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# Gastrointestinal (GI) Tolerability of Sodium Zirconium Cyclosilicate (ZS-9) in Hyperkalemia: Pooled Analysis of Two Phase 3 Studies

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Hyperkalemia (HK; serum potassium [K+] ≥5.1mEq/L) increases the risk of mortality and limits use of lifesaving renin-angiotensin-aldosterone inhibitors (RAASi) in patients (pts) with chronic kidney disease, diabetes, and heart failure. Approved drugs for treating HK are organic polymers like sodium polystyrene sulfonate (SPS) and patiromer. However, there are safety concerns with SPS such as GI toxicity when used in combination with sorbitol, as well as poor patient satisfaction. Sodium zirconium cyclosilicate (ZS-9) is an oral, sorbitol-free, inorganic cation trap that selectively binds K+ throughout the GI tract. In 2 large, double-blind, randomized, placebo-controlled, Phase 3 trials, ZS-9 rapidly normalized and maintained serum K+ in HK pts (ZS-003 [NEJM]; HARMONIZE [JAMA]). GI tolerability of ZS-9 was compared with that of placebo (PBO) in pt pooled from these 2 studies. Pts received ZS-9 or placebo three times daily for initial 48h, followed by oncedaily extended treatment for up to 28 days. Analysis included pts treated with once-daily 10g ZS-9 (n=114) or PBO (n=301) in extension phases. A total of 4 pts (3.5%) treated with ZS-9 experienced GI AEs vs 20 pts (6.6%) treated with PBO. The incidences of constipation, diarrhea, nausea, and vomiting in 10g ZS-9 pts were, respectively 2.6%, 0%, 0.9%, and 0% vs, respectively, 2.3%, 2.0%, 0.7%, and 0.7% in PBO pts. ZS-9 was well tolerated, with a GI AE profile similar to that of PBO, suggesting it is suitable for chronic use. ZS-9 is a potential new medical therapy for HK and may avoid known, and potentially severe GI tolerability issues seen with organic polymers. With this tolerability profile, ZS-9 may represent another therapeutic option for patients.

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