Hyperkalemia, defined as serum potassium (s-K+) exceeding 5.0 mEq/L, is a common, sometimes fatal, electrolyte disorder seen most frequently in patients with chronic kidney disease (CKD), congestive heart failure heart failure, or diabetes mellitus. Cardiac arrhythmias can be a fatal complication of hyperkalemia therefore correcting elevated s-K+ levels is essential for preventing serious complications. Risks of developing hyperkalemia include impaired renal function or use of drugs that disrupt or block the renin-angiotensin-aldosterone system (RAAS) such as, angiotensinogen-converting enzyme inhibitors (ACEi), angiotensinogen receptor blockers (ARB), mineralocorticoid receptor antagonists. In one study, 11% of patients taking ACEi developed hyperkalemia during a one year period. Treatment with RAAS inhibitors is still strongly recommended in patients with CKD, heart failure, and diabetes mellitus with microalbuminuria.

Management of hyperkalemia in the outpatient setting primarily consists of decreasing or discontinuing medications that result in potassium (K+) retention, decreasing dietary intake of K+, or increasing K+ excretion. Decreasing K+ substances from the diet has not been shown to be effective in reducing s-K+ levels, primarily because these diets are difficult to adjust. Decreasing or discontinuing RAAS inhibitors may increase patients’ risk for disease state related complications in those CKF, heart failure or diabetes mellitus. Increasing K+ excretion can be accomplished with using loop or thiazide diuretics or exchange resins. Loop or thiazide diuretics may be an option, however, their use may be contraindicated or intolerable in some patients. Historically, sodium polystyrene sulfonate (SPS) has been used for acute and long-term management of hyperkalemia, but this nonspecific polymeric exchange resin has several drawbacks. SPS has a lower selectivity for K+ ions in the presence of other cations (e.g. calcium, magnesium) which can result in electrolyte imbalances. SPS has also been associated with poor gastrointestinal tolerability and serious gastrointestinal adverse events. Additionally, there have been concerns about the true efficacy of SPS, illustrated by a prospective study that found marginal increases in K+ excretion compared to laxatives alone. Another exchange resin includes a nonspecific sodium-cation exchange polymer, patiromer (Veltassa®), which essentially functions as a K+ binding agent. Unfortunately, Veltassa® carries a black box warning for decreased absorption of co-administered medications. Thus, it is recommended to administer other oral medications at least 6 hours apart from Veltassa®. Veltassa® also binds magnesium in the colon, which has been shown in some cases to cause hypomagnesemia. Treatment options for hyperkalemia are currently limited, therefore a safer more specific treatment for hyperkalemia is warranted.

Lokelma® (sodium zirconium cyclosilicate) is a novel K+ binding agent approved for the treatment of hyperkalemia in adults in non-acute settings. It was developed to overcome the gaps and limitations to current available therapies. Due to its novel chemical structure, Lokelma® has higher specificity for K+ ions compared to SPS and patiromer. The purpose of this article is to review the safety and efficacy of sodium zirconium cyclosilicate (ZS-9) for the treatment of hyperkalemia.

**Mechanism of Action**

ZS-9 selectively binds K+ in exchange for hydrogen and sodium inside the gastrointestinal tract, lowering the free concentration of K+ available for absorption, which leads to a reduction in s-K+ concentrations. Selectivity for K+ is retained even in the presence of other cations such as calcium and magnesium.

**Pharmacodynamics**

In healthy adult subjects, ZS-9 administered as 5 g or 10 g once daily for four days caused a dose-dependent increase in fecal K+ excretion. Corresponding dose-dependent decreases in urinary K+ excretion and s-K+ were also observed. ZS-9 has been observed to cause small dose-dependent increases in serum bicar-
bonate levels (5 g once daily = +1.1 mEq/L, 10 g once daily = +2.3 mEq/L, 15 g once daily = +2.6 mEq/L, placebo = +0.6 mEq/L). However, the clinical significance of this finding is unclear. No clinically relevant effects in serum calcium, magnesium, sodium, or kidney function parameters have been detected in trials.\(^{13}\)

**Pharmacokinetics**

ZS-9 is insoluble and not systemically absorbed and is therefore not subject to enzymatic metabolism.\(^{13}\) As expected, SZ-9 concentrations in the urine and blood were similar in treated patients and untreated patients.\(^{13}\)

### CLINICAL TRIALS

The safety and efficacy of ZS-9 for the treatment of hyperkalemia has been evaluated in one phase II trial, two published phase III trials, and one published subgroup analysis of CHF patients. The following section will discuss these trial results for ZS-9. Additionally, two trials evaluating the long-term safety and efficacy of ZS-9 are underway (NCT02107092, NCT02163499). A summary of sodium ZS-9 efficacy for the treatment of hyperkalemia is summarized in Table 1 and safety data in Table 2.

#### Phase II Trial

A phase II trial conducted by Ash et al. sought to determine the safety, efficacy, and optimal dosing of ZS-9 in 90 patients with stage 3 CKD (eGFR 30-60 ml/min/1.73 m\(^2\)) and mild-to-moderate hyperkalemia (5.0-6.0 mEq/L).\(^{15}\) Exclusion criteria included pseudohyperkalemia, treatment with SPS or phosphate binders within 7 days of enrollment, severe acidosis, acute kidney injury, or hyperkalemia-related electrocardiogram changes. Patients were randomly allocated to ZS-9 or placebo in a 2:1 ratio per cohort [cohort 1: ZS-9 0.3 g (n=12), placebo (n=6); cohort 2: ZS-9 3 g (n=24), placebo (n=12); cohort 3: ZS-9 10 g (n=24), placebo (n=12)]. The three cohorts were treated sequentially with at least one week between cohorts for safety monitoring. In each cohort, patients received either ZS-9 or placebo three times daily with meals for 48 hours. After the 48 hours, patients with normalized s-K+ (defined as 3.5-4.9 mEq/L) were discharged and patients with s-K+ (≥5.0 mEq/L) continued to receive additional treatment. Patients could receive a minimum of 6 doses (over 48 hours) or a maximum of 12 doses (over 96 hours). Patients returned on days 5 to 7 for the end-of-study visit. The primary endpoint was the rate of s-K+ decline in the first 48 hours. Secondary endpoints included changes in s-K+ at various time points, urine excretion of K+ and sodium, serum electrolytes (Ca\(^2+\), Mg\(^2+\), and Na\(^+\)), and kidney function parameters. Treatment was discontinued at any time during the study if s-K+ was >6.5 or <3.5 mEq/L. Across all arms, 56% had diabetes and 62% were receiving a RAAS inhibitor.

For the primary outcome, the rate of s-K+ decline was significantly higher in the ZS-9 3 g group (p=0.048) and ZS-9 10 g group (p<0.0001) compared to placebo. No specific rates of change were provided in the study’s results. Regarding secondary outcomes, compared to placebo, mean s-K+ declined significantly from baseline in the ZS-9 10 g group by -0.11±0.46 mEq/L at 1 hour (p=0.02), -0.52±0.49 mEq/L at hour 4 on day 2 (p=0.001), -0.62±0.45 mEq/L at hour 8 on day 2 (p<0.001), and -0.92±0.52 mEq/L at hour 14 on day 2 (p<0.001) compared to placebo. No significant differences were observed at any time point with ZS-9 0.3 g or ZS-9 3 g dose compared to placebo.

Twenty-four-hour urinary K+ excretion decreased significantly in the ZS-9 10-g group (-15.8 mEq/L) compared to placebo (+8.9 mEq/L, p<0.001). There were no differences in 24-hour urinary sodium excretion in any of the ZS 9 dose groups compared to placebo. No clinically relevant changes were seen in serum calcium, magnesium, or sodium in any of the treatment groups. A dose-dependent effect was seen with ZS-9 on blood urea nitrogen, with the greatest effect seen in the ZS-9 10 g group, which resulted in significant decreases seen at all measurements on days 2 to 7 compared to placebo. Serum bicarbonate increased approximately 10% with ZS-9 10 g, from 27.4 mEq/L at baseline to 30.1 mEq/L on day 2 (p=0.05) and day 3 (p=0.067). No significant changes in serum creatinine, 24-hour urea nitrogen, urine creatinine, or urinary sediment were observed at any of the three doses of ZS-9. The authors reported 23 treatment-emergent adverse events (TEAEs) from the 80 patients (19% of patients experienced ≥1 TEAE). The percentage of patients in each group who experienced at least one TEAE were 10%, 8%, 13%, 33% in patients treated with placebo, ZS-9 0.3 g, 3 g, 10 g, respectively. Three TEAEs were judged to be possibly related to the study treatment, mild constipation (3 g ZS-9), and nausea and vomiting (placebo). No serious TEAEs were reported. Additionally, there were no reports of clinically relevant hypocalcemia (≤8.0 mg/dl), hypomagnesemia (≤1.2 mEq/l), or hypokalemia (≥3.0 mEq/l) in any of the treatment groups.

#### Phase III Trials

The first phase III trial was conducted by Packham et al. which evaluated the safety and efficacy of ZS-9 for treatment of hyperkalemia (5.0-6.5 mEq/L) with a multicenter, two-stage, double-blind study design.\(^{16}\) In the initial phase, 752 patients with hyperkalemia were randomly allocated to receive either ZS-9 1.25 g (n=154), 2.5 g (n=141), 5 g (n=157), 10 g (n=143) three times daily or placebo (n=158) for 48 hours. For the maintenance phase, patients in the ZS-9 groups who achieved normokalemia (3.5-4.9 mEq/L) were then randomly allocated in a 1:1 ratio to receive either their original dose of ZS-9 or placebo. All patients who were in placebo group during the initial phase were randomly allocated to receive either 1.25 g (n=45) or 2.5 g (n=50) of ZS-9 during the maintenance phase. Treatment, ZS-9 1.25 g (n=95), 2.5 g (n=104), 5 g (n=65), 10 g (n=63), or placebo (n=216), was administered once daily before breakfast from days 3 to 14. The primary outcome of the initial phase was the exponential rate of change during the first 48 hours of treatment. The primary outcome for the maintenance phase was the between-group difference in the exponential rate of change in the mean s-K+ level during the 12-day treatment interval, analyzed separately for each treatment dose, compared to placebo. Exclusion criteria included patients with pseudohyperkalemia signs and symptoms (excessive fist clenching hemolyzed blood specimen, severe leukocytosis or thrombocytosis), treatment with resins within 7 days, on dialysis, insulin-dependent diabetes mellitus, and women who are pregnant or lactating. Of the patients in the initial phase, 60% had diabetes, 40% had heart failure, and 67% had receipt of therapy with a RAAS inhibitor.

For the initial primary outcome, the mean exponential rates of change from baseline per hour were -0.11% in the 1.25 g group, -0.16% in the 2.5 g group, -0.21% in the 5 g group, and -0.30% in the 10 g group compared to -0.09% in the placebo group (p<0.05 for all doses compared to placebo). The mean baseline s-K+, 5.3 mEq/L, decreased to 4.9 mEq/L in the 2.5 g group, 4.8 mEq/L in the 5 g group, and 4.6 mEq/L in the 10 g
group. The s-K+ absolute mean reductions were 0.46 mEq/L in the 2.5 g group, 0.54 mEq/L in the 5 g group, and 0.73 mEq/L in the 10 g group compared to a mean reduction of 0.25 mEq/L in the placebo group (p<0.001 for all comparisons). Notably, patients in the 1.25 g group achieved a mean s-K+ of 5.1 mEq/L, with a nonsignificant mean reduction of 0.3 mEq/L compared to placebo (p>0.05).

For the primary outcome in maintenance phase, the mean exponential rate of change in s-K+, expressed as a percent difference, was +0.09% per hour in the 5 g group compared to +0.47% per hour in the placebo group (p=0.008), and +0.14% per hour in the 10 g group compared to +1.04% per hour in the placebo group (p<0.001). The mean exponential rate of change in s-K+ per hour in the 1.25 g and 2.5 g groups not significantly different compared to placebo (no specific rates or p values were provided). For the secondary outcome, the 5 g daily dose and 10 g daily dose of ZS-9 were significantly superior to placebo in maintenance of normokalemia (p=0.008 for 5 g group; p<0.001 for 10 g group). Of note, hyperkalemia redeveloped within one week after all ZS-9 doses were discontinued.

In both phases of the study the incidence of adverse events reported appeared to be similar between patients treated with ZS-9 compared to those who received placebo (initial phase: 12.9% in the ZS-9 groups versus 10.8% with placebo; maintenance phase: 25.1% in the ZS-9 groups versus 24.5% with placebo). The most common adverse event for all dose groups for both phases was diarrhea (initial phase: 1.8% with all doses of ZS-9 compared to 2.5% with placebo; maintenance phase: 1.7% with all doses of ZS-9 versus 2.2% with placebo). There were two cases of hypokalemia (one with 10 g in the initial phase, one with 2.5 g in the maintenance phase), which resolved without K+ supplementation. Mean dose-dependent increases in serum bicarbonate were seen from baseline to the end of the maintenance phase (ZS-9 1.25 g: +0.75 mEq/L; ZS-9 2.5 g: +0.7 mEq/L; ZS-9 5 g: +0.9 mEq/L; ZS-9 10 g: +2.4 mEq/L); the average increase in serum bicarbonate with placebo was 0.775 mEq/L for comparison. No treatment-related serious adverse events occurred in any of the ZS-9 dose groups.

HARMONIZE

The HARMONIZE trial was a phase III trial that evaluated the safety and efficacy of ZS-9 in a two-part study.17 The study included a 48 hour open-label phase and a 28-day randomized, double-blind, placebo-controlled phase. The objective was to evaluate ZS-9’s efficacy at maintaining normokalemia (defined as s-K+ 3.5 - 5.0 mEq/L) following 48 hours of therapy for acute hyperkalemia (≥5.1 mEq/L). During the open-label phase, 258 patients with hyperkalemia received 10 g of ZS-9 three times daily for 48 hours. Patients who achieved normokalemia were then randomly allocated in a 4:4:4:7 ratio to either 5 g (n=45), 10 g (n=51), 15 g (n=56), or placebo (n=85) daily for 28 days. There were no specified primary endpoints in the open-label phase. However, secondary endpoints included absolute and percentage change from baseline s-K+ at various time intervals, proportion of patients who achieved normokalemia at 24 and 48 hours, time to normalization, and the exponential rate of change in s-K+.

The primary outcome for the maintenance phase was the mean s-K+ level in each ZS-9 group versus placebo during days 8 through 29 of the randomized phase. The 258 patients (mean age 64 years, 58% male, 83% Caucasian) were enrolled in the open-label phase, 66% had CKD, 36% had heart failure, 66% had diabetes, and 70% were on RAAS inhibitor therapy. Mean baseline s-K+ was 5.6 mEq/L, 39% had moderate hyperkalemia (s-K+ 5.5-5.9 mEq/L), 15% had severe hyperkalemia (s-K+ ≥6 mEq/L). During the open-label phase, ZS-9 10 g decreased s-K+ by a mean of 0.2 mEq/L at 1 hour and 0.4 mEq/L at 2 hours compared to baseline (p<0.001 for both time points). Absolute change in s-K+ was -0.7 mEq/L (12%) at 24 hours and -1.1 mEq/L (-19%) at 48 hours compared to baseline (p<0.001 for both groups). Median time to normokalemia was 2.2 hours, with 84% of patients achieving normokalemia by 24 hours, and 98% by 48 hours. At 48 hours, the mean exponential rate of change in s-K+ was -0.3% per hour (95% CI, -0.4% to -0.3% per hour).

In the maintenance phase, 237 patients were randomly allocated to maintenance treatment. Fourteen patients were excluded from enrolling in the maintenance phase; notably, 9 patients had hyperkalemia (s-K+ >6.2 mEq/L) and 2 had severe hypokalemia (s-K+ <3.0 mEq/L). For the primary outcome, s-K+ was significantly lower during days 8-29 with all three ZS-9 arms (5 g = 4.8 mEq/L (95% CI, 4.6-4.9 mEq/L), 10 g = 4.5 mEq/L (95% CI, 4.4-4.6 mEq/L), and 15 g = 4.4 mEq/L (95% CI, 4.3-4.5 mEq/L) compared to placebo [5.1 mEq/L (95% CI, 5.0-5.2 mEq/L); p < .001 for all doses]. Higher doses of ZS-9 resulted in greater decreases in s-K+ revealing a dose-dependent effect; however, no comparison statistics were completed between the ZS-9 groups. Among secondary outcomes, a greater proportion of patients achieved mean s-K+ <5.1 mEq/L during days 8-29 with all ZS-9 doses (5 g = 80%, 10 g = 90%, and 15 g = 94%) compared to placebo (46%; p<0.001 for all doses). The mean change in s-K+ from baseline at the beginning of the maintenance phase was +0.3 mEq/L in the 5 g group, +0.1 mEq/L in the 10 g group, and -0.1 mEq/L in the 15 g group compared to +0.6 mEq/L with placebo (p=0.007 in the 5 g group; p<0.001 in the 10 g and 15 g group).

Adverse events were similar between ZS-9 and placebo, although edema was more common in patients who received 15 g of ZS-9 compared to those who received a lower dose of ZS-9 [edema incidence: 5 g = 2% (1/45), 10 g = 6% (3/51), 15 g = 14% (8/56), placebo = 2% (2/85)]. Mild hypokalemia (3.0-3.4 mEq/L) developed in 10% of patients in the 10 g group and 11% of patients in the 15 g ZS-9 group, versus none in the 5 g or placebo group. No severe hypokalemia (<3.0 mEq/L) occurred in any of the groups. There were no serious treatment-emergent adverse events that were deemed related to study treatment with any of the ZS-9 doses. In summary, ZS-9 was shown to be safe and efficacious in treating hyperkalemia and maintaining normal s-K+ levels for up to 29 days.

HARMONIZE: Post-hoc Analysis

A pre-specified subgroup analysis of the HARMONIZE trial evaluated the management of hyperkalemia in patients with heart failure with daily ZS-9 over 28 days.18 The open-label phase of HARMONIZE treated 94 heart failure patients with hyperkalemia (≥5.1 mEq/L) with ZS-9 10 g three times daily for 48 hours. Patients who achieved normokalemia were randomly assigned to receive 5 g (n=18), 10 g (n=18), 15 g (n=25), or placebo (n=26) daily for 28 days. The primary outcome was mean s-K+ from days 8 to 29 after randomization. Additional outcomes included the proportion of patients that were normokalemic (s-K+ <5.1 mEq/L) during days 8 to 29 and adverse events. Across all groups, 76% had chronic kidney disease, 71% had diabetes mellitus, and 69% were treated with RAAS inhibitor.

http://pharmacy.ufl.edu/pharmanote/
### Table 1 | Summary of Sodium Zirconium Cyclosilicate Primary Outcome Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subject Populations</th>
<th>Interventions</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ash et al.15</td>
<td>Stage 3 CKD&lt;sup&gt;a&lt;/sup&gt; and hyperkalemia (s-K⁺ = 5.0-6.0 mEq/L)</td>
<td>• ZS-9 0.3 g TID (n=12)</td>
<td>Rate of s-K⁺ reduction in the first 48 hours</td>
<td>• ZS-9 3 g vs placebo; p=0.048</td>
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<tr>
<td></td>
<td></td>
<td>• ZS-9 3 g TID (n=24)</td>
<td></td>
<td>• ZS-9 10 g vs placebo; p&lt;0.0001</td>
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<td></td>
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<td>• ZS-9 10 g TID (n=24)</td>
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<tr>
<td></td>
<td></td>
<td>• Placebo (n=30)</td>
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<tr>
<td>Packham et al.16</td>
<td>Initial phase: Patients with hyperkalemia (5.0-6.5 mEq/L)</td>
<td>• ZS-9 1.25 g TID (n=154)</td>
<td>Exponential rate of change (per hour) in mean s-K⁺ compared to placebo over 48 hours</td>
<td>• ZS-9 2.5 g: -0.16%</td>
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<td></td>
<td></td>
<td>• ZS-9 2.5 g TID (n=141)</td>
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<td>• ZS-9 5 g: -0.21%</td>
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<td>• ZS-9 5 g TID (n=157)</td>
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<td>• ZS-9 10 g: -0.30%</td>
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<td>• ZS-9 10 g TID (n=143)</td>
<td></td>
<td>Placebo: -0.09%</td>
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<td></td>
<td></td>
<td>• Placebo (n=158)</td>
<td></td>
<td>(p&lt;0.001 for each comparison to placebo)</td>
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<td></td>
<td>Maintenance phase: Patients with a s-K⁺ (3.5-4.9 mEq/L) after the initial 48 hour treatment phase</td>
<td>• ZS-9 1.25 g TID (n=95)</td>
<td>Exponential rate of change (per hour) in mean s-K⁺ in each ZS-9 arm compared to placebo over 12 days</td>
<td>ZS-9 5 g: +0.09% vs +0.47% for placebo (p=0.008)</td>
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<td></td>
<td></td>
<td>• ZS-9 2.5 g TID (n=104)</td>
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<td>ZS-9 10 g:+0.14% vs. +1.04% for placebo (p&lt;0.001)</td>
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<td></td>
<td></td>
<td>• ZS-9 5 g TID (n=65)</td>
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<td>(results for ZS-9 1.25 and 2.5 g not reported)</td>
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<tr>
<td></td>
<td></td>
<td>• ZS-9 10 g TID (n=63)</td>
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<td>• Placebo (n=216)</td>
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<tr>
<td>HARMONIZE17</td>
<td>Randomized phase: Patients with a s-K⁺ of 3.5-5 mEq/L after an open-label treatment phase with ZS-9 10 g TID for hyperkalemia (≥5.1 mEq/L)</td>
<td>• ZS-9 5 g QD (n=45)</td>
<td>Mean s-K⁺ in each ZS-9 arm compared to placebo during days 8-29</td>
<td>• ZS-9 5 g: 4.8 mEq/L (95% Cl 4.6-4.9mEq/L)</td>
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<td>• ZS-9 10 g QD (n=50)</td>
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<td>• ZS-9 10 g: 4.5 mEq/L (95% Cl 4.4-4.6 mEq/L)</td>
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<td>• ZS-9 15 g QD (n=54)</td>
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<td>• ZS-9 15 g: 4.4 mEq/L (95% Cl 4.3-4.5 mEq/L)</td>
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<td>• Placebo (n=82)</td>
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<td>Placebo: 5.1 mEq/L (95% Cl 5.0-5.2 mEq/L)</td>
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<td>(p&lt;0.001 for each comparison to placebo)</td>
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<tr>
<td>Anker et al.18</td>
<td>Randomized phase: HF patients who achieved normal s-K⁺ (3.5-5 mEq/L) after treatment with ZS-9 10 g TID for 48 hours for hyperkalemia (≥5.1 mEq/L)</td>
<td>• ZS-9 5 g daily (n=18)</td>
<td>Mean s-K⁺ in each ZS-9 arm compared to placebo during days 8-29</td>
<td>• ZS-9 5 g: 4.7 mEq/L (95% Cl 4.5-4.9mEq/L)</td>
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<tr>
<td></td>
<td></td>
<td>• ZS-9 10 g daily (n=18)</td>
<td></td>
<td>• ZS-9 10 g: 4.5 mEq/L (95% Cl 4.3-4.6 mEq/L)</td>
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<tr>
<td></td>
<td></td>
<td>• ZS-9 15 g daily (n=25)</td>
<td></td>
<td>• ZS-9 15 g: 4.4 mEq/L (95% Cl 4.2-4.5 mEq/L)</td>
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<td>• Placebo (n=26)</td>
<td></td>
<td>Placebo: 5.1 mEq/L (95% Cl 5-5.2 mEq/L)</td>
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<td>(p&lt;0.001 for each comparison to placebo)</td>
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</table>

* a: eGFR between 30 and 59 mL/min/1.73 m²

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; TID = three times daily; QD = every day; s-K⁺ = serum potassium; ZS-9 = sodium zirconium cyclosilicate
In the open-label phase, mean baseline s-K+ was 5.6 mEq/L (95% CI 5.5-5.7 mEq/L) and the mean normalized concentration was 4.4 mEq/L (95% CI 4.3-4.5 mEq/L) after 48 hours. During the open-label phase, the median time to normalization of s-K+ was 2 hours. By the end of the 48 hour open-label phase 99% of patients achieved s-K+ <5.1 mEq/L. For the primary outcome, all ZS-9 treatment groups achieved significantly lower mean s-K+ concentrations in a dose-dependent manner [5g = 4.7 mEq/L (95% CI 4.5-4.9 mEq/L), 10 g = 4.5 mEq/L (95% CI 4.3-4.6 mEq/L), 15 g = 4.4 mEq/L (95% CI 4.2-4.5 mEq/L)] compared to placebo [5.2 mEq/L (95% CI 5.0-5.4 mEq/L); p<0.001 for doses]. Higher proportions of patients who received ZS-9 maintained normokalemia during the 28-day treatment phase (5 g = 83%, 10 g = 89%, 15 g = 92%) compared to the placebo group (40%; p<0.01 for all doses) across all active treatment arms.

### Adverse Effects and Precautions

The most common adverse reactions seen in clinical trials were edema and gastrointestinal adverse events. Mild to moderate edema was seen in some patients during clinical trials, more commonly in those who received 15 g once daily. Signs of edema should be monitored, especially in patients prone to fluid retention or having sodium limitations (e.g., heart failure, CKD) as each dose of Lokelma® contains about 400 mg of sodium. ZS-9 transiently increases gastric pH, which may alter the absorption of co-administered drugs with pH-dependent solubility. Other drugs that do not have pH-dependent solubility can be taken with ZS-9. Allopurinol, aspirin, captopril, cyclosporine, digoxin, ethyl estradiol, lisinopril, magnesium, metformin, phenytoin, prednisone, propranolol, quinapril, spironolactone, and ticagrelor did not show in vitro interactions when administered with ZS-9. Losartan, glipizide, and levothyroxine showed in vitro interactions, but did not demonstrate changes in exposure when administered with ZS-9 in healthy volunteers. However, in vivo increases in systemic exposure with weak acids, such as furosemide and atorvastatin, and decreases in systemic exposure with weak bases, such as dabigatran, were observed when administered with ZS-9. These observations are consistent with the hypothesis that ZS-9 can elevate gastric pH and affect systemic exposure of co-administered drugs with pH-dependent solubility. Therefore, oral medications that exhibit pH-dependent solubility should be administered at least two hours before or two hours after ZS-9 administration.

### Dosing and Administration

For initial treatment of hyperkalemia, the current recommended dose of ZS-9 is 10 g administered three times daily for up to 48 hours. For maintenance treatment, the recommended dose is 10 g once daily. Lokelma is supplied in a 5-gm or 10-gm white powder for oral suspension and is administered after dissolving in at least three tablespoons of water.

### Cost and Availability

The cost of a 30-day supply of Lokelma® is $650-730 at local pharmacies. Whereas the cost of a 30-day supply of Veltassa® is $820-920 at local pharmacies and the average retail price for a 30-day supply of SZS is approximately $50. However, pricing of Lokelma® can vary and is subject to change based on individual insurance coverage. The manufacturer of Lokelma®, Astrazeneca, currently does not have a patient assistance program for patients.

### Clinical Implications

Data from the current clinical trials support ZS-9’s use for treatment of hyperkalemia. Key populations such as patients with CKD and those receiving treatment with RAAS inhibitors were included in these studies where this drug would be useful. Also, current published trials have only reported on relative short-term safety and efficacy with ZS-9. Additional unpublished trials will add information about long-term use of ZS-9. A recently completed two-stage (acute and extended) phase III trial (NCT02163499) evaluated the safety and efficacy of ZS-9 titrated to s-K+ ≤5.0 mEq/L (max 15 g daily) for 12 months in 751 outpatients with hyperkalemia. An open-label extension trial (NCT02107092) is evaluating the safety and efficacy of ZS-9 10 g once daily for 11 months in 123 patients. Until the results of these trials are published, the long-term safety of ZS-9 use is unknown. At this time, limited knowledge and costs may be a barrier to its use.

### Conclusion

ZS-9 is a novel, non-absorbed K+ binding agent indicated

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**Table 2 | Common Adverse Effects of Sodium Zirconium Cyclosilicate**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>5 g QD ZS-9 (n=45)</th>
<th>5 g TID ZS-9 (n=267)</th>
<th>10 g QD ZS-9 (n=50)</th>
<th>10 g TID ZS-9 (n=488)</th>
<th>15 g QD ZS-9 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values predicted are actual incidences.

Data from the trial conducted by Anker et al. overlaps with the HARMONIZE trial because it evaluated a subset of patients from the HARMONIZE trial. ZS-9 = sodium zirconium cyclosilicate; TID = three times daily; QD = once daily.
for management of hyperkalemia in ambulatory patients. ZS-9 has been found to be effective and safe in general populations including patients with CKD and in those on treatment with RAAS inhibitors. ZS-9 has a predictable reduction in s-K+ levels and a favorable safety profile. However, additional studies are needed to assess reduction of complications associated with hyperkalemia, such as cardiac arrhythmias.

**References**

Incorporating Pharmacogenetics to Provide Drug Therapy Recommendations for Post-Operative Pain Management Following Total Knee Arthroplasty

The cytochrome P450 2D6 (CYP2D6) enzyme biotransforms tramadol, codeine, hydrocodone, and oxycodone into more potent opioid metabolites. CYP2D6 genotype may affect the concentration of tramadol, codeine, hydrocodone, and oxycodone metabolites and influence the effectiveness and safety of these opioid analgesics. Specifically, patients with genotypes leading to increased metabolism (called ultra-rapid metabolizers) are at increased risk for toxic opioid concentrations, respiratory depression, and death. Conversely, patients with genotypes leading to loss of or significant reductions in CYP2D6 activity (called poor or intermediate metabolizers) may receive inadequate pain relief because of lower levels of active metabolites.

The UF Health Precision Medicine Program (PMP), in collaboration with orthopedic surgeons, is conducting a pilot project study involving CYP2D6 genetic testing for patients scheduled to undergo total hip or knee arthroplasty to assist with post-operative pain management.

In this article, we present a case for a patient who received CYP2D6 genotyping prior to total knee arthroplasty as part of this program.

Patient Presentation

A 75-year-old female with a history of osteoporosis and fibromyalgia presented for total knee arthroplasty. The patient has tried anti-inflammatory medications, left knee arthroscopy, and physical therapy without significant relief.

Pharmacogenetic Test Results

CYP2D6*4/*4; poor metabolizer phenotype; little to no CYP2D6 enzyme activity.

Drug Therapy Recommendation provided by the PMP Team

This patient’s CYP2D6 PM status is associated with little to no CYP2D6 activity and increased risk for inadequate pain relief with tramadol, codeine, hydrocodone, and to a lesser extent, oxycodone. For post-operative pain we recommended a non-CYP2D6-mediated opioid, such as hydromorphone or morphine, because of her CYP2D6 genotype.

Discussion

Currently, tramadol is recommended as the preferred opioid analgesic in this setting, because of its dual opioid and non-opioid mechanism of action. However, a non-CYP2D6-mediated opioid analgesic was recommended for this patient because of her CYP2D6 genotype. This case provides an example of the additional clinical insight that genotype can provide to help guide drug therapy decisions.

References