materials were reviewed:

- Original NDA 207078 (dated 05/26/2015)
- Complete Response Letter (dated 05/26/2016)
- ZS Pharma response to Complete Response Letter (dated 09/12/2016)
  \\CDSESUB1\evsprod\NDA207078\0030\m1\us\multiple-module-document-0030.pdf
- Safety Update Report, includes safety data obtained from original NDA submission, 120-day safety update, and from ongoing study ZS-005 (dated 08/31/2016)

  \\CDSESUB1\evsprod\NDA207078\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperkalemia\5353-rep-analys-data-more-one-stud\crl-safety-update\safety-update-report.pdf

Standard MedDRA queries for fluid overload, cardiac failure and hypertension were based on MedDRA 18.1. Laboratory values were change from baseline in systolic/diastolic blood pressure and body weight. Subgroup analysis of AEs focused on risk factors for edema including chronic kidney disease, chronic heart failure, diabetes and concomitant use of calcium channel blockers or diuretics.

Overview of Studies

The clinical development program included two phase 1 studies (ZS-006, ZS-009), one phase 2 study (ZS002), two randomized, placebo-controlled phase 3 studies (ZS003, ZS004) and two open-label long terms safety studies (ZS004E, ZS005). As of 7 December 2015, a total of 1,760 subjects with hyperkalemia and 210 healthy volunteers have been exposed to at least 1 dose of ZS.

A description of the phase 3 studies is provided in **Table 1**. A total of 1,273 subjects have received at least 1 dose of ZS in the extended dosing phase. Among the completed phase 3 studies, a total of 527 subjects received at least 1 dose of ZS during Extended Dosing (Studies ZS-003 and ZS-004 = 479 subjects and Study ZS-004E = 48 subjects treated with placebo in Study ZS-004 who received ZS in Study ZS-004E).

Table 1. Completed and Ongoing Phase 3 Clinical Trials (Reviewer's Table)

	ZS-003	**ZS-004**	**ZS-004E**	**ZS-005**
Status	Completed	Completed	Completed	On-going
Design	Two phase (Acute and Subacute), randomized, double-blind Subacute Phase (12 days): randomized withdrawal for subjects who received ZS during Acute Phase	Two phase (Acute and Maintenance) Acute Phase: single ZS treatment group, open-label Maintenance Phase (28 days): randomized, double-blind, placebo-controlled	An open-label extension to Study ZS-004	Phase 3, multicenter, prospective, open-label maintenance study
Number Subjects	753 acute/ 543 extended dosing	258 acute/237 extended dosing	123 extended dosing	751 acute/ 746 extended dosing
Acute Phase	TID for 48 hours (fixed doses) 1.25 g 2.5 g 5 g 10 g Placebo	10 g TID for 48 hours	10 g TID 1-2 days	10 g TID for 24, 48, or 72 hours
Extended Dosing Phase	QD for 12 days (fixed doses) 1.25 g 2.5 g 5 g 10 g Placebo	QD for 28 days (fixed doses) 5 g 10 g 15 g Placebo	11 months 10 g QD with adjustment based on i-STAT potassium	12 months 5 g QD with adjustment based on i-STAT potassium

Cross reference: Tables 3-2 and 6-1 in Integrated Summary of Safety-Safety Update (31 August 2016) and Table 1-2 in 2.7.4 Summary of Clinical Safety (30 March 2015)
Abbreviations: QD, once daily; TID, three times per day

Fluid Retention, Edema and Heart Failure AEs in ZS-004

The main evidence for the fluid retention AEs came from Study ZS-004 because this randomized study contained a placebo control arm and subjects were dosed with ZS or placebo for 28 days. Standard MedDRA Query for Hemodynamic edema, effusions and fluid overload is shown in Table 2. More subjects in the ZS arms had an edema/fluid retention AEs compared to placebo [14 (9%) *vs*. 2 (2%)]. Subjects with AEs mainly came from the 15 g ZS dose [9 (16%)]. There was no pattern to the time of onset of edema. None of the AEs were serious.

Table 2. Edema and Fluid Retention AEs in Study ZS-004 (Reviewer's Table)

MedDRA HLT and PT	Acute Phase Treatment 10 g ZS TID (2 days) Maintenance Phase Treatment (28 days)									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	***2***	***4.4***	***3***	***5.9***	***9***	***16.1***	***14***	***9.2***	***2***	***2.4***
Oedema NEC	1	2.2	3	5.9	8	14.3	12	7.9	2	2.4
Generalised oedema	0	0	0	0	2	3.6	2	1.3	0	0
Oedema	1	2.2	0	0	1	1.8	2	1.3	0	0
Oedema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Total fluid volume increased	1	2.2	0	0	1	1.8	2	1.3	0	0
Fluid overload	1	2.2	0	0	0	0	1	0.7	0	0
Fluid retention	0	0	0	0	1	1.8	1	0.7	0	0
Joint related signs and symptoms	0	0	0	0	1	1.8	1	0.7	0	0
Joint swelling	0	0	0	0	1	1.8	1	0.7	0	0

Cross-reference: Table 12-12 in ZS-004 Clinical Study Report (03December2014)
Abbreviations: HLT, high level term; PT, preferred term, NEC, not elsewhere classified

Subjects who have comorbid diseases such as chronic kidney disease (CKD), heart failure or diabetes are at risk for developing edema. In study ZS-004, subject with these risk factors who were taking ZS experienced fluid retention at a higher incidence than those taking placebo (**Table 3**). All 14 subjects with fluid retention AEs who took ZS had CKD at baseline. Of the 14 subjects with AEs, 8 (9.4%) subjects had baseline glomerular filtration rate (GFR) ≤30 ml/min/1.73 m^2 and were taking ZS (6 taking 15 g QD, 2 taking 10 QD). Four subjects (5%; 3 in ZS groups, 1 in placebo) had baseline GFR between 30 and 60 ml/min/1.73 m^2 and 2 subjects (3%; 1 each in ZS and placebo groups) had baseline GFR ≥60 ml/min/1.73m^2.

Subgroup analysis was also performed by concomitant medications that could increase the risk of fluid retention (**Table 4**). Subjects taking concomitant calcium channel blocker (CCB) with ZS were more likely to experience fluid retention than those taking placebo with a CCB.

Table 3. Fluid Retention AEs by Subgroup in Study ZS004 (Reviewer's Table)

Subgroup	Acute Phase Treatment 10 g ZS TID (2 days)									
	Maintenance Phase Treatment (28 days)									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Number in subgroup (n)/Total (N)	***2/45***	***4.4***	***3/51***	***5.9***	***9/56***	***16.1***	***14/152***	***9.2***	***2/85***	***2.4***
Patients with CKD (N=152)	2/29	6.9	3/36	8.3	9/37	24.3	14/102	13.7	1/50	2.0
Subjects with No CKD (N=85)	0/16	0	0/15	0	0/19	0	0/50	0	1/35	2.9
Subjects with HF (N=87)	1/18	5.6	2/18	11.1	5/25	20	8/61	13.1	1/26	3.9
Subjects with No HF (N=150)	1/27	3.7	1/33	3.0	4/31	12.9	6/91	6.6	1/59	1.7
Subjects with DIAB (N=157)	2/26	7.7	3/38	7.9	7/39	17.9	12/103	11.7	0/54	0
Subjects with No DIAB (N=80)	0/19	0	0/13	0	2/17	11.8	2/49	4.1	2/31	6.5

Abbreviations: CKD, chronic kidney disease with glomerular filtration rate less than 60 ml/min; HF, heart failure as reported at baseline; DIAB, diabetes as reported at baseline.

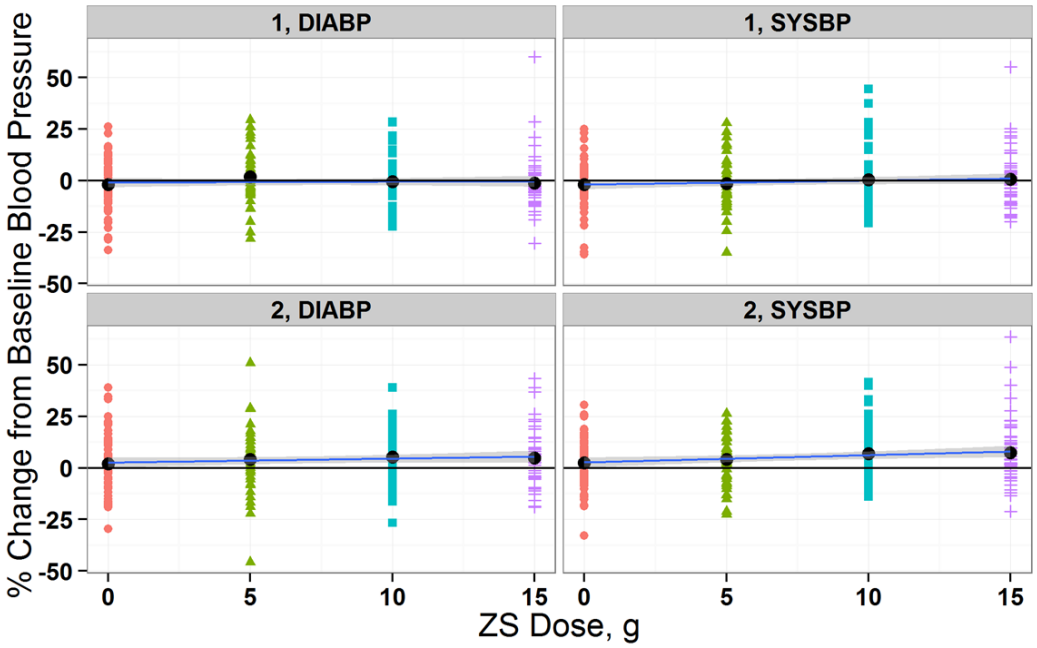
Table 4. Fluid Retention AEs by Concomitant Medication (Reviewer's Table)

	Concomitant Medications (ANL02FL="Y")			
	Taking Diuretics (N=63)	Not Taking Diuretics (N=174)	Taking CCB (N=75)	Not Taking CCB (N=162)
Subjects with Edema	5 (7.9%)	11 (5.7%)	9 (12%)	7 (4.3 %)
By Treatment				
Placebo	2/29 (6.9%)	0/58	0/22	2/63 (3.2%)
ZS Groups	3/34 (8.8%)	11/116 (9.5%)	9/53 (16.9%)	5/99 (5.0%)

Abbreviations: ANLO2FL, indicator of concomitant medication; CCB, calcium channel blocker

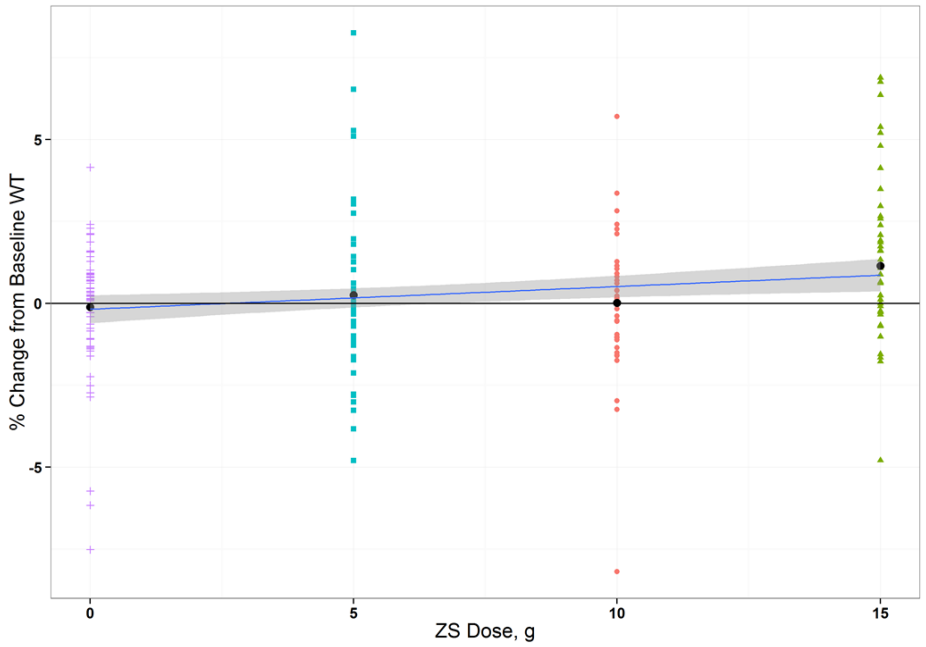
There is a trend for dose-related increases in systolic blood pressure (**Figure 1**) and weight gain (**Figure 2**), which provides supportive evidence that ZS causes fluid retention.

Figure 1. Change from Baseline in Blood Pressure in the Acute (Top Panel) and Extended Dosing (Bottom Panel) Phases of Study ZS-004 (Reviewer's Figure).
(Note: doses in the X-axis refer to the randomized fixed doses in the extended dosing phase—all subjects received 10 g TID in the acute phase)



Shown are observed data by dose group in extended dosing phase and linear regression trend line with 95% confidence interval. Abbreviations: DIABP, diastolic blood pressure; SYSBP, systolic blood pressure; 1, indicator for acute phase; 2, indicator for extended dosing phase.

Figure 2. Trend for Dose-Response in Weight Gain during ZS Dose in Extended Dosing Phase (Reviewer's Figure)



Shown are observed data by dose group and linear regression trend line with 95% confidence interval.
Abbreviations: WT, body weight

In study ZS-004, there were four subjects with treatment-emergent heart failure AEs—all subjects had a history of congestive heart disease at baseline. All events were in the ZS treatment arms (**Table 5**).

Table 5. Adverse Events in the Cardiac Failure SMQ in Study ZS-004 in Subjects with Congestive Heart Disease at Baseline (Reviewer's Table)

MedDRA HLT and PT	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%	n/N*	%
Heart failures NEC	***1/18***	***5.6***	***1/18***	***5.6***	***2/25***	***8.0***	***4/61***	***6.6***	***0/26***	***0***
Cardiac failure	0	0	0	0	1/25	4.0	1/61	1.6	0	0
Cardiac failure acute	0	0	1	5.6	0	0	1/61	1.6	0	0
Cardiac failure congestive	1/18	5.6	0	0	1/25	4.0	2/61	3.3	0	0
Serious adverse event	1/18	5.6					1/61	1.6	0	0
Led to discontinuation							0	0	0	0

Cross-reference: Table 12-8 in ZS-004 Clinical Study Report (03December2014)
Abbreviations: HLT, high level term; PT, preferred term, NEC, not elsewhere classified, N*, number of subjects with a history of congestive heart disease at baseline; n, number of subjects with adverse event

Fluid Retention, Edema and Heart Failure AEs in Long-Term Safety Studies (ZS-004E and ZS-005)

Both ZS-004E and ZS-005 studies were open-label, uncontrolled safety studies (**Table 1**). In the extended dosing phases, subjects received either 10 g QD (ZS-004E) or 5 g QD (ZS-005). ZS doses were adjusted based on the i-STAT potassium values.

- In ZS-004E, K>5.5 mmol/L, dose titrated to 15 g QD and K between 3 and 3.4 mmol/L, dose titrated to 5 g QD.
- In ZS-005, K>5.0 mmol/L (5 g QD/QOD) or 5.5 mmol/L (10 mg QD), dose titrated by 5 g QD to maximum dose of 15 mg QD between 3 and 3.4 mmol/L, dose titrated by 5 g QD minimum dose of 5 mg QOD.

When the combined ZS exposure across Studies ZS-004 and ZS-004E was totaled with the ZS exposure from Study ZS-005, the overall extent of exposure as of 7 December 2015 was > 30 days for 765 subjects, > 90 days for 615 subjects, > 180 days for 432 subjects, > 270 days for 308 subjects, and > 360 days for 145 subjects (**Table 6**). Most subjects were able to maintain normkalemia on doses between 5 to 10g QD, with ≤13% subjects taking 15g QD and <2% taking 5g QOD.

Table 6. Extent of Exposure and Distribution of Doses in Long-Term Safety Studies (ZS-004E and ZS-005, Reviewer's Table)

Days of Treatment	ZS-004E N=123 10 g QD Titration[1]	ZS-005 (7DEC2015) N=746 5 g QD Titration[1]
>30 d >90 d >180 d >270 d >360 d	113 (92%) 89 (72%) 68 (55%) 61 (50%) 0	652 (87%) 526 (71%) 364 (49%) 247 (33%) 145 (19%)
Distribution of doses at EoT: 5 mg QOD 5 mg QD 10 mg QD 15 mg QD	 1.6% 12% 73% (starting dose) 13%	 0.7% 62% (starting dose) 32% 6%[2]

[1]ZS dose was adjusted based on the i-STAT potassium values. In ZS-004E, K>5.5 mmol/L, dose titrated to 15 g QD and K between 3 and 3.4 mmol/L, dose titrated to 5 g QD. In ZS-005, K>5.0 mmol/L (5 g QD/QOD) or 5.5 mmol/L (10 mg QD), dose titrated by 5 g QD to maximum dose of 15 mg QD between 3 and 3.4 mmol/L, dose titrated by 5 g QD minimum dose of 5 mg QOD.
[2]Shown as 10% in Table 5-3 in the Responses to Issues in CR Letter (12 September 2016)
Cross-reference: Table 6-2 in Integrated Summary of Safety-Safety Update (31August 2016)
Abbreviations: QD, once daily; QOD, once every other day; EoT, end of treatment

In these long term safety studies at maintenance doses <15 mg QD in most subjects, edema incidence was 8-11% (**Table 7**). Edema was treated as customary for this patient population by the investigator in 57% of subjects in ZS-004E and 59% of subjects in ZS-005; thus, the incidence of clinically significant edema (i.e., requiring intervention) was 6.5% in ZS-004E and 4.7% in ZS-005. No subjects in ZS-004E or the ongoing ZS-005 discontinued study medication due to edema and none of the AEs were serious.

Table 7. Edema and Fluid Retention AEs in Long-Term Safety Studies (ZS-004E and ZS-005, Reviewer's Table)

MedDRA HLT and PT	ZS-004E N=123		ZS-005 (7Dec2015) N=746	
	n	%	n	%
Oedema NEC	14	11.4	59	7.9
Oedema	4	3.3	16	2.1
Oedema peripheral	10	8.1	45	6.0
Generalized edema	0	0	1	0.1
Total fluid volume increased	1	0.8	0	0

Cross-reference: Table 6-3 in Responses to Issues in CR Letter (12 September 2016) and Table 8-9 in Integrated Summary of Safety-Safety Update (31 August 2016)
Abbreviations: HLT, high level term; PT, preferred term, NEC, not elsewhere classified

In studies ZS-004E and ZS-005, heart failure events (associated with the PTs, cardiac failure, cardiac failure acute or congestive) were reported in 5/123 (4.1%) and 25/746 (3.4%) of subjects, respectively (**Table 8**). There were 2 subjects reporting pulmonary edema; one event was considered serious. In study ZS-004E, all subjects reporting heart failure and pulmonary edema AEs had a history of congestive heart disease at baseline. Medical history of subjects in ZS-005 is not available because the study is ongoing and electronic datasets have not been submitted.

Table 8. Adverse Events Suggestive of Heart Failure in Long-Term Studies (Reviewer's Table)

MedDRA HLT and PT	ZS-004E (N=123)		ZS-005 (7Dec2015) (N=746)	
	n	%	n	%
Heart failures NEC	5	4.1	25	3.4
Cardiac failure	3	2.4	6	<1
Cardiac failure acute	0	0	4	<1
Cardiac failure congestive	2	1.6	15	2.0
Pulmonary edemas	2	1.6	0	0
Serious adverse event	4	3.3	15	2.0
Led to discontinuation	1	<1	10	1.3

Cross-reference: Table 6-7 in Responses to Issues in CR Letter (12 September 2016) and Table 8-9 in Integrated Summary of Safety-Safety Update (31 August 2016)
Abbreviations: HLT, high level term; PT, preferred term, NEC, not elsewhere classified

Conclusion

- Edema/fluid overload was observed at a higher frequency in the ZS groups compared to the placebo group in Study ZS-004, particularly at the highest dose evaluated for extended use (15 g once daily).
- In uncontrolled long term safety studies at maintenance doses <15 mg QD in most patients, edema (includes preferred terms of edema, peripheral edema and generalized edema) incidence is 8-11%. Approximately 60% of subjects required medical treatment for edema. The incidence for adverse events associated with the MedDRA HLT heart failure is 3-4%. The distinction between AEs related to either edema or heart failure may be arbitrary.

Without a placebo control in the long term safety studies, the interpretation of these findings is limited.

- Warning and Precaution statement is warranted to address potential for edema/fluid overload.

Labeling

The applicant submitted the following labeling statements for sections 5 Warnings and Precautions and 6 Adverse Reactions as shown in the following text highlighted using grey shading.

5 WARNINGS AND PRECAUTIONS

None

Reviewer's comment: The submitted label does not include any statements about sodium absorption leading to edema. I recommend adding such a statement to section 5 Warnings and Precautions.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

(b) (4)

Reviewer's comments:

(b) (4)

Laboratory Abnormalities

In clinical trials (b) (4) developed hypokalemia with a serum potassium value less than 3.5 mEq/L, which was resolved with dose (b) (4) discontinuation of LOKELMA.

Reviewer's comments:

- *Hypokalemia reflects completed studies (ZS-002, ZS-003, ZS-004 and ZS-004E). The overall incidence of hypokalemia is* (b) (4) *(* (b) (4) *%).* (b) (4)

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/s/

CHRISTINE E GARNETT
01/18/2017

ALIZA M THOMPSON
01/18/2017

Office of Drug Evaluation-I: Decisional Memo

Date	May 26, 2016
From	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	207078
Applicant Name	ZS Pharma, Inc.
Date of Submission	May 26, 2015
PDUFA Goal Date	May 26, 2016
Proprietary Name	Lokelma
Established (USAN) Name	Sodium zirconium cyclosilicate powder for suspension
Dosage Forms/ Strengths	Powder for suspension, 5 gram and 10 gram packets
Proposed Indication	…is a (b) (4) indicated for the treatment of hyperkalemia (b) (4)
Action:	*Complete response*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Brian Proctor
Medical Officer Clinical Review**	Shen Xiao
Clinical Pharmacology Review	Ju-Ping Lai; Lars Johannesen; Jeffry Florian; Rajnikanth Madabushi
Statistical Review	Thomas Birkner; James Hung
Pharmacology Toxicology	Phillip Gatti; Tom Papoian
Chemistry Manufacturing and Controls	Mohan Sapru; Maryam Changi; Thomas Wong, Raymond Frankewich; Wendy Wilson; Vidya Pai; Kasturi Srinivasachar; Steven Fong; Lane Christensen
ONDQA Biopharmaceutics Review	Gerlie Gieser; Elsbeth Chikhale
Method Validation	Laura Pogue; Michael Trehy
Office of Scientific Investigation	Sharon Gershon; Janice Pohlman; Kassa Ayalew
Division of Medication Error Prevention and Analysis	Tingting Gao; Chi-Ming (Alice) Tu
Office of Prescription Drug Promotion	Puja Shah
Division of Risk Management	Kimberly Lehrfeld; Leah Hart; Doris Auth
OSE PMs	Tri Bui Nguyen; Darrell Lyons
Epidemiology Reviewer	Veronica Sansing; Margie Goulding; Tamra Meyer
Pharmacovigilance	Amy Chen; Susan Lu; Monica Munoz
Cross-Discipline Team Leader	Aliza Thompson
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge

**Christine Garnett provided a number of supplemental analyses for the assessment of safety.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Sodium zirconium cyclosilicate (ZS) is a new molecular entity for the treatment of hyperkalemia. Hyperkalemia, generally defined as a serum potassium > 5 mEq/L, typically occurs in patients with acute or chronic kidney disease (CKD) or heart failure, particularly in those taking renin-angiotensin-aldosterone system (RAAS) inhibitors and/or mineralocorticoid receptor antagonists. Because marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis, therapies are needed to both treat and control hyperkalemia in order to avoid life-threatening elevations.

The review team is unanimous in its agreement that the NDA provides substantial evidence of ZS's effectiveness in lowering serum potassium in patients with hyperkalemia. Although a serum potassium concentration is not a measure of how patients feel, function, or survive, it is an accepted surrogate endpoint in this population.

Zirconium cyclosilicate is not absorbed, but binds ~3 mEq potassium per gram, exchanging it for sodium and hydrogen ions, carrying potassium out in the stool. The proposed initial dose of 10 g TID for 2 days is capable of binding ~100 mEq potassium. Because this quantity is in excess of any plausible intake, it lowers the serum potassium by about 1 mEq/L. To put a 100 mEq decrease into perspective, a typical 70 kg male, 50 to 59 years of age, has a total body potassium of approximately 3,000 mEq (Kehayias JJ et al. *Am J Clin Nutr* 1997;66:904-10). Thus, 100 mEq represents roughly 3% of total body potassium.

The known risks are related to zirconium cyclosilicate's pharmacodynamic effects: hypokalemia and sodium/fluid retention. The Division believes that both of these risks can be addressed adequately through labeling and monitoring, and I agree. There is concern about use in patients with impaired colonic motility, although no adverse effects were actually observed in the studies.

Typical of drugs in this class (patiromer; sodium polystyrene sulfonate), a major concern is its ability to bind other drugs administered by the oral route. As noted by Dr. Stockbridge, *in vitro* studies suggest more of a problem than the *in vivo* studies. Much of the *in vitro* effect appears to be related to pH changes that are buffered *in vivo*. Changes in pH, however, do not explain all of the disparities between the *in vitro* and *in vivo* results. There is agreement that drug-drug interactions (DDI) need to be better characterized prior to approval. As noted by Dr. Stockbridge, the most extreme method of risk mitigation would be to separate administration of zirconium cyclosilicate from administration of all oral drugs. Presumably, the applicant will be able to reduce the list of DDIs down to a manageable few. The applicant recently submitted new data on DDIs. Although these studies constitute a major amendment that could have been reviewed within a 90-day extension of the PDUFA goal date, there are also unresolved facility issues, and, to our knowledge, the applicant has not provided the information necessary to resolve these. Without the possibility of an approval on this first cycle, an extension would not have been appropriate.

The drug's actual benefit to patients is difficult to characterize. RAAS inhibitors, mineralocorticoid receptor antagonists, and, most recently, sacubitril/valsartan, have been shown to decrease morbidity and/or mortality in patients with CKD and/or heart failure, but their use can be limited by hyperkalemia in some patients. In essence, by helping to manage the hyperkalemia, ZS could help to enable the use of these drugs in such patients. The drug's risks are manageable, as noted above. Aside from the potential for hypokalemia and sodium/fluid retention, we are not aware of any potential for irreversible harm. The label will urge appropriate patient monitoring.

Importantly, significant inspectional observations at the manufacturing facility were cited on Form FDA 483 to the firm; therefore, the NDA cannot be approved unless and until these issues are corrected. In addition, the DDI will need to be better characterized to permit the writing of adequate instructions for use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis. The goal of therapy is to initiate treatments for hyperkalemia before life-threatening elevations occur.	Hyperkalemia can be a serious condition. In rare cases, it is life-threatening.
Current Treatment Options	Approved cation exchange agents for removing excess potassium from the body include sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, and patiromer (Veltassa), approved in October 2015. Limitations of these agents include a relatively slow onset of action (both agents), poorly characterized efficacy (SPS), and safety concerns such as intestinal necrosis (SPS), the potential for drug-drug interactions with other orally administered medications (both agents), hypomagnesemia (both agents), other non-specific binding to cations (SPS), volume overload secondary to an increase in sodium load (SPS), hypokalemia (both agents), and GI intolerance (both agents).	Given the limitations of available therapies, there is need for additional agents that are effective in lowering serum potassium and maintaining target potassium levels in patients with hyperkalemia.
Benefit	Support for efficacy is provided by the applicant's two phase 3 trials, as well as a phase 2 trial. These trials demonstrated statistically significant and clinically meaningful effects on serum potassium at the doses proposed for use in patients with hyperkalemia. The proposed initial dose of 10 g TID for 2 days is capable of binding ~100 mEq potassium (~3% of total body potassium), and lowers the serum potassium by about 1 mEq/L. The drug's actual benefit to patients is difficult to characterize. A number of drugs have been shown to decrease morbidity and/or mortality in patients with CKD and/or heart failure, but their use can be limited by hyperkalemia in some patients. In essence, by helping to manage the hyperkalemia, ZS could help to enable the use of these drugs in such patients.	The application provides substantial evidence of ZS's effectiveness in lowering serum potassium levels in patients with hyperkalemia, an accepted surrogate endpoint in this population, as well as substantial evidence of effectiveness in maintaining treated patients in the target potassium range.

Risk	Hypokalemia was observed in clinical trials, but was generally mild (i.e., serum potassium levels of 3-3.4 mEq/L). The frequency of hypokalemia was dose-related. Fewer than 1% of patients who received ZS 10 g TID for the acute treatment of hyperkalemia developed a serum potassium < 3.5 mEq/L. In patients randomized to treatment with higher doses of ZS (10 g and 15 g QD), ~ 10% of subjects developed a serum potassium < 3.5 mEq/L. Fluid retention, edema, and weight gain, presumably resulting from sodium exchange, occurred fairly frequently. Fluid retention and edema were dose-related. Patients with renal impairment, heart failure, and those taking calcium channel blockers are more susceptible. ZS's potential to interact with other orally administered medications remains an outstanding issue.	These risks are mostly related to the drug's pharmacodynamic effects. They are to some degree predictable, and can be mitigated or prevented with appropriate monitoring. ZS's potential to interact with other orally administered medications needs to be resolved prior to approval.
Risk Management	Labeling should contain adequate information on the risks of hypokalemia, sodium absorption (leading to edema, volume overload, and occasionally heart failure), and DDIs. Patients with colonic motility disorders could incur risks from local effects.	Appropriate monitoring paradigms will be provided to mitigate risk. Because the potential for ZS to interact with other orally administered medications remains an outstanding issue, recommendations for mitigating DDIs cannot be made at this time.

2. Background

Sodium zirconium cyclosilicate (ZS) powder for oral suspension is a cation exchanger with a proposed indication: LOKELMA™ (sodium zirconium cyclosilicate) powder for oral suspension is a (b) (4) indicated for the treatment of hyperkalemia (b) (4)

The product entraps potassium in exchange for hydrogen and sodium, increasing fecal potassium excretion through binding of potassium in the gastrointestinal tract. Potassium

binding reduces the concentration of potassium in the gastrointestinal lumen, thereby lowering serum potassium levels. Zirconium cyclosilicate also has the capacity to selectively entrap monovalent cations, specifically ammonium ions.

Disease background: Hyperkalemia is generally defined as a serum potassium in excess of 5 mEq/L. Because the extracellular potassium concentration is tightly regulated by the movement of transcellular potassium and urinary excretion, hyperkalemia is rarely a problem in the general population. Hyperkalemia is not unusual, however, in patients with acute or chronic kidney disease or heart failure, particularly in those who are taking renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors, i.e., angiotensin converting enzyme inhibitors or angiotensin receptor blockers) or mineralocorticoid antagonists (spironolactone and others). Of note, such patients often take multiple medications, some of which convey important morbidity and mortality benefits. Marked elevations in serum potassium concentration can cause cardiac arrhythmias (sometimes fatal), conduction abnormalities, muscle weakness, and paralysis. Thus, a distinction is made between acute treatment and chronic treatment. The latter can be construed as an "enabling" therapy for some patients. Control of serum potassium can enable the use of a number of drugs that tend to increase serum potassium, some of which have important benefits.

Approved oral treatments for hyperkalemia include sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, and patiromer (Veltassa), approved in October, 2015. Use of SPS has been limited by tolerability and safety concerns (i.e., colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy. Of note, SPS and patiromer share the liability of potential binding to co-administered oral medications. For SPS, binding of concomitant medications has not been well studied. Based on *in vitro* studies, the current label for patiromer includes a Boxed Warning about patiromer's potential to bind co-administered oral medications. Presumably, once the DDI data for ZS are reviewed, important DDIs might need to be noted in a similar Boxed Warning.

An important issue for the use of these agents is their time to onset of action. According to the patiromer label, statistically significant reductions in serum potassium initially occur 7 hours after initiating therapy with patiromer; however, the mean effect was small at this time point (-0.2 mEq/L). Thus, its labeling includes a Limitation of Use: "Veltassa should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action."

Regulatory background: The important interactions with the applicant are well summarized by the Dr. Thompson. With respect to discussions about potential drug-drug interactions, the applicant was advised to conduct *in vitro* drug-drug interaction studies at a pre-IND meeting in 2010. The applicant submitted the *in vitro* studies in their NDA application; however, the review team noted that the test conditions used in these studies were inadequate. The applicant was advised to repeat the *in vitro* studies using physiologically relevant conditions. As discussed later, the results of these studies raised significant concerns regarding the potential of ZS to interact with other orally administered drugs, and prompted the need for additional clinical studies.

Sodium zirconium cyclosilicate is not currently marketed in any country.

3. Product Quality

Because of objectionable conditions identified during inspection of the drug substance manufacturing, release, and stability testing facility (ZS Pharma Inc., Coppell, TX), the Office of Process and Facilities has issued a 'Withhold" recommendation for the facility. Thus, from a product quality perspective, the application cannot be approved until satisfactory resolution of all of the inspectional observations cited in FDA Form 483.

Drug Substance: The active moiety is a negatively charged covalent framework of interconnecting channels and cavities that house positive ions. As noted in the review, "Electrostatic interactions between the framework and the cations allow for mobility and possibility of exchange for other cations that would fit and pass the free pore openings of ~ 3.0 Å, providing the compound with its distinctive ion-exchange selectivity features." The Quality Review explains that the active moiety must be accompanied by sodium ions to balance the charge as well as interstitial water to support the structure.

The drug substance is a free flowing white crystalline powder with molecular formula $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet n\,H_2O$ ($n' = 2–3$). The basic unit has a relative molecular mass of (b) (4) daltons. The structure is insoluble and collapses above 300°C. Potassium ion exchange capacity is (b) (4) mEq/g

Drug Product: The drug product consists of the drug substance (b) (4) The drug product is packaged in (b) (4) foil pouch at 2 strengths: 5 g and 10 g of sodium zirconium cyclosilicate. Proposed labeling instructs patients to suspend the contents in ≥ 45 mL water and drink immediately.

Facilities review/inspection: When the NDA was submitted, the applicant provided attestation that the drug substance manufacturing, release and stability testing facility in Coppell, TX was inspection-ready. As discussed in the product quality review, however, this was not the case. The Applicant was warned at the mid-cycle meeting that that if the manufacturing facility had not passed inspection by the PDUFA date, the NDA would not be approved.

Having received a go-ahead from the applicant that the facility was ready for inspection, the pre-approval inspection at ZS Pharma Inc., Coppell, TX was conducted from March 17-29, 2016. At the conclusion of the inspection, the inspector issued an FDA Form 483 citing several deficiencies. As noted on pages 41-42 of the Product Quality Review:

"…Significant inspectional observations were cited on Form FDA 483 to the firm. The observations included deficiencies related to buildings and facilities, inadequate environmental controls, inadequate production and process controls, inadequate lab controls, inadequate process validation, deficiencies in records and reports and issues with the quality assurance systems."

The firm responded to the deficiencies, and their response was reviewed by the district in detail. Although many problems were addressed satisfactorily, there were continued concerns with

respect to: a) procedures in place for cleaning and maintaining process equipment; b) assessment of impact of adequate validation, control and monitoring of software used for manufacturing and quality control operations; and c) inadequate response to support validation of test methods used in manufacture.

Thus, the ZS Pharma, Inc. Coppell TX, site is considered unacceptable to support this NDA at this time.

There are no other outstanding issues related to labeling and elemental impurity specifications that need to be listed as deficiencies in the complete response letter.

4. Nonclinical Pharmacology/Toxicology

The application can be approved from a pharmacology-toxicology perspective. A mass balance study in rats showed that ZS-9 is not absorbed. Following single dose administration, ~97-101% of the administered dose was recovered from feces and 0.1-0.3% was recovered from urine.

Long-term toxicology studies included a 39-week repeat-dose study in dogs and a 26-week repeat-dose study in rats. Tubulointerstitial inflammation and lipid vacuolation were observed in the adrenal cortex following chronic administration to dogs. These effects were greatly reduced with potassium supplementation, suggesting that the observed findings reflected adaptive responses to the drug's potassium-lowering effect.

Developmental and reproductive toxicity data were provided from studies in rats and rabbits. These data have little relevance, however, given the absence of systemic absorption.

Sodium zirconium cyclosilicate was not genotoxic in the reverse mutation test (Ames assay), chromosome aberration, or rat micronucleus assays. Importantly, the drug did not cause gastrointestinal irritation or alterations in a 39-week toxicity study in dogs. Carcinogenicity was not assessed because it was not genotoxic, was not absorbed from the gastrointestinal tract, and not found to cause local adverse effects in the gastrointestinal tract in the 39-week dog study.

An acceptable established pharmacologic class for the drug would be "potassium binder."

5. Clinical Pharmacology

Two major issues are pending from a clinical pharmacology perspective: the potential for drug-drug interactions and the maximum recommended daily dose.

Pharmacodynamics: In healthy adults, zirconium cyclosilicate 5 g or 10 g daily X 4 days caused a dose-dependent increase in fecal potassium excretion. Corresponding dose-dependent decreases in urinary and serum potassium were also observed. In patients with hyperkalemia treated with zirconium cyclosilicate 10 g TID for 2 days, decreases in serum potassium were

observed after 1 hour and potassium continued to decline over the treatment period. As discussed in the clinical pharmacology review, the starting potassium level and effect size are closely correlated.

Pharmacokinetics: As discussed in Section 4, the drug is not significantly absorbed; therefore, conventional PK studies were not conducted.

The applicant is recommending (b) (4)

The Clinical Pharmacology review team is recommending that the label specify a recommended starting dose of 10 g TID for 48 hours. For extended treatment, the Clinical Pharmacology Team is recommending a dose of 10 g QD, with monitoring of serum potassium levels and dose adjustment as needed at (b) (4) or longer intervals to a maximum dose of 15 g QD or a minimum dose of 5 g every other day.

The review team explains their rationale for the proposed regimen:

Starting dose: Essentially, the review team finds (b) (4)

The review team's analyses focused on 2 populations: patients with baseline potassium > 5.5 mEq/L and patients with baseline potassium ≤ 5 mEq/L. For patients with baseline potassium concentrations > 5.5 mEq/L, a greater proportion achieved the target potassium (3.5 – 5 mEq/L) when initiated on a dose of 10 g TID as compared to 5 g TID, 77% vs. 47%, respectively. Moreover, for patients with baseline potassium concentrations ≤ 5.5 mEq/L, a greater proportion achieved the target potassium concentration with 10 g TID as compared to 5 g TID, 85% vs. 71%, respectively. The risk of hypokalemia at the 10-g dose appears to be low. (b) (4)

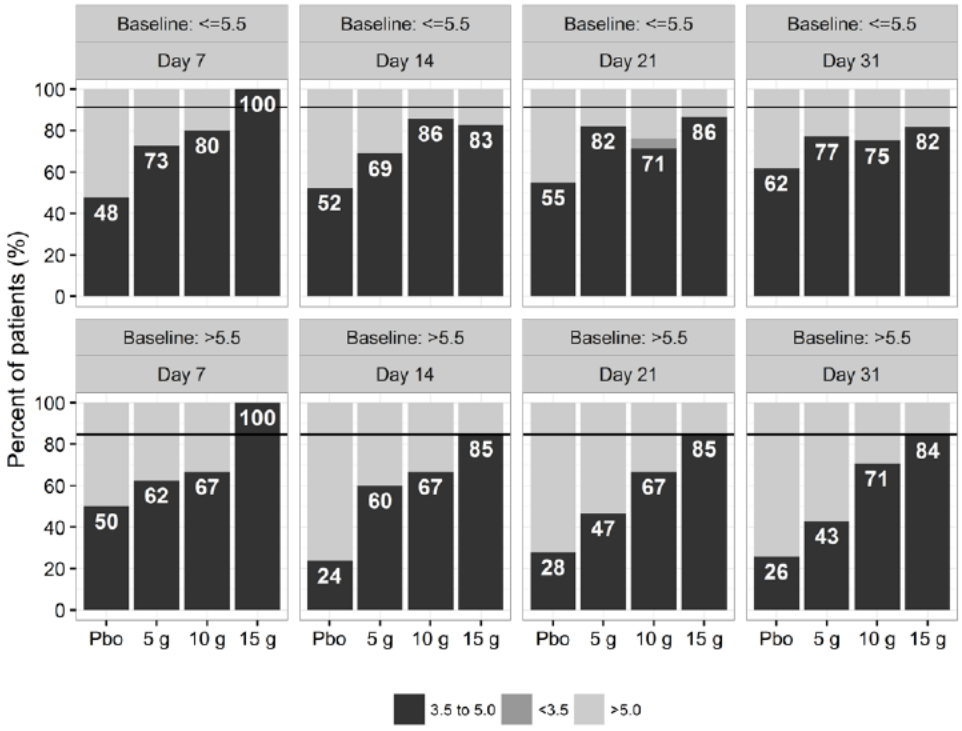
With respect to the 15-g dose, there was an increased incidence of edema compared to the lower doses. Thus, a starting dose of 10 g once daily seems preferable.

Maintenance dose: Again, the review team's analyses focused on populations with baseline potassium > 5.5 mEq/L and ≤ 5 mEq/L.

As shown in Figure 1, among patients with higher baseline potassium concentrations (bottom panel), there was a dose-dependent increase in the proportion of patients achieving the target range of 3.5 – 5.0 mEq/L. Based on this analysis, it appears that some patients who do not achieve adequate control at 10 g will achieve control at 15 g.

In contrast, among subjects with lower baseline potassium concentrations (≤ 5.5 mEq/L, top panel), daily doses of 5, 10 and 15 g appear to provide similar efficacy, especially at Days 21 and 31. Although the incidence of hypokalemia is greater at 10 g than 5 g, cases reported in the development program were mild.

Figure 1: Study ZS-004: Percentage of patients achieving different potassium concentrations during maintenance by time and baseline potassium (Clinical Pharmacology Review, Figure 4)



(b) (4)

As pointed out by Dr. Thompson, the critical issues for prescribers are to gauge when to check potassium levels after a dosing change, and how often to monitor during steady state. I agree with their analysis; however, there can be reasons to check before (b) (4) days. These are areas of ongoing discussion with the review team prior to finalizing labeling. Given that these decisions are related to the clinical scenario, Dr. Thompson believes that the label should provide a fair amount of latitude in making these decisions, and I agree.

Drug-drug interactions: Zirconium cyclosilicate was screened *in vitro* for potential interactions with drugs commonly co-administered in the to-be-marketed population. Of 39 drugs screened for interactions:

- 9 (aluminum, amlodipine, calcium carbonate, dabigatran, E- and Z-norgestimate, levothyroxine, lithium, prasugrel, and warfarin) showed a significant decrease in concentration (30% to 99%) in one or more media in the presence of zirconium cyclosilicate;
- 7 (atorvastatin, edoxaban, erythromycin, furosemide, lanthanum, sevelamer, and valsartan) showed a significant increase in concentration or binding capacity (40 to 564%) in the presence of zirconium cyclosilicate; and
- 5 (clopidogrel, docusate, glipizide, ketoconazole, and losartan) showed inconsistent findings over different pH ranges in different media in the presence of zirconium cyclosilicate.

According to the clinical pharmacology review, zirconium cyclosilicate can change the pH of the test media. Thus, the applicant conducted additional studies in which drugs that showed >10% change in concentration in the presence of zirconium cyclosilicate were tested at varying pH's. The applicant interpreted the results as showing that the observed interactions can be explained solely on the basis of drug-induced changes in pH, i.e., pH-mediated changes in solubility. The clinical pharmacology review team disagrees with their interpretation of the study. They agree that many of these interactions result from pH changes, but some drugs exhibited concentration changes in the presence of zirconium cyclosilicate that could not be explained solely by changes in pH. This concern was communicated to the applicant, most recently at the Late Cycle Meeting on March 23, 2016.

After the Late Cycle Meeting, the applicant submitted the results of additional studies, including human *in vivo* studies, as a major amendment. Because these study reports were submitted late in the review cycle, they are not addressed in the clinical pharmacology review, and recommendations for mitigating drug-drug interactions cannot be made at this time. The late submission would have triggered a 3-month goal date extension; however, given the inspection findings at drug substance manufacturing, release and stability testing facility, a complete response will be issued instead.

Demographic interactions/specific populations. The drug is neither absorbed nor metabolized. It is eliminated through the fecal route. Elimination and pharmacodynamic effects (i.e., potassium lowering) are not expected to be affected by intrinsic factors that are usually of concern, such as age, gender, race, hepatic, and renal impairment.

Bridging between the formulation(s) tested in clinical studies and the to-be-marketed formulation: As noted in the clinical pharmacology review, the potassium exchange capacity (KEC) of the to-be-marketed product (target = (b) (4) mEq/g; range of (b) (4) mEq/g) is similar to the KEC of the products used in the phase 3 trials (average KEC of (b) (4) mEq/g in studies ZS003 and ZS004, respectively).

QT assessment: Because the drug product is not significantly absorbed, a Thorough QT study was not conducted. Nevertheless, the applicant performed extensive analyses of zirconium cyclosilicate's effect on the QT interval. These analyses, described in the clinical review, show that zirconium cyclosilicate can affect the QT interval principally indirectly through its potassium lowering effect.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Much of this information comes directly from the excellent CDTL review of Dr. Thompson. Two phase 3 studies, Studies ZS-003 and ZS-004, provide evidence of effectiveness. Study ZS-002, a US-only, phase 2 study, provides additional support for efficacy, and is described in the clinical and statistical reviews and discussed briefly later in this section.

Each of the studies included an acute phase (48 hours in Studies ZS-003 and ZS-004; 48 to 96 hours in Study ZS-002) in order to normalize potassium values. In the phase 3 studies, subjects who completed the acute phase with normalized potassium values were eligible for extended dosing and were randomized to treatment for an additional 12 days in Study ZS-003 (subacute phase) and an additional 28 days in Study ZS-004 (maintenance phase). Both studies employed a randomized, withdrawal design (although the dosing interval was changed). In Studies ZS-002 and ZS-003, the acute phase was conducted in a randomized, placebo-controlled, double-blind fashion. The acute phase of Study ZS-004 was open-label, with all patients receiving ZS 10 g.

Study ZS-003

Study ZS-003 was a two-part, randomized, double-blind, placebo-controlled, dose-ranging trial, conducted between November 2012 and October 2013 at 65 sites in the US, South Africa and Australia. The study randomized 754 patients.

In the "acute" phase, subjects with hyperkalemia (potassium 5.1-6.5 mEq/L) were randomized 1:1:1:1:1 to 1 of 4 doses of ZS (1.25, 2.5, 5, or 10 g) or placebo. The test drugs were administered TID with meals for 48 hours (Figure 2).

The second "subacute" phase was a randomized withdrawal: patients treated with ZS who achieved a potassium level between 3.5 and 5.0 mEq/L were re-randomized to remain on the ZS dose they were taking or switch to placebo. *Of note, however, the dosing frequency was changed from TID to QD in all patients.* Patients originally randomized to placebo TID were randomized to ZS 1.25 or 2.5 g QD, but these patients were not included in the analysis for the sub-acute phase. See Figure 2.

Figure 2: Dosing Groups in Study ZS-003 (from Dr. Thompson)

Acute Phase: Thrice Daily Treatment X 48 Hours									
Placebo		ZS 1.25 g TID		ZS 2.5 g TID		ZS 5 g TID		ZS 10 g TID	
									
Subacute Phase: Daily Treatment X 12 Days									
ZS 1.25g	ZS 2.5g	Placebo	ZS 1.25g	Placebo	ZS 2.5g	Placebo	ZS 5g	Placebo	ZS 10g

The 1° endpoint for the acute phase was the difference in the exponential rate of change in serum potassium concentration (based on central laboratory values) during the initial 48 hours of study drug treatment between the placebo arm and ZS treatment arms. For the subacute phase, the 1° endpoint was the difference in the exponential rate of change in serum potassium levels (based on central laboratory values) over the 12-day treatment interval between the placebo and ZS treatment arms.

The statistical methodology is complex, but well-described in the statistical review. In both the acute and subacute phases of the study, the 1° endpoint was tested against placebo starting with the highest acute phase dose and proceeding through lower doses until statistical significance was no longer achieved. No multiple comparison control procedure was pre-specified for testing secondary endpoints.

Study ZS-004

Study ZS-004 was also a two-part trial with an open-label acute phase and a month-long randomized, double-blind, placebo-controlled withdrawal phase. The study was conducted at 44 sites in the United States, South Africa, and Australia between March and August 2014. The study enrolled 258 patients.

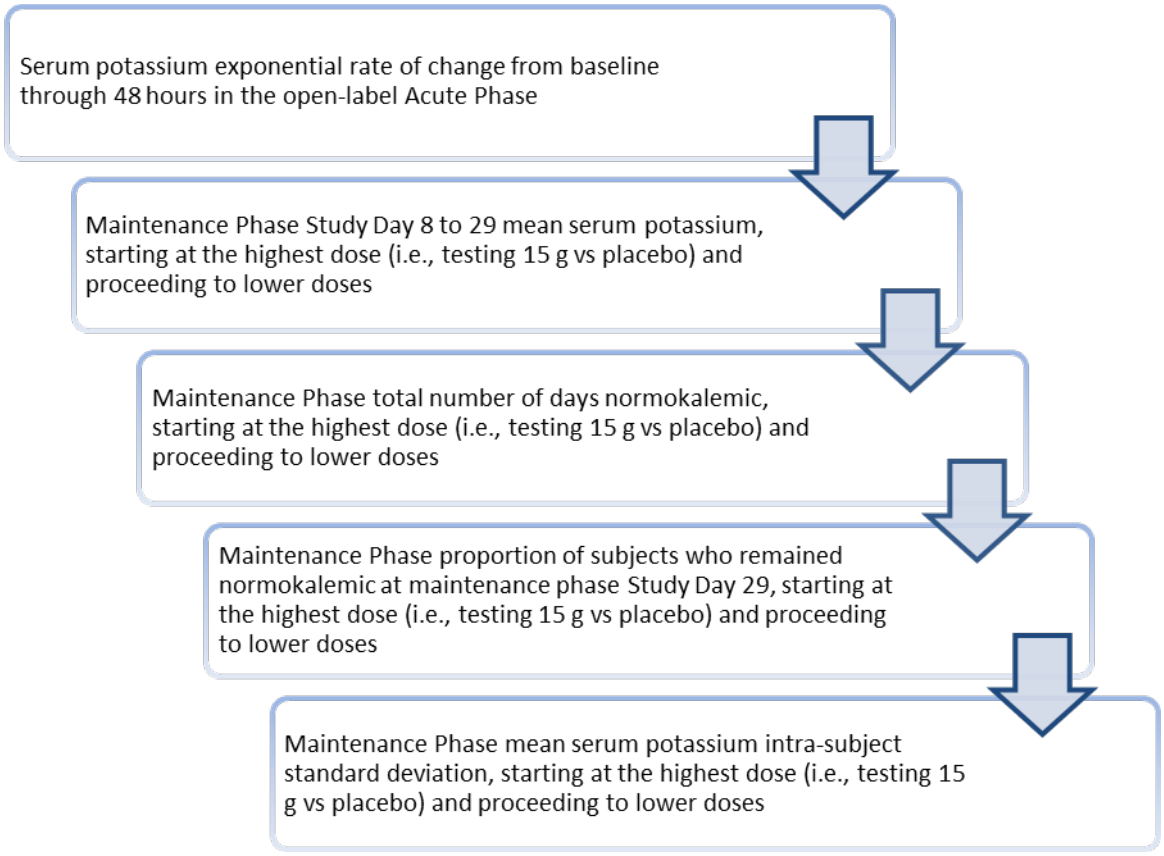
In the initial "acute phase" of the trial, patients with hyperkalemia (mean potassium values $\geq$ 5.1 mEq/L at screening) received open-label ZS, 10 g TID, for 24-72 hours. In the second "maintenance" phase, patients who achieved normokalemia (potassium of 3.5 to 4.9 mEq/L on the morning of Study Day 2, 3 or 4) were randomized 4:4:4:7 to receive one of three doses of ZS (5 g, 10 g, and 15 g) or placebo QD X 28 days.

The 1° endpoint was the model-based least squares mean of all available central potassium values obtained during the maintenance phase from Days 8 to 29. The primary population for the efficacy analysis was the maintenance phase intent-to-treat population. Secondary efficacy endpoints for the maintenance phase included the number of normokalemic days during maintenance phase (Days 8 to 29), the proportion of subjects who remained normokalemic at

maintenance phase (Day 29), and the maintenance phase mean potassium intra-subject standard deviation.

The pre-specified hierarchical testing procedure used to control type-1 error is shown in Figure 3, from the CDTL review. Additional detail on statistical methodology is provided in the statistical review.

Figure 3: Hierarchical testing procedure to control the type 1 error in Study ZS-004
Source: CDTL



Phase 3 Trial Results:

Demographics: In the acute phase of Study ZS-004, mean age of patients was 64 years, 58% of subjects were male, 83% were Caucasian, and 14% were Black or African American. The most common causes of hyperkalemia were (categories are not mutually exclusive): use of RAAS inhibitors (70%), chronic kidney disease (69%), diabetes mellitus (66%), and heart failure (36%). Baseline demographic characteristics were quite similar in the acute phase of Study ZS-003.

Degree of hyperkalemia: Mean baseline potassium in the acute phase of Study ZS-004 was 5.6 (range 5.1-7.4 mEq/L). Baseline potassium was < 5.5 mEq/L in 46% of patients; 39% had a

baseline potassium ≥ 5.5 to < 6.0 mEq/L, and 15% had a baseline potassium ≥ 6.0 mEq/L. Baseline potassium concentrations were less elevated in Study ZS-003; depending on treatment group, 15% to 28% of subjects had a potassium > 5.5 mEq/L in the acute phase of the study.

Disposition:

Approximately 97% of patients completed the open-label acute phases of both studies.

Of the 258 subjects enrolled in the open-label acute phase of the Study ZS-004, most (237, 92%) entered the maintenance phase of the study. As discussed in the clinical review, reasons for not entering the maintenance phase reported for two or more subjects included hypokalemia, hyperkalemia, and withdrawal of consent (in the acute phase).

For Study ZS-003, approximately 25% of the 595 subjects treated with ZS in the acute phase were not continued in the subacute phase. In almost all cases, the underlying reason was hypokalemia or hyperkalemia. As previously noted, patients needed to achieve a potassium concentration in the target range (3.5 to 5.0 mEq/L) in order to be randomized into the subacute phase. As shown in Table 1, hypo/hyperkalemia was strongly dose-related (the lower the ZS dose, the less likely patients were to achieve the target K+ concentration).

Table 1: Study ZS-003: Reasons Subjects from the Acute Phase Did Not Enter the Subacute Phase

Reason, n (%)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 158)	ZS 10 g TID (N = 143)
Did not enter subacute Phase	60 (39.0)	37 (26.2)	19 (12.0)	16 (11.2)
Consent withdrawn	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.7)
Sponsor's decision	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypo- or hyperkalemia	60 (39.0)	36 (25.5)	18 (11.4)	15 (10.5)

Source: Clinical Study Report for Study ZS-003, Table 10-2, page 69

Subject disposition in the maintenance phase of Study ZS-004 is shown in Table 2. Across the treatment groups, a similar proportion of study subjects completed the maintenance phase of the study (high 80% range). Relative to Study ZS-004, a higher proportion of subjects completed the subacute phase of Study ZS-003 (range 91 to 98% depending on the treatment arm). As previously noted, the subacute phase of Study ZS-003 was 12 days, whereas the maintenance phase of Study ZS-004 was 28 days. Other differences between the designs of the studies likely contributed to the lower discontinuation rate in Study ZS-003.

Table 2: Study ZS-004: Disposition in the Maintenance Phase

Disposition, n (%)	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo	ZS 5 g QD	ZS 10 g QD	ZS 15 g QD
Randomized	85	45	51	56
Completed Maintenance Phase	75 (88.2)	40 (88.9)	44 (86.3)	49 (87.5)
Discontinued Maintenance Phase	10 (11.8)	5 (11.1)	7 (13.7)	7 (12.5)
Adverse event	0 (0.0)	3 (6.7)	0 (0.0)	1 (1.8)
Consent withdrawn	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Subject compliance	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator's decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Sponsor's decision	2 (2.4)	0 (0.0)	2 (3.9)	1 (1.8)
Hypo- or hyperkalemia	3 (3.5)	0 (0.0)	3 (5.9)	1 (1.8)
Met ECG withdrawal criteria	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.6)
Other	2 (2.4)	1 (2.2)	2 (3.9)	1 (1.8)

Source: Clinical Study Report for ZS-004, Table 10-3, page 84

Efficacy Findings:

As shown in the Table 3, below, Study ZS-003 met its 1° endpoint in both phases of the trial. The 10, 5, and 2.5 g TID doses were statistically significantly superior to placebo for the exponential decrease in serum potassium during the acute phase; the 10 and 5 g QD doses were statistically significantly superior to placebo during the subacute phase.

Table 3: Study ZS-003: *P*-values for the 1° Efficacy Endpoints in the Acute and Subacute phases

Exponential rate of change in serum potassium	
Acute phase (48 hours)	Subacute phase (12 days)
ZS 10 g: $p < 0.05$ ZS 5 g: $p < 0.05$ ZS 2.5 g: $p < 0.05$ ZS 1.25 g: $p = 0.50$	ZS 10 g: $p < 0.05$ ZS 5 g: $p < 0.05$ ZS 2.5 g: $p = 0.84$

Source: Adapted from the statistical review, Table 15, page 23

As shown below, Study ZS-004 also met its 1° endpoint, as well as the first endpoint in the hierarchical testing procedure. During Days 8 to 29 of the maintenance phase, all three ZS doses (5, 10, and 15 g QD) maintained mean potassium at lower levels than placebo (placebo

least squares mean = 5.1 mEq/L vs. 4.8, 4.5, and 4.4 mEq/L for 5, 10, and 15 g ZS, respectively, $p \leq 0.001$ for all doses).

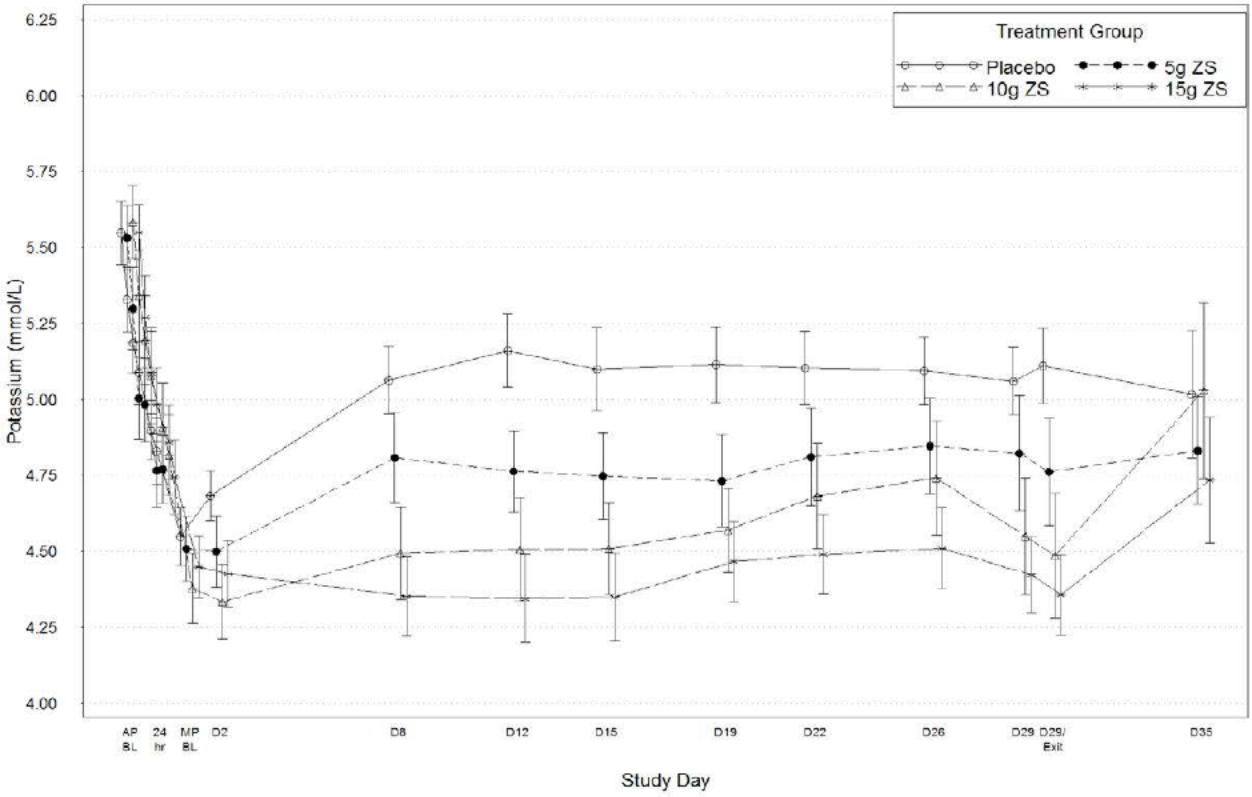
Table 4: Study ZS-004: *P*-values for the First 4 Endpoints Specified in the Hierarchical Testing Procedure

Endpoint	Observed *p*-value
Acute phase: potassium exponential rate of change from baseline through 48 hours (Null hypothesis: exponential rate of change from baseline equals 0)	< 0.0001
1° Efficacy Endpoint	
Maintenance phase Days 8-29 mean serum potassium (Null hypothesis: ZS 15 g QD = placebo)	< 0.0001
Maintenance phase Days 8-29 mean serum potassium (Null hypothesis: ZS 10 g QD = placebo)	< 0.0001
Maintenance phase Days 8-29 mean serum potassium (Null hypothesis: ZS 5 g QD = placebo)	0.0001

Source: Clinical Study Report for ZS-004, Table 11-7, page 94; Results confirmed by Dr. Birkner

Figure 4 shows the mean potassium concentrations over time in Study ZS-004. During the open-label acute phase in which all subjects were treated with ZS 10 g TID, mean potassium levels fell by approximately 1 mEq/L. Following the switch to a once daily regimen of ZS or placebo, mean potassium levels rose in the placebo and ZS 5 g treatment arms but not to pre-treatment levels. In contrast, mean potassium levels in the 10 and 15 g ZS treatment groups remained close to levels achieved at the end of the acute treatment period. The dose-response is quite clear in the figure.

Figure 4: Maintenance Phase: Mean (±2 SEM) Serum Potassium by Time – ITT Population
Source: Clinical Study Report for ZS-004, Figure 11-3, page 104



The results for the 2° endpoints in Study ZS-004 were also positive. The mean number of normokalemic days was statistically significantly greater in each of the ZS treatment groups than in the placebo group, and effect size tended to be related to dose (7.4 days for placebo, 13.4 days for ZS 5 g, 13.9 days for ZS 10 g, and 16.8 days for ZS 15 g, all out of 22 days).

Study ZS-002

Data from the phase 2 ZS-002 study also provide support for efficacy. Briefly, the study was a placebo-controlled, dose-ranging trial to assess the safety, tolerability, and efficacy of 3 different doses of ZS administered TID for 48 hours in subjects with moderate chronic kidney disease and hyperkalemia (baseline potassium 5 to 6.0 mEq/L). The 1° efficacy endpoint was the difference in the exponential rate of change in potassium levels during the initial 48 hours between placebo-treated subjects and ZS-treated subjects. An intent-to-treat analysis with a closed testing procedure was used to test doses from highest the lowest. The study met its 1° efficacy endpoint for the 10 g ($p < 0.0001$) and 3 g ($p = 0.048$) TID doses, but not the 0.3 g TID dose.

According to the applicant, (b) (4)

(b) (4) dosages lower than 3 g were evaluated in phase 3.

Subpopulations:
Efficacy was observed across subgroups examined by age, sex, race, geographic region (US vs non-US), comorbidities (i.e., diabetes, chronic kidney disease, and heart failure) and concomitant medications (i.e., RAAS inhibitor use). Patients with higher baseline serum potassium levels appeared to have greater reductions in potassium than patients with lower levels. In addition, some analyses suggested a larger treatment effect in Blacks/African Americans than in the population as a whole; however, these analyses were based on small numbers of subjects.

Data supporting durability of effect:
As noted above, Studies ZS-003 and ZS-004 indicate that the potassium lowering effect is durable through up to 12 and 28 days of treatment, respectively.

An open-label, uncontrolled extension study to Study ZS-004, submitted as part of the applicant's 120-day safety update, provides efficacy data beyond 28 days. The 1° objective of Study ZS-004E was to evaluate safety and tolerability during dosing of ZS for up to 11 months. The 2° objective was to evaluate the efficacy of ZS in maintaining normokalemia during this interval.

The applicant's analyses of these data suggest that ZS is effective in maintaining potassium levels near the target range during up to 11 months of extended treatment. According to Dr. Xiao's clinical review, the applicant focused on cut-points of ≤ 5.1 and ≤ 5.5 mEq/L, as opposed to defining the normal range as 3.5 to 5.0 as was the case in Study ZS-004. Because of the high drop-out rate in the trial (36%), the interpretation of the results is not straightforward. According to Dr. Xiao's review, lack of efficacy did not appear to be the issue underlying the dropouts. The main reasons for dropout included progression of chronic kidney disease, adverse events, and patient compliance. As also noted in Dr. Xiao's review, an ongoing long-term open-label study (ZS005) is expected to provide additional information on maintenance of potassium control during long-term treatment.

Conclusion: The Division believes that the applicant has provided substantial evidence of the effectiveness of ZS in lowering serum potassium levels in patients with hyperkalemia, an accepted surrogate endpoint in this population, and in maintaining normokalemia in patients with hyperkalemia. I agree with their assessment.

8. Safety

This information comes from the reviews of Drs. Xiao and Thompson, with supplemental analyses by Dr. Garnett. A total of 1,592 subjects with hyperkalemia received ZS in the clinical trials. Of this total, 1,009 subjects were enrolled in trials reviewed in this NDA (i.e., Studies ZS-002, ZS-003, ZS-004 and ZS-004E). The other 583 subjects are enrolled in Study ZS-005, an ongoing, open-label study evaluating long-term safety and efficacy of ZS. Data submitted by the

applicant include 262 patients with hyperkalemia who have been treated for ≥ 6 months and 79 who have been treated for ≥ 1 year.

Safety topics of interest:

The review by Dr. Xiao (with supplemental analyses by Dr. Christine Garnett) focuses on expected risks related to the drug's mechanism of action, based in part on experience with the approved potassium cation exchange resins. These risks include hypokalemia, gastrointestinal (GI) toxicity, sodium absorption leading to heart failure, edema and volume overload, binding of non-potassium cations, and alkalosis.

The applicant evaluated the potential of ZS to interact with orally administered medications *in vitro*, and subsequently in drug-drug interaction (DDI) studies in healthy volunteers. At this point, the Division does not believe that DDI have been adequately investigated. As noted above, the applicant has submitted additional data, and they remain under review.

Hypokalemia: Potassium levels were monitored in the phase 3 trials and the open-label extension study, ZS-004. During the subacute phase of Study ZS-003, potassium was measured on Days 1, 2, and 3, and then on Days 6 and 12. During the extended dosing phase of Study ZS-004, serum potassium was measured on Days 1 and 2 and then every 3 to 4 days for the duration of the 28-day treatment period. During Study ZS-004E, potassium was measured weekly starting at Day 8 through Day 57 and then approximately every 28 days.

Confirmed hypokalemia was defined as 2 potassium values obtained 10 minutes apart, both < 3.5 mEq/L, or a single value < 3.5 mEq/L in the absence of a confirmatory sample.

The review team believes that the adverse event and laboratory data are reassuring with respect to precipitation of hypokalemia:

- Acute phase: During the acute phases of the short-term studies (Studies ZS-004, ZS-003 and ZS-002), potassium values < 3.5 mEq/L were observed in 0.4% of ZS-treated subjects (4/913). For the high-dose group (10 g TID), the frequency was 0.7%. No subject had a potassium < 3.0 mEq/L as assessed by the central laboratory.
- Extended dosing: Through 12 days of QD dosing in Study ZS-003 and up to 28 days of QD dosing in Study ZS-004, 4% of ZS-treated subjects overall had a potassium < 3.5 mEq/L. Hypokalemia was strongly dose-related, with frequencies of 0.5%, 6.1%, and 19.6% for ZS doses of 2.5, 10, and 15 g daily, respectively. Ten subjects had reported potassium values < 3.0 mEq/L in studies ZS-002, ZS-003, and ZS-004, but only one had a value <3.0 as assessed by the central laboratory. (Other values < 3.0 mEq/L had been found on samples assessed by i-STAT.)

Of the dosing regimens evaluated in all of the phase 3 studies, the regimen evaluated in Study ZS-004 was more closely aligned with the regimen to be recommended in labeling. As expected, the incidence of confirmed hypokalemia in Study ZS-004 was dose-related: 13.7% of

subjects in the 10 g QD group and 19.6% of subjects in the 15 QD group. One of these patients was discontinued from treatment because of QTc prolongation.

- Long-term treatment: During long-term treatment in Study ZS 004E (median treatment duration: 252 days; range 1 to 338 days), 7 of 123 (5.7%) subjects were reported to have a potassium value < 3.5 mEq/L, and in one of these subjects, potassium was < 3.0 mEq/L (2.8 mEq/L).

Based on the above, it is clear that ZS can cause hypokalemia, as expected on the basis of its mechanism of action. Occasionally, hypokalemia can be severe. Proper monitoring should largely ameliorate the risk, and instructions will be included in labeling.

Volume overload and edema: Dr. Christine Garnett performed a number of analyses to assess the potential risk of sodium absorption, focusing on Study ZS-004, which evaluated the highest dose used in the extended dosing phase (15 g QD). Dr. Garnett ran a standard MedDRA query (SMQ) for hemodynamic edema, effusions, and fluid overload, and found a dose-dependent increase in the incidence of these adverse events in Study ZS-004: 4.4%, 5.9%, and 16.1% for the ZS 5, 10, and 15 g QD treatment groups, respectively (Table 5). The frequency in the placebo group was 2.4%.

Table 5: Standard MedDRA Query: Hemodynamic edema, effusions and fluid overload by treatment group in Study ZS-004

MedDRA high-level term; preferred term	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	2	4.4	3	5.9	9	16.1	14	9.2	2	2.4
Edema	1	2.2	3	5.9	8	14.3	12	7.9	2	2.4
generalized edema	0	0	0	0	2	3.6	2	1.3	0	0
edema	1	2.2	0	0	1	1.8	2	1.3	0	0
edema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Total fluid volume increased	1	2.2	0	0	1	1.8	2	1.3	0	0
fluid overload	1	2.2	0	0	0	0	1	0.7	0	0
fluid retention	0	0	0	0	1	1.8	1	0.7	0	0
Joint related signs and symptoms	0	0	0	0	1	1.8	1	0.7	0	0
joint swelling	0	0	0	0	1	1.8	1	0.7	0	0

Source: Dr. Christine Garnett

Other analyses, including analyses of weight and blood pressure, also suggest that ZS provides a sodium load to patients, particularly at the 15-g dose.

Dr. Garnett also assessed the risk of edema/fluid overload by subgroup (Table 6). Not surprisingly, patients with chronic kidney disease (CKD), chronic heart disease (CHD) and diabetes appear to be at higher risk. It is interesting, however, that all of these adverse events were reported in patients with CKD, and in such patients, the risk was striking: 24% at the 15-g dose. There were no adverse events for edema/fluid overload in patients without CKD. It would be useful to assess these adverse events in subgroups of age. Medical judgment suggests that older patients would be more vulnerable, but it would be useful to assess the data. If present, greater vulnerability with advancing age would be worth noting in labeling.

Table 6: Standard MedDRA Query: Hemodynamic edema, effusions and fluid overload by subgroup in Study ZS-004

Population	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Total (N=237)	2/45	4.4	3/51	5.9	9/56	16.1	14/152	9.2	2/85	2.4
CKD (yes) (N=152)	2/29	6.9	3/36	8.3	9/37	24.3	14/102	13.7	1/50	2.0
CKD (no) (N=85)	0/16	0	0/15	0	0/19	0	0/50	0	1/35	2.9
CHD (yes) (N=87)	1/18	5.6	2/18	11.1	5/25	20	8/61	13.1	1/26	3.9
CHD (no) (N=150)	1/27	3.7	1/33	3.0	4/31	12.9	6/91	6.6	1/59	1.7
Diabetes (yes) (N=157)	2/26	7.7	3/38	7.9	7/39	17.9	12/103	11.7	0/54	0
Diabetes (no) (N=80)	0/19	0	0/13	0	2/17	11.8	2/49	4.1	2/31	6.5

Source: Dr. Christine Garnett

Heart failure:

Heart failure was reported in 2.6% of patients in the ZS groups vs. 0% in the placebo group (4 patients vs. 0, Table 7, from Dr. Christine Garnett). The numbers of adverse events are too small to assess a dose-response.

Table 7: Cardiac Failure: Adverse Events in Study ZS-004

MedDRA High-level term; preferred term	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Heart failure (all)	1	2.2	1	2.0	2	3.6	4	2.6	0	0
Cardiac failure	0	0	0	0	1	1.8	1	0.7	0	0
Cardiac failure acute	0	0	1	2.0	0	0	1	0.7	0	0
Cardiac failure congestive	1	2.2	0	0	1	1.8	2	1.3	0	0

In the open-label Study ZS-004E, 5 patients (4.1%) reported heart failure, numbers that are difficult to interpret without a control group.

I have some concern that ZS could precipitate CHF in vulnerable patients. I recognize that the number of CHF adverse events is low, but given the drug's mechanism of action, and given that sodium retention/fluid retention is clearly drug-related (and dose-related), it would be foolish to think that the difference in adverse events for CHF, even as small as it is, represents play of chance. The label should reflect this.

GI safety and tolerability: Given that ZS is not absorbed but remains in the intestinal lumen, there was interest in assessing the frequency of GI adverse events. The frequencies of GI adverse events were fairly low in all treatment groups, and not greater with ZS than with placebo.

Clinically significant alkalosis: Because ZS binds ammonium ions, it has the potential to increase serum bicarbonate levels, leading to a metabolic alkalosis. During ≤ 12 days of dosing in Study ZS-003 and ≤ 28 days in Study ZS-004, ZS caused a small, dose-dependent increase in mean serum bicarbonate concentrations (1.1, 2.3, and 2.6 mEq/L at 5, 10, and 15 g QD, compared with a mean change of 0.6 mEq/L in patients treated with placebo). Of the 59 subjects treated with ZS 15 g, 1 (1.8%) had a shift to a value above the normal range, compared to 3 of 301 subjects (1.0%) in the placebo group. No subject had a reported bicarbonate > 35 mEq/L. In summary, there does not appear to be much risk of clinically significant alkalosis at the doses proposed for use.

Other cations: The clinical review team found no clinically meaningful changes in magnesium in the phase 3 trials. Small dose-related decreases in mean calcium values were observed in the ZS treatment arms (-0.13, -0.18, and -0.28 mg/dL in the ≤ 3, 5, and 10 g TID dose groups compared with a change of -0.07 mg/dL in the placebo group). No subjects developed a calcium < 7.0 mg/dL during the acute or extending dosing phases of the phase 3 trials.

9. Advisory Committee Meeting

As noted in the CDTL review, the NDA was not presented to the FDA Cardiovascular and Renal Drugs Advisory Committee. Although the drug is a new molecular entity with a novel structure, we thought that the efficacy and safety were well characterized, straightforward, and in no way controversial. The clinical trials were conventional in both their designs and their 1° endpoints. We did not anticipate novel efficacy or safety issues that would warrant discussion.

10. Pediatrics

As noted in the CDTL review, there was no agreed-upon pediatric study plan prior to submission of the NDA. In order to address the PREA requirement, the applicant has proposed to conduct a deferred, open-label, dose-escalation safety and pharmacodynamic study in children with hyperkalemia, aged 0 to (b) (4) Although there are aspects of the protocol that require further discussion, the overall design of the study is acceptable.

Key considerations include the following:

(b) (4)

11. Other Relevant Regulatory Issues

Financial disclosures and Good Clinical Practice: Disclosure of financial arrangements was adequate. Although 2 investigators who participated in Study ZS-004 had financial interests or arrangements to disclose, based on the site analyses performed by Dr. Birkner, data from their sites had no impact on the overall efficacy results.

Office of Scientific Investigations (OSI) audits: OSI conducted inspections at 3 clinical investigator sites and also performed an inspection of the sponsor. Two of the clinical sites received a classification of "No Action Indicated." A Form FDA 483 was issued for minor deficiencies at a third clinical site, deficiencies that OSI considered unlikely to affect the integrity of the data submitted in support of the NDA.

Application Integrity Policy: The applicant's firm is not listed on FDA's Application Integrity Policy list (i.e., FDA's list of firms that were notified that FDA is deferring substantive scientific review of one or more of the firm's applications and/or is proceeding to withdraw the approved applications).

12. Labeling

Prescribing Information:

Marked up labeling was sent via email to the Applicant on April 26, 2016. At this time, as noted by the CDTL, principal outstanding issues include:

- Dosage and Administration. As discussed in Section 5 (Clinical Pharmacology) the applicant is proposing a maximum recommended daily dose of (b) (4) g once daily during maintenance treatment, whereas the clinical pharmacology team is recommending a maximum daily dose of 15 g once daily during the maintenance phase.
- Warnings and Precautions. At this time, the review team believes that a Warning and Precaution related to sodium absorption leading to edema is warranted. I will add that the warning should also note the possibility of precipitation of heart failure in susceptible individuals. The review team has also proposed a Warning and Precaution related to worsening of gastrointestinal motility, and specifically, avoiding use of the drug in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because the drug may be ineffective and may worsen gastrointestinal conditions (patiromer contains a similar warning).
- Drug-drug interactions. As discussed in Section 5 (Clinical Pharmacology): Dosing instructions for mitigating drug interaction potential cannot be made until clinical pharmacology has completed its reviewed of the results of *in vivo* DDI studies that were submitted late in the review cycle.

Substantial edits were also made to other sections of the label by members of the review team and Michael Monteleone, Associate Director for Labeling; a number of these edits addressed concerns raised by the Office of Prescription Drug Promotion.

On May 19, 2016, ZS Pharma submitted a response to the draft labeling sent by the Division. It seems clear that additional work needs to be completed before there can be alignment on labeling.

Proprietary name:

The proposed name, “Lokelma,” has been deemed acceptable by the Division of Medication Error Prevention and Analysis.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS):

Product labeling is expected to be adequate to ensure that the product’s benefits outweigh its risks in the postmarketing setting, such that a REMS is not deemed to be necessary at this time.

Postmarketing Requirements (PMRs) and Commitments (PMCs):

When approved for the treatment of hyperkalemia in adults, a PMR should be issued to conduct a two-part, safety and pharmacodynamic study in children 0 to (b) (4) years of age with hyperkalemia to satisfy PREA.

14. Recommended Comments to the Applicant

See the *Complete Response* letter, to be issued today.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
05/26/2016

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	N. Stockbridge
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	207078 000
Applicant	ZS Pharma
Date of Submission	16 September 2016
PDUFA Goal Date	16 March 2017
Proprietary Name / **Non-Proprietary Name**	Lokelma Sodium zirconium cyclosilicate
Dosage Form(s) / Strength(s)	Powder for suspension, 5 and 10 g
Applicant Proposed Indication(s)/Population(s)	Hyperkalemia
Action/Recommended Action	*Complete Response*
Approved/Recommended Indication/Population(s) (if applicable)	

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Thompson

There is a detailed CDTL memo of Dr. Thompson's with which I am in complete agreement. The CMC review is, at this time, incomplete. Draft labeling was shared with the sponsor last week; the major point of contention there is with management of drugs whose absorption is sensitive to pH. While it is possible to identify some of the drugs with the potential for being affected to a clinically significant degree, the review team and I agree that a more reliable strategy is to avoid taking most drugs at the same time as Lokelma, except when one is sure it is safe to do so. Effectiveness of Lokelma administered once a day should make this strategy reasonably easy to implement, once one is past the initial thrice daily regimen.

The original Complete Response largely concerned CMC issues, and these remain unresolved. A "withhold" recommendation remains for the ZS site for drug substance manufacturing, release, and stability testing following a reinspection in January. (b) (4)

The Agency had advocated for the availability of a 15-g dosing regimen, and ZS has lowered heavy metal specifications in order to make this dose acceptable. The current product specifications are compatible with proposed dosing recommendations (b) (4)

The review team and I do not favor approval at this time. A reinspection would be necessary to give the district office confidence that the CMC issues have been fully addressed, and more data are necessary to ensure the specific activity issue is understood and mitigated. In my view, it is the lack of data on the specific activity issue that argues in favor of a second complete response instead of a clock extension.

There are two other approved potassium binders, so it is reasonable to issue a Complete Response on this one until remaining CMC issues are resolved.

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/s/

NORMAN L STOCKBRIDGE
03/13/2017

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	N. Stockbridge
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	207078 000
Applicant	ZS Pharma
Date of Submission	26 May 2015
PDUFA Goal Date	26 May 2016
Proprietary Name / **Non-Proprietary Name**	Lokelma Sodium zirconium cyclosilicate
Dosage Form(s) / Strength(s)	Powder for suspension, 5 and 10 g
Applicant Proposed Indication(s)/Population(s)	Hyperkalemia
Action/Recommended Action	*Complete Response*
Approved/Recommended Indication/Population(s) (if applicable)	

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Xiao, Garnett
Statistical Review	Birkner
Pharmacology Toxicology Review	Gatti
OPQ Review	Frankewich, Wong, Pai, Gieser, Changi, Pogue, Sapru
Clinical Pharmacology Review	Lai, Johannesen
OPDP	Shah
OSI	Gershon
CDTL Review	Thompson
OSE/DMEPA	Gao

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment
Lokelma is clearly effective in reducing serum potassium, binding about 3 mEq per gram, and doses of 10 g thrice daily for two days and 5-15 g once daily are well tolerated. Patients require monitoring to adjust the dose to keep the serum potassium in the normal range and to mitigate edema resulting from the sodium load. What needs to be done to manage drug interactions remains to be determined.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Hyperkalemia conveys risk of proarrhythmia.	Hyperkalemia is a self-evidently valid surrogate for a life-threatening condition.
Current Treatment Options	Sodium polystyrene sulfonate and patiromer are approved, non-absorbable potassium binders. The former was never very well worked up and both have safety and GI tolerability issues[1].	Unmet medical need persists.
Benefit	Three studies established the nature, time, and dose-dependence of Lokelma's effects on serum potassium.	Lokelma is effective and appropriate instructions for use are known.
Risk	GI tolerability is good, so there is risk of inducing hypokalemia. Lokelma exchanges sodium and hydrogen ions for potassium, sometimes enough of the former to precipitate edema in vulnerable patients. The extent to which Lokelma affects absorption of other drugs is still being assessed; the main effect seems to be through pH, not nonspecific binding.	Risks have been adequately assessed in the development program.

[1] See p 4 of the CDTL memo for a more thorough discussion.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	Instructions for use limit the potential for hypokalemia, via dose adjustment and monitoring of serum potassium. Edema can also be monitored clinically.	Strategies for management of hypokalemia and edema are adequately developed. Potential drug interactions can be managed by shifting the time of dosing.

2. Background

Zirconium cyclosilicate is manufactured to have a pore size specific, for all intents and purposes, for potassium, which it binds (about 3 mEq/g) in exchange for sodium and hydrogen. It is intended for the treatment of hyperkalemia, including chronic use.

3. Product Quality

A manufacturing site was not ready for inspection, as had been alleged at submission, and did not get declared ready until late. It was promptly inspected and was found to have numerous problems, documented in product quality and CDTL reviews, some of which could not be satisfactorily resolved during this review cycle. This might have been the sole basis for a CR action.

4. Nonclinical Pharmacology/Toxicology

Zirconium cyclosilicate is not absorbed. In animals and man its effects given alone are attributable to resulting systemic decrease in potassium and increase in sodium. There was no GI irritation, so carcinogenicity studies were deemed unnecessary.

5. Clinical Pharmacology

Lokelma is unequivocally effective. The proposed initial dose of 10 g tid for 2 days, capable of binding ~100 mEq of potassium, which is far in excess of any plausible intake, drives the serum potassium down about 1 mEq/L. Subsequent doses of 5-15 g qd[2] seem to be in the useful maintenance range, and are more in line with dietary intake of potassium. I note that total serum potassium is about 4 mEq/L x 5 L or 20 mEq, which is on the order of daily intake; serum potassium is rapidly buffered by vast extravascular (mostly intracellular) potassium, and equilibration following a change in the binder dose takes a week or more.
In vitro studies suggest more of a problem with drug-drug interaction than do in vivo studies. Much of the in vitro effect seems to relate to pH changes which are buffered in vivo. This does not completely explain all of the in vitro-in vivo results. This remains an open issue, but the final recourse is separating Lokelma administration from other drugs; the only question is whether the list of affected drugs is large enough to warrant shifting all of them.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

See Section 5 for a discussion of effects on serum potassium.
Chronic use of Lokelma or another tolerated potassium binder may enable use of or higher doses of RAAS inhibitor therapy in populations that previously could not tolerate the

[2] The sponsor recommended a maintenance dose cap (b) (4), but the review team and I believe the 15 g qd dose is useful. This remains to be negotiated, and trace element specifications may need tightening to make the 15-g dose acceptable.

hyperkalemia. Many patients on RAAS inhibitors were in phase 3 studies. Whether such use is clinically of net benefit remains to be determined.

8. Safety

Lokelma is quite effective and well tolerated, so hypokalemia is possible. The studies seemed to have established a reasonable basis for developing instructions for monitoring and dose adjustment.
The small effect on QT is expected from changes in electrolytes.
At a dose of 10 g qd, the sodium load should be about 30 mEq (same as potassium binding) or ~700 mg. This is enough to precipitate edema in a vulnerable population (e.g., dihydropyridine use, renal impairment, or heart failure).

9. Advisory Committee Meeting

No AC was held. The regulatory pathway was clear, and there were no novel safety issues warranting discussion.

10. Pediatrics

Data needed to support use in children will need to be obtained post-marketing. Effectiveness can be readily extrapolated; dose-response and tolerability will need to be determined.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Two substantial issues remain to be resolved. One is the option of a 15-g/day maintenance dose, which the review team thinks is appropriate. This dose may require further reduction in the trace element specifications. The other is whether concomitant drugs (some or many) need to be spaced away from the Lokelma dose; information to determine that is under review.

13. Postmarketing

Labeling is thought to be adequate to manage identified risks. The only anticipated post-marketing requirement will be to conduct a study of use in children (PREA).

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/s/

NORMAN L STOCKBRIDGE
05/21/2016

Cross-Discipline Team Leader Review

Date	May 20, 2016
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA #	207078
Applicant	ZS Pharma Inc
Date of Submission	May 26, 2015
PDUFA Goal Date	May 26, 2016
Proprietary Name / Non-Proprietary Name	Lokelma / sodium zirconium cyclosilicate
Dosage form(s) / Strength(s)	Powder for Oral Suspension / 5 g and 10 g packets
Applicant Proposed Indication(s)/Population(s)	Treatment of hyperkalemia (b) (4)
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	

This secondary review is based on the following:

Material Reviewed/Consulted	
Quality Assessment (2/3/16 and 5/10/16)	Raymond Frankewich, Thomas Wong, Vidya Pai, Gerlie Gieser, Maryam Changi, Laura Pogue, and Mohan Sapru
Pharmacology Toxicology Review (1/8/16)	Philip Gatti and Thomas Papoian
Clinical Pharmacology Review (5/9/16)	Ju-Ping Lai, Lars Johannesen, Jeffry Florian, and Rajnikanth Madabushi
Clinical Review (4/7/2016)	Shen Xiao
Safety Analyses	Christine Garnett and Ana Szarfman
Statistical Review (2/8/2016)	Thomas Birkner and Hsien Ming Hung
Division of Medication Error Prevention and Analysis Review (8/11/15 & 11/15/15)	Tingting Gao and Chi-Ming (Alice) Tu
Office of Prescription Drug Promotion Review (1/8/16)	Puja Shah
Office of Scientific Investigations Clinical Inspection Summary (4/6/2016)	Sharon Gershon and Susan Thompson

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

On May 26, 2015, ZS Pharma Inc submitted NDA 207078 for sodium zirconium cyclosilicate (Lokelma) for the treatment of hyperkalemia (b) (4) Hyperkalemia, often defined as a serum potassium > 5 mmol/L, is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on renin-angiotensin-aldosterone system inhibitors. Because marked elevations in serum potassium can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis, therapies are needed to treat hyperkalemia before life-threatening elevations occur.

The review team is in agreement that the application provides substantial evidence of ZS's effectiveness in lowering serum potassium in patients with hyperkalemia, an accepted surrogate endpoint in this population, and in maintaining normokalemia in these patients. However, as discussed below, there are a number of outstanding issues that prevent approval at this time.

- *Facility inspections.* As discussed in Section 3, objectionable conditions were identified during inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX). Because of the inspection findings, the Office of Process and Facilities has issued a 'Withhold" recommendation for the facility. From a product quality perspective, the application cannot be approved until satisfactory resolution of all of the inspectional observations cited in FDA Form 483.
- *Drug-drug interactions.* As discussed in Section 5, the results of *in vitro* screening tests raise concern for a potential risk of drug interactions. Of the 39 drugs that were screened for interactions in an *in vitro* test system, nine exhibited a significant decrease in concentration (30% to 99%) in one or more media in the presence of ZS, seven exhibited a significant increase in concentration or binding capacity (40% to 564%), and five exhibited inconsistent findings over different pH ranges in different media. Although many of these interactions appear to be the result of pH changes caused by ZS, there are drugs that showed concentration changes that cannot be explained solely by pH changes. The Applicant has conducted additional evaluations, including *in vivo* drug-drug interaction studies. Because the *in vivo* study reports were submitted late in the review cycle, these study reports are not addressed in the Clinical Pharmacology Review and recommendations for mitigating drug interaction potential cannot be made at this time.
- *Dosing regimen.* As discussed in Section 5, the Clinical Pharmacology Review team is recommending a different dosing regimen than what is proposed by the Applicant. Obviously, agreement will need to be reached on the recommended dosing regimen in labeling.

Benefit-Risk Summary and Assessment

Although there are outstanding issues that prevent approval at this time, it is important to note that a number of issues have been adequately resolved during the current review cycle. As previously indicated, there is widespread agreement among the members of the review team that the application provides substantial evidence of ZS's effectiveness in treating hyperkalemia. I also believe that the risks of this product (beyond its potential for drug-drug interactions) have been adequately characterized during the current review cycle. In brief, these risks include (1) the risk of hypokalemia, which appears to be manageable with appropriate monitoring of serum potassium, and (2) the risk of sodium absorption leading to edema and fluid overload, particularly at the highest dose recommended for extended use. The Clinical Reviewer believes that both of these risks can be adequately addressed via labeling. I agree.

For a summary of the evidence and uncertainties and my conclusions and reasons, see the table below. I thank and commend the review team for their work on what has proven to be a challenging application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis. The goal of therapy is to initiate treatments for hyperkalemia before life-threatening elevations occur.	Hyperkalemia can be a serious condition.
Current Treatment Options	Approved cation exchange agents for removing excess potassium from the body include sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, and patiromer (Veltassa), approved in October 2015. Potential limitations of these agents include a relatively slow onset of action (both agents), poorly characterized efficacy (SPS), and safety concerns such as intestinal necrosis (SPS), the potential for drug-drug interactions with other orally administered medications (both agents), hypomagnesemia (patiromer and SPS)/other non-specific binding to cations (SPS), volume overload secondary to an increase in sodium load (SPS), hypokalemia (both agents) and GI tolerability (both agents).	Given the limitations of available therapies, there is need for additional agents that are effective in lowering serum potassium and maintaining target potassium levels in patients with hyperkalemia.
Benefit	Support for efficacy is provided by the applicant's two phase 3 trials, as well as a phase 2 trial. These trials demonstrated statistically significant and clinically meaningful effects on serum potassium at the doses proposed for use in patients with hyperkalemia.	The application provides substantial evidence of ZS's effectiveness in lowering serum potassium in patients with hyperkalemia, an accepted surrogate endpoint in this population, as well as substantial evidence of effectiveness in maintaining treated patients in the target potassium range.

Risk	Hypokalemia was observed in clinical trials, but for the most part was mild (i.e., serum potassium levels of 3-3.4 mmol/L). The incidence of hypokalemia varied depending on the stage of the trial and the dose that was studied. Less than 1% of subjects who were administered ZS 10 g three times a day for the acute treatment of hyperkalemia developed a serum potassium < 3.5 mmol/L. In subjects randomized to treatment with higher doses of ZS (10 g and 15 g once daily), approximately 10% of subjects developed a serum potassium < 3.5 mmol/L. Edema and weight gain, presumably resulting from sodium absorption from the product, was observed in clinical trials, particularly at the highest dose evaluated for extended use (15 g once daily). Subgroup analyses suggest that patients more severe renal impairment, those with diabetes and those with heart failure, as well as patients taking a calcium channel blocker may be particularly susceptible to the risk of edema and fluid overload. ZS's potential to interact with other orally administered medications remains an outstanding issue.	Hypokalemia is a risk of treatment with ZS, but with appropriate monitoring, this risk is manageable. Edema and fluid overload resulting from sodium absorption from the product is a risk, particularly at the highest dose recommended for extended use and in certain populations. This risk can also be adequately managed with appropriate monitoring of patients. ZS's potential to interact with other orally administered medications needs to be resolved prior to approval.
Risk Management	Labeling should contain adequate information on risks including the risk of hypokalemia and sodium absorption from the product leading to edema and fluid overload.	Identified risks related to hypokalemia and sodium absorption from the product can be adequately managed by labeling. Because ZS's potential to interact with other orally administered medications remains an outstanding issue, recommendations for mitigating drug interaction potential cannot be made at this time.

2. Background

Sodium zirconium cyclosilicate (ZS) powder for oral suspension is an inorganic cation exchanger with a high capacity to selectively entrap monovalent cations, specifically potassium and ammonium ions, as it traverses the intestinal tract. The proposed indication is for the treatment of hyperkalemia, (b) (4)

Therapeutic context: Hyperkalemia is typically defined as a serum potassium > 5 mmol/L and is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors). Marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis. Hence, the goal is to initiate treatments for hyperkalemia before life-threatening elevations occur.

Approved oral treatments for removing excess potassium from the body include sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, and patiromer (Veltassa), approved in October 2015. To date, use of SPS has been limited by tolerability and safety concerns (i.e., colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy. Based on findings in in vitro studies, the current label for patiromer includes a Boxed Warning about patiromer's potential to bind other co-administered oral medications.[1] Common adverse reactions seen in clinical trials with patiromer include gastrointestinal adverse reactions and hypomagnesemia. An important issue related to the use of these agents to treat hyperkalemia is the time to onset of a clinically relevant effect on serum potassium levels. According to the patiromer label, statistically significant reductions in serum potassium were first observed 7 hours after initiating therapy with patiromer; however, even at this point, the mean effect was small (-0.2 mmol/L).

Regulatory background: There were a number of interactions with the Applicant over the course of development. The Clinical Review contains an overview of discussions pertaining to a number of key topics, while the Clinical Pharmacology Review contains a focused overview of communications between the Applicant and the Agency pertaining to drug-drug interactions.

With regard to important milestones and agreements:

- An IND to develop ZS as a treatment for hyperkalemia was submitted in December 2010. The IND (108951) was initially placed on clinical hold because of adverse kidney/bladder findings in the nonclinical program, an issue that was adequately resolved via changes to the formulation (see Section 4 for further discussion).
- Meetings were held to discuss the product's overall development program (September 2012) and the data supporting a future NDA (July 2014). Neither of the phase 3

[1] For the most part, the drug-drug interaction potential of Kayexalate has not been evaluated. Based on the findings in the patiromer program, a PMR was issued for DDI studies of Kayexalate.

protocols were conducted under Special Protocol Assessment; however, during the course of other interactions, the Division confirmed that the primary endpoints used in the phase 3 trials and overall design of the development program were acceptable for a drug being developed to treat hyperkalemia.

With regard to discussions pertaining to ZS's drug interaction potential, the Applicant was advised to conduct *in vitro* drug-drug interaction studies at a pre-IND meeting in 2010. The Applicant submitted the result of *in vitro* studies in their NDA application; however, early in the course of the review, the Clinical Pharmacology Review team noted that the *in vitro* test conditions that were used in these studies were inadequate. Hence, in the filing letter, the Applicant was advised to repeat their *in vitro* studies using physiologically relevant conditions. As discussed later in this review, the results of these screening studies, which were submitted approximately 5 months into the review cycle, raised significant concern about the potential of ZS to interact with other orally administered medications and prompted the need for further evaluation via *in vivo* studies in humans.

Marketing history: ZS is not currently marketed in any country.

3. Product Quality

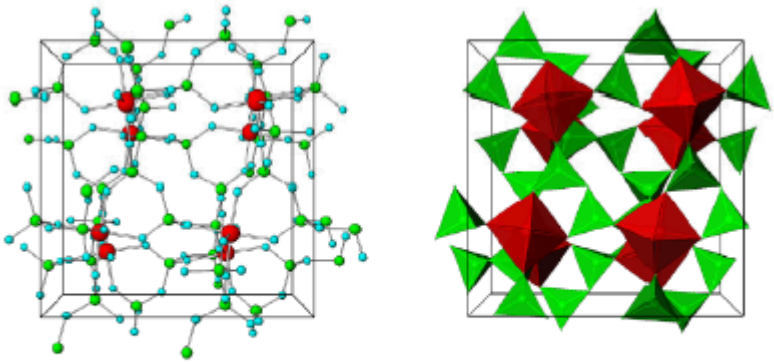
From a product quality perspective, the application cannot be approved at this time. As discussed below, objectionable conditions were identified during inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX). Because of the inspection findings, the Office of Process and Facilities has issued a 'Withhold" recommendation for the facility. From a product quality perspective, the application cannot be approved until satisfactory resolution of all of the inspectional observations cited in FDA Form 483.

Drug Substance: As discussed in the Quality Review, the drug substance structure can be viewed as a covalent framework. This framework consists of channels and cavities that interconnect and house positive ions that counter-balance the negative charge of the framework. According to the review, "Electrostatic interactions between the framework and the cations allow for mobility and possibility of exchange for other cations that would fit and pass the free pore openings of ~ 3.0 Å, providing the compound with its distinctive ion-exchange selectivity features." The applicant asserts, and the Quality Review team agrees, that the negatively charged framework (b) (4) constitutes the active moiety. The Quality Review further notes that the active moiety must be accompanied by sodium ions to balance the charge and interstitial water to support the structure.

The drug substance is a free flowing white crystalline powder. The molecular formula of the basic unit of the drug substance is $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet n'H_2O$ ($n' = 2–3$). Other notable attributes are as follows:

- The basic unit has a relative molecular mass of (b) (4) Daltons.
- The structure is insoluble and collapses above 300 °C.
- Potassium ion exchange capacity is (b) (4) mmol/g

A representation of the structure of sodium zirconium cyclosilicate is shown below. Because very fine particles can lead to systemic absorption of sodium zirconium cyclosilicate, no more than 3% of particles have a diameter below 3 µm.



In the diagram on the left the $[Zr(O)_6]^{-2}$ octahedron is represented by the red and blue ball-and-sticks, and the $[Si(O)_4]^{0}$ tetrahedron is represented by the green-and-blue:

Figure 1: Representation of the structure of sodium zirconium cyclosilicate

Source: CMC review dated February 3, 2016, page 11

Drug Product: The drug product consists of the drug substance (b) (4) The drug product is packaged in (b) (4) foil pouch to produce two strengths: 5 g and 10 g of sodium zirconium cyclosilicate. Proposed labeling instructs patients to empty the entire packet into a drinking glass, add about 3 tablespoons (1.5 ounces) of water or more if desired, stir well and drink the suspension immediately.

Expiration Date and Storage Conditions: Stability data support the proposed product shelf-life of (b) (4) months, when packaged in (b) (4) foil pouches and stored at 25ºC.

Facilities review/inspection: At the time of NDA submission, the Applicant attested that the manufacturing and testing facilities were ready for inspection. However, as discussed in the Product Quality review, the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX) was not inspection-ready when the site was visited for inspection. At the Mid-Cycle Meeting, the Applicant was warned that that if their manufacturing facility had not passed inspection by the PDUFA date, then the application could not be approved during the current review cycle. The pre-approval inspection the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX) was subsequently conducted from March 17-29, 2016. At the conclusion of the inspection, the inspector issued FDA Form 483. According to the Product Quality Review (see pages 41-42):

> *"…Significant inspectional observations were cited on Form FDA 483 to the firm. The observations included deficiencies related to buildings and facilities, inadequate environmental controls, inadequate production and process controls,*

inadequate lab controls, inadequate process validation, deficiencies in records and reports and issues with the quality assurance systems.

The firm responded to the inspectional observations, and the firm's response was reviewed by the district in detail. While many observations were satisfactorily addressed, there were continued concerns with the firm's responses with regards to a) procedures in place for cleaning and maintaining process equipment. b)assessment of impact of adequate validation, control and monitoring of software used for manufacturing and quality control operations, c)inadequate response to support validation of test methods used in manufacture.

[redacted] (b) (4) *The risks presented by this* [redacted] (b) (4) *are yet to be adequately reviewed and mitigated by the applicant and verified in practice. The field investigators recommend a Withhold for the Pre-Approval Inspection and this has been confirmed by the DAL-District following review of EIR and firm's response. The facilities review team also concurs with the Withhold recommendation and will request that the corrective actions to the Form 483 be verified on a follow up inspection. Thus, the ZS Pharma, Inc. Coppell TX, site is considered unacceptable to support this NDA at this time."*

Other outstanding issues: According to the Quality Review, there are also outstanding issues related to labeling and elemental impurity specifications that should be listed as deficiencies in the complete response letter.

- Labeling: During the review period, the Applicant was advised to delete the term [redacted] (b) (4) from the product name because the term is not appropriate for the nomenclature of this product. Although the Applicant has agreed to make this change, to date, the container labels have not been changed.
- Elemental Impurity Specifications: If the maximum daily dose during maintenance therapy is increased to 15 g, as recommended by the Clinical Pharmacology Review team, potential daily exposures [redacted] (b) (4) for each of these elements. Therefore, if a 15 g dosage strength is to be approved, the Applicant will need to revise the acceptance criteria for these elements in order to comply with Q3D recommended PDE limits.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Gatti's review, the application can be approved from a pharmacology-toxicology perspective.

ADME: A non-GLP mass balance study in rats did not suggest significant systemic absorption of ZS-9. Following single dose administration, ~97-101% of the administered

dose was recovered from feces and 0.1-0.3% was recovered from urine collected over a three-day period.

Toxicity studies: Initial toxicology studies used formulations that contained sodium zirconium cyclosilicate [redacted] (b) (4) In initial repeat-dose toxicology studies in dogs and rats, the formulations caused renal tubular degeneration/necrosis and pyelitis. These adverse renal effects were not observed in subsequent repeat-dose toxicology studies of longer duration using newer formulations of the product [redacted] (b) (4)

Long-term repeat dose toxicity studies included a 39-week repeat-dose study in dogs and a 26-week repeat-dose study in rats. Findings seen in toxicology studies were thought to reflect adaptive responses to the drug's effect on serum potassium and included decreased urine potassium levels, decreased serum aldosterone concentrations, increased serum HCO3 concentrations, increased urine sodium excretion, and decreased urine hydrogen ion excretion. Tubulointerstitial inflammation and lipid vacuolation in the adrenal cortex were also observed during chronic administration in dogs, effects which were greatly reduced when the animals received the same dose with potassium supplementation.

Pharmacology: In a 5-day pharmacology study in normal rats, ZS-9 increased fecal potassium excretion and decreased urinary potassium excretion but did not affect urinary or fecal calcium or magnesium excretion or blood levels of these parameters. According to Dr. Gatti's review, the potassium exchange capacities (KEC) of the lots used in nonclinical studies were [redacted] (b) (4) mmol/g; the average KECs of the products used in the two phase 3 studies were higher ([redacted] (b) (4) mmol/g).

Reproductive toxicology: Per Dr. Gatti, sodium zirconium cyclosilicate was not teratogenic in rats or rabbits, did not have adverse effects on fertility in rats, and was not associated with detrimental effects in a rat pre/postnatal study.

Genotoxicity and Carcinogenicity: Sodium zirconium cyclosilicate was not genotoxic in the reverse mutation test (Ames assay), chromosome aberration or rat micronucleus assays. Since sodium zirconium cyclosilicate is not absorbed from the GI tract, is not genotoxic, and did not cause local gastrointestinal irritation/alterations in the chronic toxicity study in dogs, carcinogenicity studies were not performed.

5. Clinical Pharmacology

As discussed in the Clinical Pharmacology Review, there are two major outstanding issues from a clinical pharmacology perspective. The first pertains to the product's drug-drug interaction potential and how best to mitigate the risk; the second pertains to the recommended dosing regimen. Both of these issues are discussed in greater detail below.

General clinical pharmacology considerations:

- Mechanism of Action: ZS is a cation exchanger that entraps potassium in exchange for hydrogen and sodium. ZS increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. ZS and the entrapped potassium are then excreted from the body in the feces. Binding of potassium reduces the concentration

of free potassium in the gastrointestinal lumen, thereby lowering serum potassium levels. ZS has high capacity to selectively entrap monovalent cations, specifically potassium and ammonium ions.

- Pharmacodynamics: In a study in healthy adult subjects, ZS administered as 5 g or 10 g once daily for four days caused a dose-dependent increase in fecal potassium excretion. A corresponding dose-dependent decrease in urinary potassium excretion and serum potassium was also observed. In patients with hyperkalemia treated with ZS 10 g three times a day for 48 hours, reductions in serum potassium were observed one hour after initiation of therapy and continued to decline over the 48-hour treatment period. As discussed in the Clinical Pharmacology Review, there is a close correlation between starting serum potassiums and effect size. Specifically, patients with higher starting serum potassiums have greater reductions in serum potassium, a finding that was also seen with patiromer.
- PK: As discussed in Section 4, no significant systemic absorption was observed in a non-GLP mass balance study in rats. In a clinical study in patients with hyperkalemia in which zirconium concentrations were measured in the urine and blood, zirconium concentrations were either undetectable or around the lower limit of quantification of the assay suggesting minimal absorption of zirconium from the product. Accordingly, conventional ADME studies were not conducted.

General Dosing Instructions: The Applicant is recommending (b) (4)

The Clinical Pharmacology Review team is recommending that the label specify a recommended starting dose of 10 g three times a day for 48 hours. For extended treatment, the Clinical Pharmacology Review team is recommending a dose of 10 g once daily, with monitoring of serum potassium levels and dose adjustment as needed at (b) (4) or longer intervals to a maximum of 15 g once daily or a minimum of 5 g every other day.

The Clinical Pharmacology Review contains the team's rationale for the proposed regimen, some of which is summarized below.

- Starting dose: Analyses performed by the review team focused on two populations: subjects with baseline serum potassium concentrations > 5.5 mmol/L and those with baseline serum potassium concentrations ≤ 5 mmol/L.

  As shown in Figure 3 of the Clinical Pharmacology Review, among subjects with baseline serum potassium concentrations >5.5 mmol/L, a greater proportion achieved the target serum potassium of 3.5 – 5 mmol/L when initiated on ZS 10 g three time a day as compared to 5 g three times a day (77% and 47%, respectively). The review also notes that a numerically higher proportion of subjects with baseline serum potassium concentrations ≤ 5.5 mEq/L achieved target potassium concentrations with 10 g three times a day as compared to 5 g three times a day (85% vs. 71%) and that the

risk of hypokalemia at the 10 g dose appears to be low. As noted by the Clinical Pharmacology Review team, based on these analyses, there does not appear to be an obvious advantage to having two different starting doses in labeling.

- Maintenance dose: Again, analyses performed by the review team focused on two populations: those with baseline serum potassium concentrations > 5.5 mmol/L and those with baseline serum potassium concentrations ≤ 5 mmol/L.

  As shown in the figure below, among subjects with higher baseline serum potassium concentrations, there is a dose-dependent increase in the proportion of subjects achieving the target range of 3.5 – 5.0 mmol/L mEq/L. Based on this analysis, it appears that some patients who are unable to achieve adequate control at 10 g once daily, will achieve control using the 15 g dose. In contrast, among subjects with lower baseline potassium concentrations, doses of 5, 10 and 15 g once daily appear to provide similar efficacy. Although the incidence of hypokalemia is greater at the 10 g as compared to the 5 g dose, the cases that were seen in the development program were mild. Finally because of the increased incidence of edema at the 15 g dose as compared to lower doses, a starting dose of 10 g once daily seems preferable to a starting dose of 15 g once daily.

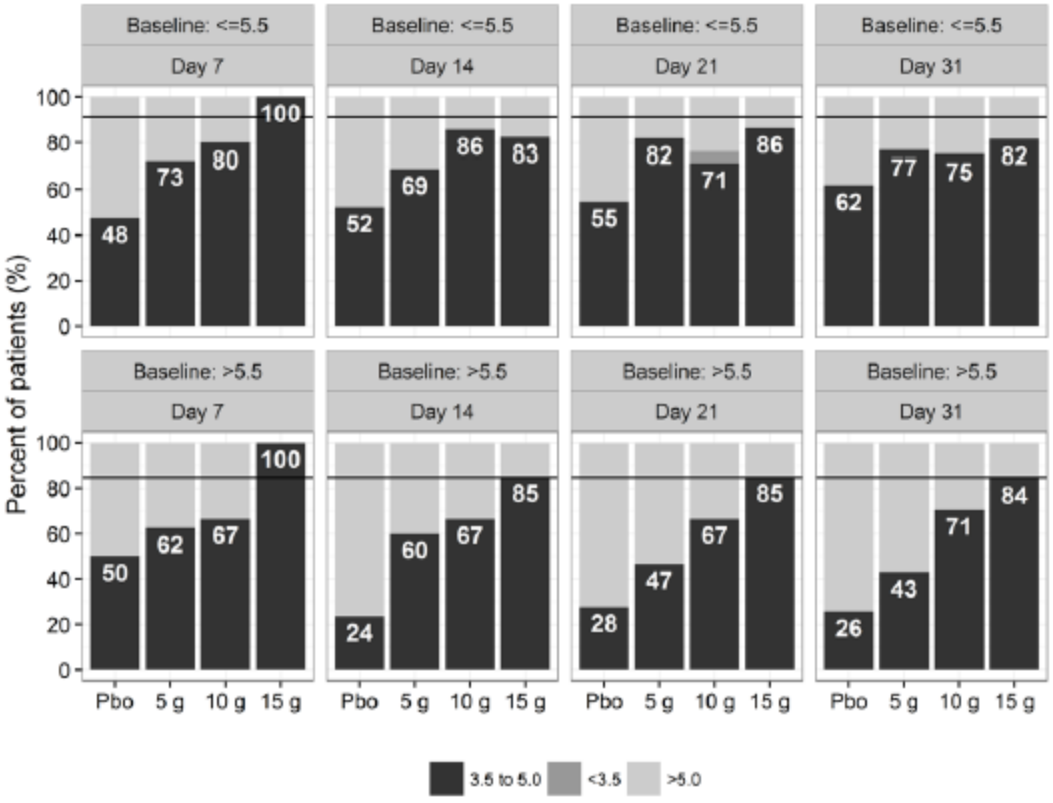


Figure 2: Percentage of patients achieving different serum potassium concentrations (3.5 to 5.0, < 3.5 and > 5 mmol/L) in the maintenance phase of Study ZS-004 by time and baseline serum potassium

Source: Clinical Pharmacology Review, Figure 4, page 14; Top panel: Patients with baseline serum potassium ≤ 5.5 mmol/L; Bottom panel: Patients with baseline serum potassium > 5.5 mEq/L. The solid

horizontal line represents the percentage of patients in the target range of 3.5 – 5.0 mEq/L at the end of the acute phase i.e., 10 g TID for 2 days).

Reviewer's comment: I think it is important that the label provide recommendations on reasonable time intervals before considering uptitration and the average time to reach steady state potassium levels following a dose change. A related but somewhat separate issue is how frequently serum potassium levels should be monitored in patients. While I believe the label should state that serum potassium levels need to be monitored, I do not think the label should provide more specific recommendations regarding the frequency of that monitoring.

Drug-drug interactions: As has been the practice to date with potassium and phosphate binders, an *in vitro* test system was initially used to screen for potential interactions between ZS and orally administered compounds that are commonly co-administered in the target population. Of the 39 compounds that were screened for interactions using physiologically relevant conditions:

- nine drugs (aluminum, amlodipine, calcium carbonate, dabigatran, E- and Z-norgestimate, levothyroxine, lithium, prasugrel and warfarin) exhibited a significant decrease in concentration (30% to 99%) in one or more media in the presence of ZS;
- seven drugs (atorvastatin, edoxaban, erythromycin, furosemide, lanthanum, sevelamer and valsartan) exhibited a significant increase in concentration or binding capacity (40% to 564%) in the presence of ZS;
- five drugs (clopidogrel, docusate, glipizide, ketoconazole and losartan) exhibited inconsistent findings over different pH ranges in different media in the presence of ZS.

According to the Clinical Pharmacology Review, because ZS changes the pH of the test media the Applicant conducted additional studies in which drugs that showed greater than a 10 % change in concentration in the presence of ZS were tested under conditions where the pH of the test media was adjusted but ZS was not added. The Applicant believes that these studies demonstrate that the observed *in vitro* DDI findings are solely the result of drug-induced changes in pH and associated pH- mediated solubility changes. The Clinical Pharmacology Team is not convinced. According to the Clinical Pharmacology Review, although many of these interactions appear to be the result of pH changes caused by ZS, there are drugs that showed concentration changes in the presence of ZS that cannot be explained solely by pH changes. This concern has been raised during discussions with the Applicant, and, most recently, at the Late Cycle Meeting held on March 23, 2016.

Following the Late Cycle Meeting, the Applicant submitted the results of additional testing, including the results of *in vivo* studies conducted in humans. Because the *in vivo* study reports were submitted late in the review cycle, these study reports are not addressed in the Clinical Pharmacology Review and recommendations for mitigating drug interaction potential cannot be made at this. Of note, at the Late Cycle Meeting, the Applicant was told that the late submission of the *in vivo* data would constitute a major amendment to the application and result in a three-month clock extension; however, given the inspection findings at the drug substance manufacturing, release and stability testing facility, a CR should be issued instead.

Demographic interactions/specific populations. Elimination and pharmacodynamic effects (i.e., potassium lowering) are not expected to be affected by intrinsic factors that are traditionally considered, such as age, gender, hepatic impairment, and renal impairment.

Bridging between the formulation(s) tested in clinical studies and the to-be-marketed formulation: As noted in the Clinical Pharmacology Review, the potassium exchange capacity (KEC) of the to-be-marketed product (target KEC of (b) (4) mmol/g; range of (b) (4) (b) (4) mmol/g) is similar to the KEC of the products used in the phase 3 trials (average KEC of (b) (4) mmol/g in ZS-003 and ZS-004, respectively).

QT assessment: Because the drug product is not significantly absorbed, no Thorough QT study was conducted. However, the Applicant did perform extensive analyses of ZS's effect on the QT interval. These analyses, which are described on pages 122-127 of the Clinical Review, indicate that ZS can affect the QT interval, an effect that appears to be mediated via changes in serum potassium and calcium. For the most part, the change in QT interval in subjects treated with ZS was small; however a small number of subjects in the phase 3 trials developed QT intervals > 500 ms or an increase from baseline > 60 ms. As shown in the table below, the proportion of subjects in the phase 3 trials who developed a QT interval > 500 ms or an increase > 60 ms was slightly greater in the ZS as compared to placebo treatment arms.

Table 1: Potentially clinically significant QTc interval changes in Studies ZS-003 and ZS-004

Parameter QTc[a] Interval Criteria, n (%)	Placebo[b] (N = 301)	Starting Dose of ZS in Extension			
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Subjects with baseline QTc Interval ≤ 500 msec	n = 290	n = 195	n = 107	n = 113	n = 54
Maximum QTc interval > 500 msec	0 (0.0)	2 (1.0)	3 (2.8)	2 (1.8)	2 (3.7)
Maximum QTc increase from baseline > 30 msec	31 (10.7)	23 (11.8)	12 (11.2)	25 (22.1)	16 (29.6)
Maximum QTc increase from baseline > 60 msec	3 (1.0)	4 (2.1)	4 (3.7)	5 (4.4)	2 (3.7)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 30 msec	0 (0.0)	2 (1.0)	2 (1.9)	1 (0.9)	1 (1.9)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 60 msec	0 (0.0)	2 (1.0)	2 (1.9)	1 (0.9)	0 (0.0)

Source: ISS, Table 12-5, page 119; based on acute phase baseline

6. Clinical Microbiology

ZS is not an antimicrobial therapy.

7. Clinical/Statistical- Efficacy

Principal support for efficacy is provided by two phase 3 studies, ZS-003 and ZS-004, described below. Additional support for efficacy is provided by Study ZS-002, a phase 2 study that is described in the Clinical and Statistical reviews and briefly discussed elsewhere in this review.

Overview of Phase 3 Trials

Study ZS-003

Study ZS-003 was a two-part trial, randomized, placebo-controlled, double-blind, dose-ranging trial. The study was conducted between November 2012 and October 2013 (first subject enrolled and last subject completed, respectively) at 65 sites in the United States, South Africa and Australia.

In the Acute phase, subjects with hyperkalemia (potassium 5.1-6.5 mmol/l) were randomized 1:1:1:1:1 to receive one of four doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered three times daily with meals for 48 hours. In the second phase (termed the "Subacute phase"), patients treated with ZS who achieved a potassium level between 3.5 and 5.0 mmol/L were re-randomized to receive once daily placebo or 1.25 g, 2.5 g, 5 g or 10 g of once daily ZS for 12 days, as shown in the table below.

Table 2: Dosing Groups in Study ZS-003

Acute Phase Treatment									
Placebo		ZS 1.25 g TID		ZS 2.5 g TID		ZS 5 g TID		ZS 10 g TID	
									
Subacute Phase Treatment *									
ZS 1.25 g QD	ZS 2.5 g QD	Placebo	ZS 1.25 g QD	Placebo	ZS 2.5 g QD	Placebo	ZS 5 g QD	Placebo	ZS 10 g QD

*Source: Table generated by CDTL; *Acute phase placebo subjects re-randomized to 1.25 g or 2.5 g ZS were not included in the efficacy analysis for the Subacute phase.*

The primary efficacy endpoint in the acute phase was the difference in the exponential rate of change in serum potassium levels (based on central laboratory values) during the initial 48 hours of study drug treatment between the placebo arm and ZS treatment arms. For the Subacute phase, the primary efficacy endpoint was the difference in the exponential rate of change in serum potassium levels (based on central laboratory values) over the 12-day treatment interval between the placebo and ZS treatment arms.

See the Statistical Review for a description of the random effects models used to test the primary efficacy endpoints in the acute and Subacute phases of the trial. In both phases, the primary efficacy endpoint was tested against placebo starting with the highest acute phase dose and proceeding to lower doses until statistical significance was no longer achieved. No multiple comparison control procedure was pre-specified for testing secondary endpoints.

Study ZS-004

Study ZS-004 was a two-part trial with an open-label acute phase and a month long randomized, double-blind, placebo-controlled withdrawal phase. The study was conducted between March and August 2014 (first subject enrolled and last subject completed, respectively) at 44 sites in the United States, South Africa and Australia.

In the first part of the trial (termed the “acute phase”), subjects with hyperkalemia (mean i-STAT potassium value ≥ 5.1 mmol/l at screening) received open-label ZS at a dose of 10 g three times a day for 24-72 hours. In the second phase (termed the “maintenance phase”), subjects who achieved normokalemia (potassium of 3.5 to 4.9 mmol/l on the morning of Study Day 2, 3 or 4) were randomized 4:4:4:7 to receive one of three doses of ZS (5 g, 10 g, and 15 g) or placebo once daily for 28 days.

The primary endpoint was the model-based least squares mean of all available serum potassium values (based on central potassium values) during the maintenance phase from Days 8 to 29; the primary population for the efficacy analysis was the maintenance phase Intent-to-Treat population. Secondary efficacy endpoints for the maintenance phase

included the number of normokalemic days during maintenance phase Study Days 8 to 29, the proportion of subjects who remained normokalemic at maintenance phase Study Day 29, and the maintenance phase mean serum potassium intra-subject standard deviation.

The pre-specified hierarchical testing procedure used to control type 1 error is shown in the figure below. For information on the model used to test the first endpoint in the testing chain (the exponential rate of change in serum potassium in the acute phase), and additional detail regarding the statistical methodology used to test the trial's primary endpoint, see the Statistical Review.

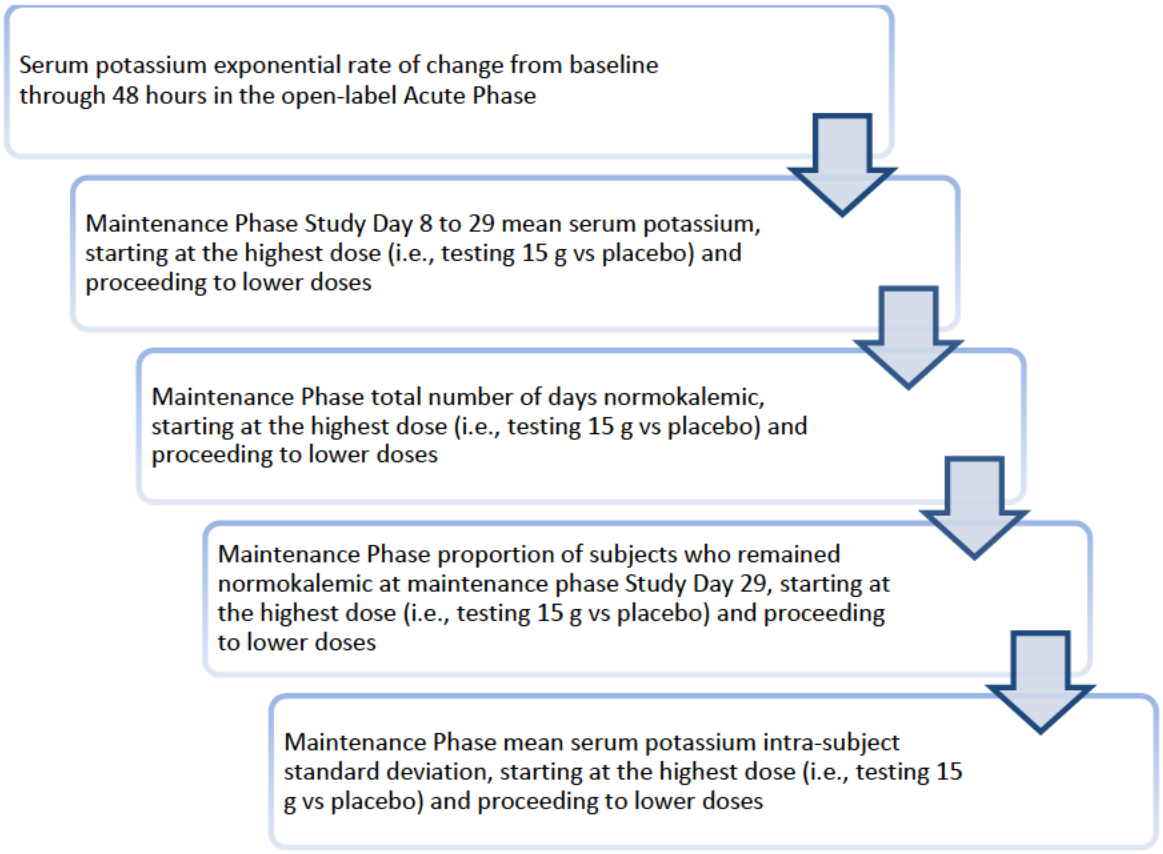


Figure 3: Hierarchical testing procedure to control the type 1 error in Study ZS-004

Source: Figure generated by CDTL

Phase 3 Trial Results

Demographics: Both the clinical and statistical reviews contain information on key demographic characteristics by trial, study phase and treatment arm. In the acute phase of Study ZS-004, the mean age of patients was 64 years, 58% of subjects were men, 83% were Caucasian, and 14% were Black or African American. The most commonly reported causes of hyperkalemia were as follows (categories are not mutually exclusive): use of RAAS inhibitor medication (70%), CKD (69% based on an eGFR < 60 mL/min), diabetes mellitus (66%) and heart failure (36%). For the most part, baseline demographic characteristics were similar in the acute phase of Study ZS-003.

With regard to baseline potassium levels, the baseline average serum potassium in the acute phase of Study ZS-004 was 5.6 (range 5.1-7.4 mmol/L) and 46% of subjects had a baseline serum potassium < 5.5 mmol/L, 39% had a baseline serum potassium ≥5.5 to < 6.0 mmol/L, and 15% had a baseline serum potassium ≥ 6.0 mmol/L. Baseline serum potassium levels tended to be lower in Study ZS-003; depending on the treatment arm, between 15% and 28% of subjects had a serum potassium > 5.5 mmol/L in the acute phase of the study.

Disposition:
Approximately 97% of subjects completed the open-label acute phase of Study ZS-004; a similar proportion of subjects completed the placebo-controlled acute phase of Study ZS-003 (range of 96 to 99% depending on the treatment arm).

Of the 258 subjects enrolled in the open-label Acute Phase of the study ZS-004, 92% (237 subjects) entered the maintenance phase of Study ZS-004. As discussed in Dr. Xiao's clinical review, reasons for not entering the maintenance phase reported for two or more subjects included hypokalemia, hyperkalemia, and withdrawal of consent (in the acute phase).

In contrast to Study ZS-004, out of the 595 subjects treated with ZS in the Acute Phase of Study ZS-003, only 75% (447 subjects) continued into the Subacute Phase. The main reason given for not entering the Subacute phase was "hypo-or hyperkalemia." A previously noted, patients needed to achieve a potassium level in the target range (between 3.5 and 5.0 mmol/L) in order to be randomized into the Subacute Phase. As shown in the table below, many subjects who did not achieve this target level were in the lower dose groups.

Table 3: Subjects treated with ZS in the Acute Phase who did not enter the Subacute phase by reason

Reason, n (%)	**ZS 1.25 g TID (N = 154)**	**ZS 2.5 g TID (N = 141)**	**ZS 5 g TID (N = 158)**	**ZS 10 g TID (N = 143)**
Did not enter Subacute Phase	60 (39.0)	37 (26.2)	19 (12.0)	16 (11.2)
Consent Withdrawn	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.7)
Sponsor's Decision	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypo- or Hyperkalemia*	60 (39.0)	36 (25.5)	18 (11.4)	15 (10.5)

*Source: Clinical Study Report for ZS-003, Table 10-2, page 69; *Of the 158 patients in the placebo arm, 61 (39%) did not enter the Subacute Phase for this reason.*

Subject disposition in the maintenance phase of Study ZS-004 is shown in the table below. Across the treatment arms, a similar proportion of study subjects completed the maintenance phase of the study (~86-89%). Relative to Study ZS-004, a higher proportion of subjects completed the Subacute phase of Study ZS-003 (range 91 to 98% depending on the treatment arm). As previously noted, the maintenance phase of Study ZS-004 was 28 days whereas the Subacute phase of Study ZS-003 was only 12 days; other differences in the design of the two studies likely also contributed to the lower discontinuation rate in Study ZS-003.

Table 4: Disposition in the Maintenance Phase of Study ZS-004

Disposition, n (%)	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo	ZS 5 g QD	ZS 10 g QD	ZS 15 g QD
Randomized	85	45	51	56
Completed Maintenance Phase	75 (88.2)	40 (88.9)	44 (86.3)	49 (87.5)
Discontinued Maintenance Phase	10 (11.8)	5 (11.1)	7 (13.7)	7 (12.5)
Adverse event	0 (0.0)	3 (6.7)	0 (0.0)	1 (1.8)
Consent withdrawn	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Subject compliance	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator's decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Sponsor's decision	2 (2.4)	0 (0.0)	2 (3.9)	1 (1.8)
Hypo- or hyperkalemia	3 (3.5)	0 (0.0)	3 (5.9)	1 (1.8)
Met ECG withdrawal criteria	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.6)
Other	2 (2.4)	1 (2.2)	2 (3.9)	1 (1.8)

Source: Clinical Study Report for ZS-004, Table 10-3, page 84

Efficacy Findings:
As shown in the table below, Study ZS-003 met its primary endpoint in both phases of the trials. Based on the prespecified closed testing procedure, the 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were statistically significantly superior to placebo for the exponential decrease in serum potassium during the Acute Phase and the 10 g and 5 g QD doses of ZS were statistically significantly superior to placebo for the exponential decrease in serum potassium during the Subacute Phase.

Table 5: Primary Efficacy Endpoints findings in Acute and Subacute phases of Study ZS-003

Exponential rate of change in serum potassium	
Acute phase (48 hours)	**Subacute phase (12 days)**
ZS 10 g: $p < 0.0001$ ZS 5 g: $p < 0.0001$ ZS 2.5 g: $p = 0.0009$ ZS 1.25 g: $p = 0.50$	ZS 10 g: $p < 0.0001$ ZS 5 g: $p = 0.008$ ZS 2.5 g: $p = 0.84$

Source: Dr. Birkner's Review, Table 15, page23

As shown below, Study ZS-004 also met its primary endpoint, as well as the first endpoint in the hierarchical testing procedure. During Study Days 8 to 29 of the maintenance phase, all three doses (5 g, 10 g, and 15 g) of once daily ZS maintained mean serum potassium at lower levels than placebo (placebo LS Mean of 5.1 mmol/L vs. 4.8, 4.5, and 4.4 mmol/L for 5 g, 10 g, and 15 g, respectively, p-value ≤ 0.001 for all doses).

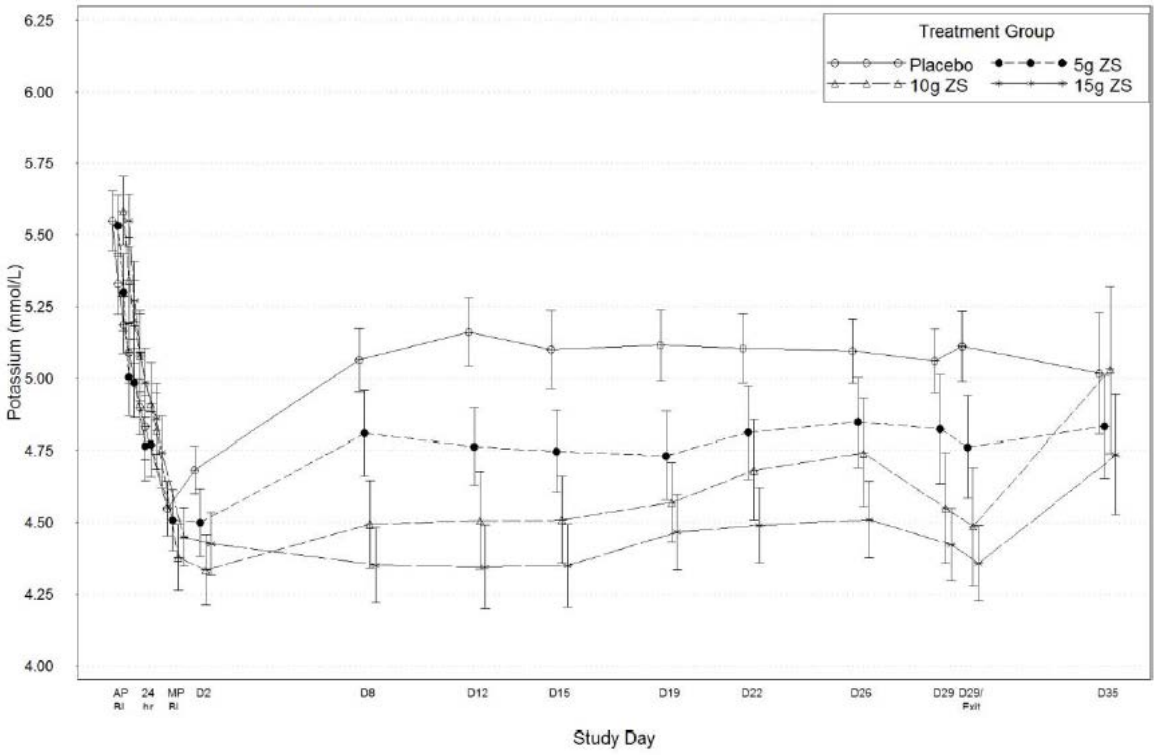
Table 6: Results for the First Four Endpoints Specified in the Hierarchical Testing Procedure for Study ZS-004

Endpoint	Observed p-value
Acute Phase serum potassium exponential rate of change from baseline through 48 hours (Null hypothesis: exponential rate of change from baseline equals 0)	< 0.0001
Primary Efficacy Endpoint	
Maintenance Phase Days 8-29 mean serum potassium (Null hypothesis: ZS 15 g QD = placebo)	< 0.0001
Maintenance Phase Days 8-29 mean serum potassium (Null hypothesis: ZS 10 g QD = placebo)	< 0.0001
Maintenance Phase Days 8-29 mean serum potassium (Null hypothesis: ZS 5 g QD = placebo)	0.0001

Source: Clinical Study Report for ZS-004, Table 11-7, page 94; Results confirmed by Dr. Birkner

Mean potassium over time in Study ZS-004 are shown in the figure below. During the open-label acute phase, in which all subjects were treated with ZS 10 g TID, potassium levels fell. Following the switch to a once daily regimen of ZS or placebo, mean potassium levels rose in the placebo and ZS 5 g treatment arms but not to pre-treatment levels. In contrast, mean potassium levels in the 10 and 15 g ZS treatment groups remained close to levels achieved at the end of the acute treatment period.

Table 7: Maintenance Phase: Mean Serum Potassium Over Time – ITT Population



Source: Clinical Study Report for ZS-004, Figure 11-3, page 104

The results of the hierarchical testing procedure for secondary efficacy endpoints in Study ZS-004 are shown in the table below. The mean number of normokalemic days was statistically significantly greater in each of the ZS treatment groups as compared to placebo and increased with increasing dose of ZS (7.4/22 days for placebo, 13.4/22 days for ZS 5 g, 13.9/22 days for ZS 10 g, and 16.8/22 days for ZS 15 g). In addition, statistically significantly higher proportions of subjects had mean serum potassium levels in the normal range (3.5 mmol/L-5.0 mmol/L) at maintenance phase Study Day 29/Exit while on ZS as compared to placebo (71%, 76%, and 85% at the 5 g, 10 g and 15 g dose, respectively, compared with 48% on placebo).

Table 8: Results of Hierarchical Testing Procedure for the Secondary Efficacy Endpoints in Study ZS-004

Secondary Maintenance Phase Efficacy Endpoints	P-value
Maintenance Phase Days 8-29 total number of days normokalemic (Null hypothesis: ZS 15 g QD = placebo)	< 0.0001
Maintenance Phase Days 8-29 total number of days normokalemic (Null hypothesis: ZS 10 g QD = placebo)	< 0.0001
Maintenance Phase Days 8-29 total number of days normokalemic (Null hypothesis: ZS 5 g QD = placebo)	0.0001
Maintenance Phase Day 29/Exit proportion of subjects normokalemic (Null hypothesis: ZS 15 g QD = placebo)	< 0.0001
Maintenance Phase Day 29/Exit proportion of subjects normokalemic (Null hypothesis: ZS 10 g QD = placebo)	0.002
Maintenance Phase Day 29/Exit proportion of subjects normokalemic (Null hypothesis: ZS 5 g QD = placebo)	0.015
Maintenance Phase mean S-K intra-subject standard deviation (Null hypothesis: ZS 15 g QD = placebo)	0.33
Maintenance Phase mean S-K intra-subject standard deviation (Null hypothesis: ZS 10 g QD = placebo)	-
Maintenance Phase mean S-K intra-subject standard deviation (Null hypothesis: ZS 5 g QD = placebo)	-

Source: Clinical Study Report for ZS-004, Table 11-7, page 94; Results confirmed by Dr. Birkner

Data from phase 2 supporting dose-response and dose selection for phase 3

Study ZS-002, a phase 2 study discussed in the clinical and statistical reviews also provides support for efficacy, as well as the basis for dose selection in phase 3. In brief, Study ZS-002 was a placebo-controlled, dose-ranging trial evaluating the safety, tolerability, and efficacy of three different doses of ZS administered three times daily for 48 hours to subjects with moderate chronic kidney disease and hyperkalemia (serum potassium between 5 to 6.0 mmol/L). The primary efficacy endpoint was the difference in the exponential rate of change in serum potassium levels during the initial 48 hours of study drug treatment between placebo-treated subjects and ZS-treated subjects. The primary endpoint analysis was performed in the ITT population and a closed testing procedure was used to test from the highest to lowest dose for the primary efficacy endpoint. The study met its primary efficacy endpoint at the 10 g ($p < 0.0001$) and 3 g ($p = 0.048$) three times daily doses, but not at the 0.3 g three times daily dose. According to the sponsor, (b) (4) dosages lower than 3 g were also evaluated in phase 3.

Subpopulations

As might be expected given the drug's mechanism of action, efficacy was observed across the subgroups that were examined, including subgroups defined by age, race, sex, region

(US vs non-US), comorbidities (i.e., diabetes, chronic kidney disease, and heart failure) and concomitant medications (i.e., RAAS inhibitor use). Patients with higher baseline serum potassium levels appeared to have greater reductions in serum potassium than patients with lower levels. In addition, some analyses suggested a larger treatment effect in Blacks/African Americans than in the population as a whole; however, these analyses were based on a small number of subjects. For additional information on the results of subgroup analyses, see pages 34-40 of the Statistical Review and pages 53-56 and 78-80 of the Clinical Review.

Data supporting durability of efficacy

Data from studies ZS-003 and ZS-004 indicate that the potassium lowering effect is durable over up to 12 and 28 days of treatment, respectively (see previously presented efficacy findings).

Data on efficacy beyond 28 days is provided by an open-label uncontrolled extension study to Study ZS-004 which was submitted as part of the applicant's 120-day safety update. The primary objective of Study ZS-004E was to evaluate safety and tolerability during extended dosing of ZS for up to 11 months). The secondary objective was to evaluate the efficacy of ZS in maintaining normokalemia during this time interval.

As discussed on pages 87-88 of the Clinical Review, the applicant's analyses of these data suggest that ZS is effective in maintaining potassium levels near the target range during up to 11 months of extended treatment.[2] However, the late date at which the statistical analysis plan was finalized (approximately 1 week prior to trial database lock) and the high drop-out rate in the trial (only 64% of the 125 subjects who enrolled in the trial completed the extended dosing phase) complicate interpretation of these analyses. According to the Clinical Review, review of the reasons for dropout did not suggest that lack of efficacy was responsible for dropouts and the main reasons for dropout included progression of chronic kidney disease, adverse events, and patient compliance. As also noted in Dr. Xiao's review, an ongoing long-term open label study (Study ZS005) is expected to provide additional information on the maintenance of potassium control during long-term treatment with ZS.

Conclusions on Substantial Evidence of Effectiveness: The review team believes that the application provides substantial evidence of ZS's effectiveness in lowering serum potassium levels in patients with hyperkalemia, an accepted surrogate endpoint in this population, and in maintaining normokalemia in patients with hyperkalemia. I agree with their assessment.

[2] According to the Clinical Review, the applicant focused on cut-points of ≤ 5.1 and ≤ 5.5 mmol/L, as opposed to defining the normal range as 3.5 to 5.0, as was done in ZS-004, and using a cut-point of ≤ 5.0.

8. Safety

Adequacy of exposure and safety assessments
The size of the safety database, clinical safety assessments, and duration of exposure are adequate to assess common adverse reactions and the safety topics of interest as outlined below.

According to Dr. Xiao's review, as of July 15 2015, 1,592 subjects with hyperkalemia have been exposed to at least one dose of ZS in clinical trials. Of these, 1,009 subjects were enrolled in trials that have been completed and that were reviewed as part of this NDA (i.e., studies ZS-002, ZS-003, ZS-004 and ZS-004E). The remaining subjects (583 subjects) are enrolled in Study ZS-005, an ongoing open-label study evaluating the long-term safety and efficacy of ZS. As of the aforementioned data cut-off date, a total of 262 patients with hyperkalemia have been treated with ZS for at least 6 months and 79 for one year.

Safety topics of interest
Dr. Xiao's review focuses on potential risks of ZS given the drug's mechanism of action, and the experience with the approved potassium cation exchange resins. These potential risks include hypokalemia, adverse GI effects, sodium absorption leading to edema and fluid overload, non-specific binding to other cations, and the risk of clinically significant alkalosis. ZS's potential to interact with other oral medications was explored initially via *in vitro* studies, and, subsequently via DDI studies in normal healthy volunteers; for further discussion of evaluations focused on ZS's DDI potential, see the Clinical Pharmacology Section of this review.

Hypokalemia: Serum potassium levels were monitored in the phase 3 trials and the open-label extension study, ZS-004.[3] As a whole, analyses of the adverse event and laboratory data were reassuring as relates to the risk of hypokalemia.

- Acute phase (pooled data): In the acute phase of the short-term studies (Studies ZS-004, ZS-003 and ZS-002), 0.4% of subjects treated with ZS (4/913) developed a serum potassium < 3.5 mmol/L, including three out of 425 subjects treated with ZS 10 g TID (0.7%) and one subject treated with ZS 3 g TID. No subject developed a serum potassium < 3.0 mmol/L.
- Extended dosing (pooled data): During up to 12 days of once daily dosing in Study ZS-003 and up to 28 days of once daily dosing in Study ZS-004, 19 out of 479 (4%) subjects treated with ZS developed a serum potassium < 3.5 mmol/L including one (0.5%), seven (6.1%), and 11 (19.6%) subjects treated with ZS 2.5 g, 10 g, and 15 g once daily, respectively. No subject developed a serum potassium < 3 mmol/L as

[3] During the Subacute phase of Study ZS-003, serum potassium was measured daily for the first 3 days after initiating once daily dosing and then on days 6 and 12 of once daily dosing. During the extended dosing phase of Study ZS-004, serum potassium was measured on days 1 and 2 and then every three to four days for the duration of the 28-day treatment period. During Study ZS 004E, serum potassium was measured weekly starting at day 8 through day 57 and then approximately every 28 days.

assessed by central laboratory values, although, as discussed below, some of these subjects had a potassium < 3.0 mml/L on i-STAT.

- Acute and extended dosing phases of Study ZS-004: Of the dosing regimens evaluated in the phase 3 studies, the dosing regimens evaluated in Study ZS-004 more closely match the regimen recommended in labeling. The incidence of hypokalemia in Study ZS-004 is shown in the table below. Of the 11 subjects who developed confirmed hypokalemia in Study ZS-004 (defined as 2 serum potassium values taken 10 minutes apart that were both < 3.5 mmol/L or a single value < 3.5 mmol/L in the absence of a second sample), five were in the ZS 10 g QD group and six were in the ZS 15 QD group (corresponding to ~10% of subjects enrolled in each of these treatment arms). Five of the 11 subjects with confirmed hypokalemia were managed with dose reductions, while six were not. Of the five who were managed with dose reductions, four were able to complete dosing and one was discontinued from treatment for meeting protocol-specified stopping rules for QTc prolongation. Of the six subjects who were not managed with dose reductions, four were discontinued for hypokalemia with a serum potassium of < 3.0 mmol/L on i-STAT (and a somewhat higher value on central measurement), one was discontinued for meeting protocol specified stopping rules for QTc prolongation and one completed dosing.

Table 9: Hypokalemia in Study ZS-004

	Acute Phase Treatment 10 g ZS									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	N	%	n	%	n	%	n	%	n	%
Confirmed hypokalemia[1]	0	0	5	9.8	6	10.7	11	7.24	0	0
Any values <3.5 mmol/L	0	0	7	13.7	11	19.6	18	11.8	0	0
Any values <3.0 mmol/L	0	0	1	2.0	0		1	<1	0	0

Source: Analysis performed by Dr. Christine Garnett; [1]defined as 2 K values taken 10 min apart that were both <3.5mmol/L or a single K value <3.5 mmol/L in absence of a second sample.

- Long-term treatment: During long-term treatment in Study ZS 004 E (median days on treatment= 252; range= 1 to 338 days), seven of 123 (5.7%) subjects developed a serum potassium level < 3.5 mmol/L (defined as two serum potassium values taken 10 minutes apart that were both < 3.5 mmol/L or a single serum potassium value < 3.5 mmol/L in the absence of a second sample). Of these subjects, one developed a potassium level <3.0 mmol/L and was discontinued from the study after 8 days of dosing with ZS 10 g QD due to hypokalemia (potassium value of 2.8 mmol/L). Four of the six subjects who developed a serum potassium between 3 and 3.4 mmol/L had their dose reduced. According to the provided narrative for the subject who developed a serum potassium of 2.8 mmol/L, the subject had received placebo during the extended dosing phase of Study ZS-004 and was initiated on ZS 10 g once daily upon enrollment into Study ZS-004E. At the time of initiation of ZS in Study ZS-004E, his serum potassium was in the normal range (baseline serum potassium for ZS-004E of 4.3 mmol/L based on central laboratory assessment).

Sodium absorption leading to edema and fluid overload:

As described in the Clinical Review, a number of analyses were performed to assess for potential risk associated with sodium absorption from ZS. These analyses, which were performed by Dr. Christine Garnett, focused on the data from Study ZS-004. This study evaluated a higher once daily dose than Study ZS-003 (15 gm once daily as compared to 10 gm once daily) and evaluated a longer duration of treatment than Study ZS-003 (28 days as compared to 12 days). The dosing regimen used in Study ZS-004 also more closely mirrors the regimen that will be used in clinical practice (for the most part, the doses evaluated in Study ZS-003 were lower than those recommended in labeling). Dr. Garnett's analyses, discussed below, show a dose-dependent increase in the incidence of AEs of edema/fluid overload.

As shown in the table below, based on the MedDRA SMQ for Haemodynamic oedema, effusions and fluid overload, there was a dose-dependent increase in the incidence of AEs of edema/fluid overload in Study ZS-004, ranging from 4.4% in subjects treated with ZS 5 g once daily (the incidence in the placebo arm was 2.4%) to 16.1% of subjects administered ZS 15 g once daily.

Table 10: MedDRA SMQ Haemodynamic oedema, effusions and fluid overload: Adverse events by treatment arm in Study ZS-004

MedDRA HLT and PT	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	***2***	**4.4**	**3**	**5.9**	**9**	**16.1**	**14**	**9.2**	**2**	**2.4**
Oedema NEC	1	2.2	3	5.9	8	14.3	12	7.9	2	2.4
Generalised oedema	0	0	0	0	2	3.6	2	1.3	0	0
Oedema	1	2.2	0	0	1	1.8	2	1.3	0	0
Oedema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Total fluid volume increased	1	2.2	0	0	1	1.8	2	1.3	0	0
Fluid overload	1	2.2	0	0	0	0	1	0.7	0	0
Fluid retention	0	0	0	0	1	1.8	1	0.7	0	0
Joint related signs and symptoms	0	0	0	0	1	1.8	1	0.7	0	0
Joint swelling	0	0	0	0	1	1.8	1	0.7	0	0

Source: Analysis performed by Dr. Christine Garnett

Analyses of Study ZS-004 using the MedDRA SMQ for cardiac failure are shown below. Although reports of edema were not uncommon, reports of AEs specifically mentioning cardiac failure or other AEs included in the SMQ for cardiac failure (such as pulmonary edema) were uncommon in Study ZS-004. During the extended dosing phases of the phase 3 trials, SAEs such as congestive heart failure, pulmonary edema and generalized edema were reported in a few subjects (including subjects receiving placebo and those assigned to lower and higher ZS dose groups); however, for the most part, the reported AEs were mild to moderate in severity.

Table 11: **MedDRA SMQ for Cardiac Failure: Adverse events in Study ZS-004**

MedDRA HLT and PT	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	**2**	**4.4**	**4**	**7.8**	**9**	**16.1**	**15**	**9.9**	**2**	**2.4**
Oedema NEC	1	2.2	3	5.9	7	12.5	11	7.2	2	2.4
Oedema	1	2.2	0	0	1	1.8	2	1.3	0	0
Oedema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Heart failures NEC	1	2.2	1	2.0	2	3.6	4	2.6	0	0
Cardiac failure	0	0	0	0	1	1.8	1	0.7	0	0
Cardiac failure acute	0	0	1	2.0	0	0	1	0.7	0	0
Cardiac failure congestive	1	2.2	0	0	1	1.8	2	1.3	0	0

Source: Analysis performed by Dr. Christine Garnett

AEs of edema, heart failure and pulmonary edema were reported in the long-term extension Study, ZS-004E, a study that lacked a control arm (see table below). Three SAEs of cardiac failure, with onset from 6 to 103 days were reported in Study ZS-004E; one SAE lead to permanent discontinuation of study drug.

Table 12: MedDRA SMQ Cardiac Failure: Adverse events in Study ZS-004E

MedDRA HLT and PT	ZS (N=123)	
	n	%
Oedema NEC	14	11.4
Oedema	4	3.3
Oedema peripheral	10	8.1
Heart failures NEC	5	4.1
Cardiac failure	3	2.4
Cardiac failure congestive	2	1.6
Pulmonary oedemas	2	1.6

Source: Analysis performed by Dr. Christine Garnett

Dr. Garnett also performed analyses to evaluate whether certain subgroups were more vulnerable to the sodium load provided by ZS. As shown in the following table, the risk of edema/fluid overload appeared to be more pronounced in subjects with CKD, diabetes and, to a lesser extent, in those with a reported history of heart failure. In other subgroup analyses described in the Clinical Review, the risk of edema associated with ZS treatment appeared to be greater in subjects with lower as compared to higher levels of GFR and in those who were not taking a diuretic at baseline or who were on a calcium channel blocker at baseline.

Table 13: MedDRA SMQ Haemodynamic oedema, effusions and fluid overload: Adverse events by Subgroup in Study ZS-004

Subgroup	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total	**2**	**4.4**	**3**	**5.9**	**9**	**16.1**	**14**	**9.2**	**2**	**2.4**
Patients with CKD (N=152)	2	4.4	3	5.9	9	16.1	14	9.2	1	1.2
Patients with No CKD (N=85)	0		0		0		0		1	1.2
Patients with CHD (N=87)	1	2.2	2	3.9	5	8.9	8	5.6	1	1.2
Patients with No CHD (N=150)	1	2.2	1	2.0	4	7.1	6	4.0	1	1.2
Patients with DIAB (N=157)	2	4.4	3	5.9	7	12.5	12	7.9	0	
Patients with No DIAB (N=80)	0		0		2	3.6	2	1.3	2	2.4

Source: Analysis performed by Dr. Christine Garnett
Abbreviations: ZS=sodium zirconium cyclosilicate; CKD=chronic kidney disease, CHD=chronic heart disease, DIAB=diabetes.

Other analyses that were performed, including analyses of vital sign data (changes in body weight and blood pressure), are also described in the Clinical Review. Like the AE analyses, the weight and blood pressure analyses suggest that the product provides a sodium load to patients, particularly at the 15 g dose.

GI safety and tolerability: Analyses pertaining to GI safety and tolerability are provided on pages 107 to 109 of the Clinical Review; analyses performed by Dr. Garnett using the MedDRA SOC Gastrointestinal Disorders are shown below. The analyses shown in the Clinical Review and those performed by Dr. Garnett do not suggest an increased incidence of GI adverse events in the ZS treatment arms as compared to placebo.

Table 14: MedDRA SOC Gastrointestinal Disorders: Adverse Events by treatment arm in the Acute Phase of Study ZS-003

MedDRA Preferred Term	Acute Phase (48 h)									
	1.25 g ZS TID (N=154)		2.5 g ZS TID (N=141)		5 g ZS TID (N=157)		10 g ZS TID (N=143)		Placebo (N=158)	
	n	%	n	%	n	%	n	%	n	%
Diarrhoea	5	3	2	1	3	2	1	1	4	3
Nausea	2	1	0		1	1	0		1	1
Abdominal pain	1	1	0		0		0		0	
Constipation	1	1	1	1	1	1	3	2	1	1
Abdominal pain upper	0		0		0		1	1	0	
Frequent bowel movements	0		0		1	1	0		0	
Gastritis	0		0		0		0		1	1
Vomiting	0		0		0		1	1	2	1

Source: Analysis performed by Dr. Christine Garnett

Table 15: MedDRA SOC Gastrointestinal Disorders: Adverse Events by treatment arm in the SubAcute Phase of Study ZS-003

MedDRA Preferred Term	Acute Phase (48 h)											
	2.5 g ZS TID				5 g ZS TID				10 g ZS TID			
	Subacute Phase (14 days)											
	ZS QD		Placebo		ZS QD		Placebo		ZS QD		Placebo	
	N=54		N=46		N=65		N=68		N=63		N=61	
	n	%	n	%	n	%	n	%	n	%	n	%
Vomiting	2	4	1	2	3	5	0		0		0	0
Diarrhoea	2	4	2	4	2	3	3	4	0		0	0
Dyspepsia	0		0		2	3	0		0		0	0
Abdominal distension	0		0		1	2	0		0		0	0
Constipation	0		0		0		0		2	3	0	0
Flatulence	0		0		0		1	1	0		0	0
Gastric ulcer	0		0		0		1	1	0		0	0
Nausea	2	4	1	2	0		0		1	2	0	0

Source: Analysis performed by Dr. Christine Garnett; 1.25 g ZS QD vs placebo comparison results not shown

Table 16: MedDRA SOC Gastrointestinal Disorders: Adverse Events by treatment arm in Study ZS-004

MedDRA Preferred Term	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment (30 days)									
	5 g ZS QD (N=45)		10 g ZS QD (N=51)		15 g ZS QD (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	N	%	n	%
Diarrhea	1	2.2	0	0	3	5.4	4	2.6	2	2.3
Constipation	1	2.2	1	2.0	1	1.8	3	2.0	7	8.2
Dyspepsia	2	4.4	0	0	0	0	2	1.3	0	0
Vomiting	1	2.2	1	2.0	0	0	2	1.3	1	1.2
Diverticulum intestinal	1	2.2	0	0	0	0	1	0.7	0	0
Small intestinal obstruction	1	2.2	0	0	0	0	1	0.7	0	0
Stomatitis	0	0	0	0	1	1.8	1	0.7	0	0
Abdominal pain	1	2.2	0	0	0	0	1	0.7	1	1.2
Rectal haemorrhage	0	0	0	0	0	0	0	0	1	1.2
Dry mouth	0	0	0	0	0	0	0	0	1	1.2

Source: Analysis performed by Dr. Christine Garnett; AEs are pooled from the acute and maintenance phases

Clinically significant alkalosis: Because ZS binds ammonium, ZS has the potential to increase serum bicarbonate levels. During up to 12 days of dosing in Study ZS-003 and up to 28 days in Study ZS-004, ZS caused a small dose-dependent increase in serum bicarbonate concentrations (1.1 mmol/L at 5 g once daily and 2.3 mmol/L at 10 g once daily and 2.6 mmol/L at 15 g once daily as compared with a mean increase of 0.6 mmol/L in patients treated with placebo). One subject out of 59 (1.8%) treated with ZS 15 g had a shift from the normal range to a value above the normal range for serum bicarbonate as compared to three subjects out of 301 (1.0%) in the placebo arm. No subject developed a serum bicarbonate > 35mmol/L. In summary, safety analyses do not suggest a risk of clinically significant alkalosis at the doses proposed for use.

Other Cations: According to the Clinical Review, no clinically meaningful changes in serum magnesium were observed during the phase 3 trials. Small dose-related mean decreases in calcium values were observed in the ZS treatment arms (-0.13 mg/dL, -0.18 mg/dL and -0.28 mg/dL in the $\leq$ 3 g, 5 g and 10 g TID dose groups as compared with a change of -0.07 mg/dL in the placebo arm). No subject developed a calcium < 7.0 mg/dL during the Acute or Extending Dosing Phases of the phase 3 trials.

Other notable findings: The clinical review also contains analyses of deaths, SAES, discontinuations due to AEs and common AEs. These analyses do not raise significant safety concerns.

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because the clinical trial design and efficacy endpoints are acceptable.

10. Pediatrics

There was no agreed-upon pediatric study plan prior to NDA submission. To address its PREA requirement, the Applicant has proposed to conduct a deferred, open-label, dose-escalation safety and pharmacodynamic study in children 0 to (b) (4) years of age with hyperkalemia. As noted in the PeRC PREA template, there are aspects of the protocol that require further discussion; however, the overall design of the deferred study that will be conducted to address the applicant's PREA requirement is acceptable.

Key considerations related to the design of the trial include the following:

(b) (4)

For additional information on outstanding issues related to the design of the pediatric trial, see the PeRC template

11. Other Relevant Regulatory Issues

Financial disclosures and Good Clinical Practice: According to Dr. Xiao's review, the applicant has adequately disclosed financial arrangements with clinical investigators and studies were conducted in compliance with U.S. regulations pertaining to Good Clinical Practice. Two investigators who participated in Study ZS-004 had financial interests or arrangements to disclose; however, based on the site analysis performed by Dr. Birkner, data from these investigator sites had no impact on the overall efficacy results.

Office of Scientific Investigations (OSI) audits: Three clinical investigator site inspections and a sponsor inspection were conducted. According to OSI, no objectionable conditions or deficiencies were observed during the sponsor inspection and no significant deficiencies were noted at two of the clinical sites that were inspected (the sites received a classification of "No Action Indicated"). At the third clinical site, minor deficiencies were observed during the inspection with respect to failure to follow the investigational plan and incomplete drug

disposition records, and a Form FDA 483 was issued. OSI considers these issues to be minor and believes that they are unlikely to significantly impact the integrity of the data submitted in support of the NDA. I agree with this assessment.

Application Integrity Policy (AIP): The applicant's firm is not listed in FDA's Application Integrity Policy list (i.e., the FDA's list of firms that were notified that FDA is deferring substantive scientific review of one or more of the firm's applications and/or is proceeding to withdraw the approved applications).

12. Labeling

Prescribing Information
Marked up labeling was sent via email to the Applicant on April 26, 2016. At this time, key outstanding issues include:

- Dosage and Administration. As discussed in Section 5 (Clinical Pharmacology) the applicant is proposing a maximum recommended daily dose of (b) (4) g once daily during maintenance treatment, whereas the clinical pharmacology team is recommending a maximum daily dose of 15 g once daily during the maintenance phase, as well as other changes to the dosing regimen proposed by the Applicant.
- Warnings and Precautions. At this time, the review team believes that a Warning and Precaution related to sodium absorption leading to edema and fluid overload is warranted. The review team has also proposed a Warning and Precaution related to Worsening of Gastrointestinal Motility, and specifically, avoiding use of the drug in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because the drug may be ineffective and may worsen gastrointestinal conditions (patiromer's labeling contains a similar warning).
- Drug-drug interactions. As discussed in Section 5 (Clinical Pharmacology), dosing instructions for mitigating drug interaction potential cannot be made until Clinical Pharmacology has completed its review of the *in vivo* DDI studies that were submitted late in the review cycle.

Substantial edits were also made to other sections of the label by members of the review team and Michael Monteleone, Associate Director for Labeling. A number of these edits addressed concerns raised by the Office of Prescription Drug Promotion. At this time, the Applicant has not responded to the proposed revisions and the label has not been reviewed by the Division Director or Signatory.

For documentation purposes and to facilitate review of the label following resubmission of the application, a copy of the track change version of the label that was sent to the Applicant via email on April 26, 2016 will be uploaded into DARRTS. It is important to note, however, that the version of the label that was sent on April 26 does not reflect the team's current thinking (discussed above) on the maximum recommended dose and need for a Warning and Precaution related to sodium absorption and edema/fluid overload.

> *Reviewer's update: On May 19, 2016, ZS Pharma submitted a response to the draft labeling sent by the Division on April 26, 2016. Based on a quick look at the Applicant's submission, it appears that we are far from reaching alignment on labeling.*

Other Labeling

- Proprietary name. The proposed proprietary name, Lokelma, has been deemed acceptable by the Office of Medication Error Prevention and Risk Management.
- Patient labeling. None.
- Carton and container labeling. DMEPA's recommendations pertaining to container labels, carton labeling, and professional samples were conveyed to the Applicant in an advice letter dated January 5, 2016. According to DMEPA, the Applicant has not yet responded to their recommendations or submitted updated labeling addressing their recommendations. As previously noted, per the Product Quality Review, the term (b) (4) also still needs to be deleted from the product name on the container labels.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
At this time, product labeling is expected to be adequate to ensure that the product's benefits outweigh its risks in the postmarket setting.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
Upon approval for the treatment of hyperkalemia in adults, a PMR should be issued to conduct a two-part, safety and pharmacodynamic study in children 0 to (b) (4) years of age with hyperkalemia. (b) (4)

14. Recommended Comments to the Applicant

Comments that should be conveyed to the applicant in the regulatory action letter include:

Deficiencies and information needed to resolve each deficiency: List to be generated with the review team.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALIZA M THOMPSON
05/20/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207-078
Priority or Standard	Standard
Submit Date(s)	May 26, 2015
Received Date(s)	May 26, 2015
PDUFA Goal Date	May 26, 2016
Division/Office	DCRP/ODEI/OND
Reviewer Name(s)	Shen Xiao M.D, PhD
Review Completion Date	April 7, 2016
Established Name	Sodium zirconium cyclosilicate
(Proposed) Trade Name	Lokelma™
Applicant	ZS Pharma, Inc.
Formulation(s)	Suspension solution
Dosing Regimen	Powder: 5g or 10g Packets
Proposed Indication(s)	Treatment of Hyperkalemia
Intended Population(s)	Adult patients with hyperkalemia
Recommendation on Regulatory Action	Approvable
Recommended Indication	Adult patients with hyperkalemia

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Glossary

AC	advisory committee
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CKD	Chronic Kidney disease
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
DN	Diabetic Nephropathy
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	good clinical practice
HF	Heart Failure
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment

PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
RAAS	Renin Angiotensin Aldosterone System
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Sodium zirconium cyclosilicate (proposed proprietary name: LOKELMA) is a potassium binder. The proposed indication is as follows: "LOKELMA™ (sodium zirconium cyclosilicate, ZS) is a (b) (4) indicated for the treatment of hyperkalemia (b) (4) ." Sodium zirconium cyclosilicate is a power for suspension. The proposed dosing regimen is as follows: (b) (4)

LOKELMA™ is a new molecular entity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of ZS was evaluated in three short-term studies (Studies ZS002, ZS003, and ZS004) and one long-term study (Study ZS004E). The data from these studies, as described below, provide substantial evidence of the effectiveness of ZS in reducing serum potassium levels in patients with hyperkalemia.

- These studies show that ZS has a dose-dependent effect in lowering serum potassium levels in patients with hyperkalemia.
- The serum potassium lowering effect has a relatively rapid onset, starting ~ 1 hour after administration of the first dose of ZS 10 g; the largest mean change from baseline was observed between 38 and 48 hours after initiation of therapy (ZS 10 g TID).
- During continued treatment, efficacy was maintained with doses of ZS 5 g, 10 g and 15 g administered QD, as demonstrated by a sustained reduction in serum potassium levels and the percentage of patients who maintained normokalemia (71%, 76%, and 85% of subjects, respectively, in comparison with 48% of subjects treated with placebo). Following discontinuation of ZS treatment, serum potassium levels rose, providing further support for persistence of efficacy.
- Efficacy findings, including both a lowering of serum potassium levels and the achievement and maintenance of normokalemia were consistent among the various subgroups that were examined (age, gender, race, primary diseases and concurrent use of RAAS inhibitors).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

- LOKELMA™ (sodium zirconium cyclosilicate, ZS) is a selective potassium trap. The proposed indication is for the treatment of patients with hyperkalemia (b) (4) The intended population is patients with hyperkalemia in the setting of various primary diseases such as chronic kidney disease, heart failure, and diabetes. From a clinical perspective, I recommend that LOKELMA™ be approved for the treatment of hyperkalemia in adults, assuming the potential risk of drug-drug interactions can be adequately resolved.

- The treatment of hyperkalemia is based on the severity of hyperkalemia and the cause. For patients with mild to moderate elevations in potassium levels and no electrocardiographic (ECG) abnormalities (the targeted populations for this product), cation-exchange resins and/or diuretics are often used to increase potassium excretion. Diuretics can cause volume depletion and may not be effective or appropriate in some patients. Two cation-exchange resins, sodium polystyrene sulfonate and patiromer, are currently approved for the treatment of hyperkalemia in the U.S. Major safety concerns for sodium polystyrene sulfonate include volume overload/sodium retention and adverse GI effects including rare cases of colonic necrosis. At present, the main safety concern for patiromer is the potential to bind other orally administered medications, potentially decreasing their absorption and reducing their effectiveness. From an efficacy perspective, the time to the onset of patiromer's initial effect on serum potassium levels is about 7 hours; whereas the time to onset of sodium polystyrene sulfonate's effect is not well characterized.

- In clinical trials, LOKELMA demonstrated clinically important and statistically significant reductions in serum potassium levels and enabled the majority of subjects to reach and/or remain in the target potassium range. LOKELMA's serum potassium lowering effect has a relatively rapid onset, starting ~ 1 hour after administration of the first dose. As a whole, efficacy findings were consistent among the various subgroups that were examined (age, gender, race, primary diseases such as heart failure, chronic kidney disease, diabetes, etc., and concurrent use of RAAS inhibitors). In a long-term (12-month), open-label, uncontrolled study, ZS was effective in maintaining normokalemia over time. Following the completion of ZS treatment, serum potassium levels rose, indicating that in this population, hyperkalemia will likely recur once treatment with ZS is withdrawn.

- At this time, the major safety concern for LOKELMA™ is the potential for clinically important drug-drug interactions. An *in vitro* system was used to screen for potential drug-drug interactions. Of the 39 drugs that were screened, 22 drugs showed a positive interaction (either decreased or increased drug concentrations in the presence of

LOKELMA). These drugs included important anti-coagulants and anti-platelet agents (warfarin and prasugrel), anti-hypertensive agents (amlodipine and valsartan), as well as other therapeutic classes of drugs. The applicant has recently submitted the results of drug-drug interaction studies conducted in humans; the clinical pharmacology team is currently reviewing the results of these studies. Hence, LOKELMA's potential to interact with other oral medications remains an outstanding issue.

The other major drug-related adverse effect (AE) was a dose-dependent increase in the incidence of edema events, including general edema and peripheral edema, in LOKELMA treated patients. In the two phase 3 studies, the incidence was highest in the ZS 15 g (14.3%, 8 subjects) and ZS 10 g (5.3%, 6 subjects) once daily treatment groups. In contrast, the incidence was similar among the placebo (1.7%, 5 subjects), ZS ≤ 2.5 g once daily (1.0%, 2 subjects) and ZS 5 g once daily (0.9%, 1 subject) treatment groups. There was no pattern in the time to onset of these AEs and most of the AEs were considered to be mild to moderate in severity. None of the AEs were considered to be serious and only one AE was categorized as severe. In a long-term study (Study ZS004-E), the incidence of AEs of edema (including general edema and peripheral edema) and fluid overload was 13%. One subject had a SAE of pulmonary edema. For the most part, edema and heart failure-related events resolved without requiring study drug withdrawal. Approximately 50% of the edema events resulted in any treatment, typically a small adjustment in diuretic dosing. Analyses of vital sign data (changes in body weight and blood pressure) and, to some extent, other laboratory data (changes in hemoglobin and hematocrit) also indicate that sodium is absorbed from the product. Patients who have severe heart failure and those with significant impairment in renal function are expected to be at greatest risk.

The incidence of hypokalemia in subjects treated with ZS in the development program was, as a whole, low. In the extended dosing phase of the short-term studies (up to 12 days in study ZS-003 and up to 28 in study ZS-004), 19 out of 479 (4%) subjects developed a serum potassium level less than 3.5 mmol/L. Most of these events were mild (serum potassium between 3.0 and 3.4 mmol/L) and could be managed with a dose reduction; no subject developed a serum potassium level less than 3 mmol/L as assessed by central laboratory values. In the long-term extension study (Study ZS 004 E), 7 of 123 (5.7%) subjects had a serum potassium level less than 3.5 mmol/L including one subject who had a serum potassium level of 2.8 mmol/L. As noted in the review, other factors may have contributed to the low serum potassium value in this subject. Of note, a dose-related increase in QTc interval was also observed during the Acute Phase of the short-term studies, consistent with the ZS-induced decrease in serum potassium values. However, the increase in QTc interval was small and no cases of cardiac arrhythmias or sudden unexpected cardiac deaths were observed.

Nonclinical studies indicate that treatment with high doses of ZS results in an increase in serum bicarbonate. In the clinical development program, treatment with ZS was associated with a slight increase in serum bicarbonate levels; however, there were no cases of clinically significant metabolic alkalosis. Of note, some patients with hyperkalemia (such as those with severe renal impairment) are acidotic and one could speculate that increasing bicarbonate in these patients may be beneficial.

- In summary, the data from the clinical development program indicate that LOKELMA™ is effective in lowering serum potassium levels in patients with hyperkalemia. The potential for clinically significant drug-drug interactions remains an outstanding safety concern that should be revolved prior to approval. Overall, LOKELMA™ has a favorable benefit/risk profile as a treatment for hyperkalemia. No postmarketing studies are needed and labeling should be adequate to address risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe hyperkalemia can cause muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias including fatal cardiac arrhythmias such as asystole or ventricular fibrillation.	Hyperkalemia should be treated and severe hyperkalemia should be avoided.
Current Treatment Options	• Treatments vary depending on the cause and severity of hyperkalemia. In patients with mild and moderate hyperkalemia, treatments are often given to increase potassium removal from the body, such as diuretics or oral potassium binders. Diuretics can cause volume depletion and may not be effective or appropriate in some patients. At present, there are two potassium binders approved for the treatment of hyperkalemia. Potential limitations of these binders include a relatively slow onset of action (several hours), and safety concerns such as volume overload/sodium retention, adverse GI effects, and drug-drug interactions.	New potassium binders are needed to safely and effectively remove potassium in patients with hyperkalemia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In clinical trials, LOKELMA was effective in lowering potassium levels in patients with hyperkalemia. Many of the patients enrolled in the clinical trials were able to achieve target potassium levels. • There appears to be a relatively rapid onset of effect (potassium levels start to fall ~ 1 hour after taking LOKELMA).	Efficacy was demonstrated for the treatment of mild to moderate hyperkalemia.
Risk	• LOKELMA's potential to interact with other oral medications remains an outstanding issue. • Sodium absorption from the product leading to edema and weight gain was observed in the clinical trials, particularly at the highest dose tested for extended use (15 g daily). Patients with severe heart failure and those with significant renal impairment may be at particular risk of volume overload.	LOKELMA's potential to interaction with other oral medications will need to be resolved prior to approval. The Applicant has recently submitted additional information to address this issue; the Clinical Pharmacology Reviewer is currently reviewing this information. Labeling should contain adequate information on risks associated with sodium absorption from the product.
Risk Management	• Labeling should contain appropriate information on potential risks (see risks above).	No measures, beyond labeling, are needed to address risk.

2 Therapeutic Context

2.1. Analysis of Condition

Hyperkalemia is typically defined as a serum potassium (S-K) value > 5.0 mmol/L. It 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 (e.g., treatment with angiotensin-converting enzyme inhibitors [ACEs], angiotensin-receptor blockers [ARBs], mineralocorticoid receptor antagonists), or, most commonly, due to reduced kidney function. Often the cause is multifactorial (e.g., reduced kidney function combined with drug treatment such as ACEs or ARBs).

Hyperkalemia can result in impairment of neuromuscular, cardiac, and gastrointestinal organ systems. Symptoms of hyperkalemia are non-specific and generally include malaise and muscle weakness or signs of cardiac arrhythmias such as palpitations, bradycardia, or tachycardia. Hyperkalemia is detected via blood testing, often during routine screening for a medical disorder or after complications (such as cardiac arrhythmias) have developed. Of greatest concern is the effect of hyperkalemia on the cardiac system, where impairment of cardiac conduction sometimes leads to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. Because of the potential for fatal cardiac arrhythmias, severe hyperkalemia represents an acute metabolic emergency that must be immediately corrected. In many cases, the underlying cause of hyperkalemia remains unchanged, so even after acute restoration of normokalemia, continued treatment to avoid recurrence of hyperkalemia may be needed.

2.2. Analysis of Current Treatment Options

As discussed above, the treatment of hyperkalemia is based on the severity of hyperkalemia. For patients with severe hyperkalemia, treatment focuses on immediate stabilization of the myocardial cell membrane, rapid shifting of potassium into the intracellular space, and total body potassium elimination. For patients with moderate elevations in potassium levels and no electrocardiographic (ECG) abnormalities, a cation-exchange resin or diuretic can be used to increase excretion. Hemodialysis is also used in patients with renal failure or when pharmacologic therapy is not sufficient. These treatments for hyperkalemia are summarized in the table below.

Table 1: Currently Available Treatments for Hyperkalemia

Hyperkalemia	Treatments	Comments
Severe with ECG changes or related symptoms	Calcium iv	Ameliorates cardiac toxicity via stabilization of the myocardial cell membrane.
	Insulin+glucose infusion	Enhances potassium uptake by cells, thus decreasing the serum concentration.
	Sodium bicarbonate infusion	Used in patients with severe metabolic acidosis; raises blood pH thus shifting extracellular potassium into cells.
	Hemodialysis	For patients with renal failure and/or when the aforementioned therapies are not sufficient.
Moderate elevation with normal ECG	Diuretics	For patients who are not volume depleted with relatively preserved renal function; increases urinary potassium excretion by the kidney.
	Cation exchange resins	Includes sodium polystyrene sulfonate and patiromer

(Reviewer table)

Two cation-exchange resins, sodium polystyrene sulfonate and patiromer, are currently approved for the treatment of hyperkalemia in the U.S.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LOKELMA™ (sodium zirconium cyclosilicate) is a NME and is not currently marketed in the US.

3.2. Summary of Pre-submission/Submission Regulatory Activity

IND 108951 for ZS-9 (micro porous zirconium silicate) was submitted for the treatment of hyperkalemia in December 2010. The IND was initially placed on clinical hold because of concern that there was little to no safety margin for the proposed doses in the first in human study; the safety concern was resolved with additional animal studies.

A meeting was held in September 2012 to discuss development plans and a preNDA meeting was held in January 2015. Key discussions and agreements that were reached with the Agency at these and other meetings are summarized below:

Efficacy:
At a meeting in September 2012, the sponsor proposed to conduct two adequate and well-controlled trials to establish efficacy: one placebo-controlled trial, and a trial comparing their product with Kayexalate (SPS). The minutes note the following:

The Agency indicated that if the final results of a completed trial, trial ZS-002, supported the efficacy of ZS-9 for the treatment of hyperkalemia and the type 1 error rate was properly controlled, then only one additional controlled study of ZS-9 may be needed to establish the product's effectiveness. However, this advice assumes that the design of these trials allows one to identify a reasonable dosing strategy (starting dose, maximum dose and dose titration algorithm).

Because SPS's effect size is not known, the Division did not think that a non-inferiority trial comparing the sponsor's product to SPS could be used to establish the efficacy of ZS-9 if the sponsor was interested in labeling indicating that treatment for more than several days is effective in lowering potassium levels, then the sponsor should consider conducting a trial with a treatment phase followed by a randomized withdrawal phase.

The Agency agreed that enrolling subjects with hyperkalemia independent of underlying disease would support a label claim for the treatment of hyperkalemia, independent of etiology.

The Agency indicated that a critical issue is whether the product has an important effect on potassium in those subjects with the highest levels of serum potassium. Therefore, in addition to determining the mean effect on potassium, the sponsor should also characterize the distribution of the effect.

Safety:

- Sodium absorption: At a meeting in July 2014, the Division indicated that the NDA should contain information on the expected amount of sodium absorption (in mg) associated with the full range of proposed acute and maintenance doses of ZS. The Division also indicated that the NDA should contain information on the rates and outcomes of adverse events related to fluid overload and heart failure in clinical trials and advised the sponsor on specific analyses that should be performed.

- QT: At a meeting in July 2014, the Division indicated that the proposed clinical studies should be adequate to characterize the effect of ZS on the QT interval if ZS is not absorbed in humans and analyses of group and individual data indicate that increases in the QT interval associated with clinical administration of ZS are a function of a reduction in serum potassium (SK) and /or serum Ca levels. At the preNDA meeting, the sponsor asked whether the Division agreed that the effect of ZS on the QT interval had been well

characterized and that a thorough QT study was not needed. The Division responded that a thorough QT study may not be needed and advised the sponsor to submit information from all subjects with QT information for Agency review. The Division also advised the sponsor on specific analyses that should be performed.

- DDI: At a meeting in 2013, the Agency recommended that the sponsor evaluate the interaction potential of ZS in vitro using drugs belonging to the following classes that may be co-prescribed in the proposed patient population – antihypertensives, antiplatelet agents, anticoagulants, antibiotics, anti-diabetic agents, lipid lowering agents and immunosuppressants. The sponsor agreed. The Division indicated that if an in vitro study suggested a significant interaction with a drug, then the sponsor should continue testing drugs from the same class until one is identified that is free of an interaction potential.

  At the preNDA meeting, the Agency asked the sponsor to perform additional studies to rule out a significant interaction with at least one drug from the following classes of agents/therapeutic areas: calcium channel blocker, novel oral anti-coagulant, agents used to treat gout, and agents used to treat seizures. The Agency also indicated that the sponsor could choose to evaluate additional classes of drugs based on commonly administered medications in their clinical trials.

  The sponsor agreed to perform the recommended in vitro drug interaction studies, but also stated that the data from studies conducted thus far indicate that the potential for interaction can be ruled out based on the molecular size and charge of the interacting moiety. The Agency asked the sponsor to submit the data from these drug interaction experiments in the NDA and noted that these data may be critical for providing information on concomitant use with agents that were not studied during development. If the data are persuasive, then the Agency would not ask for further drug-drug interaction studies.

Other:

- Breakthrough Therapy and Priority Review: At the Pre-NDA meeting, ZS Pharma inquired about priority review and breakthrough therapy designation for their product. The Division stated that it was unlikely that the sponsor's product would meet the criteria for priority review or Breakthrough designation. The Division also noted that one of the advantages of breakthrough therapy designation is more frequent interactions with the Agency, especially at the early stages of development; the Division questioned the value of this designation so late in the development cycle of the product.

- Late submission of data: At the Pre-NDA meeting, the Division agreed that the Sponsor could submit long-term dosing data from Studies ZS-004E and ZS-005 in the 120-Day Safety Update, as well as additional information on the sodium load associated with administration of their product. The sponsor also asked if they could submit additional drug-drug interaction data in the update. They noted that they had tested their product

with approximately 20 different drugs and had found no drug-drug interactions. The sponsor believes that because of the size and ionic charge of their drug, the likelihood of any other drug-drug interactions is minimal. The Agency advised the sponsor to submit the data as part of the NDA; if the data are persuasive, then the Agency would not require further drug-drug interaction studies.

- Advisory Committee Meeting: At the Pre-NDA meeting, the Sponsor asked about the need for an Advisory Committee Meeting to discuss their application. The Division indicated that based on the data presented thus far, an Advisory Committee Meeting was unlikely.

- PREA: The applicant submitted a request for a full waiver in July 2013. The request for a full waiver was denied, and the Agency encouraged the sponsor to submit a revised pediatric drug development plan. In July 2014, the sponsor submitted a revised plan, which contained a request for deferral of pediatric studies until after the approval of the product for adult use.

3.3. Foreign Regulatory Actions and Marketing History

At present, LOKELMA™ (sodium zirconium cyclosilicate) is not approved in any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three domestic clinical study sites (Sites# 001, 081 and 4032) were selected for audit based on the enrollment of large numbers of study subjects and more favorable efficacy findings in Study ZS003 or Study ZS004. No regulatory violations were found during the inspections of two sites. These inspections were classified as NAI. Minor regulatory violations were observed during the inspection of one site (Site# 4032 in Los Angeles) and a two- observation Form FDA 483 was issued for failure to follow the investigational plan and failure to maintain accurate records with respect to drug disposition records. Those findings are unlikely to have a significant impact on the efficacy or safety outcome of the study. No regulatory violations were found during the inspection at the Applicant. The Applicant inspection was classified NAI. OSI recommends the data be considered acceptable in support of the NDA.

4.2. Product Quality

LOKELMA ™ is a free flowing, odorless, tasteless, insoluble white powder. It will be administrated orally as a suspension with water. The active ingredient in LOKELMA™ is sodium zirconium cyclosilicate. ZS has a mean particle size of 20 µm and includes no more than 3% of particles with a diameter below 3 µm. It is a non-absorbed, "cation trap" that binds potassium. The sodium content of sodium zirconium cyclosilicate is no more than (b)(4)%.

From a CMC perspective, approval is pending the results of a pre-approval inspection of the drug substance manufacturing and testing facility, and resolution of issues related to elemental impurities.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review indicates that sodium zirconium cyclosilicate can be approved from a pharmacology/toxicology perspective. Use of the drug for periods longer than 6 months is not limited from a pharmacology/toxicology perspective.

General toxicology studies in two species (rat and dog) were conducted to support use of sodium zirconium cyclosilicate for humans. The toxicological effects observed were secondary to hypokalemia produced by the drug. No other safety signals were identified. With regard to reproductive effects, sodium zirconium cyclosilicate was not teratogenic in rats or rabbits. No effect on fertility was observed in rats. A pre/postnatal study in rats did not show any detrimental effects. Since the drug is not absorbed from the GI tract, there is no plasma exposure in the animals. However, the studies do show that any secondary effects of the drug on reducing potassium absorption do not impair reproductive function or induce teratogenic effects.

Because the drug is not absorbed from the GI tract, is not genotoxic and does not result in local gastrointestinal effects (i.e., necrosis/regeneration, irritation, inflammation or hyperplasia), carcinogenicity studies of sodium zirconium cyclosilicate were not requested by the Agency or performed by the Sponsor. In the 39-week dog repeat-dose toxicity study, there was no indication of GI inflammation which would indicate possible pre-cancerous effects.

4.5. Clinical Pharmacology

The Clinical Pharmacology review has not been finalized.

A major safety concern is the potential for drug-drug interactions. In *in vitro* studies, 22 out of 39 screened drugs showed a positive interaction with ZS. The results of *in vivo* studies were recently submitted to the NDA; the clinical pharmacology reviewer has not yet completed her review of these studies. This issue (i.e., the potential for clinically significant drug-drug interactions) will need to be resolved prior to approval.

4.5.1. Mechanism of Action

ZS is a non-absorbed inorganic cation exchanger that binds potassium in exchange for hydrogen and sodium. It may also bind ammonium cations. ZS binds potassium throughout the gastrointestinal tract thereby lowering serum potassium levels. ZS and the trapped cations are then excreted from the body in the feces. According to the Applicant, the binding effect of ZS is not significantly affected in the presence of other cations such as calcium and magnesium based on the both in vitro and in vivo studies.

4.5.2. Pharmacodynamics

ZS causes a dose-dependent reduction in serum potassium levels of potassium. The onset of the effect occurs ~ 1 hour after oral administration. There is a close correlation between the baseline serum potassium level and the effect size; patients with higher starting serum potassium levels have greater reductions in serum potassium.

4.5.3. Pharmacokinetics

As ZS is not absorbed systemically, the pharmacokinetics of this product were not evaluated in clinical studies. An in vivo mass balance study in rats showed that ZS was recovered in the feces with no evidence of systemic absorption.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Information on clinical trials pertinent to the evaluation of efficacy and safety is provided in the table below.

Table 2: Listing of Completed Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
ZS-002	A multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating study to investigate the safety, tolerability and pharmacodynamics of ZS in subjects with mild hyperkalemia in chronic kidney disease and moderate kidney dysfunction	Administered orally, TID in conjunction with meals for at least 48 hours or up to 96 hours for subjects whose serum potassium (S-K) had not normalized.	Difference in exponential rate of change in S-K levels during initial 48 hours between the placebo and the ZS arms	2 days during Acute Phase and 28 days during Maintenance Phase.	90 randomized 90 treated	subjects with moderate CKD (GFR between 30 to 60 mL/min) and hyperkalemia (S-K between 5 and 6 mmol/L)	9 sites in the United States
ZS-003	A phase 3, multicenter, two-phase, multi-dose, randomized, double-blind, placebo controlled study to investigate the safety and efficacy of ZS in Subjects with mild to moderate hyperkalemia.	Administered orally in conjunction with meals (TID for acute phase for 48 hours and QD in withdraw phase for 12 days)	Difference in exponential rate of change in S-K levels during initial 48 hours and the end of withdraw phase between the placebo and the ZS arms	48 hours for acute phase and 12 days for randomized withdrawal phase	754 randomized and 753 treated in Acute Phase; 543 randomized and 543 treated in Subacute Phase	subjects with mild to moderate hyperkalemia (S-K between 5.0 and 6.5 mmol/L)	65 sites in the United States, Australia, and South Africa
ZS004	A phase 3, multicenter,	Administered	Difference in	TID for 48	258/251 in	Subjects with	44 sites in

	multi-phase, multi-dose, randomized, double-blind, placebo controlled maintenance study to investigate the safety and efficacy of ZS in subjects with hyperkalemia	orally, just before meals. Subjects who developed potassium values between 3.0 and 3.4 mmol/L were to have dosing reduced to QOD.	exponential rate of change in S-K levels in the end of withdraw phase between the placebo and the ZS	hours, QD for 28 days	first phase and 237 treated in maintenance phase	hyperkalemia (S-K ≥ 5.1 mmol/L) (Maintenance Phase).	the United States, Australia, and South Africa
ZS004E	Open-label extension study of Study ZS004	Administered orally, once a day just before breakfast	long-term safety, tolerability, and efficacy follow-up data including the proportions of subjects with average S-K ≤ 5.1 and 5.5 mmol/L	10 g QD may be up to 15g, down to 5g Q.O.D based on S-K for 11 months	123	Normal level of S-K between 3.5 to 5.0 mmol/L	30 sites in the United States, Australia, and South Africa

5.2. Review Strategy

The efficacy review focused on the results of the two phase 3 trials, ZS003 and ZS004. Study ZS002, a phase 2 study, was reviewed for supportive evidence of efficacy, while study ZS004E, the extension study of ZS004, was reviewed for evidence of long-term efficacy. The safety review utilized data from all of the clinical trials listed in Section 5.1. Study ZS005, another long-term study, is currently ongoing; data from this trial were not included in the NDA.

In this review, the results of the Applicant's analyses are presented along with reviewer commentary. Key efficacy analyses were confirmed by the FDA statistician, Dr. Thomas Birkner. Analyses related to submission specific safety concerns were conducted by Dr. Christine Garnett, a clinical analyst in the Division of Cardiovascular and Renal Products.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study ZS003

6.1.1. Study Design

Overview and Objective
Study ZS003 was a phase 3, multi-center, two-phase, multi-dose, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (microporous, fractionated, protonated zirconium silicate) in subjects with mild to moderate hyperkalemia.

The purpose and major objective of this study were to evaluate the safety and efficacy of four different doses of ZS administered 3 times daily for 48 hours in the Acute Phase for subjects with mild to moderate hyperkalemia (potassium level between 5.0 -6.5 mmol/l as determined by i-STAT) at baseline, and the safety and efficacy of four different doses of ZS administered once daily for 12 additional days in a subsequent Subacute Phase for subjects completing the Acute Phase and achieving serum potassium (S-K) levels within the normal range (3.5 – 5.0 mmol/l).

Trial Design
Study ZS003 enrolled 750 subjects with mild to moderate hyperkalemia (i- STAT potassium levels between 5.0-6.5 mmol/l, inclusive) and randomized them 1:1:1:1:1 to receive one of four doses of ZS (1.25g, 2.5g, 5g, and 10g) or placebo control, administered 3 times daily with meals for an initial 48 hours (Acute Phase). The Acute Phase of the study was followed by a Subacute Phase (randomized withdrawal phase). The Subacute Phase included subjects who became normokalemic (i-STAT potassium values 3.5 to 4.9 mmol/l, inclusive) on active drug and those

who became normokalemic on placebo. The former were randomized in a 1:1 ratio to the same dose of ZS they received during the acute phase but administered once a day or placebo. Subjects on placebo during the Acute Phase who were normokalemic in the morning of Study Day 3 were randomized to receive either 1.25 or 2.5 g ZS qd.

Reviewer's Comment: The inclusion of a placebo-control group enables a more reliable estimate of the treatment effect on potassium levels but also resulted in the exclusion of subjects with more severe hyperkalemia since it would have been unethical to randomize subjects with severe hyperkalemia to receive placebo.

Key inclusion criteria:

- Over 18 years of age
- Mean i-STAT potassium values between 5.0 – 6.5 mmol/l inclusive, at screening (Study Day 0).
- 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 screening.

Key exclusion criteria:

- Pseudohyperkalemia signs and symptoms, such as excessive fist clinching hemolyzed blood specimen, severe leukocytosis or thrombocytosis.
- Subjects treated with lactulose, xifaxan or other non-absorbed antibiotics for hyperammonemia within the last 7 days.
- Subjects treated with resins (such as Sevelamer acetate or Sodium polystyrene sulfonate [SPS; e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within the last 7 days.
- Subjects with a life expectancy of less than 3 months.
- Women who are pregnant, lactating, or planning to become pregnant.
- Subjects with diabetic Ketoacidosis.
- 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.
- Known hypersensitivity or previous anaphylaxis to ZS or to components thereof.
- Previous treatment with ZS.
- Treatment with a drug or device within the last 30 days that has not received regulatory approval at the time of study entry.
- Subjects with cardiac arrhythmias that require immediate treatment.
- Subjects on insulin where a stable dose has not yet been established
- Subjects on dialysis

Reviewer's comment: For the most part, the entry criteria were reasonable. Although the study population is reasonably representative of the patient population that is likely to receive the

drug post-approval, some population that are likely to use the drug were excluded (such as patients on dialysis).

Dose selection: The ZS doses (1.25 g, 2.5 g, 5 g, and 10 g) were selected based on efficacy data obtained from the phase 2 study (ZS-002) in which ZS dosages of 3 g and 10 g TID significantly decreased S-K in subjects with mild to moderate hyperkalemia and moderate CKD within 48 hours of treatment in a dose-dependent manner. According to the Applicant, (b) (4) the lower ZS dosages of 1.25 g and 2.5 g were included to better define the dose-response relationship as well as define the minimum effective dose.

Reviewer's comment: The applicant's rationale for dose selection was reasonable.

Study treatments: As previously noted, subjects were randomized to receive treatment with 1 of 4 doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo, administered TID for the initial 48 hours (Acute Phase), followed by a randomized dose of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered QD in the morning for 12 days (Subacute Phase). In the Acute Phase, study drug was to be taken at breakfast, lunch, and dinner, with the exception of Study Day 1 when breakfast was provided after the 2-hour post Dose 1 S-K collection. On Study Days 1 and 2, lunch was provided after the 4-hour post Dose 1 blood collection and within 30 minutes before administration of Dose 2. During the Subacute Phase, study drug was to be taken in conjunction with breakfast.

For doses administered in the clinic, the study coordinator/clinic staff added ~180 ml purified water to the IP bottle, capped the bottle, and shook it for at least 30 seconds to form a slurry/suspension immediately prior to administration. The dosing bottle was then sequentially rinsed with 2 X ~30 ml of purified water, and each rinse was to be consumed by the subject. Clinic staffs were to use the in-clinic dose preparation procedure to instruct the subject on how to make up the dose at home. Bottles of water containing ~ 240 ml (~8 ounce) were to be given to each subject for use at home.

Dose modification and discontinuation: Subject who developed potassium values > 7.0 or < 3.0 mmol/l as determined by i-STAT, or a significant cardiac arrhythmia (see below) were to receive appropriate medical treatment and be discontinued from study drug. The following rules were also implemented during the Acute and Subacute Phases:

- *Acute Phase:* If a subject developed potassium values between 3.0 - 3.4 mmol/l as determined by i-STAT, the next dose of study drug was to be skipped. The subject would be eligible for enrolment onto the Subacute Phase if the potassium level, as determined by i-STAT, had normalized (3.5 – 4.9 mmol/l) on the morning of Study Day 3.

- *Subacute Phase*: If a subject developed potassium values < 3.4 mmol/l as determined by i- STAT the subject was to be discontinued from the study.

The following cardiac events were to result in immediate discontinuation from the study (regardless of the study phase):

- Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter or new paroxysmal supraventricular tachycardia [except sinus tachycardia], 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])
- Acute congestive heart failure
- Significant increase in PR interval (to more than 0.25 s in the absence of preexisting atrioventricular block), widening of the QRS complex (to more than 0.14 s in the absence of pre-existing bundle branch block) or peaked T-wave

Dietary restrictions/instructions: As listed above, study drug was to be taken at breakfast, lunch, and dinner. No special dietary restrictions were requested in this study.

Subject completion, discontinuation, or withdrawal: Subjects who had i-STAT potassium values > 6.5 mmol/L at the 4-hour post Dose 1 time point on Study Day 1 were considered treatment failures and were to be withdrawn from the study. Similarly, subjects who had i-STAT potassium values ≥ 6.2mmol/L, 90 minutes after the 2nd dose on Study Day 1 were to be withdrawn from the study. On Study Day 2, subjects who had i-STAT potassium values ≥ 6.2mmol/L prior to dosing or at the 4-hour post Dose 1 time point were to be withdrawn from the study. Subjects who developed cardiac arrhythmias as described under the stopping criteria described above were also to be withdrawn from the study and receive standard of care treatment.

Every reasonable effort was made to maintain protocol compliance and participation in the study. If a subject withdrew or was prematurely terminated from the study for any reason, the reason for early study withdrawal was to be recorded. If withdrawal was the result of a serious adverse reaction, the subject was to be followed until the condition resolved, as determined by the investigator. The investigator or Sponsor could have withdrawn 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 was censored at time of withdrawal and, if possible, a final evaluation (End of Study procedures) was made. After subjects were withdrawn from the study, no subjects were replaced regardless of the reason for withdrawal.

Randomization and Blinding: As previously noted, ZS003 was a double-blind trial. There was a one-time randomization at which subjects were assigned their Acute Phase treatment and Subacute Phase (randomized withdrawal phase) treatment. Randomization was blinded and the randomization code was to be held by a third party not associated with clinical management of the study.

There was only one randomization number assigned per subject, which covered both the Acute and Subacute treatments. For both the Acute- and Subacute Phases, identical-appearing ZS and placebo bottles were labeled with a unique numeric code. Each subject was assigned a specific investigational product (IP) numeric code contained within the bottle label. The assignment of unique numeric codes to active product or placebo was to be securely retained until such time as designated by the Statistical Analysis Plan.

Emergency unblinding by the site was not permitted. The iDMC was allowed to request a code break, either for an individual subject or on a group basis. The iDMC was allowed to request to break the blind if: there was an imbalance in safety parameters between groups; if stopping criteria were met and/or; in case of single or multiple significant AEs/SARs that might be drug-related. If unblinded was needed (either of an individual subject or on a group basis), the chair of the iDMC was to request unblinding from the Sponsor's Chief Medical Officer (CMO). In such cases, the CMO would request unblinding from the third party keeper of the randomization codes.

Investigators and study administrative structure: The study was overseen by ZS Pharma, Inc. and conducted by investigators who were contracted by and under the direction of the Sponsor. The Sponsor was responsible for the operational aspects of the trial, including medical and clinical monitoring for the study.

An Independent Data Monitoring Committee (iDMC), separate from the Sponsor, was established to review safety data on an ongoing basis and make recommendations regarding the safe conduct of the study. Blinded safety data for review were prepared and provided to the iDMC (b) (4) after 200, 400, and 600 subjects had completed the study.

Reviewer's Comment: No major recommendations regarding study conduct were made based on these reviews of the safety data.

Procedures and schedule: The schedule of study assessments for the Acute Phase and the Subacute Phase are summarized in the following two tables.

Table 3: Schedule of Assessments in the Acute Phase

Study Day		0[a]	1	2	3	9
Parameter		Screening 8:00 AM (± 120 minutes)	8:00 AM – 12:00 PM (± 120 minutes)		8:00 AM (± 120 minutes)	EOS for subjects not entering the Subacute Phase
Written informed consent	X					
Eligibility criteria		X				
Demographics		X				
Medical history		X				
Physical examination		X			X	X
Study drug administration			X[b]	X[b]		
Electrocardiogram		X	X[c]	X	X	X
Vital signs		X			X	X
Concomitant medications		X	X	X	X	X
Adverse events			X	X	X	X
Serum potassium		X[d]	X[e,f]	X[e]	X[g]	
Serum chemistry[h,i]		X			X	X
Hematology[h,i]		X			X	X
Zr whole blood and urine[j]		X	X	X	X	X
Urinalysis[h]		X			X	X
Urine culture		X				X[k]
Urine hCG[l]		X				X[k]
Urinary sediment		X			X	X
Study drug reconciliation						X

EOS = End of Study Visit; hCG = human chorionic gonadotropin; Zr = zirconium

a. Procedures for Study Day 0 and Study Day 1 may have been combined (conducted on the same day) if all screening procedures were completed and the results of local laboratory tests were received prior to the first dose of study drug at 8:00 AM (± 120 minutes).
b. Study drug was to be administered orally in conjunction with breakfast, lunch, and dinner on Study Days 1 and 2.
c. Only for subjects with i-STAT potassium between 6.1 and 6.5 mmol/L, inclusive, at the 4-hour post Dose 1 time point.
d. Potassium was to be measured at time 0, 30, and 60 (± 10) minutes on Study Day 0 in addition to the standard serum chemistry panel. Samples were to be analyzed by i-STAT, and by the local and central laboratories.
e. Potassium was to be measured prior to, and 1, 2, and 4 hours (± 15 minutes) post Dose 1 on Study Day 1, and prior to and 1 and 4 hours (± 15 minutes) post Dose 1 on Study Day 2. Samples were to be analyzed by i-STAT and the central laboratory.
f. If the i-STAT potassium value was > 6.5 mmol/L at the 4 hour post Dose 1 time point, subjects were to be withdrawn from the study. If the potassium value was between 6.1 and 6.5 mmol/L, inclusive, then another potassium sample was to be collected 90 minutes post Dose 2. If the i-STAT potassium value was ≥ 6.2 mmol/L at the 90-minute post Dose 2 time point, the subject was to be discontinued from the study.
g. Potassium was to be measured once before breakfast in the morning of Study Day 3 (and Study Day 9 for subjects not entering the Subacute Phase) as part of the serum chemistry panel. Samples were to be analyzed by i-STAT and the central laboratory.
h. Parameters that were to be measured are detailed in Table 9-6.
i. Serum clinical chemistry and hematology parameters were to be measured fasting (nothing by mouth except water, black coffee, or tea, with or without milk and/or sugar, and essential medications only from 11:00 PM on the previous day) on Study Days 0, 3, and 9 (EOS visit for subjects not entering the Subacute Phase), 15, and 21. On Study Day 0, the serum chemistry and hematology samples for both the central and local laboratories were collected at the same time as the 60-minute screening potassium sample once it seemed likely that the mean i-STAT potassium value was ≥ 5.0 mmol/L.
j. Two whole blood (3 mL) and 2 urine (5 mL) samples were to be collected at screening and prior to Dose 1 on Study Days 1, 2, 3, and 9.
k. For subjects not enrolled in the Subacute Phase.
l. For women of childbearing potential.

Applicant's table from CSR Study ZS003, table 9-3, Page 45

Table 4: Schedule of Assessments in Subacute Phase

Study Day	3	4-6	7-8	9	10-14	15	21
Parameter	8:00 AM (± 120 minutes)			8:00 AM (± 120 minutes)		8:00 AM (± 120 minutes)	8:00 AM – EOS (± 120 minutes)
Eligibility criteria	X						
Urine dipstick[a]	X					X	X
Physical examination[a]	X					X	X
Study drug administration	X[b,c]	X[b,c]	X[b,d]	X[b,c]	X[b,d]		
Electrocardiogram[a]	X			X		X	X
Vital signs[a]	X			X		X	X
Concomitant medications	X	X		X		X	X
Adverse events	X	X		X		X	X
Serum potassium[e]	X[f,g]	X[e]		X[f]		X[f]	X[f]
Blood urea nitrogen		X[h]					
Serum chemistry[a,i]	X			X		X	X
Hematology[a,i]	X			X		X	X
Zr whole blood and urine[j]	X			X		X	X
Urinalysis[a,i]	X			X		X	X
Urinary sediment	X			X		X	X
Urine culture							X
Urine hCG							X[k]
Study drug reconciliation						X	

EOS = End of Study Visit; hCG = human chorionic gonadotropin; Zr = zirconium

a. Physical examination, electrocardiogram, vital signs, urinalysis, serum clinical chemistry, and hematology parameters were to be measured fasting (nothing by mouth except water, black coffee, or tea, with or without milk and/or sugar, and essential medications only from 11:00 PM on the previous day).
b. Study drug was to be administered orally in conjunction with, or before, breakfast on Study Days 3-14.
c. Study drug was to be administered at the site.
d. Study drug was to be administered at home.
e. Samples were to be analyzed by i-STAT and the central laboratory.
f. Potassium was to be measured once, before breakfast, in the morning as part of the serum chemistry panel. Samples were to be analyzed by i-STAT and the central laboratory.
g. If the i-STAT potassium value was < 4 mmol/L, the subject was to remain at the site and an additional potassium sample was to be collected 4 hours post dose.
h. Analyzed by the central laboratory together with the S-K pre-breakfast assessment.
i. Parameters that were to be measured are detailed in the attached table.
j. Two whole blood (3 mL) and 2 urine (5 mL) samples were to be collected prior to Dose 1 on Study Days 3 and 9 and in the morning of Study Days 15 and 21.
k. For women of childbearing potential.

Applicant's table from CSR Study ZS003, table 9-4, Page 46

Concurrent Medications: All subjects were to continue the treatments they were on upon admission into the study. All concomitant medications taken by the subject from 30 days prior to Study Day 0 until the End of Study Visit (7 days after the last dose of study drug; Study Day 9 for subjects not entering the Subacute Phase and Study Day 21 for subjects entering the Subacute Phase) were to be recorded. Whenever possible, all blood draws collected prior to meals were to be collected prior to insulin/insulin analogue treatment. From Study Day 0

through Study Day 21, the time of dosing with insulin/insulin analogues was to be recorded if administered at the site or prior to the visit on days that blood samples were to be collected.

Study Endpoints
As agreed with the Division, the primary efficacy endpoint for the Acute Phase was the difference in the exponential rate of change in S-K values during the initial 48 hours of study drug treatment between the placebo-treated subjects and the ZS-treated subjects.

The primary efficacy endpoint for the Acute Phase was the difference in the exponential rate of change in S-K values during the initial 48 hours of study drug treatment between the placebo-treated subjects and the ZS-treated subjects.

The primary efficacy endpoint for the Subacute Phase was the difference in the exponential rate of change in S-K values over the 12-day treatment interval between those on subacute therapy and randomized withdrawal, separately for the 4 Acute Phase active treatments (excluding Acute Phase placebo).

Secondary endpoints in the acute phase included S-K at other time points, time to normalization of S-K (as defined by S-K levels of 3.5 – 5.0 mmol/l), time to a decrease of 0.5 mmol/l in S-K levels, proportion of subjects who achieve normalization in S-K levels after 48 hours of treatment with ZS or placebo. Other endpoints included S-Ca, S-Na, S-Cr, S-NH4, Blood urea nitrogen (BUN), well as the type, incidence, timing, severity, relationship, and resolution of all treatment emergent adverse events.

Secondary endpoints in the Subacute phase included time remaining normokalemic (3.5 – 5.0 mmol/l), time to relapse (as defined by return to baseline S-K level), S-K at other time points, time to a decrease of 0.5 mmol/l in S-K levels, proportion of subjects with normalized S-K levels after 12 days of sub-acute treatment with ZS or placebo control. Other endpoints included S-Ca, S-Na, S-Cr, SNH4, BUN, as well as the type, incidence, timing, severity, relationship, and resolution of all treatment-emergent adverse events.

The secondary endpoints in both phases were pre-specified but there was no plan to control the type I error in testing these endpoints. For further discussion of key endpoint analyses, please see the section on the Statistical Analysis Plan.

Statistical Analysis Plan
The statistical analysis plan was on finalized on March 14, 2013. The database was locked and unblinded on November 6, 2013.

The statistical analysis plan specified the following populations for key efficacy and safety analyses.

"Intent-to-Treat Population": This was the primary population for efficacy analyses. The analysis plan defined the "ITT" Population as all subjects who were randomized, received any study drug, and had S-K values determined after 48 hours of treatment.

For the Acute Phase, subjects were considered evaluable for the primary endpoint if:

- They received the TID study drug, and
- They had S-K values determined after 48 hours of acute treatment.

For the subsequent Subacute Phase, subjects were considered evaluable for the primary endpoint if:

- They received the QD study drug, and
- They had a post-baseline S-K assessment during the Subacute Phase.

Modified Intent-to-Treat Population: The statistical analysis plan defined a Modified Intent-to-Treat Population, which was to consist of all subjects in the ITT Population who were dosed as randomized and met all eligibility criteria.

Reviewer's comment: As < 10% of the subjects in the ITT Population were considered unavailable based on this criterion, only the ITT population was analyzed.

Safety Population: The Safety Population was defined as all randomized subjects who received study drug. Randomized subjects who did not receive study drug were excluded from this population.

Reviewer's comment: A total of 753 of 754 randomized subjects received study drug.

Efficacy Analysis: Separate analyses were performed for the Acute and Subacute Phases. All potassium analyses were based on the S-K values from the central laboratory.

Acute Phase Analyses: As previously noted, the primary endpoint in the Acute Phase was the difference in the exponential rate of change in S-K values during the initial 48 hours of study drug treatment between the placebo-treated subjects and the ZS-treated subjects. The baseline S-K was computed by taking the mean of 3 different S-K values, recorded 30 minutes apart (time 0, 30, and 60 minutes) on Day 0 and then averaged with the S-K value taken just before administration of the first dose on Study Day 1; a 5% relative reduction in S-K was deemed to be a minimally significant difference between treatment and placebo control over the first 48 hours.

The analysis plan specified that an exponential model (SAS PROC MIXED) was to be used to evaluate the primary efficacy endpoint; the model controlled for each etiology (CKD, congestive heart disease, diabetes mellitus, and RAAS inhibitor medication).

As previously noted, there was no pre-specified plan to control the type 1 error in testing secondary endpoints in the Acute Phase.

Subacute Phase Analyses: The primary efficacy endpoint for the Subacute Phase was the difference in the exponential rate of change in S-K values over the 12-day treatment interval between those on subacute therapy and randomized withdrawal, separately for the 4 Acute Phase active treatments (excluding Acute Phase placebo). An exponential model (SAS PROC MIXED) was used to evaluate the primary efficacy endpoint. The same model was used as for the Acute Phase.

A Kaplan-Meier life table and log rank test, as well as a proportional hazard model (SAS PROC PHREG), was used to compare each ZS dose versus corresponding placebo control for Study Days 3 through 14 with respect to maintaining normokalemic control (defined as S-K between 3.5 and 5.0 mmol/L), time to a 0.5 mmol/L increase, and time to relapse (return to original S-K baseline), which served as secondary efficacy endpoints; the models included the baseline S-K value and etiology covariates as described above. The total number of days maintaining normokalemic control was compared for each ZS dose versus corresponding placebo control using a linear regression model (SAS PROC REG); the same baseline S-K value covariates and etiology covariates were included as previously described. In addition, a Fisher Exact test was used to compare each ZS dose versus placebo control for the proportion of subjects in the 4 cohorts (representing each ZS dose) that remained normokalemic at the end of the Subacute Phase on Study Day 14 in addition to a logistic regression model (SAS PROC LOGISTIC) for End of Study normokalemic control; the same baseline S-K value covariates and etiology covariates were included.

Type I Error Control: Type I error for the Acute Phase and the Subacute Phase testing of the primary efficacy endpoint was controlled at 0.05 by the use of a closed procedure applied in a prospectively defined manner detailed in the statistical analysis plan. The predefined closed testing order first tested the highest Acute Phase dose, then the highest Subacute Phase dose, then the next highest dose (Acute then Subacute) in the order presented below, until the lowest dose was reached as follows:

- ZS 10 g TID versus placebo TID
- ZS 10 g QD versus corresponding placebo QD
- ZS 5 g TID versus placebo TID
- ZS 5 g QD versus corresponding placebo QD
- ZS 2.5 g TID versus placebo TID
- ZS 2.5 g QD versus corresponding placebo QD
- ZS 1.25 g TID versus placebo TID
- ZS 1.25 g QD versus corresponding placebo QD

Determination of Sample Size: Separate sample size calculations were performed for the Acute and Subacute Phases. Sample size for the exponential rate of change during the Acute Phase was calculated using the program for sample size calculation of a random slopes model (http://hedwig.mgh.harvard.edu), with parameters estimates based on Study ZS-002 data. When the model was fit to the ZS-002 data, with time measured in days, the variance of the intercept was 0.00802, the variance of the slope was 0.00130 and the covariance was -0.00045, the residual variance was 0.00473. Based on these parameters, there was 90% power to detect a difference in slopes of 0.0183/day. On the log potassium scale, this was a reduction of 1.83%/day. For the percentage normokalemic at the end of the Acute Phase, any 20% absolute gain after 48 hours in the percentage with normokalemic control from placebo control to any ZS dose could have been detected with at least 90% power for a two-sided test with 0.05 Type I error.

For the Subacute Phase, it was estimated that at least 100 of the 150 treated Acute Phase subjects would achieve normokalemia for each ZS dose group. With the parameters above, there was a 90% chance of detecting a difference in slopes of 0.0205/day. On the log potassium scale, this was a slope of 2.05%/day. For the Subacute Phase, it was projected that there was at least 80% power to detect a 0.6 effect size (based on a 3-day difference with a 5-day standard deviation) for cumulative days normokalemic.

Protocol Amendments
The original protocol, dated October 30, 2012, had 3 major amendments (identified as Amendments 1, 2, and 3) and 4 site-specific amendments (identified as Amendments 3a, 3b, 3c, and 3d). Most of the modifications related to changes in entry criteria and clarifications regarding study procedures. The study endpoint was not modified and from, an efficacy perspective, the changes that were made would not impact the interpretability of the efficacy findings. Amendments 3a and 3c allowed for the collection of information on zirconium levels as specified below.

Amendment No. 3a (1 April 2013; Study Sites 006 and 081 only):

- Added collection of whole blood and urine samples for analysis of zirconium levels on Study Days 0, 1, 2, 3, and 9 in the Acute Phase and also on Study Days 15 and 21 in the Subacute Phase.
- Included details of the collection procedures and processing for the whole blood and urine samples for zirconium analysis.

Amendment No. 3c (10 May 2013; selected sites in the US only): Allowed ZS Pharma to implement the collection of whole blood and urine samples for analysis of zirconium levels at additional sites in the US as needed with IRB approval without requiring a revision to the protocol. The selected sites were to be defined outside of the protocol document.

Statistical Analysis Plan Amendments
The statistical analysis plan was initially drafted on November 20, 2012, amended twice prior to database lock (on September 8 and October 29, 2013) and unblinded on November 6, 2013.

Amendment No. 1 (8 September 2013): Removed some of the pre-specified analyses related to urinalysis data; according to the amendment, these analyses were removed because of inconsistent reporting of urinalysis data across sites.

Amendment No. 2 (29 October 2013): This amendment addressed the analysis and display of eGFR data and clarified the modeling of the primary efficacy endpoint for the Acute and Subacute Phases. The primary efficacy models for the Acute and Subacute Phases were clarified as follows:
Acute Phase:

- Baseline polypharmacy was replaced by baseline RAAS inhibitor medication as an indicator variable
- Baseline S-K was evaluated as a continuous variable consistent with ZS-002
- Baseline eGFR was evaluated as a continuous variable consistent with baseline S-K
- Separate models were run to include all Acute Phase data starting with Study Day 1/hour 0 through Study Day 2/hour 0 as well as through the end of acute treatment (primary)

Subacute Phase:

- Separate analyses were conducted to correspond to the 5 original acute treatments
- Baseline polypharmacy was replaced by baseline RAAS inhibitor medication as an indicator variable
- Baseline S-K (both Acute and Subacute) was evaluated as a continuous variable consistent with ZS-002
- Baseline eGFR (both Acute and Subacute) was evaluated as a continuous variable consistent with baseline S-K
- Separate models were run to include all Subacute Phase data starting with Study Day 3/hour 0 through Study Day 8/hour 0 as well as through the end of subacute treatment (primary)

The changes described above do not affect the ability to interpret the study findings.

Data Quality and Integrity: Sponsor's Assurance
In accordance with a Clinical Monitoring Plan, clinical research associates periodically visited the investigational sites to verify eCRF entries against source documents and ensure that appropriate data were collected and documented. GCP audits of some study sites were performed by an independent auditor.

Secure data transfer between the central laboratory and the Data Management CRO was performed in accordance to a Data Transfer Agreement. According to the study report, secure data transfers from the Data Management CRO and Biostatistics were downloaded "on an as needed basis" until study database lock. A final data transfer of the locked database from the Data Management CRO and Biostatistics was performed in accordance with a Data Transfer Agreement.

According to the Applicant's study report, the Acute and Subacute Phase databases were simultaneously locked and the phase-specific randomization code for this study was not revealed until the following preconditions were fulfilled:

- All follow-up was obtained.
- All data were entered in the database.
- All adverse events were coded.
- All data queries were resolved.
- The database was officially locked.
- Decisions had been made, agreed upon, and documented as to the impact of all protocol deviations and violations.
- Written authorization from the study's project leader was obtained.

6.1.2. Study Results

Compliance with Good Clinical Practices
According to the Applicant, the trial was conducted in accordance with the U.S. regulations governing the protection of human subjects (21 CFR part 50) and IRBs (21 CFR part 56) and 21 CFR parts 54 and 312; the Declaration of Helsinki and its most recent update (Seoul, 2008) concerning medical research in humans; and the International Conference on Harmonisation (ICH) E6 (R1) Guideline for Good Clinical Practice (GCP).

According to the Applicant, no person or entity debarred under 21 US Code 335a (k) participated in the planning, operation, analysis, or reporting of this study.

Financial Disclosure
A list of investigators and sub-investigators for Study ZS003 was included in the submission. According to the Applicant, there were no financial interests or arrangements to disclose from investigators that participated in the Study ZS-003 as described in the table below.

Table 5: Clinical Investigator Financial Disclosure in Study ZS003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 65		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer's table

Patient Disposition

A total of 1433 subjects were screened for entry into the study. Of these, 679 failed to meet the entry criteria, primarily because average i-STAT values were not within the specified range (628 subjects).

Acute Phase: A total of 754 subjects were randomized into the Acute Phase of the study. Of these, one subject randomized to ZS 5 g TID was never dosed and was excluded from all efficacy and safety analyses.

The disposition of subjects entering the Acute Phase is shown in the table below. Greater than 95% of subjects in each of the treatment groups completed the Acute Phase of the study

(range: 96% to 99%). A total of 18 subjects (including one subject who was never dosed) prematurely discontinued during the Acute Phase of the study. The percentage of subjects discontinuing treatment prematurely was low in all of the treatment arms, but somewhat higher in the ZS treatment arms (range of 2 % to 4%) as compared to the placebo arm (< 1%). Among subjects treated with ZS, the most common reason for premature discontinuation was "consent withdrawn" (6 subjects). Four ZS-treated subjects (one in the ZS 1.25 gm dose group and three in the 2.5 gm dose group) and one placebo-treated subject prematurely discontinued from the Acute Phase of the study because of hyperkalemia (potassium value range of 6.2 to 6.8 mmol/L).

Table 6: Subject Disposition in Acute Phase – All Randomized Subjects

Disposition, n (%)	Placebo	ZS 1.25 g TID	ZS 2.5 g TID	ZS 5 g TID	ZS 10 g TID
Randomized	158	154	141	158	143
Treated	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)
Completed Acute Phase	157 (99.4)	150 (97.4)	137 (97.2)	152 (96.2)	140 (97.9)
Discontinued Acute Phase	1 (0.6)	4 (2.6)	4 (2.8)	6 (3.8)	3 (2.1)
Adverse event	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.7)
Consent withdrawn	0 (0.0)	1 (0.6)	1 (0.7)	4 (2.5)	0 (0.0)
Subject compliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Sponsor's decision	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Hypo- or hyperkalemia	1 (0.6)	1 (0.6)	3 (2.1)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)[a]	0 (0.0)

Applicant's table from Study ZS003 Study Report, Table 10-1, page 68.

Subacute Phase: All subjects who completed the Acute Phase and had i-STAT potassium values within the normal range (3.5 to 4.9 mmol/L, inclusive) on the morning of Study Day 3 were eligible to enter into the Subacute Phase. Greater proportions of subjects in the placebo (38.6%) and the lowest ZS dose group (1.25 g TID: 39.0%) did not achieve normokalemia following Acute Phase treatment and did not enter the Subacute Phase compared with the higher ZS dose groups (2.5 g TID: 25.5%; 5 g TID: 11.4%; 10 g TID: 10.5%). A summary of the proportions of subjects who did not enter the Subacute Phase by reason is presented in the following table.

Among subjects in the ZS 10 g TID group who did not enter the Subacute Phase, two had i-STAT potassium values < 3.5 mmol/L (range: 3.2 and 3.3 mmol/L). All other subjects who did not enter the Subacute Phase because of not achieving normokalemia had potassium values >5.0 mmol/L and did not qualify for the Subacute Phase.

Table 7: Subjects Did Not Enter Subacute Phase By Reason – All Randomized Subjects

Reason, n (%)	Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 158)	ZS 10 g TID (N = 143)
Did not enter Subacute Phase	61 (38.6)	60 (39.0)	37 (26.2)	19 (12.0)	16 (11.2)
Consent Withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.7)
Sponsor's Decision	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypo- or Hyperkalemia	61 (38.6)	60 (39.0)	36 (25.5)	18 (11.4)	15 (10.5)

Applicant's table from Study ZS003 Study Report, Table 10-2, page 69.

A summary of subject disposition for the Subacute Phase of the study is presented in the following table. Of the 579 subjects who completed ZS TID dosing during the Acute Phase, 447 continued into the Subacute Phase and were randomized to continue on the same ZS dose they received in the Acute Phase but administered QD or placebo. Greater than 90% of the subjects in each of the treatment groups completed the Subacute Phase of the study.

Eleven subjects (4.8%) in the ZS QD groups and 11 (5.1%) in the corresponding placebo groups prematurely discontinued from the study. Among the ZS treatment arms, the most common reason for premature discontinuation was an adverse event (7 subjects). Among the placebo treatment arms, the most common reasons for premature discontinuation were consent withdrawn (5 subjects) and adverse events (4 subjects). No dose-related trends were apparent among the treatment groups for the reasons leading to discontinuation. One subject in the ZS 10 g TID/Placebo group had a potassium value below the normal range (3.4 mmol/L), 4 hours after the first dose of placebo in the Subacute Phase and was prematurely discontinued from the study; the S-K value based on central laboratory measurement at this time point was 4.0 mmol/L. No other subjects were prematurely discontinued from the study due to hypokalemia or hyperkalemia.

Table 8: Subject Disposition in Subacute Phase – All Randomized Acute Phase ZS Subjects

	Acute Phase Treatment							
	ZS 1.25 g TID		ZS 2.5 g TID		ZS 5 g TID		ZS 10 g TID	
	Subacute Phase Treatment							
Disposition, n (%)	Placebo	ZS QD	Placebo	ZS QD	Placebo	ZS QD	Placebo	ZS QD
Randomized	41	49	46	54	68	65	61	63
Treated	41 (100)	49 (100)	46 (100)	54 (100)	68 (100)	65 (100)	61 (100)	63 (100)
Completed study	38 (92.7)	48 (98.0)	43 (93.5)	52 (96.3)	66 (97.1)	59 (90.8)	58 (95.1)	61 (96.8)
Discontinued study	3 (7.3)	1 (2.0)	3 (6.5)	2 (3.7)	2 (2.9)	6 (9.2)	3 (4.9)	2 (3.2)
Adverse event	1 (2.4)	1 (2.0)	1 (2.2)	1 (1.9)	1 (1.5)	4 (6.2)	1 (1.6)	1 (1.6)
Consent withdrawn	1 (2.4)	0 (0.0)	2 (4.3)	0 (0.0)	1 (1.5)	0	1 (1.6)	1 (1.6)
Protocol violation	1 (2.4)	0 (0.0)	0	0	0 (0.0)	1 (1.5)	0	0
Investigator's decision	0	0	0	1 (1.9)[a]	0	0	0	0
Hypo or hyperkalemia	0	0	0	0	0	0	1 (1.6)	0
Death	0	0	0	0	0	1 (1.5)	0	0

Applicant's table from Study ZS003 Study Report, Table 10-3, page 70.

A summary of subject disposition for the Acute Phase placebo subjects is summarized in the following table. Of the 157 subjects who completed placebo dosing during the Acute Phase, 96 continued into the Subacute Phase and were randomized to either ZS 1.25 g QD or 2.5 g QD. The majority of the subjects in both treatment groups completed the Subacute Phase of the study (≥96%). One subject in the Placebo/ZS 1.25 g QD group received a single dose in the Subacute Phase, despite having an elevated potassium value (5.4mmol/L) at the end of the Acute Phase, and was prematurely discontinued from the study. No other subjects were prematurely discontinued from the study due to hypokalemia or hyperkalemia.

Table 9: Subject Disposition –Randomized Acute Phase Placebo Subjects

	Acute Phase Treatment: Placebo	
	Subacute Phase Treatment	
Disposition, n (%)	ZS 1.25 g QD	ZS 2.5 g QD
Randomized	46	50
Treated	46 (100)	50 (100)
Completed study	44 (95.7)	49 (98.0)
Discontinued study	2 (4.3)	1 (2.0)
Consent withdrawn	1 (2.2)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (2.0)
Hypo- or hyperkalemia	1 (2.2)	0

Applicant's table from Study ZS003 Study Report, Table 10-4, page 71

Protocol Violations/Deviations

Across the Acute and Subacute Phases of the study, 11 subjects had major deviations identified based on blinded review of the data. Deviations observed during the Acute Phase included not fasting for the baseline S-K value (1 placebo subject), not fasting for Study Day 3 S-K value (1 ZS 1.25 g TID subject), dosed while S-K > 7.0 mmol/L (1 ZS 1.25 g TID subject), received incorrect study drug (1 ZS 5 g TID subject), received SPS within 7 days (1 ZS 10 g TID subject), and < 80% dosing compliance (1 ZS 10 g TID subject).

Deviations observed during the Subacute Phase included i-STAT potassium value did not qualify for Subacute Phase (1 ZS 1.25 g TID/Placebo subject and 1 Placebo/ZS 1.25 g QD subject) and received incorrect study drug (2 ZS 5 g TID/5 g QD subjects and 1 ZS 5 g TID/Placebo subject).

Reviewer comments: The small number of subjects who had major protocol deviations should have no impact on the overall efficacy and safety results of the study.

Table of Demographic Characteristics

Acute phase: A summary of demographic and other baseline characteristics for the Acute Phase of the study is presented by treatment group in the following table for the ITT Population.

The demographic characteristics were generally similar among the Acute Phase treatment groups. Among the Acute Phase treatment groups, mean age ranged from 65.2 to 66.2 years (overall range: 22 to 93 years). The majority of the subjects in each of the treatment groups were male (range: 53.9% to 64.5%) and most were White (range: 83.9% to 88.7%). Among the treatment arms, between 19 % to 28% of subjects baseline S-K values (per central laboratory) > 5.5 mmol/L. Based on the investigator, the most common etiology of elevated S-K within each of the Acute Phase treatment groups (subjects could have multiple etiologies) was CKD (based on eGFR < 60 mL/min, ~75%; range: 71% to 80%). Other etiologies of elevated S-K included use of RAAS inhibitor medication (~67%; range: 63% to 71%), and diabetes mellitus (~60%; range: 57% to 61%).

Table 10: Demographic and Other Baseline Characteristics in Acute Phase –ITT Population

Demographic/baseline characteristic		Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 143)
Gender	Male	98 (62.0)	83 (53.9)	91 (64.5)	96 (61.1)	80 (55.9)
	Female	60 (38.0)	71 (46.1)	50 (35.5)	61 (38.9)	63 (44.1)
Age (years)	Mean (SD)	65.6 (12.2)	65.4 (13.1)	65.9 (11.7)	65.2 (11.9)	66.2 (12.2)
	Median	66.5	66.0	67.0	66.0	68.0
	Min, max	27.0, 88.0	22.0, 93.0	27.0, 91.0	24.0, 89.0	31.0, 91.0
Race[a], n (%)	White	136 (86.1)	131 (85.1)	125 (88.7)	132 (84.1)	120 (83.9)
	African American	17 (10.8)	20 (13.0)	11 (7.8)	20 (12.7)	19 (13.3)
	Asian	2 (1.3)	0	5 (3.5)	3 (1.9)	2 (1.4)
	American Indian or Alaska Native	2 (1.3)	0	0	1 (0.6)	1 (0.7)
	Native Hawaiian or Other Pacific Islander	1 (0.6)	3 (1.9)	0	0	1 (0.7)
	Multiple race	0	0	1 (0.7)	1 (0.6)	0
	Others	0	0	1 (0.7)	0	0
Chronic Kidney Diseases	< 15 mL/min	15 (9.5)	8 (5.3)	15 (10.9)	8 (5.2)	10 (7.0)
	15-29+ mL/min	44 (27.8)	42 (27.8)	38 (27.5)	43 (27.9)	42 (29.4)
	30-59+ mL/min	61 (38.6)	73 (48.3)	48 (34.8)	64 (41.6)	50 (35.0)
	≥ 60 mL/min	38 (24.1)	28 (18.5)	37 (26.8)	39 (25.3)	41 (28.7)
Chronic Heart Failure		66 (41.8)	57 (37.0)	54 (38.3)	64 (40.8)	59 (41.3)
Diabetes mellitus		96 (60.8)	94 (61.0)	84 (59.6)	96 (61.1)	81 (56.6)
Baseline of Serum Potassium (mmol/L)	≤5.3	95 (60.1)	76 (49.4)	72 (51.1)	90 (57.3)	94 (65.7)
	5.4-5.5	22 (13.9)	38 (24.7)	29 (20.6)	36 (22.9)	27 (18.9)
	> 5.5	41 (25.9)	40 (26.0)	40 (28.4)	31 (19.7)	22 (15.4)
RAAS medication		101 (63.9)	109 (70.8)	97 (68.8)	99 (63.1)	96 (67.1)

a. Categories are not mutually exclusive.
Reviewer's table based on Study Report of Statistical Table 14.1.4A

Subacute phase: A summary of demographic and other baseline characteristics for the Subacute Phase is presented by treatment group in the following table for the Acute Phase ZS subjects ITT Population. The demographic and other baseline characteristics of the Subacute Phase ITT Population were generally similar to those noted for the Acute Phase ITT Population. The overall distributions of Subacute Phase baseline S-K (per central laboratory) and eGFR values, as well as etiologies of elevated S-K were similar among the Subacute Phase treatment groups.

Table 11: Subacute Phase- Demographic and Other Baseline Characteristics - ITT Population

	Acute Phase Treatment: Placebo	
	Subacute Phase Treatment	
Demographic Parameter Statistic	**ZS 1.25 g QD (N = 46)**	**ZS 2.5 g QD (N = 50)**
Age at screening (years)		
Mean (SD)	66.8 (12.36)	66.7 (13.55)
Median	68.0	69.5
Min, max	27.0, 87.0	35.0, 88.0
Gender, n (%)		
Male	25 (54.3)	31 (62.0)
Female	21 (45.7)	19 (38.0)
Race,[a] n (%)		
White	39 (84.8)	45 (90.0)
Black or African American	6 (13.0)	5 (10.0)
Asian	1 (2.2)	0
Weight at baseline[b] (kg)	n = 44	n = 50
Mean (SD)	85.8 (23.72)	83.7 (19.22)
Median	84.1	81.0
Min, max	50.8, 183.7	44.5, 129.0
Acute S-K baseline, n (%)		
≤ 5.3 mmol/L	35 (76.1)	36 (72.0)
5.4-5.5 mmol/L	7 (15.2)	6 (12.0)
> 5.5 mmol/L	4 (8.7)	8 (16.0)
Subacute S-K baseline, n (%)		
≤ 5.3 mmol/L	45 (97.8)	49 (98.0)
5.4-5.5 mmol/L	0	0
> 5.5 mmol/L	1 (2.2)	1 (2.0)
Acute eGFR at baseline, n (%)		
< 15 mL/min	3 (6.5)	1 (2.0)
15-29+ mL/min	14 (30.4)	8 (16.0)
30-59+ mL/min	17 (37.0)	24 (48.0)
≥ 60 mL/min	12 (26.1)	17 (34.0)
Subacute eGFR at baseline, n (%)		
< 15 mL/min	3 (6.5)	1 (2.0)
15-29+ mL/min	12 (26.1)	7 (14.0)
30-59+ mL/min	20 (43.5)	21 (42.0)
≥ 60 mL/min	11 (23.9)	20 (40.0)
Etiology,[a] n (%)		
CKD	28 (60.9)	24 (48.0)
CHF	18 (39.1)	19 (38.0)
Diabetes mellitus	26 (56.5)	27 (54.0)
RAAS medication	28 (60.9)	34 (68.0)

a. Categories are not mutually exclusive.
b. Weight at baseline was the measurement taken at screening

Applicant's table from CSR Study ZS003, Table 11-6, page 78.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the Acute Phase, 2 of the 3 daily doses were administered at the site by study staff and the third dose was taken at home. Within each of the Acute Phase treatment groups, > 96.2% of subjects received all 3 doses of study drug on Study Days 1 and 2.

During the Subacute Phase, the majority (> 90%) of the subjects within each of the treatment groups was dosed on each of the 12 days.

Major concomitant medications that could affect the study results include RAAS inhibitors, diuretics, and insulin. Use of RAAS inhibitors and insulin were similar among the different group. Furosemide, torsemide, Bumex, and HCTZ were initiated in sixteen subjects during the trial, including 3 placebo subjects, 6 subjects on ZS 1.25 g, 1 on 2.5 g, 2 on 5 g, and 4 on 10 g. The initiation of diuretics in these patients would not be expected to have a significant impact on the efficacy results. No rescue medication was used in the study.

Efficacy Results – Primary Endpoint
The efficacy findings for the primary endpoint, described below, were confirmed by the FDA statistical reviewer, Dr. Thomas Birkner.

The primary efficacy endpoint for the Acute Phase was the difference in the exponential rate of change in S-K values during the initial 48 hours of study drug treatment between the placebo-treated subjects and the ZS-treated subjects. The primary efficacy endpoint for the Subacute Phase was the difference in the exponential rate of change in S-K values over the 12-day treatment interval between those on subacute therapy and randomized withdrawal, separately for the 4 Acute Phase active treatments (excluding Acute Phase placebo). Type I error for the Acute Phase and the Subacute Phase testing of the primary efficacy endpoint was controlled at 0.05 by the use of a closed procedure. The predefined closed procedure order first tested the highest Acute Phase dose, then the highest Subacute Phase dose, then the next highest dose (Acute then Subacute), until statistical significance was no longer achieved.

Based on the closed testing procedure, the 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were statistically significantly superior to placebo for the exponential decrease in S-K during the Acute Phase and the 10 g and 5 g QD doses of ZS were statistically significantly superior to placebo for the exponential decrease in S-K during the Subacute Phase. Thus, the first 5 significance tests met the pre-specified closed testing procedure requirements as shown in the following table.

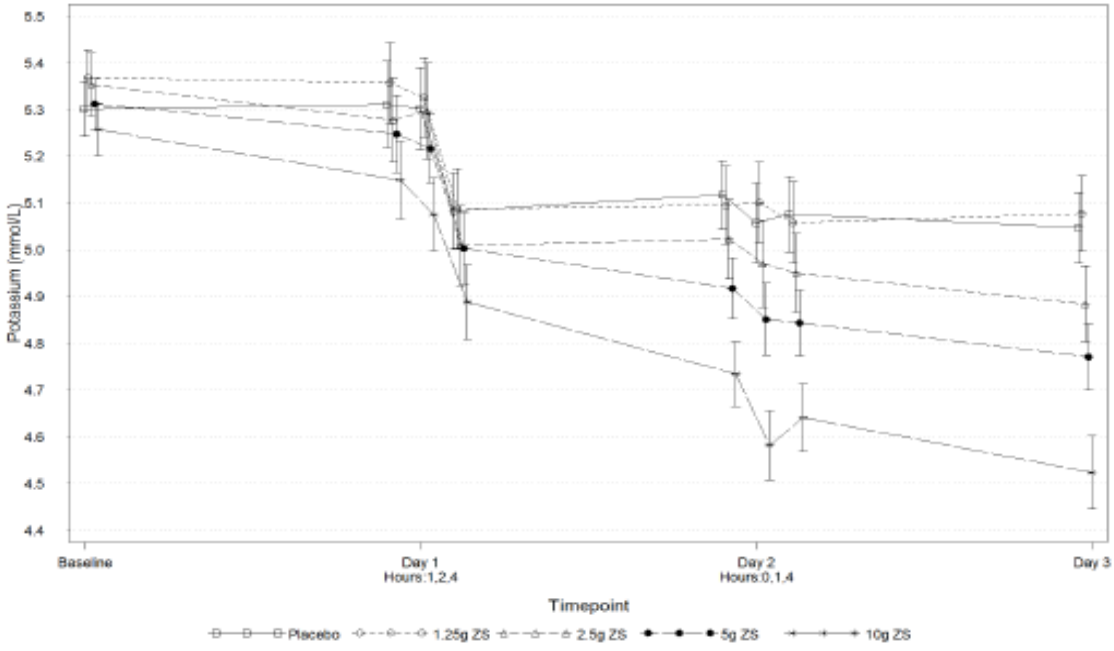
Table 12: Closed Testing Procedure and the Exponential Rate of Change in Serum Potassium during Acute and Subacute Phases

Treatment Group	Exponential Decrease in S-K p-value
Acute Phase: ZS 10 g TID versus placebo TID	10^{-31}
Subacute Phase: ZS 10 g QD versus corresponding placebo QD	10^{-23}
Acute Phase: ZS 5 g TID versus placebo TID	< 0.0001
Subacute Phase: ZS 5 g QD versus corresponding placebo QD	0.0083
Acute Phase: ZS 2.5 g TID versus placebo TID	0.0009
Subacute Phase: ZS 2.5 g QD versus corresponding placebo QD	Not significant (p = 0.4761)
Acute Phase: ZS 1.25 g TID versus placebo TID	Not significant (p = 0.0874)
Subacute Phase: ZS 1.25 g QD versus corresponding placebo QD	Not significant (p = 0.1900)

Applicant's table from CSR Study ZS003, Table 11-7, page 80.

Acute Phase: Based on the closed testing procedure, the 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were statistically significantly superior to placebo for the exponential decrease in S-K over the initial 48 hours of treatment. Mean (± 2 × standard error). S-K values over the initial 48 hours of treatment are described in the following figure. Statistically significant differences from placebo were also observed for these ZS dose groups in the exponential decrease in S-K over the initial 24 hours of treatment (Study Day 2: 0 hour; 10 g [p < 0.0001], 5 g [p < 0.0001], and 2.5 g [p = 0.0315] TID).

Figure 1: Acute Phase- Mean Serum Potassium over Initial 48 Hours – ITT Population

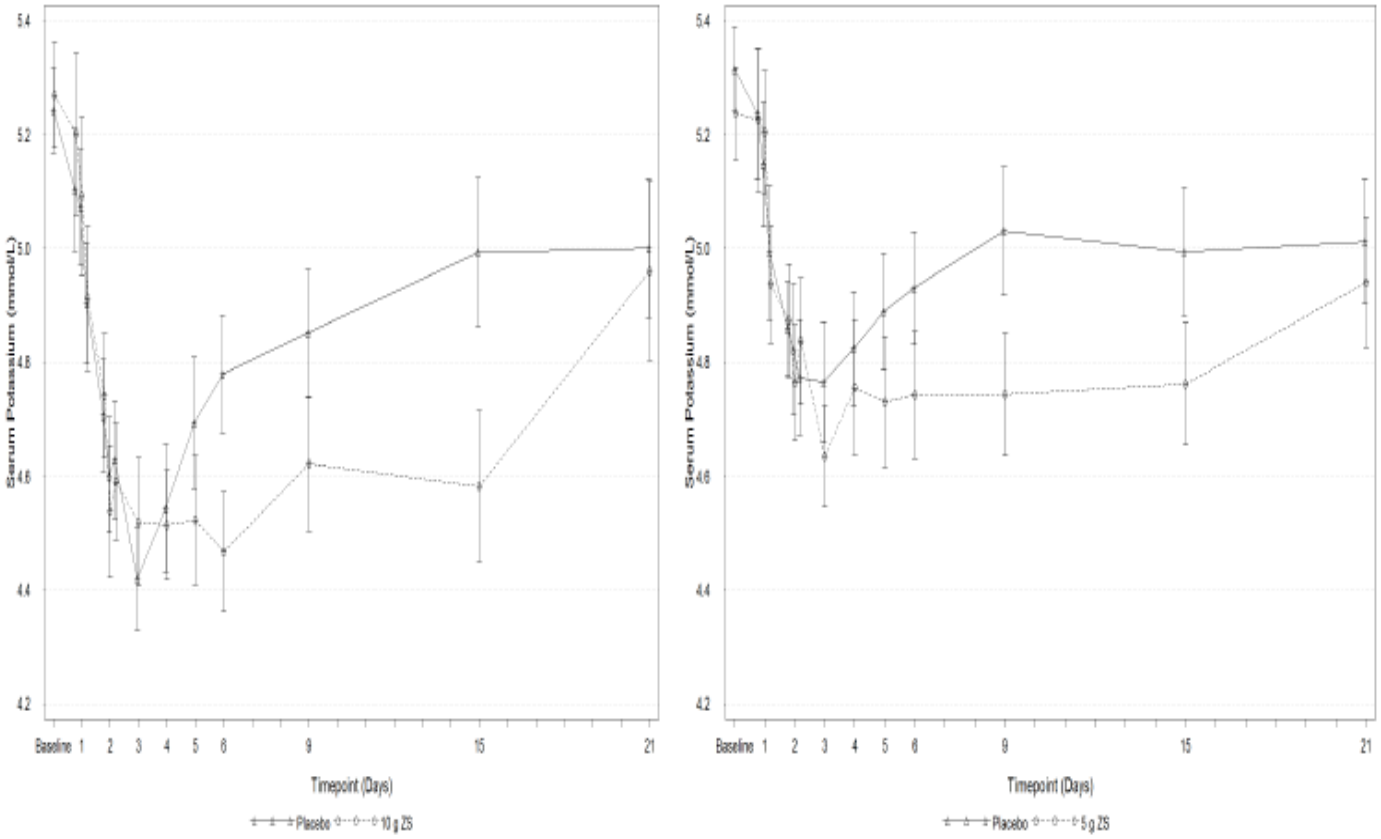


Applicant's figure from CSR Study ZS003, Figure 11-1, page 81.

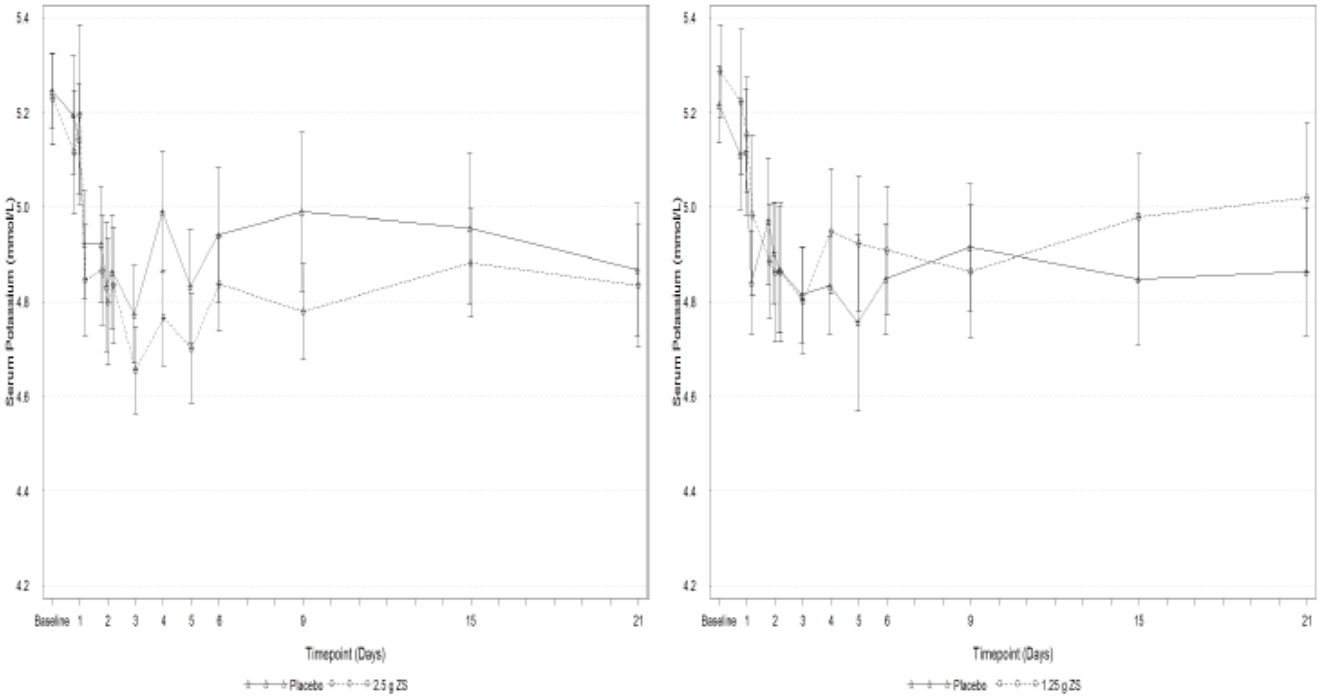
Subacute phase: Based on the closed testing procedure, the 10 g QD and 5 g QD doses of ZS were statistically significantly superior to placebo for the exponential decrease in S-K over the Subacute Phase 12-day treatment interval. Mean (± 2 × standard error) S-K values over the Subacute Phase are described in the following figures. A statistically significant difference from placebo was observed in the exponential decrease in S-K from baseline over the first 5 days of the Subacute Phase for the ZS 10 g QD dose group ($p < 0.0001$), but not for the ZS 5 g QD dose group ($p = 0.0936$).

Figure 2: Subacute Phase-Mean (± 2 Standard Errors) Serum Potassium (mmol/L) Over Time - ITT Population

Placebo versus ZS 10 g QD **Placebo versus ZS 5g QD**



Placebo versus ZS 2.5 g QD **Placebo versus ZS 1.25 g QD**



Applicant's figure from Study ZS003 Study Report, Figure 11-2, pages 85-86.

Data Quality and Integrity – Reviewers' Assessment

Review of the submitted data did not raise concern for data quality or integrity issues. As noted in section 4.1, according to OSI, the study appears to have been conducted adequately, and the data submitted by the Applicant may be used in support of the indication.

Efficacy Results – Secondary and other relevant endpoints

Acute phase: There was no prospective plan to control the type 1 error in testing secondary endpoints. The results of secondary endpoint analyses, as reported by the Applicant, are provided below.

- Mean Change (Absolute and Percent) From Baseline in Serum Potassium Values: Mean baseline S-K values were similar among the Acute Phase treatment groups, ranging from 5.3 to 5.4mmol/L. For the 10 g TID dose of ZS, the S-K lowering effect started immediately from placebo noted for the mean change from baseline 1 hour after the first dose of study drug. The difference from placebo was observed at all scheduled time points from 1 hour to 48 hours after the initial dose. Similar results were observed for percent change from baseline. The largest mean decrease from baseline in S-K was at 48 hours after the first dose of study drug in the ZS 10 g TID dose group (-0.73 mmol/L).

  The S-K lowering effect of ZS was also observed in the ZS 5 g TID and 2.5 g TID groups. For the 5 g TID dose of ZS, the first difference from placebo was noted for the mean

change from baseline 2 hours after the first dose of study drug. The difference from placebo was observed at all scheduled time points from 24 to 48 hours after the initial dose. Similar results were observed for percent change from baseline. The largest mean decrease from baseline in S-K was at 48 hours after the first dose of study drug in the ZS 5 g TID dose group (-0.54 mmol/L).

For the 2.5 g TID dose of ZS, the first difference from placebo was noted for the mean change from baseline 4 hours after the first dose of study drug. The difference from placebo was observed at all scheduled time points from 4 hours to 48 hours after the initial dose. Similar results were observed for percent change from baseline. The largest mean decrease from baseline in S-K was at 48 hours after the first dose of study drug in the ZS 2.5 g TID dose group (-0.46 mmol/L).

- Time to 0.5 mmol/L decrease in S-K Values: The time to a 0.5 mmol/L decrease in S-K values was reduced with the ZS 10 g, ZS 5 g, and ZS 2.5 g TID doses compared to placebo. No difference from placebo was observed for the ZS 1.25 g TID dose.

- Time to Normalization in Serum Potassium Values: Time to normalization of S-K values (defined as S-K values between 3.5 and 5.0 mmol/L, inclusive) was reduced with the ZS 10 g TID dose as compared to placebo. No differences from placebo were observed for the ZS 5 g, 2.5 g, or 1.25 g TID doses.

- Percentage of Normokalemic Subjects: The percentage of normokalemic subjects across all treatment groups was different 2 hours following the first dose of study drug and from pre-dose on Study Day 2 (24-hour time point) through pre-dose on Study Day 3 (48-hour time point). For the ZS 10 g TID dose, the difference from placebo in percentage of normokalemic subjects was different 2 hours following the first dose on Study Day 1 and from pre-dose on Study Day 2 through pre-dose on Study Day 3. The percentage of normokalemic subjects in the ZS 10 g TID dose group was > 75% at each scheduled time point on Study Days 2 and 3.

  For the ZS 5 g TID dose, the difference from placebo in percentage of normokalemic subjects was different from pre-dose on Study Day 2, 4 hours after the first dose on Study Day 2, and pre-dose on Study Day 3. The percentage of normokalemic subjects in the ZS 5 g TID dose group was > 65% at each scheduled time point on Study Days 2 and 3.

  For the ZS 2.5 g TID dose, the difference from placebo in percentage of normokalemic subjects was from 4 hours after the first dose on Study Day 2 and pre-dose on Study Day

3. The percentage of normokalemic subjects in the ZS 2.5 g TID dose group was > 60% from 1 hour after the first dose on Study Day 2 through pre-dose on Study Day 3.

In compared to the placebo, the 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were significantly increased the percentage of normokalemic subjects at 48 hours after the first dose of study drug based on a logistic regression model with factors for Acute Phase baseline S-K, Acute Phase baseline eGFR, etiology, and age.

Subacute Phase: As in the Acute Phase, there was no prospective plan to control the type 1 error in testing secondary endpoints. The results of secondary endpoint analyses, as reported by the Applicant, are provided below.

- Time to Relapse in Serum Potassium Values: Time to relapse in S-K values (return to Acute Phase S-K baseline value) during the Subacute Phase was significantly later with continued ZS QD treatment than with placebo for subjects who received ZS 5 g TID and ZS 2.5 g TID in the Acute Phase, but not for the ZS 10 g QD group, which is most likely due to the extended effect of ZS dosing during the Acute Phase within the placebo group. Median time to relapse from the Subacute Phase baseline was 18.0, 6.0, 12.0, and 2.0 days in the ZS 10 g, 5 g, 2.5 g, and 1.25 g QD groups, respectively. Median time to relapse from the Subacute Phase baseline for subjects randomized to placebo was 12.0, 2.0, 1.0, and 3.0 days among subjects who received ZS 10 g, 5 g, 2.5 g, and 1.25 g TID, respectively, in the Acute Phase.

- Total Number of Days Normokalemic: Subjects in the ZS 10 g QD, 5 g QD, and 2.5 g QD groups each had a significant greater total number of days normokalemic (S-K values between 3.5 and 5.0 mmol/L, inclusive) compared to their corresponding placebo groups during the Subacute Phase. There was no difference between the ZS 1.25 g QD and 2.5 g QD groups in the total number of days normokalemic (S-K values between 3.5 and 5.0 mmol/L, inclusive) during the Subacute Phase.

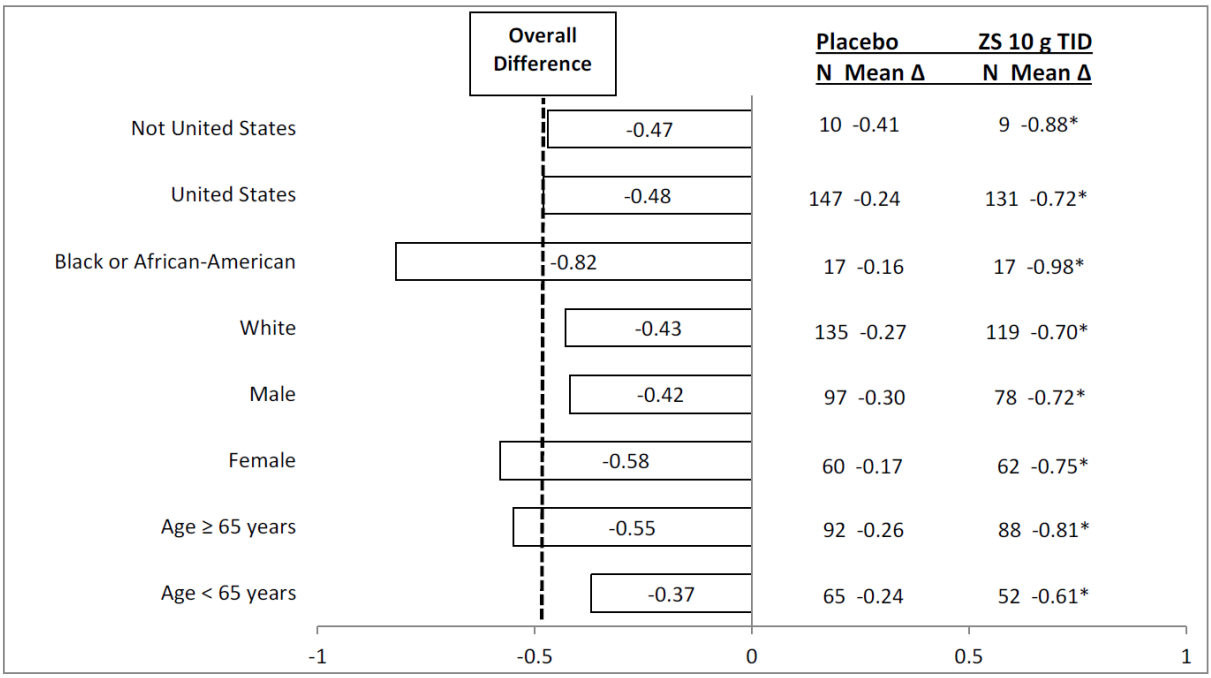
- Percentage of Subjects Within Each Treatment Group Who Retained Normal Serum Potassium Values at End of Treatment and the End of the Subacute Phase: A significantly greater proportion of subjects in the ZS 10 g QD and 5 g QD groups retained normal S-K values (S-K values between 3.5 and 5.0 mmol/L, inclusive) at the end of treatment in the Subacute Phase (Subacute Day 12) compared to their corresponding placebo groups. There were no differences between any of the ZS QD dose groups and their corresponding placebo groups for the proportions of subjects who retained normal S-K values at the end of the Subacute Phase. There were no differences between the ZS 1.25 g QD and 2.5 g QD groups in the percentage of subjects who retained normal S-K values at the end of treatment in the Subacute Phase (Subacute Day 12) or at the end of the Subacute Phase (Subacute Day 18).

- Mean Change (Absolute and Percent) From Baseline in Serum Potassium Values: Among subjects who received ZS 10 g TID during the Acute Phase, significant differences versus placebo for change in S-K values from the Subacute Phase baseline to Subacute Phase Days 2, 3, 6, and 12 were observed. Mean increases (0.28 to 0.58 mmol/L) from the Subacute Phase baseline were observed on these days for subjects randomized to placebo in the Subacute Phase compared with small, variable mean changes (-0.06 to 0.10 mmol/L) in subjects randomized to ZS 10 g QD in the Subacute Phase. There were no differences between the ZS 1.25 g QD and 2.5 g QD dose groups for mean change or mean percent change from the Subacute Phase baseline to scheduled visits during the Subacute Phase.

- Time to Increase in Serum Potassium Values of 0.5mmol/L: Time to first increase of ≥ 0.5 mmol/L in S-K during the Subacute Phase was later with continued ZS QD treatment than with placebo for subjects who received ZS 10 g TID in the Acute Phase. No other treatment group differences were observed. Median time to increase of ≥ 0.5mmol/L in S-K from the Subacute Phase baseline was 18.0, 18.0, 12.0, and 18.0 days in the ZS 10 g, 5 g, 2.5 g, and 1.25 g QD groups, respectively. Median time to increase of ≥ 0.5 mmol/L in S-K from the Subacute Phase baseline for subjects randomized to placebo in the Subacute Phase was 3.0, 6.0, 12.0, and 18.0 days among subjects who received ZS 10 g, 5 g, 2.5 g, and 1.25 g TID, respectively, in the Acute Phase.

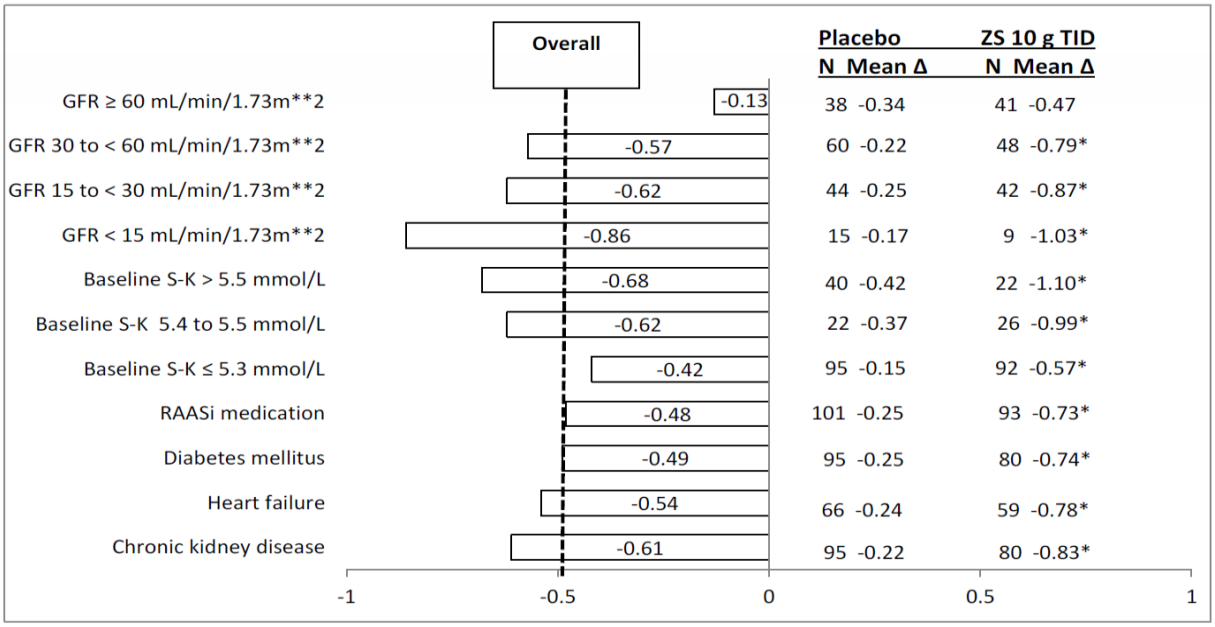
Subgroup Analysis: Efficacy of ZS in the subgroup analysis was assessed by demographic characteristics (age, gender, race, and geographic region) and by baseline eGFR, baseline S-K, concomitant diseases, and use of RAAS inhibitor medication. Efficacy was observed across the subpopulations that were examined.

Table 13: Differences between ZS 10 g TID and Placebo for Mean Change in Serum Potassium (mmol/L) from Baseline to 48 Hours by Demographic Characteristics (Acute Phase, ITT Population)



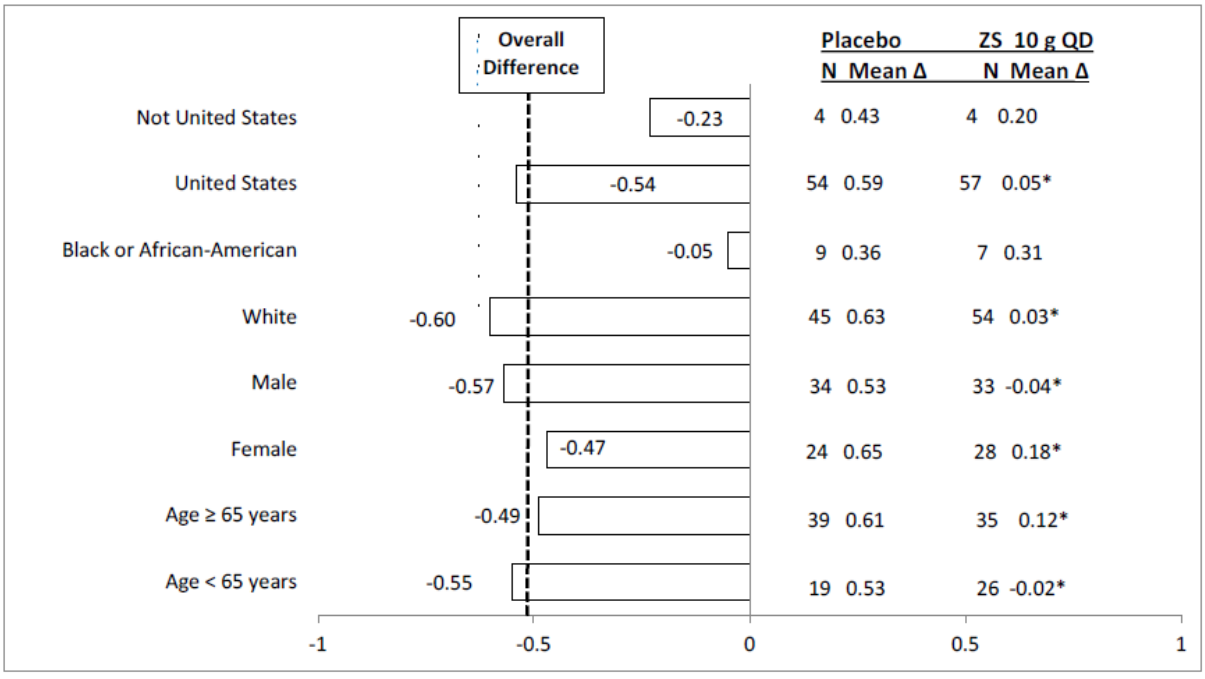
Applicant's Figure from SCE figure 3-7, page 55.

Table 14: Differences between ZS 10 g TID and Placebo for Mean Change in Serum Potassium (mmol/L) from Baseline to 48 Hours by Baseline Characteristics (ITT Population)



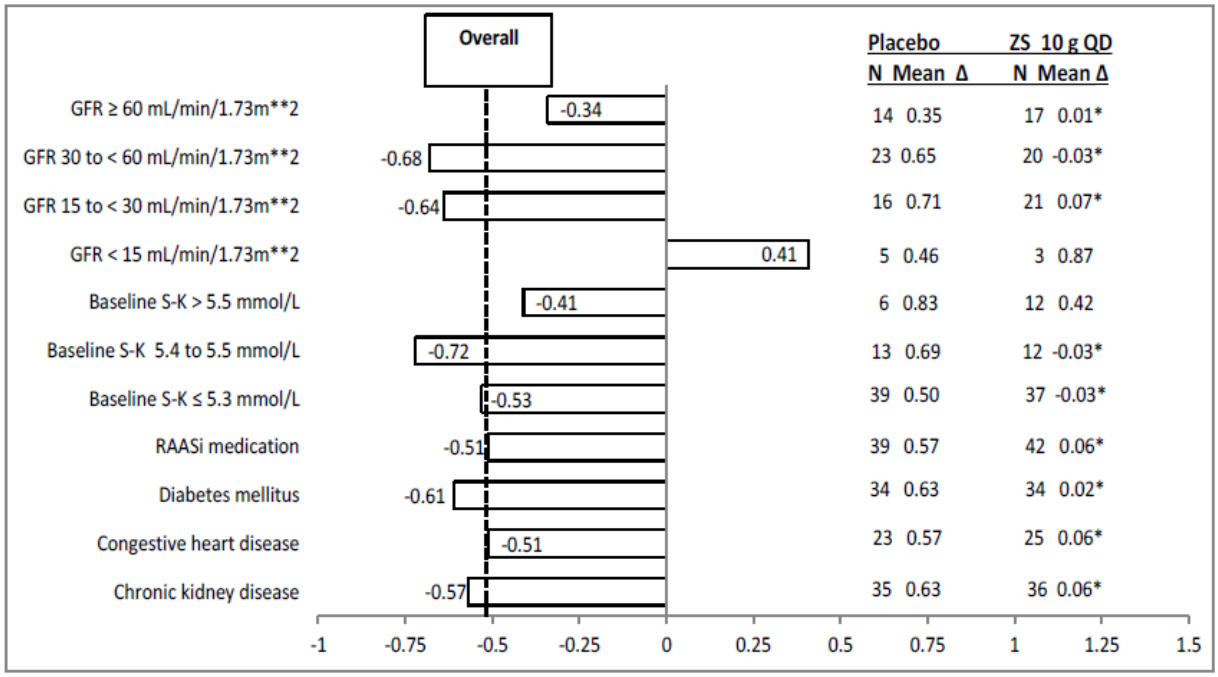
Applicant's Figure from SCE figure 3-8, page 56.

Table 15: Differences between ZS 10 g QD and Placebo for Mean Change in Serum Potassium (mmol/L) from Baseline to Study Day 12 by Demographic Characteristics (ITT Population)



Applicant's Figure from SCE figure 3-12, page 60.

Table 16: Differences between ZS 10 g QD and Placebo for Mean Change in Serum Potassium (mmol/L) from Baseline to Day 12 by Subpopulation (ITT Population)



Applicant's Figure from SCE figure 3-13, page 61.

Durability of Response

This was a short-term study. As such, it does not provide significant insight into the durability of the treatment effect during long-term use.

Persistence of Effect

There was a dose-dependent increase in the time to relapse in S-K values (return to acute phase S-K baseline value) after subjects switched to placebo in the Subacute Phase. The mean time to relapse was 12 days in subjects treated with ZS 10g tid in the Acute Phase, 2 days in subjects treated with ZS 5g tid, and 1 day in subjects treated with ZS 2.5g tid.

Additional Analyses Conducted on the Individual Trial

None.

6.2. Study ZS004

6.2.1. Study Design

Overview and Objective
Study ZS004 was a phase 3 multicenter, multi-phase, multi-dose prospective, randomized double-blind, placebo-controlled, maintenance study to investigate the safety and efficacy of ZS in subjects with hyperkalemia.

The stated purpose and major objectives of the study were to evaluate the safety and efficacy of three different doses of ZS administered once daily for 28 days in maintaining normokalemia (serum potassium between 3.5 – 5.0 mmol/l, inclusive) in subjects achieving normokalemia following two days of acute therapy.

Trial Design
Study ZS004 had two phases: an open label acute phase and a maintenance phase.

Acute Phase**:** During the Acute Phase (Study Days 1 and 2), subjects were to receive open-label ZS at a dose of 10g three times a day for 48 hours. On each day, the first dose was to be administered at the site and the second and third doses were to be taken at home just before lunch and the evening meal, respectively. Potassium values were measured as fasting, 2 times at 0 and 60 minutes (± 10 minutes) for establishment of a baseline, at 1, 2, and 4 hours (± 15 minutes) after the first dose on Acute Phase Study Day 1, before (0 hour) and 1 hour (± 15 minutes) after the first dose on Acute Phase Study Day 2, and after 48 hours of treatment in the morning of Acute Phase Study Day 3.

Subjects who had i-STAT potassium values ≥ 6.1 mmol/L on Acute Phase Study Day 1 at the 4-hour post Dose 1 time point were to remain at the site and take the second dose of study drug 4 hours after the first dose. Ninety minutes after Dose 2, another blood sample and an electrocardiogram (ECG) were to be obtained. If the i-STAT potassium value was > 6.2 mmol/L at the 90-minute post Dose 2 time point, the subject was to be discontinued from the study and receive standard of care treatment. If the i-STAT potassium value was ≤ 6.2 mmol/L, and the ECG did not meet any of the ECG stopping criteria, the subject was allowed to continue in the study. Subjects whose i-STAT potassium value was not within the normal range (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) by the morning of Acute Phase Study Day 3 were to be withdrawn from the study, receive standard of care treatment at the discretion of their physician, and return to the site for an End of Study Visit 7 (± 1) days later on Acute Phase Study Day 9.

Maintenance Phase: All subjects who completed the Acute Phase and had i-STAT potassium values within the normal range (3.5 to 5.0mmol/L, inclusive) on the morning of Acute Phase

Study Day 3 were to be randomized to 1 of 3 doses of ZS (5 g, 10 g, and 15 g) or placebo administered QD. Study drug was to be administered at the site in the morning on Maintenance Phase Study Days 1 (Acute Phase Study Day 3), 2, 5, 8, 12, 15, 19, 22, and 26. On all other days, subjects were to take study drug at home, just before breakfast. Subjects who developed i-STAT potassium values between 3.0 and 3.4 mmol/L, inclusive, during the Maintenance Phase, were to have study drug dosing reduced from QD to every other day (QOD) for the remainder of the study.

Subjects were to return to the site on Maintenance Phase Study Days 2, 5, 8, 12, 15, 19, 22, 26, and 29 in a fasting state for potassium measurements. Maintenance Phase subjects who completed the Maintenance Phase Study Day 29 visit or who discontinued due to hypo- or hyperkalemia were to be offered participation in an open-label extension study (ZS-004E) designed to evaluate the long-term safety and efficacy of ZS in maintaining normokalemia. All study subjects who did not enter the extension study were to be followed for a total of 7 (± 1) days after the last dose of study drug.

Key inclusion /exclusion criteria:

- Mean i-STAT potassium values ≥ 5.1 mmol/l inclusive, at screening
- Other entry criteria were similar to Study ZS003

Dose Selection: The Acute Phase ZS dose (10 g TID) was selected based on efficacy data obtained from the phase 3 study (ZS-003) in which ZS dosages of 5 g and 10 g 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 10 g ZS dose. The Maintenance Phase ZS doses (5 g, 10 g or 15 g QD for 28 days) were selected based on results from the Maintenance Phase of the phase 3 study (ZS-003) to ensure optimal control of S-K values throughout the 28-day Maintenance Phase. Based on data from ZS-003, combined with modeling, it was estimated that the 2 top doses of ZS (10 g and 15 g QD) would be able to maintain the majority of subjects within the normokalemic range throughout the 28-day period. The 5 g QD dose was included to try to establish a minimum effective dose.

Study treatments: As previously noted, all subjects received 10 g ZS administered TID for the initial 48 hours (Acute Phase). In the Acute phase, the first daily dose was to be taken in the clinic ~1 hour before breakfast and the second and third daily doses were be taken at home just before lunch and dinner. In the Maintenance phase, subjects received a randomized dose of ZS (5 g, 10 g, or 15 g) or placebo administered QD in the morning, just before breakfast, for 28 days. The dose preparations were exact the same as the prior study, Study ZS 003.

Dose Modification and Discontinuation: If a subject developed i-STAT potassium values < 3.0 mmol/L at any time during the study or > 6.2 mmol/L during the Maintenance Phase, or a

clinically significant cardiac arrhythmia (see discussion of Study ZS003 for the definition), the subject was to receive appropriate medical treatment and be discontinued from study drug.
Randomization and Blinding: During the Acute Phase, all subjects were treated with open-label ZS 10 gm tid. Subjects who achieved normokalemia (i-STAT potassium between 3.5 mmol/L and 5.0 mmol/L, inclusive) on the morning of Acute Phase Study Day 3, were randomized to 1 of 3 doses of ZS (5 g, 10 g, and 15 g) or placebo in a 4:4:4:7 ratio.

To obtain a subject's blinded treatment assignment, the site contacted the IVRS/IWRS. The IVRS/IWRS provided a Maintenance Phase kit assignment (Week 1) for the subject; a new kit number was assigned weekly during the Maintenance Phase via the IVRS/IWRS using the kit number based on the randomization. Maintenance Phase kits were dispensed by designated and trained site pharmacy staff. The randomization code was held by (b) (4) which was not associated with the clinical management of the study.

Blinding was maintained during the Maintenance Phase via the use of identical-appearing ZS and placebo sachet that were packaged into kits that were uniquely coded and assigned through the randomization and subsequent visits via the IVRS/IWRS. The assignment of unique numeric codes to active product or placebo was securely retained until such time as designated by the statistical analysis plan. Rules for unblinding the study were similar to the rules for unblinding Study ZS003.

Investigators and study administrative structure:
The study was overseen by the applicant and conducted by investigators contracted by and under the direction of the applicant. The study was conducted at 44 investigational sites in the US, Australia, and South Africa. The study had an IDMC whose function was similar to that in Study ZS003.

Procedures and schedule:
The schedule of study assessments for the Acute Phase and the Maintenance Phase are summarized in the following two tables.

Table 17: Open-Label Acute Phase (AP)

AP Study Day Parameter	SCRN[10]	1	2	3[7]	9 (EOS)[9]
			In-clinic		for subjects NOT entering the DBRMP
Written informed consent	X				
Eligibility criteria		X[10]			
Demographics		X[10]			
Medical History		X[10]			
Physical exam including weight		X[10]		X	X
Access IVRS/IWRS		X		X[11]	
Study drug (IP) administration[5]		X	X		
ECG		X[10]		X	X
Vital signs		X[10]		X	X
Concomitant medications		X[10]	X	X	X
Adverse events and non-protocol Physician/ER visits		X	X	X	X
Potassium[4]		X[2]	X[3]	X[8]	X[8]
Serum chemistry[1,4]		X[10]		X	X
Hematology[1,4]		X[10]		X	X
Urinalysis including sediment[1,4]		X[10]		X	X
Urine culture		X[10]			X
Urine HCG		X[6, 10]			X[6]
IP Reconciliation					X

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 will be measured predose (0 hour) and 1 hour (± 15 min) post 1st 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. 11 Access IVRS/IWRS on AP Study Day 3 or if subject permanently discontinues dosing before the end of the AP dosing period

Applicant's table from Study ZS004 Study protocol, table 5.1, page 19

Table 18: DB Randomized Maintenance Phase (DBRMP)

DBRMP Study Day[7]	1	2	5	8	12	15	19	22	26	29	35 (EOS)[8]
Eligibility criteria	X										
Physical exam including weight[3]	X					X				X	X
Access IVRS/IWRS[9]	X			X		X		X			
Study drug (IP) administration[4]	X	X	X	X	X	X	X	X	X		
ECG[3]	X			X		X		X		X	X
Vital signs[3]	X					X				X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events and non-protocol Physician/ER visits	X	X	X	X	X	X	X	X	X	X	X
Potassium[6]	X[2]	X	X	X	X	X[2]	X	X	X	X[2]	X[2]
Serum chemistry[1, 3]	X					X				X	X
Hematology[1, 3]	X					X				X	X
Urinalysis[1, 3]	X					X				X	X
Urinary sediment	X					X				X	X
Urine Culture										X[10]	X
Urine HCG										X[10]	X[5]
IP Reconciliation										X	

1. All blood potassium samples are analyzed by i-STAT and by the Central Laboratories.
2. Potassium will be measured fasting, prior to the 1st 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

Applicant's table from Study ZS004 Study protocol, table 5.2, page 21

Concurrent Therapy: All subjects were to continue the treatments they were on upon admission into the study. Whenever possible, all blood draws collected prior to meals were to be collected prior to insulin/insulin analogue treatment. From Acute Phase Study Day 1 through Maintenance Phase Study Day 28, the time of dosing with insulin/insulin analogues was to be recorded if administered at the site.

During the study, subjects were not to receive alternative treatment for hyperkalemia while taking study drug. If dosing with study drug was discontinued or the subject completed dosing, the subject may have received alternative treatment for hyperkalemia if clinically indicated prior to completing the End of Study Visit. Any alternative treatment administered after the end of study drug administration and prior to the End of Study Visit was to be recorded in the concomitant medication CRF (and as an adverse event, if applicable).

Recordkeeping and Monitoring: Similar to Study ZS003.

Study Endpoints

The primary efficacy endpoint in the study was the mean S-K value of ZS administered once a day in comparison with the placebo 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 ≥ 5.1mmol/l) at baseline.

Other major endpoints are listed below. As discussed under "Statistical Analysis Plan", a hierarchical testing procedure was used to control the type 1 error in testing some of these endpoints.

- 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; and time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/l, inclusive).

- Maintenance Phase: the mean cumulative days of normokalemic in this phase; 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; and the proportion of subjects who remain normokalemic at DBRMP Study Days 8, 15, 22 and 29 days.

Exploratory endpoints not related to potassium for both study phases included: 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; and incidence of hospitalization and ER visits.

For a more detailed discussion of the primary endpoint analysis, see the discussion of the statistical analysis plan below.

Statistical Analysis Plan
The analyses described in this section were based on the final statistical analysis plan. The statistical analysis plan was finalized on July 17, 2014; the database was locked and unblinded on August 29, 2014.

The statistical analysis plan specified the following populations for key efficacy and safety analyses.

Acute Phase "Intent-to-Treat" Population: This population was to be used for analyses of Acute Phase efficacy and included all subjects who were who received at least 1 Acute Phase dose administration and had any post-baseline S-K values after receiving the investigational product during the first 48 hours.

Maintenance Phase Intent-to-Treat Population: This population was to be used for the primary analyses of Maintenance Phase efficacy and included all randomized subjects who received at least 1 Maintenance Phase dose administration and who had at least 1 observed S-K value on or after Maintenance Phase Day 8.

Maintenance Phase Modified Intent-to-Treat Population: The Maintenance Phase Modified ITT Population included all subjects who were included in the Maintenance Phase ITT Population and had no significant protocol deviations that may have been expected to bias the subject's S-K assessments. Subjects were to be analyzed according to randomized treatment assignments.

Reviewer's comment: Analyses for the Maintenance Phase Modified ITT Population were only to be executed if at least 5% of the Maintenance Phase ITT Population required exclusion and were only to be used for assessment of efficacy. As < 5% of the subjects in the ITT Population would have required exclusion, only the ITT Population was analyzed.

Acute Phase Safety Population: This population was to be used for analyses of Acute Phase safety and was defined as all subjects who received at least 1 Acute Phase dose administration.

Maintenance Phase Safety Population: This population was to be used for analyses of Maintenance Phase safety and included all randomized subjects who received at least 1 Maintenance Phase dose administration.

Efficacy Endpoint Analyses: The primary efficacy endpoint was the model-based least squares mean (LSMEAN) of all available S-K values inclusive of Maintenance Phase Study Days 8 to 29.

As described below, a pre-specified hierarchical testing procedure was used to test the first secondary endpoint for the Acute Phase first (the exponential rate of change in S-K values during the initial 48 hours of study drug treatment), followed by the primary endpoint for the Maintenance Phase and 3 secondary endpoints for the Maintenance Phase (total number of days normokalemic, proportions normokalemic at Study Day 29/Exit, and mean S-K standard deviation). For each endpoint, the comparisons to placebo were from highest to lowest ZS dose. Thus, in total, there were 13 treatment comparisons in the hierarchy, which was deemed to be the practical limit to the number of such comparisons.

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

- Acute Phase S-K exponential rate of change from baseline through 48 hours
- Maintenance Phase Study Day 8 to 29 mean S-K
  (Null hypothesis: 15 g = placebo)
- Maintenance Phase Study Day 8 to 29 mean S-K
  (Null hypothesis: 10 g = placebo)
- Maintenance Phase Study Day 8 to 29 mean S-K
  (Null hypothesis: 5 g = placebo)
- Maintenance Phase total number of days normokalemic
  (Null hypothesis: 15 g = placebo)
- Maintenance Phase total number days normokalemic
  (Null hypothesis: 10 g = placebo)
- Maintenance Phase total number days normokalemic
  (Null hypothesis: 5 g = placebo)
- Maintenance Phase Study Day 29/Exit proportion of subjects normokalemic
  (Null hypothesis: 15 g = placebo)
- Maintenance Phase Study Day 29/Exit proportion of subjects normokalemic
  (Null hypothesis: 10 g = placebo)
- Maintenance Phase Study Day 29/Exit proportion of subjects normokalemic
  (Null hypothesis: 5 g = placebo)
- Maintenance Phase mean S-K intra-subject standard deviation
  (Null hypothesis: 15 g = placebo)
- Maintenance Phase mean S-K intra-subject standard deviation
  (Null hypothesis: 10 g = placebo)
- Maintenance Phase mean S-K intra-subject standard deviation
  (Null hypothesis: 5 g = placebo)

Determination of Sample Size: The sample size was based on the mean S-K during Maintenance Phase Study Days 8 through to 29. To optimize the comparison of 3 active doses versus placebo control, the placebo group had 1.73 × the number of subjects per active dose. A 4:4:4:7 allocation best approximated the optimum Dunnett's allocation. A sample size of 232 Maintenance Phase subjects (49 per active dose and 85 placebo controls) had 90% power and 5% Type 1 error for a 2-sided hypothesis test to detect a mean 0.3 mmol/L advantage for Maintenance Phase Study Days 8 through 29 for any active dose versus 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 had 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 Maintenance Phase for a pooled 6-day standard deviation.

Protocol Amendments
The original protocol, dated 8 July 2013, had 3 amendments (identified as Amendments 1, 2, and 3). Most of the modifications related to changes in entry criteria, sample collections, and safety monitory procedures and clarifications regarding study procedures. The study endpoint was not modified and from, an efficacy perspective, the changes that were made would not be expected to impact the interpretability of the efficacy findings.

Data Quality and Integrity: Sponsor's Assurance
The methods for assuring data quality and integrity were similar to those used in Study ZS003.

6.2.2. Study Results

Compliance with Good Clinical Practices
Similar to Study ZS003.

Financial Disclosure
A list of investigators was provided for Study ZS004. The financial disclosure information for this study is summarized in the table below. According to the Applicant, two investigators who participated in Study ZS004 had financial interests or arrangements to disclose.

- (b) (6) and sub-investigator (b) (6) from study site (b) (6): Consulting fee of $ 49,713.84; Honorarium fee of $3500.00; and expense reimbursement of $14,880.10. The total is $68,093.94.
- (b) (6) from study site (b) (6): Significant Equity Interest $> 50,000.00.

Table 19: Clinical Investigator Financial Disclosure in Study ZS004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 40		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): 2 Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer table

Based on the site analysis performed by the statistical reviewer, Dr. Thomas Birkner, sites 4058 and 4200 contributed two subjects each to the primary analysis population (N = 231). Data from these sites had no impact on the overall efficacy results.

Reviewer comments: *Given Dr. Birkner's findings, the aforementioned financial arrangements do not raise concerns about the reliability of the data submitted in support of this application*.

Patient Disposition

Overall, 425 subjects were screened for entry into the study. Of these, 167 failed to meet the entry criteria, primarily due to average i-STAT values not being within an acceptable range (160 subjects), and were not enrolled in the study.

Acute phase: A total of 258 subjects enrolled in the Open-Label Acute Phase of the study. The vast majority of these subjects completed the Acute Phase of the study (97.3%). Of the seven

subjects who prematurely discontinued during the Acute Phase of the study, five withdrew consent and two discontinued because of hyperkalemia (both had i-STAT potassium values of 6.3mmol/L, 90 minutes after the second dose of ZS on Acute Phase Study Day 1).

Maintenance phase: Of the 251 subjects who completed the Acute Phase, 240 were eligible to enter the Maintenance Phase. A summary of the proportions of subjects who did not enter the Maintenance Phase by reason is presented in the table below. Among the 11 subjects who were ineligible to enter the Maintenance Phase, two had i-STAT potassium values < 3.5 mmol/L (3.2 and 3.4 mmol/L). All other subjects who did not enter the Maintenance Phase because they did not achieve normokalemia (i.e., had i-STAT potassium values ≥5.1 mmol/L).

Table 20: Subjects Who Did Not Enter Maintenance Phase– All Subjects

Reason, n (%)	ZS 10 g TID (N =258)
Discontinued prematurely	7 (2.7)
Completed Acute Phase	251
Ineligible to enter Maintenance Phase:	
Hypokalemia	2 (0.8)
Hyperkalemia	9 (3.5)
Eligible to enter Maintenance Phase	240
Eligible, but did not enter Maintenance Phase: Consent withdrawn	1 (0.4)
Investigator's decision	1 (0.4)[a]
Met ECG withdrawal criteria	1 (0.4)[b]
Entered Maintenance Phase	237 (91.9)

a. The investigator decided not to randomize the subject in the Maintenance Phase due to difficulty in performing venipuncture.
b. Subject met criterion for increase in QTc interval > 25 msec to more than 500 msec.

Applicant's table from CSR Study ZS004, table 10-2, Page 82.

Of the 251 subjects who completed ZS 10 g TID dosing during the Acute Phase, 237 continued into the Maintenance Phase and were randomized in accordance with the protocol and randomization schedule to either placebo or ZS (5 g, 10 g, or 15 g QD). Among these 237 subjects, 85 were randomized to placebo, 45 to ZS 5 g QD, 51 to ZS 10 g QD, and 56 to ZS 15 g QD. The majority of the subjects in each of the treatment groups completed the Maintenance Phase of the study (range: 86.3% to 88.9%). No dose-related trends were apparent among the treatment groups for the reasons leading to discontinuation.

Three placebo subjects were prematurely discontinued from the Maintenance Phase due to hyperkalemia (i-STAT range: 6.3 to 6.6mmol/L). Four ZS subjects (3 ZS 10 g QD and 1 ZS 15 g QD) were prematurely discontinued from the Maintenance Phase due to hypokalemia (i-STAT range: 2.8 to 2.9mmol/L, later checked were 3.0mmol/L). Applicant decision led to premature discontinuation of 5 subjects (2 placebo, 2 ZS 10 g QD, and 1 ZS 15 g QD) enrolled within 6 days

of each other. The i-STAT potassium values for each of these subjects prior to dosing on Acute Phase Study Day 1 were substantially higher (range: 0.7 to 2.7 mmol/L difference) than the S-K values reported from the central laboratory. In addition, all 5 subjects had central laboratory S-K values within the normal range (range: 4.0 to 4.8 mmol/L). Although the sponsor monitored the site and identified no violations associated with study procedures for obtaining and processing the samples, it was decided to prematurely discontinue the subjects from the study following the evaluation as none of these subjects were hyperkalemic at baseline based on central laboratory data. The decision was made without unblinding the data. Three other subjects enrolled at this site, several days prior to those noted above, had i-STAT potassium values that were similar with the S-K values from the central laboratory and were allowed to complete the study as these subjects were hyperkalemic based on central laboratory values (S-K between 5.1 and 5.6 mmol/L) at study entry.

Adverse events led to premature discontinuation from the Maintenance Phase in 4 ZS-treated subjects (3 ZS 5 g QD and 1 ZS 15 g QD). These AEs included small intestinal obstruction, renal failure, confusional state, and generalized edema. In addition, 3 ZS-treated subjects (1 ZS 5 g QD and 2 ZS 15 g QD) were prematurely discontinued from the study because they met the predefined stopping rule for QTc prolongation. None of these subjects developed any new cardiac arrhythmias. Two subjects were unable to complete their End of Study Visits because of hospitalization: one subject in the ZS 10 g QD group had cellulitis and one in the ZS 15 g QD group was hospitalized for dyspnea.

Table 21: Maintenance Phase-Subject Disposition – All Subjects

Disposition, n (%)	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo	ZS 5 g QD	ZS 10 g QD	ZS 15 g QD
Randomized	85	45	51	56
Treated	85 (100.0)	45 (100.0)	51 (100.0)	56 (100.0)
Completed Maintenance Phase	75 (88.2)	40 (88.9)	44 (86.3)	49 (87.5)
Discontinued Maintenance Phase	10 (11.8)	5 (11.1)	7 (13.7)	7 (12.5)
Adverse event	0 (0.0)	3 (6.7)	0 (0.0)	1 (1.8)
Consent withdrawn	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Subject compliance	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator's decision	0 (0.0)	0 (0.0)	0 (0.0)	1(1.8)[a]
Sponsor's decision	2 (2.4)	0 (0.0)	2 (3.9)	1(1.8)
Hypo- or hyperkalemia	3 (3.5)	0 (0.0)	3(5.9)[b]	1 (1.8)
Met ECG withdrawal criteria	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.6)
Other[c]	2 (2.4)	1 (2.2)	2 (3.9)	1 (1.8)

a. The investigator decided to withdrawal the subject from the study due to pre-existing clinical status.
b. One subject who prematurely discontinued due to hypokalemia subsequently died 4 days after last dose due to myocardial infarction.
c. Placebo (1 subject had family emergency/gone for 1 month; 1 subject had to leave town), ZS 5 g QD (1 subject moving out of state), ZS 10 g QD (1 subject leaving for other residence; 1 subject hospitalized for treatment of cellulitis), and ZS 15 g QD (1 subject hospitalized due to dyspnea).

Applicant's table from CSR Study ZS004, table 10-3, Page 84

Protocol Violations/Deviations

There were no major protocol deviations. Deviations in a few patients were noted during the study including the mistiming or omission of study procedures or deviations in study drug dosing. These deviations should have no impact on the overall efficacy and safety results of the study.

Table of Demographic Characteristics

Acute phase:

- Demographics: A summary of demographic and other baseline characteristics for the Acute Phase of the study is provided in the table below. Age ranged from 22 to 89 years, with a mean age of 64.0 years. The majority of the subjects were male (57.8%) and most were White (83.3%). Baseline S-K values (per central laboratory) were < 5.5 mmol/L for 46.1% of subjects, ≥5.5 to < 6.0 mmol/L for 38.8% of subjects, and ≥ 6.0 mmol/L for 15.1% of subjects. The most common etiologies of elevated S-K (subjects could have had

multiple etiologies; the etiology was determined by the investigator) were use of RAAS inhibitor medication (69.8%), CKD (based on eGFR < 60 mL/min, 69.4%), and diabetes mellitus (65.9%).

Table 22: Acute Phase-Demographic and Other Baseline Characteristics – Safety Population

Demographic Parameter **Statistic**	**ZS 10 g TID** **(N = 258)**
Age at screening (years)	
Mean (SD)	64.0 (12.72)
Median	65.0
Min, max	22, 89
Gender, n (%)	
Male	149 (57.8)
Female	109 (42.2)
Race,[a] n (%)	
White	215 (83.3)
Black or African American	37 (14.3)
Asian	5 (1.9)
Native Hawaiian or other Pacific Islander	1 (0.4)
Other	2 (0.8)
Multiple races indicated	1 (0.4)
Ethnicity, n (%)	
Hispanic	105 (40.7)
Not Hispanic	153 (59.3)
Weight at baseline[b] (kg)	n = 257
Mean (SD)	87.85 (22.856)
Median	85.00
Min, max	41.8, 195.0
Acute Phase S-K baseline, n (%)	
< 5.5 mmol/L	119 (46.1)
5.5-< 6.0 mmol/L	100 (38.8)
≥ 6.0 mmol/L	39 (15.1)
Acute Phase eGFR at baseline, n (%)	
< 60	179 (69.4)
≥ 60	72 (27.9)
Missing	7 (2.7)
Etiology,[a] n (%)	
RAAS inhibitor medication	180 (69.8)
Diabetes mellitus	170 (65.9)
CKD	169 (65.5)
HF	94 (36.4)
Insulin use, n (%)	
Acute Phase insulin use prior to any blood draw	27 (10.5)

a. Categories are not mutually exclusive.
b. Weight at baseline was the measurement taken at screening.
Applicant's table from CSR Study ZS004, table 11-3, Page 87

- Prior and Concomitant Medications: The most common (> 50% of subjects) types of medications received during the Acute Phase included agents acting on the renin-angiotensin system (66.7%), drugs used in diabetes (62.4%), and lipid-modifying agents (57.4%).

Table 23: Acute Phase-Concomitant Medications (Safety Population)

Anatomic Therapeutic Class, n (%)	**ZS 10 g TID (N = 258)**
Any Medication	251 (97.3%)
Agents acting on the renin-angiotensin system	172 (66.7)
Drugs used in diabetes	161 (62.4)
Lipid modifying agents	148 (57.4)
Beta blocking agents	117 (45.3)
Antithrombotic agents	109 (42.2)
Vitamins	101 (39.1)
Calcium channel blockers	98 (38.0)
Diuretics	98 (38.0)
Drugs for acid-related disorders	86 (33.3)
Analgesics	75 (29.1)
Antianemic preparations	62 (24.0)
Antihypertensives	44 (17.1)
Psychoanaleptics	44 (17.1)

Applicant 's table from CSR Study ZS004, table 11-4, Page 88

Maintenance Phase:

- Demographics: A summary of demographic and other baseline characteristics for the Maintenance Phase is provided in the table below. Demographic characteristics were generally similar among the Maintenance Phase treatment groups. Among the treatment groups, mean age ranged from 61.5 to 64.9 years (overall range: 22 to 89 years). The majority of the subjects in each of the treatment groups were White (range: 80.0 to 86.3%). The proportions of male subjects tended to be higher in the ZS 15 q QD group (71.4%) compared with the placebo (51.8%) and the lower ZS dose (5 g QD: 60.0%; 10 g QD: 52.9%) groups. Greater proportions of subjects in the ZS 15 g QD group had HF, CKD (based on eGFR < 60 mL/min) and diabetes mellitus compared with the placebo group.

Table 24: Maintenance Phase-Demographic and Other Baseline Characteristics

Demographic Parameter Statistic	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo (N = 85)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 51)	ZS 15 g QD (N = 56)
Age at screening (years)				
Mean (SD)	64.3 (12.13)	61.5 (16.89)	63.8 (9.97)	64.9 (12.85)
Median	66.0	64.0	65.0	64.5
Min, max	23, 87	22, 89	44, 85	25, 85
Gender, n (%)				
Male	44 (51.8)	27 (60.0)	27 (52.9)	40 (71.4)
Female	41 (48.2)	18 (40.0)	24 (47.1)	16 (28.6)
Race,[a] n (%)				
White	73 (85.9)	36 (80.0)	44 (86.3)	46 (82.1)
Black or African American	10 (11.8)	8 (17.8)	5 (9.8)	9 (16.1)
Asian	3 (3.5)	0 (0.0)	1 (2.0)	1 (1.8)
Native Hawaiian or other Pacific Islander	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (2.2)	1 (2.0)	0 (0.0)
Multiple races indicated	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic	38 (44.7)	19 (42.2)	23 (45.1)	21 (37.5)
Not Hispanic	47 (55.3)	26 (57.8)	28 (54.9)	35 (62.5)
Weight at baseline[b] (kg)	n = 85	n = 45	n = 51	n = 55
Mean (SD)	85.12 (18.575)	89.57 (23.907)	87.38 (25.62)	87.17 (18.63)
Median	84.30	87.30	84.40	84.50
Min, max	52.0, 134.5	53.5, 185.4	46.2, 175.2	44.5, 137.8
Acute Phase S-K baseline, n (%)				
< 5.5 mmol/L	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 - < 6.0 mmol/L	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥ 6.0 mmol/L	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)
Acute Phase eGFR at baseline, n (%)				
< 60 mL/min	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥ 60 mL/min	28 (32.9)	12 (26.7)	13 (25.5)	15 (26.8)
Missing	5 (5.9)	2 (4.4)	0 (0.0)	0 (0.0)
Etiology,[a] n (%)				
RAAS inhibitor medication	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)
Diabetes mellitus	54 (63.5)	26 (57.8)	38 (74.5)	39 (69.6)
CKD	50 (58.8)	29 (64.4)	36 (70.6)	37 (66.1)
HF	26 (30.6)	18 (40.0)	18 (35.3)	25 (44.6)

Maintenance Phase-Demographic and Other Baseline Characteristics – (continued)

Demographic Parameter Statistic	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo (N = 85)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 51)	ZS 15 g QD (N = 56)
Insulin use, n (%)				
Acute Phase insulin use prior to any blood draw	5 (5.9)	5 (11.1)	9 (17.6)	6 (10.7)
Maintenance Phase insulin use prior to any blood draw	1 (1.2)	5 (11.1)	2 (3.9)	0 (0.0)

a. Categories are not mutually exclusive.
b. Weight at baseline was the measurement taken at screening.

Applicant's table from CSR Study ZS004, table 11-5, Page 90

- Maintenance Phase: Prior and Concomitant Medications: As in the acute phase, the most common (> 50% of subjects in each treatment group) types of medications received during the Maintenance Phase in each of the treatment groups included agents acting on the renin-angiotensin system (range: 57.1 to 70.6%), drugs used in diabetes (range: 55.6 to 72.5%), and lipid modifying agents (range: 51.1 to 62.7%).

Table 25: Concomitant Medications Reported By ≥ 15% of Subjects in Any Treatment Group

Anatomic Therapeutic Class, n (%)	**Acute Phase Treatment: ZS 10 g TID**			
	Maintenance Phase Treatment			
	Placebo (N = 85)	**ZS 5 g QD (N = 45)**	**ZS 10 g QD (N = 51)**	**ZS 15 g QD (N = 56)**
Any Medication	82 (96.5)	45 (100.0)	50 (98.0)	53 (94.6)
Agents acting on the renin-angiotensin	60 (70.6)	30 (66.7)	35 (68.6)	32 (57.1)
system	51 (60.0)	25 (55.6)	37 (72.5)	36 (64.3)
Drugs used in	52 (61.2)	23 (51.1)	32 (62.7)	33 (58.9)
diabetes Lipid	37 (43.5)	22 (48.9)	26 (51.0)	26 (46.4)
modifying agents	31 (36.5)	15 (33.3)	27 (52.9)	29 (51.8)
Beta blocking agents	35 (41.2)	21 (46.7)	18 (35.3)	24 (42.9)
Antithrombotic	31 (36.5)	13 (28.9)	22 (43.1)	27 (48.2)
agents Diuretics	31 (36.5)	17 (37.8)	17 (33.3)	27 (48.2)
Calcium channel blockers	31 (36.5)	13 (28.9)	16 (31.4)	20 (35.7)
Vitamins	33 (38.8)	15 (33.3)	13 (25.5)	15 (26.8)
Drugs for acid-related disorders	23 (29.1)	13 (28.9)	12 (23.5)	12 (21.4)
Analgesics	13 (15.3)	11 (24.4)	8 (15.7)	12 (21.4)
Antianemic	16 (18.8)	7 (15.6)	8 (15.7)	9 (16.1)
preparations	18 (21.2)	6 (13.3)	5 (9.8)	9 (16.1)
Antihypertensives	13 (15.3)	5 (11.1)	8 (15.7)	7 (12.5)
Psychoanaleptics	12 (14.1)	8 (17.8)	2 (3.9)	7 (12.5)
Antigout preparations	4 (4.7)	5 (11.1)	10 (19.6)	10 (17.9)

Applicant's table from CSR Study ZS004, table 11-6, Page 92

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the Acute Phase, the first of the 3 daily doses was administered at the site by study staff and the second and third doses were taken at home. Of the 258 subjects dosed during the Acute Phase of the study, 96.9% received all 3 doses of study drug on Acute Phase Study Days 1 and 2.

The proportions of subjects dosed on each day during the Maintenance Phase ranged from 88 to 100% in the placebo group, 89 to 100% in the ZS 5 g QD group, 73 to 100% in the ZS 10 g QD group, and 75 to 98% in the ZS 15 g QD group (1 subject in the ZS 15 g QD group was not dosed on the first day of the Maintenance Phase, but was dosed on subsequent Maintenance Phase days). According to the Applicant, the somewhat lower percentages observed in the ZS 10 g QD and 15 g QD groups can be attributed to subjects who reduced their dosing from QD to QOD, but remained in the calculation for days they did not receive dosing.

Major concomitant medications that could affect the study results include RAAS inhibitors, diuretics and insulin. RAAS inhibitor use was similar among the different group. The use of

diuretics and insulin during the maintenance phase was also, as a whole, similar among the groups. No rescue medication was used in the study.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the model-based least squares mean of all available S-K values during Extended Dosing Study Days 8 to 29 in comparison with the placebo group. As shown in the table below, each ZS group had a statistically significantly smaller mean S-K value than the placebo group. Among the ZS groups, the mean S-K value decreased with increasing dose of ZS (4.8 mmol/L for ZS 5 g QD, 4.5 mmol/L for ZS 10 g QD, and 4.4 mmol/L for ZS 15 g QD).

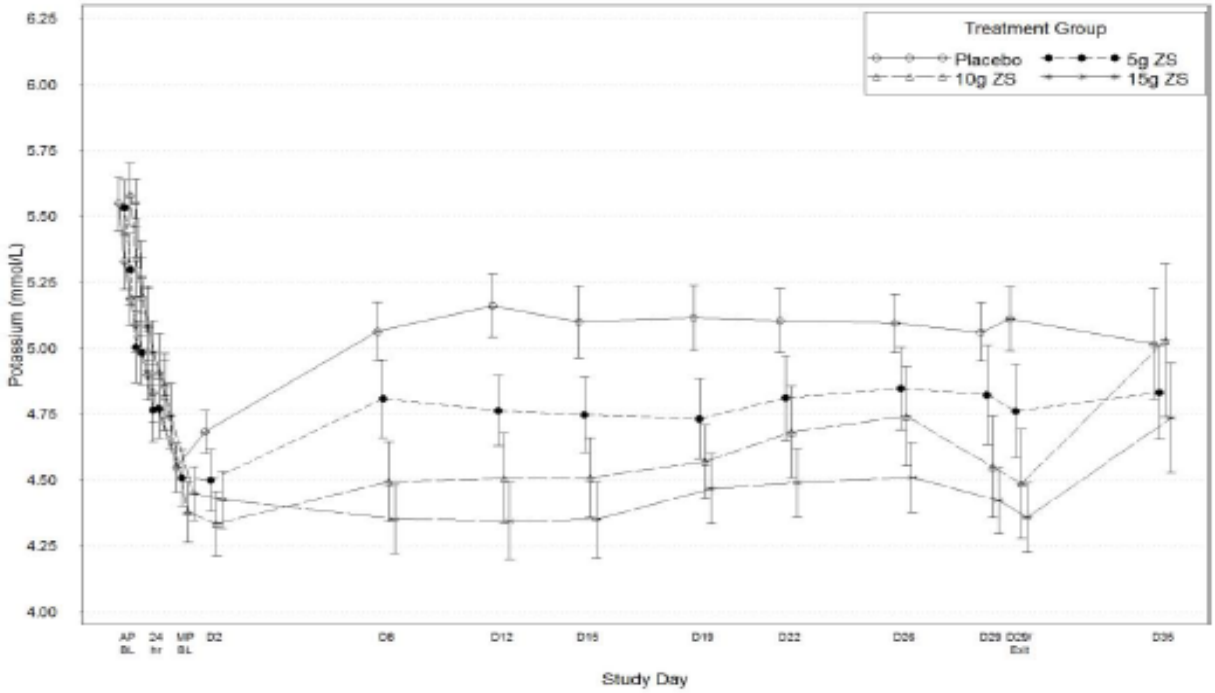
Table 26: Mean Serum Potassium between Maintenance Phase Study Days 8 and 29 (ITT Population)

Statistic[a]	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo (N = 82)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 50)	ZS 15 g QD (N = 54)
Back-transformed from model				
Least squares mean	5.0603	4.7544	4.5081	4.3742
95% confidence interval	4.9646, 5.1578	4.6350, 4.8769	4.4005, 4.6184	4.2754, 4.4753
Log-transformed (as modelled)				
Least squares mean (standard error)	1.6214 (0.00968)	1.5591 (0.01290)	1.5059 (0.01226)	1.4757 (0.01159)
95% confidence interval	1.6023, 1.6405	1.5336, 1.5845	1.4817, 1.5300	1.4529, 1.4986
t-test p-value (ZS versus placebo)		0.0001	< 0.0001	< 0.0001

Applicant's table from CSR Study ZS004, table 11-14, Page 103 confirmed by Statistical reviewer, Dr. Thomas Birkner

The mean S-K values during the Maintenance Phase are summarized graphically over time by treatment group in the figure below. Just as the similar to the table above, there was a dose dependent significantly smaller mean S-K value than the placebo group. At the last visit after the withdrawal of all the treatment, the S-K values were the same.

Figure 3: Mean Serum Potassium over Time in Maintenance Phase – ITT Population



Note: Vertical bars represent ± 2 standard errors.
Applicant's Figure from CSR Study ZS004, Figure 11-3, Page 104

Data Quality and Integrity – Reviewers' Assessment
Review of the submitted data did not raise concern for data quality or integrity issues. As previously discussed, according to OSI, the study appears to have been conducted adequately, and the data submitted by the Applicant may be used in support of the indication.

Efficacy Results – Secondary and other relevant endpoints
Acute phase: The statistical analysis plan included a plan to control the type I error in testing the first secondary endpoint, the exponential rate of change in S-K values during the initial 48 hours of study drug treatment. Other secondary endpoints in the acute phase were not tested using a plan that controlled the error rate. For completeness, the results of the secondary endpoint analyses, as described by the applicant, are discussed below:

- The mean exponential rate of change to 24 and 48 hours after start of dosing shown an statistically significant improvement from baseline in S-K with ZS 10 g TID. The mean decreases and mean percent decreases from baseline in S-K were observed from 1 hour through 48 hours after the start of ZS 10 g TID dosing
- An estimated 66.1% of subjects had normalized S-K values 24 hours after the first dose of ZS, and 88.0% of subjects had normalized S-K values 48 hours after the first dose of ZS. The Kaplan-Meier estimate of the percentage of normokalemic subjects was 84.28% at 24 hours and 97.62% at 48 hours after the first dose of ZS.

- The median time to normalization of S-K values during the Acute Phase was approximately 2.2 hours after the first dose of ZS.
- The proportion of subjects with ≥ 1 mmol/L decrease in S-K from the Acute Phase baseline at 48 hours after the first dose of ZS was 57.0%.
- The proportion of subjects with ≥ 0.5 mmol/L decrease in S-K from the Acute Phase baseline at 48 hours after the first dose of ZS was 89.6%.
- The proportion of subjects with Acute Phase baseline S-K ≥ 6.0 mmol/L and ≥ 0.5 mmol/L decrease in S-K from the Acute Phase baseline at 2 and 48 hours after the first dose of ZS was 73.7% and 94.6%, respectively.
- The proportion of subjects with Acute Phase baseline S-K ≥ 6.0 mmol/L and ≥ 1.0 mmol/L decrease in S-K from the Acute Phase baseline at 2 and 48 hours after the first dose of ZS was 23.7% and 89.2%, respectively.

Maintenance Phase**:** The hierarchical testing procedure specified the testing of the following three secondary endpoints: 1) total number of days normokalemic, 2)proportions normokalemic at Study Day 29/Exit, and 3)mean S-K standard deviation. For completeness, the applicant's analyses of all of the Secondary endpoints are discussed briefly below:

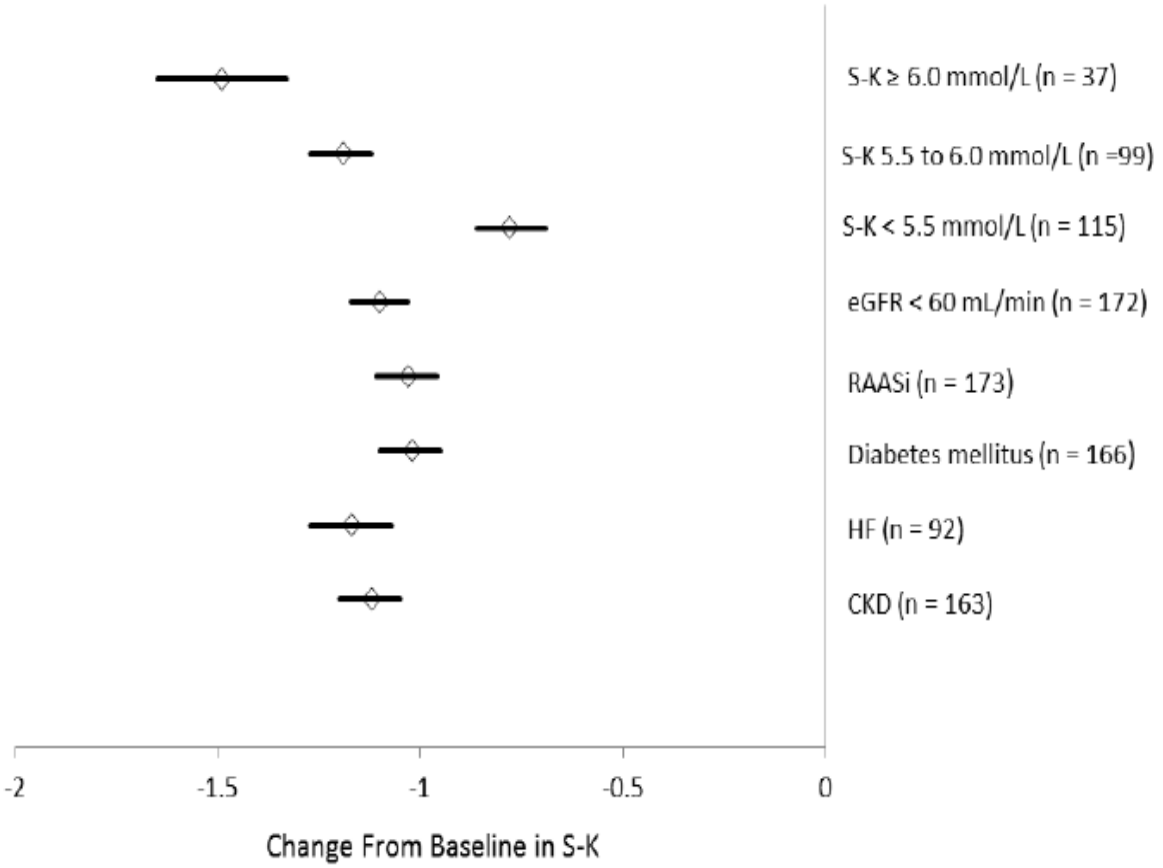
- The mean number of normokalemic days from Maintenance Phase Study Days 8 to 29 was statistically significant greater in each ZS group versus placebo. The mean number of normokalemic days increased with increasing dose of ZS (13.4/22 days for ZS 5 g QD, 13.9/22 days for ZS 10 g QD, and 16.8/22 days for ZS 15 g QD) compared with 7.4/22 days for placebo.
- The mean decrease and mean percent decrease in S-K were greater in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups than in the placebo group on Day 29. The mean decrease and mean percent decrease in S-K increased with increasing dose of ZS. The differences from placebo were also observed for all ZS groups from Maintenance Phase Study Day 2 through Study Day 26.
- The mean increase and mean percent increase in S-K were different in the placebo group as compared to smaller mean increases and mean percent increases in the ZS 5 g QD and ZS 10 g QD groups, and as compared to the mean decrease and mean percent decrease in the ZS 15 g QD group on Day 29. The differences from placebo were also observed for the ZS 15 g QD group from Maintenance Phase Study Day 2 through Study Day 26. For the ZS 5 g QD and ZS 10 g QD groups, differences from placebo were statistically significant from Maintenance Phase Study Day 2 through Study Day 22.
- Time to hyperkalemia (defined as S-K ≥ 5.1 mmol/L) during the Maintenance Phase was later with continued ZS QD treatment than with placebo for subjects who received ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD. Median time to hyperkalemia from the Maintenance Phase baseline was 7 and 14 days in the placebo and ZS 5 g QD groups, respectively. Fewer than 50% of subjects in the ZS 10 g QD and ZS 15 g QD groups had a hyperkalemic event before the end of the Maintenance Phase; therefore, the median in these 2 groups was not reached.

- Time to relapse (defined as return to S-K value measured at Acute Phase baseline) during the Maintenance Phase was later with continued ZS QD treatment than with placebo for subjects who received ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD. Median time to relapse from the Maintenance Phase baseline was 19 and 29 days in the placebo and ZS 5 g QD groups, respectively. Fewer than 50% of subjects in the ZS 10 g QD and ZS 15 g QD groups had relapsed at the end of the Maintenance Phase; therefore, the median in these 2 groups was not reached.
- The proportion of subjects who remained normokalemic was statistically significantly larger in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups (71.1%, 76.0%, and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects) on day 29.

Subgroup Analysis: Subgroup analyses evaluated demographic characteristics (age, gender, race, and geographic region) and the impact of baseline eGFR, baseline S-K, concomitant diseases, and use of RAAS inhibitor medication. Efficacy was observed across all of the subpopulations.

In the acute phase, significant reduction in S-K was observed for all demographic subpopulations (data not shown). For the various baselines, the mean reduction in S-K at 48 hours was greater in patients with higher Acute Phase baseline S-K values (S-K ≥ 6.0: -1.49 mmol/L; S-K ≥ 5.5 to < 6.0: -1.19 mmol/L; S-K < 5.5: -0.78 mmol/L). No other notable interactions were observed. Data are summarized in the figure below.

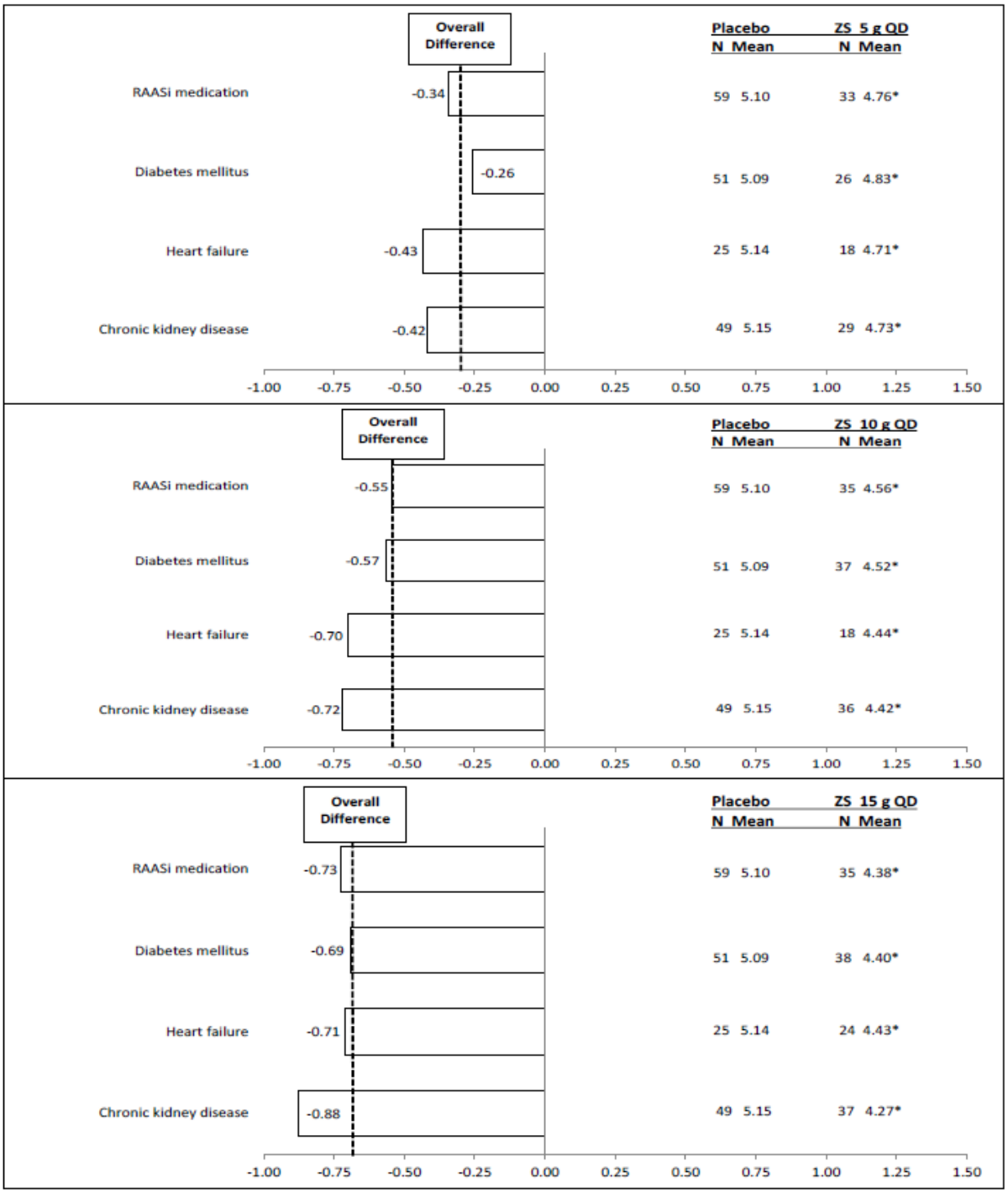
Figure 4: Mean Change in Serum Potassium from Baseline to 48 Hours after Start of ZS Dosing by Baseline Subpopulations - ITT Population



Applicant's figure from CSR Study ZS004, Figure 11-6, page 122

In the maintenance phase, as would be expected, the drug appeared to be effective in all of the subgroups that were examined. The treatment differences between each ZS group and placebo group for mean S-K during the maintenance phase (Study Days 8 and 29, inclusive) are summarized by subpopulation in the following figure.

Figure 5: Treatment Group Differences for Mean Serum Potassium during Study Days 8 and 29 - ITT Population



Applicant's figure from CSR Study ZS004, Figure 11-7, page 124

Other Data analysis issues:

- Regarding the handling of dropouts or missing data, the dropout rates in both acute phase and maintenance phase were low; less than 1% of central laboratory S-K values were missing. Therefore, missing data is not a major issue affecting interpretation of the efficacy results.

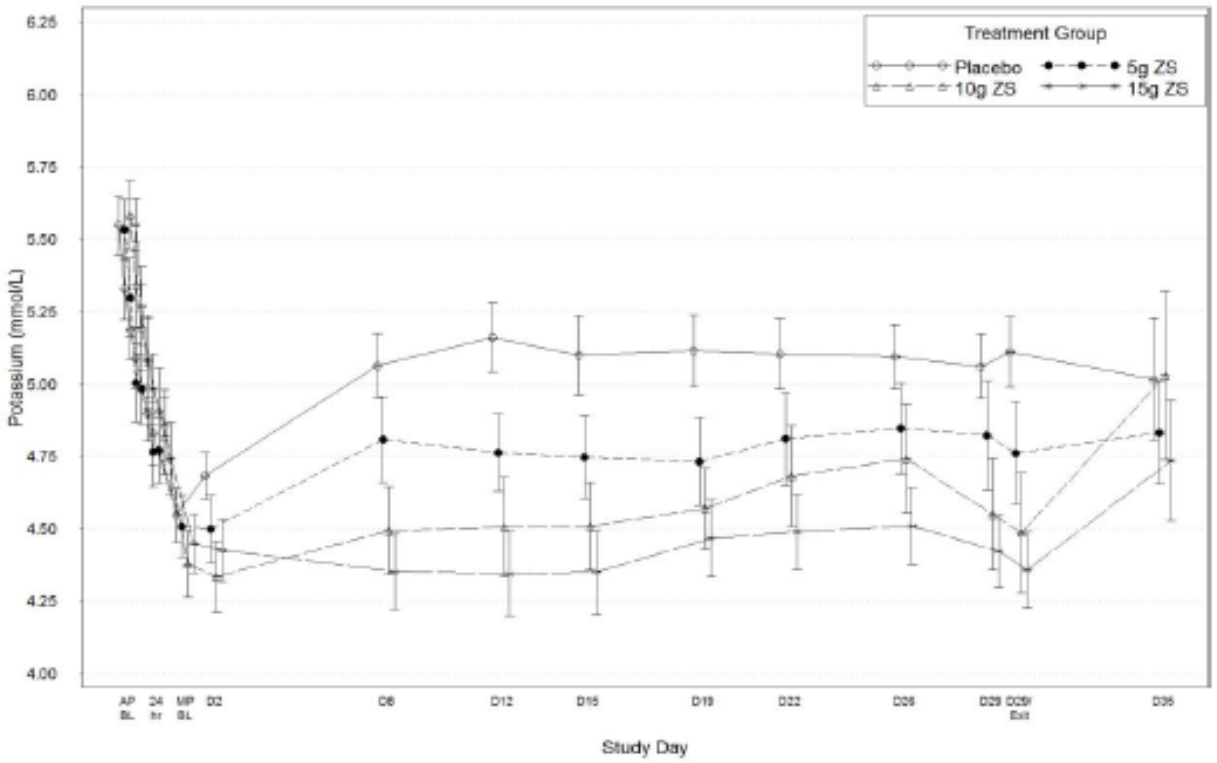
Dose/Dose Response

See Section 7.1.4, Dose and Dose-Response.

Durability of Response

As shown in the figure below, the dose-dependent potassium lowering effect was observered over the 28-day Extended Dosing treatment period.

Figure 6: Mean Serum Potassium over Time in Maintenance Phase – ITT Population



Applicant's Figure from CSR Study ZS004, Figure 11-3, page 104

Persistence of Effect

Similar to Study ZS003, there was a dose-dependent increase in the time to relapse in S-K values (return to acute phase S-K baseline value) after subjects switched to placebo in the Subacute Phase.

Time to relapse (defined as return to S-K value measured at Acute Phase baseline) during the Maintenance Phase was later with continued ZS QD treatment than with placebo for subjects who received ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD. Median time to relapse from the Maintenance Phase baseline was 19 and 29 days in the placebo and ZS 5 g QD groups, respectively. Fewer than 50% of subjects in the ZS 10 g QD and ZS 15 g QD groups had relapsed at the end of the Maintenance Phase, which indicated a persistence effect in the higher dose groups.

Additional Analyses Conducted on the Individual Trial
None.

6.3. Study ZS004E

6.3.1. Study Design

Overview and Objective
Study ZS004E was an open-label extension to Study ZS-004; the first subject was enrolled on 10 May 2014 and the last subject completed on 14 July 2015. The primary objective was to generate open-label long-term safety and tolerability data; however the study also provides data supporting long-term efficacy.

The stated efficacy objectives in this study were to evaluate the proportion of subjects with average serum potassium (S-K) ≤ 5.1 mmol/L from Extended Dosing Phase Days 8 through Month 11 (Day 337) and the proportion of subjects with average S-K ≤ 5.5 mmol/L from Extended Dosing Phase Days 8 through Month 11 (Day 337)

Reviewer's comment: The study was completed after the NDA was submitted; the final study report and associated datasets were submitted by the sponsor on September 23, 2015 as part of the 120-day safety update.

Trial Design
The study was conducted at 30 sites in the U.S., Australia and South Africa. All subjects who completed Study ZS-004 Extended Dosing Phase Study Day 29 Visit and had an i-STAT potassium value that was between 3.5 and 6.2 mmol/L, inclusive, or who discontinued during Study ZS-004 due to hypo- or hyperkalemia and had a mean i-STAT potassium value from 2 consecutive measurements at 0 and 60 minutes on Acute Phase Study Day 1/Extended Dosing Phase Study Day 1 that was between 3.5 and 6.2 mmol/L, inclusive, were eligible to participate.

In this study, subjects received up to 11 months (336 days) of additional treatment with open-label ZS. As discussed below, subjects had their potassium levels monitored periodically during the study and the dose of study drug was to be titrated based on the result.

Key entry criteria: Completed the Extended Dosing Phase Study Day 29 Visit of Study ZS004 or discontinued Study ZS-004 during the Extended Dosing Phase because of hypo- or hyperkalemia, had an i-STAT potassium value between 3.5 and 6.2 mmol/L, and was able to start dosing in Study ZS-004E within 2 days after the last dose of study drug in Study ZS-004.

Study treatments: Subjects who continued into the extension study began dosing in Study ZS-004E within 2 days after the last dose of study drug in Study ZS-004.

- Subjects who had i-STAT potassium values between 3.5 and 5.5 mmol/L, inclusive, at the Study ZS-004 Extended Dosing Phase Study Day 29 Visit started on open-label ZS at a dose of 10 g QD.
- Subjects with i-STAT potassium values > 5.5 mmol/L at the Study ZS-004 Extended Dosing Phase Study Day 29 Visit underwent an Acute Phase, where they received ZS 10 g three times a day (TID) for 24 (3 doses) or 48 hours (6 doses), depending on their daily i-STAT potassium measurement. Subjects who attained normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) after either 24 or 48 hours of treatment entered the Extended Dosing Phase. Any subject whose i-STAT potassium level was not within the normal range (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) on the morning of Acute Phase Study Day 3 exited from the study and did NOT progress into the Extended Dosing Phase.
- Subjects who discontinued during Study ZS-004 due to hypo- or hyperkalemia, a baseline potassium value was determined within 1 day of taking the first dose of ZS by taking 2 potassium measurements (i-STAT and central laboratory) at 0 and 60 minutes (± 10 minutes). If the mean i-STAT value was between 3.5 and 5.5 mmol/L, inclusive, subjects entered the Extended Dosing Phase and received ZS 10 g QD; if the mean i-STAT potassium value was > 5.5 mmol/L, subjects entered the Acute Phase.

Subjects took the first dose of the Extended Dosing Phase study drug in the clinic (Extended Dosing Phase Study Day 1) and thereafter took the study drug at home, in the morning just before breakfast, except on days with scheduled clinic visits, when study drug was taken in the clinic.

Potassium levels were monitored during the study (see discussion under “Procedures and schedule”) and the dose of the drug was to be titrated based on the potassium value.

- If a subject’s i-STAT potassium value increased above 5.5 mmol/L during the Extended Dosing Phase treatment at 10 g QD, the dose would be increased to 15 g QD.
- If the i-STAT potassium value decreased to between 3.0 and 3.4 mmol/L, inclusive, the dose of ZS would be decreased in 5 g QD decrements.
- If a subject was on a 5 g QD dose and still developed i-STAT potassium values between 3.0 and 3.4 mmol/L, inclusive, the dose would be reduced to QOD.

Procedures and schedule: S-K measurements were to be collected weekly throughout the first 8 weeks of the Extended Dosing Phase, every 4 weeks thereafter to Study Day 337 and at End of Study. Other laboratory evaluations included measurements of sodium, calcium, magnesium, bicarbonate, phosphorus, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). Safety evaluations also included physical examinations, weight, vital signs, 12-lead ECGs, and standard laboratory parameters (hematology, serum chemistry, and urinalysis).

Any time the ZS dose was adjusted or a renin-angiotensin-aldosterone system (RAAS) inhibitor or diuretic dose was adjusted or initiated, the subject returned to the site 7 (± 1) days later for a potassium measurement and recording of adverse events and concomitant medications.

All subjects withdrawn from the study prior to completion were to return to the site 7 (± 1) days after the last dose of study drug for an End of Study Visit. For an overview of study procedures, see the table below.

Table 27: Study Procedure in Maintenance Phase in Study ZS004 E

MP Study Day[6]	1[9]	8	15	22	29	36	43	50	57, 85, 113	141	169, 197, 225, 253, 281, 309	337	(EOS)[11]
Visit window (days)		+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	+/-1	
		In-clinic											
Eligibility criteria	X												
Demographics	X												
Medical History	X												
Physical exam[3]	X		X		X		X		X	X	X	X	X
Study drug administration[4]	X	X	X	X	X	X	X	X	X	X	X		
ECG[3]	X		X		X		X		X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Potassium[2,3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[1, 3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[1,3]	X				X				X	X	X	X	X
Urinalysis including sediment	X				X				X	X	X	X	X
Urine Culture	X												X
Urine HCG[5]	X												X
IP Reconciliation												X[12]	
North America Only													
S-Aldo[3,7] & P-Renin[3,7]	X				X					X	X[13]	X	
S-Insulin[3]	X				X					X		X	
P-PTH[3] & HbA1c[3,10]	X				X					X		X	
S-Galectin-3[3,8] & BNP[3]	X												
Urine chemistry	X				X					X		X	

1. Parameters to be measured are detailed in Appendix 1.
2. Potassium will be measured fasting before dosing, as part of the serum chemistry panel. All potassium samples will be analyzed by i-STAT and the central laboratory
3. Physical Exam, ECG, Vital signs, urinalysis, urine chemistry, serum clinical chemistry including S-Aldo, S-Galectin-3, S-Insulin, P-Renin, P-PTH, P-BNP, HbA1c as well as 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 prior to sample collection at the clinic)
4. All doses of study drug will be administered orally in conjunction with, or before breakfast. Any time the ZS dose is adjusted or a RAAS inhibitor or diuretic dose is adjusted or initiated, the subject will return to the site 7 (± 1) days later for a potassium measurement and recording of adverse events and concomitant medications.
5. For women of childbearing potential using kits supplied by the central laboratory
6. From MP Day 8 through MP Day 337, visits may occur within ± 1 day of the scheduled visit
7. S-Aldo is collected into serum separator tubes; P-Renin is collected into EDTA tubes. Both samples are collected prior to 10am after at least 2 hours in the upright position. Samples are to be aliquoted immediately after processing and frozen until sent for analysis. At least 1ml of the processed sample is required.
8. Process to serum/plasma and freeze within 2 hours of collection Protocol Number ZS-004E (Amendment 5)
9. 9 Only collected as a baseline measurement if not previously collected at ZS-004 DBRMP Study Day 29 visit or AP Study Day 1
10. 2 ml WHOLE blood collected into K2EDTA tube frozen
11. EOS occurs 7 ± 1 day after the last administration of IP
12. IP (investigational product) reconciliation will occur periodically at the discretion of the site monitor
13. Collect aldosterone and renin samples only on Day 253

Applicant's table from Study ZS004E, Protocol and Amendment, table 5-2, page 489

Study Endpoints: The primary efficacy endpoint was the proportion of subjects with average S-K ≤ 5.1 mmol/L during Extended Dosing Phase Study Days 8 to 337, inclusive.

The secondary efficacy endpoint was the proportion of subjects with average S-K ≤ 5.5 mmol/L during Extended Dosing Phase Study Days 8 to 337, inclusive.

Statistical analysis plan:
The analyses described in this section are based on the final statistical analysis plan that was finalized and submitted on June 15, 2015. The database was locked on July 23, 2015.
As previously, noted, the primary objective of the study was to generate open-label long-term safety and tolerability data and hence the late data at which the statistical analysis plan was finalized is less of concern. According to the statistical analysis plan, an overall Type I error rate of 5% was to be maintained using a hierarchical order for hypotheses testing. The primary endpoint was tested first, followed by the secondary endpoint.

Two separate baselines were identified for S-K analyses in this study: the Acute Phase baseline is the average 0-hr and 60-minute S-K values prior to Acute Phase dosing in Study ZS-004 and Extended Dosing Phase baseline is the last S-K value from a regularly scheduled visit in Study ZS-004 that was within 1 day of the last dose or the S-K value prior to Extended Dosing for subjects who were treated in the Acute Phase of Study ZS-004E. The proportions of subjects who were normokalemic, hypokalemic, or hyperkalemic at each scheduled Extended Dosing Phase visit were summarized. The proportion of subjects who remained normokalemic at the Extended Dosing Study Day 337/Exit time point was analyzed using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint in Study ZS004.

6.3.2. Study Results

Patient Disposition
A total of 123 subjects met the i-STAT potassium value criterion and entered Study ZS-004E. Of the 123 subjects who entered Study ZS-004E, 48 had received placebo, 21 had received ZS 5 g QD, 21 had received ZS 10 g QD, and 33 had received ZS 15 g QD during Study ZS-004. Each of these subjects had completed Study ZS-004, except for 1 placebo subject who prematurely discontinued due to hyperkalemia. Subject disposition is summarized in the table below.

Table 28: Patients Disposition – All Enrolled Patients

Disposition, n (%)	ZS QD
Entered Extended Dosing	123
Treated	123 (100)
Completed Extended Dosing Phase	79 (64.2)[a]
Discontinued Extended Dosing Phase	44 (35.8)
Adverse event	7 (5.7)
Consent withdrawn	9 (7.3)
Subject compliance	3 (2.4)
Investigator's decision	3 (2.4)
Lost to follow-up	2 (1.6)
Hypo- or hyperkalemia	2 (1.6)[b]
Expected progression of chronic kidney disease	12 (9.8)
Met electrocardiogram withdrawal criteria	3 (2.4)[c]
Other	3 (2.4)[d]

a. Includes 15 subjects who completed 56 days of dosing under the original protocol, 7 subjects who completed 140 days of dosing under Amendment 1 of the protocol, and 57 subjects who completed 336 days of dosing under Amendment 3 of the protocol.

b. One subject who prematurely discontinued due to hyperkalemia also had a serious adverse event of hyperkalemia recorded, with an action taken of study drug withdrawn.

c. All 3 subjects who prematurely discontinued due to meeting ECG withdrawal criteria also had adverse events of electrocardiogram QT prolonged (2 subjects) and right bundle branch block (1 subject) recorded, with an action taken of study drug withdrawn.

d. One withdrawn at the request of the subject's primary care physician who felt the subject's edema had worsened, 1 withdrawn as the subject's primary care physician had introduced a potassium supplement to medications, and 1 withdrawn in error as the investigator mistakenly thought the subject met ECG stopping criteria.

Applicant's table from CSR Study ZS004E, table 10-1 page 45

Demographic Characteristics

Among the Extended Dosing Phase ITT Population in Study ZS-004E, age ranged from 22 to 85 years, with a mean age of 64 years. The majority of the subjects were male (58%) and most were White (88%). Baseline S-K values (per central laboratory) from the Acute Phase of Study ZS-004 were < 5.5 mmol/L for 45% of subjects, ≥ 5.5 to < 6.0 mmol/L for 44% of subjects, and ≥ 6.0 mmol/L for 12% of subjects. The most common etiologies of elevated S-K (subjects could have multiple etiologies) were CKD (based on eGFR < 60 mL/min, 74%), use of RAAS inhibitor medication (69%), and diabetes mellitus (66%).

Efficacy Findings

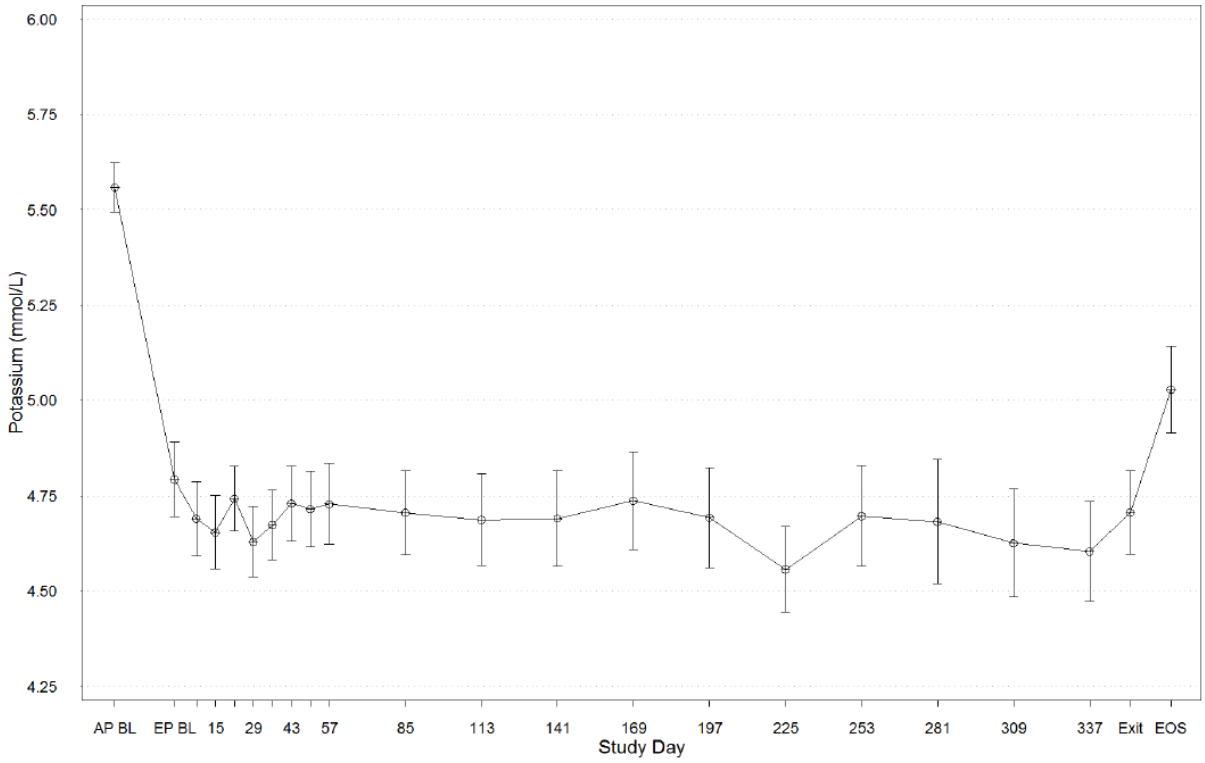
Analyses conducting by the applicant indicate that the treatment effect persists during extended dosing with ZS for up to 11 months and that S-K values increase after the withdrawal of ZS as shown in the following figure. Results were consistent across subgroups defined by age and baseline presence of CKD, HF, diabetes mellitus, and RAAS inhibitor use.

- Across Extended Dosing Study Days 8 to 337, 88.3% (95% CI: 81.2%, 93.5%) of subjects had average S-K values ≤ 5.1 mmol/L. The LS mean from a logistic regression analysis, which adjusted for baseline covariates, was 92.8% (95% CI: 84.7%, 96.8%).

- The proportions of subjects with S-K values ≤ 5.1 mmol/L were relatively constant among the Extended Dosing Phase time points, ranging from 77.1% to 87.5%.
- Across Extended Dosing Study Days 8 to 337, 100% (95% CI: 97.0%, 100.0%) of subjects had average S-K values ≤ 5.5 mmol/L.
- The proportions of subjects with S-K values ≤ 5.5 mmol/L were relatively constant across the Extended Dosing Phase time points, ranging from 91.4% to 98.5%.

Serum potassium levels rose after coming off treatment. According to the Applicant, there was a mean increase of 0.39 mmol/L in S-K values from Extended Dosing Study Day 337 to the End of Study assessment, which was 7 days after the last dose per protocol.

Figure 7: Mean Serum Potassium (mmol/L) Over Time in Study ZS004 E - ITT Population



AP BL = Study ZS-004 AP baseline; EP BL = Study ZS-004E Extended Dosing baseline; Exit = last visit of Extended Dosing Phase within 1 day of last dose of ZS. Vertical bars represent ± 2 standard errors.
Applicant' figure from CSR Study ZS004E, figure 11-1, page 88

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. Primary Endpoints

Both pivotal trials (Studies ZS 003 and ZS 004) assessed effects on serum potassium as the primary endpoint(s), although the analyses used differed. A summary table of the primary endpoints findings across trials is provided below. As shown in the table, all of the trials met their primary endpoint. Collectively, these trials provide substantial evidence that sodium zirconium cyclosilicate is effective in lowering serum potassium levels, an accepted surrogate endpoint for drugs intended to treat hyperkalemia.

7.1.2. Secondary and Other Endpoints

For the most part, secondary endpoints, which also assessed effects on serum potassium levels, were not tested within a plan that controlled that type 1 error rate. Of the studies discussed above, only Study ZS004 had protocol-specified secondary endpoints with adequate multiplicity adjustment. These 3 secondary endpoints were the total number of days normokalemic; proportions normokalemic at Study Day 29/Exit; and the mean S-K intra-subject standard deviation calculated among subjects with ≥ 2 values on or after Extended Dosing Study Day 8). For each of these endpoints, the comparison was made between the placebo arm and the ZS arm, staring with the highest dose and them moving to lower doses. Results are summarized below:

- The mean number of normokalemic days from Maintenance Phase Study Days 8 to 29, was statistically significant greater in each ZS group versus placebo (P< 0.001 in all treatment groups). The mean number of normokalemic days increased with increasing dose of ZS (13.4/22 days for ZS 5 g QD, 13.9/22 days for ZS 10 g QD, and 16.8/22 days for ZS 15 g QD) compared with 7.4/22 days for placebo.
- The proportion of subjects who remained normokalemic was statistically significantly larger in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups (71.1%, 76.0%, and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects) on day 29.
- For the intra-subject standard deviation among subjects with ≥ 2 S-K values on or after Maintenance Phase Study Day 8, a statistically significantly larger intra-subject standard deviation was observed for the ZS 10 g QD group (0.08 mmol/L) versus placebo (0.06 mmol/L).

7.1.3. Subpopulations

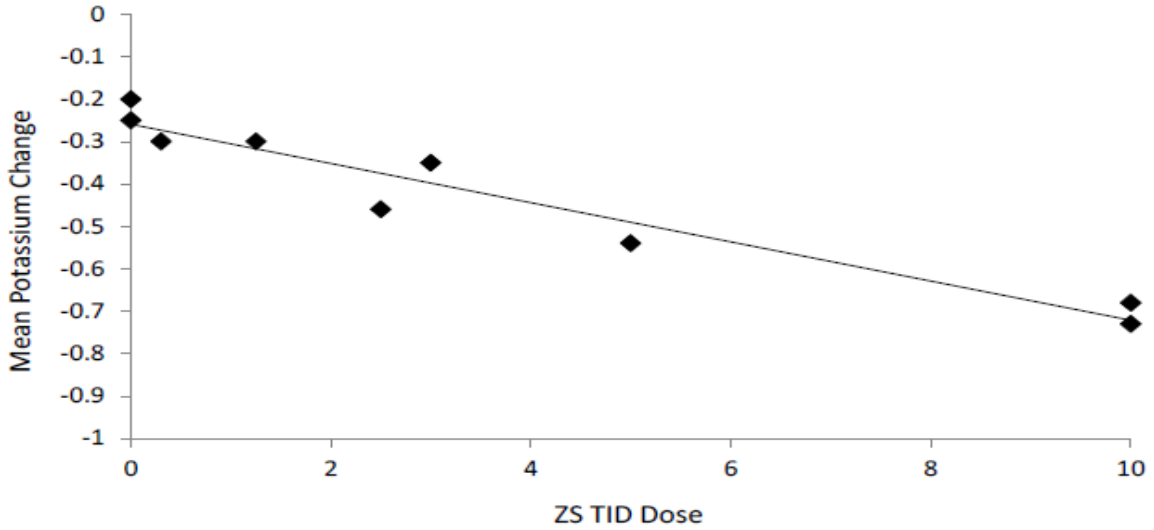
Subgroup analyses were conducted in Studies ZS003 and ZS004. Because of important differences in study design, including differences in inclusion criteria (e.g. S-K values could be >6.5 mEq/L in Study ZS004), study duration, and dosages, study results were not pooled across the trials. These analyses examined the effect of treatment by age, gender, race, baseline eGFR, baseline S-K, concomitant diseases, and use of RAAS inhibitor medication. In general, the magnitude of the treatment effect appeared to be greater among subjects with higher baseline

serum potassium values. Otherwise, there were no significant differences among the subgroups. See Sections 6.1.2 and 6.2.2 for additional information on the results of subgroup analyses.

7.1.4. Dose and Dose-Response

As ZS is not systemically absorbed, pharmacokinetic data were not collected; hence, the following analyses focus on the dose -response relationship for potassium lowering.
Data on the dose-response relationship during initial therapy are provided by Studies ZS002 and ZS003. As shown in the figure below, the reduction in mean serum potassium from baseline to 48 hours after start of dosing increased with larger doses of ZS. This dose response was observed across multiple endpoints and subpopulations. Of note, the incidence of hypokalemia during the initial 48 hours throughout the program was also low (0.4%; 4/913) and no patient had a serum potassium value less than 3.0 mmol/L. Based on the efficacy, safety and tolerability profile, the Applicant has proposed a recommended starting dose of ZS 10 g TID for acute treatment of hyperkalemia.

Figure 8: Mean Change in Serum Potassium from Baseline to 48 Hours after Start of Dosing (Acute Phase for Placebo-Controlled Studies ZS-002 and ZS-003, ITT Population)

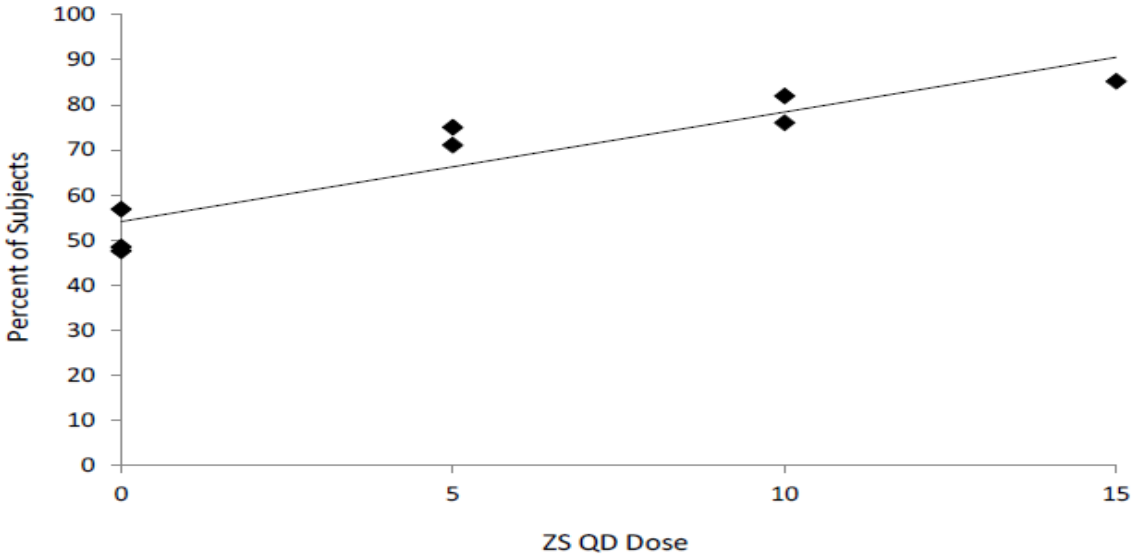


Applicant's Figure: CSR Study ZS-002 Statistical Table 14.2.1; CSR Study ZS-003 Statistical Table 14.2.1A

According to the Applicant's analyses, dosing TID should be continued until normal S-K levels have been achieved, which in most patients will occur within 24 hours (84% in Study ZS-004). For patients who are still hyperkalemic at 24 hours, the Applicant believes another 24 hours of ZS 10 g TID dosing should be given. According to the Applicant's analyses, 98% of subjects were normokalemic after 48 hours of ZS 10 g TID dosing in Study ZS-004, hence most patients would be expected to achieve target potassium levels over this time frame.

To evaluate the dose-response relationship in the maintenance phase, the Applicant examined the proportions of normokalemic subjects at the end of treatment during maintenance phase by treatment arm (placebo, ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups) from Studies ZS-003 and ZS-004. As shown in the figure below, the proportion of normokalemic subjects at the end of the maintenance phase treatment increased with larger doses of ZS, although the relationship was somewhat shallow.

Figure 9: Proportion of Normokalemic Subjects at End of Treatment (Maintenance Phase for Completed Studies, ITT Population)



Applicant's Figure: CSR Study ZS-003 Statistical Tables 14.2.3.3S and 14.2.3.4S; CSR Study ZS-004 Statistical Table 14.2.2.11.1

Given that patient's responses are likely to be variable, the Applicant has proposed a titration strategy for the maintenance phase, starting with 5 g QD, with up titration in 5 g increments or down to 5 g QOD as needed to maintain the target serum potassium level. Although the Applicant initially proposed a maximum dose of 15 g QD in the label, the Applicant has recently informed the Division that they intend to revise their draft label to recommend a maximum dose of (b) (4) gm, but has not yet provided supportive analyses.

Dosing down titration from QD to QOD was assessed in Study ZS-004. Per the protocol, if a subject developed i-STAT potassium values between 3.0 and 3.4 mmol/L during the maintenance phase, the study medication could be reduced from QD to QOD with the same dose level for the remainder of the study. None of the subjects who received the ZS 5 g QD dose required adjustment from QD to QOD. A total of 8 subjects treated with ZS 10 g QD and 10 subjects treated with ZS 15 g QD had their QD dosing adjusted to QOD. Sixteen (88.9%) of the 18 total subjects who had their QD dosing adjusted to QOD were able to complete dosing in the

study and 2 subjects in the ZS 15 g QD group were discontinued from the study (1 due to meeting protocol-specified stopping rules for prolonged QTc interval and 1 due to a treatment-emergent adverse event of generalized edema).

Reviewer's comment: Based on the information summarized above, the Applicant's proposed starting doses for acute and maintenance treatment and dose titration strategy seem reasonable; however input is needed from clinical pharmacology on the Applicant's proposal, as well as appropriate intervals for dose titration. The maximum dose for the maintenance phase remains an outstanding issue.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Onset of Efficacy: The mean change from baseline in S-K to 1, 2, 4, 24, and 48 hours after the start of dosing with placebo control were measured in Studies ZS002, ZS003 and without placebo control in Study ZS004. The S-K lowering effect of ZS 10 g was relatively rapid, with a significant difference from placebo starting at 1 hour after the start of dosing in both Studies ZS-002 and ZS-003. A significant mean decrease from baseline in S-K was also observed at 1 hour after the start of dosing in Study ZS-004.

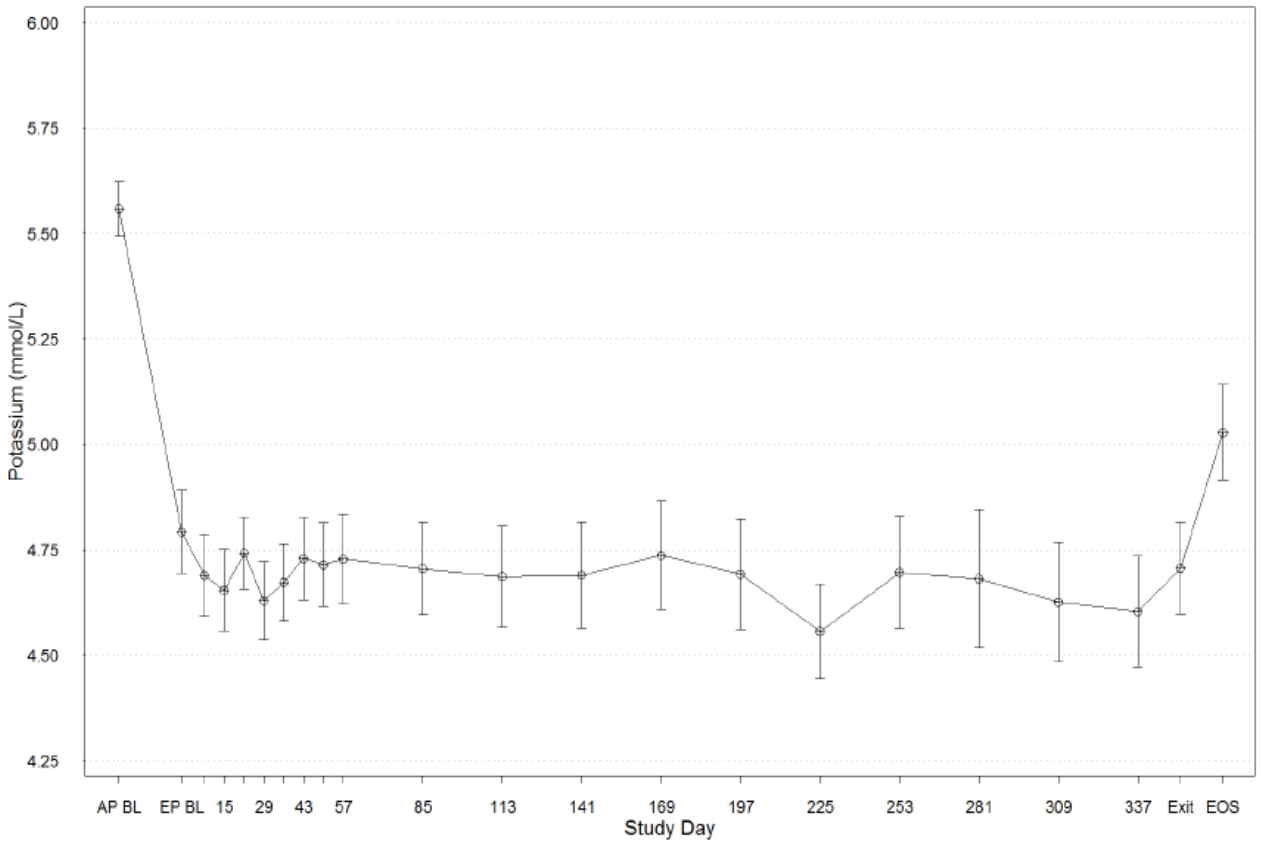
Duration and Durability of Efficacy Effects: Available data indicate persistence of clinical efficacy with continuous treatment during extended dosing. Study ZS-004 met its primary efficacy endpoint, which evaluated the mean S-K value during Extended Dosing Study Days 8 to 29 in the ZS as compared to placebo treatment groups ($p \leq 0.0001$ for each ZS dose group). In Study ZS-004, the proportion of subjects who remained normokalemic at end of treatment was greater in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups (71.1%, 76.0%, and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects).

The Applicant believes that because efficacy/control of serum potassium levels was well-maintained over the 28-day Extended Dosing treatment period in Study ZS-004, control would also be maintained during longer treatment durations unless underlying comorbidities (e.g., deteriorating kidney function) change. In the latter setting, the dose could be up-titrated (assuming the previous dose was well-tolerated and the patient was not at the maximum dose).

In a long-term study, Study ZS004 E, extended dosing with ZS for up to 11 months was effective in maintaining normokalemia. Across Extended Dosing Study Days 8 to 337, 88.3% (95% CI: 81.2%, 93.5%) of subjects had average S-K values ≤ 5.1 mmol/L. The LS mean from a logistic regression analysis, which adjusted for baseline covariates, was 92.8% (95% CI: 84.7%, 96.8%). Results were consistent across subgroups defined by age and baseline presence of CKD, HF, diabetes mellitus, and RAAS inhibitor use. In addition, the proportions of subjects with S-K values ≤ 5.1 mmol/L were relatively constant among the Extended Dosing Phase time points, ranging from 77.1% to 87.5%. The effectiveness of ZS in maintaining normokalemia was also

demonstrated by the proportion of subjects with average S-K values ≤ 5.5 mmol/L during Extended Dosing Study Days 8 to 337. Across Extended Dosing Study Days 8 to 337, 100% (95% CI: 97.0%, 100.0%) of subjects had average S-K values ≤ 5.5 mmol/L. The proportions of subjects with S-K values ≤ 5.5 mmol/L were relatively constant across the Extended Dosing Phase time points, ranging from 91.4% to 98.5%. Therefore, ZS was effective in maintaining normokalemia for up to 12 months (1 month in Study ZS-004, 11 months in Study ZS-004E) in subjects with hyperkalemia. The mean change of S-K values over time is described in the figure below.

Figure 10: Mean Serum Potassium (mmol/L) Over Time in Study ZS004 E - ITT Population



Applicant's Figure from ZS-004E Clinical Study Report, Figure 11-1, page 88.
Abbreviations: AP = Acute Phase; BL = baseline; EP = Extended Dosing Phase; EOS = end of study
AP BL = Study ZS-004 AP baseline; EP BL = Study ZS-004E Extended Dosing baseline; Exit = last visit of Extended Dosing Phase within 1 day of last dose of ZS. Vertical bars represent ± 2 standard errors.

Reviewer comment: The dropout rate was high in this open-label extension study. Of the enrolled 125 subjects, only 79 (64.2%) completed the study. Review of the reasons for dropout does not suggest that lack of efficacy was responsible for dropout; main reasons for dropout included progression of chronic kidney disease, adverse events, and patient compliance. See Section 6.3.2 for additional information on patient disposition in Study ZS004 E. Of note, another long-term open label study (Study ZS005) is currently ongoing. This study should provide

additional information on persistence of efficacy over time.

7.2. Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

Dialysis patients were not included in the clinical trials. Given the ability to titrate therapy based on response, it seems likely that physicians will be able to individualize care for this population.

7.2.2 Other Relevant Benefits

None.

7.3 Integrated Assessment of Effectiveness

Sodium zirconium cyclosilicate (ZS) is a selective cation exchanger that entraps potassium in the gastrointestinal tract in exchange for sodium and hydrogen. The efficacy of ZS was evaluated in three short-term studies (Study ZS002, ZS003, and ZS004) and one long-term study (Study ZS004E).

Each of the short-term study included an Acute Phase (48 hours up to 96 hours in Study ZS-002 and 48 hours in Studies ZS003 and ZS004). The purpose of the Acute Phase was to achieve normalization of serum potassium values. In Studies ZS003 and 004, subjects who completed the Acute Phase with a normalized serum potassium value were eligible for extended dosing. In Study ZS003, subjects were randomized to treatment for an additional 12 days whereas in Study ZS004 subjects were randomized to treatment for an additional 28 days. Both of these phase 3 trials employed a randomized, withdrawal design in the extended dosing phase.

The aforementioned studies provide substantial evidence of the effectiveness of ZS in reducing serum potassium levels in patients with hyperkalemia. Key efficacy findings, which support the conclusion that ZS has a clinically meaningful effect on serum potassium levels in this population are summarized below:

- Both phase 3 trials met their primary endpoints in the acute phase (Study ZS003) and maintenance phase (Studies ZS003 and ZS004). Specifically, in Study ZS003, ZS at doses of 10 g TID, 5 g TID, and 2.5 g TID was statistically significantly superior to placebo for the exponential decrease in S-K during the Acute Phase; at doses of 10 g and 5 g QD, ZS was statistically significantly superior to placebo for the exponential decrease in S-K during the maintenance Phase(up to Day 12). In Study ZS004, each ZS group had a statistically significantly smaller mean S-K value than the placebo group from Day 8 to Day 29. Among the ZS groups, the mean S-K value decreased with increasing dose of ZS (4.8 mmol/L for ZS 5 g QD, 4.5 mmol/L

for ZS 10 g QD, and 4.4 mmol/L for ZS 15 g QD). As a whole, these data indicate a dose-dependent effect on lowering of serum potassium levels in patients with hyperkalemia.

- The serum potassium lowering effect has a relatively rapid onset, starting ~ 1 hour after administration of the first dose of ZS 10g (0.11 mmol/L change from baseline in Study ZS003 and 0.23 mmol/L change from baseline in Study ZS004).
- With regard to subgroup analyses, a greater reduction in serum potassium levels was observed in patients with higher baseline serum potassium values; otherwise, efficacy findings were consistent among the various subgroups that were examined (age, gender, race, primary diseases and concurrent use of RAAS inhibitors).
- In the long-term open-label study (Study ZS004E), ZS was effective in maintaining normokalemia for up to 12 months. The results were consistent across subgroups defined by age and baseline presence of CKD, HF, diabetes mellitus, and RAAS inhibitor use. Following the completion of ZS treatment, significant increases in S-K were observed, indicating that hyperkalemia will likely recur once treatment with ZS is withdrawn.

In conclusion, the submitted data provide substantial evidence of ZS's effectiveness in lowering serum potassium levels in patients with hyperkalemia. There should be further internal discussion about how to present the efficacy findings in labeling since clinicians may find it difficult to interpret some of the pre-specified efficacy analyses.

8. Review of Safety

8.1. Safety Review Approach

Safety analyses focused on the data from 3 completed multicenter studies that evaluated the efficacy and safety of ZS (Study ZS-002, ZS-003, and ZS-004), as well as the data from a completed open-label extension study to Study ZS-004 (Study ZS-004E). The results of the latter study were provided in the applicant's 120 day safety update. In addition, one open-label study to evaluate the long-term safety and efficacy of ZS is ongoing in the US, Australia, and South Africa (Study ZS-005). Interim data from this study, which were provided in the 120-day safety update, were also reviewed.

Given the drug's mechanism of action and sodium counterion, potential safety concerns include hypokalemia, sodium absorption resulting in volume overload, GI safety and tolerability, and clinically significant alkalosis. The safety review focused on these potential safety concerns.

8.2. Review of the Safety Database

8.2.1. **Overall Exposure**

As of 15 July 2015, a total of 1,592 subjects with hyperkalemia have been exposed to at least 1 dose of ZS in clinical trials (1,009 subjects from Studies ZS-002, ZS-003, ZS-004/ZS-004E and 583 subjects from Study ZS-005). An additional 30 healthy volunteers were exposed to ZS in Study ZS-006.

Table 29: Overall Exposure –safety population

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review N=1622 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=1622)	Active Control (n=0)	Placebo (n=188)
Normal Volunteers	30	0	0
Controlled trials conducted for this indication	1592	0	188
All other than controlled trials conducted for this indication	0	0	0
Controlled trials conducted for other indications	0	0	0

Source: Reviewer's table.

Table 30: Duration of Exposure

Number of patients exposed to the study drug		
>=6 months	>=12 months	>=18 months
N=262	N=79	N=0

Source: Reviewer's table.

8.2.2. **Relevant characteristics of the safety population:**

Subject characteristics for the individual studies are described in the efficacy section. In the following tables, demographic characteristic are pooled across the completed studies contributing to the safety database. The vast majority of patients were Caucasian and the majority of subjects had baseline S-K values (per central laboratory) ≤ 5.5 mmol/L (range: 59.1% to 67.6% in the Acute Phase). As also shown in the tables, many subjects were enrolled at sites located in the US (~91% in the Acute Phase).

Reviewer's comment: As noted above, few Black or African American subjects were enrolled. Patients with hyperkalemia in the setting of end-stage kidney disease were not studied and other settings in which hyperkalemia may be seen, such as hyperkalemia in the ICU setting, are

not represented. Otherwise, the safety data appear to be collected from a broad population of patients with hyperkalemia. The safety findings should be generalizable to the U.S. population of patients with hyperkalemia.

Table 31: Acute Phase-Demographic and Other Baseline Characteristics (All Completed Studies)

Demographic Parameter Statistic	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Age at screening (years)				
Mean (SD)	66.3 (12.11)	66.3 (12.06)	65.2 (11.91)	65.2 (12.62)
Median	67.0	68.0	66.0	66.0
Minimum, maximum	27, 96	22, 93	24, 89	22, 93
Age category, n (%)				
< 65	75 (39.9)	125 (37.8)	71 (45.2)	189 (44.5)
≥ 65	113 (60.1)	206 (62.2)	86 (54.8)	236 (55.5)
Gender, n (%)				
Male	121 (64.4)	194 (58.6)	96 (61.1)	238 (56.0)
Female	67 (35.6)	137 (41.4)	61 (38.9)	187 (44.0)
Race, [a] n (%)				
White	165 (87.8)	292 (88.2)	132 (84.1)	358 (84.2)
Black or African American	18 (9.6)	31 (9.4)	20 (12.7)	56 (13.2)
Asian	2 (1.1)	5 (1.5)	3 (1.9)	7 (1.6)
American Indian or Alaska Native	2 (1.1)	0 (0.0)	1 (0.6)	2 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.5)	3 (0.9)	0 (0.0)	2 (0.5)
Other	0 (0.0)	1 (0.3)	1 (0.6)	2 (0.5)
Multiple races	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Weight at baseline, n (%)				
< 85 kg	86 (45.7)	180 (54.4)	76 (48.4)	216 (50.8)
≥ 85 kg	100 (53.2)	150 (45.3)	80 (51.0)	205 (48.2)
Acute S-K at baseline (mmol/L)				
Mean (± SD)	5.28 (0.368)	5.33 (0.386)	5.31 (0.337)	5.42 (0.441)
Minimum, maximum	4.5, 6.4	4.3, 6.5	4.5, 6.2	4.1, 7.2
Acute S-K baseline, n (%)				
< 5.5 mmol/L	127 (67.6)	213 (64.4)	104 (66.2)	251 (59.1)
5.5 - < 6.0 mmol/L	57 (30.3)	99 (29.9)	46 (29.3)	128 (30.1)
≥ 6.0 mmol/L	4 (2.1)	19 (5.7)	7 (4.5)	46 (10.8)
Acute eGFR at baseline (mL/min/1.73 m^2)				
Mean (± SD)	n = 185 44.56 (23.367)	n = 310 43.51 (22.599)	n = 146 44.65 (24.523)	n = 406 46.60 (29.024)
Minimum, maximum	6.1, 125.8	4.1, 122.3	6.6, 124.0	4.7, 149.3
Acute eGFR at baseline, n (%)				
< 60 mL/min/1.73 m^2	149 (79.3)	260 (78.5)	115 (73.2)	304 (71.5)
≥ 60 mL/min/1.73 m^2	39 (20.7)	65 (19.6)	39 (24.8)	114 (26.8)
Missing	0 (0.0)	6 (1.8)	3 (1.9)	7 (1.6)
Etiology by history, [a] n (%)				
CKD	102 (54.3)	199 (60.1)	95 (60.5)	261 (61.4)
Heart failure	78 (41.5)	132 (39.9)	64 (40.8)	166 (39.1)
Diabetes mellitus	116 (61.7)	200 (60.4)	97 (61.8)	262 (61.6)
RAAS inhibitor medication	120 (63.8)	234 (70.7)	99 (63.1)	296 (69.6)

ISS Statistical Tables 2.1.1, 2.1.1a, and 5.2.1.1

a. Categories are not mutually exclusive.

Table 32: Concomitant Medications by Anatomic Therapeutic Class Reported by ≥ 20% of Subjects in Any Treatment Group (Safety Population; All Completed Studies)

Anatomic Therapeutic Class Level 2, n (%)	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Any Medication	183 (97.3)	325 (98.2)	157 (100.0)	413 (97.2)
Agents acting on the renin-angiotensin system	115 (61.2)	227 (68.6)	94 (59.9)	287 (67.5)
Lipid-modifying agents	127 (67.6)	218 (65.9)	100 (63.7)	260 (61.2)
Drugs used in diabetes	104 (55.3)	172 (52.0)	80 (51.0)	242 (56.9)
Beta-blocking agents	94 (50.0)	163 (49.2)	76 (48.4)	192 (45.2)
Anti-thrombotic agents	98 (52.1)	162 (48.9)	62 (39.5)	189 (44.5)
Vitamins	88 (46.8)	145 (43.8)	64 (40.8)	175 (41.2)
Diuretics	64 (34.0)	123 (37.2)	58 (36.9)	155 (36.5)
Calcium channel blockers	63 (33.5)	129 (39.0)	47 (29.9)	150 (35.3)
Drugs for acid-related disorders	56 (29.8)	117 (35.3)	47 (29.9)	139 (32.7)
Analgesics	65 (34.6)	98 (29.6)	53 (33.8)	127 (29.9)
Anti-anemic preparations	39 (20.7)	69 (20.8)	33 (21.0)	91 (21.4)
Psychoanaleptics	39 (20.7)	63 (19.0)	32 (20.4)	75 (17.6)

ISS Statistical Table 2.2.1

Table 33: Demographic and Other Baseline Characteristics (Safety Population; Completed Studies ZS-003, ZS-004 and ZS-004E)

Demographic Parameter Statistic	Placebo[a] (N = 301)	Starting Dose of ZS in Extended Dosing				Titration
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Age at screening (years)						
Mean (SD)	65.6 (12.33)	65.7 (13.42)	63.4 (13.84)	64.7 (11.23)	64.9 (12.85)	64.0 (12.41)
Median	66.0	68.0	65.0	66.0	64.5	64.0
Min, max	22, 93	22, 91	22, 89	31, 91	25, 85	22, 85
Age category, n (%)						
< 65	130 (43.2)	75 (37.7)	53 (48.2)	51 (44.7)	28 (50.0)	62 (50.4)
≥ 65	171 (56.8)	124 (62.3)	57 (51.8)	63 (55.3)	28 (50.0)	61 (49.6)
Gender, n (%)						
Male	178 (59.1)	115 (57.8)	60 (54.5)	62 (54.4)	40 (71.4)	71 (57.7)
Female	123 (40.9)	84 (42.2)	50 (45.5)	52 (45.6)	16 (28.6)	52 (42.3)
Race,[b] n (%)						
White	251 (83.4)	177 (88.9)	93 (84.5)	99 (86.8)	46 (82.1)	109 (88.6)
Black or African American	36 (12.0)	19 (9.5)	15 (13.6)	13 (11.4)	9 (16.1)	11 (8.9)
Asian	10 (3.3)	1 (0.5)	1 (0.9)	1 (0.9)	1 (1.8)	2 (1.6)
American Indian/Alaska Native	2 (0.7)	0	0	0	0	0
Native Hawaiian/Pacific Islander	2 (0.7)	2 (1.0)	0	0	0	0
Other	2 (0.7)	0	1 (0.9)	1 (0.9)	0	1 (0.8)
Multiple races	1 (0.3)	0	0	0	0	0
Weight at AP baseline, n (%)	n = 299	n = 197	n = 110	n = 112	n = 55	n = 122
< 85 kg	152 (50.5)	114 (57.3)	56 (50.9)	58 (50.9)	28 (50.0)	60 (48.8)
≥ 85 kg	147 (48.8)	83 (41.7)	54 (49.1)	54 (47.4)	27 (48.2)	62 (50.4)
S-K at AP baseline, n (%)						
< 5.5 mmol/L	206 (68.4)	145 (72.9)	69 (62.7)	68 (59.6)	24 (42.9)	55 (44.7)
5.5 - < 6.0 mmol/L	81 (26.9)	51 (25.6)	34 (30.9)	34 (29.8)	26 (46.4)	54 (43.9)
≥ 6.0 mmol/L	14 (4.7)	3 (1.5)	7 (6.4)	12 (10.5)	6 (10.7)	14 (11.4)
eGFR at AP baseline, n (%)						
< 60 mL/min/1.73 m^2	213 (70.8)	141 (70.9)	77 (70.0)	86 (75.4)	41 (73.2)	92 (74.8)
≥ 60 mL/min/1.73 m^2	79 (26.2)	56 (28.1)	30 (27.3)	28 (24.6)	15 (26.8)	31 (25.2)
Missing	9 (3.0)	2 (1.0)	3 (2.7)	0	0	0
Etiology by history,[b] n (%)						
CKD	181 (60.1)	117 (58.8)	68 (61.8)	74 (64.9)	37 (66.1)	78 (63.4)
Heart failure	106 (35.2)	75 (37.7)	45 (40.9)	44 (38.6)	25 (44.6)	52 (42.3)
Diabetes mellitus	190 (63.1)	113 (56.8)	62 (56.4)	74 (64.9)	39 (69.6)	82 (66.7)
RAAS inhibitor medication	206 (68.4)	131 (65.8)	71 (64.5)	79 (69.3)	33 (58.9)	84 (68.3)
Geographic region, n (%)						
United States	272 (90.4)	188 (94.5)	98 (89.1)	101 (88.6)	41 (73.2)	96 (78.0)
Other countries	29 (9.6)	11 (5.5)	12 (10.9)	13 (11.4)	15 (26.8)	27 (22.0)
Diuretic use, n (%)	118 (39.2)	70 (35.2)	48 (43.6)	44 (38.6)	24 (42.9)	56 (45.5)

a. Following treatment with ZS TID during the Acute Phase.
b. Categories are not mutually exclusive.

ISS Statistical Tables 2.1.2, 2.1.2a, 5.2.2.1, and 8.1.2

Table 34: Concomitant Medications by Anatomic Therapeutic Class Reported by ≥ 20% of Subjects in Any Treatment Group (Safety Population, Completed Studies)

Anatomic Therapeutic Class Level 2, n (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extended Dosing				Titration
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Any Medication	292 (97.0)	195 (98.0)	110 (100.0)	112 (98.2)	53 (94.6)	119 (96.7)
Agents acting on the renin-angiotensin system	200 (66.4)	128 (64.3)	66 (60.0)	78 (68.4)	32 (57.1)	84 (68.3)
Drugs used in diabetes	163 (54.2)	103 (51.8)	56 (50.9)	69 (60.5)	36 (64.3)	79 (64.2)
Lipid modifying agents	188 (62.5)	125 (62.8)	65 (59.1)	73 (64.0)	33 (58.9)	77 (62.6)
Diuretics	115 (38.2)	70 (35.2)	47 (42.7)	42 (36.8)	24 (42.9)	62 (50.4)
Analgesics	95 (31.6)	68 (34.2)	37 (33.6)	32 (28.1)	15 (26.8)	58 (47.2)
Calcium channel blockers	106 (35.2)	74 (37.2)	33 (30.0)	47 (41.2)	27 (48.2)	57 (46.3)
Vitamins	118 (39.2)	83 (41.7)	42 (38.2)	51 (44.7)	27 (48.2)	56 (45.5)
Beta blocking agents	125 (41.5)	104 (52.3)	53 (48.2)	60 (52.6)	26 (46.4)	55 (44.7)
Anti-thrombotic agents	123 (40.9)	98 (49.2)	43 (39.1)	57 (50.0)	29 (51.8)	55 (44.7)
Drugs for acid related disorders	105 (34.9)	63 (31.7)	29 (26.4)	32 (28.1)	20 (35.7)	47 (38.2)
Anti-anemic preparations	60 (19.9)	38 (19.1)	25 (22.7)	22 (19.3)	12 (21.4)	44 (35.8)
Other anti-hypertensives	31 (10.3)	29 (14.6)	21 (19.1)	21 (18.4)	12 (21.4)	29 (23.6)
Psychoanaleptics	54 (17.9)	35 (17.6)	21 (19.1)	24 (21.1)	9 (16.1)	26 (21.1)

a. Following treatment with ZS TID during the Acute Phase.
Reviewer's table based on ISS Statistical Table 2.2.2 and Study ZS-004E CSR Statistical Table 14.1.4.2

8.2.3. Adequacy of the safety database

Based on the number of subjects with exposures to the appropriate dose(s), patients demographics and disease characteristics, the safety database appears to be adequate to evaluate the safety of this product when administered for extended periods (i.e., for 6 months or more).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In my review of the submitted data, I did not identify any problems or major discrepancies that might confound the safety evaluation of this product. The quality and integrity of the data included in the submission are acceptable.

8.3.2. Categorization of Adverse Events

In general, the Applicant's approach for recording, coding, and categorizing AEs, as well as their approach to safety analyses, seemed reasonable and appropriate.

The Applicant presented the overall treatment-emergent adverse event profile by ZS dose using the Medical Dictionary for Regulatory Activities (MedDRA) 17.0 coded terms at the System Organ Class and Preferred Term levels. Because adverse event and medical history data for

Studies ZS-002 and ZS-003 were originally coded for presentation in the individual CSRs using MedDRA Version 15.1E, these data were updated to MedDRA Version 17.0 to be consistent with Study ZS-004 and Study ZS-004E.

For Safety Assessments, an adverse event was defined as any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related. An adverse event was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. TEAEs were defined as adverse events that began on, or after, the date/time of the first dose of study drug.
All adverse events were to be recorded on the designated study electronic case report form 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 adverse event was to be followed by the investigator until event resolution, the subject was lost to follow-up, the adverse event was otherwise explained, or not considered clinically significant by the investigator. Abnormal laboratory findings considered by the investigator to be clinically significant (ie, those that were unusual or unusually severe for the population being studied) were also to be recorded as adverse events.

Investigators were to assess the intensity of an adverse event as mild, moderate, or severe; and the relationship of the adverse event to the study drug as either not related or unlikely, possibly, probably, or definitely related. A serious adverse event was defined as an adverse event that suggested a significant hazard or side effect, regardless of the relationship to study drug. A serious adverse event included, but was not limited to 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; and a congenital anomaly/birth defect.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points described in the protocols seem reasonable. A full physical examination, including vital signs (blood pressure, respiratory rate, heart rate, and temperature) and weight (weighed on the same scale in the same state of dress), was performed at specified time points during each of the studies. Blood and urine samples were collected for determination of the clinical laboratory tests displayed in the following table. To ensure consistency in measurements, all samples were analyzed by a central laboratory. Standard 12-lead ECGs were also obtained.

Table 35: Clinical Laboratory Tests

Clinical Chemistry	Urinalysis
Potassium	pH
Total protein	Specific gravity
Albumin	Glucose
Bicarbonate	Ketones
Blood urea nitrogen (BUN)	Bilirubin
Creatinine	Urobilinogen
Total bilirubin	Blood
Alkaline phosphatase	Urine sediment
Glucose	Urine culture
Sodium	Urine pregnancy test
Inorganic phosphate	
Calcium (total)	**Urine Chemistry**[a]
Magnesium	Potassium
Gamma-glutamyl transferase (GGT)	Sodium
Alanine aminotransferase (ALT)	Creatinine
Aspartate aminotransferase (AST)	Albumin
Estimated glomerular filtration rate[b]	Protein
Hematology	Urea nitrogen
Hemoglobin	
Hematocrit	
Erythrocyte count (RBC)	
Differential leukocytes	
Total leukocytes (WBC)	
Platelets	

a. 24-hour urine potassium, sodium, creatinine, and urea nitrogen collected in Study ZS-002; urine potassium, sodium, creatinine, albumin, and protein were collected on Acute Phase Study Day 1 and Extended Dosing Study Day 29 in Study ZS-004.
b. Estimated glomerular filtration rate calculated in Study ZS-003 and ZS-004; 24-hour creatinine clearance calculated in Study ZS-002.

8.4. Safety Results

8.4.1. Deaths

Two deaths were reported (0.2%; 2/1,009) in the completed studies. One subject in Study ZS-003 died due to respiratory arrest and 1 subject in Study ZS-004 died due to myocardial infarction. No deaths were reported in Study ZS-004E.

As of 15 July 2015, there have been 3 deaths in Study ZS-005, which is ongoing: 1 attributed to hemorrhagic cystitis, 1 attributed to interstitial lung disease, and 1 attributed to a cardiovascular event.

Reviewer comments: Review of the provided narratives did not suggest a causal link to the study drug.

8.4.2. Serious Adverse Events

None of the ZS-treated subjects experienced a serious treatment-emergent adverse event during the Acute Phase of treatment.

During Extended Dosing in the short-term studies, the overall incidence of serious treatment-emergent adverse events was somewhat higher among ZS-treated subjects in the 5 g and 15 g QD dose groups and similar between placebo and subjects in the ZS 2.5 g and 10 g QD dose groups (1.7% in the placebo group, 3.0% in the ≤ 2.5 g QD group, 7.3% in the 5 g QD group, 2.6% in the 10 g QD group, and 5.4% in the 15 g QD group).

In the completed long-term study, Study ZS-004E, 24 (19.5%) subjects experienced treatment-emergent serious adverse events. Most of these serious adverse events were reported in only a single subject; 2 (1.6%) subjects each experienced serious adverse events of cardiac failure congestive, pneumonia, urinary tract infection, and chronic obstructive pulmonary disease.
A summary of all serious treatment-emergent adverse events reported in any Extended Dosing treatment group from Studies ZS-003 and ZS-004 (pooled data) and corresponding incidence rates from Study ZS-004E are summarized in the table below using Preferred Terms. The overall incidence of serious events was higher during Study ZS-004E (19.5%) compared with the Extended Dosing ZS treatment groups from Studies ZS-003 and ZS-004 pooled (range of 2.6% to 7.3%). This is not unexpected given the longer duration of Study ZS-004E. Among the serious events reported in Study ZS-004E that were not reported in any of the Extended Dosing ZS treatment groups from Studies ZS-003 and ZS-004 pooled, all were reported by 1 (< 1%) subject each, except for the event of chronic obstructive pulmonary disease (reported by 2 subjects in Study ZS-004E).

Table 36: Summary of All Serious Treatment-Emergent Adverse Events in Extending Phase in Pooled Studies (Safety Population, by preferred term)

		Starting Dose of ZS in Extended Dosing				Titration
	Placebo[a] (N = 301)	≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Any Event, n (%)	5 (1.7)	6 (3.0)	8 (7.3)	3 (2.6)	3 (5.4)	24 (19.5)
Preferred Term, n (%)						
Cardiac failure congestive	1 (0.3)	0	1 (0.9)	0	0	2 (1.6)
Pneumonia	1 (0.3)	1 (0.5)	1 (0.9)	0	1 (1.8)	2 (1.6)
Urinary tract infection[b]						
All events	0	1 (0.5)	0	0	0	2 (1.6)
Supported events	0	1 (0.5)	0	0	0	-
Chest pain	0	1 (0.5)	0	0	0	1 (0.8)
Myocardial infarction	0	0	0	1 (0.9)	0	1 (0.8)
Pulmonary oedema	0	0	1 (0.9)	0	0	1 (0.8)
Hyperkalemia	1 (0.3)	1 (0.5)	0	0	0	1 (0.8)
Diastolic dysfunction	0	0	1 (0.9)	0	0	0
Small intestinal obstruction	0	0	1 (0.9)	0	0	0
Generalized oedema	0	0	0	0	1 (1.8)	0
Malaise	1 (0.3)	0	0	0	0	0
Hepatotoxicity	0	0	1 (0.9)	0	0	0
Cellulitis	0	0	0	1 (0.9)	0	0
Gastroenteritis	1 (0.3)	0	0	0	0	0
Nocardiosis	0	0	1 (0.9)	0	0	0
Gout	0	0	0	1 (0.9)	0	0
Loss of consciousness	0	0	1 (0.9)	0	0	0
Confusional state	0	0	1 (0.9)	0	0	0
Renal failure	0	0	1 (0.9)	0	0	0
Urinary retention	0	1 (0.5)	0	0	0	0
Dyspnea	0	2 (1.0)	0	0	1 (1.8)	0
Respiratory arrest	0	0	1 (0.9)	0	0	0
Hospitalization	0	0	1 (0.9)	0	0	0

a, Following treatment with ZS TID during the Acute Phase.
b. Preferred terms associated with urinary tract infections are presented for all reported events and reported events that were supported by urinalysis and/or urine culture results.
Applicant's table 9-9 from ISS, page 64.

Reviewer comments: These SAEs are not unexpected events in this patient population. I reviewed the provided narratives and did not identify an obvious causal link to the study drug. Because safety signals can be obscured by splitting similar preferred terms, with similar meanings, into multiple categories, additional analyses were conducted to evaluate safety topics of interest (see Section 8.1 "Analysis of Submission-Specific Safety Issues").

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

In the Acute Phase, as shown in the table below, less than 1% of the subjects in any of the treatment groups experienced treatment-emergent adverse events that led to premature discontinuation from study drug. No dose-related trends were apparent for the events that led to premature discontinuation from study drug.

Table 37: Acute Phase- Summary of TEAEs Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population; All Completed Studies)

	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Any Event, n (%)	1 0.5)	3 (0.9)	1 (0.6)	2 (0.5)
System Organ Class Preferred Term, n (%)				
Cardiac disorders	0 0.0)	1 (0.3)	1 (0.6)	0 (0.0)
Atrial flutter	0 0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Bradycardia	0 0.0)	0 (0.0)	1 (0.6)[a]	0 (0.0)
Gastrointestinal disorders	0 0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Diarrhea	0 0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Vomiting	0 0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Investigations	1 0.5)	1 (0.3)	0 (0.0)	1 (0.2)
Electrocardiogram QT prolonged	0 0.0)	0 (0.0)	0 (0.0)	1 (0.2)[c]
Hyperkalemia	1 (0.5)[b]	1 (0.3)[b]	0 (0.0)	0 (0.0)
Nervous system disorders	0 0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Lethargy	0 0.0)	1 (0.3)[a]	0 (0.0)	0 (0.0)

a. Event started during Acute Phase, but subject was discontinued during Extended Dosing.
b. Action taken for event was recorded by the investigator as "drug withdrawn." However, these subjects were indicated as having completed the Acute Phase and did not enter Extended Dosing due to hyperkalemia.
c. Action taken for event was recorded by the investigator as "drug withdrawn." However, this subject was indicated as having completed the Acute Phase and did not enter Extended Dosing due to meeting ECG withdrawal criteria.

Applicant's table 9-12 from ISS, page 68

In the extended dosing phases of Studies ZS-003 and ZS-004, the incidence of treatment-emergent adverse events leading to premature discontinuation of study drug was higher in the ZS 5 g QD (5.5%) and 15 g QD (5.4%) groups compared with the placebo (0.3%) and other ZS treatment groups, including the ZS 10 g QD group (≤ 1.0%). One subject was withdrawn from the study due to general edema in the highest dose group. Two subjects in the dose of 5 g group and one subject in the dose of 2.5 g group were withdrawn due to pulmonary edema, dyspnea, and diastolic dysfunction. The 3 subjects from the low groups may not be drug-related.

Electrocardiogram QT prolongation led to premature discontinuation of study drug in 4 ZS-treated subjects in Study ZS-004 (1 in Acute Phase [ZS 10 g TID] and 3 in Extended Dosing [1 ZS 5 g QD and 2 ZS 15 g QD]). These discontinuations were based on stopping rules pre-specified in the protocol regarding heart-rate corrected QT (> 25 msec increase to more than 500 msec or >

25 msec increase in a subject with baseline value > 500 msec). Three of the 4 events were mild, 1 was moderate in severity, and none were considered serious.

Table 38: Extended Dosing-Summary of TEAEs Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population; Completed Studies ZS-003 and ZS-004)

	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Any Event, n (%)	1 (0.3)	2 (1.0)	6 5.5)	0 (0.0)	3 (5.4)
System Organ Class Preferred Term, n (%)					
Cardiac disorders	0 (0.0)	0 (0.0)	2 1.8)	0 (0.0)	0 (0.0)
Diastolic dysfunction	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Long QT syndrome	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (0.5)	2 1.8)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	1 (0.5)[b]	1 0.9)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (0.5)	0 0.0)	0 (0.0)	1 (1.8)
Chest pain	0 (0.0)	1 (0.5)	0 0.0)	0 (0.0)	0 (0.0)
Generalized edema	0 (0.0)	0 (0.0)	0 0.0)	0 (0.0)	1 (1.8)
Infections and infestations	1 (0.3)	0 (0.0)	0 0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.3)	0 (0.0)	0 0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	2 (3.6)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	2 (3.6)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	2 1.8)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	2 1.8)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.5)	1 0.9)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	1 (0.5)	0 0.0)	0 (0.0)	0 (0.0)
Pulmonary edema	0 (0.0)	0 (0.0)	1 0.9)	0 (0.0)	0 (0.0)

a Following treatment with ZS TID during the Acute Phase.
b Action taken for event was recorded by the investigator as "drug withdrawn." However, the investigator indicated "investigator decision" as the reason for premature discontinuation at the end of study.
Applicant's table 9-13 from ISS, page 70

In the long-term extension study of Study ZS-004E, eleven (8.9%) subjects prematurely discontinued study drug due to treatment-emergent adverse events. Two subjects discontinued due to an adverse event of electrocardiogram QT prolonged; these discontinuations were based on stopping rules prespecified in the protocol regarding heart-rate corrected QT (> 25 msec increase to more than 500 msec or > 25 msec increase in a subject with baseline value > 500 msec). All other treatment-emergent adverse events that led to premature discontinuation of study drug were reported by no more than 1 subject each. One subject was withdrawn from study treatment for an AE of cardiac failure in the first 30 days.

Table 39: Extended Dosing Phase, Summary of TEAEs Leading to Premature Discontinuation of Study Drug Presented by Preferred Term (Safety Population; Study ZS-004E)

	ZS QD; Extended Dosing Phase Days				
	1 to 30 (N = 123)	31 to 90 (N = 116)	91 to 180 (N = 91)	181 to EOS (N = 69)	Total (N = 123)
Any Event, n (%)	5 (4.1)	2 (1.7)	1 (1.1)	3 (4.3)	11 (8.9)
Preferred Term, n (%)					
Electrocardiogram QT prolonged	0	1 (0.9)	0	1 (1.4)	2 (1.6)
Acute myocardial infarction	0	1 (0.9)	0	0	1 (0.8)
Bundle branch block right	1 (0.8)	0	0	0	1 (0.8)
Cardiac failure	1 (0.8)	0	0	0	1 (0.8)
Blindness unilateral	1 (0.8)	0	0	0	1 (0.8)
Drug hypersensitivity	0	0	0	1 (1.4)	1 (0.8)
Diabetic foot infection	0	0	1 (1.1)	0	1 (0.8)
Localized infection	1 (0.8)	0	0	0	1 (0.8)
Hyperkalemia	0	0	0	1 (1.4)	1 (0.8)
Chronic obstructive pulmonary disease	1 (0.8)	0	0	0	1 (0.8)

Reviewer table modified from CSR of Study ZS004 E, table 12-7, page 118

8.4.4. Significant Adverse Events

During the Acute Phase of the completed studies, only 1 subject reported treatment-emergent adverse events that were considered by the investigator to be severe. One subject in the ZS 10 g TID group experienced severe episodes of vomiting and diarrhea on Study Day 1. Both events were considered possibly related to study drug and led to premature discontinuation of study drug.

In the maintenance phase of the short-term studies, one subject had peripheral edema in the placebo group, one had dyspnea in dose of 1.25 g group, and one had general edema in the dose of 15 g group that were considered to be severe.

In Study ZS-004E, 20 (16.3%) subjects had treatment- emergent adverse events during the Extended Dosing Phase that were considered to be severe; for the most part, these events were not unexpected events in the study population. For further discussion of the risk of hypokalemia, and sodium absorption leading to volume overload, see Section 8.5.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the Acute Phase, the overall incidence of treatment-emergent adverse events was similar among the treatment groups, with the lowest incidence observed in the placebo (10.6%) and the ZS 10 g TID (10.4%) groups. The only treatment-emergent adverse event reported by ≥ 2.0%

of subjects in any treatment group was diarrhea, which was experienced in 2.1% of subjects in the placebo group, 2.4% of subjects in the ZS ≤ 3 g TID group, 1.9% of subjects in the ZS 5 g TID group, and 1.2% of subjects in the ZS 10 g TID group. The overall incidence of gastrointestinal disorders was similar among the treatment groups (5.3% placebo; 3.6% ZS ≤ 3 g TID, 3.8% ZS 5 g TID, and 4.5% ZS 10 g TID).

Table 40: Summary of Drug-Related TEAEs by Preferred Term (Safety Population; All Completed Studies) in Acute Phase

	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Any Event, n (%)	7 (3.7)	11 (3.3)	9 (5.7)	10 (2.4)
Total Events	6 (3.2)	6 (1.8)	5 (3.2)	9 (2.1)
Diarrhea	2 (1.1)	3 (0.9)	3 (1.9)	4 (0.9)
Nausea	2 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)

Applicant's table from ISS table 9-3, page 55.

During extended dosing, study drug was administered QD for an additional 12 days in Study ZS-003 and an additional 28 days in Study ZS-004. The overall incidence of treatment-emergent adverse events was highest in the ZS 15 g QD group (44.6%), followed by the ZS 5 g QD (34.5%), ZS 10 g QD (31.6%), placebo (26.6%), and ZS ≤ 2.5 g QD (23.6%) groups. The Applicant's summary of treatment-emergent adverse events reported in ≥ 2.0% of subjects in any treatment group is shown in the table below. The analysis approach splits terms that represent similar medical concepts. Nonetheless, the analysis shows a higher incidence of edema-related adverse events in the high dose group as compared to the other groups.

Table 41: Extended Dosing-Summary of TEAES Reported by ≥ 2.0% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (Safety Population; Completed Studies ZS-003 and ZS-004)

		Starting Dose of ZS in Extension			
	Placebo[a] (N = 301)	≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Any Event, n (%)	80 (26.6)	47 (23.6)	38 (34.5)	36 (31.6)	25 (44.6)
System Organ Class Preferred Term, n (%)					
Blood and lymphatic system disorders	1 (0.3)	0 (0.0)	4 (3.6)	0 (0.0)	3 (5.4)
Anemia	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	3 (5.4)
Gastrointestinal disorders	20 (6.6)	10 (5.0)	8 (7.3)	4 (3.5)	5 (8.9)
Constipation	7 (2.3)	2 (1.0)	0 (0.0)	3 (2.6)	1 (1.8)
Diarrhea	6 (2.0)	4 (2.0)	2 (1.8)	0 (0.0)	2 (3.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)	0 (0.0)
Nausea	2 (0.7)	5 (2.5)	0 (0.0)	1 (0.9)	1 (1.8)
Vomiting	2 (0.7)	3 (1.5)	4 (3.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	7 (2.3)	5 (2.5)	2 (1.8)	10 (8.8)	10 (17.9)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.6)
Generalized edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)
Edema peripheral	5 (1.7)	2 (1.0)	0 (0.0)	5 (4.4)	6 (10.7)
Infections and infestations	22 (7.3)	16 (8.0)	13 (11.8)	9 (7.9)	9 (16.1)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.6)
Nasopharyngitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.4)
Upper respiratory tract infection	3 (1.0)	0 (0.0)	3 (2.7)	2 (1.8)	1 (1.8)
Urinary tract infection	4 (1.3)	10 (5.0)	6 (5.5)	4 (3.5)	0 (0.0)
Investigations	10 (3.3)	7 (3.5)	4 (3.6)	3 (2.6)	2 (3.6)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	2 (3.6)
Renal and urinary disorders	6 (2.0)	5 (2.5)	7 (6.4)	1 (0.9)	2 (3.6)
Renal failure	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Vascular disorders	4 (1.3)	1 (0.5)	3 (2.7)	2 (1.8)	3 (5.4)
Hypertension	4 (1.3)	1 (0.5)	2 (1.8)	2 (1.8)	2 (3.6)

[a] Following treatment with ZS TID during the Acute Phase.
Applicant's table 9-6 from ISS, page 59

In Study ZS-004E, the overall incidence of treatment-emergent adverse events was 66.7%. In the Applicant's analysis, shown below, adverse events are shown by PT term. Focusing on PT terms, alone, the most common AEs (≥ 5%) were hypertension (12.2%), urinary tract infection (8.9%), edema peripheral (8.1%), and constipation (5.7%). However, as previously noted, this analysis ignores the fact that similar medical concepts are being split across PT terms (e.g., oedema, oedema peripheral, and cardiac failure).

Table 42-Extended Dosing-Summary of TEAEs Reported by ≥ 2.0% of ZS Subjects Overall Presented by Preferred Term (Safety Population; Study ZS-004E)

	ZS QD; Extended Dosing Phase Days				
	1 to 30 (N = 123)	31 to 90 (N = 116)	91 to 180 (N = 91)	181 to EOS (N = 69)	Total (N = 123)
Any Event, n (%)	47 (38.2)	38 (32.8)	37 (40.7)	30 (43.5)	82 (66.7)
Preferred Term, n (%)					
Hypertension	5 (4.1)	4 (3.4)	2 (2.2)	4 (5.8)	15 (12.2)
Urinary tract infection	1 (0.8)	0	6 (6.6)	4 (5.8)	11 (8.9)
Oedema peripheral	5 (4.1)	1 (0.9)	2 (2.2)	2 (2.9)	10 (8.1)
Constipation	0	2 (1.7)	3 (3.3)	2 (2.9)	7 (5.7)
Anemia	1 (0.8)	1 (0.9)	2 (2.2)	2 (2.9)	6 (4.9)
Muscle spasms	3 (2.4)	1 (0.9)	0	2 (2.9)	6 (4.9)
Upper respiratory tract infection	3 (2.4)	2 (1.7)	0	0	5 (4.1)
Diarrhea	0	1 (0.9)	1 (1.1)	2 (2.9)	4 (3.3)
Nausea	3 (2.4)	1 (0.9)	0	1 (1.4)	4 (3.3)
Vomiting	1 (0.8)	0	0	3 (4.3)	4 (3.3)
Oedema	3 (2.4)	1 (0.9)	0	0	4 (3.3)
Gout	1 (0.8)	1 (0.9)	4 (4.4)	1 (1.4)	4 (3.3)
Hyperlipidemia	0	1 (0.9)	1 (1.1)	1 (1.4)	4 (3.3)[a]
Headache	4 (3.3)	0	0	0	4 (3.3)
Cardiac failure	3 (2.4)	0	0	0	3 (2.4)
Abdominal pain	0	1 (0.9)	0	2 (2.9)	3 (2.4)
Seasonal allergy	1 (0.8)	1 (0.9)	0	1 (1.4)	3 (2.4)
Gastroenteritis	1 (0.8)	1 (0.9)	1 (1.1)	1 (1.4)	3 (2.4)
Influenza	1 (0.8)	1 (0.9)	0	1 (1.4)	3 (2.4)
Pneumonia	1 (0.8)	1 (0.9)	1 (1.1)	0	3 (2.4)
Blood urea increased	2 (1.6)	0	1 (1.1)	0	3 (2.4)
Hypomagnesaemia	2 (1.6)	0	2 (2.2)	0	3 (2.4)
Arthralgia	0	1 (0.9)	1 (1.1)	1 (1.4)	3 (2.4)
Back pain	1 (0.8)	2 (1.7)	0	0	3 (2.4)
Dizziness	1 (0.8)	0	1 (1.1)	0	3 (2.4)[a]
Chronic obstructive pulmonary disease	2 (1.6)	0	1 (1.1)	0	3 (2.4)
Cough	0	2 (1.7)	1 (1.1)	0	3 (2.4)

a. Subjects with a missing start date are counted in the total but not in the time periods; therefore, the total number of subjects with an event may be greater than the sum of subjects with the event across the time periods.

From Study ZS-004E CSR Statistical Table 14.3.2.1

In comparison with the short-term studies, the incidence of TEAEs in Study ZS-004E (both TEAEs overall and specific TEAEs) was higher. However, as noted by the Applicant, the higher incidence of these events is not unexpected given the increased duration of observation in Study ZS-004E and the underlying comorbidities in these subjects.

Table 43: Extended Dosing-Summary of TEAEs Reported by ≥ 2.0% of Subjects in Pooled Studies ZS-003 and ZS-004 by Preferred Term with Corresponding Incidence Rates from Study ZS-004E (Safety Population)

		Starting Dose of ZS in Extended Dosing				Titration
	Placebo[a] (N = 301)	≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Any Event, n (%)	80 (26.6)	47 (23.6)	38 (34.5)	36 (31.6)	25 (44.6)	82 (66.7)
Preferred Term, n (%)						
Hypertension	4 (1.3)	1 (0.5)	2 (1.8)	2 (1.8)	2 (3.6)	15 (12.2)
Urinary tract infection	4 (1.3)	10 (5.0)	6 (5.5)	4 (3.5)	0	11 (8.9)
Oedema peripheral	5 (1.7)	2 (1.0)	0	5 (4.4)	6 (10.7)	10 (8.1)
Constipation	7 (2.3)	2 (1.0)	0	3 (2.6)	1 (1.8)	7 (5.7)
Anemia	0	0	1 (0.9)	0	3 (5.4)	6 (4.9)
Upper respiratory tract infection	3 (1.0)	0	3 (2.7)	2 (1.8)	1 (1.8)	5 (4.1)
Diarrhea	6 (2.0)	4 (2.0)	2 (1.8)	0	2 (3.6)	4 (3.3)
Nausea	2 (0.7)	5 (2.5)	0	1 (0.9)	1 (1.8)	4 (3.3)
Vomiting	2 (0.7)	3 (1.5)	4 (3.6)	0	0	4 (3.3)
Influenza	0	0	0	1 (0.9)	2 (3.6)	3 (2.4)
Nasopharyngitis	1 (0.3)	0	0	0	3 (5.4)	2 (1.6)
Electrocardiogram QT prolonged	0	0	1 (0.9)	0	2 (3.6)	2 (1.6)
Renal failure	0	0	3 (2.7)	0	0	2 (1.6)
Fatigue	0	0	0	1 (0.9)	2 (3.6)	1 (0.8)
Dyspepsia	0	0	4 (3.6)	0	0	0
Generalized oedema	0	0	0	0	2 (3.6)	0

a Following treatment with ZS TID during the Acute Phase.
Applicant's table 7-6 from 120 day safety update, page 38.

Reviewer comments: See submission specific safety issues for further discussion of safety topics of interest.

8.4.6. **Laboratory Findings**

The Applicant's evaluation of clinical laboratory parameters included mean changes from baseline, shifts from baseline relative to the normal range, and potentially clinically significant values.

Hematology: Hematology parameters, including hematocrit, hemoglobin, red blood cell, white blood cell and platelet counts were evaluated. During Acute and Extended Dosing, small numeric decreases from baseline in hemoglobin and hematocrit were observed in ZS-treated subjects, especially in the high dose groups (-0.3 to -0.6 g/dl for hemoglobin and -0.8% to -1.6% for hematocrit). As this product is not absorbed, the reductions in these parameters may reflect hemodilution. The proportions of subjects meeting the applicant's definition of treatment-emergent potentially clinically significant hemoglobin and hematocrit values are summarized in the following tables.

Table 44: Acute Phase- Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Hematology Values (Safety Population; Studies ZS003 and ZS004)

Parameter PCS Criterion, n/N (%)	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Hemoglobin				
Low < 8 g/dL	0/174 (0.0)	1/304 (0.3)	1/142 (0.7)	6/389 (1.5)
High > 20 g/dL	0/175 (0.0)	0/305 (0.0)	0/142 (0.0)	0/391 (0.0)
Hematocrit				
Low < 28%	3/170 (1.8)	3/295 (1.0)	3/139 (2.2)	7/373 (1.9)
High > 55%	0/175 (0.0)	0/304 (0.0)	0/142 (0.0)	2/391 (0.5)

Reviewer's table

Table 45: Extended Dosing-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Hematology Values (Safety Population; Studies ZS-003 and ZS-004)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
Hemoglobin					
Low < 8 g/dL	1/281 (0.4)	3/191 (1.6)	1/107 (0.9)	3/111 (2.7)	2/53 (3.8)
High > 20 g/dL	0/282 (0.0)	0/192 (0.0)	0/108 (0.0)	0/111 (0.0)	0/53 (0.0)
Hematocrit					
Low < 28%	11/278 (4.0)	12/184 (6.5)	5/104 (4.8)	2/105 (1.9)	3/49 (6.1)
High > 55%	1/282 (0.4)	0/191 (0.0)	0/108 (0.0)	0/111 (0.0)	0/53 (0.0)

Reviewer's table

As compared to the incidence in the short-term studies, in the long-term study, Study ZS004E, the incidence of potentially clinically significant low hemoglobin and hematocrit values was higher (see table below). Since such laboratory findings can be seen in this population, it is unclear what, if anything, to make of this finding.

Table 46: Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Hematology Values in Pooled Studies ZS-003 and ZS-004 with Corresponding Incidence Rates from Study ZS-004E (Safety Population)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extended Dosing				Titration
		≤ 2 5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS 004E (N = 123)
Hemoglobin						
Low < 8 g/dL	1/281 (0.4)	3/191 (1.6)	1/107 (0.9)	3/111 (2.7)	2/53 (3.8)	5/113 (4.4)
High > 20 g/dL	0/282 (0.0)	0/192 (0.0)	0/108 (0.0)	0/111 (0.0)	0/53 (0.0)	0/113(0.0)
Hematocrit						
Low < 28%	11/278 (4.0)	12/184 (6.5)	5/104 (4.8)	2/105 (1.9)	3/49 (6.1)	9/109 (8.3)
High > 55%	1/282 (0.4)	0/191 (0.0)	0/108 (0.0)	0/111 (0.0)	0/53 (0.0)	1/109 (0.9)

Reviewer's table

Clinical Chemistry: Chemistry parameters, including general electrolytes, acid-base, renal and hepatic function were evaluated. Effects on potassium are discussed under submission specific safety concerns.

- Mean dose-related increases in bicarbonate were observed among the ZS treatment groups (range: 0.4 to 1.6 mmol/L) compared with a small mean decrease in the placebo group in the Acute Phase. In the extended phase, mean dose-related increases in bicarbonate were observed among the ZS 5 g, 10 g, and 15 g QD treatment groups (range: 1.1 to 2.6 mmol/L) compared with smaller increases noted for the placebo and the lower ZS dose group (0.6 mmol/L for each). See also the discussion under submission specific safety concerns.
- A mean increase in serum sodium concentration (maximum mean increase of 2 mmol/L, corresponding to an approximately 1.4% change from baseline) were observed in each of the ZS as well as the placebo groups. Mean values in each of the treatment groups remained within the normal range and, during the Acute and Extending Dosing Phases, no subject developed a treatment-emergent potentially clinically significant low or high value for sodium.
- Dose-related mean decreases in calcium values were observed. Although marginally larger mean decreases were noted in the ZS ≤ 3 g (-0.13 mg/dL), 5 g (-0.18 mg/dL) and 10 g (-0.28 mg/dL) TID groups compared with placebo (-0.07 mg/dL), the mean calcium values for each of the treatment groups were all within the normal range. During the Acute and Extending Dosing Phases, no subject developed a treatment-emergent potentially clinically significant low value for calcium (< 7.0 mg/dL).
- Mean phosphorus values remained relatively unchanged in the ZS 5 g, 10 g, and 15 g QD groups (≤ 0.01 mg/dL) whereas small mean increases were observed in the placebo (0.17 mg/dL) and lower ZS dose (0.16 mg/dL) groups.
- No clinically meaningful changes were noted for magnesium during Acute phase and Extended Dosing. During the Acute and Extending Dosing Phases, no subject developed a treatment emergent potentially clinically significant low or high value for magnesium (<0.9 mg/dL).

Data on mean changes from baseline in clinical chemistry parameters and the proportions of subjects who had changes in these parameters beyond some threshold are summarized in the tables below (tables show data from the Acute and Extending Dosing Phases).

Table 47: Acute Phase-Mean Change from Baseline to End of Acute Phase in Chemistry Values (Safety Population; Studies ZS003 and ZS004)

Parameter Statistic	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Bicarbonate (mmol/L)	n = 171	n = 302	n = 145	n = 391
BL Mean (SD)	23.9 (3.56)	23.3 (3.75)	23.3 (3.13)	23.0 (3.98)
Mean (SD) Δ to End of AP	-0.2 (2.28)	0.4 (2.32)	1.0 (2.42)	1.6 (2 40)
BUN (mg/dL)	n = 183	n = 309	n = 146	n = 405
BL Mean (SD)	33.61 (17.925)	33.65 (17.598)	36.20 (18.570)	35.16 (20.680)
Mean (SD) Δ to End of AP	0.81 (6.859)	0.25 (6.882)	-1.10 (6.696)	-1.95 (5.722)
Calcium (mg/dL)	n = 183	n = 309	n = 146	n = 405
BL Mean (SD)	9.50 (0.580)	9.44 (0.546)	9.41 (0.500)	9.44 (0.604)
Mean (SD) Δ to End of AP	-0.07 (0.371)	-0.13 (0.354)	-0.18 (0.343)	-0.28 (0.364)
Magnesium (mg/dL)	n = 183	n = 309	n = 146	n = 404
BL Mean (SD)	1.97 (0.295)	1.94 (0.272)	1.99 (0.296)	1.97 (0.294)
Mean (SD) Δ to End of AP	-0.05 (0.159)	-0.04 (0.155)	-0.06 (0.160)	-0.05 (0.140)
Sodium (mmol/L)	n = 183	n = 309	n = 146	n = 405
BL Mean (SD)	138.7 (3.26)	138.9 (3.23)	138.9 (3.21)	138.2 (3.42)
Mean (SD) Δ to End of AP	-0.2 (2.66)	-0.4 (2.57)	0.5 (2.82)	1.3 (3 18)
Phosphate (mg/dL)	n = 183	n = 309	n = 146	n = 405
BL Mean (SD)	3.76 (0.719)	3.76 (0.791)	3.75 (0.750)	3.83 (0.790)
Mean (SD) Δ to End of AP	0.25 (0.630)	0.18 (0.558)	0.23 (0.578)	0.15 (0.582)
Glomerular Filtration Rate (mL/min/1.73m^2)	n = 185	n = 310	n = 146	n = 406
BL Mean (SD)	44.56 (23.367)	43.51 (22.599)	44.65 (24.523)	46.60 (29.024)
Mean (SD) Δ to End of AP	0.10 (9.327)	0.09 (7.275)	0.44 (8.640)	0.84 (8.360)

Applicant's table 10-5 from ISS, page 93

Table 48: Acute Phase-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Chemistry Values (Safety Population; Studies ZS003 and ZS004)

Parameter PCS Criterion, n/N (%)	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Bicarbonate				
Low < 15 mmol/L	1/172 (0.6)	1/310 (0.3)	1/146 (0.7)	1/391 (0.3)
High > 35 mmol/L	0/173 (0.0)	0/312 (0.0)	0/146 (0.0)	0/398 (0.0)
Calcium				
Low < 7.0 mg/dL	0/185 (0.0)	0/318 (0.0)	0/146 (0.0)	0/409 (0.0)
High > 11.0 mg/dL	0/183 (0.0)	0/318 (0.0)	0/147 (0.0)	0/410 (0.0)
Magnesium				
Low < 0.9 mg/dL	0/185 (0.0)	0/319 (0.0)	0/147 (0.0)	0/411 (0.0)
High > 4.0 mg/dL	0/185 (0.0)	0/319 (0.0)	0/147 (0.0)	0/411 (0.0)
Phosphate				
Low < 2.0 mg/dL	0/184 (0.0)	0/319 (0.0)	0/147 (0.0)	0/411 (0.0)
High > 6.5 mg/dL	1/184 (0.5)	3/316 (0.9)	0/146 (0.0)	4/407 (1.0)
Sodium				
Low < 120 mmol/L	0/185 (0.0)	0/319 (0.0)	0/147 (0.0)	0/411 (0.0)
High > 160 mmol/L	0/185 (0.0)	0/319 (0.0)	0/147 (0.0)	0/411 (0.0)

Applicant's table 10-6 from ISS, page 94

Table 49: Extended Dosing-Mean Change from Baseline in Chemistry Measurements (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter Statistic	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
Bicarbonate (mmol/L)	n = 279	n = 193	n = 102	n = 109	n = 52
BL Mean (SD)	23.1 (3.54)	23.6 (3.33)	23.3 (3.70)	22.5 (3.96)	22.6 (4.31)
Mean (SD) Δ to End of Dosing	0.6 (2.59)	0.6 (2.33)	1.1 (2.77)	2.3 (2.70)	2.6 (2.78)
BUN (mg/dL)	n = 285	n = 196	n = 104	n = 111	n = 52
BL Mean (SD)	34.62 (19.270)	31.82 (17.487)	36.61 (20.957)	37.24 (20.444)	36.42 (20.282)
Mean (SD) Δ to End of Dosing	-0.03 (8.452)	-0.84 (8.658)	-1.29 (8.561)	-2.67 (10.322)	-1.58 (10.670)
Calcium (mg/dL)	n = 279	n = 193	n = 104	n = 109	n = 52
BL Mean (SD)	9.48 (0.540)	9.46 (0.582)	9.40 (0.611)	9.39 (0.611)	9.38 (0.667)
Mean (SD) Δ to End of Dosing	-0.13 (0.413)	-0.12 (0.376)	-0.20 (0.472)	-0.18 (0.421)	-0.21 (0.421)
Magnesium (mg/dL)	n = 279	n = 193	n = 104	n = 109	n = 52
BL Mean (SD)	1.96 (0.291)	1.95 (0.297)	1.98 (0.313)	1.99 (0.290)	2.01 (0.302)
Mean (SD) Δ to End of Dosing	-0.02 (0.188)	-0.04 (0.176)	-0.03 (0.240)	-0.07 (0.222)	-0.04 (0.174)
Phosphate (mg/dL)	n = 279	n = 193	n = 104	n = 109	n = 52
BL Mean (SD)	3.76 (0.716)	3.66 (0.690)	3.90 (0.955)	3.77 (0.779)	3.88 (0.932)
Mean (SD) Δ to End of Dosing	0.17 (0.553)	0.16 (0.548)	0.00 (0.729)	0.01 (0.708)	0.00 (0.701)
Sodium (mmol/L)	n = 279	n = 193	n = 104	n = 109	n = 52
BL Mean (SD)	138.7 (3.07)	139.1 (3.48)	138.3 (3.63)	138.2 (3.69)	137.7 (3.52)
Mean (SD) Δ to End of Dosing	0.2 (2.84)	0.3 (3.02)	1.0 (3.17)	1.9 (3.47)	2.0 (2.96)
Glomerular Filtration Rate ($mL/min/1.73m^2$)	n = 279	n = 193	n = 104	n = 109	n = 52
BL Mean (SD)	45.83 (26.693)	48.43 (24.812)	45.26 (28.974)	43.42 (27.310)	45.56 (30.963)
Mean (SD) Δ to End of Dosing	-0.68 (10.896)	-0.30 (8.301)	-0.19 (10.002)	1.35 (8.817)	1.39 (9.366)

a .Following treatment with ZS TID during the Acute Phase.
Applicant's table 10-8 from ISS, page 96

Table 50: Extended Dosing, Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Chemistry Values (Safety Population; Studies ZS-003 and ZS-004)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
Bicarbonate					
Low < 15 mmol/L	1/285 (0.4)	0/196 (0.0)	2/103 (1.9)	2/112 (1.8)	0/54 (0.0)
High > 35 mmol/L	0/287 (0.0)	0/196 (0.0)	0/104 (0.0)	0/114 (0.0)	0/56 (0.0)
Calcium					
Low < 7.0 mg/dL	0/287 (0.0)	0/195 (0.0)	0/104 (0.0)	0/114 (0.0)	0/55 (0.0)
High > 11.0 mg/dL	0/285 (0.0)	0/194 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)
Magnesium					
Low < 0.9 mg/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)
High > 4.0 mg/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)
Phosphate					
Low < 2.0 mg/dL	0/287 (0.0)	1/195 (0.5)	0/106 (0.0)	1/114 (0.9)	0/56 (0.0)
High > 6.5 mg/dL	3/286 (1.0)	0/195 (0.0)	1/104 (1.0)	2/113 (1.8)	1/55 (1.8)
Sodium					
Low < 120 mmol/L	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)
High > 160 mmol/L	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)

a. Following treatment with ZS TID during the Acute Phase.
Applicant's table 10-9 from ISS, page 98

As compared to the incidence in the short-term studies, in the long-term study, Study ZS004E, the incidence of potentially clinically significant chemistry parameters was somewhat higher (see table below), likely reflecting the increased duration of observation and underlying comorbidities in the population.

Table 51: Extended Dosing-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Values for Bicarbonate, Calcium, Magnesium, Phosphate, and Sodium in Pooled Studies ZS-003 and ZS-004 with Corresponding Incidence Rates from Study ZS-004E (Safety Population)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extended Dosing				Titration
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Bicarbonate						
Low < 15 mmol/L	1/285 (0.4)	0/196 (0.0)	2/103 (1.9)	2/112 (1.8)	0/54 (0.0)	7/120 (5.8)
High > 35 mmol/L	0/287 (0.0)	0/196 (0.0)	0/104 (0.0)	0/114 (0.0)	0/56 (0.0)	0/120 (0.0)
Calcium						
Low < 7.0 mg/dL	0/287 (0.0)	0/195 (0.0)	0/104 (0.0)	0/114 (0.0)	0/55 (0.0)	2/120 (1.7)
High > 11.0 mg/dL	0/285 (0.0)	0/194 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/120 (0.0)
Magnesium						
Low < 0.9 mg/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	1/121 (0.8)
High > 4.0 mg/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
Phosphate						
Low < 2.0 mg/dL	0/287 (0.0)	1/195 (0.5)	0/106 (0.0)	1/114 (0.9)	0/56 (0.0)	2/119 (1.7)
High > 6.5 mg/dL	3/286 (1.0)	0/195 (0.0)	1/104 (1.0)	2/113 (1.8)	1/55 (1.8)	11/119 (9.2)
Sodium						
Low < 120 mmol/L	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
High > 160 mmol/L	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)

a. Following treatment with ZS TID during the Acute Phase.

Applicant's table 7-19 from 120 day update, page 57

No clinically meaningful changes were observed in other clinical chemistry parameters that were assessed during the acute phase, extending phase and long-term study (see table below). The higher incidence of abnormalities in GGT and glucose observed in Study ZS-004E as compared with the shorter-term Extended Dosing Studies likely reflects the increased duration of observation and underlying comorbidities of the population.

Table 52: Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Values for Other Clinical Chemistry Variables in Pooled Studies ZS-003 and ZS-004 with Corresponding Incidence Rates from Study ZS-004E (Safety Population)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extension				Titration
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Albumin						
Low < 2.0 g/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
High > 6.0 g/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
Bilirubin						
High > 3 × ULN	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
Alkaline phosphatase						
High > 3 × ULN	2/287 (0.7)	0/196 (0.0)	1/106 (0.9)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
ALT						
High > 3 × ULN	1/287 (0.3)	0/195 (0.0)	1/106 (0.9)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
AST						
High > 3 × ULN	1/286 (0.3)	0/195 (0.0)	1/106 (0.9)	0/113 (0.0)	1/56 (1.8)	0/121 (0.0)
Protein						
Low < 4.0 g/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
High > 10.0 g/dL	0/287 (0.0)	0/196 (0.0)	0/106 (0.0)	0/114 (0.0)	0/56 (0.0)	0/121 (0.0)
GGT						
High > 3 × ULN	3/283 (1.1)	0/194 (0.0)	1/106 (0.9)	1/111 (0.9)	0/55 (0.0)	4/118 (3.4)
Glucose						
Low < 60 mg/dL	6/286 (2.1)	4/192 (2.1)	1/104 (1.0)	6/113 (5.3)	1/56 (1.8)	7/118 (5.9)
High > 300 mg/dL	6/281 (2.1)	5/195 (2.6)	2/104 (1.9)	4/111 (3.6)	0/53 (0.0)	10 118 (8.5)

a. Following treatment with ZS TID during the Acute Phase.

Applicant's table from 120 day update table 7-20, page 58

Urinalysis: Urine parameters that were assessed included pH, gravity, and chemistry values; findings related to these parameters are summarized below:

- Urine pH: In the acute phase, consistent with the small mean increase in serum bicarbonate observed in the ZS 10 g QD group, a small mean increase from baseline in urine pH was also observed (0.12) in this dose level; mean small decreases in urine pH were observed in the other treatment groups. Similar finding was observed in the extending dosing phase. Specifically small mean increases in serum bicarbonate were observed in the ZS 10 g and 15 g QD group, and small mean increases from baseline in urine pH were also observed in these treatment groups (point estimates of 0.06 and 0.13, respectively); mean decreases in urine pH observed in the other treatment groups were generally similar.
- Urine gravity: No clinically significant trends were apparent in analyses of mean changes from baseline in specific gravity either in the Acute or Extending Dosing phases.
- Urine potassium: Mean reductions from baseline in urinary potassium were observed in the ZS 10 g QD (-17 mmol/L; % decrease of 35%) and the ZS 15 g QD (-15 mmol/L; % decrease of 29%) groups compared with the placebo group (-5 mmol/L; % increase of 3%). There were no significant changes in other low dose groups.

- Urine sodium: There were no significant changes from baseline between any of the ZS treatment groups and the placebo group in urinary sodium.
- Urinary albumin (based on spot urine): Mean increases from baseline in urinary albumin were observed within each of the ZS dose groups, with a significant difference noted for the ZS 15 g QD group (28 mg/dL) compared with the mean decrease observed in the placebo group (-3 mg/dL). There was no dose-response relationship with regard to changes in urinary albumin. The underlying variability of the urinary albumin data may limit meaningful conclusions for this parameter as there were some differences in mean and median changes within each treatment group.
- In the long-term study, Study ZS004E, no trends were apparent in the analyses of mean changes from baseline in specific gravity or for post-baseline shifts relative to the normal range in urine pH or specific gravity. According to the Applicant's analyses, mean reductions from both Acute Phase and Extended Dosing Phase baseline for urinary potassium were observed throughout the Extended Dosing Phase in Study ZS-004E. Small increases from Acute Phase baseline and small decreases from Extended Dosing Phase baseline were observed for urinary sodium. Consistent mean increases in urinary creatinine from Acute Phase baseline were observed that were significant at Extended Dosing Study Days 29, 57, and 337/Exit; no significant changes from Extended Dosing Phase baseline were observed.

8.4.7. **Vital Signs**

This section discusses the Applicant's analyses of vital sign data; for FDA analyses of blood pressure and weight data, see Section 8.5 Analysis of submission-specific safety issues.

In the Acute phase, there were no obvious clinically meaningful differences between the placebo and the ZS treatment groups in the mean changes from baseline to the end of the Acute Phase in blood pressure, heart rate, respiration rate, or temperature. Mean body weight tended to increase in the ZS treatment arms, whereas in the placebo group it remained stable. The point estimate for the mean reduction in blood pressure was also lower in the placebo as compared to the 5 and 10 g TID dose groups; however the standard deviation was large. The proportions of subjects meeting the threshold for potentially clinically significant values for high blood pressure appeared to be somewhat greater in the ZS 10 mg as compared to the placebo group; however this difference was based on a small number of events. These data are summarized in the table below.

Table 53: Acute Phase-Mean Change from Baseline to End of Acute Phase in Vital Sign Measurements (Safety Population; All Completed Short-term Studies)

Parameter Statistic	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Systolic blood pressure (mmHg)	n = 176	n = 313	n = 142	n = 403
BL Mean (SD)	138.6 (20.98)	137.7 (18.59)	137.4 (18.12)	139.8 (20.54)
Mean (SD) Δ to End of AP	-3.0 (17.05)	-2.2 (16.73)	-1.3 (15.42)	-1.1 (17.26)
Diastolic blood pressure (mmHg)	n = 176	n = 313	n = 142	n = 403
BL Mean (SD)	77.3 (11.22)	76.5 (10.64)	77.5 (10.51)	78.5 (11.02)
Mean (SD) Δ to End of AP	-1.6 (9.25)	-0.4 (9.27)	-1.3 (8.44)	-1.1 (9.03)
Heart rate (bpm)	n = 176	n = 313	n = 142	n = 403
BL Mean (SD)	69.7 (11.85)	68.6 (10.87)	68.1 (10.47)	69.0 (10.96)
Mean (SD) Δ to End of AP	0.8 (8.45)	0.9 (9.10)	1.7 (8.90)	-0.2 (8.88)
Respiration rate (breaths/min)	n = 144	n = 277	n = 142	n = 377
BL Mean (SD)	16.7 (2.27)	16.4 (1.94)	16.3 (2.06)	16.6 (2.09)
Mean (SD) Δ to End of AP	0.1 (1.88)	0.1 (1.61)	0.0 (1.90)	0.0 (2.15)
Temperature (°F)	n = 175	n = 312	n = 142	n = 398
BL Mean (SD)	97.788 (0.5433)	97.788 (0.6570)	97.813 (0.6720)	97.719 (0.8151)
Mean (SD) Δ to End of AP	-0.007 (0.6176)	-0.040 (0.6500)	-0.080 (0.6703)	-0.006 (0.7495)
Weight (kg)	n = 173	n = 309	n = 141	n = 396
BL Mean (SD)	88.867 (22.3728)	86.208 (20.3660)	89.930 (23.2972)	86.964 (22.6376)
Mean (SD) Δ to End of AP	0.009 (1.2108)	0.118 (1.1079)	0.289 (1.1833)	0.275 (1.0906)

Applicant's table from ISS table 11-1, page 111

Table 54: Acute Phase-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Vital Sign Values (Safety Population; All Completed Short-term Studies)

Parameter PCS Criterion, n/N (%)	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Systolic blood pressure (mmHg)				
Low: ≤ 90 mmHg and decreased ≥ 20 mmHg from initial value	2/177 (1.1)	1/319 (0.3)	0/142 (0.0)	0/410 (0.0)
High: ≥ 180 mmHg and increased ≥ 20 mmHg from initial value	1/169 (0.6)	0/313 (0.0)	1/140 (0.7)	8/396 (2.0)
Diastolic blood pressure (mmHg)				
Low: ≤ 50 mmHg and decreased ≥ 15 mmHg from initial value	3/177 (1.7)	3/319 (0.9)	0/142 (0.0)	0/409 (0.0)
High: ≥ 105 mmHg and increased ≥ 15 mmHg from initial value	0/176 (0.0)	2/317 (0.6)	0/141 (0.0)	2/406 (0.5)
Heart rate (bpm)				
Low: Value ≤ 50 bpm and decreased ≥ 15 bpm from initial value	2/172 (1.2)	3/308 (1.0)	1/137 (0.7)	1/400 (0.3)
High: Value ≥ 120 bpm and increased ≥ 15 bpm from initial value	0/177 (0.0)	0/319 (0.0)	0/143 (0.0)	0/412 (0.0)

Applicant's table from ISS table 11-2, page 112

As in the Acute Phase, in the extending dosing phase, there appeared to be a small dose-dependent effect on the mean change from baseline in blood pressure and weight. No obvious dose-related trends were observed among the placebo and the ZS treatment groups for the proportions of subjects with potentially clinically significant values for blood pressure or heart rate. These data are summarized in the tables below.

Table 55: Extended Dosing-Mean Change from Baseline to End of Extended Dosing in Vital Sign Measurements (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter Statistic	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Systolic blood pressure (mmHg)	n = 287	n = 195	n = 107	n = 108	n = 52
BL Mean (SD)	137.9 (17.15)	139.7 (17.42)	140.5 (20.57)	140.3 (19.42)	139.5 (24.28)
Mean (SD) Δ to End of Dosing	-2.9 (16.28)	-2.7 (18.06)	-0.4 (18.80)	-0.7 (17.38)	1.5 (19.55)
Diastolic blood pressure (mmHg)	n = 287	n = 195	n = 107	n = 108	n = 52
BL Mean (SD)	78.4 (9.97)	78.4 (11.13)	79.0 (12.18)	78.1 (10.78)	78.6 (10.22)
Mean (SD) Δ to End of Dosing	-2.1 (9.79)	-1.7 (10.12)	-1.7 (10.37)	-0.5 (9.50)	0.0 (9.79)
Heart rate (bpm)	n = 287	n = 195	n = 107	n = 108	n = 52
BL Mean (SD)	69.5 (10.92)	68.8 (11.32)	67.2 (10.91)	67.7 (10.74)	71.5 (12.13)
Mean (SD) Δ to End of Dosing	0.1 (9.72)	-0.9 (9.37)	0.5 (11.02)	-0.4 (10.38)	0.3 (9.13)
Respiration rate (breaths/min)	n = 286	n = 195	n = 107	n = 108	n = 52
BL Mean (SD)	16.5 (2.09)	16.4 (2.20)	16.4 (2.10)	16.4 (1.96)	17.0 (2.11)
Mean (SD) Δ to End of Dosing	0.0 (2.06)	-0.1 (1.97)	0.2 (2.43)	0.1 (1.99)	-0.3 (2.63)
Temperature (°F)	n = 286	n = 194	n = 107	n = 107	n = 52
BL Mean (SD)	97.765 (0.6711)	97.806 (0.6261)	97.681 (0.8934)	97.651 (0.8081)	97.704 (0.7686)
Mean (SD) Δ to End of Dosing	-0.045 (0.6623)	0.008 (0.6856)	-0.038 (0.9117)	0.080 (0.6473)	-0.126 (0.6401)
Weight (kg)	n = 286	n = 194	n = 107	n = 106	n = 50
BL Mean (SD)	87.617 (20.7548)	83.256 (19.9712)	86.913 (22.9465)	88.674 (22.9649)	88.482 (18.6468)
Mean (SD) Δ to End of Dosing	-0.133 (2.1588)	0.163 (1.6305)	0.420 (2.0371)	0.765 (2.0229)	0.990 (2.2416)

a. Following treatment with ZS TID during the Acute Phase.

Applicant's table 11-3 from ISS, page 113

Table 56: Extended Dosing-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant Vital Sign Values (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Systolic blood pressure (mmHg)					
Low: ≤ 90 mmHg and decreased ≥ 20 mmHg from initial value	1/296 (0.3)	2/199 (1.0)	0/108 (0.0)	0/113 (0.0)	0/55 (0.0)
High: ≥ 180 mmHg and increased ≥ 20 mmHg from initial value	9/291 (3.1)	6/195 (3.1)	6/105 (5.7)	5/109 (4.6)	3/53 (5.7)
Diastolic blood pressure (mmHg)					
Low: ≤ 50 mmHg and decreased ≥ 15 mmHg from initial value	2/295 (0.7)	3/199 (1.5)	3/108 (2.8)	1/113 (0.9)	1/56 (1.8)
High: ≥ 105 mmHg and increased ≥ 15 mmHg from initial value	0/292 (0.0)	1/196 (0.5)	0/107 (0.0)	0/113 (0.0)	0/55 (0.0)
Heart rate (bpm)					
Low: Value ≤ 50 bpm and decreased ≥ 15 bpm from initial value	3/288 (1.0)	1/195 (0.5)	1/103 (1.0)	1/109 (0.9)	0/54 (0.0)
High: Value ≥ 120 bpm and increased ≥ 15 bpm from initial value	0/296 (0.0)	0/199 (0.0)	0/109 (0.0)	0/114 (0.0)	0/56 (0.0)

a. Following treatment with ZS TID during the Acute Phase.

Applicant's table 11-4 from ISS, page 114

In the long-term study, Study ZS004E, no clinically significant mean changes from either baseline in blood pressure, heart rate, respiration rate, weight, and temperature were observed. No clinically meaningful differences were observed between the shorter-term Extended Dosing Studies (Studies ZS003 and ZS004) and Study ZS-004E in mean changes from baseline in vital sign parameters.

The proportions of subjects with treatment-emergent potentially clinically significant vital sign values for the Extended Dosing treatment groups from Studies ZS-003 and ZS-004 pooled, with corresponding incidence rates from Study ZS-004E is provided in the table below. The higher incidence observed in Study ZS-004E compared with the shorter-term Extended Dosing studies may reflect the increased duration of observation and underlying comorbidities in the population.

Table 57: Proportions of Subjects With Treatment-Emergent Potentially Clinically Significant Vital Sign Values in Pooled Studies ZS-003 and ZS-004 With Corresponding Incidence Rates From Study ZS-004E (Safety Population)

Parameter PCS Criterion, n/N (%)	Placebo[a] (N = 301)	Starting Dose of ZS in Extended Dosing				Titration
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Systolic blood pressure (mmHg)						
Low: ≤ 90 mmHg and decreased ≥ 20 mmHg from initial value	1/296 (0.3)	2/199 (1.0)	0/108 0.0)	0/113 (0.0)	0/55 (0.0)	1/118 (0.8)
High: ≥ 180 mmHg and increased ≥ 20 mmHg from initial value	9/291 (3.1)	6/195 (3.1)	6/105 5.7)	5/109 (4.6)	3/53 (5.7)	15 118 (12.2)
Diastolic blood pressure (mmHg)						
Low: ≤ 50 mmHg and decreased ≥ 15 mmHg from initial value	2/295 (0.7)	3/199 (1.5)	3/108 2.8)	1/113 (0.9)	1/56 (1.8)	2/119 (1.6)
High: ≥ 105 mmHg and increased ≥ 15 mmHg from initial value	0/292 (0.0)	1/196 (0.5)	0/107 0.0)	0/113 (0.0)	0/55 (0.0)	3/119 (2.4)
Heart rate (bpm)						
Low: Value ≤ 50 bpm and decreased ≥ 15 bpm from initial value	3/288 (1.0)	1/195 (0.5)	1/103 1.0)	1/109 (0.9)	0/54 (0.0)	5/117 (4.1)
High: Value ≥ 120 bpm and increased ≥ 15 bpm from initial value	0/296 (0.0)	0/199 (0.0)	0/109 0.0)	0/114 (0.0)	0/56 (0.0)	2/117 (1.6)

a Following treatment with ZS TID during the Acute Phase.
Applicant's table 7-22 from 120 day safety update, page 62

8.4.8. **Electrocardiograms (ECGs)**

In Study ZS003, a standard 12-lead electrocardiogram was to be recorded at Screening and Study Days 2, 3 and 9 for subjects NOT entering the extended Phase, and on Study Days 0, 2, 3, 9, 15 and 21 for subjects entering the extended Phase. ECGs were performed prior to breakfast on each day at the same time as the S-K samples were taken. For subjects who had i-STAT potassium levels between 6.1 and 6.5mmol/l at the 4 hour post 1st dose time point on Study Day 1, an additional ECG was recorded 1 hour post 2nd dose. As in Study ZS003, in Study ZS004, ECGs were recorded at screening and Study Days 2, 3 and 9 for subjects NOT entering the randomized Maintenance Phase, and on the Maintenance Phase Study Days 1, 8, 15, 22, 29, and 35 (EOS) for subjects not entering the open-label ZS-004E extension study. For subjects who had 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 was recorded 1.5 hours post 2nd dose.

PR interval, QRS duration and heart rate in the short-term studies: In the Acute and Extended Dosing Phases, there were no obvious drug effects on the PR interval, QRS duration and heart rate (as assessed by mean changes from baseline).

QTc in the short-term studies: In the Acute Phase, mean increases from baseline to the end of the Acute Phase in QTc interval were observed in each of the treatment groups, with greater increases noted with increasing ZS dose. The mean increase in QTc interval in the ZS 5 g TID

and 10 g TID dose groups were 4.2 and 9.1 msec, respectively, compared with 0.1 msec in the placebo group. The overall incidence of maximum QTc intervals > 500 msec was 1 (0.5%) subject in the placebo group and 5 (1.2%) subjects in the ZS 10 g TID group. Few subjects experienced increases from baseline of > 60 msec (≤ 2.2% in each of the treatment groups with no clinically meaningful differences between placebo and any of the ZS dose groups). These data are summarized in the tables below.

Table 58: Acute Phase-Mean Change from Baseline to End of Acute Phase in Electrocardiogram Measurements (Safety Population; All Completed Studies)

Parameter Statistic	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
PR interval (msec)	n = 177	n = 313	n = 143	n = 389
BL Mean (SD)	170.6 (37.95)	171.1 (37.68)	172.2 (30.61)	171.2 (34.86)
Mean (SD) Δ to End of AP	2.1 (21.83)	1.4 (20.67)	-0.8 (17.31)	2.5 (27.59)
QRS duration (msec)	n = 188	n = 325	n = 152	n = 414
BL Mean (SD)	98.1 (21.73)	97.6 (23.72)	97.8 (24.63)	95.6 (23.41)
Mean (SD) Δ to End of AP	-0.6 (7.66)	-0.2 (8.63)	-0.8 (8.24)	2.1 (10.17)
QTc (msec)[a]	n = 188	n = 325	n = 151	n = 414
BL Mean (SD)	420.5 (28.24)	420.8 (31.10)	424.0 (28.89)	422.5 (31.36)
Mean (SD) Δ to End of AP	0.1 (17.65)	1.6 (16.80)	4.2 (18.34)	9.1 (21.57)
Heart rate (bpm)	n = 188	n = 325	n = 151	n = 414
BL Mean (SD)	67.2 (12.17)	66.0 (11.30)	66.2 (12.37)	66.0 (10.69)
Mean (SD) Δ to End of AP	0.6 (8.50)	1.3 (7.59)	1.4 (8.27)	1.1 (6.85)

a. QT is corrected for heart rate according to Bazett's formula.
Applicant's table from ISS, table 12-1, page 115

Table 59: Acute Phase-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant QTc Interval Values (Safety Population; All Completed short-term Studies)

Parameter QTc[a] Interval Criteria, n (%)	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)
Subjects with baseline QTc Interval ≤ 500 msec	n = 185	n =323	n =149	n =416
Maximum QTc interval > 500 msec	1 (0.5)	0 (0.0)	0 (0.0)	5 (1.2)
Maximum QTc increase from baseline > 30 msec	9 (4.9)	25 (7.7)	10 (6.7)	44 (10.6)
Maximum QTc increase from baseline > 60 msec	3 (1.6)	2 (0.6)	2 (1.3)	9 (2.2)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 30 msec	1 (0.5)	0 (0.0)	0 (0.0)	3 (0.7)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 60 msec	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.7)

a. QT is corrected for heart rate according to Bazett's formula.
Applicant's table from ISS, table 12-2, page 116

Mean increases from the Acute Phase baseline to the end of the Extended Dosing Phase in QTc interval were observed in each of the treatment groups, with greater increases noted with increasing ZS dose. The mean increase in QTc interval was 3. 7 msec in the ZS 5 g QD group as compared to 1.5 msec in the placebo group; mean increases of 5.7 and 11.9 msec were observed in the ZS 10 g and 15 g QD groups, respectively. A similar finding was not observed in the Extended Dosing Phase (i.e., almost all of the increase in the QTc interval occurred during the Acute Phase, with little additional change during the Extended Dosing Phase). Of note, when the baseline value was defined as the value at the beginning of the Extending Dosing

Phase, a mean increase from baseline to the end of the Extended Dosing Phase in QTc interval was observed only in the ZS 15 g QD group (5.6 msec). Mean decreases in QTc interval were observed in the ZS 5 g QD (-1.4 msec), ZS 10 g QD (-4.3 msec), and placebo groups (-3.4 msec).

The overall incidence of maximum QTc intervals > 500 msec ranged from 1.5% to 5.4% among the ZS dose groups as compared to 0.7% of the placebo subjects. The incidence of increases from the Extended Dosing Phase baseline in QTc interval of > 30 msec was highest in the ZS 15 g QD group (23.2%). Increases from baseline in QTc intervals > 60 msec were infrequent, and no dose-response relationship was observed. No subject had a clinically significant arrhythmia observed on ECG or reported an as adverse event. These data are summarized in the tables below.

Table 60: Extended Dosing-Mean Change from Acute Phase Baseline to End of Extended Dosing in Electrocardiogram Measurements (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter Statistic	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
PR interval (msec)	n = 276	n = 183	n = 101	n = 103	n = 49
BL Mean (SD)	171.9 (29.64)	174.3 (33.95)	169.0 (32.59)	171.2 (30.04)	174.3 (43.72)
Mean (SD) Δ to End of Dosing	-0.2 (17.59)	0.4 (28.95)	0.1 (19.34)	0.3 (16.99)	-4.5 (18.69)
QRS duration (msec)	n = 289	n = 196	n = 107	n = 112	n = 54
BL Mean (SD)	95.6 (21.45)	97.1 (23.25)	93.1 (22.32)	98.9 (27.14)	100.1 (24.52)
Mean (SD) Δ to End of Dosing	-0.3 (9.34)	0.9 (10.10)	1.2 (7.60)	-1.2 (16.41)	0.1 (10.83)
QTc (msec)[b]	n = 288	n = 196	n = 107	n = 112	n = 54
BL Mean (SD)	421.6 (32.71)	421.8 (29.37)	424.5 (28.55)	425.1 (28.16)	429.4 (29.33)
Mean (SD) Δ to End of Dosing	1.5 (25.73)	1.9 (19.81)	3.7 (18.49)	5.7 (31.14)	11.9 (24.39)
Heart rate (bpm)	n = 288	n = 196	n = 107	n = 112	n = 54
BL Mean (SD)	66.8 (11.09)	65.5 (11.13)	65.8 (12.45)	64.3 (10.54)	69.1 (12.21)
Mean (SD) Δ to End of Dosing	1.0 (8.86)	0.2 (7.83)	-0.4 (10.22)	0.4 (6.94)	0.6 (8.55)

a Following treatment with ZS TID during the Acute Phase.
b QT is corrected for heart rate according to Bazett's formula.

Applicant's table 12-4 from ISS, page 118

Table 61: Extended Dosing-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant QTc Interval Values Based on Acute Phase Baseline (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter QTc[a] Interval Criteria, n (%)	Placebo[b] (N = 301)	Starting Dose of ZS in Extension			
		≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Subjects with baseline QTc Interval ≤ 500 msec	n = 290	n = 195	n = 107	n = 113	n = 54
Maximum QTc interval > 500 msec	0 (0.0)	2 (1.0)	3 (2.8)	2 (1.8)	2 (3.7)
Maximum QTc increase from baseline > 30 msec	31 (10.7)	23 (11.8)	12 (11.2)	25 (22.1)	16 (29.6)
Maximum QTc increase from baseline > 60 msec	3 (1.0)	4 (2.1)	4 (3.7)	5 (4.4)	2 (3.7)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 30 msec	0 (0.0)	2 (1.0)	2 (1.9)	1 (0.9)	1 (1.9)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 60 msec	0 (0.0)	2 (1.0)	2 (1.9)	1 (0.9)	0 (0.0)

a QT is corrected for heart rate according to Bazett's formula.
b Following treatment with ZS TID during the Acute Phase.

Applicant's table 12-5 from ISS, page 119

Table 62: Extended Dosing-Mean Change from Extended Dosing Baseline to End of Extended Dosing in Electrocardiogram Measurements (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter Statistic	Placebo[a] (N = 301)	Starting Dose of ZS in Extension			
		ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
PR interval (msec)	n = 280	n = 185	n = 102	n = 107	n = 49
BL Mean (SD)	174.3 (32.60)	175.9 (35.90)	168.9 (32.46)	175.2 (29.27)	173.8 (38.05)
Mean (SD) Δ to End of Dosing	-1.5 (16.69)	-1.0 (31.08)	0.6 (19.48)	-3.2 (16.02)	-4.0 (15.95)
QRS duration (msec)	n = 290	n = 196	n = 108	n = 112	n = 54
BL Mean (SD)	96.1 (19.88)	97.7 (23.21)	94.0 (21.88)	100.7 (27.10)	100.9 (24.79)
Mean (SD) Δ to End of Dosing	-0.8 (8.86)	0.3 (8.02)	0.5 (8.65)	-2.9 (17.40)	-0.7 (10.16)
QTc (msec)[b]	n = 290	n = 196	n = 108	n = 112	n = 54
BL Mean (SD)	426.4 (28.06)	423.7 (27.55)	429.4 (30.66)	435.0 (29.68)	435.6 (26.17)
Mean (SD) Δ to End of Dosing	-3.4 (16.01)	0.0 (15.85)	-1.4 (19.15)	-4.3 (30.96)	5.6 (17.59)
Heart rate (bpm)	n = 290	n = 196	n = 108	n = 112	n = 54
BL Mean (SD)	67.8 (10.60)	67.3 (10.82)	65.8 (10.75)	66.0 (9.70)	68.3 (12.72)
Mean (SD) Δ to End of Dosing	-0.1 (6.94)	-1.6 (7.72)	-0.6 (7.72)	-1.3 (6.40)	1.4 (7.21)

a Following treatment with ZS TID during the Acute Phase.
b QT is corrected for heart rate according to Bazett's formula.

Applicant's table 12-7 from ISS, page 121

Table 63: Extended Dosing-Proportions of Subjects with Treatment-Emergent Potentially Clinically Significant QTc Interval Values Based on Extended Dosing Baseline (Safety Population; Completed Studies ZS-003 and ZS-004)

Parameter QTc[a] Interval Criteria, n (%)	**Placebo[b] (N = 301)**	**Starting Dose of ZS in Extension**			
		≤ 2.5 g QD (N = 199)	**5 g QD (N = 110)**	**10 g QD (N = 114)**	**15 g QD (N = 56)**
Subjects with baseline QTc Interval ≤ 500 msec	n = 295	n = 197	n = 108	n = 112	n = 56
Maximum QTc interval > 500 msec	2 (0.7)	3 (1.5)	3 (2.8)	3 (2.7)	3 (5.4)
Maximum QTc increase from baseline > 30 msec	15 (5.1)	17 (8.6)	11 (10.2)	8 (7.1)	13 (23.2)
Maximum QTc increase from baseline > 60 msec	0 (0.0)	3 (1.5)	2 (1.9)	1 (0.9)	0 (0.0)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 30 msec	1 (0.3)	3 (1.5)	2 (1.9)	1 (0.9)	3 (3.6)
Maximum QTc interval > 500 msec and maximum QTc increase from baseline > 60 msec	0 (0.0)	2 (1.0)	2 (1.9)	1 (0.9)	0 (0.0)

a. QT is corrected for heart rate according to Bazett's formula.
b. Following treatment with ZS TID during the Acute Phase.

Applicant's table 12-8 from ISS, page 122

ECG parameters in Study ZS004E: No clinically significant mean changes from baseline in PR interval, QRS duration, or heart rate were observed in Study ZS004E. Statistically significant small mean increases in QTc interval were observed at several time points during extended dosing and were attributed to resolving hyperkalemia. No clinically important differences were observed between the shorter-term Extended Dosing Studies and Study ZS-004E in mean changes from baseline in ECG parameters. No new clinically significant cardiac arrhythmias were observed in Study ZS-004E.

The incidence of maximum QTc intervals > 500 msec was 4.9% in Study ZS004E with a magnitude ranging from 503 to 537 msec. Four subjects experienced a maximum QTc interval > 500 msec and a > 30 msec increase. One subject had a > 60 msec increase from the Acute Phase baseline in QTc interval to a maximum QTc interval > 500 msec. Each of the subjects with an increase in QTc of > 30 msec with a corresponding QTc interval > 500 msec had multiple comorbidities and was receiving numerous concomitant medications. Three subjects reported a cardiac adverse event (including one with right bundle branch block and two with QT prolonged) and met the ECG withdrawal criteria.

Table 64: Proportions of Subjects with Treatment-Emergent QTc Interval Values Meeting Predefined Criteria (Safety Population; Study ZS-004E)

QTc Interval Criteria, n (%)	ZS QD (N = 123)	
Maximum QTc interval > 500 msec	6 (4.9)	
	Change From AP Baseline	**Change From ED Baseline**
Maximum QTc increase from baseline > 30 msec	45 (36.6)	38 (30.9)
Maximum QTc increase from baseline > 60 msec	9 (7.3)	6 (4.9)
Maximum QTc interval > 500 msec with change from baseline > 30 msec	4 (3.3)	3 (2.4)
Maximum QTc interval > 500 msec with change from baseline > 60 msec	1 (0.8)	1 (0.8)

Note: AP Baseline is the value prior to Acute Phase dosing in Study ZS-004; ED Baseline is the value on or before the last regularly scheduled day of dosing in Study ZS-004. QT is corrected for heart rate according to Bazett's formula.
Applicant table from CSR Study ZS004E, table 12-27, page 152

Correlation of QTc Changes with Serum Potassium and Serum Calcium: In order to further evaluate the effect of ZS on the QT interval, an analysis was performed to assess whether the increases in QT interval associated with ZS administration were a function of the reduction in S-K and/or serum calcium levels. The 48-hour Acute Phases of Studies ZS-003 (n = 696) and ZS-004 (n = 250), during which subjects were dosed TID, were pooled for analysis. All subjects (n = 946) were evaluated for changes in QTc interval (Bazett's correction), S-K, and serum calcium from pre-dose to 48 hours. A linear regression analysis of change in QTc interval (dependent outcome) on change in S-K (independent variable) was performed and corresponding Pearson correlation coefficient and regression R-squared values were calculated. A parallel analysis was conducted for change in QTc interval on change in serum calcium. For each linear regression model, a prediction equation was drawn with 95% and 99% confidence intervals; the predicted QTc change (or level) was computed for a decrease of -2 mEq/L in S-K and a decrease of -1 mEq/L in serum calcium.

After 48 hours of treatment with ZS TID, the change in S-K was significantly correlated with change in QTc with a Pearson correlation coefficient of -0.14 ($p < 0.0001$). Similarly, the change in serum calcium was also significantly correlated with change in QTc with a Pearson correlation coefficient of -0.17 ($p < 0.0001$). In all scenarios involving the change in QTc or the QTc outcome at 48 hours with the 48- and 24-hour changes in S-K, no clinically significant QTc changes ≥ 30 msec or QTc outcomes ≥ 500 msec were predicted. Similar findings were observed for the 48-hour changes in serum calcium. As expected, a correlation between decrease in S-K and increase in QTc interval was observed across the clinical trial program.

Reviewer comments: ZS's effect on serum potassium levels results in changes in the QT interval (i.e., prolongation). No direct drug-related ECG abnormality findings were observed. No cases of serious cardiac arrhythmias, including Torsades des Pointes ventricular tachycardia, or sudden unexpected cardiac death have been reported.

8.4.9. **QT**

Given the nature of the product (i.e., its very low systemic absorption), a thorough QT study was conducted.

8.4.10. **Immunogenicity**

Sodium Zirconium Cyclosilicate is a small molecule that is not significantly absorbed. Therefore, it is not expected to have immunogenic potential. Neither the non-clinical studies nor the clinical studies suggest an increase in adverse events of potential immunogenic etiology.

8.5. **Analysis of Submission-Specific Safety Issues**

Given the mechanism of action of this product and the experience with the larger pharmacologic class, the following potential safety concerns were evaluated: hypokalemia, volume overload, GI tolerability and safety, and clinically significant alkalosis. Many of the analyses described below were performed by Dr. Christine Garnett. Drug-drug interactions are another potential safety concern for this class of agents; this potential risk is still being evaluated by the clinical pharmacology review.

8.5.1. **Hypokalemia**

In the acute phase of the short-term studies (up to 48 hours), 4 of 913 (0.4%) subjects developed a serum level of potassium less than 3.5 mmol/L including 3 subjects (0.7%) treated with ZS 10 g TID (one Study ZS003) and 1 (0.3%) treated with 3 g TID.

In the extended dosing phase (up to 12 days in study ZS-003 and up to 28 in study ZS-004), there was a dose-related increase in the number of subjects with serum potassium levels less than 3.5 mmol/L. Overall, 19 out of 479 (4%) subjects developed a serum potassium level less than 3.5 mmol/L including 11 (19.6%), 7 (6.1%), and 1 (0.5%) subjects treated with ZS 15 g, 10 g, and 2.5 g QD, respectively. No subject developed a serum potassium level less than 3 mmol/L as assessed by central laboratory values.

Dose reductions from QD to QOD occurred in 2 of five ZS 10 g QD subjects who developed a S-K value < 3.5 mmol/L and in 3 of the 6 ZS 15 g QD subjects. Four of the 5 subjects with dose reductions were able to complete dosing (2 ZS 10 g QOD and 2 ZS 15 g QOD subjects) and 1 was discontinued due to meeting protocol-specified stopping rules for prolonged QTc interval. Among the 6 subjects with confirmed low S-K values who did not have dose reductions, 1 completed dosing, 4 prematurely discontinued due to hypokalemia (i-STAT < 3.0 mmol/L, although central laboratory S-K in all cases was ≥ 3.0 mmol/L), and 1 discontinued due to meeting protocol-specified stopping rules for prolonged QTc interval.

In the long-term (Study ZS 004 E, up to 11 months durations): 7 of 123 (5.7%) subjects had a serum potassium level less than 3.5 mmol/L including one subject who had a serum potassium level of less than 2.8 mmol/L.

Reviewer's comment: The incidence of hypokalemia was low in the clinical development program. The available data indicate that the risk of hypokalemia can be adequately managed with periodic monitoring of serum potassium levels.

8.5.2. **Volume overload and edema:**

To evaluate the risk of clinically significant volume overload , the following data were analyzed: AEs of edema and heart failure, vital sign data (including changes in blood pressure and body weight), laboratory data (including changes in hemoglobin, hematocrit, and urinary sodium excretion), and diuretic use. The results of these analyses are discussed below.

Edema: In the short-term studies (ZS003 and ZS004), there was a dose-dependent increase in the incidence of AEs of edema (preferred terms of "general edema" and "peripheral edema"). The incidences were 1.3%, 1.0%, 1.8%, 5.3%, 14.3% in the placebo and 2.5 g, 5 g, 10 g, and 15 g qd ZS doses, respectively. There was no pattern in the time to onset of these AEs and most of the AEs were mild to moderate in severity. None of the AEs were considered to be serious and only one AE was categorized as severe. In the long-term study ZS004-E, the incidence of edema (including general edema, peripheral edema) and fluid overload was 13%; one subject had a SAE of pulmonary edema.

A number of subgroup analyses (based on demographic characteristics, comorbidities, renal function, and concomitant medications) were conducted in order to evaluate whether certain subpopulations may at greater risk of clinically significant volume overload. Analyses focused on the data from Study ZS004 as the highest dose of 15 g was administered in this study.

In subgroup analyses of Study ZS004, the incidence of edema was greater in patients with CKD, diabetes and in those with a reported history of heart failure who were treated with ZS than in patients who were treated with placebo, particularly at the 15 gm dose (see table below).

Table 65: Edema in Patients with Different Comorbidities (Study ZS004)

Subgroup	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	n	%	n	%	n	%
Total Edema	**1**	**2.2**	**3**	**5.9**	**8**	**14.3**	**12**	**7.9**	**2**	**2.4**
Patients with CKD (N=152)	1	2.2	3	5.9	8	14.3	12	7.9	1	1.2
Patients with No CKD (N=85)	0		0		0		0		1	1.2
Patients with CHD (N=87)	1	2.2	2	3.9	5	8.9	8	5.3	1	1.2
Patients with No CHD (N=150)	0		1	2.0	3	5.4	4	2.6	1	1.2
Patients with DIAB (N=157)	1	2.2	3	5.9	6	10.7	10	6.6	0	
Patients with No DIAB (N=80)	0		0		2	3.6	2	1.3	2	2.4

Source: Dr. Christine Garnett
Abbreviations: ZS=sodium zirconium cyclosilicate; CKD=chronic kidney disease, CHD=chronic heart disease, DIAB=diabetes. Edema included MedDRA Preferred Terms of general edema and peripheral edema.
Reviewer's analysis based on Applicant's datasets AE.xpt and ADSL.xpt.

In a subgroup analysis in which patients were stratified by baseline GFR levels, the risk of edema associated with ZS treatment appeared to be greatest in subjects with GFRs < 30 mL/min/1.73m^2.

Table 66: Edema in Patients with Different Degrees of Renal Impairment (Study ZS004)

	Baseline GFR, ml/min/1.73m^2		
	<=30 (N=85)	>30 to <60 (N=77)	>=60 (N=68)
Subjects with Edema	8 (9.4%)	4 (5.2%)	2 (2.9%)
By Treatment			
Placebo	0/24	1 /28 (3.6%)	1/28 (3.6%)
ZS Groups	8/61 (13.1%)	3/49 (6.1%)	1/40 (2.5%)

Source: Dr. Christine Garnett
Abbreviations: GFR=glomerular filtration rate; ZS=sodium zirconium cyclosilicate. Reviewer's analysis based on Applicant's datasets AE.xpt and ADSL.xpt.

The risk of edema associated with ZS treatment also appeared to be greater in patients not taking diuretics at baseline and those who were on calcium channel blockers at baseline.

Table 67: Edema in Patients with Concomitant Medications (Study ZS004)

	Concomitant Medications (ANL02FL="Y")			
	Taking Diuretics (N=63)	Not Taking Diuretics (N=174)	Taking CCB (N=75)	Not Taking CCB (N=162)
Subjects with Edema	4 (6.3%)	10 (5.7%)	8 (10.7%)	6 (3.7%)
By Treatment				
Placebo	2/29 (6.9%)	0/58	0/22	2/63 (3.2%)
ZS Groups	2/34 (5.6%)	10/116 (8.6%)	8/53 (15.1%)	4/99 (4.0%)

Source: Dr. Christine Garnett
Abbreviations: CCB=calcium channel blockers; ZS=sodium zirconium cyclosilicate. Notes: ANL02FL indicates that medication taken during the Extended Dosing Phase. 7/8 subjects with edema were taking amlodipine. Reviewer's analysis based on Applicant's datasets AE.xpt, ADSL.xpt, and ADCM.xpt.

Heart failure: The incidence of heart failure AEs was higher in the ZS as compared to the placebo groups. However, the total number of AEs was low as shown in the following table. In the short-term studies, all of the events were considered mild or moderate in severity, with the exception of 1 severe event of dyspnea in the middle dose group. In the long-term study, Study ZS-004E, 6 (4.9%) subjects reported AEs of cardiac failure (broad SMQ). Three subjects had severe events (2 cardiac failure congestive and 1 cardiac failure) that were serious and required or prolonged hospitalization, 2 (cardiac failure congestive) of which resulted in dose interruption and 1 (cardiac failure) that resulted in premature discontinuation from study drug. The remaining non-serious events were considered mild or moderate in severity, with the exception of 1 severe event of cardiac failure.

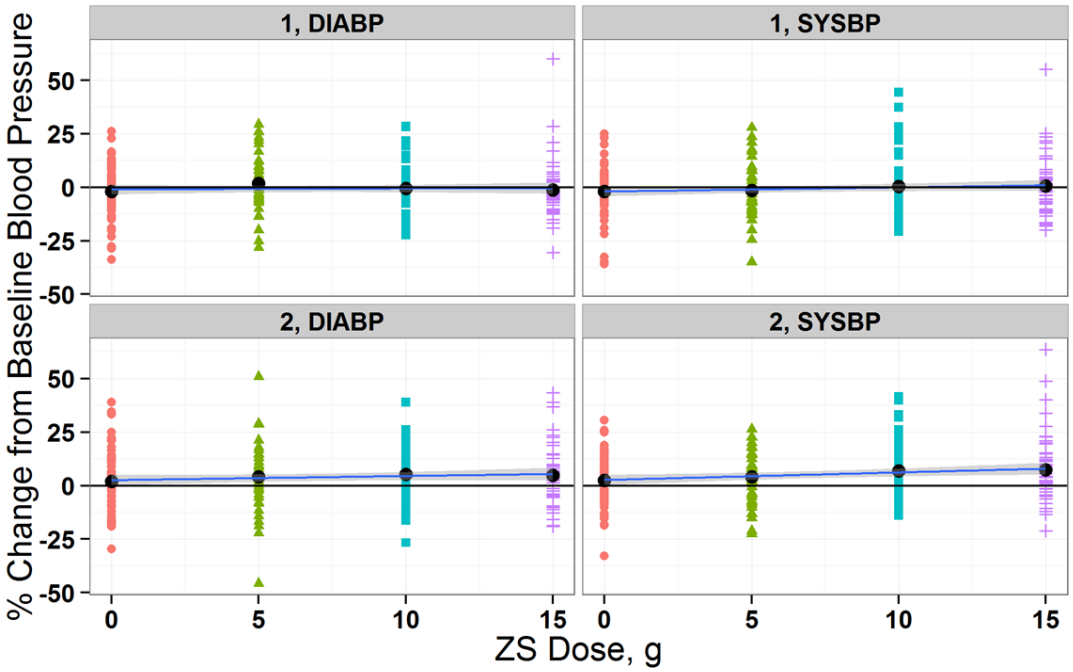
Table 68: Treatment-Emergent Adverse Events Related to Cardiac Failure (Pooled Studies)

Events with preferred term	**Placebo (n=301)**	**ZS Dose Levels in Short-Term Studies**				**Long term Study** (n=123)
		≤ 2.5 g qd (n=199)	5 g qd (n=110)	10 g qd (n=114)	15 g qd (n=56)	
Cases, n (%)	1 (0.3)	2 (1.0)	2 (1.8)	2 (1.8)	2 (3.6)	6 (4.9)
Cardiac failure	0	0	0	0	1	3
Cardiac failure acute	0	0	0	1	0	0
Cardiac failure congestive	1	0	1	0	1	2
Dyspnea	0	2	1	1	0	0
Pulmonary edema	0	0	1	0	0	2
Rales	0	0	1	0	0	0

Reviewer's table

Changes in Blood Pressure: There was a trend towards a dose-dependent increase in blood pressure in the extended dosing phase of the short-term studies (see figure below). In the short term studies (analyses performed on pooled data), the incidence of hypertension AEs was 1.3% (4/301), 1.8% (2/110), 1.8% (2/114), and 3.6% (2/56) in placebo, ZS 5g, ZS 10g, and ZS 15g, respectively. In the long term study (ZS004 E), 13% of subjects were reported to have a hypertension AE. Hypertension AEs were mild to moderate in severity and none were considered to be serious.

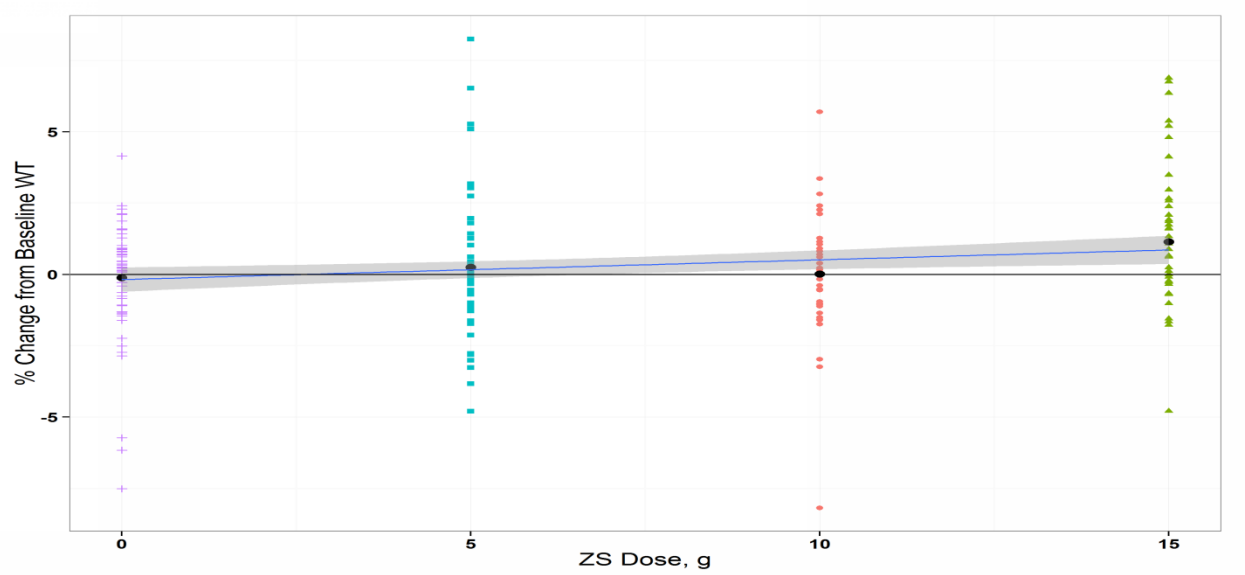
Figure 11: Trend for dose-dependent increase in BP during Extended Dosing Phase (Study ZS004)



Source: Dr. Christine Garnett
Abbreviations: 1 = acute phase; 2 = extended dosing phase; DIABP=diastolic blood pressure, SYSBP=systolic blood pressure; ZS=sodium zirconium cyclosilicate. Linear regression trend line is shown by the solid line with 95% confidence shown by shading. The mean percent increase in blood pressure is shown by the solid black points. Reviewer's analysis based on Applicant's dataset ADVS.xpt.

Changes in Body Weight: There was a trend towards an increase in body weight in the extended dosing phase of Study ZS004 as shown in the following figure. The 15 g dose had the largest increase in body weight at the end of the extended dosing phase, with a mean increase of +1.15 kg.

Figure 12: Trend for Dose-dependent Increase in Body Weight at End of Extended Dosing Phase (Study ZS004)



Source: Dr. Christine Garnett
Abbreviations: WT=body weight; ZS=sodium zirconium cyclosilicate. Linear regression trend line is shown by the solid line with 95% confidence shown by shading. The mean percent increase in weight is shown by the solid black points. Reviewer's analysis based on Applicant's dataset ADVS.xpt.

Changes in Hemoglobin/Hematocrit: In the short-term studies, there was a slight mean decrease in hemoglobin and hematocrit from baseline in the high dose group in comparison to the placebo and low dose groups as shown in the table below. As discussed in Section 8.1.1, there was also a dose-dependent increase in the proportion of patients with a hemoglobin < 8g/dl in the 10 g and 15 g doses groups in comparison with placebo (3/11, 2.7%; 2/53, 3.8% vs 1/281, 0.4%, respectively). As previously noted, these findings may reflect hemodilution.

Table 69: Hemoglobin and Hematocrit Changes

		Placebo (N=301)	<= 2.5 g (N=199)	5 g (N=110)	10 g (N=114)	15 g (N=56)
Hemoglobin Mean (SD)	Baseline	12.4 (1.9)	12.5 (2.1)	12.4(1.9)	12.3 (1.9)	12.5(2.2)
	Change to End	-0.4(0.6)	-0.5 (0.6)	-0.5 (0.8)	-0.5(0.8)	-0.6 (1.1)
Hematocrit Mean (SD)	Baseline	38.3(5.9)	38.5 (6.3)	38.4(5.7)	37.8(5.9)	38.6 (7.0)
	Change to End	-1.0 (2.1)	-1.3(2.0)	-1.3(2.5)	-1.2 (2.5)	-1.6 (3.2)

Reviewer's table

Urinary Sodium Excretion: Urine sodium excretion was measured in Study ZS 0004. In comparison with placebo, there was a slight increase in urinary sodium excretion in the 5 g

and 15 g dose groups but not in the 10 g group. Interpretation of these data is complicated by the use of diuretics in ~40% of patients. A separate study, Study ZS006, was conduct in healthy volunteers to evaluate the effect of ZS on urinary sodium excretion. In this study, subjects were administered doses of 5 g and 10 g QD or placebo for 4 days. There was no obvious effect on urinary sodium excretion in this study.

Diuretic Use: The proportion of patients using diuretics at the baseline was similar to the withdrawal phase, which was about 40%.

Reviewer comments: As a whole, the available data, including analyses of AEs of edema, and vital sign data (changes in body weight and blood pressure) and, to some extent other laboratory data, indicate that sodium is absorbed from the product. However, safety analyses do not raise concern for significant risk in the population that was studied.

8.5.3. **GI events**

The incidence of GI AEs was similar in the placebo and treatment groups and there was no evidence of a dose-response relationship. One subject on ZS 10 g TID developed severe vomiting and diarrhea on Day 1 that led to discontinuation. See Section 8.3.4 for additional information.

8.5.4. **Alkalosis**

As ZS binds protons in the GI tract, ZS has the potential to cause alkalosis. In the acute phase of the short-term studies, small mean dose-related increases in bicarbonate were observed in the ZS treatment groups; however values remained in the normal range. In the maintenance phase of these trials, mean dose-related increases in bicarbonate were observed in the ZS 5 g, 10 g, and 15 g treatment groups as shown in the table below. The overall increase was small and most of the values remained in the normal range; three patients treated with placebo and one treated with ZS 15 g had a shift from the normal range to a value above the normal range for serum bicarbonate. No patient had a serum bicarbonate> 35mmol/L.

Table 70: Change in Serum Bicarbonate from Baseline

Change in serum bicarbonate	Placebo (N = 301)	ZS ≤ 2.5 g QD (N = 199)	ZS 5 g QD (N = 110)	ZS 10 g QD (N = 114)	ZS 15 g QD (N = 56)
Baseline, mean (sd)	23.1 (3.5)	23.6 (3.3)	23.3 (3.7)	22.5 (4.0)	22.6 (4.3)
Change (sd) from baseline	0.6 (2.6)	0.6 (2.3)	1.1 (2.8)	2.3 (2.7)	2.6 (2.8)

Reviewer's table

Reviewer comments: Based on the aforementioned findings, alkalosis is not a major safety concern.

8.6. Specific Safety Studies/Clinical Trials

None.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

In the one-year, long-term extension study, Study ZS004 E, one case of adenocarcinoma of the colon was reported. No other malignant tumor was reported.

8.7.2. Human Reproduction and Pregnancy

There is no information on drug exposure in pregnant or lactating woman.

8.7.3. Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The potential for abuse and dependence with ZS has not been evaluated in clinical studies. However, due to the insolubility and lack of absorption of ZS, drug abuse or development of drug dependence seems unlikely.

No subjects received > 2 × the intended dose. No information is available from ZS clinical studies with respect to overdose.

In the randomized withdrawal phases in both Studies ZS003 and ZS 004, no withdrawal or rebound effect was observed. Due to its insolubility and mechanism of action, it is unlikely that ZS would cause a withdrawal effect or rebound.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The drug is not currently marketed.

8.8.2. Expectations on Safety in the Postmarket Setting

Assuming adequate monitoring of serum potassium levels, the risk of hypokalemia should be low.

8.9. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

A total of 1,592 subjects with hyperkalemia have been exposed to at least 1 dose of ZS in clinical trials. This includes patients with hyperkalemia in the setting of CKD, heart failure, diabetes, and hypertension treated with RAAS inhibitor therapy. Although most of the experience has been with short-term administration, data were also submitted for 262 subjects who have been exposed to ZS for ≥ 6 months and 79 subjects who have been exposed for one year in two long-term extension studies (Study ZS004E, which is completed, and Study ZS005, which is ongoing).

Given the drug's mechanism of action and experience with potassium binders, potential safety concerns included hypokalemia, sodium absorption resulting in volume overload, GI safety and tolerability, and clinically significant alkalosis. Findings related to these issues are summarized below.

- Sodium absorption leading to volume overload: In the short-term studies (ZS003 and ZS004), there was a dose-dependent increase in the incidence of AEs of edema (preferred terms of "general edema" and "peripheral edema"). The incidences were 1.3%, 1.0%, 1.8%, 5.3%, 14.3% in the placebo and 2.5 g, 5 g, 10 g, and 15 g qd ZS doses, respectively. There was no pattern in the time to onset of these AEs and most of the AEs were mild to moderate in severity. None of the AEs were considered to be serious and only one AE was categorized as severe. The incidence of AEs suggestive of heart failure was, as whole, low, though possibly somewhat higher in the ZS as compared to placebo treatment groups. In the long-term study (Study ZS004-E), the incidence of AEs of edema (including general edema and peripheral edema) and fluid overload was 13%. One subject had a SAE of pulmonary edema.

  For the most part, edema and heart failure-related events resolved without requiring study drug withdrawal. Approximately 50% of the edema events resulted in any treatment, typically a small adjustment in diuretic dosing. Analyses of vital sign data (changes in body weight and blood pressure) and, to some extent, other laboratory data (changes in hemoglobin and hematocrit) also indicate that sodium is absorbed from the product. Patients who have severe heart failure and those with significant impairment in renal function are expected to be at greatest risk.

- Hypokalemia: In the clinical trials, serum potassium levels were monitored regularly. The incidence of hypokalemia in subjects treated with ZS in the development program was, as a whole, low. In the extended dosing phase of the short-term studies (up to 12 days in study ZS-003 and up to 28 in study ZS-004), 19 out of 479 (4%) subjects developed a serum potassium level less than 3.5 mmol/L. Most of these events were mild (serum potassium between 3.0 and 3.4 mmol/L) and could be managed with a dose reduction; no subject developed a serum potassium level less than 3 mmol/L as assessed by central laboratory values. In the long-term extension study (Study ZS 004 E), 7 of 123 (5.7%) subjects had a serum potassium level less than 3.5 mmol/L including one subject who had a serum potassium level of 2.8 mmol/L. As noted in the review, other factors may have contributed to the low serum potassium value in this subject. Of note, a dose-related increase in QTc interval was also observed during the Acute Phase of the short-term studies, consistent with the ZS-induced decrease in serum potassium values. However, the increase in QTc interval was small and no cases of cardiac arrhythmias or sudden unexpected cardiac deaths were observed.

- Clinically Significant Metabolic Alkalosis: Nonclinical studies indicate that treatment with high doses of ZS results in an increase in serum bicarbonate. In the clinical development program, treatment with ZS was associated with a slight increase in serum bicarbonate levels; however, there were no cases of clinically significant metabolic alkalosis. Of note, some patients with hyperkalemia (such as those with severe renal impairment) are acidotic and one could speculate that increasing bicarbonate in these patients may be beneficial.

- GI safety and tolerability: The incidence of GI AEs was similar in the placebo and ZS treatment groups and there was no evidence of a dose-response relationship.

No other significant safety concerns were identified during review of the clinical safety database. The main outstanding issue at this time is the potential risk of clinically significant drug-drug interactions; this potential risk is currently being evaluated by the clinical pharmacology reviewer.

9. Advisory Committee Meeting and Other External Consultations

None.

10. Labeling Recommendations

Labeling will be discussed separately.

11. Risk Evaluation and Mitigation Strategies (REMS)

None.

12. Post-marketing Requirements and Commitments

Pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) are deferred until after approval of the product for adults. There are ongoing discussions with the applicant about the design of their pediatric development program.

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/s/

SHEN XIAO
04/07/2016

ALIZA M THOMPSON
04/07/2016