PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of Safety, Effectiveness and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: A Real-World Study Protocol
AUTHORS	Shen, Nan; Meng, Qingyang; Zhang, Lihong; Zhu, Qiang; Shan, Chunyan; Cai, Xudong; Xie, Hua; Yang, Jing; Luo, Xun; Wang, Jianmin; Ye, Jianming; Wan, Xin; Tian, Shaojiang; Zuo, Li; Wu, Yifan; Lin, Yongqiang; Yu, Xiaoyong; Li, Qing; Liu, Xinyu; Shi, Zhenwei; Zhou, Jingwei; Long, Gang; Liu, Chunyan; Cao, Yanping; Zhao, Jiangrong; Wang, Nian-Song; Xing, Changying; Jiang, Xinxin; Wu, Henglan; Hu, Yao; Li, Lu; Wang, Zhaohua; He, Jingdong; Cao, Juan; Wu, Fenglei; Ma, Cong; Yin, Xun; Li, Zhongxin; Wang, Huimin; Lin, Hong-li

VERSION 1 – REVIEW

REVIEWER	Imamura, Teruhiko University of Toyama
REVIEW RETURNED	02-Dec-2022

GENERAL COMMENTS	The authors reported here a protocol of prospective single-arm study to observe the safety and efficacy of SZC in patients with hyperkalemia in the manuscript entitled “XXX”. The adverse events during SZC therapy and the efficacy of SZC to normalize hyperkalemia and maintain serum potassium levels have already been reported by phase II/III trials. Thus, the novelty of this study is unclear. Also, patients with a history of hyperkalemia within the past one year seem to be included, irrespective of the current existence of hyperkalemia. Some of them, particularly those with currently normal serum potassium levels, might not be appropriate candidates for SZC.

REVIEWER	Shrestha, Dhan Mangalbare Hospital, Department of Emergecny Medicine
REVIEW RETURNED	17-Dec-2022

GENERAL COMMENTS	Thank you for the opportunity to review this protocol. The authors planned this big real-world study in china to study the safety and effectiveness of SZC among the Chinese population for China's drug review and approval process. The protocol looks pretty much clear and reflects the idea/research question. When I reviewed the paper I noticed some minor typo-related issues (inconsistencies in placing references before/after the full stop), non-uniform references (eg. Reference 32), and similar minor write-up-related issues, which need proofread.

	Best wishes ahead for the study conduction and successful completion of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Comments to the authors.

1. The adverse events during SZC therapy and the efficacy of SZC to normalize hyperkalemia and maintain serum potassium levels have already been reported by phase II/III trials. Thus, the novelty of this study is unclear.

Response: Thank you for your comment. We agree that phase II/III clinical trials have been conducted to evaluate the effectiveness and safety profiles of SZC in HK patients globally. However, there are no previously reported II/III clinical studies which have reported safety and efficacy on SZC in Chinese population. In addition to this, conducting post-market real world studies can provide a better perspective regarding the product safety profile in a broader population and closer to the clinical practice. This is the first study to evaluate safety, effectiveness and treatment patterns of SZC in real-world settings in large population of HK patients in China and is expected to enhance and supplement currently available SZC safety and tolerability data from the already conducted pre-market phase II/III clinical studies. We have elaborated the same in the revised manuscript (Page 6 line 23 to Page 7 line 2; Page 11 line 16 to line 23).

2. Patients with a history of hyperkalemia within the past one year seem to be included, irrespective of the current existence of hyperkalemia. Some of them, particularly those with currently normal serum potassium levels, might not be appropriate candidates for SZC.
   Response: Thank you for your comment. However, eligible patients will be identified by physicians in each study site by assessing the patients or reviewing the medical record. As the present study requires that the enrolled patients are undergoing SZC treatment and there is a strict indication management system in China due to which SZC cannot be administered to non-hyperkalemia patients, this setting is more in line with the clinical practice of China's real-world studies. Also, patients with normal serum potassium levels will not be included in the study during enrolment. As already mentioned in the manuscript, all the eligible patients will be tested for safety outcomes, sK levels, SZC treatment (as applicable) and other related variables from enrolment (Day 1 to Month 6 if data available). In addition to this, monthly serum potassium tests will be regularly performed to intensify serum potassium monitoring according to clinical practice. We have described these details in the revised manuscript (Page 7 line 11 to line 14; Page 7 line 24).

Reviewer 2: Comments to the authors.

1. I noticed some minor typo-related issues (inconsistencies in placing references before/after the full stop), non-uniform references (eg. Reference 32), and similar minor write-up-related issues, which need proofreading.

Response: Thank you for your comment. We have checked the manuscript for typo-related and write-up-related issues and corrected them in the revised manuscript.

We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Thank you
Sincerely,
Nan Shen,
The first affiliated hospital of Dalian medical university

Email: 373929986@qq.com