Background: Hyperkalemia (HK) increases mortality and limits use of life-saving RAAS inhibitors, yet current therapies are limited. ZS-9 is a nonsystemic cation exchanger designed to entrap excess potassium (K⁺). In a Phase 2 trial in chronic kidney disease (CKD) patients with HK, ZS-9 10g led to a rapid and sustained decrease in serum K⁺ (s-K⁺), with a favorable safety profile (Ash et al. ASN 2013). Here we present mean rate of s-K⁺ decline.

Methods: Patients (glomerular filtration rate, 30-60 mL/min/1.73 m²; s-K⁺, 5-6 mEq/L) were randomized 2:1 to ZS-9 (0.3g [n=12], 3g [n=24], or 10g [n=24]) or placebo (n=30) given orally TID for ≥ 2 days with regular meals (8 am, 12 pm, 6 pm) as in-patients. Serum K⁺ was measured 0.5 hr, 1 hr, and 2 hr after 1st dose and 4 hr after all 6 doses. Rate of decline for ZS-9 10g averaged over two on-drug daytime treatment periods (Hours 0-14 and 24-38) and two off-drug nighttime rebound periods were compared with placebo by unpaired t-test.

Results: At baseline, mean s-K⁺ was 5.1 mEq/L for placebo and ZS-9 10g. Mean daytime rate of decline was -0.01 mEq/L/hr and -0.04 mEq/L/hr in the two groups, respectively (p=0.001). This is illustrated by the widening difference between mean s-K⁺ values between the two groups (Fig.).

![Graph showing serum potassium decline](image)

Conclusions: In CKD patients with HK, ZS-9 led to a predictable rate of decline in s-K⁺ during daytime treatment periods. ZS-9 may allow for rapid and predictable treatment of HK. ZS-9 is being studied in a two-stage Phase 3 trial that just completed (N=753).