Acid-Base Balance in Phase 2 and Phase 3 Trials of ZS-9 for Hyperkalaemia in Patients With Chronic Kidney Disease

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BACKGROUND

- Metabolic acidosis is common in patients with chronic kidney disease (CKD) and hyperkalemia. It becomes more common with advancing stages of CKD,[1-3] and contributes to progressive decline of the estimated glomerular filtration rate (eGFR).[4] Furthermore, ameliorating metabolic acidosis is kidney-protective.[4]
- ZS-9 is a selective cation exchanger designed to entrap excess potassium (K^+) in exchange for sodium and hydrogen (Fig. 1). ZS-9 absorbs ammonium as well as K^+. This unique, microporous sirconium silicate compound builds on a long history of Zr use in dialysis and other biomedical applications. ZS-9 is insoluble, highly stable, and not systemically absorbed.
- In a Phase 2, multicenter, randomized, double-blind, controlled study, ZS-9 5g and 10g significantly reduced K^+ vs. placebo over 48 h with excellent tolerability in patients with CKD.[5]
- A two-stage Phase 3 trial that has just completed (N=753) provides a larger dataset with which to evaluate ZS-9's effects in patients with all-cause hyperkalemia, and the impact on acid-base balance.[6]

Objectives

- To evaluate relevant acid-base related laboratory values from patients treated with ZS-9 in the Phase 2 and Phase 3 clinical studies.

Methods

- For Study 002, patients (eGFR, 30-60 mL/min/1.73 m^2; serum K^+, 5-6 mmol/L) were randomized 2:1 to ZS-9 (n=60; 0.3g [n=12], 3g [n=24], or 10g [n=24]) or placebo (n=30) given orally three times daily for 2 days (and up to 2 more days if K^+ ≥5.0 mmol/L) with regular meals (8am, 12pm, 6pm) as inpatients (**Fig. 1**).
- For Study 003, multiple acute (TID) and extended (QD) treatment regimens of ZS-9 were evaluated (**Fig. 2**). Patients who achieved normokalemia (K+ 3.5-5.0 mEq/L) in the acute phase were re-randomized to either the same dose or ZS-9 or placebo (QD dosing) for the extended phase.
- Serum and urine samples were collected and evaluated with standard laboratory procedures. Differences between groups were compared by unpaired t-test.

Figure 1. ZS-9 is a first-in-class selective potassium trap

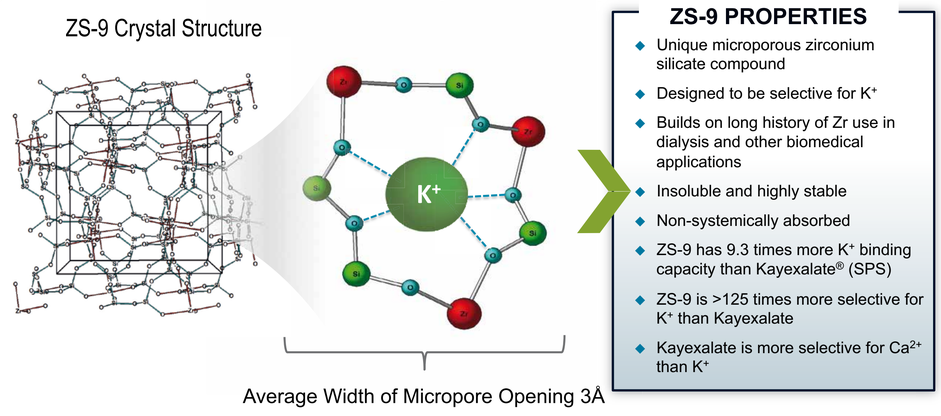


Figure 2. ZS-002 study schematic

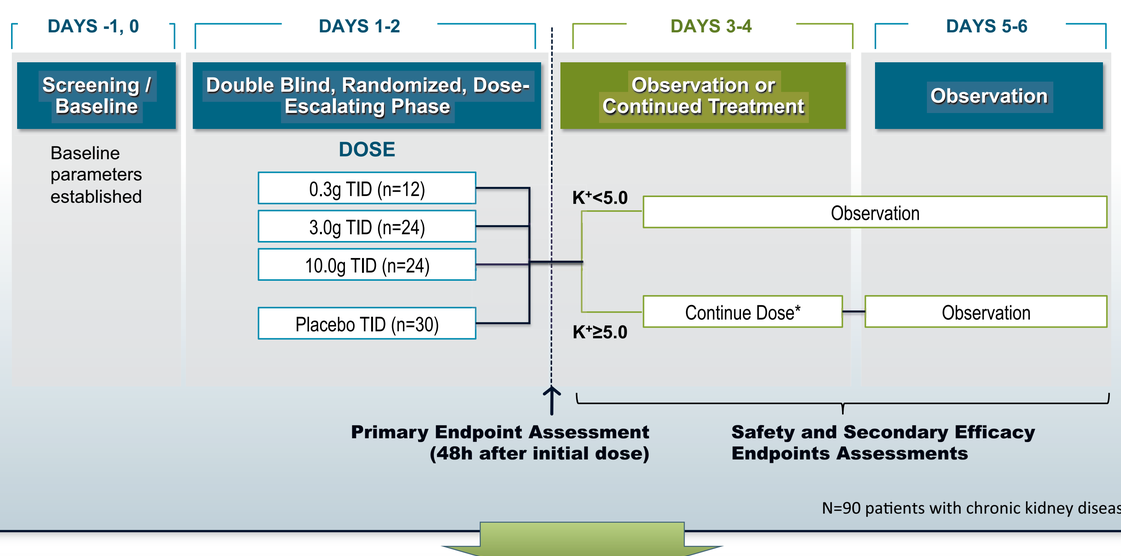


Figure 5. ZS-003 study schematic

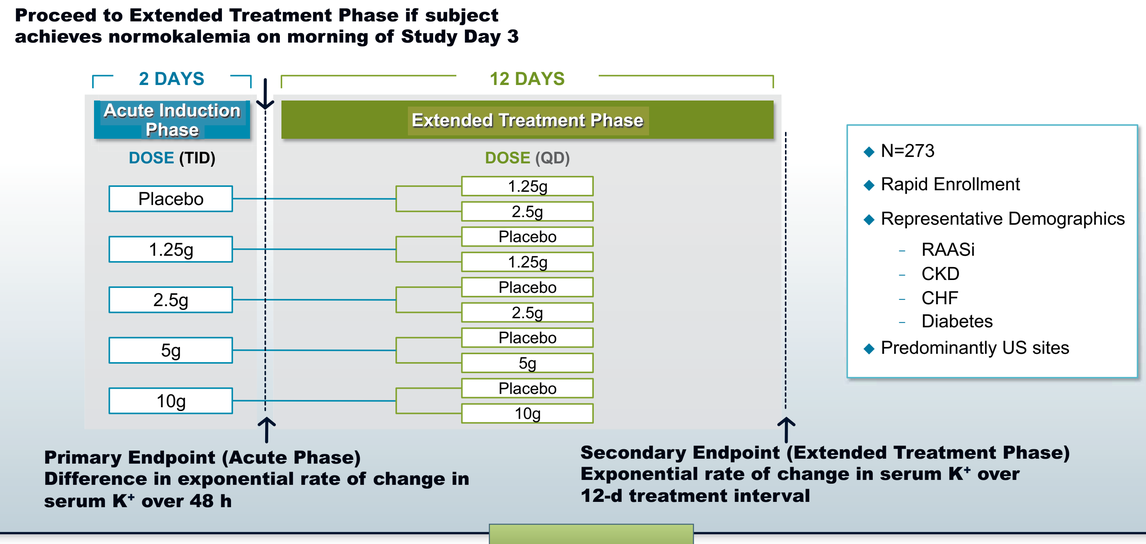


Figure 3. ZS-002: Serum bicarbonate elevation and BUN decline at 48 h

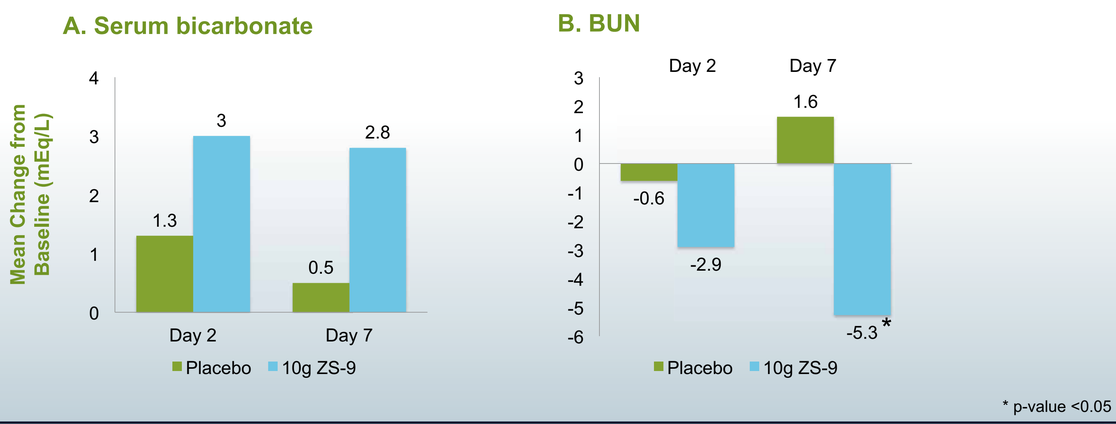


Figure 6. ZS-003: Changes in serum bicarbonate and BUN persisted through Day 21.

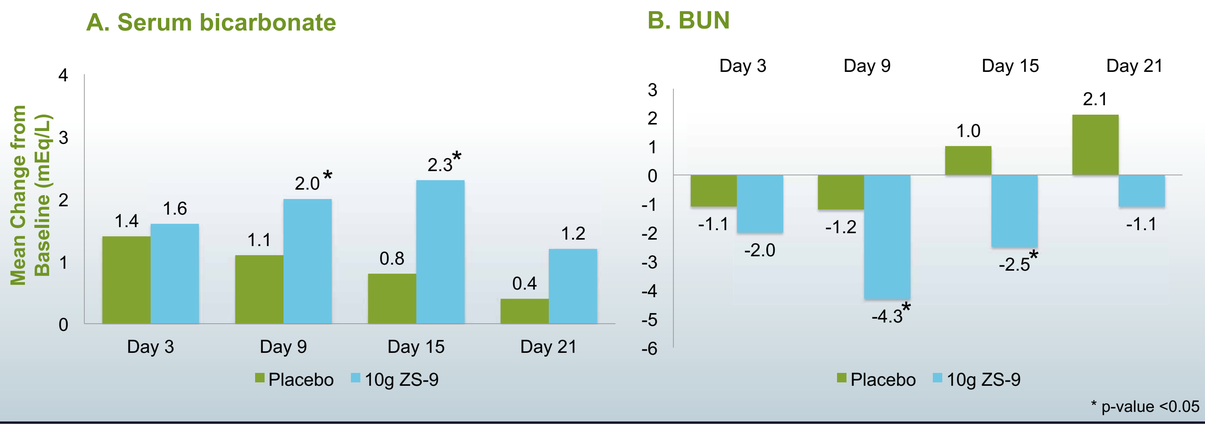


Figure 4. ZS-002: ZS-9 10g Increases Urinary pH Relative to Placebo

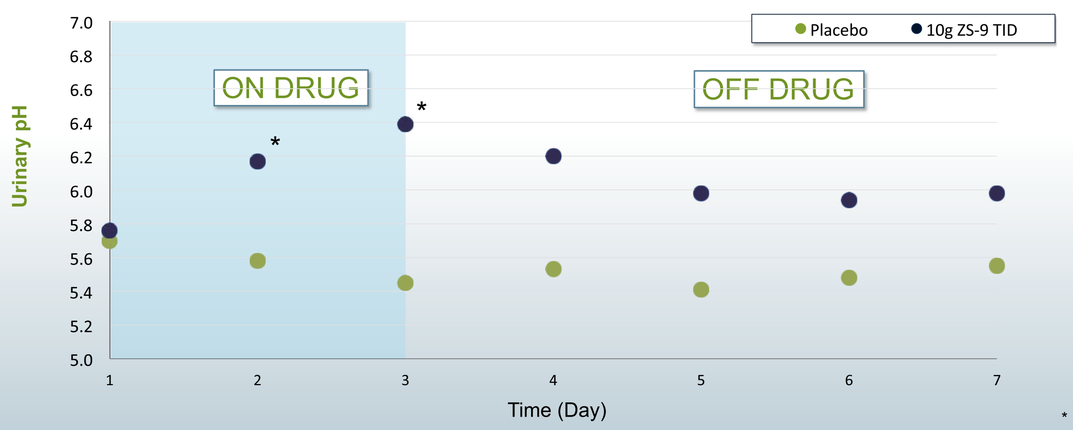
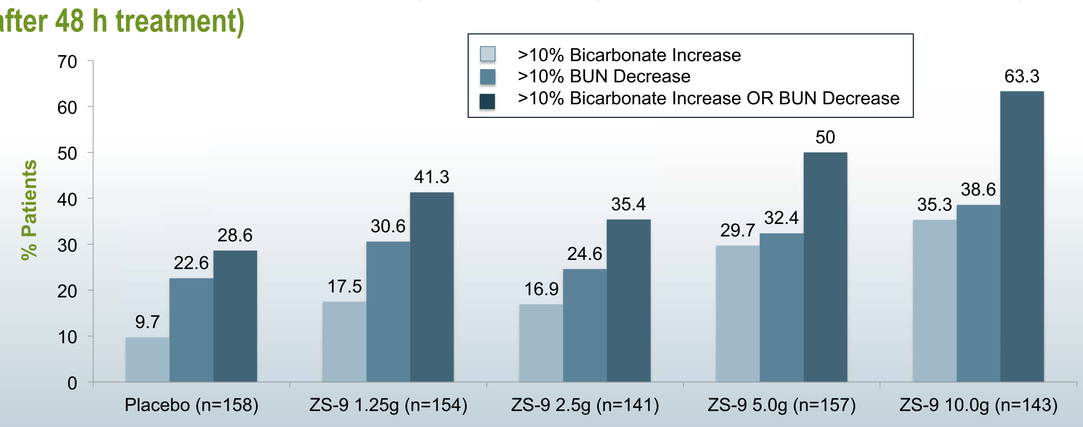


Figure 7. Patients in ZS-003 had significant changes in bicarbonate and BUN at Day 3 (after 48 h treatment)



RESULTS

ZS-002

- At baseline, mean urinary pH (5.8 and 5.7) and mean bicarbonate (28.1 mg/dL and 27.4 mg/dL) were similar between ZS-9 and placebo groups, respectively.
- Bicarbonate increased more with ZS-9 10g than with placebo from Days 2-7. After 48 h (14 h after the last dose of ZS-9 10g) bicarbonate increased by +3.4 mg/dL with ZS-9 10g vs. +0.4 mg/dL with placebo (**Fig. 3A**).
- ZS-9 10g significantly reduced mean blood urea nitrogen (BUN) from baseline vs. placebo ($p<0.05$ for all evaluations between Days 2-7; **Fig. 3B**).
- ZS-9 10g significantly increased mean urinary pH versus placebo at Day 2 (6.2 vs. 5.6, $p<0.01$) and Day 3 (6.4 vs. 5.7, $p<0.01$). Urinary pH remained higher in the ZS-9 10g group vs. placebo through Day 7 (**Fig.** 4).

ZS-003

- Patients treated with ZS-9 10g demonstrated a significant increase in bicarbonate compared with placebo at Day 6 ($p<0.05$). This difference persisted through Day 21 (**Fig. 6A**).
- Similarly, reduction of mean BUN by ZS-9 10g from baseline vs. placebo persisted through Day 21 (**Fig. 6B**).
- Changes in bicarbonate and BUN appear to be dose-dependent. After 48 h, 35.3% of patients in the ZS-9 10g group experienced >10% increase in serum bicarbonate; 38.6% of the group experienced >10% decrease in BUN (**Fig. 7**). 50% of ZS-9 5g patients and 63.3% of ZS-9 10g patients had either >10% bicarbonate increase or >10% BUN decrease after 48 h of treatment ($p<0.0001$).

CONCLUSIONS

- ZS-9 10g significantly increases urinary pH and serum bicarbonate and reduces BUN vs. placebo in patients after 48 h (ZS-002); these changes persist to Day 21 (ZS-003), and suggest that ZS-9 may improve acid-base balance in patients with hyperkalaemia.
- The improvement in metabolic acidosis may be explained by removal of ammonium by ZS-9, as illustrated by the significant reduction in BUN (ZS-003).
- The ZS-9 5g and 10g dose groups exhibited the greatest effects on serum bicarbonate increase and BUN reduction; these effects were also observed in patients treated with lower doses (1.25g and 2.5g), compared with placebo (ZS-003).
- As studies have suggested that amelioration of metabolic acidosis is kidney-protective,[4] longer-term analyses are needed to determine whether persistent improvements in acid-base balance as a result of ZS-9 treatment might help delay progression of CKD in non-dialysis dependent CKD patients.

References

1. Eustace JA, Astor B, Muntner PM, et al. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int.* 2004;65:1031. 2. Warnock DG. Uremic acidosis. *Kidney Int*. 1988;34:278. 3. Welbourne T, Weber M, Bank N. The effect of glutamine administration on urinary ammonium excretion in normal subjects and patients with renal disease. *J Clin Invest*. 1972;51:1852. 4. Goraya N, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int.* 2014 Apr 2. doi: 10.1038/ki.2014.83. [Epub ahead of print] 5. Ash SR, Singh B, Lavin PT, et al. *J Am Soc Nephrol*. 2013;24:2B (abstract). Presented as a late-breaker oral presentation at the American Society of Nephrology Kidney Week, Nov 5 – 10, 2013, Atlanta, GA. 6. Singh B, Rasmussen HS, Lavin PT, et al. Presented as a late-breaker oral presentation at the American Society of Hypertension Annual Meeting, May 16 – 20, 2014, New York, NY.

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