ACHIEVEMENT OF NORMAL SERUM POTASSIUM WITH SODIUM ZIRCONIUM CYCLOSILICATE (ZS-9) IN A SUBGROUP OF PATIENTS WITH STAGE 4/5 CHRONIC KIDNEY DISEASE AND BASELINE POTASSIUM ≥ 5.5 MMOL/L FROM THE PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED HARMONIZE STUDY

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Introduction and Aims: Hyperkalaemia (serum K+ >5.0 mmol/L) is associated with increased risk of mortality (Goyal, 2012; Torlen, 2012) and limits renin-angiotensin-aldosterone system (RAAS) inhibitor therapies in patients with heart failure, diabetes, and chronic kidney disease (CKD). Hyperkalaemia becomes more frequent as renal function deteriorates. Current treatments with non-specific resins such as sodium polystyrene sulfonate have questionable efficacy and are associated with serious gastrointestinal (GI) adverse events (AEs). Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation exchanger that traps excess K+ in the GI tract and has demonstrated efficacy and safety in three prospective randomized placebo-controlled trials (Ash, KI 2015; Packham, NEJM 2014; Kosiborod, JAMA 2014). In the Phase 3 HARMONIZE study, treatment of hyperkalaemic patients with ZS-9 resulted in acute reduction of serum K+ within 48 hours, followed by maintenance of normokalaemia for 28 days (Kosiborod, JAMA 2014). Here we present a subgroup analysis of patients with Stage 4/5 CKD and baseline K+ ≥ 5.5 mmol/L from the HARMONIZE study.

Methods: HARMONIZE was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate long-term efficacy and safety of ZS-9 in patients with hyperkalaemia (serum K+ ≥5.1 mmol/L). All patients received 10g of ZS-9 thrice daily (TID) for 48 hours in the acute open-label phase (N=258). Patients achieving normokalaemia (serum K+ 3.5-5.0 mmol/L) were then re-randomized to one of 3 ZS-9 doses (5, 10, or 15 g) once daily (QID) or placebo for 28 days in the maintenance phase. In this study, we evaluated the mean change in serum K+ during the acute phase and proportion of patients achieving normokalaemia at 24 and 48 hours.

Results: Of 258 patients, 64 had Stage 4/5 CKD and baseline K+ ≥5.5 mmol/L. Mean baseline K+ was 5.9 mmol/L. Significant reductions in serum K+ (-0.2, -0.5, -0.6, -0.8, and -1.3 mmol/L) were observed at 1, 2, 4, 24, and 48 hours, respectively (P<0.001; Figure). The proportion of patients achieving normokalaemia was 69% and 93% by 24 and 48 hours, respectively. ZS-9 was generally well tolerated with a low rate of AEs in the overall study population.

Conclusions: Our study demonstrated that ZS-9 rapidly restored normokalaemia in patients with Stage 4/5 CKD and high baseline serum K+. Thus, ZS-9 may fulfill an important unmet clinical need in this population of high-risk patients and may potentially minimize the need for emergency intervention with renal replacement therapy.

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