PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patiromer utility as an adjunct treatment in patients needing urgent hyperkalaemia management (PLATINUM): design of a multicentre, randomised, double-blind, placebo-controlled, parallel group study
AUTHORS	Rafique, Zubaid; Farrell, Alex; Budden, Jeffrey; Quinn, Carol Moreno; Duanmu, Youyou; Safdar, Basmah; Bischof, Jason; Driver, Brian; Herzog, Charles; Weir, Matthew R.; Singer, Adam J.; Boone, Stephen; Soto, Karina; Peacock, Frank

VERSION 1 – REVIEW

REVIEWER	Sinagra, Gianfranco Azienda Sanitaria Universitaria Integrata di Trieste
REVIEW RETURNED	19-Mar-2023

GENERAL COMMENTS	The authors proposed here a trial design investigating the potential of Patiromer for treating hyperK in the ED. Despite the potential relevance of their study, since no well-powered investigations on this clinically frequent topic are actually lacking, the study design lacks of some important aspects: - In the study aim the authors report "additional medical interventions", whereas the primary study endpoint is a combination of them and K reduction. I would be more precise in the introduction, reporting for instance "a measure of net clinical benefit" or something indicating the double components of the endpoint - blinding process should be better specified in methods - expected dyalisis as exclusion criteria is potentially misleading since up to half of the patients can be on chronic dyalisis. Be more precise (for instance expected dyalisis within ... hours/emergent) - the primary endpoint has been previously validated as the authors correctly stated. However, it remains not properly intuitive for readers and I am not completely convinced that two co-primary endpoints (additional medical interventions and K changes) would have been more incisive. However, at least the authors should more deeply discuss why they opted for this definition in discussion - It is unclear whether the follow-up ends at discharge or at day 15. If the last is correct, how the authors planned to contact the patient if already discharged. Moreover, since the endpoints are assessed earlier, where is the need to keep the follow-up active so long? - I agree that strict re-assessment of patients in the ED is essential. However, I am afraid that defining multiple bi-hour assessment of K among the endpoints (4-6-8 hour) might be confusing for the readers. I would consider to be reduce the timepoints (eventually only one at hour 4 or 6 might be reasonable) and rather prefer other clinical measures of efficacy and safety

	- is the study investigator initiated or sponsored?

REVIEWER	Humphrey, Toby
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	Thank you for the opportunity to review this paper. I am happy for it to be accepted for publication. I could not see Figure 3 unfortunately (it just showed a black square) but hopefully this explained the primary endpoint or showed a worked example as this was the only part of the paper/protocol that I was not entirely clear on.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Gianfranco Sinagra, Azienda Sanitaria Universitaria Integrata di Trieste Comments to the Author:	**Author response**
The authors proposed here a trial design investigating the potential of Patiromer for treating hyperK in the ED. Despite the potential relevance of their study, since no well-powered investigations on this clinically frequent topic are actually lacking, the study design lacks of some important aspects: - In the study aim the authors report "additional medical interventions", whereas the primary study endpoint is a combination of them and K reduction. I would be more precise in the introduction, reporting for instance "a measure of net clinical benefit" or something indicating the double components of the endpoint	Thank you for this comment – we have added further details to the primary objective within the study aims section (page 6): "The primary objective is to determine if patiromer, as adjunct to intravenous (IV) insulin, glucose and inhaled beta-agonist therapy, lowers K^+ and reduces the need for additional medical interventions for the management of hyperkalaemia."
- Blinding process should be better specified in methods	Thank you for this comment – we have added further details on blinding and the circumstances under which unblinding is permissible (pages 11–12): "Participants, site personnel, clinical providers and the Sponsor will be blinded to the study drug. The clinical trial supply management team will provide blinded sachets of patiromer and placebo, and the site investigational pharmacists will maintain the blinding. In the case of a medical emergency, the Investigator may request that the blind be broken if it is considered important to the management of the medical emergency, or for study-specific suspected unexpected serious adverse reaction (SUSAR) and aggregate safety reporting to Health Authorities. In such cases, the Investigator will be unblinded via the IWRS."
- Expected dialysis as exclusion criteria is potentially misleading since up to half of the patients can be on chronic dialysis. Be more precise (for instance expected dialysis within ... hours/emergent)	Thank you for this comment – we currently state in the methods that the exclusion criteria include "expected dialysis during the first 6 hours of study treatment", however we have added clarification regarding patients undergoing chronic dialysis (page 10):

	"expected dialysis during the first 6 hours of study treatment"
- The primary endpoint has been previously validated as the authors correctly stated. However, it remains not properly intuitive for readers and I am not completely convinced that two co-primary endpoints (additional medical interventions and K changes) would have been more incisive. However, at least the authors should more deeply discuss why they opted for this definition in discussion	Thank you for this comment – we fully agree the use of net clinical benefit is an important aspect of the PLATINUM trial. We currently provide an explanation within the endpoints section of the methods describing the reasoning behind the use of net clinical benefit as an outcome "Assessment of the efficacy of K^+ binders in the ED can be confounded owing to repeat administrations of insulin and/or albuterol. Therefore, net clinical benefit is used to simultaneously assess both the number of additional potassium-lowering medications required and the change in serum K^+." Further explanation of the endpoint is also provided within the discussion "This novel method of assessing the effect of K^+ binders considers the overall benefit of both lowering serum K^+ and simultaneously reducing the number of interventions required. Hence, net clinical benefit combines two potential merits of a novel agent and will also be useful in future trials as a method to investigate the effect of K^+ binders to treat hyperkalaemia." As one of the aims of the study is to establish net clinical benefit as a new evaluation parameter for acute hyperkalaemia treatment investigations, the impact on the study results of utilizing net clinical benefit rather than two separate, co-primary endpoints as suggested, will be further explored within the primary results manuscript.
- It is unclear whether the follow-up ends at discharge or at day 15. If the last is correct, how the authors planned to contact the patient if already discharged. Moreover, since the endpoints are assessed earlier, where is the need to keep the follow-up active so long?	Thank you for this comment – we have added details into the methods describing how follow-up will be achieved. The 14-day follow-up is to enable full capture of any further K^+ lowering interventions or adverse events following discharge (page 10): "Participants who prematurely discontinue study drug will remain in the study to be monitored and assessed for safety and efficacy. The 14-day follow-up will be conducted via a phone call."
- I agree that strict re-assessment of patients in the ED is essential. However, I am afraid that defining multiple bi-hour assessment of K among the endpoints (4-6-8 hour) might be confusing for the readers. I would consider to be reduce the timepoints (eventually only one at hour 4 or 6 might be reasonable) and rather prefer other clinical measures of efficacy and safety	Thank you for this suggestion – we have chosen these timepoints based on the data from the pilot study (Rafique et al 2020), which demonstrated that patiromer significantly reduced serum potassium within 2 hours but did not show a difference at 6 hours. Therefore, we feel that inclusion of the 4-, 6-, and 8-hour timepoints is important in this much larger, more rigorous study in order to ensure, as far as

	possible, that we can fully answer the aims of the study. However, we have added further explanation to the study aims that the primary endpoint is net clinical benefit at the 6-hour timepoint. Further, as the trial has already begun recruitment and these timepoints are specified within the current version of the protocol, we are unable to change these at this point in the study. We have however noted your feedback regarding the potential for confusion and we will take this on board when publishing the primary results of the trial.
- Is the study investigator initiated or sponsored?	Thank you for this suggestion – this is an investigator-initiated and sponsored trial. This work was executed by Comprehensive Research Associates, LLC and was funded by Vifor Fresenius Medical Care Renal Pharma Ltd. (Page 20)
Reviewer 2: Toby Humphrey **Comments to the Author:**	**Author response**
Thank you for the opportunity to review this paper. I am happy for it to be accepted for publication. I could not see Figure 3 unfortunately (it just showed a black square [in the system-generated PDF]) but hopefully this explained the primary endpoint or showed a worked example as this was the only part of the paper/protocol that I was not entirely clear on.	Thank you for this comment and general approval of the manuscript – we can confirm the figure presents correctly in the version submitted, however we are happy to provide an alternative file type if required. The figure simply presents the equation for calculating net clinical benefit, as an alternative to the description provided within the manuscript text.

VERSION 2 – REVIEW

REVIEWER	Sinagra, Gianfranco Azienda Sanitaria Universitaria Integrata di Trieste
REVIEW RETURNED	11-May-2023

GENERAL COMMENTS	The authors fully addressed my previous comments. I have no additional concerns.

VERSION 2 – AUTHOR RESPONSE