Author’s response to reviews

Title: Efficacy and safety of sodium zirconium cyclosilicate in patients with baseline serum potassium level ≥5.5 mmol/L: pooled analysis from two phase 3 trials

Authors:

Alpesh Amin (anamin@uci.edu)
Jose Menoyo (jmenoyo@zspharma.com)
Bhupinder Singh (100gfr@gmail.com)
Christopher Kim (seoungk@uw.edu)

Version: 2 Date: 19 Sep 2019

Author’s response to reviews:

September 19, 2019

Jing Zhang
Assistant Editor
BMC Nephrology

Dear Dr. Zhang,

Thank you for the opportunity to resubmit our revised manuscript (BNEP-D-19-00437R1) titled “Efficacy and safety of sodium zirconium cyclosilicate in patients with baseline serum potassium level ≥5.5 mmol/L: pooled analysis from two phase 3 trials” to be considered for publication in BMC Nephrology.

My coauthors and I appreciate the input from the editors and peer reviewers and have revised the manuscript to address their comments. Revisions to the manuscript are shown as tracked changes. The revised text in the manuscript is also quoted in the responses to the reviewers’ comments that the changes address.

The point-by-point responses to the reviewer comments are included on the following pages. Please note that the page numbers listed in the responses refer to the locations in the revised manuscript with tracked changes.

Thank you for your consideration of this revised manuscript.

Sincerely,
The authors describe the effect of ZS in hyperkalemic subjects pooled from 2 separate studies.

1. On page 3: the reviewer agree with the idea the drug works in the small bowel. However this is an inference based on the rapidity of action. The authors may wish to soften the statement about where it works and this is inferred, unless there is direct information available.

Authors’ response: Thank you for your comment. As suggested, we have softened the language used in this sentence in the introduction (page 3, paragraph 3) to read as follows:

“SZC is thought to start binding potassium in the upper gastrointestinal tract, which most likely accounts for its rapid onset of action [11, 12] (AstraZeneca, unpublished observations).”


2. Is there any differences in men versus women and how they respond?

Authors’ response: Given the mechanisms of action of SZC (i.e., highly selective for charge and size and non-absorbable), we do not expect a difference in treatment response between men and women. Hence, a formal analysis of any difference between men and women has not been performed. A statement related to this has been added to the discussion section (page 12, paragraph 1):

“Given the mechanism of action of SZC, we do not expect a difference in the treatment response between men and women. Further analysis would need to be carried out to verify this more formally.”

3. While 66% of patients were on RAASi, did the type of RAASi or combination influence the results? Any difference for example if spironolactone was used?

Authors’ response: Thank you for raising these great questions about concomitant use of RAASi or mineralocorticoid receptor antagonists. In the current analysis, only 11 patients received spironolactone at baseline; no formal subanalysis was conducted.
In a previous pooled analysis of the ZS-003 and HARMONIZE studies (Kosiborod M, et al Circulation. 2015;132(suppl):A13555), patients with baseline mineralocorticoid-receptor antagonist (MRA) use (n = 19) demonstrated a median time to normokalemia of 3.8 hours; however, the number of patients was small (n = 19) and no formal comparison was done with the overall group.

4. Any comments about the low magnesium and calcium (has this been reported before?).

Authors’ response: SZC does not bind calcium or magnesium, and across the clinical development program no clinically significant cases of SZC-related hypocalcemia or hypomagnesemia have been reported. Although 1 case of hypocalcemia and 3 cases of hypomagnesemia were reported in this analysis, the mild reductions in magnesium and calcium observed here may have been caused by general dilution as SZC was administered in 240 mL of water. Water intake was reduced to 45 mL for subsequent studies.

5. Was there an influence of the type or dose of diuretic used. Those on higher doses of loop diuretics might have had a better response?

Authors’ response: A formal analysis of any potential additional benefit of diuretics (type or dose) in reducing potassium levels was not performed. However, 78 patients (nearly half) of the patients in the analysis were on and remained on stable diuretic regimen throughout the studies. Nearly 80% of those receiving diuretics were receiving loop diuretics (furosemide, bumetanide, furosemide sodium, or torasemide).

Reviewer #2 (Giuseppe Regolisti)

In this paper the Authors present the results of a post-hoc pooled analysis of the data from 170 patients with a serum potassium concentration (sK) > 5.5 mmol/L, collected in the 48-hour correction phase of ZS003 and HARMONIZE studies.

They found that sK decreased significantly in all patients 4 hours after the first 10 g dose of SZC, and the decrease was greater in patients with higher baseline sK. Moreover, approximately 80% of the patients achieved sK < 5.5 mmol/L, and 38% achieved sK < 5.0 mmol/L at this time point. By 48 hours, 98% of the patients achieved sK < 5.5 mmol/L, and 85% achieved sK < 5.0 mmol/L. Median time to sK < 5.5 mmol/L was 2.0 (95% CI, 1.1-2.0) hours, and median time to sK < 5.0 mmol/L was 21.6 (95% CI, 4.1-22.4) hours. Median time to these sK values were higher in patients with higher baseline sK. Adverse events, mainly gastrointestinal in nature, were reported in 15 patients (8.8%); no serious adverse events were reported.

The Authors conclude that the administration of a single dose of SZC 10 g obtains a rapid and significant sK decrease in patients with clinically significant hyperkalemia, and that SZC 10 TID obtains sK normalization by 48 hours in 85% of these patients with an acceptable safety profile.
This paper is clear, concise and well written. It extends the results of a previous pooled analysis by Kosiborod et al (ref. 7 in the manuscript) of the same data, which had been carried out in 45 patients with sK > 6.0 mmol/L from the ZS003 and HARMONIZE studies.

I have only one comment:

1. I suggest that the Authors specify if any sK data were missing at the specified time points. This is relevant, because the Authors used a paired t-test to analyze changes in sK vs baseline at each time points in subgroups of patients with different ranges of baseline sK. If the number of missing data were relevant, perhaps the use of a linear mixed model for repeated measure with baseline sK as a covariate may be preferable.

Authors’ response: Thank you for this very insightful comment. As we went back and reanalyzed the data, we found that there were only a few missing observations in the source data. More specifically, from the 170 patients in the analysis, 2 observations were missing at 2, 4, 24, and 25 hours, and 3 observations were missing at 48 hours. There were no missing observations at 1 hour. Given the limited number of data points that were missing, we did not feel that this warranted the use of an alternative statistical model.

Reviewer #3 (Zubaid Rafique)

This is a nice review of the efficacy of SZC in the first 48 hrs. My comments are as follows:

1. This is a post hoc pooled analysis without a control arm for comparison. Therefore, the conclusion needs to be a little more restrained. Ln 248 (conclusion) states "rapid reduction in serum K" is not based on data; there was no rate-of-change calculation comparing to control arm, so it would be prudent to delete "rapid" from the Conclusion section and everywhere else in the manuscript.

Authors’ response: Thank you for your comment. In the primary ZS-003 analysis, one of the two data sets pooled for the current analysis, SZC was associated with a significant greater rate of exponential change in mean serum K+ at 48 hours versus placebo, indicating a “rapid” reduction in serum K+ in this earlier analysis. However, as the exponential rate of change was not calculated in the current analysis, “rapid” has been removed throughout the manuscript as appropriate and the text in the conclusions (page12, paragraph 2) has been revised to read as follows:

“Patients with baseline serum K+ level ≥5.5 mmol/L who received SZC 10 g experienced decreases in serum K+ levels from baseline within 1 hour of treatment, and most patients (85%) who received SZC 10 g TID achieved normokalemia within 48 hours. The reduction of serum K+ levels among patients with serum K+ level ≥5.5 mmol/L with SZC was achieved with an acceptable safety profile, consistent with that observed in prior studies.”
2. Results section reports decrease in K within 1 and 2 hrs. It would be helpful to have a figure showing K change over the first 4 hrs from baseline for mild, moderate and severe hyperkalemia cohorts (5.5-6, 6-6.5 and >6.5 mEq/L).

Authors’ response: Figure 1, which shows mean serum K+ values over time, has been modified by splitting the X-axis scale to more clearly show changes in K+ from baseline over the first 4 hours. This shows that further decreases in K+ from baseline were observed at 4 hours in the overall population and in patients in the serum K+ 5.5–<6.0 and 6.0–6.5 mmol/L subgroups. In addition, text has been added to the results section to highlight these observations (page 7, paragraph 3):

“By 4 hours post dose, changes from baseline in serum K+ levels of –0.55, –0.70, and –0.82 mmol/L were observed in the 5.5–<6.0, 6.0–6.5, and >6.5 mmol/L subgroups, respectively (p ≤ 0.01 for all comparisons vs. baseline).”

3. Table 2 is misleading and needs more context. Which hyperkalemia cohort (mild, moderate, severe) got corrected (K<5.5) at 2 hrs? I understand only 80% reached that point at 4 hrs.

Authors’ response: Thank you for your comment. The proportion of patients with serum K+ ≤5.5 or ≤5.0 mmol/L at 4, 24, and 48 hours is currently displayed in Fig. 2A and 2B, respectively. For consistency within the manuscript, the proportion of patients with serum K+ ≤5.5 or ≤5.0 mmol/L at 2 hours has been added to this figure, rather than adding it to Table 2. Additional text has also been added to the results section (page 8, paragraph 2) as follows:

“A serum K+ level of ≤5.5 mmol/L was achieved by 66% of patients within 2 hours of initial treatment with SZC 10 g, and nearly 80% and 98% of patients achieved this serum K+ level within 4 and 48 hours, respectively (Fig. 2A).”

4. Ln 233 "Patiromer has demonstrated efficacy for the treatment of serum K+ levels of 5.5-<6.5 mmol/L in randomized controlled trials; however, those effects were achieved at a dosing regimen beyond what is currently indicated in its label”. Please clarify. Does this mean that the FDA approved dose is not effective in treating hyperkalemia?

Authors’ response: Thank you for your comment. This statement has been deleted from the manuscript to avoid confusion.