Reviewer's report

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

Version: 1 Date: 29 Jul 2019

Reviewer: Giuseppe Regolisti

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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. 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.

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