Poster # 1-FP

Effect of Sodium Zirconium Cyclosilicate (ZS-9) on Urinary Potassium and Sodium: An Analysis of the Phase 3 Randomised, Double-Blind, Placebo-Controlled HARMONIZE Study

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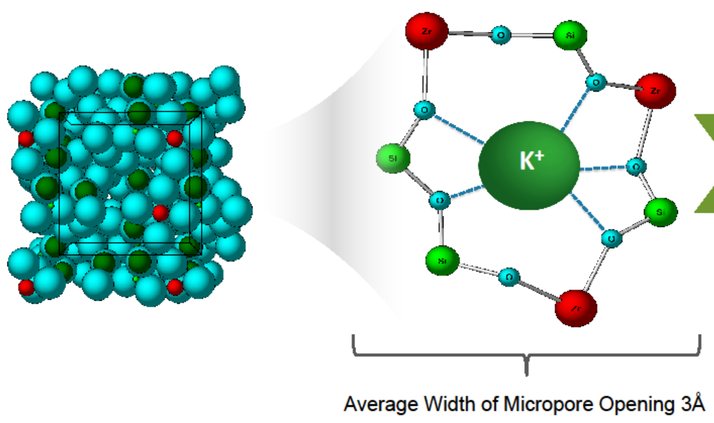
BACKGROUND

- Hyperkalaemia (HK; serum K^+ >5.0 mmol/L) is associated with an increased risk of mortality in patients with chronic kidney disease (CKD)/cardiovascular disease[1,2] and limits the use of renin-angiotensin-aldosterone system inhibitors (RAASi) that prolong life
- CKD patients have an impaired ability to eliminate excess sodium (Na^+) which may result in related complications such as edema, heart failure, and high blood pressure
- Current treatments with nonspecific resins (e.g. sodium polystyrene sulfonate [SPS]) have questionable efficacy, result in Na^+ loading, and have poor gastrointestinal (GI) tolerability
- Sodium zirconium cyclosilicate (ZS-9) is a selective K^+ ion trap (SKIT); preclinical studies have suggested that ZS-9 may allow for K^+ binding as early as the duodenum[3,4] (**Figure 1**)
- The exchange ion in ZS-9 is a balance of H^+ and Na^+, making it of interest to understand if there would be Na^+ loading from ZS-9 therapy
- In a previous Phase 2 trial, ZS-9 demonstrated reductions in urine K^+ and no increases in urinary Na^+ at any dose[5]
- In the Phase 3 HARMONIZE trial, treatment of HK patients with ZS-9 resulted in acute reduction of serum K^+ within 48 hours, followed by maintenance of normokalaemia for 28 days[6]

Figure 1. ZS-9 Crystal Structure



ZS-9 PROPERTIES

- Unique microporous zirconium silicate compound
- Designed to be selective for K^+
- Builds on long history of Zr use in dialysis and other biomedical applications
- Insoluble and highly stable
- Non-systemically absorbed
- ZS-9 has 9.3 times more K^+ binding capacity than Kayexalate® (sodium polystyrene sulfonate)
- ZS-9 is >125 times more selective for K^+ than Kayexalate
- Kayexalate is more selective for Ca^{2+} than K^+

OBJECTIVES

- Here we evaluated urine K^+ and Na^+ excretion to assess the impact of ZS-9 on systemic K^+ and Na^+ among patients from the HARMONIZE study

METHODS

- Patients (N=258) with serum K^+ ≥5.1 mmol/L were enrolled and given 10g ZS-9 orally three times daily (TID) for 48 hours (open-label phase) – (**Figure 2**)
- Following this phase, patients with serum K^+ = 3.5-5.0 mmol/L (n=237) were randomised 4:4:4:7 to ZS-9 (5g, 10g, or 15g) or placebo once daily (QD) for 28 days (randomised phase) – (**Figure 2**)
- In the present analysis, mean 24-hour urinary K^+ and Na^+ were estimated from Na^+, K^+ and creatinine concentrations in patient spot urine specimens according to the method established by Tanaka et al., 2002[6]

Figure 2. HARMONIZE Study Design

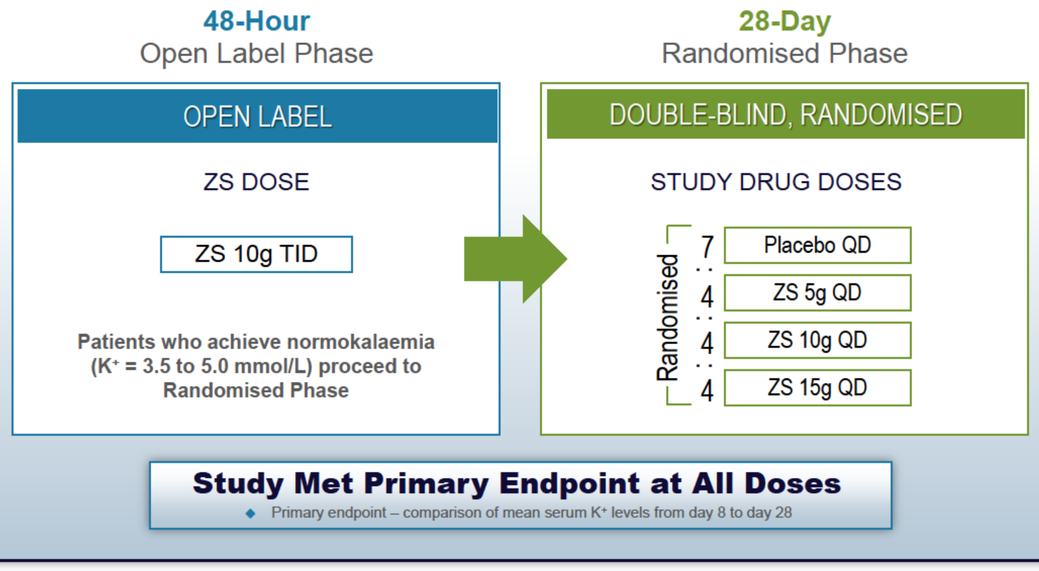


Table 1. Baseline and Demographic Characteristics

	Open Label	Randomised Phase			
	10g (n=258)	Placebo (n=85)	5g (n=45)	10g (n=51)	15g (n=56)
Median Age, years	65	66	64	65	65
Male, %	58	52	60	53	71
White, %	83	86	80	86	82
Black ,%	14	12	18	10	16
Serum K^+ <5.5 mmol/L, %	46	51	51	37	43
Serum K^+ 5.5-<6.0 mmol/L, %	39	35	38	45	46
Serum K^+ ≥6.0 mmol/L, %	15	14	11	18	11
RAAS inhibitors, %	70	72	73	71	59
Heart Failure, %	36	31	40	35	45
Diabetes Mellitus, %	66	64	58	75	70
Baseline eGFR <60, %	69	61	69	75	73
Brain Natriuretic Peptide, pg/mL	126	101	175	101	152

RESULTS

- Ninety-three of 258 patients had all data required for the calculation to estimate urinary K^+ and Na^+ (Tanaka et al, 2002[6])
- At Day 29 of the randomised phase, urinary K^+ excretion decreased by -6.6 (-12.5%), -9.7 (-20.2%), and -10.5 (-20.5%) mmol/day from baseline in the 5, 10, and 15 g ZS-9 groups, respectively, compared with -5.5 mmol/day (-10.7%) in the placebo group (**Figure 3**)
- At Day 29 of the randomised phase, urinary Na^+ did not increase in any ZS-9 dose group [-7.3 (-4.3%), -9.9 (-5.8%), and -0.9 (-0.5%) mmol/day change from baseline with 5, 10, and 15 g doses, respectively], or with placebo [-2.7 mmol/day (-1.6%)] (**Figure 4**)
- ZS-9 was well tolerated in all patients and had an AE incidence of 53.3%, 29.4%, and 44.6% in the 5g, 10g, and 15g ZS-9 doses, respectively, compared to 31.8% for the placebo (**Table 2**)

Figure 3. All ZS-9 Doses Maintained Greater Change From Baseline in Urinary K^+ Excretion Than Placebo

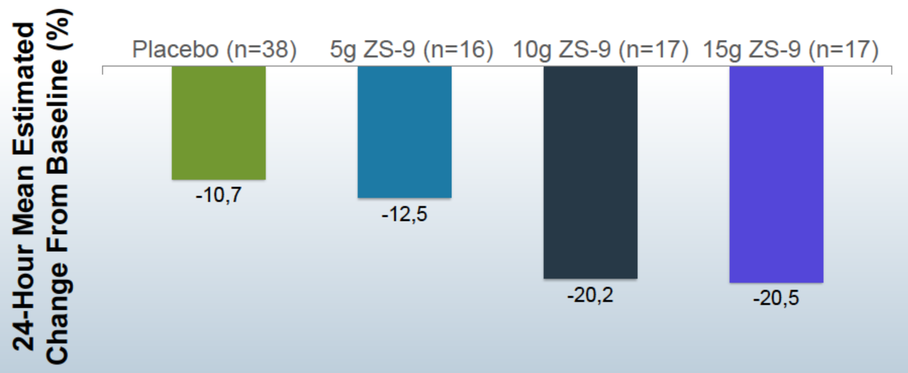


Figure 4. Urinary Sodium Excretion Did Not Increase With ZS-9 Treatment

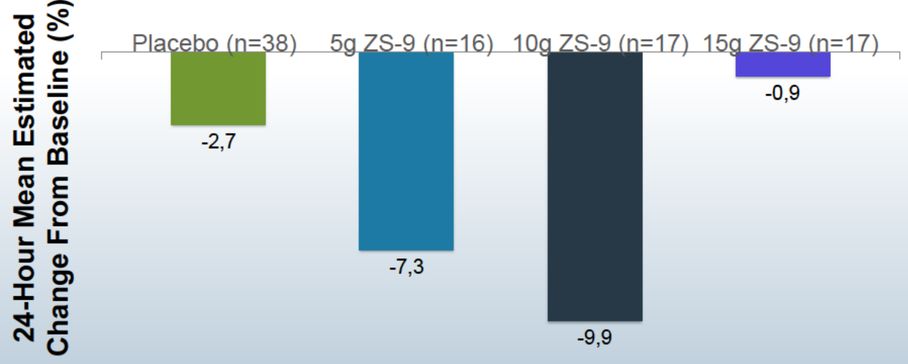


Table 2. Summary of Adverse Events Occurring in ≥5% of Patients in any Group

	Open Label	Randomised Phase			
	10g ZS-9 (n=258)	Placebo (n=85)	5g ZS-9 (n=45)	10g ZS-9 (n=51)	15g ZS-9 (n=56)
Any Event	20 (7.8)	27(31.8)	24(53.3)	15(29.4)	25(44.6)
Blood and Lymphatic System Disorders					
Anaemia	0 (0.0)	0(0.0)	0(0.0)	0(0.0)	3(5.4)
Gastrointestinal Disorders					
Constipation	2(0.8)	6(7.1)	0(0.0)	1(2.0)	1(1.8)
General Disorders and Administration Site Conditions					
Oedema[1]	0(0.0)	2(2.4)	1(2.2)	3(5.9)	8(14.3)
Metabolism and Nutrition Disorders					
Hypokalaemia (all)	0(0.0)	0(0.0)	0(0.0)	6(11.8)	7(12.5)
Hypokalaemia (reported as adverse event)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.8)
Infections and Infestations					
Nasopharyngitis	0(0.0)	1(1.2)	0(0.0)	0(0.0)	3(5.4)
Upper respiratory tract infection	1(0.4)	1(1.2)	3(6.7)	1(2.0)	1(1.8)

[1]Including generalized and peripheral edema

DISCUSSION/CONCLUSIONS

- Consistent with reductions in serum K^+, ZS-9 decreased urinary K^+ excretion in patients treated for hyperkalaemia
- ZS-9 treatment did not cause increases in urinary Na^+ excretion from baseline at any dose
- These results are consistent with findings from a previously published phase 2 trial evaluating ZS-9 that showed no apparent differences in urinary sodium excretion between placebo and any ZS-9 dose[5]
- ZS-9 treatment had a tolerability profile similar to that of placebo
- These results suggest that ZS-9 does not cause increased Na^+ load among patients with hyperkalaemia

References

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