Efficacy and Safety of ZS in Patients with Hyperkalemia: Results from the HyperkAlemia RandoMized InterventiON multi-dose ZS maintEnance (HARMONIZE) clinical trial

MIKHAIL KOSIBOROD, MD
Saint Luke’s Mid America Heart Institute,
University of Missouri - Kansas City

On behalf of Henrik S. Rasmussen, Philip T. Lavin, Wajeh Qunibi, Bruce Spinowitz, David Packham, Simon Roger, Alex Yang, Edgar Lerma, Bhupinder Singh, and the HARMONIZE Study Group
Disclosures

This study was funded by:
ZS Pharma, Inc., Coppell, Texas

Mikhail Kosiborod, MD:
Consultant for ZS Pharma, Inc.
Investigator in HARMONIZE Trial
Background

Hyperkalemia

Common, and increasing in prevalence

May lead to life-threatening cardiac arrhythmias

Associated with poor outcomes in CVD and CKD\(^1,2\)

Limits use of cardioprotective and renoprotective RAAS inhibitors\(^3,4\)

Source:  \(^1\)Jain et al, 2012;  \(^2\)McMahon et al, 2012;  \(^3\)Makani et al, 2013;  \(^4\)Takaichi et al, 2007
Current Treatment Options for Hyperkalemia are Limited

- Most acute therapies do not remove excess potassium, and impractical in outpatient setting
  - IV calcium, sodium bicarbonate, insulin and dextrose, nebulized beta-adrenergic agonists
- Dietary potassium restriction met by non-adherence, limits healthy food choices
- Sodium polystyrene sulfonate (SPS)
  - Uncertain efficacy - no rigorous clinical trials
  - Poorly tolerated
  - Reports of serious intestinal toxicity

There is a clinical need for a hyperkalemia treatment that is effective, safe and well-tolerated
Sodium Zirconium Cyclosilicate (ZS)

- First in class inorganic crystalline zirconium silicate compound
- Exchanges $K^+$ for $H^+$ and $Na^+$ in the intestine
- Highly selective for $K^+$ trapping (>125 times more than SPS)
- Insoluble, stable, does not expand in water
- Not systemically absorbed

ZS CRYSTAL STRUCTURE
HARMONIZE is a Phase 3, randomized, double blind, placebo controlled, international multicenter trial.

Ambulatory patients with prior history or laboratory evidence of hyperkalemia were recruited from 44 nephrology, cardiology, general research sites:

- **US**: 80%
- **South Africa**: 12%
- **Australia**: 8%
Key Inclusion and Exclusion Criteria

**INCLUSION CRITERIA**

- Potassium values ≥ 5.1 mEq/L, with no upper limit at entry
- Ability to have repeated blood draws
- Provision of written informed consent

**EXCLUSION CRITERIA**

- Dialysis requirement
- Cardiac arrhythmias requiring immediate treatment
- Active treatment with SPS
- Life expectancy < 3 months
- Pregnancy
### Study Design

#### 48-Hour
Open Label Phase

**OPEN-LABEL**

**ZS DOSE**

- ZS 10g TID

Patients who achieve normokalemia (K+ = 3.5 to 5.0 mEq/L) proceed to Randomized Phase

#### 28 Day
Randomized Phase

**DOUBLE-BLIND, RANDOMIZED**

**STUDY DRUG DOSES**

<table>
<thead>
<tr>
<th>Randomized</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Placebo QD</td>
</tr>
<tr>
<td>4</td>
<td>ZS 5g QD</td>
</tr>
<tr>
<td>4</td>
<td>ZS 10g QD</td>
</tr>
<tr>
<td>4</td>
<td>ZS 15g QD</td>
</tr>
</tbody>
</table>
Primary endpoint was the comparison of mean serum potassium levels between placebo and each ZS treatment group during days 8-29 of the randomized phase.

Prespecified secondary analyses included:
- In the open label phase: change from baseline in serum potassium levels at all time intervals, proportion of patients achieving normokalemia by 24 and 48 hours, time to potassium normalization.
- In the randomized phase: proportion of patients with mean potassium <5.1 mEq/L during days 8-29.

Safety and tolerability.
425 Patients were assessed for eligibility

258 enrolled and received 10g ZS

251 included in open label phase

237 into 28-day randomized phase

85 were randomized to placebo

45 were randomized to 5g ZS

51 were randomized to 10g ZS

56 were randomized to 15g ZS

167 failed screening

7 discontinued early

14 did not enter randomized phase

147 were randomized to 5g ZS

292 were randomized to 10g ZS

16 were randomized to 15g ZS

16 were randomized to placebo

278 failed screening

26 did not enter randomized phase

251 included in open label phase
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Open Label</th>
<th>Randomized Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10g (n=258)</td>
<td>Placebo (n=85)</td>
</tr>
<tr>
<td><strong>Median Age</strong> years</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td><strong>Male %</strong></td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td><strong>White %</strong></td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td><strong>Black %</strong></td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td><strong>BL Serum K+ &lt;5.5 mEq/L %</strong></td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td><strong>BL Serum K+ 5.5-&lt;6.0 mEq/L %</strong></td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td><strong>BL Serum K+ ≥6.0 mEq/L %</strong></td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td><strong>RAAS inhibitors %</strong></td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td><strong>Heart Failure %</strong></td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus %</strong></td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td><strong>Baseline eGFR &lt;60 %</strong></td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td><strong>Brain Natriuretic Peptide pg/mL</strong></td>
<td>126</td>
<td>101</td>
</tr>
</tbody>
</table>
Results: Open-Label Phase

*P value <0.001

**KEY OBSERVATIONS**

- Mean starting K+ of 5.55 mEq/L
- 0.2, 0.4, & 0.5 mEq/L potassium decline at 1, 2, & 4 hours respectively (p<0.001)
- Median time to K+ normalization 2.2 hours
- 84% of patients normalized by 24 hrs
- 98% of patients normalized by 48 hrs

| ZS DOSES: ▲ ▲ ▲ ▲ ▲ ▲ ▲ |
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**Mean Potassium (mEq/L)**

- ZS DOSES:
  - ▲
  - ▲
  - ▲

**Time (hr)**

- 0 4 8 12 16 20 24 28 32 36 40 44 48
**Results: Open-Label Phase**

**Key Observations**
- Mean starting K+ of 5.55 mEq/L
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*P value <0.001

Mean Potassium (mEq/L)

Time (hr)

ZS DOSES: ▲ ▲ ▲ ▲ ▲
**Results: Open-Label Phase**

*P value <0.001

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Mean Potassium (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>4</td>
<td>5.2</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>4.8</td>
</tr>
<tr>
<td>24</td>
<td>4.6</td>
</tr>
<tr>
<td>48</td>
<td>4.4</td>
</tr>
</tbody>
</table>

**ZS DOSES:** ▲ ▲ ▲ ▲ ▲ ▲ ▲

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Results: Open-Label Phase

*P value <0.001

![Graph showing mean potassium levels over time](image)
Open Label Phase: Consistent Efficacy in All Subgroups

*P value <0.0001

Error bars represent ±95 confidence intervals
Achieves Primary Endpoint, Mean K+ Maintenance on Days 8-29 for All Doses

Mean Potassium (mEq/L)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Baseline K+ (mEq/L)</th>
<th>Mean K+ (mEq/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5.55</td>
<td>5.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ZS 5 g</td>
<td>5.53</td>
<td>4.75*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ZS 10 g</td>
<td>5.58</td>
<td>4.51*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ZS 15 g</td>
<td>5.55</td>
<td>4.37*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Error bars represent ±95 confidence intervals
Randomized Phase: Mean Potassium Levels Over Time

* Two-sample t-test p-value <0.05

Mean Potassium (mEq/L)

ZS DOSES:
- Placebo (n=82)
- 5 g ZS (n=45)
- 10 g ZS (n=50)
- 15 g ZS (n=54)

Primary Endpoint
Randomized Phase: Proportion of Patients with Mean K <5.1 mEq/L during Days 8-29

**P value <0.001**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Percent of Study Group</th>
<th><em>(P value &lt;0.001)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46% (38/82)</td>
<td></td>
</tr>
<tr>
<td>5 g ZS</td>
<td>80%* (36/45)</td>
<td></td>
</tr>
<tr>
<td>10 g ZS</td>
<td>90%* (45/50)</td>
<td></td>
</tr>
<tr>
<td>15 g ZS</td>
<td>94%* (51/54)</td>
<td></td>
</tr>
</tbody>
</table>
Randomized Phase: Efficacy Consistent in All Subgroups

*P value < 0.001

Error bars represent ±95 confidence intervals

Mean Potassium (mEq/L)

- Placebo
- 10g ZS
Safety and Tolerability

- Tolerability profile comparable to placebo
- No treatment-related serious adverse events
- Numerically lower rates of GI AEs with ZS vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>ZS 5g</th>
<th>ZS 10g</th>
<th>ZS 15g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported AE</td>
<td></td>
<td>2 (2%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Needed Treatment Adjustment</td>
<td>2/2</td>
<td>0/1</td>
<td>0/3</td>
<td>5/8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td>0 (0%)</td>
<td>5 (10%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

- Edema numerically higher in ZS 15 g dose
- 7 out of 14 edema patients did not require treatment
- 13 of 14 edema patients had peripheral edema only and successfully completed the study
- Hypokalemia higher in ZS 10g and 15g dose groups
- All cases mild (3.0 to 3.4 mEq/L) and resolved with dose adjustments
Other Safety Data of Interest

- No changes in serum sodium, magnesium, and calcium
- No increase in urinary sodium excretion
- No differences in heart rate or blood pressure
- No difference in body weight
- No cardiac arrhythmias or EKG changes
Study Limitations

Due to focus on outpatient management of hyperkalemia, certain patient subgroups not included:

- Hospitalized patients
- Patients with life-threatening arrhythmias
- Patients on dialysis (however 36% of patients had advanced CKD [Stage IV/V])

Focus on potassium levels; not powered for mortality and other clinical events
Conclusions

Open Label: ZS rapidly lowered serum potassium to normal range in patients with hyperkalemia
◆ Significant reduction in K⁺ by 1 hr; median time to normalization 2.2 hrs
◆ 84% patients normokalemic by 24 hrs, 98% by 48 hrs
◆ Greater absolute declines in K⁺ among patients with higher K⁺ at baseline

Randomized Phase: Compared with placebo, all 3 doses of ZS resulted in
◆ Significantly lower serum potassium
◆ Higher proportion of patients with normal potassium for up to 4 weeks

Results consistent across all patient subgroups including HF, CKD, DM, RAASi

T tolerability profile comparable to placebo
Further studies are planned to evaluate the efficacy and safety of ZS over longer time periods and in additional patient populations.
Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia: The HARMONIZE Randomized Clinical Trial

M. Kosiborod and coauthors

Published online November 17, 2014
Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com
Appendix
Potassium Measurements

- All potassium levels were measured
  - in whole blood with a point-of-care device (i-STAT; Abbott Laboratories)
  - in serum via central laboratory
- Eligibility for enrollment, randomization and treatment decision were based on i-STAT values
- All statistical analysis based on central lab values
- Potassium measured at 1, 2, 4, 24, and 48 hours during open label phase
- Day 1, 2, 8, 12, 15, 19, 22, 26, 29 during randomized phase
Statistical Analysis

- Samples size of 232 patients in the randomized phase at 90% power, 0.3 mEq/L mean difference in potassium levels during days 8-29 for each ZS dose versus placebo
- Longitudinal generalized estimated equation (GEE) model was used to simultaneously compare each ZS dose (highest to lowest) versus placebo with mean day 8-29 potassium value
Patients were assessed for eligibility.

425 Patients were assessed for eligibility

258 enrolled and received 10g ZS-9 (safety population)

251 included in 48-hour open-label phase intent-to-treat population

237 randomized into 28-day randomized phase

85 randomized to placebo

10 Discontinued early
2 withdrew consent
1 due to participant compliance
2 due to unconfirmed eligibility
3 due to hyperkalemia
2 for other reasons

45 randomized to 5g ZS-9

5 Discontinued early
3 due to adverse event
1 met ECG withdrawal criteriaa
1 for other reason

3 not included in the intent-to-treat populationb

45 included in the randomized phase intent-to-treat population

51 randomized to 10g ZS-9

7 Discontinued early
2 due to unconfirmed eligibility
3 due to hypokalemia
2 for other reasons

1 not included in the intent-to-treat populationb

50 included in the randomized phase intent-to-treat population

56 randomized to 15g ZS-9

7 Discontinued early
1 due to adverse event
1 due to Investigator's decision
9 due to hyperkalemia
2 due to hypokalemia

2 not included in the intent-to-treat populationb

54 included in the randomized phase intent-to-treat population

167 failed screening
160 due to potassium values <5.1 mEq/L
1 due to prior randomization in ZS-9 study
2 withdrew consent
1 due to inability to have repeated blood draws or effective venous catheterization
1 hospitalized prior to randomization
1 due to participant compliance
1 due to Investigator's decision

7 Discontinued early
5 withdrew consent
2 due to hyperkalemia

14 did not enter randomized phase
1 met ECG withdrawal criteriaa
1 withdrew consent
1 due to Investigator's decision
9 due to hyperkalemia
2 due to hypokalemia

251 included in 48-hour open-label phase

10 Discontinued early
2 withdrew consent
1 due to participant compliance
2 due to unconfirmed eligibility
3 due to hyperkalemia
2 for other reasons

3 not included in the intent-to-treat populationb

82 included in the randomized phase intent-to-treat population

258 enrolled and received 10g ZS-9

237 randomized into 28-day randomized phase

10 Discontinued early
2 withdrew consent
1 due to participant compliance
2 due to unconfirmed eligibility
3 due to hyperkalemia
2 for other reasons

45 included in the randomized phase intent-to-treat population

50 included in the randomized phase intent-to-treat population

54 included in the randomized phase intent-to-treat population

ECG withdrawal criteria included significant increase in PR interval (>250 msec in the absence of pre-existing atrioventricular block), or widening of the QRS complex (>140msec in the absence of pre-existing bundle branch block) or peaked T-wave or an increase in QTc interval >25msec to more than 500msec or >25msec in somebody with a baseline QTc of >500msec

b due to having no follow-up potassium measurements after the maintenance phase baseline
Maintenance of Potassium Across All Subgroups on ZS – 5g

*P value <0.001

**Graph showing serum potassium levels across different subgroups: Placebo vs. 5g ZS-9.**

- **All CKD HF DM On RAASi:**
  - Placebo
  - 5g ZS-9

- **Serum Potassium (mEq/L):**
  - Range: 4.0 to 5.4

- **Significance:**
  - *P value <0.001

- **Subgroups:**
  - All
  - CKD
  - HF
  - DM
  - On RAASi

**Notes:**
- Green circle represents Placebo.
- Blue circle represents 5g ZS-9.
Maintenance of Potassium Across All Subgroups on ZS – 15g

*P value <0.001
ZS004 Mean K+ for all K+ ranges

Study 004 Mean s-K⁺ (Acute, All K⁺ ranges) – 10g
Serum Potassium (mEq/L)

Dose

<5.5 (n=119)  5.5-6.0 (n=100)  ≥6.0 (n=39)

Time (hr)

DOSES:

SOURCE:  14.2.1.2.7-9

Biostats Review and QC pending
### All ZS-004 Hypokalemia Cases Transient, With No Arrhythmias, and No Need for K+ Supplements

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Hypokalemic Instances</th>
<th># of Exposure Days*</th>
<th>Hypokalemic Instances/Exposure Days</th>
<th>Patients with Hypokalemia</th>
<th># of Patients</th>
<th>Patients with Hypokalemia /Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZS-002</td>
<td>2</td>
<td>120</td>
<td>0.2%</td>
<td>2</td>
<td>60</td>
<td>3.3%</td>
</tr>
<tr>
<td>ZS-003</td>
<td>2</td>
<td>8,330</td>
<td>&lt;0.1%</td>
<td>2</td>
<td>595</td>
<td>0.3%</td>
</tr>
<tr>
<td>ZS-004</td>
<td>11</td>
<td>4,560</td>
<td>0.2%</td>
<td>11</td>
<td>152</td>
<td>7.2%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>15</strong></td>
<td><strong>13,010</strong></td>
<td><strong>0.1%</strong></td>
<td><strong>15</strong></td>
<td><strong>807</strong></td>
<td><strong>1.8%</strong></td>
</tr>
</tbody>
</table>

0 of 807 ZS Patients With Serum K+ <3.0 mEq/L
Black Patients are at a Greater Risk for Developing Hypokalemia than Non Black

Proportion of Total Patients that are Black
Percentage of Patients

- Black Patients in Study Population: 14%
- Black Patients in Hypokalemic Population: 55%
- Black Patients in Hypokalemic Population That Discontinued Study: 75%

n = 257
11
4

*Hypokalemia was determined by two subsequent [separated by 10 minutes] Cenetro values of S-K < 3.5mmol/l
**Discontinuation from study was determined by I-STAT S-K < 3.0mmol/l