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CADTH COMMON DRUG REVIEW

Clinical Review Report

SODIUM ZIRCONIUM CYCLOSILICATE (LOKELMA)

(AstraZeneca Canada Inc.)

Indication: For the treatment of hyperkalemia in adults.

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
CI	confidence interval
CKD	chronic kidney disease
DB	double-blind
CPS	calcium polystyrene sulfonate
DM	diabetes mellitus
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ VAS	EuroQol Visual Analogue Scale
ESRD	end-stage renal disease
FAS	full-analysis set
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention-to-treat
LSM	least squares mean
NOC	Notice of Compliance
OLE	open-label extension
RAASi	renin-angiotensin-aldosterone system inhibitor
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SPS	sodium polystyrene sulfonate
SZC	sodium zirconium cyclosilicate
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Drug	Sodium zirconium cyclosilicate (Lokelma)
Indication	Treatment of hyperkalemia in adults
Reimbursement request	Corrective treatment of hyperkalemia in adults. Maintenance treatment of hyperkalemia in adults with chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 who have experienced at least 2 hyperkalemic events and are sub-optimally managed on renin angiotensin aldosterone system inhibitor (RAASi) therapy
Dosage form(s) and route of administration) and strength(s)	5 g or 10 g powder for oral suspension
NOC date	July 25, 2019
Sponsor	AstraZeneca Canada Inc.

Executive Summary

Introduction

Hyperkalemia occurs when the amount of potassium in the blood is above the normal range of 3.5 mmol/L to 5.0 mmol/L. The severity can be defined as mild (5.5 mmol/L to 5.9 mmol/L), moderate (6.0 mmol/L to 6.4 mmol/L), or severe (> 6.5 mmol/L). A high potassium level affects the propagation of electrical signals and is particularly damaging to the cardiac system. Of greatest concern is the development of life-threatening cardiac arrythmias and death.

The exact incidence of hyperkalemia in the general population is unclear; however, it is highest in patients with chronic kidney disease (CKD) or maintenance dialysis. Drug-induced hyperkalemia is more likely to happen among patients who have hypertension, diabetes, or CKD while on medications, such as renin-angiotensin-aldosterone system inhibitor (RAASis) therapies for the treatment of hypertension, congestive heart failure, or myocardial infarction. These include the commonly used angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers. Other medications, such as nonsteroidal anti-inflammatory drugs, can also increase the risk of hyperkalemia. Mild hyperkalemia can be asymptomatic, while higher potassium levels can cause nausea, muscle pain, weakness, paresthesia, or palpitations. The management of hyperkalemia depends on whether it is acute or chronic as well as on its severity. Severe hyperkalemia needs emergency treatment to correct the serum potassium level. Chronic hyperkalemia, particularly when due to CKD or the use of RAASi medications to reduce the risk of cardiovascular events, may require long-term maintenance treatment.

Sodium zirconium cyclosilicate (SZC) is a potassium binder that increases potassium excretion. Health Canada granted SZC a Notice of Compliance (NOC) on July 25, 2019 for the treatment of hyperkalemia in adults with serum potassium levels greater than 5.0 mmol/L. The dosing for the acute phase is 10 g three times daily for up to two days. Once normokalemia is achieved (3.5 mmol/L to 5.0 mmol/L), a maintenance dose may be initiated at 5 g to 10 g once daily or 5 g once every other day. Other potassium binders are also available. These include sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS), and patiromer. Maintenance treatment of mild or moderate hyperkalemia may include dietary modification to reduce potassium intake, discontinuation of potassium

supplements, and discontinuation or reduction in the dosages of medications that increase potassium, such as the RAASi therapies.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of SZC 5 g and 10 g powder for oral suspension to treat hyperkalemia in adults.

Stakeholder Engagement

Patient Input

One joint submission from two patient groups, The Kidney Foundation of Canada and Diabetes Canada, was received for this review. Information from patients was gathered from an online survey. Seven respondents participated, all of whom identified as living with CKD and four of whom also reported having diabetes. Regulating potassium levels is a concern for patients with CKD, particularly those undergoing dialysis. This can be accomplished partly through lifestyle changes; however, patients described these changes as being highly restrictive, to the point of having a negative impact on their quality of life. Two patients reported having experience with SPS, a potassium binder, for hyperkalemia. They indicated dislike for the texture and taste of the medication and a desire to have it available in pill form. Most respondents said the following concerns were important or very important to them: fatigue, interference with sleep, edema of the foot, effect on mood, interference with other medications, changes in appetite, cost, and length of time on the medication. Patients also noted concerns about side effects and drug efficacy as other important factors when choosing a new medication for CKD.

Clinician Input[1]

Two clinical experts with expertise in cardiovascular and kidney disease provided input for this review. Hyperkalemia is treated by withdrawing medications that increase potassium, in particular the RAASi therapies and mineralocorticoid receptor antagonists. However, this approach means that patients will lose the cardio- and renal protective effects of RAASi and be at higher risk of adverse clinical outcomes. Other treatments for chronic hyperkalemia include SPS, diuretics, or laxatives. All treatments include dietary counselling to modify foods that are high in potassium. The goal of treatment is to prevent life-threatening arrhythmias and enable optimal dosing of RAASi. SZC would be considered an adjunct treatment, primarily in patients who experience hyperkalemia while on RAASi. Given that hyperkalemia is usually asymptomatic, blood testing of serum potassium is needed to identify patients in need of treatment and to monitor them afterward. Patients with serum potassium levels of less than 5.5 mmol/L are least suitable for treatment. While serum potassium is the immediate, surrogate outcome to monitor hyperkalemia, the most important outcome from a clinical perspective is reduction in the risk of cardiovascular or kidney disease outcomes by continuation of optimal doses of RAASi. SZC should be prescribed in community- or hospital-based clinics by specialists in cardiology, nephrology, endocrinology, or general internal medicine.

[1] This information is based on information provided by clinical experts consulted by CADTH Common Drug Review reviewers for the purpose of this review.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The main evidence for SZC consisted of five double-blind (DB), randomized controlled trials (RCTs). Two studies had a randomized, placebo-controlled acute phase for the first two days of treatment. Four studies had a randomized, placebo-controlled maintenance phase that lasted 12 days or 28 days. Across the studies, just under 900 patients were evaluated for acute treatment, while 950 were evaluated for maintenance treatment at the Health Canada–approved doses. SZC was administered at various doses in the studies; however, in this review, only those doses approved by Health Canada (5 g and 10 g) were evaluated. A heterogeneous, older patient population with various conditions and medications was included. The mean age of patients was in their sixties to seventies. In the maintenance phase, 58% to 100% of patients had CKD; most had an estimated glomerular filtration rate (eGFR) above 15 mL/min/1.73m^2. Patients were generally in the range of mild to moderate hyperkalemia at baseline. The cause of hyperkalemia for most patients was RAASi use and/or CKD.

Efficacy Results

Acute PhaseTable 1 provides estimates for the acute-phase outcomes that were tested as part of a sequential closed statistical testing procedure to control for type I error. In studies ZS-003 (N = 301) and ZS-D9482 (N = 99), the primary outcome — the exponential rate of serum potassium change over 48 hours — demonstrated that SZC 10 g three times daily reduced serum potassium at a statistically significantly higher rate compared with placebo. In Study ZS-003, the SZC group had a 0.48 mmol/L greater decrease in serum potassium at 48 hours compared with placebo. In Study ZS-D9482, this group had about a 1 mmol/L greater decrease compared with placebo. The percentage of patients who achieved normokalemia (3.5 mmol/L to 5.0 mmol/L) at 48 hours was 86.4% with SZC versus 47.8% with placebo in Study ZS-003, and 91.7% versus 15.2% in Study ZS-D9482.

Maintenance Phase

Patients entered the maintenance phase if they achieved normokalemia after 48 hours of treatment in the acute phase. Table 2 provides estimates for the maintenance phase outcomes that were tested as part of a sequential closed statistical testing procedure to control for type I error, which included three of the four studies. Across all four studies with a maintenance phase, a consistent effect in favour of SZC was observed. In Study ZS-003 (N = 256), the exponential rate of change in serum potassium over 28 days of treatment was smaller (i.e., there was a greater degree of potassium stabilization) for SZC 5 g and 10 g compared with their corresponding placebo groups. In Study ZS-004 (N = 181), mean serum potassium through days 8 to 29 was lower for the SZC 5 g and 10 g groups compared with placebo; these groups also had more normokalemic days on day 29 (medians of 13.9 days for 10 g, 13.4 days for 5 g, and 7.4 days for placebo). Study ZS-D9480 (N = 248) also found a lower mean of serum potassium through days 8 to 29 for 5 g and 10 g compared with placebo. Compared with placebo, more patients in both dosage groups remained normokalemic at day 29, had a higher number of normokalemic days, and had a longer time to hyperkalemia. All studies conducted exploratory analyses of subgroups, such as patients with CKD, heart failure, and RAASi use, and found effects in favour of SZC. Yet there was uncertainty as to whether patients with CKD and an eGFR of less than 30 would have a similar beneficial effect and harm profile compared to patients

whose eGFRs were greater than or equal to 30 mL/min/1.73m^2. Among a dialysis population in the DIALIZE study, more patients who received SZC maintained a pre-dialysis serum potassium level of 4.0 mmol/L to 5.0 mmol/L and did not require rescue therapy compared with placebo (41.2% versus 1.0%, P < 0.001). There were limited data available for outcomes of interest to patients and clinicians, such as cardiac or renal morbidity, quality of life, or maintenance of RAASi or mineralocorticoid receptor antagonist therapies at optimal doses.

Harms Results

Table 3 provides harms data for the acute phase. Table 4 provides these for the maintenance phase.

Acute Phase

The more frequent (> 1%) adverse events (AEs) were constipation, diarrhea, vomiting, and edema. There were three withdrawals due to adverse vents (WDAEs) in patients who received SZC. No patient who received SZC had a serious adverse event (SAE), and there were no deaths. Of the notable harms, constipation, edema, hypokalemia, atrial fibrillation, palpitations, hypertension, and ventricular extrasystoles were slightly more common with SZC compared with placebo. One patient in an open-label acute-phase experienced intestinal obstruction.

Maintenance Phase

Across three studies, SAEs were experienced by six patients who received SZC 10 g, by 12 patients who received SZC 5 g, and by four patients who received placebo. There were eight patients with WDAEs in the 10 g group, 14 in the 5 g group, and four in the placebo group. In DIALIZE, SAEs were experienced by seven patients on SZC and by eight patients on placebo. There were three deaths in the maintenance phase across the four studies. One patient who received SZC 5 g died from respiratory distress; one patient receiving 10 g died of myocardial infarction; and one patient on dialysis in the DIALIZE study who received SZC died of peripheral arterial occlusive disease.

Of the notable harms, constipation was more frequent with SZC 10 g. One patient on 5 g had a small intestinal obstruction. Edema and/or peripheral edema were observed in most studies: among 20 patients in the 10 g groups, six patients in the 5 g groups, and four patients in the placebo groups. Hypokalemia was observed more frequently with higher doses. In Study ZS-004, hypokalemia occurred in eight patients in the 10 g group, and in none in the placebo and 5 g groups. In Study ZS-D9480, one patient experienced hypokalemia in the 10 g group; there were no cases in the placebo and 5 g groups. In DIALIZE, five patients in both the placebo and SZC groups experienced pre-dialysis hypokalemia.

Table 1: Summary of Key Efficacy Results in the Acute Phase

	Study ZS-003		Study ZS-D9482	
	Placebo (N = 158)	SZC 10 g (N = 143)	Placebo (N = 33)	SZC 10 g (N = 36)
Primary outcome				
Exponential rate of S-K change				
48 hours, estimate (SE)	–0.00094 (NR)	–0.00297 (NR)	–0.00012 (0.00029)	–0.00508 (0.00027)
P value	—	10^{-31}	—	< 0.0001

SE = standard error; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Table 2: Summary of Key Efficacy Results in the Maintenance Phase

Study	Primary outcome			Secondary outcomes								
	Exponential rate of S-K change (day 12 of maintenance phase)											
Study ZS-003		Estimate	P value	No secondary outcomes were part of the sequential closed statistical testing procedure.								
	Placebo (N = 68)	0.0047	—									
	SZC 5 (N = 64)	0.0009	0.0083									
	Placebo (N = 61)	0.01039	—									
	SZC 10 (N = 63)	0.00137	< 0.0001									
	LSM S-K (days 8 to 29)			Number of normokalemic days (S-K 3.5 mmol/L to 5.0 mmol/L)		Remained normokalemic						
Study ZS-004		LSM (95 % CI), mmol/L	P value	Mean (SE), days	P value	Day 29 exit		Day 35 (EOS)		No other secondary outcomes were part of the sequential closed statistical testing procedure.		
						n/N (%)	P value	n/N (%)	P value			
	Placebo (N = 85)	5.1 (5.0 to 5.2)	—	7.4 (8.0)	—	39/82 (47.6)	—	16/31 (51.6)	—			
	SZC 5 (N = 45)	4.8 (4.6 to 4.9)	0.0001	13.4 (7.6)	0.0001	32/45 (71.1)	≤ 0.05	14/22 (63.6)	0.41			
	SZC 10 (N = 51)	4.5 (4.4 to 4.6)	< 0.0001	13.9 (7.9)	< 0.0001	38/50 (76.0)	≤ 0.01	13/27 (48.1)	1.0			
	LSM S-K (days 8 to 29)			Number of normokalemic days (S-K 3.50 mmol/L to 5.0 mmol/L)			Time to hyperkalemia (S-K ≥ 5.1 mmol/L)			Achieved normokalemia		
Study ZS-D9480		LSM (SE), mmol/L	LSM difference (95% CI)	LSM (SE), days	LSM difference (95% CI)	P value	Median, days	HR (95% CI)	P value	n (%)	P value	
	Placebo (N = 50)	5.3 (0.02)	—	3.5 (1.4)	—	—	5	—	—	12 (24.0)	—	
	SZC 5 (N = 99)	4.8 (0.01)	0.90 (0.88 to 0.93)	10.8 (1.1)	7.3 (4.3 to 10.2)	< 0.001	14	0.4 (0.3 to 0.7)	< 0.001	58 (58.6)	< 0.001	
	SZC 10 (N = 99)	4.4 (0.01)	0.82 (0.80 to 0.85)	15.6 (1.1)	12.1 (9.1 to 15.0)	< 0.001	29	0.2 (0.1 to 0.3)	< 0.001	75 (77.3)	< 0.001	

CI = confidence interval; EOS = end of study; LSM = least squares mean; SE = standard error; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Table 3: Summary of Harms in the Acute Phase

	Study ZS-003		Study ZS-D9482	
	Placebo (N = 158)	SZC 10 g (N = 143)	Placebo (N = 33)	SZC 10 g (N = 36)
Patients with > 0 AEs, N (%)	17 (10.8)	17 (11.9)	1 (3.0)	5 (13.9)
Patients with > 0 SAEs, N (%)	1 (0.6)	0 (0)	0 (0)	0 (0)
WDAEs, N (%)	0 (0)	1 (0.7)	0 (0)	0 (0)
Number of deaths, N (%)	0 (0)	0 (0)	0 (0)	0 (0)

AE = adverse event; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

Table 4: Summary of Harms in the Maintenance Phase

	Study ZS-003				Study ZS-004			Study ZS-D9480			DIALIZE	
	PBO (N = 68)	SZC 5 g (N = 65)	PBO (N = 61)	SZC 10 g (N = 63)	PBO (N = 85)	SZC 5 g (N = 45)	SZC 10 g (N = 51)	PBO (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)	PBO (N = 99)	SZC (N = 96)
> 0 AEs, N (%)	16 (23.5)	14 (21.5)	15 (24.6)	21 (33.3)	27 (31.8)	24 (53.3)	15 (29.4)	10 (20.0)	28 (28.3)	44 (44.4)	46 (46.5)	40 (41.7)
> 0 SAEs, N (%)	2 (2.9)	3 (4.6)	1 (1.6)	1 (1.6)	0 (0)	5 (11.1)	2 (3.9)	1 (2.0)	4 (4.0)	3 (3.0)	8 (8.1)	7 (7.3)
WDAEs, N (%)	0 (0)	3 (4.6)	1 (1.6)	1 (1.6)	0 (0)	4 (8.9)	0 (0)	3 (6.0)	7 (7.1)	7 (7.1)	2 (2.0)	4 (4.2)
Deaths, N (%)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)

AE = adverse event; PBO = placebo; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

Critical Appraisal

The primary limitation in the evidence base is the absence of information on other co-administered interventions that could reduce potassium levels, such as dietary modifications or changes to RAASi therapy. Although there were some data about changes to RAASi therapies at the end of treatment in the acute and maintenance phases, this was a post hoc analysis; the studies were not designed to systematically evaluate this outcome. If these interventions systematically varied across the treatment groups, then bias could have been introduced; however, given the lack of detailed information, it is unknown which direction any bias would have gone. The studies included a heterogeneous patient population with diverse medical histories and concomitant medications, reflective of patients who present with hyperkalemia in clinical practice. Given the relatively small sample sizes of the subgroups, more study is warranted to identify the potential disparity in maintaining treatment effect by different level of kidney impairment as measured by eGFR categories (e.g., < 30 mL/min/1.73m^2 per the sponsor's listing request). It is also of note that the treatment effects observed in these studies were among a high percentage of patients using RAASi medications (more than 50% and up to nearly 80%). However, there are several concerns about the generalizability of the evidence base to the patient population of interest. First, none of the study sites were in Canada, and it is unclear if the clinical practices of other countries differed from Canada's with respect to dietary interventions or protocols for modifying therapies. Second, according to the clinical experts consulted for this review, the potassium cut-off used to screen patients into the studies (i.e., > 5.0 mmol/L

or > 5.1 mmol/L) was low compared with clinical practice, where intervention would typically be initiated at about 5.3 mmol/L to 5.5 mmol/L. Also, while a large percentage of patients had CKD, patient populations with other conditions associated with hyperkalemia, such as heart failure, were included. Third, the studies focused on outcomes related to potassium; however, no or limited data were available for outcomes of importance to clinicians and patients, such as need to change RAASi therapy, cardiovascular or kidney morbidity, and quality of life. Fourth, there are no direct or indirect comparative data available on other potassium binders or interventions used in the treatment of hyperkalemia.

Comparisons

No evidence from indirect treatment comparisons (ITCs) was available.

Other Relevant Evidence

Description of Studies

Two additional studies, ZS-004E and ZS-005, provided longer-term safety and efficacy data for SZC. Both were open-label, single-group, and multi-centre. Study ZS-004E was an open-label extension (OLE) of Study ZS-004, in which patients were administered SZC 10 g once daily (with possible titration down to 5 g or up to 15 g) during an extended-dosing phase that lasted up to 11 months. In Study ZS-005, patients were administered SZC during an extended-dosing phase of up to 12 months. Patients started at 5 g once daily in the extended phase, but could be titrated to 15 g based on potassium level.

Efficacy Results

During the extended-dosing phases, the proportions of patients with a mean serum potassium value of 5.1 mmol/L or less on average from day 8 to day 337 (Study ZS-004E) or day 365 (Study ZS-005) were 88.3% (95% confidence interval [CI], 81.2 to 93.5) and 86.0% (95% CI, 83.2 to 88.4), respectively.

Harms Results

During the extended-dosing phases of studies ZS-004E and ZS-005, 66.7% and 65.5% of patients reported AEs; 19.5% and 21.6% reported SAEs; and 8.9% and 13.7% reported WDAEs, respectively. Eight (1.1%) deaths were reported in Study ZS-005, none of which were considered related to the study drug. Hypertension, peripheral edema, and gastrointestinal disorders (i.e., constipation, vomiting, and diarrhea) were some of the most frequently occurring AEs in the two studies and are discussed as notable harms in this review.

Conclusions

SZC is a new potassium binder for the treatment of hyperkalemia in adults. Five studies provide evidence for its efficacy compared with placebo for the acute (initial 48 hours) and maintenance (beyond 48 hours) phases in patients with mild to moderate hyperkalemia. For the treatment of acute hyperkalemia, SZC 10 g reduced serum potassium levels at a higher rate than placebo over 48 hours. In the maintenance phase, the evidence consistently showed a potassium-lowering effect for SZC 5 g or 10 g once daily compared with placebo over both 12 days and 28 days. SZC led to a greater degree of potassium stabilization, lower mean potassium, a higher proportion of patients who remained normokalemic, a higher number of normokalemic days, and longer time to hyperkalemia. In a population of

patients requiring dialysis, more patients who received SZC had pre-dialysis potassium levels within the normal range and did not require rescue therapies. As with other potassium binders, gastrointestinal effects, such as constipation, may be more common with this medication. Other AEs that require monitoring are edema and hypokalemia, especially at the higher dose of 10 g. A key limitation of the evidence for SZC is that there were no or limited data available for outcomes of importance, such as cardiovascular and kidney morbidity, the need to modify RAASi therapies, or quality of life. While patients with eGFRs of less than 30 mL/min/1.73m^2 were included in the trials (sponsor reimbursement request), the results of subgroup analyses for these patients are uncertain due to small sample sizes and exploratory analyses. There were also no direct treatment comparisons or ITCs of SZC with other potassium binders; therefore, the benefit and safety of this medication versus other existing therapies are currently unknown. Overall, despite its demonstrated efficacy in reducing serum potassium levels, there is uncertainty as to the added clinical benefit of SZC.

Introduction

Disease Background

Potassium plays an important role in conducting electrical impulses in the body and maintaining normal cell electrophysiology. The ratio between intracellular and extracellular potassium is tightly regulated at 98:2%, with an extracellular range of 3.5 mmol/L to 5.0 mmol/L.[1,2] Hyperkalemia occurs when the extracellular potassium level goes above this normal range. A high level of potassium affects the proper propagation of electrical signals and is particularly damaging to the cardiac system. Dysfunction in cardiac electrophysiology may cause a decrease in myocardial resting membrane potential, an increase in cardiac depolarization, myocardial excitability, cardiac instability, and conduction system abnormalities, which can result in life-threatening arrhythmias.[2] Potassium has been found to follow a U-shaped association with mortality, with both low and high levels increasing the risk of death.[2]

Hyperkalemia is defined as a blood serum potassium level above the normal range of 3.5 mmol/L to 5.0 mmol/L. A high potassium level affects the propagation of electrical signals and is particularly damaging to the cardiac system. Of greatest concern is the development of life-threatening cardiac arrythmias and sudden cardiac death.[2] Mild hyperkalemia may be asymptomatic and detected upon routine lab testing only. Higher potassium blood serum levels may cause nausea, muscle pain, weakness, paresthesia, or palpitations.[3] Although there is no uniformly agreed-upon definition, hyperkalemia can be classified as mild (5.5 mmol/L to 5.9 mmol/L), moderate (6.0 mmol/L to 6.5 mmol/L), or severe (> 6.5 mmol/L).[4]

Hyperkalemia may arise from an increase in potassium intake, a decrease in potassium excretion, or an imbalance in intracellular-extracellular potassium distribution.[5] The kidney is the main route for potassium excretion; CKD is the most important risk factor for potassium elevation. Diabetes mellitus (DM) and cardiovascular disease, both of which may co-exist with CKD, are other important risk factors.[2] Diabetes mellitus results in insulin deficiency and hypertonicity, which reduces potassium distribution into the intracellular space.[2] Cardiovascular disease, such as congestive heart failure and myocardial infarction, has an effect on potassium homeostasis and may be treated with medications that increase potassium. In particular, the RAASi therapies, which include the ACEIs and angiotensin receptor blockers, are used for renal and cardio protection; however, they also increase the risk of hyperkalemia.[2] For example, a study showed that 11% of patients on an ACEI developed hyperkalemia.[6] Other risk factors are older age, metabolic acidosis, and the use of mineralocorticoid receptor antagonists or nonsteroidal anti-inflammatory drugs.[3]

The exact incidence of hyperkalemia in the general population is unclear, given that it is a transient condition and longitudinal studies to monitor for its presence are unavailable.[2,7] Among elderly patients who presented to an emergency department in southwestern Ontario from 2003 to 2010, 2.6% had potassium levels that were greater than 5.5 mmol/L; among those admitted to hospital, 3.5% had potassium levels greater than 5.5 mmol/L.[8] The incidence of hyperkalemia in patients with CKD may be higher. Patients on maintenance dialysis may have the highest incidence.[7]

Standards of Therapy

The management of hyperkalemia depends on whether it is acute or chronic as well as on its severity (i.e., the degree of potassium elevation).[3] Acute hyperkalemia occurs when

potassium is released from cells, which can happen in states of trauma, metabolic acidosis, or hemolysis and requires immediate intervention.[3] Chronic hyperkalemia occurs when there is impairment in potassium excretion (e.g., kidney disease) and/or an increase in potassium load (e.g., from a diet high in potassium or supplements) and requires ongoing management.[3] Severe hyperkalemia (serum potassium > 6.5 mmol/L) is a medical emergency whether it is due to an acute or chronic cause. In the emergency setting, patients will be hospitalized and treated with IV therapies to rapidly redistribute potassium into cells (e.g., insulin plus glucose, sodium bicarbonate, beta-adrenergic agonists), stabilize the cell membrane (e.g., IV calcium), or remove potassium from the body (e.g., hemodialysis or IV loop diuretics).

Mild or moderate forms of acute or chronic hyperkalemia may be treated with drugs that increase potassium excretion, such as oral loop or thiazide diuretics and cation-exchange resins or cation-exchange polymers. This latter group of medications, also known as potassium binders, includes SZC, SPS, CPS, and patiromer (Table 5). The potassium binders cannot be used for hyperkalemia that is a medical emergency due to their delayed onset of action.[3]

Non-pharmacological modalities are also important in the management of hyperkalemia. The first step in the management of mild or moderate hyperkalemia may include dietary modifications to reduce potassium intake, discontinuation of potassium supplements, and discontinuation or reduction in the dosages of medications that increase potassium, such as RAASi therapies.[2] While discontinuation or reduction in RAASi dosage may help to normalize potassium levels, this will result in patients losing the renal and cardio-protective effects of these medications. Therefore, it is not desired.

Drug

SZC is a microporous zirconium silicate with a specific crystal geometry that reduces potassium by selectively binding to potassium ions in the gut in exchange for sodium and hydrogen ions. SZC is a powder that is dissolved in water to create an oral suspension. It is available in 5 g or 10 g sachets. Health Canada has approved this medication for the treatment of hyperkalemia in adults (NOC received July 25, 2019).[9] For patients with potassium levels greater than 5.0 mmol/L, the dosing for the acute phase is 10 g three times daily for up to 48 hours.[10] Once normokalemia is achieved (potassium 3.5 mmol/L to 5.0 mmol/L), the maintenance dose is initiated. The dose to maintain normal potassium is 5 g to 10 g once daily, or 5 g once every other day.

The sponsor is requesting reimbursement of SZC for the corrective treatment of hyperkalemia in adults. The sponsor is also requesting reimbursement for the maintenance treatment of hyperkalemia in the following specific patient population: adults with CKD with an estimated eGFR of less than 30 mL/min/1.73 m^2 who have experienced at least two hyperkalemic events and are suboptimally managed on RAASi therapy.

Table 5 provides key characteristics of SZC, as well as those of SPS, CPS, and patiromer, which are other potassium binders approved by Health Canada for the treatment of hyperkalemia.

Table 5: Key Characteristics of SZC and Other Treatments

	SZC	SPS	CPS	Patiromer
Mechanism of action	Cation-exchange resin: microporous zirconium silicate that selectively binds potassium in the intestine (exchange of potassium with sodium and hydrogen ions)	Cation-exchange resin: binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with sodium ions)	Cation-exchange resin: binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with calcium ions)	Cation-exchange polymer: binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with calcium-sorbitol complex)
Indication[a]	Treatment of hyperkalemia in adults	Treatment of hyperkalemia	Treatment of hyperkalemia (anuria or severe oliguria; acute and chronic renal failure; dialysis)	Treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2)
Route of administration	Oral suspension	Oral suspension or enema	Oral suspension or enema	Oral suspension
Recommended dose	Acute/correction phase: 10 g t.i.d. Maintenance phase: 5 g to 10 g once daily or 5 g once every other day	Oral: 15 g one to four times daily Rectal: 30 g to 50 g once or twice daily	Oral: 15 g three to four times daily Rectal: 30 g once daily	Starting dose: 8.4 g once daily to a maximum of 25.2 g once daily
Serious side effects/safety issues	Edema due to sodium content[b] Hypokalemia	Intestinal obstruction or intestinal rupture (diarrhea may need to be induced to prevent these safety issues) Hypokalemia	GI injury (most cases occurred with concomitant use of sorbitol) Hypokalemia	GI symptoms Hypokalemia
Other	Should not be used as an emergency treatment for life-threatening hyperkalemia due to delayed onset of action	Not used for rapid correction of severe hyperkalemia Non-specific binder that binds calcium and magnesium in addition to potassium, which can cause hypocalcemia or hypomagnesemia GI side effects are common Not administered on a chronic basis	Non-specific binder that binds magnesium in addition to potassium, which can cause hypomagnesemia Risk of hypercalcemia due to calcium content	Not used for rapid reduction of potassium due to delayed onset of action (4 hours to 7 hours) Non-specific binder that binds magnesium, which can cause hypomagnesemia Contraindicated in patients with hereditary condition of fructose intolerance (contains sorbitol)

CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

[a] Health Canada indication.

[b] Each 5 g dose contains about 400 mg of sodium.[10]

Source: Product monograph for SZC;[10] product monograph for SPS;[11] product monograph for CPS;[12] product monograph for patiromer.[13]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One joint submission from two patient groups, The Kidney Foundation of Canada and Diabetes Canada, was received for this review. The Kidney Foundation of Canada (www.kidney.ca) is a national volunteer organization committed to eliminating the burden of kidney disease through: funding and stimulating innovative research for better treatments and a cure; providing education and support to prevent kidney disease in those at risk and to empower those with kidney disease to optimize their health status; advocating for improved access to high-quality health care; and increasing public awareness and commitment to advancing kidney health and organ donation. Diabetes Canada (www.diabetes.ca) is a national health charity that represents Canadians living with diabetes or prediabetes. Its mission is to prevent, care for, and cure diabetes through research and policy initiatives. This includes supporting disease management by distributing practical, evidence-based tools to health care providers, advocating for making healthy choices easier, and funding scientific research related to the disease and care of diabetes.

Both patient groups reported having received funding from AstraZeneca Canada Inc. (the manufacturer of SZC), Sanofi Canada, and Boehringer Ingelheim (Canada) Ltd. Horizon Pharma Inc., Janssen Pharmaceutical Companies, and Otsuka Canada Pharmaceutical Inc. have provided funding to The Kidney Foundation of Canada. LifeScan Canada Ltd., Novo Nordisk Canada Inc., and Sun Life Financial have provided funding to Diabetes Canada. Each organization stated that funders had no input or influence on their submission content, and that they received no outside assistance with data collection, analysis, or framing of the results.

2. Condition-Related Information

The Kidney Foundation of Canada and Diabetes Canada collaborated to distribute a self-administered questionnaire targeting people living with CKD or CKD and diabetes and their caregivers. The survey asked about their experience with CKD, medications, and expectations for new drug therapies in Canada. A few questions were specifically about SZC. The survey was open for two weeks in May 2019. It was shared through both organizations' social media channels (Twitter and Facebook) and made available on The Kidney Foundation of Canada's website. A total of seven respondents participated, all of whom identified as being a person living with CKD. The patients were between the ages of 40 and 69. About half (n = 4) had had CKD for more than 20 years. Four reported also living with diabetes.

Kidney disease is a risk factor for hyperkalemia. Kidney disease results from a variety of disorders that can affect the kidneys, most often related to an attack on the nephrons and impaired ability to eliminate waste and excess fluid. Kidney disease is often associated with other medical conditions, such as diabetes (the leading cause of kidney failure in Canada), high blood pressure, and heart disease. This is reflected in the survey results: 57% of patients reported living with diabetes, 85% had high blood pressure, 57% had high cholesterol, and 86% had high potassium levels. Kidney disease is considered CKD when

kidney damage or decreased kidney function has been present for a period of three or more months. It can range from mild to severe, and can eventually progress to kidney failure or end-stage renal disease (ESRD). Unfortunately, specific symptoms of disease are typically not seen until damage is severe. When the kidneys fail, waste accumulates in the body, creating the need for dialysis treatment or a kidney transplant.

Healthy kidneys are normally able to balance the potassium in the body. However, impaired kidney function may result in elevated potassium levels (i.e., hyperkalemia, for which the drug under review is indicated) or potassium levels that are too low (i.e., hypokalemia). Regulating potassium levels is a concern for patients with CKD, particularly for those undergoing dialysis, and can be achieved in part through lifestyle changes. However, patients described these changes as being highly restrictive, to the point of having a negative impact on their quality of life.

The survey respondents generally described living with CKD as a negative experience. Lack of energy and fatigue were reported as major issues that affected their everyday lives, including their ability to go to work or do household chores. One patient said, "I am constantly exhausted daily, cannot walk anywhere without a walker [and am] now scared to go out by myself as I may fall." There were also comments about the inability to exercise due to fatigue or exhaustion. One respondent noted issues with nausea and itchiness. When asked if there are particular challenges living with both CKD and diabetes, a respondent said, "having to adjust both meds (sic) for diabetes and kidney disease…constant pain in feet."

3. Current Therapy-Related Information

According to the patient submission, dietary restrictions constitute one way that patients in the early stages of CKD can manage their potassium levels, but this approach does not work for everyone. Limiting potassium intake is also common for patients being treated with dialysis for CKD. Seventy-two percent of survey respondents reported that they had a dietary restriction, which they described as highly restrictive and having a negative impact on quality of life. Two patients reported having experience taking SPS for hyperkalemia; one still takes this medication. One patient noted that they disliked the texture and taste of the medication for high potassium, and would prefer it in pill form. SZC is currently not available in Canada. As a result, none of the survey respondents had experience with this medication.

The survey included questions about factors that were important to patients when choosing medications to treat CKD. The following were identified as "very important" or "important" by the majority of respondents: fatigue, interference with sleep, edema of the foot, effect on mood, interference with other medications, changes in appetite, cost, and length of time on the medication. One respondent felt indifferent regarding the cost and effect on mood. Patients also cited side effects and drug efficacy as important factors when choosing a new medication for CKD.

Lastly, the patient groups highlighted the financial burden that Canadians living with CKD experience as a result of dialysis treatment, which is associated with high out-of-pocket costs for things like transportation to treatment and medication. Further, it was noted that those living with CKD are often dealing with comorbid conditions, such as diabetes, and that many would benefit from an effective and affordable treatment that could help them achieve better health outcomes and quality of life.

4. Expectations About the Drug Being Reviewed

Survey respondents would like to see therapies for CKD or diabetes that help them feel better and reduce the need for invasive therapies, such as surgery.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team, and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in the diagnosis and management of cardiovascular and kidney disease.

Description of the Current Treatment Paradigm for the Disease

Hyperkalemia is treated by withdrawing drugs that increase potassium, namely RAASi therapies and mineralocorticoid receptor antagonists. The problem with this approach is that patients lose the protection these drugs confer on the cardiovascular and renal systems. Other treatments for chronic hyperkalemia are diuretics (which may have deleterious effects associated with electrolyte disturbance), laxatives, and potassium binders. All approaches include counselling patients about moderating their intake of potassium-containing foods.

Treatment Goals

The goal of treatment is to avoid life-threatening arrhythmias and enable optimal dosing of RAASi therapies.

Unmet Needs

The withdrawal or dose reduction of RAASi therapies compromises the care of patients with cardiovascular or renal disease and leaves them at increased risk of worse clinical outcomes.

Place in Therapy

SZC would be used as an adjunct treatment for patients who require RAASi therapy and have experienced hyperkalemia. Prior to initiating therapy with SZC, clinicians would need to first understand the contributing causes of hyperkalemia and address those factors that are readily modifiable, such as reversible causes of impaired kidney function, diets high in potassium, and RAASi use. SZC may be considered once all reversible causes have been addressed, especially in patients who require continuation of RAASi therapy, but also in other patient populations who remain hyperkalemic.

Patient Population

The patients most in need of SZC are those who experience hyperkalemia while on a RAASi. To identify patients best suited for treatment, laboratory tests to measure serum potassium would be needed, as this is often the only way to detect hyperkalemia. Patients with serum potassium greater than 5.5 mmol/L would be most suitable for treatment.

Assessing Response to Treatment

Response to treatment would be assessed with serial blood testing of serum potassium. Assessments would initially be monthly, then quarterly once potassium levels become stable. Serum potassium is the immediate assessment of treatment response. However, the most clinically relevant outcome would be continued optimal use of RAASi to confer cardiovascular and renal protection. This would also be important to patients because they would have peace of mind knowing that they could continue RAASi therapy without worry of hyperkalemia.

Discontinuing Treatment

If RAASi therapy is withdrawn (e.g., no longer indicated), then therapy with SZC may be discontinued. If dialysis is initiated for kidney failure, then SZC may be discontinued, because dialysis will generally remove potassium. However, there may be cases when patients on dialysis require continued treatment for hyperkalemia.

Prescribing Conditions

Specialists in cardiology, nephrology, endocrinology, or general internal medicine are required to diagnose, treat, and monitor patients with hyperkalemia. Therefore, SZC should be prescribed by specialists in community- or hospital-based clinics.

Clinical Evidence

The clinical evidence included in the review of SZC is presented in three sections. Section 1, Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted, long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of SZC 5 g or 10 g powder for oral suspension for the treatment of hyperkalemia in adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 6.

Table 6: Inclusion Criteria for the Systematic Review

Patient population	Adults with hyperkalemia (serum potassium > 5.0 mmol/L)
	
	Subgroups:
	• baseline serum potassium level (mild hyperkalemia: 5.5 mmol/L to 5.9 mmol/L; moderate hyperkalemia: 6.0 mmol/L to 6.5 mmol/L; severe hyperkalemia: > 6.5 mmol/L)
	• number of previous hyperkalemic events
	• patients on RAASi therapy (i.e., ACEI or ARB) or mineralocorticoid receptor antagonist therapy (i.e., spironolactone)
	• patients with CKD
	  ○ mild eGFR reduction: 60 mL/min/1.73 m^2 to 89 mL/min/1.73 m^2; mild to moderate reduction: 45 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2; moderate to severe reduction: 30 mL/min/1.73 m^2 to 44 mL/min/1.73 m^2; severe reduction: 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2; kidney failure: less than 15 mL/min/1.73 m^2
	  ○ albuminuria as measured with ACR, normal to mildly increased: < 3 mg/mmol; moderately increased: 3 mg/mmol to 0 mg/mmol; severely increased: > 30 mg/mmol
	• patients with heart failure

Intervention	Correction of hyperkalemia • SZC 10 g three times daily for 24 hours to 72 hours Maintenance: • SZC 5 g to 10 g once daily

Comparators	**Pharmacological[a]:**
	• Potassium binders
	  ○ SPS
	  ○ CPS
	  ○ patiromer

	• Diuretics
	  ○ loop (furosemide)
	  ○ thiazides (hydrochlorothiazide)
	• Laxatives (e.g., lactulose)
	
	Stopping or reducing dose of RAASi or mineralocorticoid receptor antagonist therapy
	
	No treatment/placebo

Outcomes	**Efficacy:** • survival or mortality • hospitalization • quality of life[b] • arrhythmia • MACE/MAKE • progression of kidney disease • continuation or need for discontinuation of RAASi/mineralocorticoid receptor antagonist therapy at regular doses • serum potassium • onset of serum potassium reduction • normokalemia (serum potassium 3.5 mmol/L to 5.0 mmol/L) • onset of normokalemia • number of hyperkalemic events • time to requiring emergency or life-threatening hyperkalemia (e.g., renal replacement therapy, intravenous calcium, insulin, sodium bicarbonate) **Harms:** AEs, SAEs, WDAE, hypokalemia (fatigue, muscle weakness, or cramps), edema, gastrointestinal upset (including constipation and bowel obstruction)
Study design	Published and unpublished phase III and IV RCTs

ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin-to-creatinine ratio; AE = adverse event; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event; MAKE = major adverse kidney event; RAASi = renin-angiotensin-aldosterone system inhibitor; RCT = randomized controlled trial; SAE = serious adverse event; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] A low-potassium diet may be implemented in addition to pharmacological treatments.

[b] Outcome identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).[14]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Lokelma and sodium zirconium cyclosilicate. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed June 14, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of CADTH Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters):[15] health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials registries, and databases (free). Google was used to search for additional internet-based materials. In addition, the drug sponsor was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review. Differences were resolved through discussion.

Findings From the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7.

A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

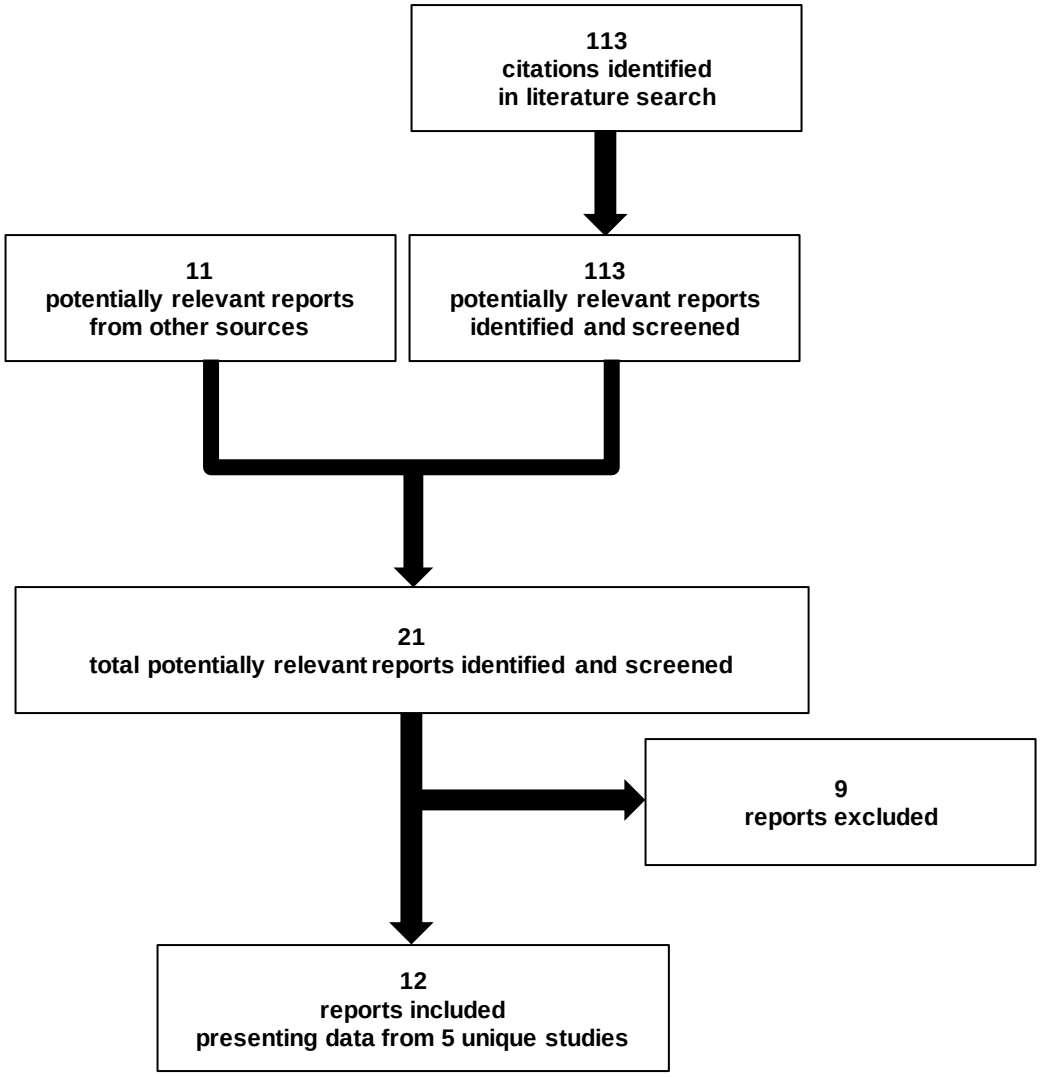


Table 7: Details of Included Studies

		Study ZS-003	Study ZS-004 HARMONIZE	Study ZS-D9480 HARMONIZE Global	Study ZS-D9482	DIALIZE
DESIGNS AND POPULATIONS	**Study design**	Two-phase, DB RCT (acute phase + maintenance phase)	Two-phase, DB RCT (acute phase was open-label; maintenance phase was randomized)	Two-phase, DB RCT (acute phase was open-label; maintenance phase was randomized)	DB RCT (acute phase)	DB RCT (maintenance phase)
	Locations	65 sites in the US, Australia, and South Africa	44 sites in the US, Australia, and South Africa	42 sites in Japan, Russia, South Korea, and Taiwan	24 sites in Japan	54 sites in Japan, Russia, the US, and the UK
	Randomized (N)	754	237 (maintenance phase)[a]	248 (maintenance phase)[b]	103	196
	Inclusion criteria	• > 18 years of age • i-STAT[c] S-K between 5.0 mmol/L and 6.5 mmol/L at screening (mean of 3 i-STAT potassium values) • ability to have repeated blood draws or effective venous catherization	• > 18 years of age • i-STAT S-K ≥ 5.1 mmol/L at screening (2 consecutive i-STAT potassium values, both ≥ 5.1 mmol/L) • ability to have repeated blood draws or effective venous catherization • for entry into maintenance phase, achieved normokalemia after acute phase	• ≥ 18 and ≤ 90 years of age • S-K ≥ 5.1 mmol/L in two consecutive i-STAT tests • ability to have repeated blood draws or effective venous catherization • for entry into maintenance phase, achieved normokalemia after acute phase	• ≥ 18 years of age • S-K levels ≥ 5.1 mmol/L and ≤ 6.5 mmol/L in two consecutive i-STAT tests • ability to have repeated blood draws or effective venous catherization	• ≥ 18 years of age • ESRD managed for ≥ 3 months before randomization by hemodialysis three times weekly • persistent hyperkalemia during the 1-week screening period (pre-dialysis S-K > 5.4 mmol/L after long interdialytic interval and S-K > 5.0 mmol/L after at least one short interdialytic interval)
	Exclusion criteria	• pseudo-hyperkalemia[d] • treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within the last 7 days • treatment with resins (e.g., sevelamer	• pseudo-hyperkalemia[d] • treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within the last 7 days • treatment with resins (e.g., sevelamer acetate, SPS), calcium acetate, calcium carbonate, or	• pseudo-hyperkalemia[d] • treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within the last 7 days • treatment with resins (e.g., sevelamer acetate, SPS), calcium	• pseudo-hyperkalemia[d] • treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within the last 7 days • treatment with resins (e.g., sevelamer acetate, SPS), calcium	• hemoglobin < 9 g/dL • non-compliance with hemodialysis during the 2 weeks prior to screening • treatment with SPS, CPS, or patiromer within 7 days before screening • myocardial infarction, acute coronary syndrome, stroke, seizure, or

		Study ZS-003	Study ZS-004 HARMONIZE	Study ZS-D9480 HARMONIZE Global	Study ZS-D9482	DIALIZE
		acetate, SPS), calcium acetate, calcium carbonate, or lanthanum carbonate within the last 7 days • insulin dose not stabilized • receiving dialysis • life expectancy < 3 months • HIV-positive (except South African sites) • diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant	lanthanum carbonate within the last 7 days • receiving dialysis • life expectancy < 3 months • diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant • randomized to Study ZS-002 or Study ZS-003	acetate, calcium carbonate, or lanthanum carbonate, within the last 7 days • receiving dialysis • life expectancy < 3 months • diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant	acetate, calcium carbonate, or lanthanum carbonate within the last 7 days • receiving dialysis • life expectancy < 3 months • active or history of diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant	thrombotic/thromboembolic event within 12 weeks before randomization • pregnancy or breastfeeding
Drugs	**Intervention**[e]	SZC orally as a suspension in purified water Acute phase (48 hours): 1.25 g, 2.5 g, 5 g, or 10 g t.i.d. Maintenance phase (days 3 to 14): 1.25 g, 5 g, or 10 g q.d.	SZC orally as a suspension in purified water Acute phase: (48 hours): 10 g t.i.d. Maintenance phase (28 days): 5 g, 10 g, or 15 g q.d.	SZC powder for oral suspension Acute phase: (48 hours): 10 g t.i.d. Maintenance phase (28 days): 5 g or 10 g q.d.	SZC powder for oral suspension 5 g or 10 g t.i.d. (48 hours)	SZC powder for oral suspension 5 g q.d. starting dose on non-dialysis days Doses titrated in 5 g increments to maximum of 15 g q.d.
	Comparator(s)	Placebo	Placebo	Placebo	Placebo	Placebo

		Study ZS-003	Study ZS-004 HARMONIZE	Study ZS-D9480 HARMONIZE Global	Study ZS-D9482	DIALIZE
DURATION	**Phase**					
	Run-in	None	None	None	None	None
	Double-blind	Acute phase: 2 days Subacute phase: 12 days	Acute phase: 2 days Maintenance phase: 28 days	Acute phase: 2 days Maintenance phase: 28 days	2 days	8 weeks (4 weeks dose titration and 4 weeks stable dose period)
	Follow-up	7 days	7 days	7 days	7 days	14 days
OUTCOMES	**Primary end point**	Acute phase: exponential rate of change in S-K in the initial 48 hours Maintenance phase: exponential rate of change in S-K over the 12-day treatment period (days 3 to 14)	LSM of all available S-K values during maintenance phase, days 8 to 29	LSM of all available S-K values during maintenance phase, days 8 to 29	Exponential rate of change in S-K during the initial 48 hours of study drug treatment	Proportion who maintained pre-dialysis S-K of 4.0 mmol/L to 5.0 mmol/L (in the stable dose evaluation period) during at least three of four hemodialysis treatments after the long interdialytic interval and who did not require rescue therapy
	Secondary and exploratory end points	Acute phase: • change in S-K at all time points • time to S-K normalization (3.5 mmol/L to 5.0 mmol/L) • time to first decrease in S-K of 0.5 mmol/L • proportion who achieved S-K normalization at the end of 24 hours & 48 hours • harms Maintenance phase:	Acute phase: • exponential rate of change in S-K during the initial 48 hours of study drug treatment • change from baseline in S-K at all measured time intervals post-dose • proportion who achieved normokalemia at 24 hours and 48 hours • time to normalization of S-K (3.5 mmol/L to 5.0 mmol/L) • harms Maintenance phase:	Acute phase: • exponential rate of change in S-K • change from baseline in S-K at all measured time intervals post-dose • proportion who achieved normokalemia at 24 hours and 48 hours • time to normalization of S-K (3.5 mmol/L to 5.0 mmol/L) • EQ-5D • harms Maintenance phase:	• proportion who achieved normokalemia at 48 hours • exponential rate of change in S-K during the initial 24 hours • proportion who achieved normokalemia at 24 hours • proportion who achieved normokalemia at each scheduled assessment after start of dosing • change from baseline in S-K at all measured time intervals post-dose	• proportion requiring any urgent rescue intervention to reduce S-K • pre- and post-dialysis S-K • harms

		Study ZS-003	Study ZS-004 HARMONIZE	Study ZS-D9480 HARMONIZE Global	Study ZS-D9482	DIALIZE
		• time to relapse of S-K (return to S-K baseline value) • total number of days remaining normokalemic (S-K 3.5 mmol/L and 5.0 mmol/L) • proportion who retained normal S-K (3.5 mmol/L and 5.0 mmol/L) at the end of the subacute phase • mean change from baseline in S-K • time to an increase in S-K of 0.5 mmol/L • harms	• number of normokalemic days during days 8 to 29 • change from acute-phase S-K baseline • change from maintenance phase S-K baseline • time to hyperkalemia (S-K ≥ 5.1 mmol/L) • time to relapse in S-K values (return to original acute-phase S-K baseline) • proportion who remained normokalemic at days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29, and 35 • harms	• proportion who remained normokalemic (S-K 3.5 mmol/L to 5.0 mmol/L) during and at end of maintenance phase • number of normokalemic days • change from acute-phase and maintenance-phase baseline S-K • time to hyperkalemia (S-K ≥ 5.1 mmol/L) • EQ-5D-5L • harms	• time to normalization of S-K (3.5 mmol/L to 5.0 mmol/L) • time to a decrease in S-K of 0.5 mmol/L • harms	
NOTES	**Publications**	Packham et al. (2015)[16]	Kosiborod et al. (2014)[17] Anker et al. (2015)[18]	None	None	Fishbane et al. (2019)[19]

CDR = CADTH Common Drug Review; CPS = calcium polystyrene sulfonate; DB = double-blind; EQ-5D = EuroQol 5-Dimensions; EQ-5D-5L = EuroQol 5-Dimensions 5 levels; ESRD = end-stage renal disease; LSM = least squares mean; q.d. = once daily; RCT = randomized controlled trial; S-K = serum potassium; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Note: Two additional reports were included (CDR submission[20] and FDA review[21,22]).

[a] 258 patients were in the open-label acute phase and received SZC 10 g t.i.d. for 48 hours.

[b] 267 patients were in the open-label acute phase and received SZC 10 g t.i.d. for 48 hours.

[c] i-STAT is a handheld analyzer that measures potassium in plasma and provides immediate results.

[d] Pseudo-hyperkalemia may arise from hemolyzed blood specimens due to excessive clenching, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis.

[e] The Health Canada product monograph for SZC indicates a dose of 10 mg three times a day for the acute phase and 5 mg to 10 mg once daily for the maintenance phase. Accordingly, this clinical report does not include data available for 1.25 g, 2.5 g, and 5 g in the acute phase or 15 g in the maintenance phase.

Sources: Clinical Study Report for Study ZS-003;[23,24] Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9480;[26] Clinical Study Report for Study ZS-D9482;[27] Fishbane et al. (2019).[19]

Description of Studies

Five DB, placebo-controlled RCTs met the inclusion criteria for the systematic review: three two-phase studies (Study ZS-003, Study ZS-004, and Study ZS-D9480), one acute-phase study (Study ZS-D9482), and one maintenance-phase study (DIALIZE). In all three two-phase studies, patients were required to achieve normokalemia (a serum potassium level of 3.5 mmol/L to 5.0 mmol/L) upon completion of the acute phase to be eligible to enter the maintenance phase. In all five included studies, patients treated with SPS within the last seven days before screening were excluded. The DIALIZE study was the only one involving patients with end-stage kidney disease on dialysis.

Study ZS-003 (NCT01737697) was a phase III study that consisted of two randomized phases, an acute phase of two days, and a maintenance phase of 12 days in adult patients (> 18 years of age) with mild to moderate hyperkalemia (serum potassium levels of 5.0 mmol/L to 6.5 mmol/L as measured by an i-STAT handheld analyzer) (Figure 2). The primary objective was to evaluate the efficacy and safety of four different doses of SZC in the acute phase. A secondary objective was to evaluate the maintenance phase. The study was conducted from November 25, 2012 to October 29, 2013 in 65 sites in the US, Australia, and South Africa. A total of 1,433 patients were screened, of whom 754 (52.6%) were randomized in a 1:1:1:1:1 ratio to placebo or SZC 1.25 g, 2.5 g, 5 g, or 10 g three times daily for the first 48 hours (days 1 and 2). The 1.25 g and 2.5 g doses are not included in this review as they are not part of Health Canada's approved dosing regimen.[10] Patients who were normokalemic (3.5 mmol/L to 5.0 mmol/L) after 48 hours were randomized in a 1:1 ratio to the same acute-phase dose or to placebo administered once daily for 12 days (days 3 to 14). An end-of-study assessment occurred seven days after the last dose of study drug (day 21 for patients enrolled in the maintenance phase; otherwise, day 9 for patients not enrolled in the maintenance phase).

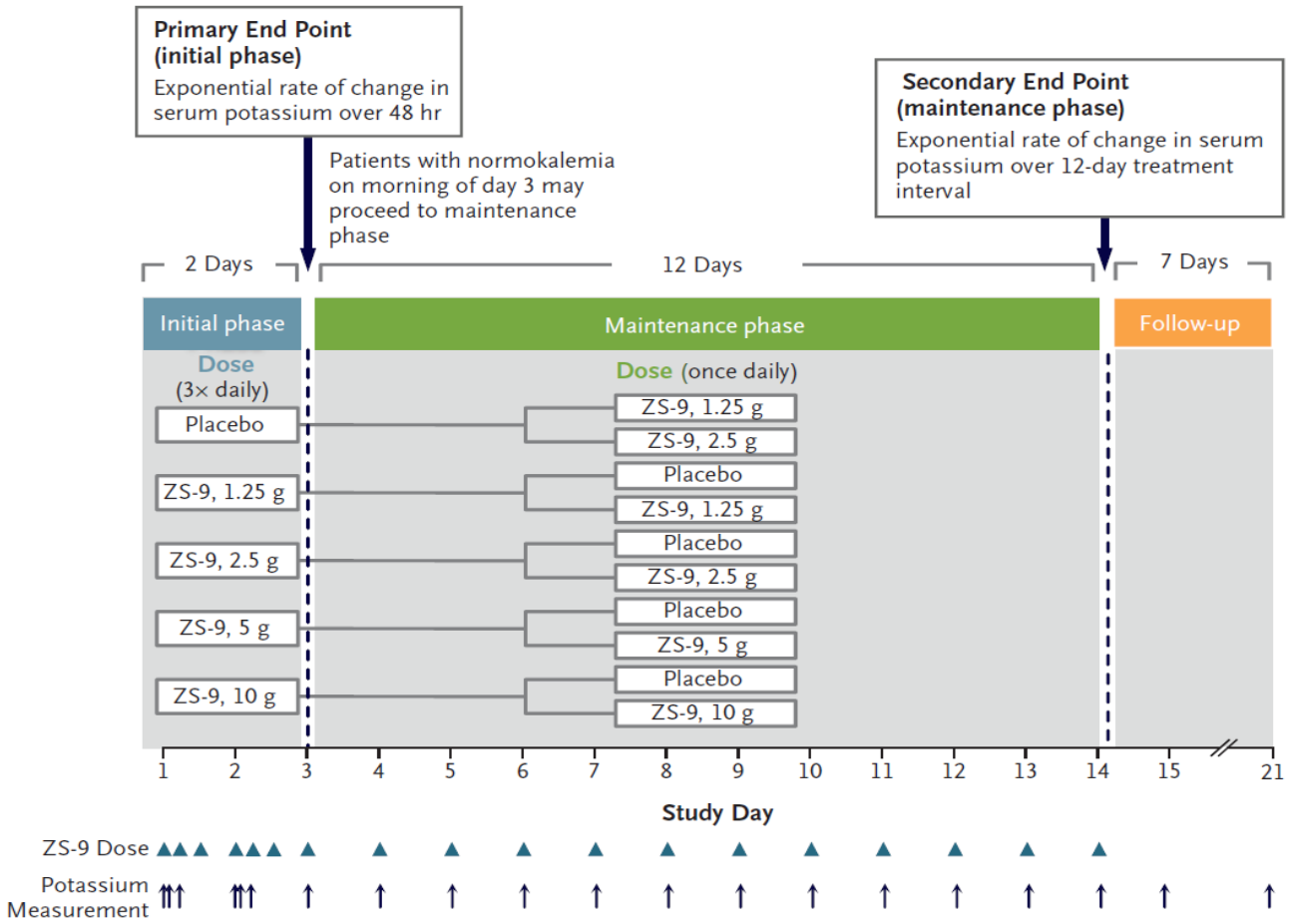
Study ZS-004 (NCT02088073), also known as HARMONIZE, was a phase III study that also consisted of two phases: an open-label acute phase of two days followed by a randomized maintenance phase that lasted 28 days (note: no design figure was available for this study). Adult patients (> 18 years of age) with serum potassium of 5.1 mmol/L or greater at screening were recruited from March 18, 2014 to August 8, 2014. The primary objective was to evaluate the efficacy and safety of three different doses of SZC during the maintenance phase. A secondary objective was to evaluate the acute phase. The study was conducted in 44 sites in the US, Australia, and South Africa. Of 425 patients screened, 258 (60.7%) entered the open-label, 48-hour acute phase and received SZC 10 g three times daily. Patients were eligible to enter the maintenance phase if they achieved normokalemia after 48 hours. A total of 237 patients were randomized in a 7:4:4:4 ratio to placebo, SZC 5 g, SZC 10 g, or SZC 15 g once daily for 28 days. The 15 g dose is not included in this review as it is not approved by Health Canada.[10] Patients who completed the maintenance phase or discontinued due to hypokalemia or hyperkalemia were offered participation in an OLE study (Study ZS-004E) to evaluate the long-term safety and efficacy of SZC. Patients who did not enter Study ZS-004E were followed for seven days after the last dose of study drug for end of study (day 35).

Study ZS-D9480, also known as HARMONIZE Global, was a phase III study conducted in Japan, Russia, South Korea, and Taiwan whose design was similar to that of Study ZS-004 (Figure 3). Adult patients (18 years to 90 years) with two consecutive serum potassium values of 5.1 mmol/L or greater were recruited between March 3, 2017 and February 14, 2018. The primary objective was to evaluate the efficacy of two different doses of SZC during the maintenance phase. Secondary objectives were to evaluate the efficacy of SZC in the acute phase and safety in both the acute and maintenance phases. A total of 472 patients were screened, and 267 (56.6%) entered the acute phase, in which patients were administered SZC 10 g three times daily for 48 hours. If patients achieved normokalemia after the acute phase, they were eligible to enter a 28-day maintenance phase in which they were randomized in a 1:2:2 ratio to placebo, SZC 5 g, or SZC 10 g once daily (N = 248). An end-of-study assessment occurred seven days after the last dose of study drug (day 35).

Study ZS-D9482 was a phase II/III study that was conducted during the acute phase in 103 Japanese patients 18 years or older with two consecutive i-STAT serum potassium values of 5.1 mmol/L to 6.5 mmol/L, inclusive (Figure 4). The study was conducted from June 14, 2017 to February 23, 2018 at 24 sites in Japan. Patients were randomized in a 1:1:1 ratio to placebo, SZC 5 g, or SZC 10 g three times daily for 48 hours. The 5 g dose is not included in this review as it is not approved by Health Canada for the acute phase. Patients were followed for seven days after the last dose (day 9).

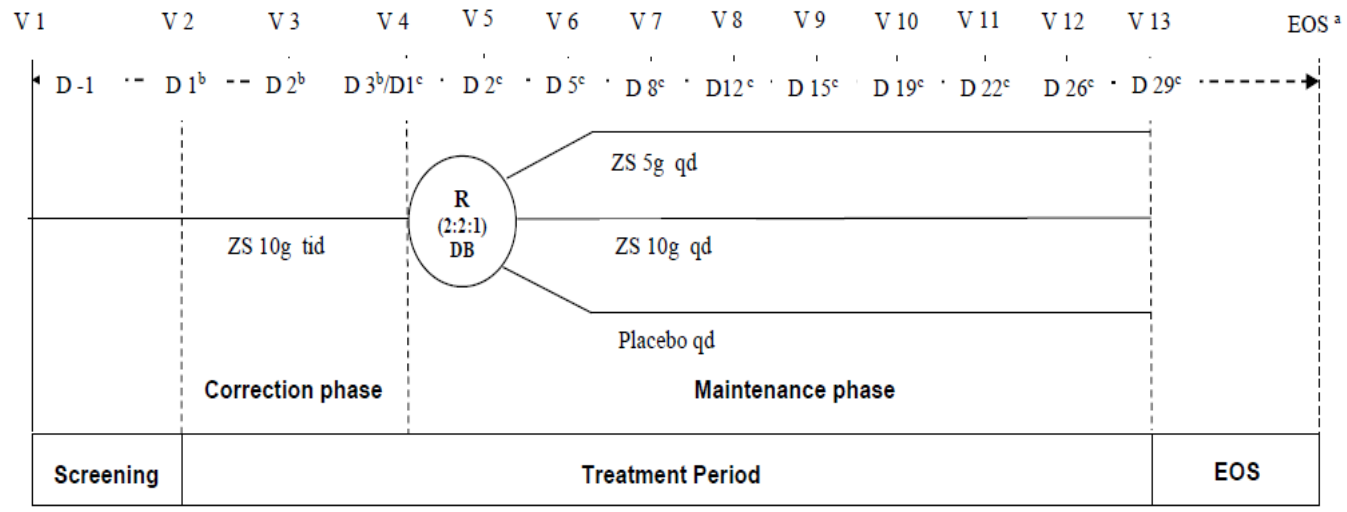
DIALIZE was a phase IIIb study that was conducted from December 14, 2017 to November 7, 2018 in patients with ESRD who were being managed with hemodialysis three times a week. The treatment period was eight weeks, with an initial four-week dose titration period followed by a four-week stable dose period, during which efficacy was evaluated (Figure 5). The study was conducted at 54 sites in the US, the UK, Japan, and Russia. A total of 196 patients were randomized in a 1:1 ratio to placebo or a starting dose of SZC 5 g once daily on non-dialysis days. The dose was titrated in 5 g increments to a maximum of 15 g once daily to maintain normokalemia (i.e., pre-dialysis serum potassium 4.0 mmol/L to 5.0 mmol/L). Patients were followed for two weeks after the last dose of study drug.

Figure 2: Study Design of Study ZS-003



Source: Extracted from N Engl J Med, Packham, D. K. et al., Sodium zirconium cyclosilicate in hyperkalemia, 372:222-231. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[16]

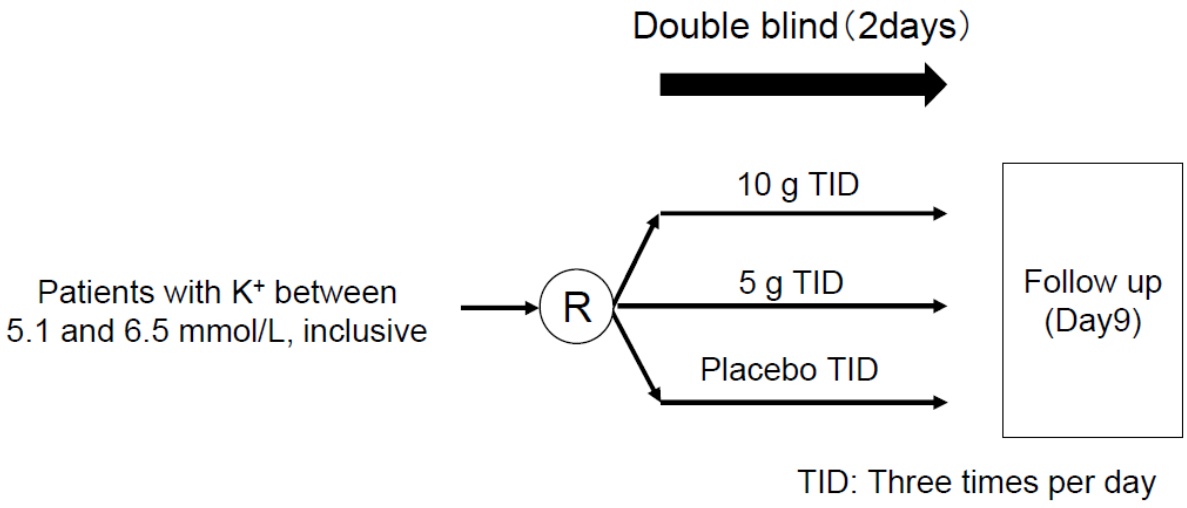
Figure 3: Study Design of Study ZS-D9480



EOS = end of study.

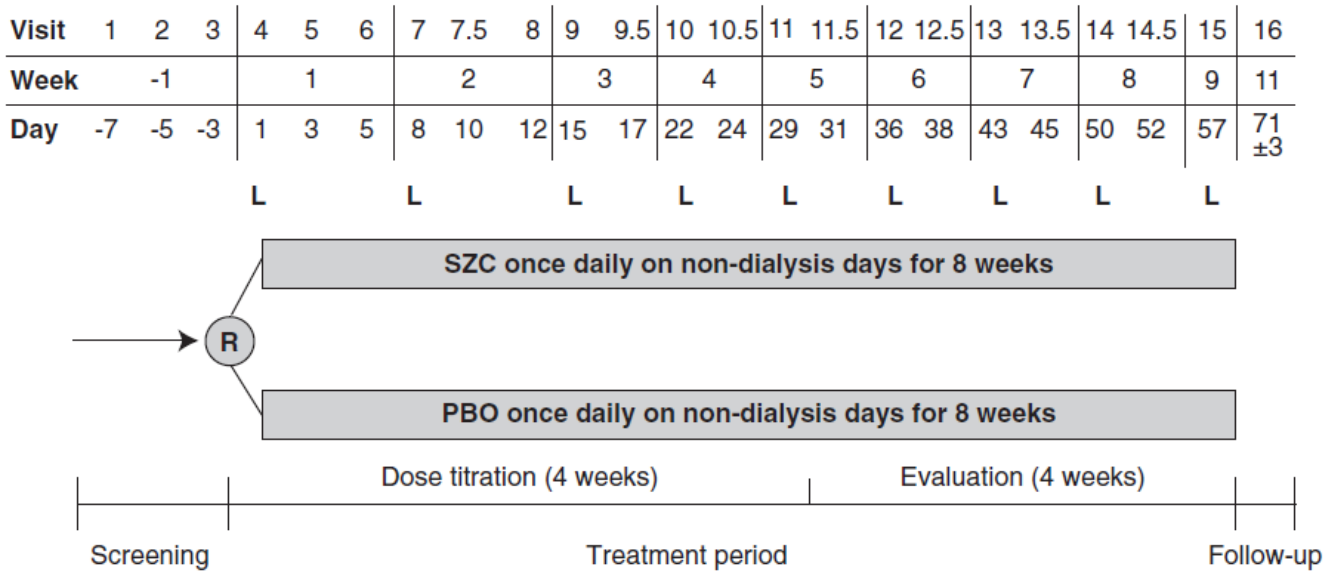
Source: Extracted from Clinical Study Report for Study ZS-D9480.[26]

Figure 4: Study Design of Study ZS-D9482



Source: Extracted from sponsor's confidential information package.[20]

Figure 5: Study Design of DIALIZE



PBO = placebo; SZC = sodium zirconium cyclosilicate.
Source: Republished with permission from the American Society of Nephrology from: A phase IIIb, randomized, double-blind, placebo-controlled study of SZC for reducing the incidence of pre-dialysis hyperkalemia, Fishbane, S. et al., JASN, 30 (6), © 2019; permission conveyed through Copyright Clearance Center, Inc.[19]

Populations

Inclusion and Exclusion Criteria: Two-Phase Studies

Study ZS-003 included adult patients over 18 years of age with mild to moderate hyperkalemia (serum potassium 5.0 mmol/L to 6.5 mmol/L as identified at the site during routine or acute visits) who were treated in an outpatient setting. At screening, potassium was recorded three times at 30-minute intervals by i-STAT. If the mean of the values was between 5.0 mmol/L and 6.5 mmol/L, the patient was randomized into the study. Patients treated with SPS within the last seven days or who were receiving dialysis were excluded. Study ZS-004 included adult patients over 18 years of age with serum potassium of 5.1 mmol/L or higher (an upper limit was not specified) identified during routine or acute visits in an outpatient setting. At screening, potassium was recorded twice at one-hour intervals by i-STAT. If both values were greater than or equal to 5.1 mmol/L, the patient entered the acute phase of the study. Patients who failed the initial screening may have been screened up to two more times during the study. Patients treated with SPS within the last seven days, who were receiving dialysis, or who were included in Study ZS-003 were excluded. Study ZS-D9480 had inclusion and exclusion criteria that were similar to those of Study ZS-004.

Inclusion and Exclusion Criteria: Single-Phase Studies

Study ZS-D9482 recruited adult patients 18 years or older with mild to moderate hyperkalemia (serum potassium 5.1 mmol/L to 6.5 mmol/L). Patients treated with SPS within the last seven days or who were receiving dialysis were excluded. DIALIZE was the only study that included patients on dialysis. Adult patients 18 years or older with ESRD who were managed for at least three months prior to randomization by hemodialysis three times weekly were screened. Patients were required to have persistent hyperkalemia during the one-week screening period, defined as pre-dialysis serum potassium greater than

5.4 mmol/L after the long interdialytic interval and greater than 5.0 mmol/L after at least one short interdialytic interval. Patients treated with SPS, CPS, or patiromer within the last seven days were excluded, as were patients with myocardial infarction, acute coronary syndrome, stroke, or thrombotic/thromboembolic event within the last 12 weeks.

Baseline Characteristics

Acute Phase

Table 8 shows the baseline characteristics of patients in the acute phase (first 48 hours). In all studies, patients were generally older (mean age in the sixties across studies, and slightly higher among the Japanese patients in Study ZS-D9482, who had mean ages in the seventies). The majority of patients were male and white, except in studies ZS-D9480 and ZS-D9482, which included more Asian patients. Baseline serum potassium indicated mild to moderate hyperkalemia; levels were 5.3 mmol/L or less in the majority of patients in ZS-003, less than 6.0 mmol/L in Study ZS-004, and less than 5.5 mmol/L in Study ZS-D9482. The most common causes of hyperkalemia were RAASi use and CKD. In Study ZS-003, RAASi was the cause of hyperkalemia in about 67% of patients. CKD was the cause in 61%, DM in 60%, and congestive heart failure in 40%. In Study ZS-004, RAASi use was again the most common cause of hyperkalemia (70%), followed by DM and CKD (66%) and heart failure (36%). In Study ZS-D9480, CKD was slightly more frequent than RAASi use (about 78% and 77%, respectively), followed by DM (64%) and congestive heart failure (19%). In Study ZS-D9482, RAASi use was present in 78% of patients, CKD in 76%, diabetes in 62%, and heart failure in 14%. Some baseline differences among groups were present (e.g., in Study ZS-003, serum potassium greater than 5.5 mmol/L was 26% in the placebo group versus 15% in the SZC 10 g group; in Study ZS-9482, serum potassium greater than 5.5 mmol/L was 46% in the placebo group versus 33% in the SZC 10 g group).

Table 8: Summary of Acute-Phase Baseline Characteristics

Characteristic	Study ZS-003		Study ZS-004[a]	Study ZS-D9480[a]	Study ZS-D9482	
	Placebo (N = 158)	SZC 10 g (N = 143)	SZC 10 g (N = 258)	SZC 10 g (N = 267)	Placebo (N = 33)	SZC 10 g (N = 36)
Mean age (SD), years	65.6 (12.2)	66.2 (12.2)	64.0 (12.7)	67.8 (10.8)	76.1 (6.8)	71.1 (7.6)
Age range, years	27 to 88	31 to 91	22 to 89	31 to 90	57 to 85	50 to 87
Male, n (%)	98 (62.0)	80 (55.9)	149 (57.8)	171 (64.0)	23 (69.7)	28 (77.8)
Race, n (%)						
White	136 (86.1)	120 (83.9)	215 (83.3)	40 (15.0)	0 (0)	0 (0)
Black	17 (10.8)	19 (13.3)	37 (14.3)	0 (0)	0 (0)	0 (0)
Asian	2 (1.3)	2 (1.4)	5 (1.9)	227 (85.0)	33 (100)	36 (100)
Other	3 (1.9)	2 (1.4)	3 (1.2)	0 (0)	0 (0)	0 (0)
S-K median (range), mmol/L	NR	NR	NR	5.6 (4.5 to 7.4)	5.5 (5.2 to 6.6)	5.4 (5.0 to 6.8)
S-K, n (%)						
≤ 5.3 mmol/L	95 (60.1)	94 (65.7)	NR	NR	NR	NR
< 5.3 mmol/L	NR	NR	NR	NR	6 (18.2)	12 (33.3)
< 5.5 mmol/L	NR	NR	119 (46.1)	NR	NR	NR
5.3 mmol/L to 5.5 mmol/L	NR	NR	NR	NR	12 (36.4)	12 (33.3)

Characteristic	Study ZS-003		Study ZS-004[a]	Study ZS-D9480[a]	Study ZS-D9482	
	Placebo (N = 158)	SZC 10 g (N = 143)	SZC 10 g (N = 258)	SZC 10 g (N = 267)	Placebo (N = 33)	SZC 10 g (N = 36)
5.4 mmol/L to 5.5 mmol/L	22 (13.9)	27 (18.9)	NR	NR	NR	NR
5.5 mmol/L to < 6.0 mmol/L	NR	NR	100 (38.8)	NR	NR	NR
> 5.5 mmol/L	41 (25.9)	22 (15.4)	NR	NR	15 (45.5)	12 (33.3)
≥ 6.0 mmol/L	0 (0)	0 (0)	39 (15.1)	NR	0 (0)	0 (0)
eGFR, n (%)						
< 15 mL/min/1.73m^2	15 (9.5)	10 (7.0)	NR	NR	11 (33.3)	9 (25.0)
15 to 29 mL/min/1.73m^2	44 (27.8)	42 (29.4)	NR	NR	11 (33.3)	13 (36.1)
30 to 59 mL/min/1.73m^2	61 (38.6)	50 (35.0)	NR	NR	11 (33.3)	11 (30.6)
< 60 mL/min/1.73m^2	NR	NR	179 (69.4)	NR	NR	NR
≥ 60 mL/min/1.73m^2	38 (24.1)	41 (28.7)	72 (27.9)	NR	0 (0)	3 (8.3)
Cause of hyperkalemia/ baseline condition, n (%)						
CKD	96 (60.8)	83 (58.0)	169 (65.5)	209 (78.3)	26 (78.8)	26 (72.2)
CHF/HF	66 (41.8)	59 (41.3)	94 (36.4)	50 (18.7)	4 (12.1)	3 (8.3)
DM	96 (60.8)	81 (56.6)	170 (65.9)	172 (64.4)	16 (48.5)	24 (66.7)
RAASi use	101 (63.9)	96 (67.1)	180 (69.8)	205 (76.8)	27 (81.8)	26 (72.2)

CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure; NR = not reported; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] The acute phases of Study ZS-004 and Study ZS-D9480 were open-label with no comparator groups.

Sources: Clinical Study Report for Study ZS-003;[23] Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9482.[27]

Maintenance Phase

Figure 9 and Table 10 provide baseline characteristics of patients in the maintenance phase (beyond 48 hours). Patients were mostly older (mean ages in the sixties) and the majority were male and white, except in Study ZS-D9480, which had mostly Asian patients. Serum potassium levels at the start of the maintenance phase were in the normal range (3.5 mmol/L to 5.0 mmol/L) for the majority of patients. (In studies ZS-003, ZS-004, and ZS-D9480, patients were required to achieve normokalemia after acute-phase treatment to enter the maintenance phase). At the acute-phase baseline, a small percentage of patients had an eGFR of less than15 mL/min/1.73m^2 (4.4% to 9.8%). Larger proportions of patients had an eGFR of 15 to 29 mL/min/1.73m^2 (27.9% to 34.9%) or 30 to 59 mL/min/1.73m^2 (32.8% to 47.1%). In DIALIZE, more patients in the placebo group had a medical history of cardiac disorders (61.6% versus 46.4%).

Table 9: Summary of Maintenance-Phase Baseline Characteristics (Studies ZS-003 and ZS-004)

Characteristic	Study ZS-003				Study ZS-004		
Acute phase	**SZC 5 g**		**SZC 10 g**		**SZC 10 g**		
Maintenance phase	**Placebo (N = 68)**	**SZC 5 g (N = 64)**	**Placebo (N = 61)**	**SZC 10 g (N = 63)**	**Placebo (N = 85)**	**SZC 5 g (N = 45)**	**SZC 10 g (N = 51)**
Mean age (SD), years	65.0 (12.6)	64.6 (11.3)	66.8 (12.5)	65.5 (12.2)	64.3 (12.1)	61.5 (16.9)	63.8 (10.0)
Age range, years	24 to 89	35 to 86	33 to 88	31 to 91	23 to 87	22 to 89	44 to 85
Male, n (%)	46 (67.6)	32 (50.0)	35 (57.4)	35 (55.6)	44 (51.8)	27 (60.0)	27 (52.9)
Race, n (%)							
White	54 (79.4)	56 (87.5)	48 (78.7)	55 (87.3)	73 (85.9)	36 (80.0)	44 (86.3)
Black	10 (14.7)	7 (10.9)	9 (14.8)	8 (12.7)	10 (11.8)	8 (17.8)	5 (9.8)
Asian	2 (2.9)	1 (1.6)	2 (3.3)	0 (0)	3 (3.5)	0 (0)	1 (2.0)
Other	2 (3.0)	0 (0)	2 (3.2)	0 (0)	1 (1.2)	1 (2.2)	1 (2.0)
S-K at AP baseline, n (%)							
≤ 5.3 mmol/L	38 (55.9)	42 (65.6)	41 (67.2)	39 (61.9)	NR	NR	NR
< 5.5 mmol/L	NR	NR	NR	NR	43 (50.6)	23 (51.1)	19 (37.3)
5.4 mmol/L to 5.5 mmol/L	17 (25.0)	14 (21.9)	13 (21.3)	12 (19.0)	NR	NR	NR
5.5 mmol/L to < 6.0 mmol/L	NR	NR	NR	NR	30 (35.3)	17 (37.8)	23 (45.1)
> 5.5 mmol/L	13 (19.1)	8 (12.5)	7 (11.5)	12 (19.0)	NR	NR	NR
≥ 6.0 mmol/L	0 (0)	0 (0)	0 (0)	0 (0)	12 (14.1)	5 (11.1)	9 (17.6)
S-K at MP baseline, n (%)							
≤ 5.3 mmol/L	64 (94.1)	62 (96.9)	61 (100)	62 (98.4)	NR	NR	NR
5.4 mmol/L to 5.5 mmol/L	3 (4.4)	1 (1.6)	0 (0)	0 (0)	NR	NR	NR
> 5.5 mmol/L	1 (1.5)	1 (1.6)	0 (0)	1 (1.6)	NR	NR	NR
Patients who were normokalemic, n (%)	55 (80.9)	57 (89.1)	59 (96.7)	57 (90.5)	NR	NR	NR
eGFR at AP baseline, n (%)							
< 15 mL/min/1.73m^2	3 (4.4)	5 (7.8)	6 (9.8)	3 (4.8)	NR	NR	NR
15 to 29 mL/min/1.73m^2	19 (27.9)	20 (31.3)	18 (29.5)	22 (34.9)	NR	NR	NR
30 mL/min to 59 mL/min/1.73m^2	32 (47.1)	21 (32.8)	21 (34.4)	23 (36.5)	NR	NR	NR
< 60 mL/min/1.73m^2	NR	NR	NR	NR	52 (61.2)	31 (68.9)	38 (74.5)
≥ 60 mL/min/1.73m^2	13 (19.1)	17 (26.6)	16 (26.2)	15 (23.8)	28 (32.9)	12 (26.7)	13 (25.5)
eGFR at MP baseline, n (%)							
< 15 mL/min/1.73m^2	2 (2.9)	5 (7.8)	5 (8.2)	3 (4.8)	NR	NR	NR

Characteristic	Study ZS-003				Study ZS-004		
Acute phase	**SZC 5 g**		**SZC 10 g**		**SZC 10 g**		
Maintenance phase	**Placebo (N = 68)**	**SZC 5 g (N = 64)**	**Placebo (N = 61)**	**SZC 10 g (N = 63)**	**Placebo (N = 85)**	**SZC 5 g (N = 45)**	**SZC 10 g (N = 51)**
15 to 29 mL/min/1.73m^2	19 (27.9)	18 (28.1)	17 (27.9)	23 (36.5)	NR	NR	NR
30 mL/min to 59 mL/min/1.73m^2	29 (42.6)	20 (31.3)	24 (39.3)	20 (31.7)	NR	NR	NR
≥ 60 mL/min/1.73m^2	17 (25.0)	19 (29.7)	15 (24.6)	17 (27.0)	NR	NR	NR
Cause of hyperkalemia, n (%)							
CKD	42 (61.8)	37 (57.8)	36 (59.0)	37 (58.7)	50 (58.8)	29 (64.4)	36 (70.6)
CHF/HF	28 (41.2)	26 (40.6)	23 (37.7)	26 (41.3)	26 (30.6)	18 (40.0)	18 (35.3)
DM	48 (70.6)	36 (56.3)	37 (60.7)	36 (57.1)	54 (63.5)	26 (57.8)	38 (74.5)
RAASi use	45 (66.2)	38 (59.4)	40 (65.6)	43 (68.3)	61 (71.8)	33 (73.3)	36 (70.6)

AP = acute phase; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure; MP = maintenance phase; NR = not reported; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Sources: Clinical Study Report for Study ZS-003;[23] Clinical Study Report for Study ZS-004.[25]

Table 10: Summary of Maintenance-Phase Baseline Characteristics (Studies ZS-D9480 and DIALIZE)

Characteristic	Study ZS-D9480			DIALIZE	
Acute phase	**SZC 10 g**			**None**	
Maintenance phase	**Placebo (N = 50)**	**SZC 5 g (N = 99)**	**SZC 10 g (N = 99)**	**Placebo (N = 99)**	**SZC 5 g to 15 g (N = 97)**
Mean age (SD), years	69.4 (10.3)	66.7 (11.4)	68.0 (10.2)	60.4 (13.2)	55.7 (13.8)
Age range, years	46 to 88	31 to 90	36 to 86	NR	NR
Male, n (%)	36 (72.0)	63 (63.6)	61 (61.6)	58 (58.6)	57 (58.8)
Race, n (%)					
White	7 (14.0)	12 (12.1)	13 (13.1)	52 (52.5)	50 (51.5)
Black	NR	NR	NR	8 (8.1)	11 (11.3)
Asian	43 (86.0)	87 (87.9)	86 (86.9)	33 (33.3)	33 (34.0)
Other	NR	NR	NR	6 (6.0)	3 (3.1)
S-K median (range) at AP baseline, mmol/L	5.7 (4.5 to 6.9)	5.6 (4.6 to 7.2)	5.6 (4.8 to 6.90)	NA	NA
S-K median (range) at MP baseline, mmol/L	4.5 (3.4 to 5.2)	4.4 (3.5 to 5.3)	4.4 (3.6 to 5.8)	NA	NA
Pre-dialysis S-K, mean (SD), mmol/L	NA	NA	NA	5.9 (0.6)	5.8 (0.6)
Post-dialysis S-K, mean (SD), mmol/L	NA	NA	NA	3.9 (0.6)	3.8 (0.6)
Cause of hyperkalemia, n (%)					
CKD	35 (70.0)	82 (82.8)	82 (82.8)	99 (100)	97 (100)
HF	8 (16.0)	18 (18.2)	19 (19.2)	NR[a]	NR[a]

Characteristic	Study ZS-D9480			DIALIZE	
Acute phase	SZC 10 g			None	
Maintenance phase	Placebo (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)	Placebo (N = 99)	SZC 5 g to 15 g (N = 97)
DM	29 (58.0)	67 (67.7)	66 (66.7)	NR	NR
RAASi use	41 (82.0)	76 (76.8)	78 (78.8)	NR	NR

AP = acute phase; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; MP = maintenance phase; NA = not applicable; NR = not reported; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] Cardiac disorders were present in 61.6% of placebo group and 46.4% of the SZC group.

Source: Clinical Study Report for Study ZS-D9480;[26] Fishbane et al. (2019).[19]

Interventions

SZC was administered orally as a suspension in all studies. The following describes study doses of SZC that are Health Canada–approved for the treatment of hyperkalemia in the acute (i.e., 10 g three times daily) and maintenance (i.e., 5 g to 10 g once daily) phases.

Two-Phase Studies

In Study ZS-003, SZC was administered in the acute phase at 10 g three times daily for two days and in the maintenance phase as 5 g or 10 g once daily for 12 days. In the acute phase, patients took doses with meals, except for the first dose, which was taken about 90 minutes prior to breakfast. The first two doses on days 1 and 2 were administered at the site; the third dose was taken at home. In the maintenance phase, patients took the dose in the morning with breakfast at the site on days 3 to 6 and day 9, and at home on days 7 to 8 and days 10 to 14. For doses taken at site, staff added about 180 mL purified water to the study drug bottle and shook for at least 30 seconds to form a suspension immediately prior to ingestion. The bottle was then sequentially rinsed twice with about 30 mL purified water and each rinse was consumed by the patient. For doses taken at home, staff instructed patients on the preparation procedure and provided patients with bottles that contained about 240 mL of water. SZC was provided as a free-flowing, odourless, tasteless, white crystalline powder. The placebo in the acute and maintenance phases was a matching oral powder with the same appearance, taste, odour, and mode of administration.

In studies ZS-004 and ZS-D9480, SZC was administered as open-label for the first two days at a dose of 10 g three times daily. In Study ZS-004, the first dose on each acute-phase day was administered at the site about one hour before breakfast, and the second and third doses were taken at home just before lunch and dinner. Patients who entered the DB randomized maintenance phase received SZC 5 g or 10 g, or matching placebo, once daily in the morning just before breakfast at the site or at home, based on pre-specified days. The study drug was provided in sachets (two sachets in the acute phase and three in the maintenance phase, packaged in single-use boxes). For doses administered at the site, staff emptied the required number of sachets into a standardized dosing vessel, filled the vessel with water to the calibration line (about 180 mL), and shook the bottle for at least 30 seconds to form a suspension immediately prior to ingestion. The bottle was then sequentially rinsed with about 30 mL water and each rinse was consumed by the patient. For doses taken at home, staff instructed patients on the preparation procedure. If the i-STAT potassium value was between 3.0 mmol/L and 3.4 mmol/L, inclusive, in the maintenance phase, then dosing of the study drug was reduced from once daily to once every other day for the remainder of the study. In Study ZS-D9480, the acute phase day 1 and day 2 first doses were administered before breakfast, and the second and third doses

of each day could be administered with or without food. During the maintenance phase of Study ZS-D9480, patients were randomized to SZC 5 g or 10 g or a matching placebo. The study drug was taken once daily in the morning with or without food. If the i-STAT serum potassium level was 3.0 mmol/L to 3.4 mmol/L, inclusive, at any time during the maintenance phase — and was confirmed with a second measurement taken 10 minutes later — then the frequency of the study drug was reduced from once daily to once every other day.

Single-Phase Studies

In Study ZS-D9482, patients received SZC 10 g or placebo as an oral suspension in water three times daily for 48 hours in the acute phase.

In DIALIZE, patients received SZC or placebo in 5 g sachets at a starting dose of 5 g and titrated up to 15 g once daily over four weeks, followed by a four-week stabilization period. Treatment was provided as a powder for oral suspension; each sachet was suspended in 45 mL water by the patient. The placebo in DIALIZE was not described. Dose adjustments were based on i-STAT pre-dialysis serum potassium levels. The first four weeks of treatment constituted a dose adjustment phase in which doses of placebo or SZC were changed once weekly if the pre-dialysis serum potassium was greater than 5.0 mmol/L after the long interdialytic interval.

Concomitant Medications or Co-Interventions Permitted

No dietary interventions or restrictions were imposed for any treatment group in either the acute or maintenance phases of studies ZS-003, ZS-004, ZS-D9480, or ZS-D9482. In DIALIZE, one of the inclusion criteria was that patients receive dietary counselling for ESRD treated with hemodialysis, as per local guidelines, including restriction in dietary potassium.

In Study ZS-003, patients continued the treatments that they were on upon admission into the study. Medications taken 30 days prior to study entry until the end-of-study visit (i.e., seven days after the last dose of study drug) were recorded. Similarly, in Study ZS-004, patients continued with treatments they were taking prior to admission into the study. Medications taken 30 days prior to study entry until day 29 of the maintenance phase for patients entering the extension phase — or at the end-of-study visit (i.e., seven days after the last dose of study drug) for patients not entering the extension — were recorded. In Study ZS-D9480, concomitant medications were allowed, although changes in RAASi or diuretic therapies were not permitted. In Study ZS-D9482, concomitant medications were allowed, and medications taken seven days prior to study entry until the end-of-study visit (i.e., seven days after the last dose of study drug) were recorded.

Table 11 and Table 12 show the percentages of patients who were using selected medications that can affect serum potassium. The majority of patients were on a RAASi. In Study ZS-003 (not shown in tables), a RAASi was used by about 64% of patients on placebo, 67% of patients on SZC 10 g, and 62% of patients on SZC 5 g. A large percentage were also on beta-blockers or diuretics — particularly furosemide, a loop diuretic. Insulin use varied among the studies. Few patients were taking anti-inflammatory drugs, tacrolimus, or cyclosporin.

Table 11: Selected Concomitant Medication Use That May Affect Potassium Levels (Study ZS-D9482)

Medication	Study ZS-D9482	
Acute phase	**Placebo (N = 33)**	**SZC 10 g (N = 36)**
RAASi, n (%)	30 (90.9)	28 (77.8)
Diuretic, n (%)		
Furosemide	6 (18.2)	6 (16.7)
Indapamide	NR	NR
Hydrochlorothiazide	NR	NR
Spironolactone	1 (3.0)	0 (0)
Eplerenone	1 (3.0)	0 (0)
Insulin, n (%)		
Long- or intermediate-acting	2 (6.1)	5 (13.9)
Rapid-acting	1 (3.0)	6 (16.7)
Mixed	1 (3.0)	2 (5.6)
Beta-blocker (oral), n (%)	9 (27.3)	10 (27.8)
Anti-inflammatory (oral), n (%)	0	1
Tacrolimus, n (%)	NR	NR
Cyclosporin, n (%)	0 (0)	1 (2.8)

NR = not reported; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Source: Clinical Study Report for ZS-D9482.[27]

Table 12: Selected Concomitant Medication Use That May Affect Potassium Levels (Studies ZS-004 and ZS-D9480)

Medication	Study ZS-004			Study ZS-D9480		
Acute phase	**SZC 10 g**			**SZC 10 g**		
Maintenance phase	**Placebo (N = 85)**	**SZC 5 g (N=45)**	**SZC 10 g (N = 51)**	**Placebo (N = 50)**	**SZC 5 g (N = 99)**	**SZC 10 g (N = 99)**
RAASi, n (%)	60 (70.6)	30 (66.7)	35 (68.6)	41 (82.0)	77 (77.8)	79 (79.8)
Diuretic, n (%)	35 (41.2)	21 (46.7)	18 (35.3)	NR	NR	NR
Furosemide	23 (27.1)	11 (24.4)	12 (23.5)	10 (20.0)	22 (22.2)	21 (21.2)
Indapamide	1 (1.2)	0 (0)	0 (0)	1 (2.0)	0 (0)	2 (2.0)
Hydrochlorothiazide	4 (4.7)	7 (15.6)	3 (5.9)	0 (0)	2 (2.0)	4 (4.0)
Spironolactone	4 (4.7)	2 (4.4)	3 (5.9)	1 (2.0)	6 (6.1)	2 (2.0)
Eplerenone	NR	NR	NR	0 (0)	3 (3.0)	1 (1.0)
Insulin, n (%)						
Long- or intermediate-acting	19 (22.4)	8 (17.8)	10 (19.6)	8 (16.0)	13 (13.1)	7 (7.1)
Rapid-acting	14 (16.5)	11 (24.4)	7 (13.7)	4 (8.0)	9 (9.1)	6 (6.1)
Mixed	2 (2.4)	0 (0)	2 (3.9)	2 (4.0)	5 (5.1)	5 (5.1)
Other[a]	4 (4.7)	3 (6.7)	8 (15.7)	NA	NA	NA
Beta-blocker (oral), n (%)	37 (43.5)	22 (48.9)	26 (51.0)	20 (40.0)	36 (36.4)	39 (39.4)
Anti-inflammatory or antirheumatic (oral), n (%)	4 (4.7)	3 (6.7)	2 (3.9)	2 (4.0)	3 (3.0)	2 (2.0)

Medication	Study ZS-004			Study ZS-D9480		
Acute phase	SZC 10 g			SZC 10 g		
Maintenance phase	Placebo (N = 85)	SZC 5 g (N=45)	SZC 10 g (N = 51)	Placebo (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)
Tacrolimus, n (%)	1 (1.2)	0 (0)	1 (2.0)	0 (0)	1 (1.0)	0 (0)
Cyclosporin, n (%)	0 (0)	1 (2.2)	0 (0)	1 (2.0)	2 (2.0)	0 (0)

NA = not applicable; NR = not reported; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

[a] Other insulins include human mixtard, human insulin, porcine insulin, and insulin.

Source: Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9480.[26]

Rescue Medication

Patients who required emergency treatment for hyperkalemia (i.e., IV calcium, insulin, glucose, beta-agonists, or dialysis) would have been discontinued from the study drug. In DIALIZE, the need for urgent rescue therapy was one of the outcomes, and it was defined as therapies needed to reduce serum potassium levels due to severe hyperkalemia (serum potassium > 6.0 mmol/L). Rescue therapies included SPS, CPS, patiromer, beta-agonists, sodium bicarbonate, insulin or glucose, or additional dialysis initiated to reduce potassium.

Stopping Criteria

In Study ZS-003, patients with an i-STAT potassium level greater than 6.5 mmol/L on day 1 (four hours after the first dose) were withdrawn from the study and received standard of care. Patients with potassium levels from 6.1 mmol/L to 6.5 mmol/L four hours after the first dose remained at the site for 90 minutes after the second dose; if potassium was greater than or equal to 6.2 mmol/L at this point, the patient was withdrawn. On day 2, patients with a potassium level greater than or equal to 6.2 mmol/L prior to dosing or four hours after the first dose of the second day were withdrawn from the study. During the acute phase, if a patient's potassium was 3.0 mmol/L to 3.4 mmol/L, they skipped the next dose. The following were other rules for withdrawal from the study: potassium greater than 7.0 mmol/L or less than 3.0 mmol/L; potassium less than 3.4 mmol/L during the maintenance phase; serious cardiac arrhythmia (i.e., ventricular tachycardia, ventricular fibrillation, new atrial fibrillation or flutter, new paroxysmal supraventricular tachycardia other than sinus tachycardia, second- or third-degree atrioventricular block, or significant bradycardia, defined as heart rate less than 40 beats per minute); acute congestive heart failure; or significant increase in PR interval (> 0.25 seconds), widening of QRS complex (> 0.14 seconds), or peaked T-wave.

Study ZS-004: Patients with i-STAT potassium greater than 6.2 mmol/L on day 1, 90 minutes after the first dose of study drug were withdrawn. Patients with potassium not within the normal range of 3.5 mmol/L to 5.0 mmol/L by the morning of day 3 were not eligible for randomization in the maintenance phase and were withdrawn. Patients with potassium levels less than 3.0 mmol/L at any time, or greater than 6.2 mmol/L during the maintenance phase, were withdrawn. Other criteria for withdrawal were: serious cardiac arrhythmia (as described in Study ZS-003); acute heart failure; significant increase in PR interval (0.25 seconds), widening of QRS complex (0.14 seconds), peaked T-wave, or increase in heart rate–corrected QT interval.

In Study ZS-D9480, patients with i-STAT potassium levels less than 3.0 mmol/L at any time, or greater than 6.2 mmol/L during the maintenance phase, were discontinued from treatment. Patients were not allowed to titrate, discontinue, switch, or start new therapy with

a RAASi or diuretic during the study. If changes to RAASi or diuretic therapy were indicated, then patients were required to discontinue the study drug. Patients were also discontinued for any of the following reasons: start of dialysis; clinically significant cardiac arrhythmia (as described in Study ZS-003); acute heart failure; significant increase in PR interval (> 0.25 seconds); widening of the QRS complex (> 0.14 seconds); peaked T-wave; or increase in heart rate–corrected QT interval (absolute > 0.55 seconds or increase of > 0.06 seconds from baseline to more than 0.5 seconds).

In Study ZS-D9482, patients with i-STAT potassium levels greater than 6.5 mmol/L were withdrawn from the study. If potassium was between 3.0 mmol/L and 3.4 mmol/L at any point on day 1 or day 2, additional doses of the study drug were withheld for that day and the patient was asked to return the next day for re-evaluation. Patients also discontinued the study drug if they developed significant cardiac arrhythmias (as described in Study ZS-003) or acute heart failure, or if they showed an increase in PR interval (0.25 seconds); a widening of QRS complex (0.14 seconds); a peaked T-wave with evaluation of potassium level; or an increase in heart rate–corrected QT interval (absolute > 0.55 seconds or increase of > 0.06 seconds from baseline to more than 0.5 seconds).

In the DIALIZE study, stopping rules were not provided.

Outcomes

In Study ZS-003, the primary outcomes were the exponential rate of change in serum potassium levels in the initial 48 hours of the acute phase and over the 12 days of the maintenance phase. (Note: these primary outcomes were based on FDA recommendations, which differed from those of the European Medicines Agency's Committee for Human Medicinal Products. The committee's recommendations used the percentage of patients achieving normokalemia as the primary outcome in the acute phase and the cumulative number of days remaining normokalemic for the maintenance phase). Other outcomes for the acute phase were: change in serum potassium, time to normalization (3.5 mmol/L to 5.0 mmol/L), time to first potassium decrease of 0.5 mmol/L, proportion of patients who achieved potassium normalization at the end of 24 hours and 48 hours, and harms. Other outcomes for the maintenance phase were time to relapse (i.e., return to potassium baseline value), number of days remaining normokalemic, proportion of patients who retained normal potassium levels at the end of the subacute phase, change in potassium from baseline, time to potassium increase of 0.5 mmol/L, and harms. Potassium levels were analyzed by both a handheld analyzer that provided results in minutes (i-STAT) and by a central laboratory. Patient eligibility and treatment decisions were based on i-STAT values, while statistical analyses were based on central laboratory values. At screening, the mean of three potassium values was taken to determine patient eligibility (5.0 mmol/L to 6.5 mmol/L). Subsequently, potassium was measured on day 1 (0 hours, 1 hour, 2 hours, and 4 hours after dose 1 and 1.5 hours after dose 2), day 2 (0 hours, 1 hour, and 4 hours after dose 1), and day 3 (0 hours and 4 hours after dose 1), and once on days 4 to 6, 9, 15, and 21. Efficacy and harms were analyzed separately for the acute and maintenance phases. Harms were recorded from the first dose of study drug to the end-of-study visit.

The primary outcome in Study ZS-004 was the least squares mean (LSM) of all available serum potassium values during the maintenance phase (days 8 to 29). Other outcomes for the acute phase were the exponential rate of change in serum potassium in the initial 48 hours of treatment, change in potassium from baseline, proportion of patients who achieved normokalemia at 24 hours and 48 hours, time to potassium normalization, and harms. Other outcomes for the maintenance phase were number of normokalemic days, change in

potassium from baseline, time to hyperkalemia (potassium ≥ 5.1 mmol/L), time to relapse (i.e., return to potassium baseline value), proportion of patients who remained normokalemic, and harms. Serum potassium was analyzed by i-STAT and central laboratory, with eligibility and treatment decision based on i-STAT values and statistical analyses based on central laboratory values. At screening, two consecutive i-STAT potassium values taken 60 minutes apart needed to be greater than or equal to 5.1 mmol/L for a patient to be eligible for entry. Potassium was measured on acute-phase day 1 (1 hour, 2 hours, and 4 hours after dose 1), day 2 (0 hours and one hour after dose 1), and day 3, followed by maintenance-phase days 2, 5, 8, 12, 15, 19, 22, 26, and 29. Health care utilization, including physician, hospital, and emergency room visits, was also monitored in this study.

The primary and secondary outcomes in Study ZS-D9480 were similar to those of Study ZS-004. Study ZS-D9480 additionally evaluated health-related quality of life (HRQoL) with the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) instrument at day 1 of the acute phase and at end of the maintenance phase. The EuroQol 5-Dimensions (EQ-5D) instrument is a generic, self-reported quality of life instrument that is applicable to a wide range of health conditions and treatments. The tool consists of a descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The EQ-5D-5L has been validated for feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from six countries with chronic conditions;[28] however, evidence of validity in patients with hyperkalemia was not identified. A Canadian-specific estimate of a minimum important difference for the EQ-5D-5L was a mean of 0.056.[29]

In Study ZS-D9482, the primary outcome was the exponential rate of change in serum potassium during 48 hours of treatment. Secondary outcomes were the exponential rate of change in potassium during the first 24 hours, the proportion of patients who achieved normokalemia at 24 hours and 48 hours, change in potassium from baseline, time to normalization of potassium, time to potassium decrease of 0.5 mmol/L, and harms. Patients were assessed at days 1, 2, and 3, and at an end-of-study visit seven days after the last dose of study drug. Serum potassium levels were measured using both the i-STAT and central laboratory, with treatment decisions based on i-STAT values and statistical analyses based on central laboratory values.

The primary outcome in DIALIZE was the proportion of patients who maintained a pre-dialysis serum potassium level of 4.0 mmol/L to 5.0 mmol/L during at least three of four hemodialysis treatments after the long interdialytic interval and who did not require rescue therapy. Secondary outcomes were the proportion of patients who required any urgent rescue intervention to reduce potassium, pre- and post-dialysis potassium levels, and harms. Rescue therapy was defined as any urgent intervention that was needed to reduce serum potassium due to severe hyperkalemia (i.e., potassium > 6.0 mmol/L) and included SPS, CPS, patiromer, beta-adrenergic agonists, sodium bicarbonate, insulin or glucose, or additional dialysis. As with the other studies, potassium was measured using both the i-STAT and central laboratory. Adverse events were recorded from the time of randomization and SAEs from the time of informed consent.

Statistical Analysis

Power Calculation

Study ZS-003: Separate sample sizes were calculated for the acute and maintenance phases. For the exponential rate of potassium change in the acute phase, the sample size

was based on a random slopes model and parameters from data obtained in Study ZS-002. Using the parameters in the model, there was 90% power to detect a difference in slopes of 0.0183 per day. For the maintenance phase, 100 of 150 patients treated in the acute phase in each dosage group were estimated to achieve normokalemia and be eligible for extended dosing. Using the parameters from the random slopes model, there was 90% power to detect a difference in slopes of 0.0205 per day.

Study ZS-004: Sample size was calculated based on serum potassium during maintenance-phase days 8 to 29. A sample of 232 patients in the maintenance phase (85 in the placebo group and 49 in each active dose group) had 90% power and 5% type I error to detect a mean difference of 0.3 mmol/L between any active dose comparator with placebo, with a two-sided hypothesis test and a sequential closed testing procedure. This sample size also had 90% power and 5% type I error to detect a four-day increase in normokalemic days between any active dose and placebo.

Study ZS-D9480: Sample size was calculated based on LSM serum potassium during maintenance-phase days 8 to 29. It was estimated that 255 patients (51 in the placebo group and 102 in each active treatment group) would provide more than 90% power to detect a mean serum potassium difference of 0.30 between each dose group and placebo, assuming an intra-patient standard deviation (SD) of 0.50 and a two-sided test at a 5% significance level. It was assumed that 95% of patients would be normokalemic after treatment with at least one dose of 10 g. Based on these estimates, 269 patients were required to enter the acute phase.

Study ZS-D9482: Sample size was calculated based on the exponential rate of change in serum potassium using a random slopes model and parameters that were estimated from Study ZS-003. Based on these estimates, 34 patients in the placebo group and in each dosage group provided more than 95% power to detect a difference in slopes of 0.055 per day and 83% power to detect a difference in slopes of 0.030 per day. The proportion of patients normokalemic at 48 hours was assumed to be 47.8% for placebo and 86.4% for 10 g. The sample size of 34 patients in each group had about 90% power to detect the difference between placebo and 10 g at a significance level of 5%.

DIALIZE: The sample size for the primary efficacy outcome was calculated as 180 patients (90 patients in each group). This sample provided a power of greater than or equal to 90% to detect a difference between placebo and SZC of 25% in the proportion of patients who maintained a pre-dialysis serum potassium of 4.0 mmol/L to 5.0 mmol/L during at least three of four hemodialysis treatments after the long interdialytic interval and who did not require rescue therapy, at a two-sided significance level of 5%.

Statistical Test or Model

Study ZS-003

An exponential model was used to analyze the primary efficacy outcome (i.e., the exponential rate of potassium change). For the acute phase, the model controlled for age, baseline eGFR, CKD, congestive heart disease, DM, and RAASi medication. For the maintenance phase, the model controlled for age, baseline serum potassium in the acute phase, eGFR in the acute- and maintenance-phase baselines, CKD, congestive heart disease, DM, and RAASi medication. Type I error was controlled at the 0.05 level by a pre-specified closed testing procedure that was sequentially applied. In the closed testing order, the highest acute-phase dose was tested first, then the highest maintenance-phase dose, followed by the next-highest acute-phase dose and then the next-highest maintenance-

phase dose, in the same pattern until the lowest dose was reached. The relevant dosages for this review were included in the following testing order: acute: 10 g three times daily versus placebo; maintenance: 10 g once daily versus placebo; acute: 5 g three times daily versus placebo; and maintenance: 5 g once daily versus placebo.

A logistic regression model was used to analyze the proportion of patients who achieved normokalemia after 48 hours. The model controlled for baseline serum potassium (≤ 5.5 mmol/L, 5.6 mmol/L to 6.0 mmol/L, and > 6.0 mmol/L), CKD, congestive heart disease, DM, and RAASi medication. Kaplan–Meier analysis, log-rank test, and proportional hazard models were applied to evaluate time to initial normalization of serum potassium, maintenance of normokalemia, time to serum potassium decrease of greater than or equal to 0.5 mmol/L, time to serum potassium increase of 0.5 mmol/L, and time to relapse (return to original serum potassium baseline); for the maintenance phase, these models adjusted for baseline serum potassium, CKD, congestive heart disease, DM, and RAASi medication.

Study ZS-004

For the maintenance-phase primary outcome of LSM potassium, the statistical model included the patient as a random effect, and fixed effects for treatment group, age, eGFR at acute-phase baseline, serum potassium at acute- and maintenance-phase baselines, CKD, heart failure, DM, and RAASi medication. The number of normokalemic days was evaluated using a linear regression model with the same covariates. For other efficacy outcomes in the maintenance phase, the proportion of normokalemic patients at the maintenance-phase day 29 exit was based on a logistic regression model that contained the same covariates. The change in serum potassium from baseline to maintenance-phase follow-up was obtained from a mixed-effects regression model with the same covariates.

The exponential rate of change in serum potassium in the acute phase was obtained from a mixed-effects model of log-transformed serial potassium values on time, age, baseline eGFR, CKD, heart failure, diabetes, and RAASi medication.

Type I error was maintained at 5% by using a pre-specified sequential closed testing order. Each test was assessed at 5% type I error rate, with the first lack of statistical significance resulting in a stop to any further testing. The order of statistical testing was: (1) acute: baseline to 48 hours; (2 to 4) days 8 to 29: mean serum potassium 15 g versus placebo, followed by 10 g versus placebo, followed by 5 g versus placebo; (5 to 7) days 8 to 29: days normokalemic on 15 g versus placebo, followed by 10 g versus placebo, followed by 5 g versus placebo; (8 to 10) day 29 exit: proportion of patients normokalemic on 15 g versus placebo, followed by 10 g versus placebo, followed by 5 g versus placebo.

Study ZS-D9480

The primary outcome was analyzed using a longitudinal mixed-effects model, with the LSM of all available log-transformed serum potassium in maintenance-phase days 8 to 29 as the end point, and adjusted for covariates (i.e., treatment group, treatment by visit interaction, acute-phase baseline serum potassium, maintenance phase serum potassium, acute-phase baseline eGFR, age category [< 55 years, 55 years to 64 years, and ≥ 65 years], country, baseline RAASi use, CKD, heart failure, and DM). Time to normalization of serum potassium was evaluated with Kaplan–Meier analysis, with all available potassium values used during the maintenance phase. If patients did not achieve normalization, or if they discontinued due to high potassium levels (> 6.2 mmol/L at the 90-minute post-dose day 2 blood draw), they were censored at the last measurement or at 48 hours, respectively.

As in Study ZS-004, type I error was maintained at 5% using a sequential closed testing order. Each test was performed at a two-sided 5% significance level; if statistical significance was not reached, further testing was stopped. The order of statistical testing was: (1) acute: mean change from baseline in serum potassium from baseline to 48 hours; (2 to 3) days 8 to 29: mean serum potassium 10 g versus placebo, followed by 5 g versus placebo; (4 to 5) day 29 exit: proportion of patients who remained normokalemic 10 g versus placebo, followed by 5 g versus placebo; (6 to 7) days 8 to 29: number of days remaining normokalemic on 10 g versus placebo, followed by 5 g versus placebo; (8 to 9) maintenance: time to hyperkalemia at 10 g versus placebo, followed by 5 g versus placebo.

Study ZS-D9482

The exponential rate of change in serum potassium to 24 hours or 48 hours was analyzed with a random-slope, mixed-effects model. Type I error was maintained at 5% with sequential, hierarchical testing. Each test was conducted at a 5%, two-sided significance level. The testing proceeded in the following order: serum potassium exponential rate of change through 48 hours, 10 g versus placebo, 5 g versus placebo. Logistic regression models, with baseline serum potassium as a covariate, were used for dichotomous outcomes. Time to normokalemia was evaluated with Kaplan–Meier and log-rank analysis.

DIALIZE

The primary outcome was analyzed with a two-sided Fisher's exact test at a 5% significance level.

Data Imputation Methods

Study ZS-003: Missing serum potassium data were replaced with plasma data by adjusting for the average paired difference between serum and plasma values collected at the same visit. No other data were imputed.

Study ZS-004: Serum potassium data missing from the central laboratory were replaced with i-STAT measurements by adjusting for the average paired difference between central laboratory and i-STAT values collected at the same visit. If both central laboratory and i-STAT potassium values were missing, then the end-of-study value was imputed if it was within one day of the last dose. No other data were imputed.

Study ZS-D9480: Missing serum potassium values from the central laboratory were replaced with i-STAT values, with adjustment for the average paired difference between central laboratory and i-STAT collected at the same visit and with the same calibration method for the potassium assay. If both central laboratory and i-STAT values were missing for the last visit on treatment, then the end-of-study value was imputed if it was within one day of a target study day and the last dose. No other data were imputed.

Study ZS-D9482: Missing serum potassium values from the central laboratory were replaced with i-STAT values, with adjustment for the average paired difference. If both central laboratory and i-STAT values were missing, the data point was left missing. For logistic regression models, patients with missing serum potassium were assumed to be non-responders.

DIALIZE: Patients who had more than one missing serum potassium measurement were classified as non-responders. `

Sensitivity Analyses

Study ZS-004: Two sensitivity analyses were conducted for the primary outcome of LSM of serum potassium during the maintenance phase. The model was repeated by adding in patients who discontinued the study drug before obtaining a serum potassium value at day 8 of the maintenance phase. First, data for these patients were imputed using an expectation-maximization algorithm that used available potassium values from patients in the same treatment group. Second, the model was run again with the following modifications: rescaling each patient's maintenance-phase day 8 to day 29 serum potassium values by subtracting the maintenance-phase baseline and dropping the maintenance-phase baseline factor from the model.

Study ZS-D9480: Sensitivity analyses were performed to test the impacts of a change in calibration method of the serum potassium assay at the central laboratory on the primary outcome and the secondary outcome of the proportion of patients who remained normokalemic. The same longitudinal mixed-effects model that was used in the primary analysis was used in sensitivity analyses.

Study ZS-D9482: Three sensitivity analyses were performed on the primary outcome to account for an assay change in the central laboratory, using i-STAT potassium values rather than central laboratory values, and using a different set of covariates. For key secondary outcomes, the same logistic regression models were applied to serum potassium values that were adjusted for the assay change and to i-STAT potassium values.

DIALIZE: A sensitivity analysis was conducted to impute i-STAT potassium values for missing central laboratory values. The i-STAT values were adjusted for the mean paired difference between central laboratory and i-STAT measurements taken at the same time. If both central laboratory and i-STAT values were missing, serum potassium values were imputed with the last observation available (i.e., last observation carried forward).

Subgroup Analyses

Subgroup data were available for the baseline serum potassium category (e.g., ≤ 5.5 mmol/L, 5.6 mmol/L to 6.0 mmol/L, and > 6.0 mmol/L), baseline eGFR category (< 15 mL/min/1.73m^2, 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2, 30 mL/min/1.73m2 to < 60 mL/min/1.73m^2, and ≥ 60 mL/min/1.73m^2), CKD, congestive heart disease, and RAASi medication. In Study ZS-D9480, an interaction term for treatment by subgroup (i.e., CKD, heart failure, RAASi use) was included in statistical models.

Analysis Populations

Study ZS-003: The primary population for efficacy outcomes were patients who were randomized, received at least one dose of study drug, and had serum potassium determined 48 hours after treatment for the acute phase or during the maintenance phase. The study termed this an intention-to-treat (ITT) population or a full-analysis set (FAS). Harms were assessed in the safety set, which included all patients who were randomized and received any study drug. For efficacy outcomes, patients were analyzed based on the group into which they were randomized; for harms, patients were analyzed based on treatment received.

Study ZS-004: The primary population for efficacy outcomes was termed by the sponsor as the ITT population in the maintenance phase. This included all randomized patients who received at least one dose of maintenance drug and had at least one serum potassium

measurement on or after day 8. The safety set for the acute and maintenance phases included all patients who received at least one dose of study drug during each phase. For efficacy outcomes, patients were analyzed based on the group into which they were randomized; for harms, patients were analyzed based on treatment received.

Study ZS-D9480: Efficacy outcomes in the maintenance phase were analyzed in the ITT population, which included all patients randomized, and was based on randomized treatment assignment. Harms in the maintenance phase were analyzed in the safety set, which included all patients who were randomized and received at least one dose of study drug, and was based on actual treatment received. In the acute phase, all patients who entered the study and received at least one dose of study drug were analyzed.

Study ZS-D9482: Efficacy outcomes were analyzed in the FAS, which included all patients randomized. Harms were assessed in the safety set, which included all patients who took at least one dose of study drug. Efficacy results were based on randomized treatment assignment, whereas harms were based on treatment actually received.

DIALIZE: Efficacy outcomes were analyzed in the FAS, which included all randomized patients, whether or not they received the study drug. Harms were assessed in the safety set, which included all randomized patients who received at least one dose of the study drug.

Results

Patient Disposition

The patient disposition in studies with an acute phase (i.e., studies ZS-003, ZS-004, ZS-D9480, and ZS-D9482) is provided in Table 13. In Study ZS-003, 301 patients were randomized to placebo or SZC 10 g three times daily for two days. One patient in the placebo group discontinued due to hyperkalemia (serum potassium 6.2 mmol/L to 6.8 mmol/L). Three patients in the active treatment group discontinued the study due to an AE, lack of adeherence, and loss to follow-up. In Study ZS-004, 258 patients entered the open-label acute phase. Seven patients discontinued the study due to withdrawal of consent (n = 5) or hypokalemia or hyperkalemia (n = 2). In Study ZS-D9480, 267 patients entered the open-label acute phase and seven discontinued due to withdrawal of consent (n = 3) or other reason (n = 4). In Study ZS-D9482, 69 patients were randomized to placebo or SZC 10 g three times daily for two days. Two patients in the placebo group discontinued the study due to hyperkalemia. No patients in the active treatment group discontinued the acute phase.

Table 13: Patient Disposition in Acute Phase

	Study ZS-003		Study ZS-004	Study ZS-D9480	Study ZS-D9482	
	Placebo	SZC 10 g	SZC 10 g	SZC 10 g	Placebo	SZC 10 g
Screened, N	1,433		425	472	151[b]	
Randomized, N (%)	754 (52.6)[a]		NA	NA	103 (68.2)[c]	
	158	143			33	36
Entered, N (%)	NA	NA	258 (60.7)	267 (56.6)	NA	NA
Treated, N (%)	158 (100)	143 (100)	258 (100)	267 (100)	33 (100)	36 (100)
Completed, N (%)	157 (99.4)	140 (97.9)	251 (97.3)	260 (97.4)	31 (93.9)	36 (100)
Discontinued treatment, N (%)	NR	NR	NR	7 (2.6)	2 (6.1)	0 (0)
Discontinued study, N (%)	1 (0.6)	3 (2.1)	7 (2.7)	7 (2.6)	2 (6.1)	0 (0)
Eligible for maintenance phase, N (%)	NR	NR	240 (93.0)	249 (95.8)	NA	NA
FAS/ITT, N	158	143	258	267	33	36
Safety, N	158	143	258	267	33	36

FAS = full-analysis set; ITT = intention-to-treat; NA = not applicable; NR = not reported; SZC = sodium zirconium cyclosilicate.

[a] Includes patients randomized to 1.25 g, 2.5 g, and 5 g.

[b] Number of patients who enrolled (i.e., provided informed consent).

[c] Includes patients randomized to 5 g.

Sources: Clinical Study Report for Study ZS-003;[23] Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9480;[26] Clinical Study Report for Study ZS-D9482.[27]

Table 14 shows the patient disposition for the maintenance phase (studies ZS-003, ZS-004, ZS-D9480, and DIALIZE). In Study ZS-003, of 138 patients who received 5 g in the acute phase and entered the maintenance phase, 133 (96.4%) were randomized to placebo or 5 g once daily for 12 days. Of 127 patients who received 10 g in the acute phase and entered the maintenance phase, 124 (97.6%) were randomized to placebo or 10 g once daily for 12 days. Five patients in the placebo groups of Study ZS-003 discontinued the study due to AE (n = 2), withdrawal of consent (n = 2), or hypokalemia or hyperkalemia (n = 1). Six patients randomized to 5 g discontinued the study due to AE (n = 4), protocol violation (n = 1), or death (n = 1). Two patients in the 10 g group discontinued due to AE (n = 1) or withdrawal of consent (n = 1). One patient randomized to 5 g died after receiving one dose of drug in the maintenance phase and was excluded from the ITT population.

In Study ZS-004, 181 patients were randomized to placebo, 5 g, or 10 g once daily for 28 days. Ten patients in the placebo group discontinued the study due to withdrawal of consent (n = 2), patient compliance (n = 1), decision by sponsor (n = 2), hypokalemia or hyperkalemia (n = 3), or other reason (n = 2). In the 5 g group, five patients discontinued due to AE (n = 3), meeting electrocardiogram (ECG) withdrawal criteria (n = 1), or other reason (n=1); in the 10 g group, seven patients discontinued due to sponsor decision (n = 2), hypokalemia or hyperkalemia (n = 3), or other reason (n = 2).

In Study ZS-D9480, 248 patients entered the maintenance phase, and all were randomized to placebo, 5 g, or 10 g once daily for 28 days. Seven patients in the placebo group discontinued treatment due to AE (n = 3), hyperkalemia (n = 2), or other reason (n = 2); nine patients in the placebo group were withdrawn from the study. In the 5 g group, 14 patients discontinued treatment due to AE (n = 6), hyperkalemia (n = 3), withdrawal by patient (n = 3), protocol violation (n = 1), or other reason (n = 1); 14 patients in the 5 g group were withdrawn from the study. In the 10 g group, 12 patients discontinued treatment due to AE (n = 7), hyperkalemia (n = 1), hypokalemia (n = 2), withdrawal by patient (n = 1), or other reason (n = 1); 11 patients in the 10 g group were withdrawn from the study.

In DIALIZE, 196 patients were randomized to placebo or SZC. Four patients in the placebo group discontinued treatment due to AE (n = 2), protocol violation (n = 1), or other reason (n = 1); three patients in the placebo group were withdrawn from the study. More patients (n = 8) in the active treatment group discontinued treatment due to AE (n = 3), patient decision (n = 3), protocol violation (n = 1), or other reason (n = 1); five patients were withdrawn from the study due to withdrawal by patient (n = 2), death (n = 1), or other reason (n = 2).

Table 14: Patient Disposition in Maintenance Phase

	Study ZS-003				Study ZS-004			Study ZS-D9480			DIALIZE	
Acute phase	**SZC 5 g**		**SZC 10 g**		**SZC 10 g**			**SZC 10 g**			**NA**	
Maintenance phase	**PBO**	**SZC 5 g**	**PBO**	**SZC 10 g**	**PBO**	**SZC 5 g**	**SZC 10 g**	**PBO**	**SZC 5 g**	**SZC 10 g**	**PBO**	**SZC 5 g to 15 g**
Screened, N	NA		NA		NA			NA			443	
Entered, N	138		127		237			248			NA	
Randomized, N (%)	133 (96.4)		124 (97.6)		237 (100)[a]			248 (100)			196 (44.2)	
	68	65	61	63	85	45	51	50	99	99	99	97
Treated, N (%)	68 (100)	65 (100)	61 (100)	63 (100)	85 (100)	45 (100)	51 (100)	50 (100)	99 (100)	99 (100)	99 (100)	96 (99.0)
Completed, N (%)	66 (97.1)	59 (90.8)	58 (95.1)	61 (96.8)	75 (88.2)	40 (88.9)	44 (86.3)	43 (86.0)	85 (85.9)	87 (87.9)	95 (96.0)	88 (90.7)
Discontinued treatment, N (%)	NR	NR	NR	NR	NR	NR	NR	7 (14.0)	14 (14.1)	12 (12.1)	4 (4.0)	8 (8.2)
Discontinued study, N (%)	2 (2.9)	6 (9.2)	3 (4.9)	2 (3.2)	10 (11.8)	5 (11.1)	7 (13.7)	9 (18.0)	14 (14.1)	11 (11.1)	3 (3.0)	5 (5.2)
FAS/ITT, N	68	64	61	63	82	45	50	50	99	99	99	97
Safety, N	68	65	61	63	85	45	51	50	99	99	99	96

FAS = full-analysis set; ITT = intention-to-treat; NA = not applicable; NR = not reported; PBO = placebo; SZC = sodium zirconium cyclosilicate.

[a] Includes patients randomized to 15 g.

Source: Clinical Study Report for Study ZS-003;[23] Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9480;[26] Fishbane et al. (2019).[19]

Exposure to Study Treatments

Acute Phase

In Study ZS-003, most patients received all three doses on day 1 (100% placebo and 98.6% SZC 10 g) and day 2 (98.7% placebo and 96.5% 10 g). In Study ZS-004, of the 258 patients in the acute phase, 96.9% received all three doses of the study drug on days 1 and 2. In Study ZS-D9480, all patients received the study drug for at least one day, and 261 (97.8%) received it for two days. In Study ZS-D9482, the mean duration of exposure was similar between the placebo and 10 g groups (mean duration: 1.9 and 2.0 days respectively; mean number of doses received: 5.6 and 6.0, respectively).

Maintenance Phase

In the 12-day maintenance phase of Study ZS-003, the mean number of doses received by the placebo, 5 g, and 10 g groups were 11.5 to 11.8. In Study ZS-004, the mean number of doses received in the 28-day maintenance phase was slightly higher in the placebo group (26.3 doses) and 5 g group (27.1 doses) compared with the 10 g group (24.5 doses). The difference was due to more patients in the 10 g group reducing their dosage from once daily to once every other day. In Study ZS-D9480, the mean duration of exposure in the placebo, 5 g, and 10 g groups was similar at 26.2 days, 26.0 days, and 26.4 days, respectively. Fourteen patients had a dose reduction from once daily to once every other day (four patients in the 5 g group and 10 patients in the 10 g group). In DIALIZE, compliance with treatment was similar between the placebo and SZC groups (98.4% and 98.9%, respectively). After completion of the dose titration period in DIALIZE, 37% of patients were stabilized on SZC 5 g once daily, 43% on 10 g once daily, and 19% on 15 g once daily. In the analyses, all doses were analyzed as one group.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows. See Appendix 3 for other detailed efficacy data.

Survival and Mortality

Survival was not assessed as an efficacy outcome in any of the studies. Mortality data are provided in the Harms section.

Hospitalization

Study ZS-004 was the only study that provided data on hospitalization and emergency room visits (Table 15). There were numerically more hospitalizations in the 5 g group (four patients) than in the placebo group (one patient) and the 10 g group (one patient). One patient in the placebo group and one in the 5 g group had an emergency room visit. An additional patient in the 10 g group was hospitalized due to an SAE during the maintenance phase, but was not included in the health care utilization data.

Table 15: Health Care Utilization in Maintenance Phase of Study ZS-004

	Study ZS-004		
Maintenance phase	**Placebo (N = 85)**	**SZC**	
		5 g (N = 45)	**10 g (N = 51)**
Hospitalizations			
Number of visits	1	4	1
Patients with visits, n (%)	1 (1.2)	4 (8.9)	1 (2.0)
Emergency room visits			
Number of visits	1	1	0
Patients with visits, n (%)	1 (1.2)	1 (2.2)	0 (0)

SZC = sodium zirconium cyclosilicate.

Source: Clinical Study Report for Study ZS-004.[25]

Quality of Life

Table 16 provides EQ-5D-5L data at baseline and day 29 in the placebo, 5 g, and 10 g groups of Study ZS-D9480, the only one that assessed quality of life.

Table 16: Health-Related Quality of Life (EQ-5D-5L) in Maintenance Phase of Study ZS-D9480

	Study ZS-D9480					
Maintenance phase	**Placebo (N = 50)**		**SZC**			
			5 g (N = 99)		**10 g (N = 99)**	
	Baseline[a]	Day 29	Baseline[a]	Day 29	Baseline[a]	Day 29
Anxiety/depression, N (%)						
Not anxious or depressed	33 (66.0)	27 (54.0)	60 (60.6)	61 (61.6)	67 (67.7)	69 (69.7)
Slightly	9 (18.0)	14 (28.0)	22 (22.2)	15 (15.2)	19 (19.2)	18 (18.2)
Moderately	1 (2.0)	0 (0)	6 (6.1)	8 (8.1)	2 (2.0)	0 (0)
Severely	0 (0)	0 (0)	2 (2.0)	2 (2.0)	0 (0)	1 (1.0)
Extremely	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Mobility						
No problems in walking about	26 (52.0)	31 (62.0)	55 (55.6)	57 (57.6)	50 (50.5)	59 (59.6)
Slight problems	9 (18.0)	6 (12.0)	26 (26.3)	19 (19.2)	23 (23.2)	21 (21.2)
Moderate problems	6 (12.0)	2 (4.0)	8 (8.1)	7 (7.1)	11 (11.1)	6 (6.1)
Severe problems	2 (4.0)	2 (4.0)	2 (2.0)	3 (3.0)	4 (4.0)	2 (2.0)
Unable to walk about	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pain/discomfort						
No pain or discomfort	24 (48.0)	27 (54.0)	52 (52.5)	54 (54.5)	45 (45.5)	45 (45.5)
Slight	14 (28.0)	11 (22.0)	28 (28.3)	24 (24.2)	32 (32.3)	35 (35.4)
Moderate	4 (8.0)	3 (6.0)	9 (9.1)	8 (8.1)	9 (9.1)	6 (6.1)
Severe	1 (2.0)	0 (0)	2 (2.0)	0 (0)	2 (2.0)	2 (2.0)
Extreme	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Self-care						
No problems washing or dressing	35 (70.0)	37 (74.0)	78 (78.8)	71 (71.7)	74 (74.7)	75 (75.8)
Slight problems	5 (10.0)	2 (4.0)	6 (6.1)	7 (7.1)	8 (8.1)	9 (9.1)

	Study ZS-D9480					
Moderate problems	3 (6.0)	2 (4.0)	6 (6.1)	6 (6.1)	4 (4.0)	3 (3.0)
Severe problems	0 (0)	0 (0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)
Unable to wash or dress	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Usual activities						
No problems	34 (68.0)	31 (62.0)	62 (62.6)	63 (63.6)	58 (58.6)	63 (63.6)
Slight problems	3 (6.0)	8 (16.0)	18 (18.2)	11 (11.1)	22 (22.2)	18 (18.2)
Moderate problems	6 (12.0)	2 (4.0)	8 (8.1)	7 (7.1)	7 (7.1)	6 (6.1)
Severe problems	0 (0)	0 (0)	3 (3.0)	5 (5.1)	1 (1.0)	1 (1.0)
Unable to do usual activities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VAS						
N	43	41	91	86	88	88
Mean (SD)	72.7 (17.3)	76.6 (14.1)	75.0 (16.4)	77.6 (16.5)	74.3 (17.4)	76.9 (16.1)

SD = standard deviation; SZC = sodium zirconium cyclosilicate; VAS = visual analogue scale.

[a] Baseline is the start of the open-label acute phase.

Source: Clinical Study Report for Study ZS-D9480.[26]

Arrhythmia and Major Adverse Cardiovascular Events

Cardiovascular outcomes, including arrhythmias, were not assessed for efficacy in the studies. Cardiovascular events are presented in the Harms section.

Kidney Disease and Major Adverse Kidney Events

Renal outcomes were not assessed for efficacy in the studies. Renal events are presented in the Harms section.

Continuation or Need for Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitor or Mineralocorticoid Receptor Antagonist Treatment at Regular Doses

Studies ZS-003, ZS-004, ZS-D9480, and ZS-D9482 were not designed to evaluate the effect of SZC on RAASi or mineralocorticoid receptor antagonist therapies, and there were no protocol-defined specifications of what constituted changes in these therapies.[30] The sponsor provided some data on changes to RAASi therapies during the acute and maintenance phases as post hoc analyses (Table 17 and Table 18, respectively). In Study ZS-003, among patients who did not continue with treatment after 48 hours, more patients in the placebo group were receiving a RAASi at the end of the acute phase than patients on SZC 10 g (24.7% versus 9.1%) (Table 17). There was no discontinuation or initiation of RAASi at the end of the acute phase of Study ZS-003. Similarly, in Study ZS-D9482, slightly more patients in the placebo group were receiving a RAASi at the end of the acute phase than were receiving SZC (84.9% versus 72.2%). Among those patients on RAASi, there were no changes to therapy in the placebo group; one patient discontinued and initiated RAASi (dose changes were classified as discontinuation followed by re-initiation) in the SZC group.

At the end of the maintenance phase of Study ZS-003, the percentage of patients receiving RAASi was 66.7% in the placebo group, 57.8% in the SZC 5 g group, and 68.3% in the SZC 10 g group (Table 18). Among those patients on RAASi, there were no changes in the SZC groups, but four patients in the placebo group had changes. In Study ZS-004, a similar

percentage of patients were on RAASi therapy at the end of the maintenance phase (70.7% in the placebo group, 68.9% in the 5 g group, and 70.0% in the 10 g group). There were no changes to RAASi therapy in the 10 g group. Two patients in the 5 g group and two in the placebo group discontinued RAASi. At the end of the maintenance phase of Study ZS-D9480, RAASi therapy was similar among groups (82% in the placebo group, 76.8% in the 5 g group, and 78.8% in the 10 g group). There were three patients with changes to RAASi therapy in the 10 g group, one with a change in the 5 g group (plus one initiation of therapy) and one in the placebo group.

Table 17: Changes to RAASi Therapy at Acute-Phase End in Patients Not Continuing to Maintenance Phase

	Study ZS-003		Study ZS-D9482	
	Placebo (N = 158)	SZC 10 g (N = 143)	Placebo (N = 33)	SZC 10 g (N = 36)
Patients not continuing to maintenance phase, n (%)	62 (39.2)	19 (13.3)	NA	NA
Receiving RAASi at end of acute phase, n (%)[a]	39 (24.7)	13 (9.1)	28 (84.9)	26 (72.2)
No change in RAASi, n (%)[b]	39 (24.7)	13 (9.1)	28 (84.9)	25 (69.4)
Any change in RAASi, n (%)[c]	0 (0)	0 (0)	1 (3.0)	1 (2.8)
Discontinuation of RAASi, n (%)	0 (0)	0 (0)	0 (0)	1 (2.8)
Initiation of RAASi, n (%)	0 (0)	0 (0)	1 (3.0)	1 (2.8)

NA = not applicable; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

[a] End of acute phase is the date of the last dose of treatment received in the acute phase.

[b] Only includes patients who were receiving RAASi at end of the acute phase.

[c] All patients included, whether receiving RAASi or not at end of acute phase. A change in dose was considered as both a discontinuation and a restarting of therapy.

Source: Sponsor response to information request.[30]

Table 18: Changes to RAASi Therapy at Maintanance-Phase End

	Study ZS-003			Study ZS-004			Study ZS-D9480		
	Placebo (N = 216)[a]	SZC 5 g (N = 64)	SZC 10 g (N = 63)	Placebo (N = 82)	SZC 5 g (N = 45)	SZC 10 g (N = 50)	Placebo (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)
Receiving RAASi at end of maintenance phase, n (%)	144 (66.7)	37 (57.8)	43 (68.3)	58 (70.7)	31 (68.9)	35 (70.0)	41 (82.0)	76 (76.8)	78 (78.8)
No change in RAASi, n (%)[b]	140 (64.8)	37 (57.8)	43 (68.3)	56 (68.3)	29 (64.4)	35 (70.0)	40 (80.0)	75 (75.8)	75 (75.8)
Any change in RAASi, n (%)[c]	4 (1.9)	0 (0)	0 (0)	2 (2.4)	2 (4.4)	0 (0)	1 (2.0)	1 (1.0)	3 (3.0)
Discontinuation of RAASi, n (%)	4 (1.9)	0 (0)	0 (0)	2 (2.4)	2 (4.4)	0 (0)	1 (2.0)	0 (0)	3 (3.0)
Initiation of RAASi, n (%)	2 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	1 (1.0)	2 (2.0)

RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

[a] Includes patients in the placebo of lower-dose groups (i.e., 1.25 g and 2.5 g).

[b] Only includes patients who were receiving RAASi at end of the maintenance phase.

[c] All patients included, whether receiving RAASi or not at end of maintenance phase. A change in dose was considered as both a discontinuation and a restarting of therapy.

Source: Sponsor response to information request.[30]

Outcomes Related to Potassium Level

Acute Phase

Study ZS-003

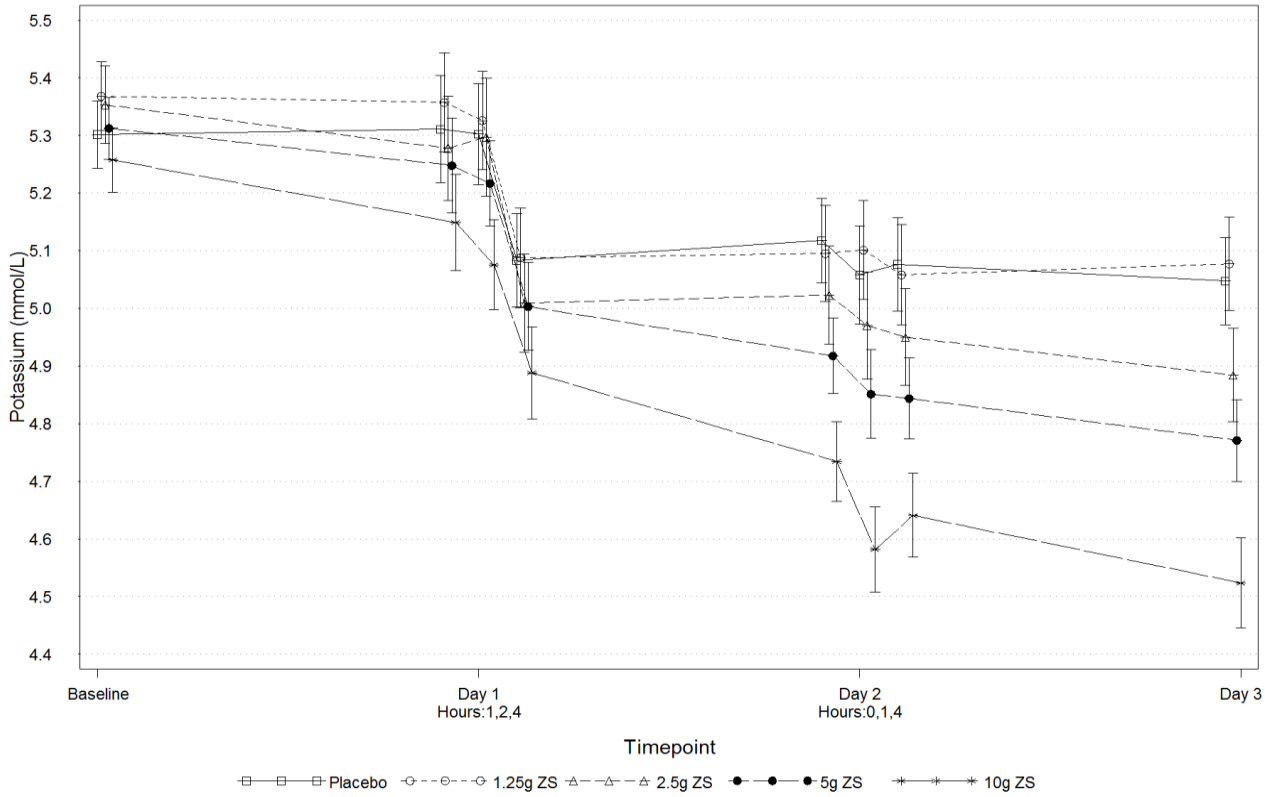
Figure 6 shows mean serum potassium levels over the acute phase of Study ZS-003. All dosage groups are displayed along with placebo groups; however, for this review, only the placebo and 10 g thrice-daily dose will be evaluated. Both groups experienced a decline in potassium from baseline. The decline in the 10 g group (line closest to the x-axis) was larger than in the placebo group (line furthest from x-axis).

For serum potassium, compared with the placebo group, the 10 g dose group had a statistically significantly higher exponential rate of change in the negative direction (slope at 48 hours: –0.003 versus –0.001, respectively) (Table 19). All other outcomes in Table 19 were outside of the sequential closed testing procedure; therefore, conclusions about statistical significance cannot be made. The mean change (SD) in serum potassium from baseline to 48 hours was –0.73 mmol/L for the 10 g group and –0.25 mmol/L for the placebo group.

A difference in mean change from baseline in potassium between the 10 g dose and placebo was observed one hour after the first dose of the study drug. The median time to serum potassium decrease of 0.5 mmol/L was 22.8 hours for 10 g and 24.8 hours for placebo. The time to serum potassium normalization (3.5 mmol/L to 5.0 mmol/L) was shorter for 10 g compared with placebo (1.1 hours versus 4.0 hours), and the proportion of patients who achieved normokalemia at 48 hours was higher in the 10 g group (86.4% versus 47.8%).

Subgroups were not part of the sequential testing procedure; therefore, the following results are descriptive only. Figure 13 in Appendix 3 shows the mean change in serum potassium from baseline to day 3 (48 hours) for 10 g three times daily versus placebo in subgroups based on eGFR, baseline serum potassium, RAASi medication use, congestive heart failure, and CKD. For all subgroups, the mean change was consistently lower for patients who received 10 g versus placebo. The largest difference was observed for patients with an eGFR of less than 15 mL/min/1.73m^2 (–0.86 mmol/L lower mean change with 10 g versus placebo). Table 43 in Appendix 3 shows the proportion of patients by subgroup who achieved normokalemia at the end of the acute phase. In all subgroups, more patients who received 10 g achieved normokalemia compared with patients who received placebo.

Figure 6: Mean Serum Potassium (± 2 Standard Error) in Acute Phase of Study ZS-003



Source: Extracted from Clinical Study Report for ZS-003.[23]

Table 19: Serum Potassium Outcomes in Acute Phase of Study ZS-003

	Study ZS-003	
	Placebo (N = 158)	**SZC 10 g (N = 143)**
Exponential rate of S-K change		
N	158	143
24 hours, estimate	–0.00126	–0.00365
P value[a]	—	< 0.0001
48 hours, estimate	–0.00094	–0.00297

	Study ZS-003	
P value	—	10^{-31}
Change from baseline S-K[a]		
Day 2 (24 hours)		
N	158	140
Mean change (SD), mmol/L	–0.18 (0.36)	–0.52 (0.36)
P value	—	≤ 0.001
Day 3 (48 hours)		
N	157	140
Mean change (SD), mmol/L	–0.25 (0.41)	–0.73 (0.50)
P value	—	≤ 0.001
Time to S-K decrease of 0.5 mmol/L[a]		
N	158	143
Median, hours	24.8	22.8
P value	—	< 0.0001
Time to S-K normalization (3.5 mmol/L to 5.0 mmol/L)[a]		
N	158	143
Median, hours	4.0	1.1
P value	—	0.0034
Percentage who achieved normokalemia (S-K 3.5 mmol/L to 5.0 mmol/L)[a]		
Day 2 (24 hours)		
N	158	140
n (%)	78 (49.4)	108 (77.1)
P value	—	≤ 0.001
Day 3 (48 hours)		
N	157	140
n (%)	75 (47.8)	121 (86.4)
P value	—	≤ 0.001

SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] Outcome was not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for Study ZS-003.[23]

Study ZS-D9482

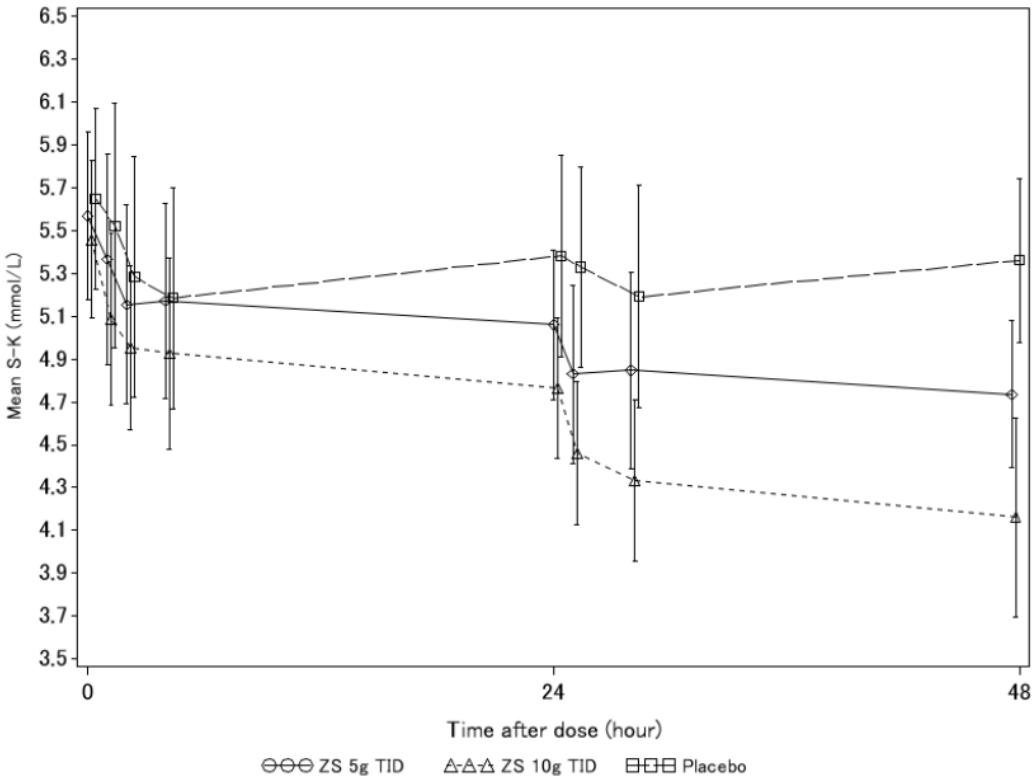
Figure 7 displays mean serum potassium over 48 hours of treatment in Study ZS-D9482. The graph shows the placebo, 5 g, and 10 g doses; however, for this review, the 5 g dose is not evaluated. The decline in the 10 g group (line closest to the x-axis) was larger than in the placebo group (line furthest from the x-axis).

The exponential rate of change in serum potassium over 48 hours was statistically significantly higher, in the negative direction, in the 10 g group compared with the placebo group (slope: –0.005 versus –0.0001) (Table 20). Sensitivity analyses of the exponential rate of change using i-STAT potassium values rather than central laboratory analyses (adjusted for the assay change in the central laboratory) or using a different set of covariates produced estimates that aligned with the primary analysis (data not shown). All other outcomes were

outside of the sequential closed testing procedure; therefore, conclusions about statistical significance cannot be made. At 48 hours, the mean change (SD) in serum potassium from baseline was –1.3 (0.5) mmol/L for the 10 g group and –0.24 (0.34) mmol/L for the placebo group. More patients achieved normokalemia in the 10 g group at 48 hours (91.7% versus 15.2%). Sensitivity analysis that used i-STAT potassium rather than central laboratory — and that adjusted for the change in assay — produced similar findings for the proportion of patients who achieved normokalemia (94.4% versus 24.2% using i-STAT potassium; 94.4% versus 18.2% adjusting for assay change). The median time to normalization was 1.8 hours for patients who received 10 g; it was 3.9 hours for those who received placebo. The median time to potassium decrease of 0.5 mmol/L or more was 2.9 hours for 10 g and 4.1 hours for placebo.

Subgroups were not part of the sequential testing procedure; therefore, the following results are descriptive only. Table 44 in Appendix 3 provides the exponential rate of change in serum potassium for patients with CKD, heart failure, or using RAASi medication. In all three subgroups, the exponential rate of change was higher in patients receiving 10 g compared with those receiving placebo. Table 45 in Appendix 3 shows the proportion of patients who achieved normokalemia at 48 hours among subgroups defined by baseline serum potassium, CKD, heart failure, use of RAASi, and eGFR. Although the sample sizes in these subgroups were small, in all cases the proportion of patients who achieved normokalemia was consistently higher in the 10 g group compared with placebo. In patients with eGFR of less than 15 mL/min/1.73m^2, normokalemia was achieved by 27.3% on placebo (N = 11) versus 100% on SZC (N = 9); for eGFR of 15 mL/min/1.73m^2 to less than 10 mL/min/1.73m^2, normokalemia was achieved by 9.1% versus 92.3%; and for eGFR of 30 mL/min/1.73m^2 to less than 60 mL/min/1.73m^2, normokalemia was achieved by 9.1% versus 81.8%.

Figure 7: Mean Serum Potassium (± Standard Deviation) in Study ZS-D9482



S-K = serum potassium; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Source: Extracted from Clinical Study Report for Study ZS-D9482.[27]

Table 20: Serum Potassium Outcomes in Study ZS-D9482

	Study ZS-D9482	
	Placebo (N = 33)	**SZC 10 g (N = 36)**
Exponential rate of S-K change		
N (%)	33 (100)	36 (100)
24 hours, estimate (SE)[a]	–0.00002 (0.00049)	–0.00403 (0.00046)
P value[b]	—	< 0.0001
48 hours, estimate (SE)[a]	–0.00012 (0.00029)	–0.00508 (0.00027)
P value	—	< 0.0001
Change from baseline S-K[b]		
N (%)	33 (100)	36 (100)
Baseline, mean S-K (SD), mmol/L	5.7 (0.4)	5.5 (NR)
24 hours, mean S-K (SD), mmol/L	5.38 (0.47)[c]	4.8 (0.3)
48 hours, mean S-K (SD), mmol/L	5.36 (0.38)[c]	4.2 (0.5)
Day 9 (EOS), mean S-K (SD), mmol/L	5.45 (0.44)	4.8 (0.4)
24 hours, mean change (SD), mmol/L	–0.22 (0.35)	–0.7 (0.4)

		Study ZS-D9482
48 hours, mean change (SD), mmol/L	–0.24 (0.34)	–1.3 (0.5)
Day 9 (EOS), mean change (SD), mmol/L	–0.20 (0.59)	–0.7 (0.5)
Percentage who achieved normokalemia (S-K 3.5 mmol/L to 5.0 mmol/L)[b]		
N	33	36
24 hours, n (%)	9 (27.3)	30 (83.3)
P value[d]	—	< 0.0001
48 hours, n (%)	5 (15.2)	33 (91.7)
P value[d]	—	< 0.0001
Day 9 (EOS), n (%)	9 (27.3)	22 (61.1)
Time to S-K normalization[b,e]		
N (%)	33 (100)	36 (100)
Median, hours	3.9	1.8
P value (log-rank, cumulative distribution)	—	0.0006
Time to S-K decrease of ≥ 0.5 mmol/L[b]		
N (%)	33 (100)	36 (100)
Median, hours	4.1	2.9
P value (log-rank, cumulative distribution)	—	0.0064

EOS = end of study; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] From a random coefficient model with patient-level random effects for time and intercept and fixed effects of intercept, time, and time by treatment interaction.

[b] Outcome was not part of the sequential closed statistical testing procedure.

[c] 31 patients were evaluated in the placebo group at 24 hours and 48 hours.

[d] From a logistic regression model that included treatment and baseline serum potassium.

[e] Time to first S-K reduction to 3.5 mmol/L to 5.0 mmol/L.

Source: Clinical Study Report for Study ZS-D9482.[27]

Studies ZS-004 and ZS-D9480

Table 21 provides data for potassium outcomes evaluated in the open-label acute phases of studies ZS-004 and ZS-D9480. These data are provided for completeness. However, no conclusions can be made about the effect of SZC, as there was no comparator.

Table 21: Serum Potassium Outcomes in the Acute Phases of Studies ZS-004 and ZS-D9480

	Study ZS-004	Study ZS-D9480
	SZC 10 g (N = 258)	**SZC 10 g (N = 267)**
Exponential rate of S-K change		
48 hours, estimate	–0.00324	–0.004 (SE 0.0001)
P value	< 0.0001	< 0.001
Change from baseline S-K		
Baseline, N (%)	258 (100)	267 (100)
Mean S-K (SD), mmol/L	5.6 (0.5)	5.7 (0.5)
48 hours, N (%)	251 (97.3)	260 (97.4)
Mean S-K (SD), mmol/L	4.5 (0.4)	4.4 (0.45)
Mean change (95% CI), mmol/L	–1.05 (–1.11 to –0.98)	–1.3 (–1.34 to –1.22)
P value	< 0.0001	< 0.001

	Study ZS-004	Study ZS-D9480
Percentage who achieved normokalemia (S-K 3.5 mmol/L to 5.0 mmol/L)		
48 hours, N	251	267
n (%)	221 (88.0)	238 (89.1)

CI = confidence interval; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Source: Clinical Study Report for Study ZS-004;[25] Clinical Study Report for Study ZS-D9480.[26]

Maintenance Phase

Study ZS-003

In Figure 8, mean serum potassium in the maintenance phase of Study ZS-003 is plotted for SZC 10 g once daily versus placebo (first panel) and 5 g once daily versus placebo (second panel). The maintenance phase was up to 12 days, followed by an end-of-study visit (shown as day 21 in plots). For both the 10 g and 5 g doses, potassium was consistently lower compared with placebo. By the end of the study, after cessation of SZC dosing, mean potassium approached placebo level.

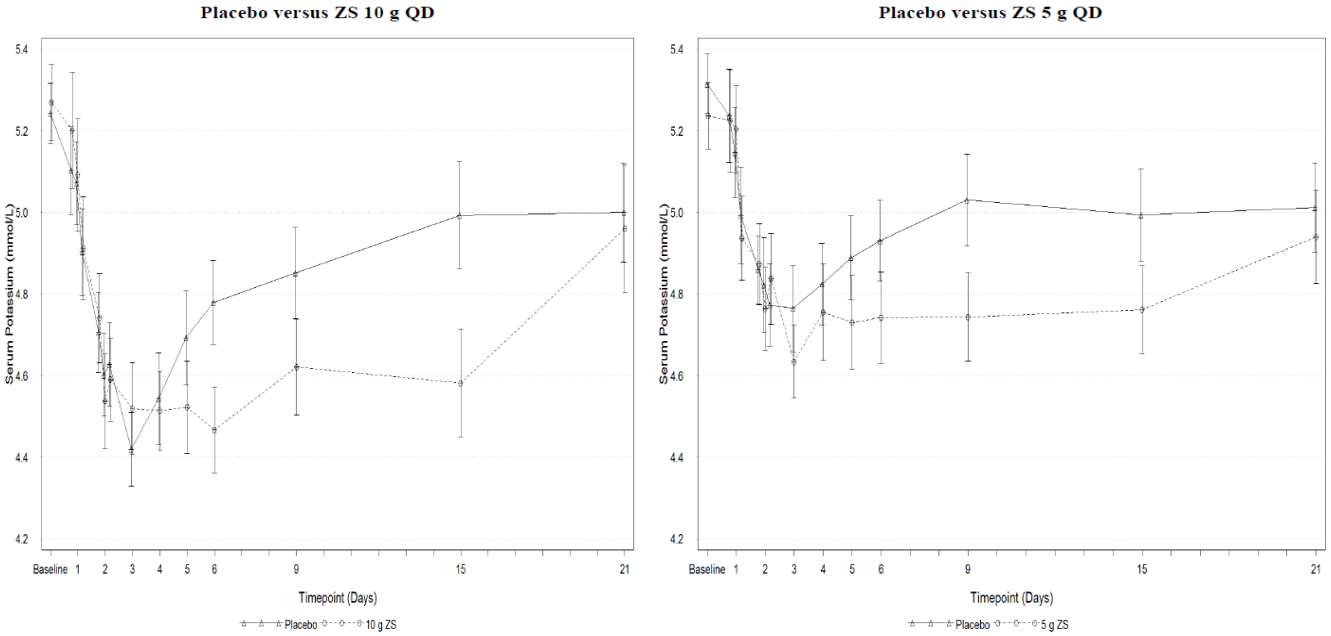
In the closed order testing procedure, the first five tests were statistically significant. For the maintenance phase, this meant that the 10 g and 5 g once-daily doses were statistically significantly different from placebo for the exponential rate of change in serum potassium. For both doses, the exponential rate of increase was slower than placebo (the 5 g slope was 0.0009 versus placebo slope of 0.005; the 10 g slope was 0.001 versus placebo slope of 0.01) (Table 22). Therefore, the change in serum potassium after achieving potassium normalization was less in the active treatment groups compared with the placebo groups. All other outcomes were outside of the sequential closed testing procedure; therefore, conclusions about statistical significance cannot be made. As shown in Table 22, both the 5 g and 10 g dosage groups had smaller changes in serum potassium from maintenance-phase baseline to day 12 (5 g versus placebo was 0.14 mmol/L versus 0.24 mmol/L; 10 g versus placebo was 0.06 mmol/L versus 0.58 mmol/L). However, at the end-of-study visit, the mean changes in serum potassium were similar between the placebo and active treatment groups, demonstrating that potassium increases after discontinuation of treatment. The median time to a potassium increase of 0.5 mmol/L was 18 days in the 5 g and 10 g groups, and three days or six days in the placebo groups. The median time for potassium to return to original acute-phase levels was six days for the 5 g group versus two days for the placebo group, and 18 days for the 10 g group versus 12 days for the placebo group. The mean number of normokalemic days was higher with active treatment (nine days for 5 g versus six days placebo, and 10 days for 10 g versus eight days for placebo). At day 12, the proportion of patients who remained normokalemic was larger in the 5 g and 10 g groups compared with placebo; however, these differences were minimal by the end-of-study visit.

Subgroups were not part of the sequential testing procedure; therefore, the following results are descriptive only. Figure 14 and Figure 15 in Appendix 3 show the mean change in serum potassium in subgroups from maintenance-phase baseline to day 12 for 10 g versus placebo and 5 g versus placebo, respectively. The subgroups were defined by eGFR, baseline serum potassium, use of RAASi medication, congestive heart disease, and CKD. Except for patients with an eGFR of less than 15 mL/min/1.73m^2, all other subgroups experienced a smaller positive change in potassium with SZC 10 g compared with placebo. In the subgroup where eGFR was less than 15 mL/min/1.73m^2, the 10 g group had a larger positive increase in potassium than placebo. Similar results were observed for the 5 g dose,

except that patients with an eGFR less than 15 mL/min/1.73m^2 or an eGFR greater than or equal to 60 mL/min/1.73m^2 had larger positive increases in potassium than placebo.

Table 46 in Appendix 3 provides the proportion of patients who achieved normokalemia at maintenance-phase day 12 for subgroups. Except for those with eGFR less than 15 mL/min/1.73m^2 (5 g: placebo = 100% [N = 2] versus SZC = 5 g 60% [N = 5]; 10 g: placebo = 60% [N = 5] and SZC 10 g = 33.3% [N = 3]), all other subgroups had higher percentages of patients achieving normokalemia in the 5 g and 10 g groups compared with placebo.

Figure 8: Mean Serum Potassium (± 2 Standard Error) in Maintenance Phase of Study ZS-003



q.d. = every day; SZC = sodium zirconium cyclosilicate.

Source: Extracted from Clinical Study Report for Study ZS-003.[23]

Table 22: Serum Potassium Outcomes in Maintenance Phase of Study ZS-003

	Study ZS-003			
	PBO (N = 68)	**SZC 5 g (N = 64)**	**PBO (N = 61)**	**SZC 10 g (N = 63)**
Exponential rate of S-K change (day 12 of maintenance phase)				
Estimate	0.00470	0.00090	0.01039	0.00137
P value	—	0.0083	—	< 0.0001
Change from maintenance baseline S-K[a]				
Day 12 (end of treatment)				
N	66	60	58	61
Mean change (SD), mmol/L	0.24 (0.58)	0.14 (0.53)	0.58 (0.49)	0.06 (0.56)
P value	—	NS	—	≤ 0.001
Day 18 (EOS)				
N	67	62	59	63
Mean change (SD), mmol/L	0.26 (0.56)	0.30 (0.54)	0.59 (0.50)	0.44 (0.65)
P value	—	NS	—	NS
Time to S-K increase of 0.5 mmol/L[a]				
Median, days	6.0	18.0	3.0	18.0
P value	—	0.2127	—	0.0008
Time to relapse of S-K (return to acute-phase baseline value)[a]				
Median, days	2.0	6.0	12.0	18.0
P value	—	0.0328	—	0.4177
Number of days normokalemic (S-K 3.5 mmol/L to 5.0 mmol/L)[a]				
N	68	64	61	63
Mean (SD), days	6.0 (4.4)	9.0 (4.2)	8.2 (4.6)	10.2 (4.0)
P value	—	0.0002	—	0.0338
Percentage who retained normal S-K (3.5 mmol/L to 5.0 mmol/L)[a]				
Day 12 (end of treatment)				
N	66	60	58	61
n (%)	32 (48.5)	45 (75.0)	33 (56.9)	50 (82.0)
P value	—	0.0033	—	0.0048
Day 18 (EOS)				
N	68	64	61	63
n (%)	37 (54.4)	37 (57.8)	37 (60.7)	39 (61.9)
P value	—	0.7282	—	1.0000

EOS = end of study; NS = not significant; PBO = placebo; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] Outcome was not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for Study ZS-003.[23]

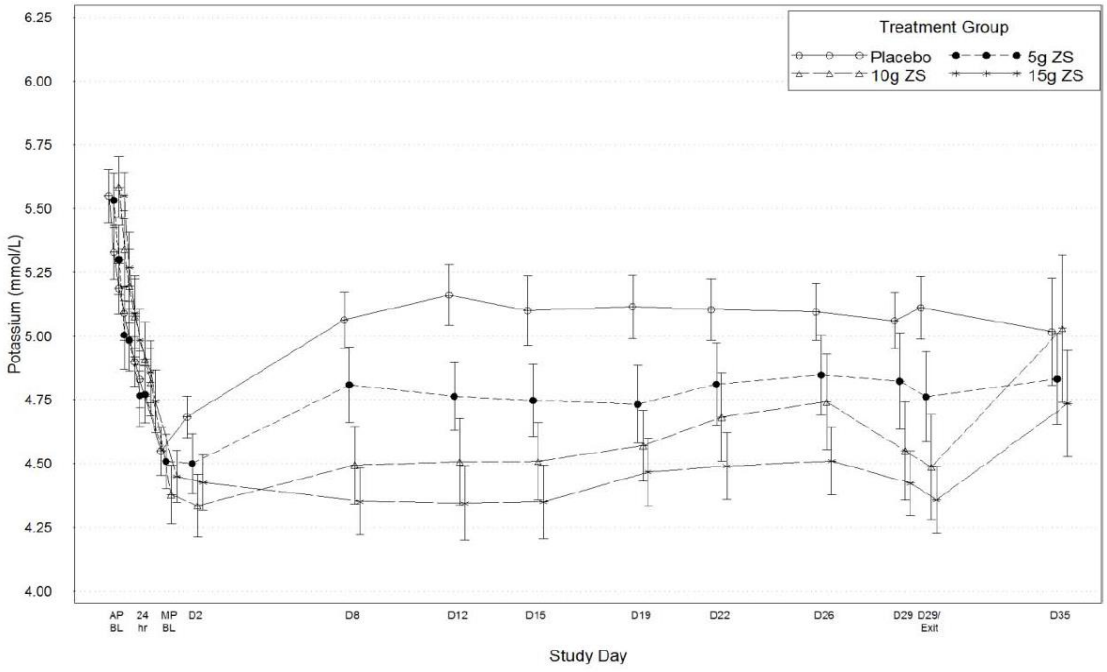
Study ZS-004

Figure 9 shows mean serum potassium over the 28-day maintenance phase and at the day 35 end-of-study visit in Study ZS-004. The placebo, 5 g, 10 g, and 15 g groups are displayed; in this review, the 15 g dose is not evaluated. The mean serum potassium was lower in the 10 g (line that is second-closest to the x-axis) and 5 g (line that is third-closest to the x-axis) groups than in the placebo group (line furthest from the x-axis). After discontinuation of active treatment, the potassium levels at the end-of-study visit on day 35 converged in all groups.

The LSM of serum potassium from day 8 to day 29 was statistically significantly lower for the 5 g group versus the placebo group (4.8 mmol/L versus 5.1 mmol/L) and for the 10 g group versus the placebo group (4.5 mmol/L vs. 5.1 mmol/L) (Table 23). In a sensitivity analysis for the LSM of serum potassium that imputed data for patients who discontinued the study drug prior to obtaining a serum potassium level at maintenance-phase day 8, the results were the same. Both dosage groups also had statistically significantly higher numbers of normokalemic days, a measurement that was assessed as part of the sequential testing procedure (13.4 days versus 7.4 days for 5 g versus placebo, and 13.9 days versus 7.4 days for 10 g versus placebo). All other outcomes were outside of the sequential testing; therefore, conclusions about statistical significance cannot be made. As shown in Table 23, the mean change in serum potassium at day 29 from maintenance-phase baseline was lower for 5 g (0.25 mmol/L) and 10 g (0.1 mmol/L) than for placebo (0.6 mmol/L). The median time to hyperkalemia (serum potassium ≥ 5.1 mmol/L) was longer for 5 g (14 days) than for placebo (seven days), and was not yet reached for 10 g. The median time for serum potassium to return to the original acute-phase baseline was 29 days in the 5 g group, 19 days in the placebo group, and not yet reached for the 10 g group. The percentages of patients who remained normokalemic at day 29 were 71.1% for 5 g, 76% for 10 g, and 47.6% for placebo.

Subgroups were not part of the sequential testing procedure; therefore, the following results are descriptive only. Figure 16 in Appendix 3 displays the LSM for serum potassium through days 8 to 29 for patients on RAASi medication, with heart failure, or with CKD for both the 5 g versus placebo and 10 g versus placebo groups. The LSM was lower for both dosage groups than for placebo. For subgroups defined by baseline serum potassium, CKD, heart failure, or use of RAASi medication, the mean change in serum potassium from maintenance-phase baseline to day 29 was numerically smaller for the 5 g and 10 g groups than for placebo (Table 47, Appendix 3). More patients with CKD, heart failure, or using RAASi medication in the 5 g and 10 g groups achieved normokalemia than patients in the placebo group.

Figure 9: Mean Serum Potassium (± 2 Standard Error) in Maintenance Phase of Study ZS-004



SZC = sodium zirconium cyclosilicate

Source: Extracted from Clinical Study Report for Study ZS-004.[25]

Table 23: Serum Potassium Outcomes in Maintenance Phase of Study ZS-004

	Study ZS-004		
	Placebo (N = 85)	**SZC 5 g (N = 45)**	**SZC 10 g (N = 51)**
LSM S-K (days 8 to 29)[a]			
N	82	45	50
LSM (95 % CI), mmol/L	5.1 (5.0 to 5.2)	4.8 (4.6 to 4.9)	4.5 (4.4 to 4.6)
P value	—	0.0001	< 0.0001
Change in S-K[b,c]			
Day 29			
N	82	45	50
Mean change (SD), mmol/L	0.6 (0.6)	0.25 (0.6)	0.1 (0.8)
P value	—	≤ 0.01	≤ 0.001
Day 35 (EOS)			
N	31	22	27
Mean change (SD), mmol/L	0.5 (0.7)	0.3 (0.5)	0.7 (0.8)
P value	---	0.2226	0.3752
Time to hyperkalemia (S-K ≥ 5.1 mmol/L) from maintenance-phase baseline[c]			
Median, days	7	14	Not reached

	Study ZS-004		
P value	—	0.0012	< 0.0001
Time to relapse of S-K (return to acute-phase baseline value) from maintenance-phase baseline[c]			
Median, days	19	29	Not reached
P value	—	0.0045	0.0001
Number of normokalemic days (S-K 3.5 mmol/L to 5.0 mmol/L)			
N	82	45	50
Mean (SE), days	7.4 (8.0)	13.4 (7.6)	13.9 (7.9)
P value	—	0.0001	< 0.0001
Percentage of patients who remained normokalemic			
Maintenance-phase baseline			
N	82	45	50
n (%)	71 (86.6)	42 (93.3)	46 (92.0)
Day 29			
N	82	45	50
n (%)	39 (47.6)	32 (71.1)	38 (76.0)
P value	—	≤ 0.05	≤ 0.01
Day 35 (EOS)			
N	31	22	27
n (%)	16 (51.6)	14 (63.6)	13 (48.1)
P value	—	0.4148	1.0000
Percentage of patients with S-K < 5.1 mmol/L (days 8 to 29)[c]			
N	82	45	50
n (%)	38 (46.3)	36 (80.0)	45 (90.0)
Percentage of patients with S-K < 5.6 mmol/L (days 8 to 29)[c]			
N	82	45	50
n (%)	70 (85.4)	44 (97.8)	50 (100)

CI = confidence interval; eGFR = estimated glomerular filtration rate; EOS = end of study; LSM = least squares mean; SE = standard error; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] From a mixed-effects model of serial S-K observations between maintenance-phase days 8 to 29 with a patient random effect and the following fixed effects: maintenance-phase treatment group, acute-phase baseline eGFR, acute-phase baseline S-K, maintenance-phase baseline S-K, age category (< 55 years, 55 years to 64 years, ≥ 65 years), use of RAASi, and disease status for chronic kidney disease, congestive heart failure, and diabetes mellitus.

[b] From maintenance-phase baseline.

[c] Outcome was not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for Study ZS-004.[25]

Study ZS-D9480

In Study ZS-D9480, the sequential testing procedure included LSM of serum potassium, the proportion of patients who remained normokalemic, the number of days remaining normokalemic, and time to hyperkalemia. Therefore, statistical inferences can be made for these outcomes. In the 28-day maintenance phase of Study ZS-D9480 (Table 24), the

primary outcome of LSM serum potassium was statistically significantly lower for 5 g versus placebo (4.8 mmol/L versus 5.3 mmol/L) and 10 g versus placebo (4.4 mmol/L versus 5.3 mmol/L). In a sensitivity analysis that used i-STAT potassium values rather than central laboratory analyses, the LSM for the 5 g and 10 g groups remained lower than for placebo (P < 0.001). In another sensitivity analysis that adjusted for the change to the potassium assay during the study, results for the 5 g and 10 g groups were also lower than for placebo (P < 0.001). At day 29, the proportion of patients who remained normokalemic was statistically significantly higher for the 5 g group (58.6%) and 10 g group (77.3%) compared with placebo (24.0%). The 5 g and 10 g groups also had higher numbers of normokalemic days (LSM 10.8 days for 5 g, 15.6 days for 10 g, and 3.5 days for placebo). The median time to hyperkalemia (serum potassium ≥ 5.1 mmol/L) was statistically significantly different for the 5 g group versus the placebo group (14 versus five days) and for the 10 g group versus the placebo group (29 versus five days).

Subgroups were not part of the sequential testing procedure; therefore, the following results are descriptive only. Table 49 in Appendix 3 provides the LSM serum potassium over maintenance days 8 to 29 for patients with CKD, heart failure, or use of RAASi medication. In the 5 g and 10 g groups, the LSMs were 4.8 mmol/L and 4.4 mmol/L, respectively, in all three subgroups. For placebo, the LSM ranged from 5.2 mmol/L to 5.4 mmol/L. The proportion of patients who achieved normokalemia was higher for 5 g and 10 g compared with placebo for all subgroups (Table 50, Appendix 3). However, none of the treatment-by-subgroup interactions were statistically significant.

Table 24: Serum Potassium Outcomes in Maintenance Phase of Study ZS-D9480

	Study ZS-D9480		
	Placebo (N = 50)	**SZC 5 g (N = 99)**	**SZC 10 g (N = 99)**
LSM S-K (days 8 to 29)			
N	49	95	96
LSM (SE), mmol/L	5.3 (0.02)	4.8 (0.01)	4.4 (0.01)
LSM difference (95% CI)[a]	—	0.90 (0.88 to 0.93)	0.82 (0.80 to 0.85)
P value	—	< 0.001	< 0.001
Change in S-K[b,c]			
Day 29			
N	41	86	88
Mean (SD), mmol/L	5.45 (0.57)	4.87 (0.56)	4.45 (0.62)
Mean change (SD), mmol/L	1.0 (0.6)	0.5 (0.6)	0.02 (0.7)
Day 35 (EOS)			
N	50	98	99
Mean (SD), mmol/L	5.31 (0.65)	5.29 (0.66)	5.21 (0.73)
Mean change (SD), mmol/L	0.88 (0.68)	0.92 (0.66)	0.77 (0.70)
Time to hyperkalemia (S-K ≥ 5.1 mmol/L)			
N	50	99	99
Median, days	5	14	29
HR (95% CI)[d]	—	0.4 (0.3 to 0.7)	0.2 (0.1 to 0.3)
P value	—	< 0.001	< 0.001

		Study ZS-D9480	
Number of normokalemic days (S-K 3.5 mmol/L to 5.0 mmol/L)			
N	50	99	97
LSM (SE), days	3.5 (1.4)	10.8 (1.1)	15.6 (1.1)
LSM difference (95% CI)[e]	—	7.3 (4.3 to 10.2)	12.1 (9.1 to 15.0)
P value	—	< 0.001	< 0.001
Percentage of patients who achieved normokalemia			
Day 29			
N	50	99	97
n (%)	12 (24.0)	58 (58.6)	75 (77.3)
P value[f]	—	< 0.001	< 0.001

CI = confidence interval; eGFR = estimated glomerular filtration rate; EOS = end of study; HR = hazard ratio; LSM = least squares mean; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; SE = standard error; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] From a mixed-effects model of serum potassium levels, with a patient random effect and fixed effects of treatment group, treatment by visit interaction, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline eGFR, age category (< 55 years, 55 years to 64 years, and ≥ 65 years), country, RAASi use, chronic kidney disease, heart failure, and diabetes mellitus.

[b] From maintenance-phase baseline.

[c] Outcome was not part of the sequential closed statistical testing procedure.

[d] From a Cox proportional hazards model that included covariates of treatment group, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline eGFR, age category (< 55 years, 55 years to 64 years, and ≥ 65 years), country, baseline RAASi use, chronic kidney disease, heart failure, and diabetes mellitus.

[e] From a linear regression model that included covariates of treatment group, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline eGFR, age category (< 55 years, 55 years to 64 years, and ≥ 65 years), country, baseline RAASi use, chronic kidney disease, heart failure, and diabetes mellitus.

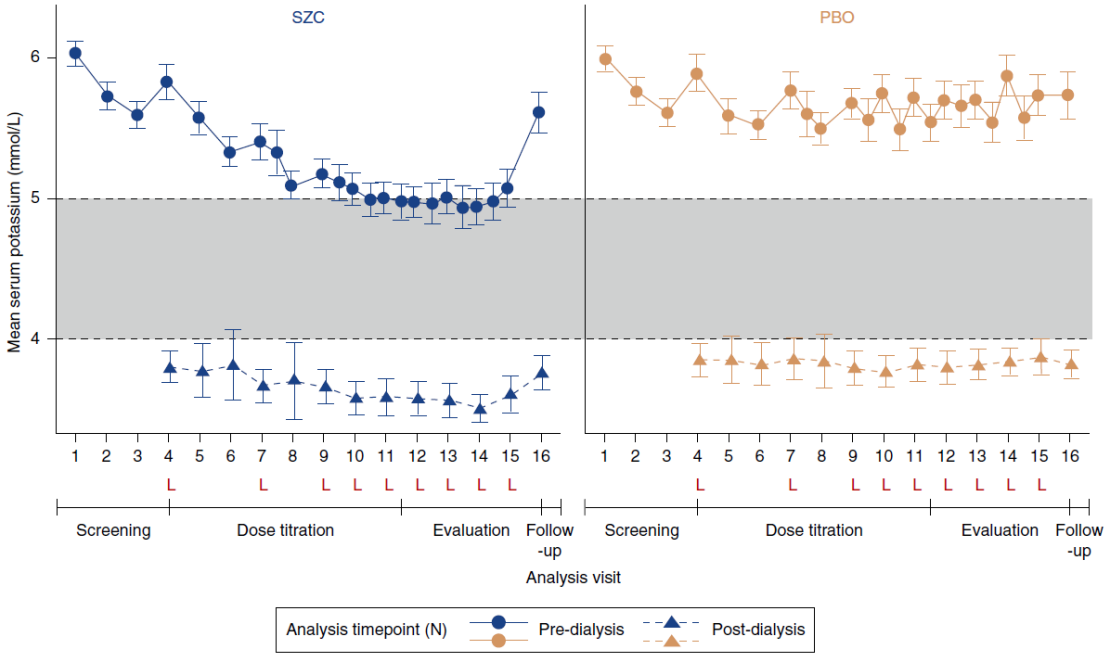
[f] From a logistic regression model that included covariates of treatment group, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline eGFR, age category (< 55 years, 55 years to 64 years, and ≥ 65 years), country, baseline RAASi use, chronic kidney disease, heart failure, and diabetes mellitus.

Source: Clinical Study Report for Study ZS-D9480.[26]

DIALIZE Study

The mean serum potassium levels before and after dialysis for patients who received SZC (first panel) or placebo (second panel) in DIALIZE is shown in Figure 10. Table 25 provides results for the efficacy outcomes in DIALIZE. The primary outcome (i.e., the proportion of patients who maintained pre-dialysis serum potassium of 4.0 mmol/L to 5.0 mmol/L and did not require urgent rescue therapy) was met by more patients in the SZC group compared to placebo (41.2% versus 1.0%, P < 0.001). In a sensitivity analysis of the primary outcome that replaced missing central laboratory potassium values with i-STAT measurements, the findings were consistent with the main analysis (42.3% versus 2.0%, P < 0.001). Urgent rescue therapy was needed by two patients in the treatment group and five in the placebo group. In post hoc analyses, pre-dialysis serum potassium was between 4.0 mmol/L and 5.0 mmol/L, or between 3.5 mmol/L and 5.5 mmol/L, more frequently with SZC than placebo (e.g., 23.7% of patients in the SZC group had at least four pre-dialysis potassium level between 4 mmol/L and 5 mmol/L, whereas there were no such patients in the placebo group). Fewer patients who received SZC also had serum potassium levels ≥ 6 mmol/L after the long interdialytic interval.

Figure 10: Mean Serum Potassium in DIALIZE



PBO = placebo; SZC = sodium zirconium cyclosilicate.

Source: Republished with permission of by the American Society of Nephrology, from A phase IIIb, randomized, double-blind, placebo-controlled study of SZC for reducing the incidence of pre-dialysis hyperkalemia, Fishbane S et al., JASN, 30 (6), © 2019; permission conveyed through Copyright Clearance Center, Inc.[19]

Table 25: Serum Potassium Outcomes and Need for Rescue Therapy in DIALIZE

	DIALIZE	
	Placebo (N = 99)	**SZC (N = 97)**
Maintained pre-dialysis S-K of 4.0 mmol/L to 5.0 mmol/L and did not require urgent rescue therapy		
N (%)	1 (1.0)	40 (41.2)
OR (95% CI)	68.8 (10.9 to 2,810.9)	
P value	< 0.001	
Need for urgent rescue therapy		
N (%)	5 (5.1)	2 (2.1)
Number of pre-dialysis S-K between 4.0 mmol/L and 5.0 mmol/L[a]		
At least 1, N (%)	26 (26.3)	76 (78.4)
At least 2, N (%)	12 (12.1)	56 (57.7)
At least 3, N (%)	1 (1.0)	40 (41.2)
At least 4, N (%)	0 (0.0)	23 (23.7)
Number of pre-dialysis S-K between 3.5 mmol/L and 5.5 mmol/L[a]		
At least 1, N (%)	67 (67.7)	92 (94.8)

	DIALIZE	
	Placebo (N = 99)	SZC (N = 97)
At least 2, N (%)	35 (35.4)	84 (86.6)
At least 3, N (%)	21 (21.2)	68 (70.1)
At least 4, N (%)	5 (5.1)	50 (51.5)
Maximum S-K ≥ 6 mmol/L after the long interdialytic interval during the stable dose evaluation period[a]		
6.0 mmol/L to 6.5 mmol/L, N (%)	30 (73.2)	11 (26.8)
6.5 mmol/L to 7.0 mmol/L, N (%)	13 (92.9)	1 (7.1)
≥ 7.0 mmol/L, N (%)	13 (86.7)	2 (13.3)

CI = confidence interval; OR = odds ratio; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

[a] Post hoc analysis.

Source: Fishbane et al. (2019).[19]

Harms

Acute Phase

Table 26 provides harms for the acute phase of Study ZS-003 and Table 27 provides harms for Study ZS-D9482. Both had comparisons with placebo. Data for the open-label, single-arm, acute phases of studies ZS-004 and ZS-D9480 are described in the text.

Adverse Events

In Study ZS-003, a similar percentage of patients in the placebo and SZC 10 g groups experienced at least one AE (10.8% and 11.9%, respectively). The most common AEs were gastrointestinal (i.e., constipation, diarrhea, and vomiting). In Study ZS-D9482, one patient in the placebo group and five patients in the SZC group experienced at least one AE. In Study ZS-004, 20 of 258 patients (7.8%) had at least one AE; the most common was diarrhea (1.2%). In Study ZS-D9480, 17 of 267 patients (6.4%) had at least one AE; the most common was edema (1.1%).

Serious Adverse Events

In Study ZS-003, one patient who received placebo experienced an SAE (acute renal failure).

Withdrawals Due to Adverse Events

In Study ZS-003, there was one WDAE (due to vomiting and diarrhea) in a patient on SZC. Studies ZS-004 and ZS-D9480 each had one WDAE; the cause in Study ZS-004 was QT prolongation.

Mortality

No deaths occurred in the acute phase.

Notable Harms

In Study ZS-003, constipation was slightly more frequent with SZC (2.1% versus 0.6%). Peripheral edema occurred in two patients on SZC and in no patients on placebo. In addition, one patient in the SZC group experienced each of hypokalemia, atrial fibrillation, palpitations, and hypertension. In Study ZS-D9482, the SZC group had one patient with

ventricular extrasystoles, two patients with hypokalemia (potassium less than 3.5 mmol/L), and one patient with hypokalemia (serum potassium level less than 3.0 mmol/L). None of these events occurred in patients on placebo. In Study ZS-004, constipation occurred in two patients; there was an ECG change in one patient; and one patient experienced hypokalemia. In Study ZS-D9480, gastrointestinal effects were experienced by three patients, including one with constipation and one with intestinal obstruction. Angina pectoris, hypertension, atrial fibrillation, palpitations, and supraventricular extrasystoles occurred in one patient. Edema was present in three patients: peripheral edema in two and peripheral swelling in one.

Table 26: Harms in Acute Phase of Study ZS-003

	Study ZS-003	
	Placebo (N = 158)	**SZC 10 g (N = 143)**
Patients with ≥ 1 AEs, N (%)	17 (10.8)	17 (11.9)
Most common AEs[a]		
Constipation	1 (0.6)	3 (2.1)
Diarrhea	4 (2.5)	1 (0.7)
Vomiting	2 (1.3)	1 (0.7)
Peripheral edema	0 (0)	2 (1.4)
SAEs		
Patients with ≥ 1 SAEs, N (%)	1 (0.6)	0 (0)
Acute renal failure	1 (0.6)	0 (0)
WDAEs		
WDAEs, N (%)	0 (0)	1 (0.7)
Vomiting and diarrhea	0 (0)	1 (0.7)
Deaths		
Number of deaths, N (%)	0 (0)	0 (0)
Notable harms		
Gastrointestinal	8 (5.1)	5 (3.5)
Constipation	1 (0.6)	3 (2.1)
Peripheral edema	0 (0)	2 (1.4)
Low potassium (below normal range)	0 (0)	1 (0.7)
Acute renal failure	1 (0.6)	0 (0)
Increased blood creatinine	1 (0.6)	0 (0)
Atrial fibrillation	0 (0)	1 (0.7)
Palpitations	0 (0)	1 (0.7)
Hypertension	0 (0)	1 (0.7)

AE = adverse event; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

Source: Clinical Study Report for Study ZS-003.[23]

Table 27: Harms in Study ZS-D9482

	Study ZS-D9482	
	Placebo (N = 33)	**SZC 10 g (N = 36)**
Patients with ≥ 1 AEs, N (%)	1 (3.0)	5 (13.9)
Most common AEs[a]		
Erythema	0 (0)	1 (2.8)
Hypoglycemia	0 (0)	1 (2.8)
Respiratory tract infection	1 (3.0)	0 (0)
Tension headache	0 (0)	1 (2.8)
Tremor	0 (0)	1 (2.8)
Ventricular extrasystoles	0 (0)	1 (2.8)
Hypokalemia (< 3.5 mmol/L)	0 (0)	2 (5.6)
Hypokalemia (< 3.0 mmol/L)	0 (0)	1 (2.8)
SAEs		
Patients with > 0 SAEs, N (%)	0 (0)	0 (0)
WDAEs		
WDAEs, N (%)	0 (0)	0 (0)
Deaths		
Number of deaths, N (%)	0 (0)	0 (0)
Notable Harms		
Ventricular extrasystoles	0 (0)	1 (2.8)
Hypokalemia (< 3.5 mmol/L)	0 (0)	2 (5.6)
Hypokalemia (< 3.0 mmol/L)	0 (0)	1 (2.8)

AE = adverse event; SAE = serious adverse event; SZC= sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

Source: Clinical Study Report for Study ZS-D9482.[27]

Maintenance Phase

Table 28, Table 29, Table 30, and Table 32 provide harms in the maintenance phases of studies ZS-003, ZS-004, ZS-D9480, and DIALIZE, respectively.

Adverse Events

In Study ZS-003, AEs were experienced by more than a fifth of patients on placebo and on SZC 5 g (23.5% and 21.5%, respectively). More patients in the SZC 10 g group experienced an AE (33.3%) than did those on placebo (24.6%). In Study ZS-004, AEs occurred in 31.8% patients on placebo, 53.3% of patients on SZC 5 g, and 29.4% of patients on SZC 10 g. In Study ZS-D9480, AEs were experienced by 20% of patients on placebo, 28.3% on 5 g, and 44.4% on 10 g. In DIALIZE, 46.5% of patients on placebo and 41.7% on SZC had an AE.

Serious Adverse Events

In Study ZS-003, SAEs were experienced by three patients in the 5 g group and two patients in the corresponding placebo group, and by one patient each in the 10 g and corresponding placebo groups. In Study ZS-004, SAEs occurred in five patients in the 5 g group, two patients in the 10 g group, and none in the placebo group. The SAEs for 5 g were

congestive cardiac failure, small intestinal obstruction, hepatotoxicity, pneumonia, and confusional state. The SAEs for 10 g were myocardial infarction and cellulitis. In Study ZS-D9480, SAEs occurred in one patient on placebo, four patients on 5 g, and three patients on 10 g. The SAEs for 5 g were infectious colitis, pneumonia, congestive cardiac failure, hypertension, and gastritis. The SAEs for 10 g were cystitis, upper respiratory tract infection, cardiac failure, and renal impairment. In DIALIZE, SAEs were experienced by eight patients on placebo and seven on SZC. The most common SAE in the active treatment group was angina pectoris; the most common SAEs in the placebo group were hyperkalemia and fluid overload.

Withdrawals Due to Adverse Events

In Study ZS-003, three patients in the 5 g group withdrew due to an AE versus none in the placebo group. The reasons for withdrawal were bradycardia; a combination of diastolic dysfunction, pulmonary edema, and renal failure; and a combination of vomiting, diarrhea, and long QT syndrome. There was also one WDAE in the 10 g group (due to gout) and one in the placebo group (due to gastroenteritis). In Study ZS-004, there were four WDAEs in the 5 g group and none in the placebo or 10 g groups. The reasons for WDAEs included small intestinal obstruction, QT prolongation, confusional state, and renal failure. In Study ZS-D9480, the placebo group had three WDAEs due to hyperkalemia and bronchial obstruction. There were seven WDAEs in both the 5 g and 10 g groups. The reasons for withdrawal in the 5 g group included pneumonia, hyperkalemia, congestive cardiac failure, ventricular extrasystoles, and peripheral edema. In the 10 g group, the reasons included hypokalemia, atrial fibrillation, cardiac failure, edema, and edema due to renal disease. In DIALIZE, WDAEs occurred in two patients in the placebo group and four in the SZC group.

Mortality

In Study ZS-003, there was one death in the 5 g group due to respiratory distress. In Study ZS-004, one death in the 10 g group occurred due to myocardial infarction. In DIALIZE, one patient on SZC died due to peripheral arterial occlusive disease.

Notable Harms

Gastrointestinal

In Study ZS-003, gastrointestinal effects were experienced by a similar number of patients in the 5 g and placebo groups (7.7% versus 7.4%), whereas in the 10 g versus placebo groups, the figures were 4.8% versus 0%. Constipation occurred in two patients receiving 10 g, but in none in the other groups. In Study ZS-004, gastrointestinal effects were experienced by 14.1% on placebo, 6.7% on 5 g, and 2.0% on 10 g. Constipation was reported by a single patient on 10 g and by six patients on placebo. Small intestinal obstruction occurred in one patient on 5 g. In Study ZS-D9480, gastrointestinal effects were more common in the 10 g (13.1%) group than in the 5 g (6.1%) or placebo (6.0%) groups. Constipation occurred in nine patients on 10 g, in one patient on 5 g, and in none in placebo. One patient on 5 g had an intestinal obstruction. In DIALIZE, three patients on placebo and four on SZC had constipation.

Cardiovascular

In Study ZS-003, one patient in the 10 g group had atrial fibrillation and one patient in the 5 g group had long QT syndrome. In Study ZS-004, one patient in the 10 g group experienced both acute cardiac failure and myocardial infarction. In the 5 g group, one patient had congestive cardiac failure and QT prolongation. Hypertension was experienced by one

patient on placebo, two patients on 5 g, and one on 10 g. In Study ZS-D9480, one patient in the 10 g group experienced angina pectoris, atrial fibrillation, and chronic/cardiac failure, and two patients experienced ventricular extrasystoles. In the 5 g group, one patient experienced angina pectoris, supraventricular extrasystoles, ventricular extrasystoles, and chronic/congestive cardiac failure. Hypertension occurred in two patients on placebo, three on 5 g, and two on 10 g. in DIALIZE, angina pectoris was the most common (n = 2) SAE in the SZC group.

Renal

In Study ZS-003, one patient in the 10 g group had renal impairment; none in the other groups had this. In Study ZS-004, two patients in the 5 g group were identified as having renal failure and one as having acute renal failure; however, neither of these events occurred in the placebo or 10 g groups. In Study ZS-D9480, renal impairment occurred in one patient on 10 g. No patients on placebo or 5 g experienced this.

Edema

In Study ZS-003, two patients in the 10 g group and two in the placebo group (of 5 g) had peripheral edema. In Study ZS-004, peripheral edema or edema occurred in three patients in the 10 g group, one patient in the 5 g group, and two patients on placebo. In Study ZS-D9480, eight patients were identified as having edema in the 10 g group; there was one in the 5 g group. Seven patients on 10 g and four on 5 g reported peripheral edema. No cases of edema occurred in the placebo group.

Hypokalemia

In Study ZS-003, one patient in the placebo group (of 10 g) had low potassium; there were no cases in the SZC groups. In Study ZS-004, hypokalemia occurred in eight patients (15.7%) in the 10 g group, and in none in the placebo or 5 g groups. In Study ZS-D9480, one patient experienced hypokalemia in the 10 g group; there were no cases in the placebo or 5 g group. In DIALIZE, five patients in both the placebo and SZC groups experienced pre-dialysis hypokalemia.

Table 28: Harms in Maintenance Phase of Study ZS-003

	Study ZS-003			
	PBO (N = 68)	**SZC 5 g (N = 65)**	**PBO (N = 61)**	**SZC 10 g (N = 63)**
Patients with ≥ 1 AEs, N (%)	16 (23.5)	14 (21.5)	15 (24.6)	21 (33.3)
Most common AEs[a]				
Atrial fibrillation	1 (1.5)	0 (0)	0 (0)	1 (1.6)
Constipation	0 (0)	0 (0)	0 (0)	2 (3.2)
Diarrhea	3 (4.4)	2 (3.1)	0 (0)	0 (0)
Dyspepsia	0 (0)	2 (3.1)	0 (0)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	1 (1.6)
Vomiting	0 (0)	3 (4.6)	0 (0)	0 (0)
Malaise	0 (0)	0 (0)	0 (0)	1 (1.6)
Peripheral edema	2 (2.9)	0 (0)	0 (0)	2 (3.2)
Upper respiratory tract infection	1 (1.5)	0 (0)	0 (0)	1 (1.6)
Urinary tract infection	0 (0)	5 (7.7)	0 (0)	4 (6.3)

	Study ZS-003			
	PBO (N = 68)	SZC 5 g (N = 65)	PBO (N = 61)	SZC 10 g (N = 63)
Bacterial urinary tract infection	1 (1.5)	1 (1.5)	0 (0)	0 (0)
Laceration	0 (0)	0 (0)	1 (1.6)	0 (0)
Blood potassium increase	1 (1.5)	1 (1.5)	0 (0)	0 (0)
Transaminases increase	1 (1.5)	0 (0)	1 (1.6)	0 (0)
Muscle spasms	1 (1.5)	0 (0)	1 (1.6)	0 (0)
Acute renal failure	0 (0)	0 (0)	1 (1.6)	0 (0)
Renal impairment	0 (0)	0 (0)	0 (0)	1 (1.6)
Cough	0 (0)	0 (0)	0 (0)	1 (1.6)
Dyspnea	0 (0)	0 (0)	0 (0)	1 (1.6)
Hypertension	1 (1.5)	0 (0)	2 (3.3)	1 (1.6)
SAEs				
Patients with ≥ 1 SAEs, N (%)	2 (2.9)	3 (4.6)	1 (1.6)	1 (1.6)
Most common SAEs[a]				
Blood potassium increase	1 (1.5)	0 (0)	0 (0)	0 (0)
Congestive cardiac failure	1 (1.5)	0 (0)	0 (0)	0 (0)
Diastolic dysfunction	0 (0)	1 (1.5)	0 (0)	0 (0)
Nocardiosis	0 (0)	1 (1.5)	0 (0)	0 (0)
Loss of consciousness	0 (0)	1 (1.5)	0 (0)	0 (0)
Renal failure	0 (0)	1 (1.5)	0 (0)	0 (0)
Pulmonary edema	0 (0)	1 (1.5)	0 (0)	0 (0)
Respiratory arrest	0 (0)	1 (1.5)	0 (0)	0 (0)
Hospitalization	0 (0)	1 (1.5)	0 (0)	0 (0)
Gastroenteritis	0 (0)	0 (0)	1 (1.6)	0 (0)
Gout	0 (0)	0 (0)	0 (0)	1 (1.6)
WDAEs				
WDAEs, N (%)	0 (0)	3 (4.6)	1 (1.6)	1 (1.6)
Most common reasons				
Chest pain and dyspnea	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	0 (0)	1 (1.5)	0 (0)	0 (0)
Diastolic dysfunction, pulmonary edema, and renal failure	0 (0)	1 (1.5)	0 (0)	0 (0)
Vomiting, diarrhea, and long QT syndrome	0 (0)	1 (1.5)	0 (0)	0 (0)
Gastroenteritis	0 (0)	0 (0)	1 (1.6)	0 (0)
Gout	0 (0)	0 (0)	0 (0)	1 (1.6)
Deaths				
Number of deaths, N (%)	0 (0)	1 (1.5)	0 (0)	0 (0)
Notable harms				
Gastrointestinal	5 (7.4)	5 (7.7)	0 (0)	3 (4.8)
Constipation	0 (0)	0 (0)	0 (0)	2 (3.2)
Atrial fibrillation	1 (1.5)	0 (0)	0 (0)	1 (1.6)
Long QT syndrome	0 (0)	1 (1.5)	0 (0)	0 (0)

	Study ZS-003			
	PBO (N = 68)	SZC 5 g (N = 65)	PBO (N = 61)	SZC 10 g (N = 63)
Congestive cardiac failure	1 (1.5)	0 (0)	0 (0)	0 (0)
Bradycardia/cardiovascular disorder	0 (0)	0 (0)	1 (1.6)	1 (1.6)
Hypertension	1 (1.5)	0 (0)	2 (3.3)	1 (1.6)
Peripheral edema	2 (2.9)	0 (0)	0 (0)	2 (3.2)
Acute renal failure	0 (0)	0 (0)	1 (1.6)	0 (0)
Renal impairment	0 (0)	0 (0)	0 (0)	1 (1.6)
Low potassium (below normal range)	0 (0)	0 (0)	1 (1.6)	0 (0)

AE = adverse event; PBO = placebo; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

Source: Clinical Study Report for Study ZS-003.[23]

Table 29: Harms in Maintenance Phase of Study ZS-004

	Study ZS-004		
	Placebo (N = 85)	SZC 5 g (N = 45)	SZC 10 g (N = 51)
Patients with ≥ 1 AEs, N (%)	27 (31.8)	24 (53.3)	15 (29.4)
Most common AEs[a]			
Constipation	6 (7.1)	0 (0)	1 (2.0)
Dyspepsia	0 (0)	2 (4.4)	0 (0)
Abdominal pain	1 (1.2)	1 (2.2)	0 (0)
Diarrhea	1 (1.2)	0 (0)	0 (0)
Nausea	1 (1.2)	0 (0)	0 (0)
Vomiting	1 (1.2)	1 (2.2)	0 (0)
Dry mouth	1 (1.2)	0 (0)	0 (0)
Rectal hemorrhage	1 (1.2)	0 (0)	0 (0)
Congestive cardiac failure	0 (0)	1 (2.2)	0 (0)
QT prolongation	0 (0)	1 (2.2)	0 (0)
Hypertension	1 (1.2)	2 (4.4)	1 (2.0)
Fatigue	0 (0)	0 (0)	1 (2.0)
Peripheral edema	2 (2.4)	0 (0)	3 (5.9)
Edema	0 (0)	1 (2.2)	0 (0)
Influenza	0 (0)	0 (0)	1 (2.0)
Nasopharyngitis	1 (1.2)	0 (0)	0 (0)
Pneumonia	0 (0)	1 (2.2)	0 (0)
Respiratory tract infection	1 (1.2)	0 (0)	0 (0)
Upper respiratory tract infection	1 (1.2)	3 (6.7)	1 (2.0)
Diverticulitis	1 (1.2)	0 (0)	0 (0)
Staphylococcal wound infection	1 (1.2)	0 (0)	0 (0)
Gout	0 (0)	1 (2.2)	1 (2.0)
Hypocalcemia	2 (2.4)	0 (0)	0 (0)
Hypoglycemia	0 (0)	1 (2.2)	0 (0)

	Study ZS-004		
	Placebo (N = 85)	**SZC 5 g (N = 45)**	**SZC 10 g (N = 51)**
Hyperglycemia	1 (1.2)	0 (0)	0 (0)
Pain in extremity	1 (1.2)	0 (0)	1 (2.0)
Back pain	1 (1.2)	0 (0)	0 (0)
Bursitis	1 (1.2)	0 (0)	0 (0)
Tendonitis	1 (1.2)	0 (0)	0 (0)
Dizziness	1 (1.2)	0 (0)	1 (2.0)
Renal failure	0 (0)	2 (4.4)	0 (0)
Dysuria	1 (1.2)	1 (2.2)	0 (0)
Hematuria	1 (1.2)	0 (0)	0 (0)
Crystal urine	1 (1.2)	0 (0)	0 (0)
Asthma	1 (1.2)	1 (2.2)	0 (0)
Dyspnea	0 (0)	1 (2.2)	0 (0)
Respiratory tract congestion	1 (1.2)	0 (0)	0 (0)
Rhinorrhea	1 (1.2)	0 (0)	0 (0)
Dermatosis	1 (1.2)	0 (0)	0 (0)
Decreased hemoglobin	1 (1.2)	0 (0)	0 (0)
Abnormal liver function tests	1 (1.2)	0 (0)	0 (0)
SAEs			
Patients with > 0 SAEs, N (%)	0 (0)	5 (11.1)	2 (3.9)
Cause of SAEs, N (%)			
Congestive cardiac failure	0 (0)	1 (2.2)	0 (0)
Myocardial infarction	0 (0)	0 (0)	1 (2.0)
Small intestinal obstruction	0 (0)	1 (2.2)	0 (0)
Hepatotoxicity	0 (0)	1 (2.2)	0 (0)
Cellulitis	0 (0)	0 (0)	1 (2.0)
Pneumonia	0 (0)	1 (2.2)	0 (0)
Confusional state	0 (0)	1 (2.2)	0 (0)
WDAEs			
WDAEs, N (%)	0 (0)	4 (8.9)	0 (0)
Cause of WDAE, N (%)			
Small intestinal obstruction	0 (0)	1 (2.2)	0 (0)
QT prolongation	0 (0)	1 (2.2)	0 (0)
Confusional state	0 (0)	1 (2.2)	0 (0)
Renal failure	0 (0)	1 (2.2)	0 (0)
Deaths			
Number of deaths, N (%)	0 (0)	0 (0)	1 (2.0)
Cause of death, N (%)			
Myocardial infarction	0 (0)	0 (0)	1 (2.0)
Notable harms			
Gastrointestinal	12 (14.1)	3 (6.7)	1 (2.0)

	Study ZS-004		
	Placebo (N = 85)	SZC 5 g (N = 45)	SZC 10 g (N = 51)
Constipation	6 (7.1)	0 (0)	1 (2.0)
Small intestinal obstruction	0 (0)	1 (2.2)	0 (0)
Acute cardiac failure	0 (0)	0 (0)	1 (2.0)
Congestive cardiac failure	0 (0)	1 (2.2)	0 (0)
Myocardial infarction	0 (0)	0 (0)	1 (2.0)
QT prolongation	0 (0)	1 (2.2)	0 (0)
Hypertension	1 (1.2)	2 (4.4)	1 (2.0)
Acute renal failure	0 (0)	1 (2.2)	0 (0)
Renal failure	0 (0)	2 (4.4)	0 (0)
Peripheral edema	2 (2.4)	0 (0)	3 (5.9)
Edema	0 (0)	1 (2.2)	0 (0)
Hypokalemia (S-K < 3.5 mmol/L)	0 (0)	0 (0)	8 (15.7)

AE = adverse event; SAE = serious adverse event; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 1% in placebo or in all SZC doses combined.

Source: Clinical Study Report for Study ZS-004.[25]

Table 30: Harms in Maintenance Phase of Study ZS-D9480

	Study ZS-D9480		
	Placebo (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)
Patients with ≥ 1 AEs, N (%)	10 (20.0)	28 (28.3)	44 (44.4)
Most common AEs[a]			
Constipation	0 (0)	1 (1.0)	9 (9.1)
Diarrhea	1 (2.0)	1 (1.0)	2 (2.0)
Nausea	1 (2.0)	0 (0)	1 (1.0)
Vomiting	1 (2.0)	1 (1.0)	0 (0)
Abdominal pain	1 (2.0)	0 (0)	0 (0)
Gastroesophageal reflux disease	1 (2.0)	0 (0)	0 (0)
Viral upper respiratory tract infection	0 (0)	1 (1.0)	2 (2.0)
Upper respiratory tract infection	0 (0)	0 (0)	3 (3.0)
Decreased appetite	1 (2.0)	0 (0)	0 (0)
Diabetes mellitus	0 (0)	2 (2.0)	0 (0)
Type 2 diabetes mellitus	0 (0)	1 (1.0)	1 (1.0)
Hyperkalemia	2 (4.0)	3 (3.0)	0 (0)
Tremor	1 (2.0)	0 (0)	0 (0)
Conjunctival edema	1 (2.0)	0 (0)	0 (0)
Ocular hyperemia	1 (2.0)	0 (0)	0 (0)
Blurred vision	1 (2.0)	0 (0)	0 (0)
Angina pectoris	0 (0)	1 (1.0)	1 (1.0)
Chronic cardiac failure	0 (0)	1 (1.0)	1 (1.0)
Ventricular extrasystoles	0 (0)	1 (1.0)	2 (2.0)

	Study ZS-D9480		
	Placebo (N = 50)	**SZC 5 g (N = 99)**	**SZC 10 g (N = 99)**
Hypertension	2 (4.0)	3 (3.0)	2 (2.0)
Increased blood pressure	0 (0)	0 (0)	2 (2.0)
Bronchial obstruction	1 (2.0)	0 (0)	0 (0)
Dyspnea	1 (2.0)	0 (0)	1 (1.0)
Nephroptosis	1 (2.0)	0 (0)	0 (0)
Renal cyst	1 (2.0)	0 (0)	0 (0)
Edema	0 (0)	1 (1.0)	8 (8.1)
Peripheral edema	0 (0)	4 (4.0)	7 (7.1)
Ankle fracture	1 (2.0)	0 (0)	0 (0)
SAEs			
Patients with > 0 SAEs, N (%)	1 (2.0)	4 (4.0)	3 (3.0)
Cause of SAEs, N (%)			
Cystitis	0 (0)	0 (0)	1 (1.0)
Infectious colitis	0 (0)	1 (1.0)	0 (0)
Pneumonia	0 (0)	1 (1.0)	0 (0)
Upper respiratory tract infection	0 (0)	0 (0)	1 (1.0)
Cardiac failure	0 (0)	0 (0)	1 (1.0)
Congestive cardiac failure	0 (0)	1 (1.0)	0 (0)
Hypertension	0 (0)	1 (1.0)	0 (0)
Gastritis	0 (0)	1 (1.0)	0 (0)
Renal impairment	0 (0)	0 (0)	1 (1.0)
Ankle fracture	1 (2.0)	0 (0)	0 (0)
WDAEs			
WDAEs, N (%)	3 (6.0)	7 (7.1)	7 (7.1)
Cause of WDAE, N (%)			
Pneumonia	0 (0)	1 (1.0)	0 (0)
Hyperkalemia	2 (4.0)	3 (3.0)	0 (0)
Hypokalemia	0 (0)	0 (0)	1 (1.0)
Atrial fibrillation	0 (0)	0 (0)	1 (1.0)
Cardiac failure	0 (0)	0 (0)	1 (1.0)
Congestive cardiac failure	0 (0)	1 (1.0)	0 (0)
Ventricular extrasystoles	0 (0)	1 (1.0)	0 (0)
Bronchial obstruction	1 (2.0)	0 (0)	0 (0)
Edema	0 (0)	0 (0)	3 (3.0)
Edema due to renal disease	0 (0)	0 (0)	1 (1.0)
Peripheral edema	0 (0)	1 (1.0)	0 (0)
Deaths			
Number of deaths, N (%)	0 (0)	0 (0)	0 (0)
Notable harms			
Gastrointestinal	3 (6.0)	6 (6.1)	13 (13.1)

	Study ZS-D9480		
	Placebo (N = 50)	SZC 5 g (N = 99)	SZC 10 g (N = 99)
Constipation	0 (0)	1 (1.0)	9 (9.1)
Intestinal obstruction	0 (0)	1 (1.0)	0 (0)
Angina pectoris	0 (0)	1 (1.0)	1 (1.0)
Atrial fibrillation	0 (0)	0 (0)	1 (1.0)
Supraventricular extrasystoles	0 (0)	1 (1.0)	0 (0)
Ventricular extrasystoles	0 (0)	1 (1.0)	2 (2.0)
Cardiac failure	0 (0)	0 (0)	1 (1.0)
Chronic cardiac failure	0 (0)	1 (1.0)	1 (1.0)
Congestive cardiac failure	0 (0)	1 (1.0)	0 (0)
Hypertension	2 (4.0)	3 (3.0)	2 (2.0)
Increased blood pressure	0 (0)	0 (0)	2 (2.0)
Renal impairment	0 (0)	0 (0)	1 (1.0)
Edema	0 (0)	1 (1.0)	8 (8.1)
Edema due to renal disease	0 (0)	0 (0)	1 (1.0)
Peripheral edema	0 (0)	4 (4.0)	7 (7.1)
Hypokalemia	0 (0)	0 (0)	1 (1.0)

AE = adverse event; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency > 1% in placebo or in all SZC doses combined.

Source: Clinical Study Report for Study ZS-D9480.[26]

Table 31: Harms in DIALIZE

	DIALIZE	
	Placebo (N = 99)	SZC (N = 96)
Patients with ≥ 1 AEs, N (%)	46 (46.5)	40 (41.7)
Most common AEs[a]		
Hypokalemia	5 (5.1)	5 (5.2)
Constipation	3 (3.0)	4 (4.2)
Diarrhea	6 (6.1)	4 (4.2)
Headache	2 (2.0)	3 (3.1)
Nasopharyngitis	5 (5.1)	3 (3.1)
Hyperkalemia	6 (6.1)	2 (2.1)
Hordeolum (stye)	0 (0.0)	2 (2.1)
Muscle spasms	2 (2.0)	2 (2.1)
Dizziness	4 (4.0)	1 (1.0)
Dyspnea	3 (3.0)	1 (1.0)
Pruritus	3 (3.0)	1 (1.0)
Shunt stenosis	3 (3.0)	1 (1.0)
SAEs		
Patients with ≥ 1 SAEs, N (%)	8 (8.1)	7 (7.3)
WDAEs		

	DIALIZE	
WDAEs, N (%)	2 (2.0)	4 (4.2)
Deaths		
Number of deaths, N (%)	0 (0)	1 (1.0)
Notable harms		
Constipation	3 (3.0)	4 (4.2)
Hypokalemia	5 (5.1)	5 (5.2)

AE = adverse event; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

[a] Frequency > 2%.

Source: Fishbane (2019).[19]

Critical Appraisal

Internal Validity

The procedures for randomization and blinding were well conducted. Randomization was performed by a third party (not associated with the clinical studies), by an interactive voice/web system, or by using the AstraZeneca global randomization system. An effort to balance the distribution of patients among treatment groups was made through block randomization in studies ZS-D9480, ZS-D9482, and DIALIZE. Investigators and patients were blinded in all studies, except during the open-label, acute phases of studies ZS-004 and ZS-D9480. To maintain blinding, placebo and SZC were identical in appearance and labelled with predetermined numeric codes. The open-label exposure to SZC in studies ZS-004 and ZS-D9480 may have had an impact on the success of blinding during the maintenance phase. Also, the disproportionate incidence of hypokalemia in patients receiving higher doses of SZC may have compromised blinding. However, given that the primary outcomes were measured objectively using the i-STAT or through central laboratory measurement of potassium, the risk of bias due to compromise in blinding is low.

Baseline characteristics were generally well balanced across groups. More patients with baseline serum potassium greater than 5.5 mmol/L received placebo during the acute phases of studies ZS-003 and ZS-D9482 (25.9% and 45.5%, respectively) than received SZC (15.4% and 33.3%), potentially causing the efficacy results for serum potassium in the acute phase to favour SZC. In the maintenance phase of Study ZS-003, 80.9% of patients who were assigned to placebo (following 5 g in the acute phase) were normokalemic. In comparison, 89.1% were normokalemic and assigned to sodium zirconium 5 g (following 5 g in the acute phase). These differences may have introduced bias in favour of SZC 5 g for the number of normokalemic days or the proportion of patients who remained normokalemic.

Patients were provided with instructions about how to prepare and take the study drug at home. The medication required some preparation (i.e., dilution in water to be consumed orally). It is unclear how well patients complied with these instructions and if compliance was consistent across groups. Concomitant medications were permitted in the studies, although studies ZS-D9480 and ZS-D9482 specifically mentioned that other potassium binders and changes to RAASi therapies or diuretics were not allowed. A restriction in changes to RAASi therapies or diuretics was not specified in studies ZS-003 or ZS-004. In addition, information or advice about dietary interventions was not provided in any of the studies. The absence of information about changes to diet or RAASi or diuretic medications is a limitation because any differences in these factors across treatment groups could introduce bias.

Potassium was measured using two methods: i-STAT, which measures potassium in plasma; and central laboratory, which measures potassium in serum. All analyses were based on *serum* potassium levels from the central laboratory, but decisions such as those related to screening or withdrawal from the study were made based on i-STAT measurements of *plasma* potassium. According to the sponsor, there is only a small difference between the measurements of potassium resulting from the two methods, with i-STAT being 0.15 mmol/L lower on average.[25] Sensitivity analyses were conducted by some of the studies that substituted i-STAT potassium values for central laboratory values, and results were found to be consistent. Therefore, the use of i-STAT values for decision-making and central laboratory values for statistical analysis should not have introduced bias.

The statistical models used in the studies were appropriate and adjusted for several important covariates. Given the many dose comparators that were incorporated into the studies, it was important that type I error was controlled to maintain a significance level of 5%. The studies controlled for type I error by following a pre-specified, sequential, closed testing procedure.

External Validity

The patients enrolled in the studies represented a heterogeneous population, with diverse comorbidities and concomitant medications that are associated with hyperkalemia in clinical practice, including CKD. Of the patients who participated in the acute phase across studies, the proportion in each treatment arm who reported having CKD at baseline ranged from 58.0% to 78.8%. The proportion of patients in a treatment arm that reported CKD at baseline, who also participated in the maintenance phase across studies, ranged from 57.8% to 100%. Therefore, the results of the included studies represent patients with hyperkalemia due to CKD as well as other causes.

Subgroup analyses showed generally consistent results in efficacy when conducted for populations of interest, such as patients with different levels of eGFR impairment, CKD, congestive heart failure, and using RAASi medication. However, of note, there is uncertainty in the maintenance of potassium at a lower level by different eGFR categories in the maintenance phase. For example, in Study ZS-003, patients with eGFR of less than 15 mL/min/1.73m^2 and an eGFR of greater than or equal to 60 mL/min/1.73m^2 had larger positive increases in potassium than those on placebo. Except for those with an eGFR of less than 15 mL/min/1.73m^2, all other subgroups had a higher percentage of patients achieving normokalemia in the 5 g and 10 g groups compared with placebo. Given the relatively small sample size, more study is warranted to identify the potential disparity in maintaining treatment effect by different level of kidney impairment as measured by eGFR categories (e.g., less than 30 mL/min/1.73m^2, per the sponsor's listing request). It is also of note that a high percentage of the patients experiencing treatment effects in these studies were using RAASi medications (more than 50% up to nearly 80%). The patients in the studies had mild to moderate hyperkalemia. The use in patients with severe hyperkalemia (greater than 6.5 mmol/L) is unclear, although potassium binders are generally not recommended in this setting due to their delayed onset of effect.

None of the study sites were in Canada, although several were in the US. Across the various study locations, there may have been variations in clinical practices concerning dietary interventions and protocols for modifying potassium-increasing medications. It is unclear if and how these may practices have differed from those in Canada. There is also concern that the potassium cut-off level used to screen patients into the studies (i.e., > 5.0 mmol/L or > 5.1 mmol/L) was too low and not relevant to clinical practice. The clinical

experts consulted for this review indicated that typically, one would consider intervening when potassium levels reach 5.3 mmol/L to 5.5 mmol/L. Aside from one study, patients receiving dialysis — a population at particularly high risk of developing hyperkalemia — were excluded. Potassium levels were frequently monitored in the studies, and patients had regular clinical visits, which may reflect clinical practice. The clinical experts indicated that potassium would not be measured as frequently in a non-emergent or acute setting.

The DIALIZE study permitted titration of the SZC dose up to 15 g once daily and combined all doses (5 g to 15 g) in analyses. The 15 g dose is not a Health Canada–approved dose. However, at the end of the dose titration period, about 19% of patients were receiving 15 g of SZC once daily; therefore, the majority were still on approved doses.

The clinical experts consulted for this review indicated that SZC would rarely be used alone to reduce potassium levels, but would be combined with other modalities, such as diuretics and dietary modifications. However, the studies examined SZC in isolation, and insufficient information was provided to assess what other types of interventions were administered and how frequently.

The outcomes in all studies focused on potassium only. While a reduction in potassium from a state of hyperkalemia is associated with reduced mortality, the studies were not designed or powered to assess other clinical outcomes of importance to clinicians and patients, such as reduction in cardiovascular or kidney morbidity or changes to RAASi therapy. Although SZC itself is not expected to have an impact on these clinical outcomes, an indirect effect can be anticipated if it prevents the need to reduce or discontinue RAASi therapies. The studies also did not assess the effect on continuation of RAASi therapy at optimal doses, although there were some data on changes to RAASi in placebo and active treatment groups. Patients indicated that their quality of life was adversely affected by having to modify their diets to reduce potassium. However, there were limited data available for HRQoL, and no clear benefit was presented. No conclusions can be drawn on this outcome.

The studies assessed acute treatment over 48 hours and maintenance treatment up to 28 days. Given that the effects of SZC on potassium level are observed over a short period of time, the study durations were reasonable. However, hyperkalemia can be a chronic issue, and typically affects patients with impaired kidney function. Therefore, patients may require treatment for an extended period — that is, beyond 28 days. In two studies, patients were given SZC once daily for 11 months or 12 months, and the results provide some evidence for long-term safety.

Indirect Evidence

No ITCs were submitted by the sponsor, and none were identified in a literature search. Palaka et al. assessed the feasibility of conducting an ITC of SZC with other cation-exchangers.[5] Ten RCTs were identified for SZC, SPS, CPS, or patiromer. However, the authors determined that an ITC was not feasible due to disconnected networks, differences in dosing of SPS, different time points of outcome assessment, and heterogeneity in patient populations.

Other Relevant Studies

Studies ZS-004E and ZS-005 provide long-term safety and efficacy data for SZC in patients with hyperkalemia.

Long-Term Extension and Single-Arm Studies

Methods

Study ZS-004E was an OLE study of Study ZS-004, which was included as a pivotal study in this review. All patients received SZC orally during the OLE, which consisted of an acute phase of up to 48 hours followed by an extended-dosing phase of up to 11 months (Table 32). The second study, Study ZS-005, was an open-label study designed to evaluate the safety and efficacy of SZC (Table 32). Randomization or enrolment in studies ZS-002, ZS-003, ZS-004, or ZS-004E was an exclusion criterion for this study. In Study ZS-005, all patients also received SZC orally for the duration of the study, which consisted of an acute phase of up to three days and an extended-dosing phase of up to 12 months. Both studies also included a follow-up visit that occurred seven (± 1) days after the end of the study.

Table 32: Overview of Other Relevant Studies

		Study ZS-004E	Study ZS-005
DESIGNS AND POPULATIONS	**Study design**	Open-label, single-group, multi-centre extension study	Open-label, single-group, multi-centre, multi-dose maintenance study
	Locations	30 sites in the US, Australia, and South Africa	56 sites in the US, Australia, Germany, UK, Netherlands, and South Africa
	Treated (N)	123	751
	Inclusion criteria	• completed extended-dosing phase of Study ZS-004 • i-STAT S-K ≥ 3.5 mmol/L and ≤ 6.2 mmol/L OR • discontinued Study ZS-004 due to hypokalemia or hyperkalemia • mean i-STAT S-K ≥ 3.5 mmol/L and ≤ 6.2 mmol/L based on two consecutive measurements at 0 min and 60 min on acute-phase study day 1/extended-dosing phase study day 1	• > 18 years of age • two consecutive i-STAT potassium values measured 60 min (± 15 min) apart, both ≥ 5.1 mmol/L (if outside Germany) or ≥ 5.1 mmol/L and ≤ 6.5 mmol/L (if in Germany), and measured within 1 day before the first dose of SZC on acute-phase day 1 • able to have repeated blood draws or effective venous catherization
	Exclusion criteria	• pseudo-hyperkalemia • alternative treatment for hyperkalemia during Study ZS-004 • insulin dose not stabilized • receiving dialysis • life expectancy < 3 months • diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant • treatment with a drug or device within the last 30 days that had not received regulatory approval at the time of study entry	• pseudo-hyperkalemia • treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonemia within the last 7 days • treatment with SPS or CPS within the last 3 days • insulin dose not stabilized • receiving dialysis • life expectancy < 3 months • HIV-positive (except South African sites) • diabetic ketoacidosis • cardiac arrhythmias that required immediate treatment • women who were pregnant, lactating, or planning to become pregnant • treatment with a drug or device within the last 30 days that had not received regulatory approval at the time of study entry • randomization/enrolment in studiesZS-002, ZS-003, ZS-004, or ZS-004E

		Study ZS-004E	Study ZS-005
Drugs	**Intervention**	SZC orally as a suspension in purified water Acute phase (days 1 and 2): 10 g t.i.d. Extended-dosing phase (up to 11 months): 10 g q.d. • if i-STAT potassium > 5. 5mmol/L, increase dose to 15 g q.d. • if i-STAT potassium ≥ 3.0 mmol/L and ≤ 3.4 mmol/L, reduce dose to 5 g q.d.	SZC orally as a suspension in purified water Acute phase (days 1 to 3): 10 g t.i.d. Extended-dosing phase (up to 12 months): starting dose of 5 g q.d., adjusted based on i-STAT potassium values
	Comparator(s)	None	None
Duration	**Phase**		
	Run-in	NA	NA
	Open-label	Acute phase: up to 48 hours Maintenance phase: up to 11 months	Acute phase: up to 72 hours Extended-dosing phase: up to 12 months
	Follow-up	7 ± 1 days	7 ± 1 days
Outcomes	**Primary end point**	Safety and tolerability (AEs) **Efficacy** • proportion of patients with average S-K ≤ 5.1 mmol/L from day 8 through month 11 • proportion of patients with average S-K ≤ 5.5 mmol/L from day 8 through month 11	Safety and tolerability (AEs)
	Other end points	**Secondary** • mean cumulative MP days normokalemic from day 8 through month 11 • percentage normokalemic at various study days • mean S-K levels relative to acute-phase and maintenance-phase baselines • mean change in S-K level from study day 337 to EOS • percentage with normal aldosterone levels (4.0 ng/dL to 31.0 ng/dL) until day 337	**Secondary** • proportion of patients who maintained normokalemia (S-K between 3.5 mmol/L and 5.0 mmol/L) until day 365 • proportion of patients who maintained normokalemia (S-K between 3.5 mmol/L and 5.5 mmol/L) until day 365
Notes	**Publications**		Spinowitz (2019)[31]

AE = adverse event; CPS = calcium polystyrene sulfonate; EOS = end of study; NA = not applicable; q.d. = every day; S-K = serum potassium; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

Populations

The key inclusion and exclusion criteria are summarized in Table 32. Briefly, patients were eligible for inclusion in Study ZS-004E if they completed the maintenance phase of the parent study (Study ZS-004) and had an i-STAT serum potassium level between 3.5 mmol/L and 6.2 mmol/L, or if they discontinued Study ZS-004 due to hypokalemia or hyperkalemia. To be eligible for inclusion in Study ZS-005, patients required an i-STAT potassium value greater than or equal to 5.1 mmol/L from two consecutive measurements. There was no upper limit on potassium level, except in Germany, where potassium had to be less than or equal to 6.5 mmol/L.

The baseline characteristics corresponding to the acute phase of Study ZS-005 and the extended-dosing phase of studies ZS-004E and ZS-005 are described in Table 33 and Table 34, respectively. The characteristics of the acute-phase population of Study ZS-005 were similar to those of the extended-dosing phase. In the extended-dosing phase (Table 34), the mean age of patients was 63.7 years, and the majority were male (57.9% and 59.8% in studies ZS-004E and ZS-005, respectively) and white (88.4% and 83.1%, respectively). At the acute-phase baseline, serum potassium levels were less than 5.5 mmol/L for 44.6% of patients in Study ZS-004E and 38.1% of patients in Study ZS-005; 5.5 to less than 6.0 mmol/L for 43.8% and 45.0%; and greater than or equal to 6.0 mmol/L for 11.6% and 16.9%, respectively. The eGFR was similar between the two studies, with about 74% of patients having an eGFR of less than 60 mL/min/1.73m^2. The most common cause of hyperkalemia in both studies was the use of a RAASi (68.6% and 70.5% for studies ZS-004E and ZS-005), followed by CKD (62.8% and 68.4%) and DM (66.1% and 62.7%).

Table 33: Summary of Baseline Characteristics in Acute Phase of Study ZS-005

	Study ZS-005
	SZC 10 g t.i.d. N = 751
Mean age (SD), years	63.6 (13.03)
Age range, years	21, 93
Male, n (%)	448 (59.7)
Race, n (%)	
White	624 (83.1)
Black	89 (11.9)
Asian	25 (3.3)
Other	13 (1.7)
S-K, n (%)	
< 5.5 mmol/L	287 (38.2)
5.5 to < 6.0 mmol/L	338 (45.0)
≥ 6.0 mmol/L	126 (16.8)
eGFR, n (%)	
< 60 mL/min/1.73m^2	552 (73.5)
≥ 60 mL/min/1.73m^2	190 (25.3)
Missing	9 (1.2)
Cause of hyperkalemia, n (%)	
CKD	513 (68.3)

	Study ZS-005
CHF	285 (37.9)
DM	471 (62.7)
Use of RAASi	527 (70.2)

CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitors; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Source: Study ZS-005 Clinical Study Report.[33]

Table 34: Summary of Baseline Characteristics in Extended-Dosing Phase of Studies ZS-004E and ZS-005

	Study ZS-004E	Study ZS-005
	SZC 10 g q.d. N = 121	SZC 5 g q.d. N = 746
Extended-dosing phase		
Mean age (SD), years	63.7 (12.29)	63.7 (13.04)
Age range, years	22, 85	21, 93
Male, n (%)	70 (57.9)	446 (59.8)
Race, n (%)		
White	107 (88.4)	620 (83.1)
Black	11 (9.1)	88 (11.8)
Asian	2 (1.7)	25 (3.4)
Other	1 (0.8)	13 (1.7)
Acute-phase baseline S-K, n (%)		
< 5.5 mmol/L	54 (44.6)	284 (38.1)
5.5 to < 6.0 mmol/L	53 (43.8)	336 (45.0)
≥ 6.0 mmol/L	14 (11.6)	126 (16.9)
eGFR, n (%)		
< 60 mL/min/1.73m2	90 (74.4)[a]	549 (73.7)
≥ 60 mL/min/1.73m2	31 (25.6)[a]	188 (25.2)
Missing	0[a]	9 (1.2)
Cause of hyperkalemia, n (%)		
CKD	76 (62.8)	510 (68.4)
CHF	50 (41.3)	283 (37.9)
DM	80 (66.1)	468 (62.7)
RAASi	83 (68.6)	525 (70.4)

CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; q.d. = every day; RAASi = renin-angiotensin-aldosterone system inhibitors; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Note: Baseline demographics for Study ZS-004E were only provided for the ITT analysis set.

[a] Acute-phase baseline from Study ZS-004.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

Interventions

Patients entering the acute phase of Study ZS-004E received 10 g of SZC three times a day with meals for either one day (three doses) or two days (six doses), depending on whether the i-STAT potassium value of the patient was greater than 5.5 mmol/L. During the extended-dosing phase, patients began on a 10 g dose of SZC once daily, with adjustments

made to the dose based on i-STAT potassium values that were outside of the normal range. An increase in dose to 15 g once daily was permitted if i-STAT potassium values were greater than 5.5 mmol/L; the dose could be decreased to 5 g once daily if the i-STAT potassium values were 3.0 mmol/L to 3.4 mmol/L.

The interventions used in Study ZS-005 were similar to those used in Study ZS-004E; however, the acute phase could be up to three days in length (nine doses), and the starting dose of SZC during the extended-dosing phase was 5 g once daily, which was also adjusted based on i-STAT values.

Outcomes

The primary efficacy outcome for Study ZS-004E was the proportion of patients with a mean serum potassium level of 5.1 mmol/L or less during the extended-dosing phase between month 1 and month 11 (day 8 to day 337). The proportion of patients who could achieve and maintain serum potassium levels of 5.5 mmol/L or less was also reported. Central laboratory data were used to determine serum potassium levels for these outcomes. The same primary efficacy end points were used for Study ZS-005, except the mean serum potassium values were evaluated from month 3 to month 12 (day 85 to day 365).

The harms or related outcomes for Study ZS-004E were AEs, vital signs, ECG, physical examination, chemistry and hematology labs, and tolerability. For the purposes of this summary, only AEs were reported.

Additional efficacy end points for Study ZS-004E included: the proportion of patients who were normokalemic (serum potassium 3.5 mmol/L to 5.0 mmol/L), hypokalemic (less than 3.5 mmol/L), or hyperkalemic (greater than 5.0 mmol/L) at each scheduled visit during the extended-dosing phase; a model-based LSM of log-transformed serum potassium; change and percentage change from acute phase and extended-dosing phase baseline in serum potassium; log-transformed serum potassium at study visits; and mean change in serum potassium.

The secondary efficacy outcomes in Study ZS-005 were similar to those of Study ZS-004E. These included: proportion of patients with mean serum potassium between 3.5 mmol/L and 5.5 mmol/L (inclusive) for months 3 to 12; mean potassium values for months 3 to 12, months 6 to 9, and months 9 to 12; and the absolute and percentage change in potassium from the acute-phase baseline. The nominal and percentage change in bicarbonate value from acute-phase baseline and the proportion of patients with normal bicarbonate values was also reported.

Statistical Analysis

The safety population of Study ZS-004E was defined as all patients who received at least one dose of SZC during the extended-dosing phase and had any post-baseline safety data. The extended-dosing phase safety population for Study ZS-005 was similar, except it did not require post-baseline safety data. These datasets were used for safety analyses of the extended-dosing phase in both studies. The extended-dosing phase ITT population was defined in both studies as including patients in the safety population who also had any post-baseline extended-dosing phase serum potassium values. This population was used for the primary efficacy analyses of the extended-dosing phase of both studies.

Statistical testing was performed for efficacy outcomes in Study ZS-004E, and an overall type I error rate of 5% was maintained using a hierarchical order for hypotheses testing.

Sample-size calculations were also performed. For the efficacy analyses in Study ZS-005, 95% CIs and t-tests (paired from baseline or independent two-group) with two-sided P values were presented where appropriate. Statistical testing was not performed for safety analyses in either study.

Patient Disposition

The patient disposition for studies ZS-004E and ZS-005 is summarized in Table 35. A total of 208 patients completed Study ZS-004; of these, 123 (59.1%) were eligible to enrol in Study ZS-004E. Two patients who received placebo during the parent study had i-STAT potassium levels greater than 5.5 mmol/L; therefore, they entered the acute phase of Study ZS-004E. The remaining 121 went directly into the extended-dosing phase. In Study ZS-005, 1,561 patients were screened and 751 (48.1%) entered the study. All patients were treated during the acute phase, and 746 (99.3%) continued into the extended-dosing phase.

The proportion of patients who completed the extended-dosing phase was similar across studies: 64.2% for Study ZS-004E and 62.5% for Study ZS-005. The most common reasons for discontinuation in Study ZS-004E and Study ZS-005, respectively, included: withdrawal of consent (7.3% and 10.9%), AEs (5.7% and 6.8%), patient compliance (2.4% and 2.3%), investigator decision (2.4% and 1.1%), and loss to follow-up (1.6% and 4.2%). Expected progression of CKD was also a common reason for discontinuation, and was almost double in Study ZS-004E (9.8%) compared to Study ZS-005 (5.4%). A greater proportion of patients in the Study ZS-004E study discontinued because they met ECG withdrawal criteria as well (2.4% versus 0.9%). Eight deaths (1.1%) led to discontinuation in Study ZS-005. No deaths were reported in Study ZS-004E.

Table 35: Patient Disposition in the Acute and Extended-Dosing Phases of Studies ZS-004E and ZS-005

	Study ZS-004E	Study ZS-005
	SZC 10 g t.i.d.	SZC 10 g t.i.d.
Acute phase		
Screened, N	208	1,561
Entered study, N (%)	123 (59.1)	751 (48.1)
Treated during AP, N (%)	2 (100)	751 (100)
Completed, N (%)	–	746 (99.3)
Discontinued, N (%)	–	5 (0.7)
Safety, N	2	751
ITT, N	2	749
	SZC 10 g q.d.	SZC 5 g q.d.
Extended-dosing phase		
Entered, N (%)	123 (100)	746 (99.3)
Treated during EDP, N (%)	123 (100)	746 (100)
Completed, N (%)	79 (64.2)[a]	466 (62.5)
Discontinued, N (%)	44 (35.8)	280 (37.5)
AE	7 (5.7)	51 (6.8)
Consent withdrawn	9 (7.3)	81 (10.9)
Patient compliance	3 (2.4)	17 (2.3)
Investigator decision	3 (2.4)	8 (1.1)
Lost to follow-up	2 (1.6)	31 (4.2)
Sponsor decision	–	5 (0.7)
Protocol violation	–	2 (0.3)
Hypokalemia or hyperkalemia	2 (1.6)[b]	14 (1.9)
Expected progression of CKD	12 (9.8)	40 (5.4)
Death	–	8 (1.1)
Met electrocardiogram withdrawal criteria	3 (2.4)[c]	7 (0.9)
Other	3 (2.4)[d]	16 (2.1)
Safety, N	123	746
ITT, N	121	734

AE = adverse event; AP = acute phase; CKD = chronic kidney disease; ECG = electrocardiogram; EDP = extended-dosing phase; ITT = intention-to-treat; q.d. = every day; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Note: See intervention subsection for details regarding dosage adjustments during the extended-dosing phase.

[a] Includes 15 patients who completed 56 days of dosing under the original protocol, seven who completed 140 days of dosing under Amendment 1 of the protocol, and 57 who completed 336 days of dosing under Amendment 3 of the protocol.

[b] One patient who prematurely discontinued due to hyperkalemia also had a serious AE of hyperkalemia recorded; the study drug was withdrawn.

[c] All three patients who prematurely discontinued due to meeting ECG withdrawal criteria also had AEs of electrocardiogram QT prolonged (two patients) and right bundle branch block (one patient) recorded; the study drug was withdrawn.

[d] One patient was withdrawn at the request of their primary care physician, who felt their edema had worsened; one was withdrawn as their primary care physician had introduced a potassium supplement to medications; and one was withdrawn in error as the investigator mistakenly thought the patient met ECG stopping criteria.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

Exposure to Study Treatments

As previously described, two patients entered the acute phase of Study ZS-004E and 751 entered the acute phase of Study ZS-005. The two patients who entered the acute phase of Study ZS-004E each required one day of dosing (with three SZC 10 g doses) to meet the criteria for entry into the extended-dosing phase. The mean (SD) number of doses and number of days on treatment were similar between the two studies, with patients having taken 3.0 (0) and 3.6 (1.47) doses in studies ZS-004E and ZS-005, respectively. Patients were on treatment for about one day, and all received 10 g SZC exclusively (Table 36).

There were more differences in terms of exposure to treatment during the extended-dosing phase of the studies (Table 36). The mean (SD) number of doses received and number of days on treatment was 208.4 (127.32) and 212.9 (129.06) in Study ZS-004E, and 278.2 (122.10) and 286.2 (122.42) in Study ZS-005. The mean (SD) dose received by patients in Study ZS-004E was 9.960 g (1.8257), which was slightly greater than what patients in Study ZS-005 received (7.18 g [2.620]). Further, the majority (73.2%) of patients in Study ZS-004E received a mean dose of 10 g SZC, whereas the majority (87.0%) of patients in Study ZS-005 received a mean dose of 5 g to less than 10 g SZC.

Table 36: Exposure to Treatment in the Extended-Dosing Phase of Studies ZS-004E and ZS-005

	Study ZS-004E	Study ZS-005
	SZC 10 g q.d. N = 123	SZC 5 g q.d. N = 746
Extended-dosing phase		
Number of doses, mean (SD)	208.4 (127.32)	278.2 (122.10)
Days on treatment, mean (SD)	212.9 (129.06)	286.2 (122.42)
Mean dose received (g), mean (SD)	9.960 (1.8257)	7.18 (2.620)
Mean dose received by patient (g), mean (SD)		
< 5 g	2 (1.6)	23 (3.1)
5 g to < 10 g	15 (12.2)	649 (87.0)
10 g	90 (73.2)	0
> 10 g	16 (13.0)	74 (9.9)

q.d. = every day; SD = standard deviation; SZC = sodium zirconium cyclosilicate.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

Efficacy

Only two patients required acute-phase dosing in Study ZS-004E. Both were treated with placebo in the parent study (Study ZS-004) and had i-STAT potassium values of 5.9 mmol/L and 5.8 mmol/L at the end of the study. After one day of dosing with SZC 10 g three times daily, both patients had i-STAT potassium values within the normal range (4.9 mmol/L and 5.0 mmol/L) and entered the extended-dosing phase. In Study ZS-005, 77.9% (95% CI, 0.748 to 0.809) of patients had serum potassium levels within the normokalemic range (3.5 mmol/L to 5.0 mmol/L) after 72 hours, and 92.5% (95% CI, 0.904 to 0.943) had serum potassium levels between 3.5 mmol/L and 5.5 mmol/L after 24 hours. By 72 hours, 98.7% (95% CI, 0.976 to 0.994) had potassium values between 3.5 mmol/L and 5.5 mmol/L.

Table 37: Acute Phase Efficacy Results in Study ZS-005

	Study ZS-005 SZC 10 g t.i.d. N = 749
Acute phase	
Proportion of patients with S-K values 3.5 mmol/L to 5.0 mmol/L	
24 hours, n	494
Proportion (95% CI)	0.660 (0.625 to 0.694)
48 hours, n	563
Proportion (95% CI)	0.753 (0.720 to 0.783)
72 hours, n	583
Proportion (95% CI)	0.779 (0.748 to 0.809)
Proportion of patients with S-K values 3.5 mmol/L to 5.5 mmol/L	
24 hours, n	692
Proportion (95% CI)	0.925 (0.904 to 0.943)
48 hours, n	732
Proportion (95% CI)	0.979 (0.965 to 0.988)
72 hours, n	738
Proportion (95% CI)	0.987 (0.976 to 0.994)

CI = confidence interval; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Source: ZS-005 Clinical Study Report.[33]

During the extended-dosing phase of Study ZS-004E, the proportion of patients with mean serum potassium values of 5.1 mmol/L or lower was 88.3% (95% CI, 0.812 to 0.935) on average, which was statistically significant ($P < 0.0001$), and 86.0% (95% CI, 0.832 to 0.884) in Study ZS-005 (Table 38). Both studies also reported the proportion of patients with serum potassium values of 5.5 mmol/L or less. Nearly all patients in both studies met these criteria (100% in Study ZS-004E and 98.5% in Study ZS-005); this was statistically significant in Study ZS-004E as well (Table 38). The proportions of patients with mean serum potassium values between 3.5 mmol/L and 5.0 mmol/L and between 3.5 mmol/L and 5.5 mmol/L were also described (Table 38). The latter was only provided for Study ZS-005. Briefly, on average during the extended-dosing phase, 79.2% (95% CI, 0.708 to 0.860) and 78.1% (95% CI, 0.749 to 0.810) of patients in Study ZS-004E and Study ZS-005 had mean serum potassium levels between 3.5 mmol/L and 5.5 mmol/L. Further, 98.5% (95% CI, 0.973 to 0.992) of patients in Study ZS-005 had mean serum potassium levels between 3.5 mmol/L and 5.5 mmol/L.

From day 8 to end of treatment, the LSM for serum potassium was similar between both studies, at 4.66 mmol/L (95% CI, 4.61 to 4.72) for Study ZS-004E and 4.70 mmol/L (95% CI, 4.68 to 4.72) for Study ZS-005. The change in serum potassium from acute baseline to the end of treatment was statistically significant in both studies ($P \leq 0.001$); the change from the extended-dosing phase baseline was statistically significant in Study ZS-005.

Table 38: Extended-Dosing Phase Efficacy Results in Studies ZS-004E and ZS-005

	Study ZS-004E SZC 10 g q.d. (N = 121)	Study ZS-005 SZC 5 g q.d. N = 749
Extended-dosing phase		
Proportion of patients with mean S-K values ≤ 5.1 mmol/L		
Day 8		
N	120	733
Proportion (95% CI)	0.875 (0.802 to 0.928)	0.767 (0.734 to 0.797)
Day 337/365 exit		
N	120	734
Proportion (95% CI)	0.783 (0.699 to 0.853)	0.827 (0.798 to 0.854)
Days 8 to 337/365 (average)		
N	120	734
Proportion (95% CI)	0.883 (0.812 to 0.935)	0.860 (0.832 to 0.884)
P value	< 0.0001	NR
Proportion of patients with mean S-K values ≤ 5.5 mmol/L		
Day 8		
N	120	733
Proportion (95% CI)	0.950 (0.894 to 0.981)	0.929 (0.908 to 0.947)
Day 337/365 exit		
N	120	734
Proportion (95% CI)	0.942 (0.884 to 0.976)	0.937 (0.917 to 0.954)
Days 8 to 337/365 (average)		
N	120	734
Proportion (95% CI)	1.000 (0.970 to 1.000)	0.985 (0.973 to 0.995)
P value	< 0.0001	NR
Proportion of patients with mean S-K values between 3.5 mmol/L and 5.0 mmol/L		
Day 8		
N	120	733
Proportion (95% CI)	0.833 (0.754 to 0.895)	0.711 (0.676 to 0.743)
Day 337/365 exit		
N	120	734
Proportion (95% CI)	0.725 (0.636 to 0.803)	0.764 (0.732 to 0.795)
Days 8 to 337/365 (average)		
N	120	734
Proportion (95% CI)	0.792 (0.708 to 0.860)	0.781 (0.749 to 0.810)
P value	NR	NR
Proportion of patients with mean S-K values between 3.5 mmol/L and 5.5 mmol/L		
Day 8		

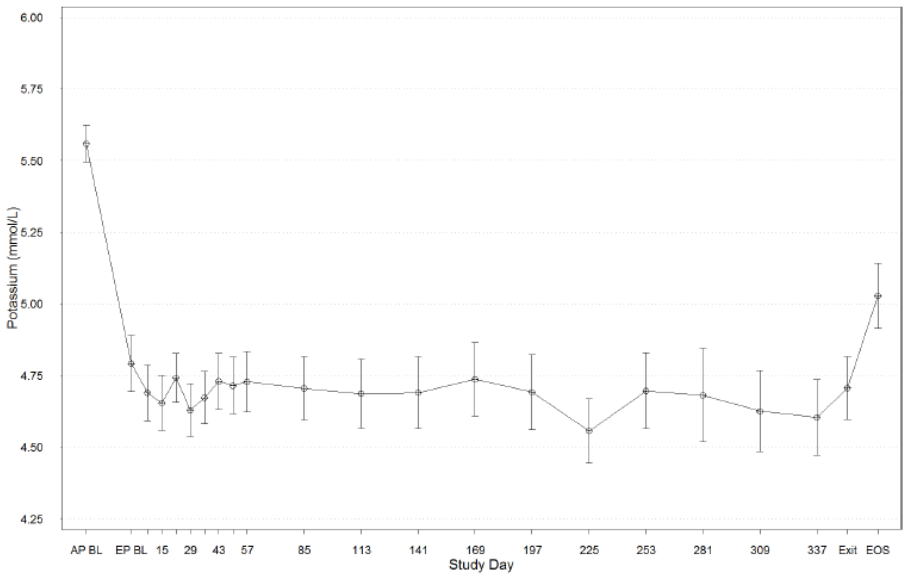
	Study ZS-004E SZC 10 g q.d. (N = 121)	Study ZS-005 SZC 5 g q.d. N = 749
N	NR	733
Proportion (95% CI)		0.929 (0.908 to 0.947)
Day 337/365 exit		
N		734
Proportion (95% CI)		0.913 (0.890 to 0.932)
Days 8 to 337/365 (average)		
N		734
Proportion (95% CI)		0.985 (0.973 to 0.992)
LSM S-K (days 8 to 337/365)		
LSM (95 % CI), mmol/L	4.6625 (4.6081 to 4.7175)	4.7022 (4.6809 to 4.7235)
Change in S-K at day 337/365 exit		
From acute-phase baseline		
N	120	734
Mean change (SD), mmol/L	–0.85 (0.698)	–0.98 (0.714)
P value	≤ 0.001	≤ 0.001
From extended-dosing phase baseline		
N	120	734
Mean change (SD), mmol/L	–0.09 (0.778)	–0.13 (0.650)
P value	NS	≤ 0.001

CI = confidence interval; LSM = least squares mean; q.d. = every day; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

The mean serum potassium levels (mmol/L) during the extended-dosing phases of studies ZS-004E and ZS-005 are presented in Figure 11 and Figure 12, respectively. The mean serum potassium levels remained within the parameters for normokalemia (3.5 mmol/L to 5.0 mmol/L, inclusive) for the duration of the extended-dosing phase in each study: 337 days for Study ZS-004E and 365 days for Study ZS-005. Mean serum potassium levels increased at the end-of-study follow-up visit and after discontinuation of treatment in both studies. In Study ZS-004E, the mean serum potassium level increased from 4.71 (95% CI, 4.60 to 4.82) to 5.03 (95% CI, 4.92 to 5.14) at end of study; in Study ZS-005, it increased from 4.61 (95% CI, 4.57 to 4.65) to 4.98 (95% CI, 4.92 to 5.03) at end of study (Table 39).

Figure 11: Mean Serum Potassium (± 2 Standard Error) in Extended-Dosing Phase of Study ZS-004E

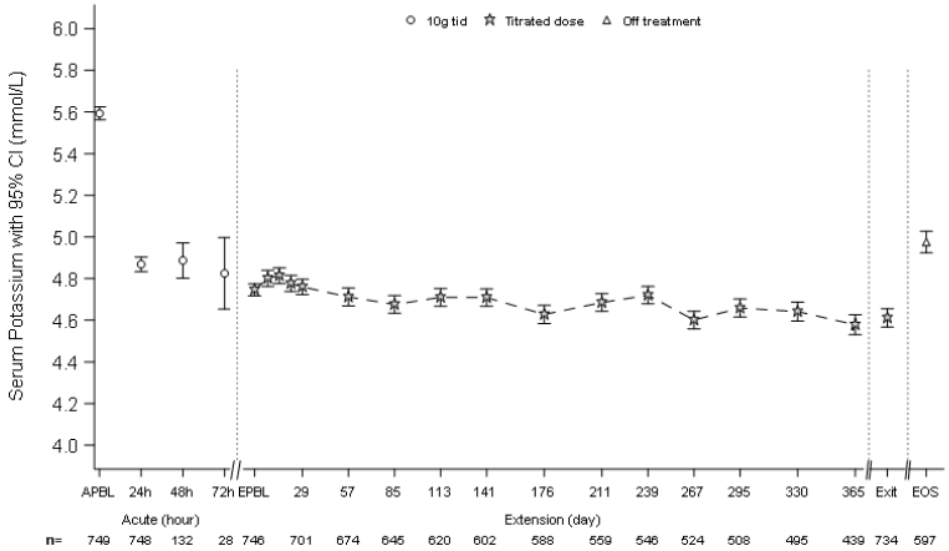


AP BL = Study ZS-004 acute-phase baseline; EOS = end of study; EP BL = Study ZS-004E extended-dosing phase baseline; SZC = sodium zirconium cyclosilicate.

Note: Vertical error bars represent ± 2 standard errors. "Exit" refers to the last visit of the extended-dosing phase within one day of the last dose of SZC.

Source: Study ZS-004E Clinical Study Report.[32]

Figure 12: Mean Serum Potassium (± 95% Confidence Interval) in Extended-Dosing Phase of Study ZS-005



AP BL = acute-phase baseline; EOS = end of study; EP BL = extended-dosing phase baseline; SZC = sodium zirconium cyclosilicate.

Note: "Exit" refers to the last visit of the extended-dosing phase within one day of the last dose of SZC. EOS includes all patient data within seven (± one) days of the last dose of SZC.

Source: Study ZS-005 Clinical Study Report.[33]

Table 39: Mean Serum Potassium Levels in Extended-Dosing Phase of Studies ZS-004E and ZS-005

	Study ZS-004E SZC 10 g q.d. N = 121	Study ZS-005 SZC 5 g q.d. N = 749
Extended-dosing phase		
Serum potassium (mmol/L)		
Extended-dosing phase baseline		
n	121	734
Mean (95% CI)	4.79 (4.69 to 4.89)	4.75 (4.72 to 4.77)
Day 337 or 365/exit		
n	120	734
Mean (95% CI)	4.71 (4.60 to 4.82)	4.61 (4.57 to 4.65)
EOS		
n	98	597
Mean (95% CI)	5.03 (4.92 to 5.14)	4.98 (4.92 to 5.03)

CI = confidence interval; EOS = end of study; q.d. = every day; SZC = sodium zirconium cyclosilicate.

Sources: Study ZS-004E Clinical Study Report[32] and Study ZS-005 Clinical Study Report.[33]

Harms

No harms data were available for the acute phase of Study ZS-004E. During the acute phase of Study ZS-005, 31 (4.1%) patients reported experiencing an AE, with the most common being nausea (n = 4), urinary tract infection (n = 4), constipation (n =2), and diarrhea (n = 2) (Table 40). One patient reported experiencing an SAE (urinary tract infection) and two reported WDAEs, and no deaths occurred. Regarding notable harms, acute renal failure, hypertension, palpitations, and peripheral edema were reported (one case each) during the acute phase in Study ZS-005. There were also 10 (1.3%) gastrointestinal-related AEs.

Table 40: Harms in Acute Phase of Study ZS-005

	Study ZS-005
Acute phase	**SZC 10 g t.i.d. N = 751**
Patients with > 0 AEs, N (%)	31 (4.1)
Most common AEs (> 1 patient)	
Constipation	2 (0.3)
Diarrhea	2 (0.3)
Nausea	4 (0.5)
Urinary tract infection	4 (0.5)
Patients with > 0 SAEs, N (%)	1 (0.1)
WDAEs, N (%)	2 (0.3)
Deaths, N (%)	0
Notable harms	
Acute renal failure	1 (0.1)
Gastrointestinal	10 (1.3)

	Study ZS-005
Acute phase	**SZC 10 g t.i.d. N = 751**
Hypertension	1 (0.1)
Palpitations	1 (0.1)
Peripheral edema	1 (0.1)

AE = adverse event; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day; WDAE = withdrawal due to adverse event.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

During the extended-dosing phase, 66.7% and 65.5% of patients in studies ZS-004E and ZS-005, respectively, reported AEs (Table 41). Rates of AEs were similar between the two studies, except for nausea, which occurred just over twice as frequently in Study ZS-005 (7.5%) as in Study ZS-004E (3.3%). Chest pain and acute renal failure were also more common in Study ZS-005 (3.8% and 4.4%, respectively) compared to Study ZS-004E (0.8% and 1.6%, respectively); they are also included as notable harms for this review. The most frequently occurring AEs in studies ZS-004E and ZS-005 were: hypertension (12.2% and 11.0%, respectively), peripheral edema (8.1% and 9.7%), urinary tract infection (8.9% and 7.9%), constipation (5.7% and 6.4%), anemia (5.7% and 5.9%), upper respiratory tract infection (4.1% and 5.0%), muscle spasms (4.9% and 3.1%), vomiting (3.3% and 4.8%), and diarrhea (3.3% and 4.4%). Hypertension, peripheral edema, and gastrointestinal disorders (constipation, vomiting, and diarrhea) were also notable harms for this review.

Serious AEs were reported by 19.5% of patients in Study ZS-004E and 21.6% of patients in Study ZS-005 during the extended-dosing phase (Table 41) Congestive cardiac failure, chronic obstructive pulmonary disease, pneumonia, and urinary tract infection were the only SAEs reported in more than one person in Study ZS-004E (each was reported in two patients, or 1.6%). The most common SAEs reported in Study ZS-005 during the extended-dosing phase were: pneumonia (1.9%), congestive cardiac failure (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and acute renal failure (1.1%). A greater proportion of patients in Study ZS-005 study reported a WDAE (13.7% versus 8.9% in Study ZS-004E), with cardiac failure (1.5%) and acute renal failure (1.2%) being the most common reasons (Table 41). The most common reason for WDAE in Study ZS-004E was an ECG with a prolonged QT interval. There were no deaths in Study ZS-004E; there were eight deaths (1.1% of patients) in Study ZS-005 (Table 41). None of the deaths were considered related to the study drug. A number of notable harms were reported in the two studies (Table 41), some of which have been previously described. Among AEs that have not yet been discussed, fatigue was twice as common in Study ZS-005 (1.9%) as in Study ZS-004E (0.8%), and hypokalemia was reported in 1.5% of patients in Study ZS-005. Cardiac disorders (8.9% in Study ZS-004E and 9.9% in Study ZS-005), gastrointestinal disorders (18.7% and 22.4%), hypertension (12.2% and 11.0%), and peripheral edema (8.1% and 9.7%) were potential safety signals to consider.

Table 41: Harms in Extended-Dosing Phase of Studies ZS-004E and ZS-005

	Study ZS-004E	Study ZS-005
	SZC 10 g q.d. N = 123	SZC 5 g q.d. N = 746
Extended-dosing phase		
Patients with > 0 AEs, N (%)	82 (66.7)	489 (65.5)
Most common AEs (≥ 2% of patients)		
Abdominal pain	3 (2.4)	7 (0.9)
Anemia	7 (5.7)	44 (5.9)
Arthralgia	3 (2.4)	19 (2.5)
Back pain	3 (2.4)	11 (1.5)
Blood urea increase	3 (2.4)	2 (0.3)
Bronchitis	1 (0.8)	18 (2.4)
Cardiac failure	3 (2.4)	5 (0.7)
Cardiac failure, congestive	2 (1.6)	24 (3.2)
Cardiac murmur	0	16 (2.1)
Cellulitis	0	21 (2.8)
Chest pain	1 (0.8)	28 (3.8)
Constipation	7 (5.7)	48 (6.4)
COPD	3 (2.4)	7 (0.9)
Cough	3 (2.4)	22 (2.9)
Diarrhea	4 (3.3)	33 (4.4)
Dizziness	3 (2.4)	17 (2.3)
Dyspnea	1 (0.8)	31 (4.2)
Edema	4 (3.3)	15 (2.0)
Edema, peripheral	10 (8.1)	72 (9.7)
Fall (injury)	0	22 (2.9)
Gastroenteritis	3 (2.4)	10 (1.3)
Gout	4 (3.3)	18 (2.4)
Headache	4 (3.3)	23 (3.1)
Hyperlipidemia	4 (3.3)	0
Hyperkalemia	1 (0.8)	19 (2.5)
Hypertension	15 (12.2)	82 (11.0)
Hypomagnesemia	3(2.4)	2 (0.3)
Influenza	3 (2.4)	10 (1.3)
Muscle spasms	6 (4.9)	23 (3.1)
Nausea	4 (3.3)	56 (7.5)
Nasopharyngitis	2 (1.6)	19 (2.5)
Pain in extremity	1 (0.8)	17 (2.3)
Pneumonia	3 (2.4)	24 (3.2)
Renal failure, acute	2 (1.6)	33 (4.4)
Seasonal allergy	3 (2.4)	2 (0.3)
Sinusitis	2 (1.6)	15 (2.0)

	Study ZS-004E	Study ZS-005
	SZC 10 g q.d. N = 123	SZC 5 g q.d. N = 746
Skin ulcer	0	19 (2.5)
Upper respiratory tract infection	5 (4.1)	37 (5.0)
Urinary tract infection	11 (8.9)	59 (7.9)
Vomiting	4 (3.3)	36 (4.8)
Patients with > 0 SAEs, N (%)	24 (19.5)	161 (21.6)
Most common SAEs (> 1 patient)		
Acute myocardial infarction	1 (0.8)	6 (0.8)
Acute respiratory failure	0	5 (0.7)
Cardiac failure	1 (0.8)	4 (0.5)
Cardiac failure, congestive	2 (1.6)	11 (1.5)
Cellulitis	0	7 (0.9)
Chest pain	1 (0.8)	11 (1.5)
COPD	2 (1.6)	3 (0.4)
Dyspnea	0	5 (0.7)
Hyperkalemia	1 (0.8)	4 (0.5)
Hypertension	0	4 (0.5)
Hypoglycemia	0	4 (0.5)
Osteomyelitis	0	8 (1.1)
Pneumonia	2 (1.6)	14 (1.9)
Renal failure, acute	0	8 (1.1)
Renal failure, chronic	0	4 (0.5)
Skin ulcer	0	4 (0.5)
Urinary tract infection	2 (1.6)	4 (0.5)
WDAEs, N (%)	11 (8.9)	102 (13.7)
Most common reasons (≥ 1% of patients)		
Cardiac failure	1 (0.8)	11 (1.5)
Electrocardiogram QT prolonged	2 (1.6)	0
Renal failure, acute	0	9 (1.2)
Deaths, N (%)	0	8 (1.1)
Myocardial infarction	0	1 (0.1)
Cystitis, hemorrhagic	0	1 (0.1)
Dyspnea and abnormal ECG	0	1 (0.1)
Cardiac arrest and toxicity to various drugs	0	1 (0.1)
Interstitial lung disease	0	1 (0.1)
Heart injury	0	1 (0.1)
Renal failure, chronic	0	1 (0.1)
Hypercapnia and respiratory failure	0	1 (0.1)
Notable Harms		
Renal failure	2 (1.6)	1 (0.1)
Acute renal failure	2 (1.6)	33 (4.4)

	Study ZS-004E	Study ZS-005
	SZC 10 g q.d. N = 123	SZC 5 g q.d. N = 746
Chronic renal failure	2 (1.6)	12 (1.6)
Cardiac disorders	11 (8.9)	74 (9.9)
Cardiac disorders in ≥ 1% of patients		
Atrial fibrillation	0	12 (1.6)
Cardiac failure	3 (2.4)	5 (0.7)
Cardiac failure, congestive	2 (1.6)	24 (3.2)
Edema	4 (3.3)	15 (2.0)
Face edema	0	2 (0.3)
Generalized edema	0	4 (0.5)
Peripheral edema	10 (8.1)	72 (9.7)
Chest pain	1 (0.8)	28 (3.8)
Fatigue	1 (0.8)	14(1.9)
Gastrointestinal disorders	23 (18.7)	167 (22.4)
Blood creatine increase	2 (1.6)	9 (1.2)
Hypertension	15 (12.2)	82 (11.0)
Hypokalemia	0	11 (1.5)

AE = adverse event; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; q.d. = once daily; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate; WDAE = withdrawal due to adverse event.

Sources: Study ZS-004E Clinical Study Report;[32] Study ZS-005 Clinical Study Report.[33]

Critical Appraisal

Internal Validity

Studies ZS-004E and ZS-005 were single-arm, open-label studies. The absence of a comparator arm limits the ability to interpret their safety and efficacy results and to estimate the effect of any possible bias introduced by the open-label design. Statistical testing was performed using a pre-specified statistical hierarchy for the primary and secondary efficacy outcomes in Study ZS-004E; however, the same was not done in Study ZS-005. In Study ZS-005, t-tests were performed where appropriate, but no adjustments for multiplicity were made. In addition, Study ZS-004E may have been underpowered, as it was reported that as few as 140 patients would be sufficient for 90% power for the primary outcome, which was based on 121 patients in the reported study results. Study ZS-005 did not perform any prospective sample-size calculations.

The discontinuation rates during the extended-dosing phase in both studies were high, at 35.8% in Study ZS-004E and 37.5% in Study ZS-005,. Further, one of the most common reasons for discontinuation was withdrawal of consent (7.3% and 10.9% in Study ZS-004E and Study ZS-005); the potential for attrition bias should be considered. Serum potassium data were imputed for missing values in Study ZS-004E. Imputation of data was not performed in Study ZS-005; however, the sponsor reported that a post hoc comparison of serum potassium values and the change from the acute phase and extended-dosing phase for those who dropped out of Study ZS-005 versus those who did not was performed. No apparent difference was observed; therefore, it was reported that missing data likely did not have an effect on the estimates.[33]

External Validity

The baseline characteristics suggest that the populations enrolled in the two studies are appropriate for the target population of SZC, except for the baseline serum potassium levels. More specifically, 44.6% and 38.1% of patients enrolled in the extended-dosing phase of studies ZS-004E and ZS-005 had acute-phase baseline serum potassium values of less than 5.5 mmol/L. According to the clinical experts assigned to this review, hyperkalemia is not of clinical concern until serum potassium values are greater than 5.5 mmol/L, which suggests that a large portion of patients included in these studies are "healthier" than the population for whom SZC would be clinically relevant, in terms of serum potassium levels.

The background care provided in the two studies may have also affected the generalizability of the study results. As per protocol, adjustments to the dosing of SZC were permitted based on patients' serum potassium levels. Concomitant medications were also permitted throughout the study, which included dose optimization of RAASi and initiation of new hyperkalemia- or hypokalemia-related treatments. As such, patients had frequent access to a clinician along with their scheduled study visits, which occurred approximately every four weeks at most. It is uncertain whether a patient would have access to this frequency of care in clinical practice, which should be considered when reviewing the results of a long-term treatment that would be used daily.

Discussion

Summary of Available Evidence

The main evidence for SZC consisted of five DB RCTs. Two studies (ZS-003 and ZS-D9482) had a randomized, placebo-controlled acute phase for the first 48 hours of treatment. Four studies (ZS-003, ZS-004, ZS-D9480, and DIALIZE) had a randomized, placebo-controlled maintenance phase that lasted 12 days or 28 days. Across the studies, 895 patients were evaluated for acute treatment and 946 for maintenance treatment at the Health Canada–approved doses. In the acute phase, SZC was administered at various doses three times daily, and in the maintenance phase, treatment was administered at various doses once daily. However, for this review, only Health Canada–approved doses were evaluated. The studies examined several efficacy outcomes related to serum potassium levels and harms.

A heterogeneous, older patient population with various conditions (e.g., CKD) and medications (e.g., RAASi) related to potassium level were included in the studies. Patients were in the range of mild to moderate hyperkalemia at baseline. The cause of hyperkalemia for most patients was CKD. The only data available for patients on dialysis were from DIALIZE, as all other studies excluded this population. Long-term data for SZC were available from one OLE of Study ZS-004 (Study ZS-004E) with 123 patients and one single-arm, open-label study (Study ZS-005) with 751 patients. In studies ZS-004E and ZS-005, patients received SZC 10 g once daily over an extended-dosing period for up to 11 months or 12 months, respectively. In both studies, treatment could be titrated down to 5 g or up to 15 g once daily; however, most patients were on 10 g or less.

Interpretation of Results

Efficacy

Acute Phase

Studies ZS-003 and ZS-D9482 found that the exponential rate of potassium change was statistically significantly higher in the negative direction (i.e., there was a greater decrease in potassium) with SZC 10 g three times daily compared with placebo over 48 hours. More than three-quarters (77%) of patients treated with SZC achieved normokalemia in 24 hours compared with half (49%) of those who received placebo. Therefore, SZC appears efficacious compared with placebo in normalizing potassium levels in the acute phase. The absence of comparisons with other potassium binders and treatments to reduce potassium levels makes it difficult to interpret the relative clinical benefit of the drug. In subgroups based on eGFR, starting serum potassium, RAASi medication use, congestive heart failure, and CKD, there was a greater decrease in serum potassium, and normokalemia was achieved by more patients who received SZC than placebo.

Maintenance Phase

Patients entered the maintenance phase of studies if they achieved normokalemia after 48 hours of treatment in the acute phase. Across the studies, a consistent effect in favour of SZC versus placebo was observed regarding stabilization of potassium level, lower mean serum potassium, more patients remaining normokalemic, higher number of days normokalemic, and longer time to return to hyperkalemia at the end of the maintenance phase. All studies conducted exploratory analyses of subgroups, such as patients with different degrees of eGFR impairment, CKD, heart failure, and use of RAASi, and found effects in favour of SZC. Given the relatively small sample size, more study is warranted to identify the potential disparity in maintaining treatment effect by different level of kidney impairment as measured by eGFR categories (e.g., < 30 mL/min/1.73m^2 per the sponsor's listing request). It is also noteworthy that many (50% to 80%) of the patients who were observed maintaining the study drug's treatment effect were using RAASi medications. Among patients on hemodialysis, DIALIZE found that more patients on SZC maintained a pre-dialysis serum potassium of 4.0 mmol/L to 5.0 mmol/L and did not require rescue therapy.

As mentioned, SZC appears to normalize serum potassium levels in the acute phase and maintains normokalemia longer than placebo. Interpreting the clinical relevance of these results is difficult because of the lack of direct or indirect comparative evidence with other treatments. Due to concerns about the safety of SPS, as described in more detail in the harms section, direct comparisons with this drug may be difficult to carry out, although comparisons with patiromer or non-pharmacological treatments for hyperkalemia would be feasible. The sponsor initiated a DB, head-to-head, RCT comparison of SPS with SZC, but the trial was terminated early by an independent data safety monitoring board due to concerns about the safety of SPS. As well, there were limited data available to measure quality of life, which was mentioned by patients as an important outcome, especially in the context of the dietary changes needed to manage hyperkalemia. One study measured HRQoL using the EQ-5D-5L. However, no apparent differences were observed between SZC versus placebo, and this study was not designed to measure quality of life. None of the studies were designed or powered for the clinical outcomes of interest, such as cardiovascular and kidney morbidity. There were limited data on hospitalizations and RAASi

dose reduction or discontinuation. The clinical experts consulted for this review indicated that a key outcome is the maintenance of optimal RAASi dose, given the morbidity and survival benefits of these drugs in patients with cardiovascular and/or kidney disease.

Of the available potassium binders (Table 5), SPS has been used for the longest time (approved by the FDA in 1958).[4] It binds to potassium in the large intestine in exchange for sodium, with one gram binding to about 0.5 mmol/L to 1.0 mmol/L potassium.[4] Among 33 outpatients with CKD whose potassium levels were 5.0 mmol/L to 5.9 mmol/L, SPS 30 g once daily for seven days decreased serum potassium levels by 1.04 mmol/L compared with placebo.[4] CPS is another potassium binder that exchanges potassium for calcium, potentially avoiding the undesirable effects of sodium retention, although it may be less effective than SPS.[34,35] Patiromer is a more recently approved binder that exchanges potassium for a calcium-sorbitol complex, with one gram binding to more than 8 mmol/L of potassium.[4] Patiromer has been found to reduce serum potassium more effectively than placebo in three RCTs of about 700 patients in total.[4] Among 243 patients with CKD and hyperkalemia, patiromer led to a mean reduction in potassium of 1.01 mmol/L by the third day.[4] Patiromer has been found to lower serum potassium and achieve normokalemia for up to 52 weeks while RAASi therapy was maintained.[2] As with SPS, SZC exchanges potassium for sodium, although it is more specific for potassium ions. One gram of SZC binds to about 3 mmol/L potassium.[4] There are currently no direct treatment comparisons or ITCs to evaluate the efficacy of SZC versus other potassium binders.

Harms

Acute Phase: The more frequent (> 1%) AEs in the acute phase were constipation, diarrhea, vomiting, and edema. There were three WDAEs in patients who received SZC. No patient who received SZC had an SAE, and there were no deaths. Of the notable harms, constipation, edema, hypokalemia, atrial fibrillation, palpitations, hypertension, and ventricular extrasystoles were slightly more common with SZC than with placebo. One patient in an open-label acute phase experienced intestinal obstruction.

Maintenance Phase

Across three studies, SAEs were experienced by six patients who received SZC 10 g, 12 patients who received SZC 5 g, and four patients who received placebo. There were eight patients with WDAEs in the 10 g group, 14 in the 5 g group, and four in the placebo group. In DIALIZE, SAEs were experienced by seven patients on SZC and eight patients on placebo. There were three deaths in the maintenance phase across the four studies. One patient who received SZC 5 g died from respiratory distress; one patient receiving 10 g died of myocardial infarction; and one patient on dialysis randomized to SZC in the DIALIZE study died of peripheral arterial occlusive disease.

Of the notable harms, constipation was more frequent with SZC 10 g. One patient on 5 g had a small intestinal obstruction. Edema or peripheral edema were observed in most studies. This is not surprising, given the mechanism of action of SZC. The clinical experts consulted for this review noted that this as an important effect that may have implications for much of the population at risk for hyperkalemia, notably those with cardiovascular and/or kidney disease. Because there is no duration of treatment specified with SZC, longer-term use with edema may affect outcomes for this patient population. Hypokalemia was observed more frequently with higher doses. In Study ZS-004, it occurred in eight patients in the 10 g group, but in none in the 5 g or placebo groups. In Study ZS-D9480, one patient in the 10 g group experienced hypokalemia; there were no cases in the 5 g or placebo groups. In

DIALIZE, five patients in both the placebo and SZC groups experienced pre-dialysis hypokalemia.

During the extended-dosing phases of studies ZS-004E and ZS-005, 66.7% and 65.5% of patients reported an AE, 19.5% and 21.6% reported an SAE, 8.9%, and 13.7% reported a WDAE, respectively. Eight (1.1%) deaths were reported in Study ZS-005, none of which were considered related to the study drug. Hypertension, peripheral edema, and gastrointestinal disorders (i.e., constipation, vomiting, and diarrhea) were some of the most frequently occurring AEs in the two studies, and were notable harms for this review. None of the SAEs were reported in more than 2% of patients in either study. The most common reasons for WDAEs included cardiac failure and acute renal failure in Study ZS-005 and an ECG with a prolonged QT interval in Study ZS-004E.

The patient input summary mentioned a dislike for the texture and taste of the potassium binder, SPS. Potassium binders are administered as an oral suspension, and palatability may be an issue. However, no data were available about patients' perspectives on taking SZC or whether they considered it palatable.

Among the other available potassium binders, patiromer has been found to have low rates of AEs, with the most common being mild to moderate constipation, diarrhea, hypokalemia, and hypomagnesemia.[4] SPS has caused electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia), gastrointestinal effects (e.g., nausea, vomiting, diarrhea, and constipation), and, of most concern, severe gastrointestinal injuries, such as ulceration, bleeding, ischemic colitis, and perforation.[4,36] In the SZC studies, two patients experienced intestinal obstruction, one each in the acute and maintenance phases. There were also gastrointestinal-related SAEs and WDAEs. Given the similar mechanism of action with potassium binders, monitoring of gastrointestinal side effects would be warranted for SZC.

Health Canada granted an NOC to SZC on July 25, 2019.[9] The Health Canada review noted the higher incidence of edema with SZC (i.e., 1.8% for 5 g, 5.3% for 10 g, and 14.3% for 15 g versus 1.7% with placebo).[9] The review indicated that 53% of edema cases were managed with a diuretic or by adjusting the diuretic dose, with the remainder not requiring any treatment. SZC is also approved for the treatment of hyperkalemia in the US and European Union.[1,21]

Conclusions

SZC is a new potassium binder for the treatment of hyperkalemia in adults. Five studies provide evidence for its efficacy compared with placebo for the acute (initial 48 hours) and maintenance (beyond 48 hours) phases in patients with mild to moderate hyperkalemia. For the acute treatment of hyperkalemia, SZC 10 g reduced serum potassium at a higher rate than placebo over 48 hours. In the maintenance phase, the evidence was consistent in showing potassium-lowering effects for SZC 5 g or 10 g once daily compared with placebo over 12 days and 28 days. SZC led to a greater degree of potassium stabilization, lower mean potassium, a higher proportion of patients who remained normokalemic, a higher number of normokalemic days, and longer time to hyperkalemia. In a population of patients requiring dialysis, more patients who received SZC had pre-dialysis potassium levels within the normal range and did not require rescue therapies. As with other potassium binders, gastrointestinal effects, such as constipation, may be more common with this medication. Other AEs that require monitoring are edema and hypokalemia, especially at the higher dose of 10 g. A key limitation in the evidence for SZC is that there were no or limited data

available for outcomes of importance, such as cardiovascular and kidney morbidity, need to modify RAASi therapies, or quality of life. While patients with eGFR of less than 30 mL/min/1.73m^2 were included in the trials (sponsor reimbursement request), the results of subgroup analyses for these patients are uncertain due to small sample sizes and exploratory analyses. There were also no direct treatment comparisons or ITCs of SZC with other potassium binders; therefore, the comparative benefit and safety of this medication versus other existing therapies are unknown. Overall, while SZC demonstrated efficacy in reducing serum potassium levels, there is uncertainty as to its added clinical benefit.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 14, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials; qualitative studies; observational studies; economic evaluations; costs and cost analysis studies, and quality of life studies.
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (MEDLINE)
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Lokelma* or ZS 9 or UXSI 9 or UXSI9 or UZSI 9 or UZSI9 or D652ZWF066).ti,ab,kf,ot,hw,rn,nm.
2	(sodium* adj3 zirconium* adj3 (cyclosilicate* or silicate*)).ti,ab,kf,ot,hw,rn,nm.
3	ZS9.ti,ab,kf,ot,hw,nm.
4	or/1-3
5	4 use medall
6	*sodium zirconium cyclosilicate/
7	(Lokelma* or ZS 9 or ZS9 or UXSI 9 or UXSI9 or UZSI 9 or UZSI9).ti,ab,kw,dq.
8	(sodium* adj3 zirconium* adj3 (cyclosilicate* or silicate*)).ti,ab,kw,dq.
9	or/6-8
10	9 use oemezd
11	10 not conference abstract.pt.
12	5 or 11
13	remove duplicates from 12

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results | lokelma OR (zirconium AND cyclosilicate)]	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search -- Studies with results | lokelma OR (zirconium AND cyclosilicate)]	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Dates for Search:	June 05, 2019 – June 14, 2019
Keywords:	[Lokelma, sodium zirconium cyclosilicate, hyperkalemia, potassium, kidney disease, and heart disease]
Limits:	Publication years: all years

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- internet search
- UpToDate.

Appendix 2: Excluded Studies

Table 42: Excluded Studies

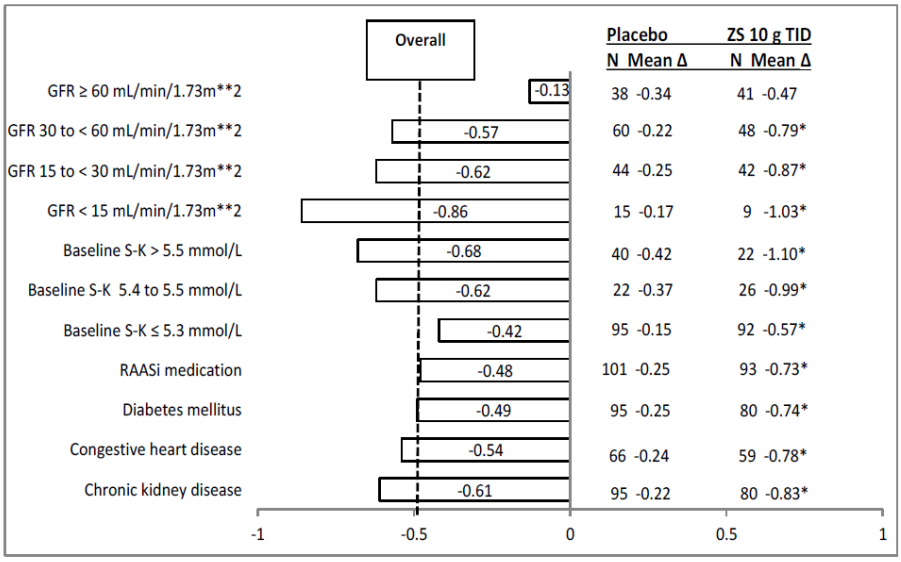
Reference	Reason for exclusion
CSR for Study ZS-004E[32]	Open-label study
CSR for Study ZS-005[33]	Open-label study
Spinowitz et al. (2019)[31]	Open-label study
Palaka et al. (2018)[5]	Review article
Anonymous (2015)[37]	Erratum
Ash et al. (2015)[38]	Phase II trial
Kosiborod et al. (2015)[39]	Editorial
Rasmussen (2015)[40]	Letter to editor
Dixon (2014)[41]	Editorial

CSR = Clinical Study Report.

Appendix 3: Detailed Outcome Data

Acute Phase

Figure 13: Mean Change in Serum Potassium from Baseline to Day 3 (48 hours) for Subgroups in Study ZS-003 (SZC 10 g Three Times Daily Versus Placebo)



GFR = glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; t.i.d. = three times a day.

Source: Extracted from Clinical Study Report for Study ZS-003.[23]

Table 43: Achievement of Normokalemia at Day 3 (48 Hours) for Subgroups in Study ZS-003

	Study ZS-003	
	Placebo	**SZC 10 g**
S-K ≤ 5.3 mmol/L		
N	95	92
n (%)	56 (58.9)	80 (87.0)
P value	—	< 0.0001
S-K 5.4 mmol/L to 5.5 mmol/L		
N	22	26
n (%)	10 (45.5)	24 (92.3)
P value	—	0.0005
S-K > 5.5 mmol/L		
N	40	22
n (%)	9 (22.5)	17 (77.3)
P value	—	< 0.0001
CKD		
N	95	80
n (%)	39 (41.1)	71 (88.8)
P value	—	< 0.0001
CHD		

	Study ZS-003	
N	66	59
n (%)	27 (40.9)	50 (84.7)
P value	—	< 0.0001
RAASi therapy		
N	101	93
n (%)	50 (49.5)	79 (84.9)
P value	—	< 0.0001
eGFR < 15 mL/min/1.73m²		
N	15	9
n (%)	4 (26.7)	9 (100.0)
P value	—	0.0006
eGFR 15 mL/min/1.73m² to < 30 mL/min/1.73m²		
N	44	42
n (%)	15 (34.1)	40 (95.2)
P value	—	< 0.0001
eGFR 30 mL/min/1.73m² to < 60 mL/min/1.73m²		
N	60	48
n (%)	29 (48.3)	41 (85.4)
P value	—	< 0.0001
eGFR ≥ 60 mL/min/1.73m²		
N	38	41
n (%)	27 (71.1)	31 (75.6)
P value	—	0.7995

CHD = congestive heart disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for Study ZS-003.[23]

Table 44: Exponential Rate of Serum Potassium Change for Subgroups in Study ZS-D9482

	Study ZS-D9482	
	Placebo	**SZC 10 g**
CKD		
N	26	26
48 hours, estimate (SE)[a]	–0.00037 (0.00029)	–0.00543 (0.00029)
P value[b]	—	< 0.05
HF		
N	4	3
48 hours, estimate (SE)[a]	–0.00014 (0.00099)	–0.00532 (0.00114)
P value[b]	—	< 0.05
RAASi medication		
N	27	26
48 hours, estimate (SE)[a]	–0.00018 (0.00031)	–0.00503 (0.00030)
P value[b]	—	< 0.05

CKD = chronic kidney disease; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor; SE = standard error; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

[a] From a random coefficient model with patient-level random effects for time and intercept and fixed effects for intercept, time, and time by treatment interaction.

[b] P values were not provided in the sponsor's submission and were inferred based on 95% confidence intervals.

Source: Clinical Study Report for Study ZS-D9482.[27]

Table 45: Achievement of Normokalemia at 48 Hours for Subgroups in Study ZS-D9482

	Study ZS-D9482	
	Placebo	**SZC 10 g**
S-K < 5.3 mmol/L		
N	6	12
Normokalemia, n (%)	3 (50.0)	10 (83.3)
S-K 5.3 mmol/L to 5.5 mmol/L		
N	12	12
Normokalemia, n (%)	2 (16.7)	12 (100)
S-K > 5.5 mmol/L		
N	15	12
Normokalemia, n (%)	0 (0)	11 (91.7)
CKD		
N	26	26
Normokalemia, n (%)	4 (15.4)	24 (92.3)
P value[a]	—	< 0.0001
HF		
N	4	3
Normokalemia, n (%)	1 (25.0)	2 (66.7)
P value[a]	—	0.1547
RAASi medication		
N	27	26
Normokalemia, n (%)	4 (14.8)	24 (92.3)
P value[a]	—	< 0.0001
eGFR < 15 mL/min/1.73m^2		
N	11	9
Normokalemia, n (%)	3 (27.3)	9 (100)
eGFR 15 30 mL/min/1.73m^2 to < 30 mL/min/1.73m^2		
N	11	13
Normokalemia, n (%)	1 (9.1)	12 (92.3)
eGFR 30 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2		
N	11	11
Normokalemia, n (%)	1 (9.1)	9 (81.8)

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

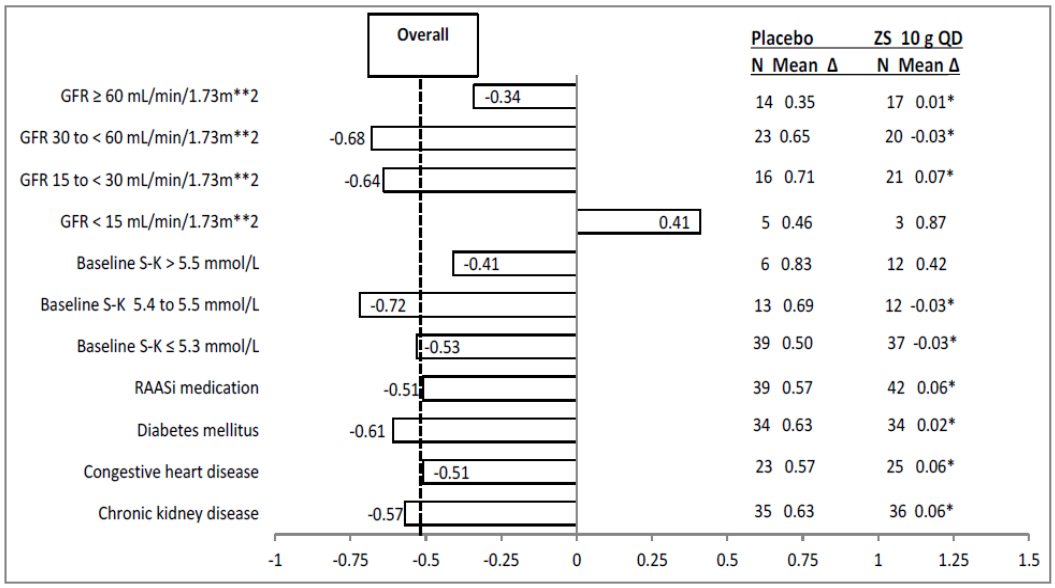
Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

[a] From a logistic regression model that included treatment and baseline S-K.

Source: Clinical Study Report for Study ZS-D9482.[27]

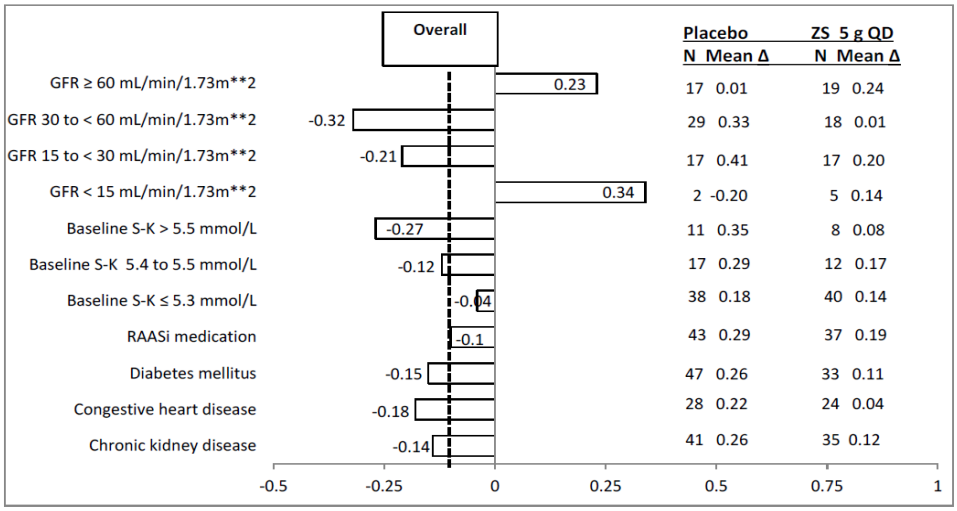
Maintenance Phase

Figure 14: Mean Change in Serum Potassium From Maintenance-Phase Baseline to Maintenance-Phase Day 12 for Subgroups in Study ZS-003 (SZC 10 g Once Daily Versus Placebo)



GFR = glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; q.d. = every day.
Source: Extracted from Clinical Study Report for Study ZS-003.[23]

Figure 15: Mean Change in Serum Potassium from Maintenance-Phase Baseline to Maintenance-Phase Day 12 for Subgroups in Study ZS-003 (SZC 5 g Once Daily Versus Placebo)



GFR = glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate; q.d. = every day.
Source: Extracted from Clinical Study Report for Study ZS-003.[23]

Table 46: Achievement of Normokalemia at Maintenance-Phase Day 12 for Subgroups in Study ZS-003

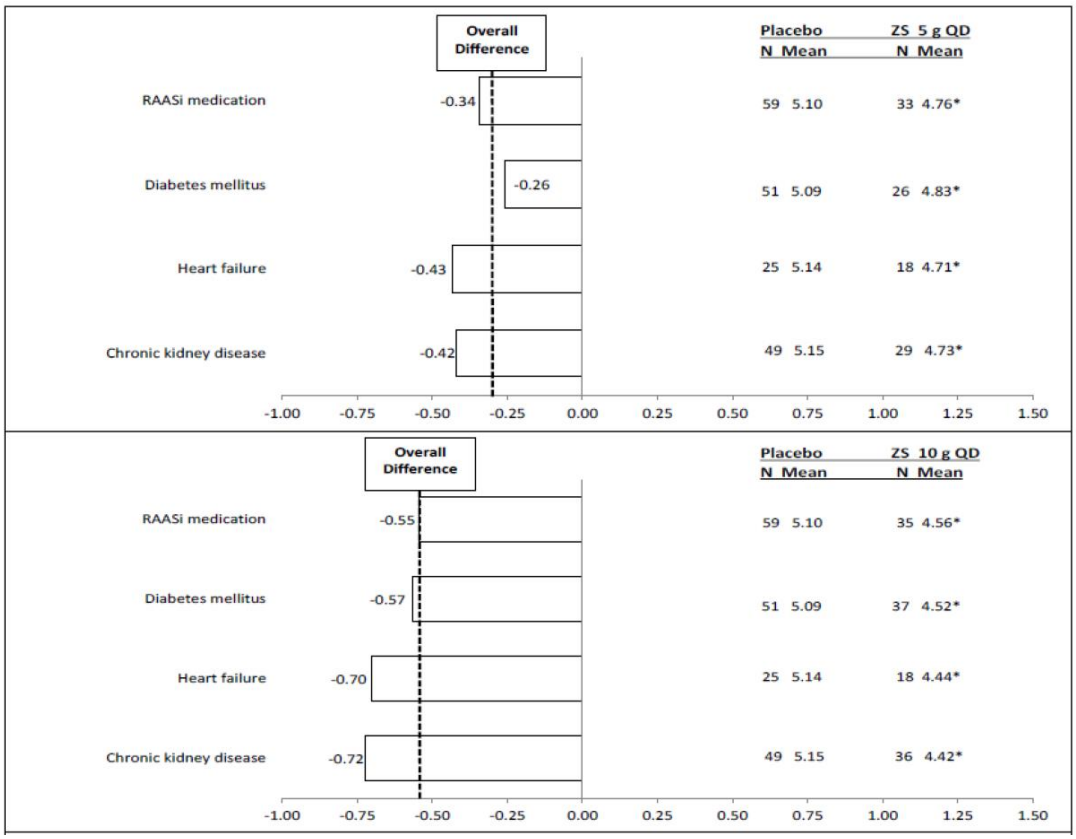
	Study ZS-003			
	Placebo	SZC 5 g	Placebo	SZC 10 g
S-K ≤ 5.3 mmol/L				
N	38	40	39	37
n (%)	21 (55.3)	29 (72.5)	26 (66.7)	34 (91.9)
P value	—	0.1569	—	0.0103
S-K 5.4 mmol/L to 5.5 mmol/L				
N	17	12	13	12
n (%)	8 (47.1)	9 (75.0)	6 (46.2)	12 (100.0)
P value	—	0.2510	—	0.0052
S-K > 5.5 mmol/L				
N	11	8	6	12
n (%)	3 (27.3)	7 (87.5)	1 (16.7)	4 (33.3)
P value	—	0.0198	—	0.6148
CKD				
N	41	35	35	36
n (%)	19 (46.3)	26 (74.3)	18 (51.4)	30 (83.3)
P value	—	0.0192	—	0.0054
CHD				
N	28	24	23	25
n (%)	13 (46.4)	20 (83.3)	11 (47.8)	21 (84.0)
P value	—	0.0090	—	0.0135
RAASi therapy				
N	43	37	39	42
n (%)	18 (41.9)	26 (70.3)	22 (56.4)	35 (83.3)
P value	—	0.0138	—	0.0140
eGFR < 15 mL/min/1.73m^2				
N	2	5	5	3
n (%)	2 (100.0)	3 (60.0)	3 (60.0)	1 (33.3)
P value	—	1.0000	—	1.0000
eGFR 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2				
N	17	17	16	21
n (%)	6 (35.3)	11 (64.7)	5 (31.3)	15 (71.4)
P value	—	0.1694	—	0.0220
eGFR 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2				
N	29	18	23	20
n (%)	10 (34.5)	15 (83.3)	13 (56.5)	19 (95.0)
P value	—	0.0022	—	0.0050
eGFR ≥ 60 mL/min/1.73m^2				
N	17	19	14	17
n (%)	13 (76.5)	15 (78.9)	12 (85.7)	15 (88.2)
P value	—	1.0000	—	1.0000

CHD = congestive heart disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Source: Clinical Study Report for Study ZS-003.[23]

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

Figure 16: Least Squares Mean Change in Serum Potassium From Day 8 to Day 29 of Maintenance Phase for Subgroups in Study ZS-004



q.d. = every day; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Note: From a mixed effect model of serial S-K observations between maintenance-phase days 8 to 29 with a patient random effect and the following fixed effects: maintenance-phase treatment group, acute-phase baseline eGFR, acute-phase baseline S-K, maintenance-phase baseline S-K, age category (< 55 years, 55 to 64 years, ≥ 65 years), use of RAASi, and disease status for CKD, CHF, and diabetes mellitus.

Source: Extracted from Clinical Study Report for Study ZS-004.[25]

Table 47: Mean Change in Serum Potassium from Maintenance-Phase Baseline to Maintenance-Phase Day 29 Exit for Subgroups in Study ZS-004

	Study ZS-004		
	Placebo	**SZC 5 g**	**SZC 10 g**
S-K < 5.5 mmol/L			
N	40	23	18
Mean change (SD), mmol/L	0.4 (0.6)	0.2 (0.5)	0.08 (0.7)
P value	—	0.1120	0.0691
S-K 5.5 mmol/L to < 6.0 mmol/L			
N	30	17	23
Mean change (SD), mmol/L	0.6 (0.6)	0.4 (0.7)	0.2 (0.9)
P value	—	0.1708	0.0635

	Study ZS-004		
S-K ≥ 6.0 mmol/L			
N	12	5	9
Mean change (SD), mmol/L	0.9 (0.5)	0.3 (0.9)	–0.1 (0.4)
P value	—	0.0666	< 0.0001
CKD			
N	49	29	36
Mean change (SD), mmol/L	0.7 (0.5)	0.2 (0.6)	–0.01 (0.7)
P value	—	0.0006	< 0.0001
HF			
N	25	18	18
Mean change (SD), mmol/L	0.7 (0.5)	0.3 (0.7)	0.08 (0.9)
P value	—	0.0120	0.0086
RAASi medication			
N	59	33	35
Mean change (SD), mmol/L	0.6 (0.5)	0.25 (0.7)	0.2 (0.8)
P value	—	0.0076	0.0086
eGFR < 60 mL/min/1.73m^2			
N	51	31	38
Mean change (SD), mmol/L	0.7 (0.5)	0.2 (0.6)	0.1 (0.8)
P value	—	0.0010	0.0004

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; S-K = serum potassium; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for ZS-004.[25]

Table 48: Achievement of Normokalemia at Maintenance-Phase Day 29 Exit for Subgroups in Study ZS-004

	Study ZS-004		
	Placebo	**SZC 5 g**	**SZC 10 g**
CKD			
N	49	29	36
Normokalemia at MP baseline, n (%)	42 (85.7)	27 (93.1)	33 (91.7)
Normokalemia at day 29 exit, n (%)	18 (36.7)	20 (69.0)	26 (72.2)
P value (day 29 exit)	—	0.0095	0.0019
HF			
N	25	18	18
Normokalemia at MP baseline, n (%)	20 (80.0)	17 (94.4)	17 (94.4)
Normokalemia at day 29 exit, n (%)	10 (40.0)	13 (72.2)	13 (72.2)
P value (day 29 exit)	—	0.0625	0.0625
RAASi medication			
N	59	33	35

	Study ZS-004		
Normokalemia at MP baseline, n (%)	49 (83.1)	31 (93.9)	32 (91.4)
Normokalemia at day 29 exit, n (%)	26 (44.1)	23 (69.7)	25 (71.4)
P value (day 29 exit)	—	0.0287	0.0113

CKD = chronic kidney disease; HF = heart failure; MP = maintenance phase; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

Source: Clinical Study Report for Study ZS-004.[25]

Table 49: LSM Serum Potassium During Maintenance-Phase Day 8 to Day 29 for Subgroups in Study ZS-D9480

	Study ZS-D9480		
	Placebo	**SZC 5**	**SZC 10**
CKD			
N	34	78	79
LSM (95% CI)[a]	5.4 (5.2 to 5.6)	4.8 (4.7 to 5.0)	4.4 (4.3 to 4.5)
Treatment-by-subgroup interaction P value	—	0.906	0.458
HF			
N	8	16	19
LSM (95% CI)[a]	5.2 (4.9 to 5.6)	4.8 (4.5 to 5.0)	4.4 (4.2 to 4.6)
Treatment-by-subgroup interaction P value	—	0.949	0.700
RAASi medication			
N	40	72	76
LSM (95% CI)[a]	5.3 (5.1 to 5.5)	4.8 (4.6 to 4.9)	4.4 (4.2 to 4.5)
Treatment-by-subgroup interaction P value	—	0.984	0.684

CI = confidence interval; CKD = chronic kidney disease; HF = heart failure; LSM = least squares mean; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

[a] From a mixed-effects model of serum potassium levels with a patient random effect and fixed effects of treatment group, treatment by visit interaction, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline estimated glomerular filtration rate, age category (< 55 years, 55 to 64 years, and ≥ 65 years), country, baseline RAASi use, CKD, HF, diabetes mellitus, and treatment by disease (CKD, HF, or RAASi) interaction.

Source: Clinical Study Report for Study ZS-D9480.[26]

Table 50: Achievement of Normokalemia at Maintenance-Phase Day 29 Exit for Subgroups in Study ZS-D9480

	Study ZS-D9480		
	Placebo	**SZC 5 g**	**SZC 10 g**
CKD			
N	35	82	80
Normokalemia, n (%)[a]	7 (20.0)	46 (56.1)	59 (73.8)
Treatment-by-subgroup interaction P value	—	0.875	0.391
HF			
N	8	18	19
Normokalemia, n (%)[a]	3 (37.5)	12 (66.7)	14 (73.7)
Treatment-by-subgroup interaction P value	—	0.564	0.189
RAASi medication			
N	41	76	76
Normokalemia, n (%)[a]	10 (24.4)	43 (56.6)	58 (76.3)
Treatment-by-subgroup interaction P value	—	0.333	0.628

CKD = chronic kidney disease; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Note: Subgroup analyses were not part of the sequential closed statistical testing procedure.

[a] From a logistic regression model that included covariates of treatment group, acute-phase baseline serum potassium, maintenance-phase serum potassium, acute-phase baseline eGFR, age category (< 55 years, 55 years to 64 years, and ≥ 65 years), country, baseline RAASi use, CKD, HF, diabetes mellitus, and treatment by disease (CKD, HF, or RAASi) interaction.

Source: Clinical Study Report for Study ZS-D9480.[26]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the EQ-5D-5L outcome measure and review its measurement properties (validity, reliability, responsiveness to change, and minimum important difference).

Findings

EuroQol 5-Dimensions 5-Levels

The EQ-5D is a generic self-reported quality of life instrument developed by the EuroQol Group that is applicable to a wide range of health conditions and treatments.[28] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, it provides valuable information from a patient perspective. The original three-level version was introduced in 1990 and was composed of five dimensions pertaining to HRQoL.[28] Respondents are to indicate their health status in terms of five HRQoL dimensions based on three levels of severity. To improve sensitivity and reduce ceiling effects, the EuroQol 5-Dimensions 3-Levels instrument was updated in 2005 and expanded to five levels per dimension, creating the EQ-5D-5L. This is what was used in Study ZS-D9480.[28]

The EQ-5D-5L consists of descriptive system and the EQ VAS. As mentioned, the descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients respond to each dimension based on five levels, where a level 1 response represents "no problems," level 2 represents "slight problems," level 3 represents "moderate problems," level 4 represents "severe problems," and level 5 represents "extreme problems" or "unable to perform," which is the worst response in the dimension.[28] Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states, respectively. The numerical values assigned to levels 1 to 5 for each dimension reflect rank-order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties. Therefore, they should not be summed or averaged, such as to produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[42] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[28,42] Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 or 21143
- a population preference–weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in terms of its feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from six countries with chronic conditions;[28] however, evidence of validity in patients with hyperkalemia was not identified. A Canadian-specific estimate of a minimal clinically important difference for the EQ-5D-5L was generated by the simulating the effects of single-level transitions in each dimension.[29] The results yielded minimal clinically important differences with a summarized mean of 0.056 (SD = 0.011) and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[29]

References

1. Hoy SM. Sodium zirconium cyclosilicate: a review in hyperkalaemia. *Drugs.* 2018;78(15):1605-1613.
2. Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. *Rev Endocr Metab Disord.* 2017;18(1):41-47.
3. Best practices in managing hyperkalemia in chronic kidney disease New York (NY): National Kidney Foundation; 2016: https://www.kidney.org/sites/default/files/02-10-7259%20Hyperkalemia%20Tool.pdf. Accessed 2019 Aug 01.
4. Liu M, Rafique Z. Acute management of hyperkalemia. *Curr Heart Fail Rep.* 2019;16(3):67-74.
5. Palaka E, Leonard S, Buchanan-Hughes A, Bobrowska A, Langford B, Grandy S. Evidence in support of hyperkalaemia management strategies: a systematic literature review. *Int J Clin Pract.* 2018;72(2).
6. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? *Arch Intern Med.* 1998;158(1):26-32.
7. Kovesdy CP. Epidemiology of hyperkalemia: an update. *Kidney Int Suppl (2011).* 2016;6(1):3-6.
8. Fleet JL, Shariff SZ, Gandhi S, Weir MA, Jain AK, Garg AX. Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. *BMJ Open.* 2012;2(6).
9. Health Canada reviewer's report: Lokelma (sodium zirconium cyclosilicate) [CONFIDENTIAL internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2019.
10. Lokelma (sodium zirconium cyclosilicate): 5 g and 10 g powder for oral suspension (draft) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2018 Jul 31.
11. Kayexalate (Sodium Polystyrene Sulfonate): cation-exchange resin cream or fine powder [presscribing information]. Laval (QC): sanofi-aventis Canada Inc.; 2018: https://pdf.hres.ca/dpd_pm/00047478.PDF. Accessed 2019 Aug 15.
12. Resonium calcium (calcium polystyrene sulfonate): cation exchange resin prepared in the calcium phase [prescribing information]. Laval (QC): sanofi-aventis Canada Inc.; 2018: https://pdf.hres.ca/dpd_pm/00047479.PDF. Accessed 2019 Aug 15.
13. Veltassa (patiromer as patiromer sorbitex calcium): 8.4 g, 16.8 g, 25.2 g powder for oral suspension [product monograph]. St. Gallen (CH): Vifor Fresenius Medical Care Renal Pharma Ltd.; 2018: https://pdf.hres.ca/dpd_pm/00047648.PDF. Accessed 2019 Aug 15.
14. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
15. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2019 Jun 11.
16. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med.* 2015;372(3):222-231.
17. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA.* 2014;312(21):2223-2233.
18. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail.* 2015;17(10):1050-1056.
19. Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol.* 2019;30(6).
20. CDR submission: Lokelma™ (sodium zirconium cyclosilicate), 5g and10g, powder for oral suspension [CONFIDENTIAL manufacturer's submission]. Mississauga (ON): AstraZeneca Canada Inc.; 2019 May 16..
21. Center for Drug Evaluation Research. Medical review(s). Lokelma™ (sodium zirconium cyclosilicate) powder for oral suspension. Company: AstraZeneca Pharmaceuticals LP. Application No.:207078. Approval date: 05/18/2018 (FDA approval package). Rockville (MD): U. S. Food and Drug Administration (FDA); 2018: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207078Orig1s000MedR.pdf. Accessed 2019 Jun 05.
22. Center for Drug Evaluation Research. Statistical review(s). Lokelma™ (sodium zirconium cyclosilicate) powder for oral suspension. Company: AstraZeneca Pharmaceuticals LP. Application No.:207078. Approval date: 05/18/2018 (FDA approval package). Rockville (MD): U. S. Food and Drug Administration (FDA); 2018: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207078Orig1s000StatR.pdf. Accessed 2019 Jun 05.
23. Clinical study report: ZS-003 US. A phase 3, multicenter, two-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (microporous, fractionated, protonated zirconium silicate), an oral sorbent, in subjects with mild to moderate hyperkalemia [CONFIDENTIAL internal manufacturer's report]. San Mateo (CA): ZS Pharma, Inc.; 2014 Nov 24. Accessed 2019 Jun 07.
24. Clinical study report: ZS-003 EU. A phase 3, multicenter, two-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (microporous, fractionated, protonated zirconium silicate), an oral sorbent, in subjects with mild to moderate hyperkalemia [CONFIDENTIAL internal manufacturer's report]. San Mateo (CA): ZS Pharma, Inc.; 2015 Aug 14. Accessed 2019 Jun 07.
25. Clinical study report: ZS-004. A phase 3, multicenter, multi-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of ZS (sodium zirconium cycosilicate), an oral sorbent, in subjects with hyperkalemia [CONFIDENTIAL internal manufacturer's report]. San Mateo (CA): ZS Pharma, Inc.; 2014 Dec 03. Accessed 2019 Jun 07.
26. Clinical study report: NCT02875834. A phase 3 multicentre, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of sodium zirconium cycosilicate (ZS) in patients with hyperkalaemia-HARMONIZE global [CONFIDENTIAL internal manufacturer's report]. Molndal (SE): AstraZeneca Inc.; 2018 Dec 05. Accessed 2019 Jun 10.

27. Clinical study report: NCT03127644. A phase 2/3 multicenter, dose-response study to assess efficacy and safety of ZS (sodium zirconium cycosilicate), in Japanese patients with hyperkalemia [CONFIDENTIAL internal manufacturer's report]. Gaithersburg (MD): AstraZeneca Inc.; 2018 Aug 10. Accessed 2019 Jun 10.

28. van Reenen M, Janssen B. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument version 2.1. Rotterdam (NL): The EuroQol Research Foundation; 2015: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. Accessed 2019 Aug 15.

29. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L Index Scores. *Value Health.* 2017;20(4):644-650.

30. AstraZeneca Canada Inc. response to July 22, 2019 request for additional information regarding Lokelma (sodium zirconium cyclosilicate) CDR review: summary of clinical clarimails/clarifaxes [CONFIDENTIAL additional manufacturer's information]. Mississauga (ON): AstraZeneca Canada Inc.; 2019 Aug 02.

31. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol.* 2019;14(6):798-809.

32. Clinical study report: ZS-004E. An open-label extension to study ZS-004, a phase 3, multicenter, multi-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of ZS (sodium zirconium cycosilicate), an oral sorbent, in subjects with hyperkalemia [CONFIDENTIAL internal manufacturer's report]. San Mateo (CA): ZS Pharma, Inc.; 2015 Sep 14. Accessed 2019 Jun 07.

33. Clinical study report: ZS-005. A phase 3 multicenter, multi-dose, open-label maintenance study to investigate the long-term safety and efficacy of ZS (sodium zirconium cycosilicate), an oral sorbent, in subjects with hyperkalemia [CONFIDENTIAL internal manufacturer's report]. San Mateo (CA): ZS Pharma, Inc.; 2017 Aug 01. Accessed 2019 Jun 07.

34. Yu MY, Yeo JH, Park JS, Lee CH, Kim GH. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. *PLoS One.* 2017;12(3):e0173542.

35. Nakamura T, Fujisaki T, Miyazono M, et al. Risks and benefits of sodium polystyrene sulfonate for hyperkalemia in patients on maintenance hemodialysis. *Drugs R D.* 2018;18(3):231-235.

36. Noel JA, Bota SE, Petrcich W, et al. Risk of hospitalization for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients of advanced age. *JAMA Intern Med.* 2019.

37. Anonymous. Erratum: Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial (JAMA (2014) 312:21 (2223-2233) DOI: 10.1001/jama.2014.15688). *JAMA.* 2015;313(5):526.

38. Ash SR, Singh B, Lavin PT, Stavros F, Rasmussen HS. A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient. *Kidney Int.* 2015;88(2):404-411.

39. Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. *N Engl J Med.* 2015;372(16):1577-1578.

40. Rasmussen H. Sodium zirconium cyclosilicate (ZS-9) treatment in patients with serum potassium >6.5 mEq/L. *J Community Hosp Intern Med Perspect.* 2015;5(4):29097.

41. Bradley SD. Zirconium cyclosilicate for treatment of hyperkalemia. *JAMA.* 2014;312(21):2217-2218.

42. 2014 Alberta population norms for EQ-5D-5L. Calgary (AB): Health Quality Council of Alberta; 2014: https://d10k7k7mywg42z.cloudfront.net/assets/542f01f2edb2f37083002e54/2014_EQ_5D_5L_report_FINALFINAL.pdf. Accessed 2019 Aug 15.