Effect of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease: NEUTRALIZE Study Design and Rationale

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Introduction

• Patients with chronic kidney disease (CKD) may develop metabolic acidosis, which is associated with increased risk of cardiovascular events, CHD progression, and mortality.
• Nearly 3 million US patients with CKD stages 3-5 have metabolic acidosis, approximately 1/3 of CKD patients with serum potassium (K+) ≥5.0 mEq/L, may have metabolic acidosis.
• In previous randomized placebo-controlled studies, sodium zirconium cyclosilicate (SZC) was associated with dose-dependent increases in serum bicarbonate in patients with CKD and hyperkalemia (HK) and this effect was also observed for up to 1 year in a larger long-term open-label maintenance study.

The NEUTRALIZE study will evaluate the efficacy of SZC in (1) correcting HK and maintaining normal serum K+ levels and (2) providing clinically meaningful increases in serum bicarbonate in patients with HK and metabolic acidosis.

Study Rationale and SZC Mechanism of Action

• SZC is a selective K+-binding agent that entraps K+ throughout the gastrointestinal (GI) tract in exchange for sodium (Na+) or hydrogen ions (H+).
• Proposed mechanisms underlying the increase in serum bicarbonate with SZC include:
  1. A correction of HK increases ammonia production in the kidney, which results in increased renal acid secretion.
  2. Direct removal of ammonium ions (NH4+) in the GI tract:
     - Due to the similar ionic diameters of NH4+ and K+, K+ interacts with NH4+ in an aqueous solution, SZC's novel profile binds both K+ and NH4+ in exchange for Na+ or H+ (Figure 1A).
     - Urea is hydrolyzed in the GI tract to release bicarbonate and NH4+, which are usually absorbed through the GI epithelium and enter the liver, where urea is synthesized.
     - However, capture of NH4+ by SZC and subsequent elimination in feces reduces NH4+ absorption and metabolism to urea, allowing for GI excretion of bicarbonate that leads to an increase in serum bicarbonate levels.
     - Overall effect of SZC binding of NH4+ is a reduction in serum acid, net acid, and increase in serum bicarbonate (Figure 1B).

Methods

• NEUTRALIZE is a prospective, randomized, double-blind, placebo-controlled, parallel-group, Multicenter Phase 3b study in US adults with CKD-associated metabolic acidosis and HK (Table 1).

Table 1. Key Patient Eligibility Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Age ≥18 years</td>
<td>Pseudohyperkalemia</td>
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<tr>
<td>Stage 3-5 or CKD eGFR 15–59 mL/min (eGFR defined according to Chronic Kidney Disease Epidemiology Collaboration formula)</td>
<td>Dialysis requirement or anticipated within 3 months; history of kidney transplant; acceleted progression of kidney function; or life expectancy &lt;3 months</td>
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<tr>
<td>Two consecutives K+ levels ≥5.0 mEq/L</td>
<td>Cardiac arrhythmias, decompensated HF, coronary revascularization, symptomatic hypotension, air embolization, or DVT propagation</td>
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<tr>
<td>Two i-STAT bicarbonate levels 16–20 mmol/L, taken 1 h apart</td>
<td>High-SAC bicarbonate levels ≥16–20 mmol/L, taken 1 h apart</td>
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<tr>
<td>Ability to undergo repeated blood draws or effective venous cannulation</td>
<td>Active or suspected diabetic ketoacidosis, history of diabetic gastroparesis, bariatric surgery, bowel obstruction, or swallowing disorders</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Active malignancy requiring treatment</td>
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Figure 1. A) Relative Diameters of SZC Pore and Major Unhydrated Cations; B) Effect of SZC on Serum Bicarbonate

- Hypothesized MOA: SZC captures NH4+ generated in the GI tract from urea hydrolyzation, leading to fecal elimination
- Increased NH4+ elimination results in reduction in serum urea, increase in serum bicarbonate, and net acid loss

Conclusions

• In the open-label correction phase, all patients will receive SZC 10 g three times daily (TID) for up to 48 h
- Patients who achieve normokalemia ≥3-STAT K+ ≥5.0 to ≤5.5 mEq/L after 24 h will enter the randomized placebo-controlled phase, while patients with ≥3-STAT K+ >5.1 mEq/L will continue SZC TID for another 24 h
- Patients with normokalemia after the open-label correction phase will be randomized 1:1 to SZC 10 g once daily (QD) or placebo QD for 4 weeks; patients with K+ ≥5.5 mEq/L at any time during the open-label correction phase will be discontinued from the study
- During the first 2 weeks of the randomized phase, the dose will be titrated as needed for abnormal ≥3-STAT K+ levels by increasing or decreasing the dose by 5 increments at 1-week intervals to between 5 to 15 QD
- Patient demographics, comprehensive medical and surgical history, and laboratory assessments will be collected at screening and at specified study visits
- Central laboratory serum K+ and ≥3-STAT bicarbonate will be used for study assessments
- The primary, secondary, and safety study objectives are summarized in Table 2
- The study will be conducted at 35 sites across the US, and patient recruitment is underway

Table 2. Study Objectives

Primary objective
To evaluate the efficacy of SZC vs. placebo in normalizing serum K+ in patients with HK and CKD-associated metabolic acidosis

Secondary objectives
To evaluate the efficacy of SZC vs. placebo in increasing serum bicarbonate in patients with HK and CKD-associated metabolic acidosis

To evaluate the efficacy of SZC vs. placebo in normalizing serum K+ and increasing serum bicarbonates in patients with HK and CKD-associated metabolic acidosis

To describe the need for rescue treatment with sodium bicarbonate for metabolic acidosis in SZC and placebo arms

Safety objective
To evaluate the safety and tolerability of SZC vs. placebo in patients with HK and CKD-associated metabolic acidosis

References

Disclosures
All authors report no conflicts of interest.

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