Efficacy and Safety of ZS-9 in Patients with Hyperkalemia: Results from the HyperkAlemia RandoMized Intervention multi-dose ZS-9 maintenance (HARMONIZE) Clinical Trial

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Background: Hyperkalemia is a common electrolyte abnormality, associated with potentially lethal cardiac arrhythmias, poor prognosis, and is difficult to manage due to lack of effective therapies. Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed zirconium-based cation exchanger that selectively binds potassium (K+) in the intestine. The long-term efficacy of ZS-9 in maintaining normokalemia has not been evaluated in clinical trials.

Methods: HARMONIZE was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate long-term efficacy and safety of ZS-9 in patients with hyperkalemia (serum K+ = 5.1 mEq/L). All patients received 10 g of ZS-9 TID for 48 hours in the acute open label phase. Patients achieving normal K+ (3.5-5.0 mEq/L) were randomized to one of 3 ZS-9 doses (5, 10, 15 g daily) or placebo for 28 days in the maintenance phase. Primary endpoint was mean K+ in each ZS-9 dose vs placebo during days 8-29 of the maintenance. Secondary endpoints included the proportion of patients achieving and maintaining normal K+ in the acute and maintenance phases respectively, and safety.

Results: Overall, 258 patients enrolled in the acute phase across 44 sites with 237 patients randomized into the maintenance phase (36% with heart failure, 64% with CKD, 64% with diabetes, 68% on RAAS inhibitors). Mean baseline K+ was 5.6 mEq/L, and was reduced to 4.5 mEq/L at 48 hrs in the acute phase.

Significant reduction in K+ was observed within 1 hour of ZS-9 administration, with 84% of patients achieving normokalemia at 24 hours and 98% at 48 hours. K+ was significantly lower with all 3 ZS-9 doses vs placebo in the maintenance phase (4.8, 4.5, 4.4 mEq/L for 5, 10 and 15g of ZS-9, respectively; 5.1 mEq/L for placebo; P =0.0001 for all comparisons). Greater proportions of patients in all 3 ZS-9 groups maintained normokalemia vs placebo (71%, 76%, 85% for 5, 10 and 15 g of ZS-9, respectively;
48% with placebo). The rate of adverse events was comparable between ZS-9 and placebo.

**Conclusion**: ZS-9 was highly effective in acutely reducing K+ levels in patients with hyperkalemia, and maintaining normokalemia for up to four weeks, with excellent tolerability.

**Disclosure**:  
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