Synoptic Clinical Study Report	
Drug Substance	Sodium zirconium cyclosilicate
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An Open-Label, Randomised, Controlled, Parallel-Design, Multicentre, Phase IV Study of Sodium Zirconium Cyclosilicate and Enhanced Nutrition Advice Compared to Standard of Care in Dialysis Patients with Hyperkalaemia (GRAZE)

Study Dates: First subject enrolled: 17 August 2021
Last subject last visit: 16 November 2021
The data presented in this report are based on a clinical data lock date of 18 February 2022.

Phase of Development: Therapeutic use (IV)

International Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

This study was performed in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Early termination of GRAZE Study

A decision was taken to terminate GRAZE Study on 19 January 2022 due to the disconnect between dietary guidelines to limit potassium intake in haemodialysis participants and clinical practice that has become increasingly clear. This recognition was the result of reviewing the responses to a survey completed by the GRAZE Investigators and discussions with various registered dietitians and non-GRAZE-associated nephrologists.

These concerns and possible steps were discussed with various advisory boards and it was even more clear that the number of unknowns and differences which exist in current clinical practice make the results unlikely to be translatable into clinical practice and, in the end, will not benefit participants.

Despite the outcomes, GRAZE was studying an important question for both participants and their physicians. Overall, 7 participants were screened, 1 of whom was randomised. As a result of the early termination of the GRAZE study and the low number of randomised participants, it was decided to issue a synoptic Clinical Study Report (CSR) instead of a full CSR.

Note: in this document, 'patient', 'participant', and 'subject' are used interchangeably.

Study centre

Initially, approximately 40 study centres were planned to enrol participants in PPD and PPD. A single participant was randomised into a study centre in PPD prior to the early study termination.

Publications

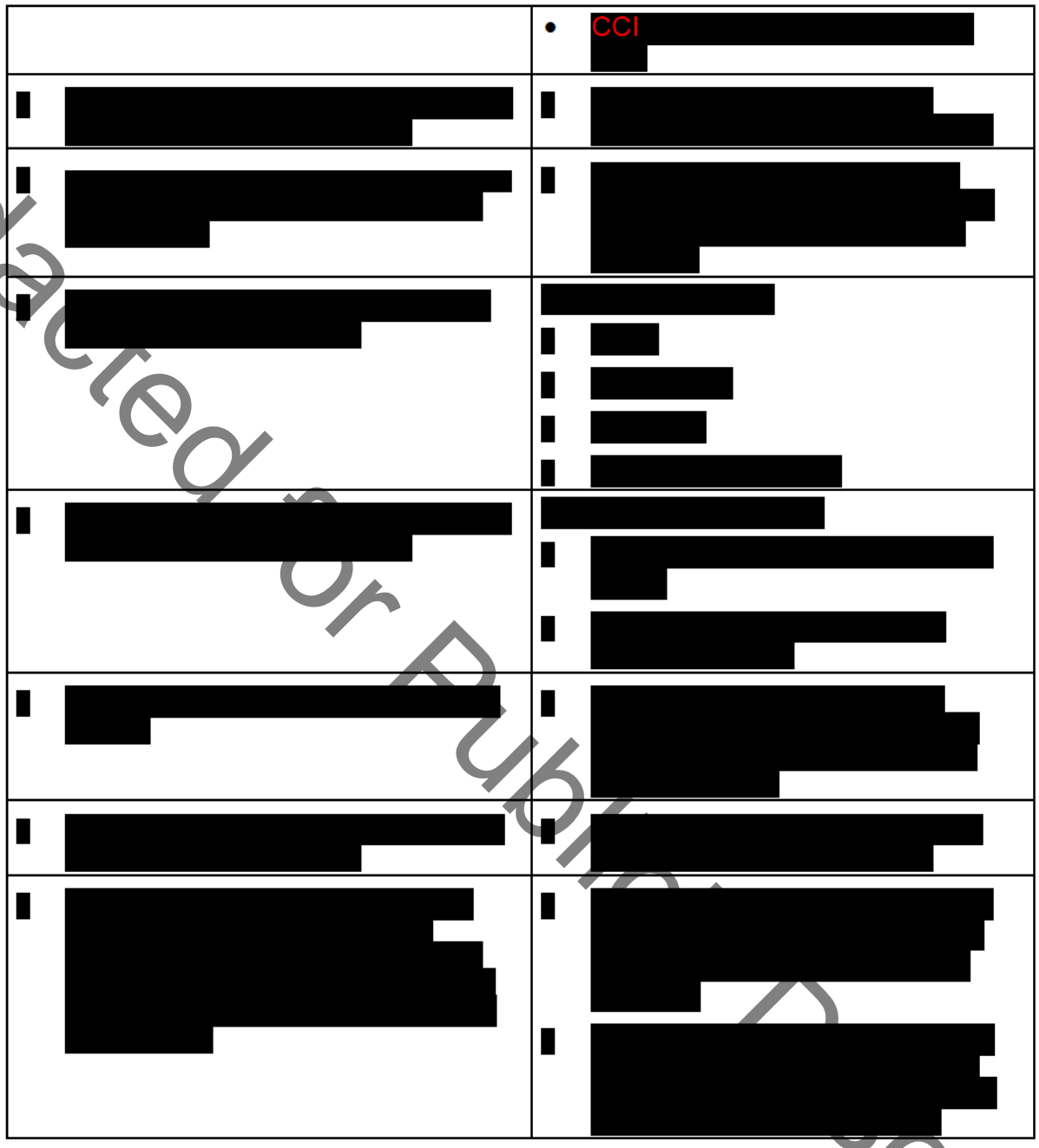
None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of the combination of sodium zirconium cyclosilicate (SZC) and enhanced nutritional advice to consume fruit and vegetables as compared to standard of care (SoC) in reducing serum potassium ($S\text{-}K^+$)	• Change in $S\text{-}K^+$ taken at long interdialytic-dialysis interval (LIDI) visits Month 3, Month 4, and Month 5 (M3, M4, and M5) compared to baseline
Secondary	

• To evaluate the effect of the combination of SZC and enhanced nutritional advice as compared to SoC on the consumption of fruit and vegetables	• Change from baseline in fruit and vegetable consumption determined by participant-reported intake using Noom app from M2 to M5
• To evaluate the effect of the combination of SZC and enhanced nutritional advice as compared to SoC on participant-reported chronic kidney disease (CKD) symptoms, physical and mental health, and satisfaction with treatment	Electronic versions of: • Kidney Disease and Quality of Life-36 item (KDQOL-36; symptoms/problems, Physical Component Summary and Mental Component Summary, Burden of Kidney Disease and Effects of Kidney Disease) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) • Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items) (TSQM-9) • Patients' Global Impression of Change (PGIC)
• To evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in maintaining S-K^+ levels within a range of 3.5 to 5.5 mmol/L, without requiring rescue therapy for hyperkalaemia (HK)	• Binary response (responder/non-responder) with criteria that at least 66% of S-K^+ values taken at LIDI visits in M3, M4, and M5 fall between 3.5 and 5.5 mmol/L • Receiving rescue therapy or a K^+ binder for HK during the final 3 months of the study was to result in a non-response
Safety	
• To assess the safety and tolerability of SZC and enhanced nutritional advice as compared to SoC	• Safety and tolerability were to be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory, interdialytic weight gain, and electrocardiogram • Assessments related to AEs cover: o Occurrence/frequency o Relationship to SZC as assessed by Investigator o Intensity o Seriousness o Death o AEs leading to discontinuation of SZC
Exploratory	
• CCI [redacted]	[redacted]



None of the efficacy objectives are reported in this synoptic CSR.

Study design

This was a Phase IV, randomised, controlled, open-label, parallel-group, multicentre, prospective study to evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in reducing S-K^+ levels in participants with HK on haemodialysis. Following the 7-day screening, all participants enrolled were to begin an up to 1-month HK Treatment Phase with SZC as per local label.

Randomisation was to occur at Visit 6. Only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC were to be randomised. Participants on 15 g SZC were to be considered as randomisation failures.

Participants were to receive dietary advice consistent with SoC at that site, including K^+ restriction. A 4-month Diet Comparison Phase was to begin next with the participants being randomised to either continue taking SZC, which could be titrated as needed to maintain target S-K^+ and were to receive enhanced nutritional advice to consume fruit and vegetables (SZC arm), or SZC was to be withdrawn and participants were to receive SoC, including dietary K^+ restriction (SoC arm).

Upon completion of the study, or early discontinuation, all participants who were to receive study drug, including those enrolled in the HK Treatment Phase but not randomised into the Diet Comparison Phase, were to proceed to the post-treatment follow-up visit after 14±3 days. After completing the study, or early discontinuation, participants were to receive SoC and standard diet advice as determined by their treating physician.

Target subject population and sample size

Participants had to be aged ≥18 years with prevalent HK (S-K^+ >5.5 mmol/L at the end of LIDI) not requiring acute treatment and receiving haemodialysis 3 times a week with stable vascular access for at least 3 months before the screening visit.

Participants were to be treated with SZC, sodium polystyrene sulfonate (sodium polystyrene sulfonate: Kayexalate™; Resonium™ A), calcium polystyrene sulfonate (Calcium Resonium™), or patiromer (Veltassa™)[1] within 4 weeks of screening.
It was planned to screen approximately 382 participants and 191 to be enrolled to achieve 162 randomised (81 per treatment arm) to study intervention.

Investigational product: dosage, mode of administration, and batch number

- **SZC:** 5 g once daily orally to establish normokalaemia (in the range commonly regarded as acceptable in these participants [3.5 to 5.5 mmol/L]); the dose would be titrated up or down weekly based on the pre-dialysis S-K^+ value after LIDI. The dose could be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days. Participants were also to receive enhanced nutritional advice to consume fruit and vegetables. The advice was to be provided by dietitians at study visits and by the Noom app between visits.

  - SZC batch numbers:
    - 5g Sachet, Labelled Kit, 6x, W0100026A
    - 5g Sachet, Labelled Kit, 10x, W0100026A.

[1] As approved and available locally

Standard of Care:

- SoC as per site practice including standard dietary advice including K^+ restriction (participants were to be encouraged to consume less than 50 mmol K^+ per day).
  This advice was to be provided by dietitians at study visits and using the Noom app.

Duration of treatment

The treatment was to have a duration of 5 months: up to 1-month HK Treatment Phase (all participants had to take SZC with standard dietary advice) in addition to 4-month Diet Comparison Phase (participants were randomised to SoC arm with standard dietary advice or to SZC arm with enhanced dietary advice).

Statistical methods

Sample size determination was based upon the primary objective of the primary estimand, i.e., *To evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in reducing S-K^+.*

With 80% power to reject the primary hypothesis, 81 randomised participants per treatment arm (162 in total) were required with a 1-sided alpha of 0.025, assuming a common standard deviation across treatment arms of 0.45 and a non-inferiority margin of 0.2. It was expected that 15% of participants who entered the HK Treatment Phase would not continue to the Diet Comparison Phase, and consequently, it was anticipated that approximately 191 participants would enter the HK Treatment Phase to achieve 162 randomised. Further, the screening failure rate was estimated to be 50%, meaning 382 participants would need to be enrolled. Participants were to be randomised into the 4-month Diet Comparison Phase until the required number of randomised participants was reached, at which point the recruitment was to stop.

Analysis populations were defined as follows: all-participants analysis set, HK treatment safety analysis set, full analysis set, and safety analysis set.

Inference concerning the primary analysis was to be performed at the 1-sided 2.5% significance level. All point estimates were to be presented together with confidence intervals of 2-sided 95% coverage, with guidance included in outputs where inference was to be based upon 1 tail of the interval.

Study population

Disposition: Overall 7 participants were screened, 1 of whom completed the HK Treatment Phase and was randomised to the SZC arm in a study centre in PPD . Of the 6 remaining participants, 4 were screen failures and 2 were enrolled in the HK Treatment Phase but did not continue due to early termination of the study by the Sponsor.

The randomised participant was a PPD who received the treatment with SZC 5 g once daily orally until the end of Month 2 in addition to enhanced nutritional advice to consume fruit and vegetables.

The participant had a medical history of PPD showed decreased S-K^+ levels: from 6.5 mmol/L on 24 August 2021 (after Visit 2) to 5.2 mmol/L on 05 October 2021 (Visit 9).

The participant completed Visit 9 but did not proceed to the other visits due to the study's early termination by the Sponsor.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

No AE, serious AE, deaths, or investigational product discontinuation occurred in this study.

Conclusion

The study early termination by the Sponsor did not allow to draw any conclusion from this study. No safety concern was reported for the single randomised and treated participant.