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**Safety and Efficacy of Sodium Zirconium Cyclosilicate for Long-Term Treatment
of Hyperkalemia in Patients with Chronic Kidney Disease:
Results from an Open-label, Phase 3 Study**

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Sodium zirconium cyclosilicate (SZC) is a potassium (K)-binder for treating hyperkalemia (HK). Patients with chronic kidney disease (CKD) are at high risk for HK. We compared the efficacy and safety of SZC in outpatients with HK ($K \geq 5.1$ mEq/L) and baseline (BL) eGFR < 30 vs ≥ 30 mL/min/1.73 m² with data from an open-label, single-arm Phase 3 trial. Patients received 10g SZC TID for 24–72h (correction phase [CP]) until K 3.5–5.0mEq/L (normokalemia; measured by point-of-care device, iSTAT; serum K also measured) then SZC was titrated to $K \leq 5.0$ mEq/L for 12mo (maintenance phase [MP]) without restricting diet or RAASi use. A post hoc analysis of patients with baseline (BL) eGFR < 30 or ≥ 30 mL/min/1.73 m² was performed. Patients with eGFR < 30 (CP, n=289; MP, n=286) vs ≥ 30 (CP, n=453; MP, n=451) were male (57% vs 61%), had mean BL eGFR of 21 vs 64 mL/min/1.73 m², more diabetes (70% vs 58%) and used RAASi (73% vs 53%), β -blockers (55% vs 37%), diuretics (55% vs 37%) and calcium channel blockers (CCB; 49% vs 25%). Mean BL iSTAT K was 5.5 mmol/L for both groups. Of patients with eGFR < 30 , 82%, 84% and 100% achieved iSTAT normokalemia at 24, 48 and 72h, respectively vs 82%, 76% and 95% for eGFR ≥ 30 . Completion rate for MP was 55% (n=158) for patients with eGFR < 30 and 67% (n=303) for eGFR ≥ 30 . Mean SZC dose from Day 15 on was higher for eGFR < 30 vs ≥ 30 groups (9.4g vs 7.5g at 12mo). Serum K was decreased from CP baseline at all time points through 12 mo in both eGFR groups. Normokalemia by serum K was maintained through 12mo in both groups. Bicarbonate increased from BL to Day 8 for both groups (1.1 vs 1.0mmol/L; $P < 0.0001$ for both) and the change was sustained in MP. AEs (83% vs 54%), serious AEs (31% vs 16%) and deaths (2% vs 0.7%) were greater in the eGFR < 30 group. Common AEs, all more frequent in patients with eGFR < 30 , were hypertension, peripheral edema, urinary tract infection, nausea and constipation. Overall, oral outpatient SZC treatment normalized K in 72h, sustained normokalemia over 12mo, and had an acceptable safety profile in patients with eGFR < 30 . Higher AE rates for the eGFR < 30 group may reflect more comorbidities, level of renal dysfunction or CCB use. SZC was effective and well-tolerated in outpatients with HK, including CKD patients with eGFR < 30 .

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