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Study Title: 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)

Protocol Reference Number: D9480C00014

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Clinical Study Protocol	
Study Intervention	Sodium zirconium cyclosilicate
Study Code	D9480C00014
Version	3.0
Date	12 Aug 2021

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)

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): US IND: 108951 / EudraCT: 2021-000457-81

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: 3.0

Study Intervention: Sodium zirconium cyclosilicate (SZC); brand name LOKELMA®

Study Phase: 4

Short Title: Sodium Zirconium Cyclosilicate and Enhanced Nutrition Study

Study physician and investigator names and contact Information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment, CSP Version 3.0	12-Aug-2021
Amendment, CSP Version 2.0	05-May-2021
CSP Version 1.0	16-Mar-2021

Amendment 2 12-August-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.1 Inclusion Criteria	Clarifications on the birth control methods allowed for female participants of childbearing potential enrolled in the United-Kingdom	Medicines and healthcare product Regulatory Agency request	Non-substantial
Section 9.3 Populations for Analyses and Appendix A 3	Clarification on screening phase definition	To allow for participants who are not consented on a LIDI day to still be eligible	Non-substantial
Section 1.3 Schedule of Activities and Appendix A 3	Further to the change in screening phase definition, the date of obtaining the ICF has been clarified	ICF can be obtained up to 7 days prior to study specific assessments	Non-substantial
Section 9.4.3.2 Secondary Endpoints	Minor editorial revisions on the statistical testing statement for the non-inferiority test	Typos, therefore have not been summarised	Non-substantial
Section 9.4.3.2 Secondary Endpoints	Update in the condition to reject the null hypothesis	The condition to reject the null hypothesis needs to match with the corrected statistical testing statement for the non-inferiority test	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Appendix C 3 Abbreviated Treatment Satisfaction Questionnaire for Medication TSQM-9	Deletion of side-effects in the instruction text	To clarify that participants are not requested to assess side-effects in this version of the TSQM	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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)

Short Title: Sodium Zirconium Cyclosilicate and Enhanced Nutrition Study

Rationale: Prescribing sodium zirconium cyclosilicate (SZC) with enhanced nutritional advice to participants with hyperkalaemia on haemodialysis will reduce serum potassium ($S\text{-}K^+$) and enable the consumption of more fruit and vegetables and result in a more satisfying diet. The study aims to show that participants using SZC achieve $S\text{-}K^+$ reduction as well as participants on standard of care (SoC) (other than potassium [K^+] binders), without the need for restricting K^+ in the diet.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in reducing $S\text{-}K^+$	• 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 [PCS] and Mental Component Summary [MCS], Burden of Kidney Disease and Effects of Kidney Disease) (Cohen et al. 2019) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) (Herdman et al. 2011) • Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items) (TSQM-9) (Atkinson et al. 2004) • 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 3.5–5.5 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 will 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 will be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory, interdialytic weight gain (IDWG), and electrocardiogram (ECG) • 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

For Exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is 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 hyperkalaemia on haemodialysis. Following 7-day screening, all participants who are enrolled will begin an up to 1-month HK Treatment Phase with SZC as per local label. Participants will receive dietary advice consistent with SoC at that site, including K^+ restriction. A 4-month Diet Comparison Phase will begin next with participants being randomised to either continue taking SZC, which can be titrated as needed to maintain target S-K^+, and receive enhanced nutritional advice to consume fruit and vegetables (SZC arm), or SZC will be withdrawn and participants will receive SoC, including dietary K^+ restriction (SoC arm).

- Approximate number of centres planned: 40
- Countries planned: US and UK

Disclosure Statement:

This is a parallel-group, non-indication-seeking intervention-model nutrition study with 2 arms that is open-label.

Number of Participants:

Approximately 382 participants will be screened and 191 enrolled to achieve 162 randomised (81 per treatment arm) to study intervention. Section 9.2, Sample Size Determination, explains how screening failures are defined.

Note: 'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

Intervention Groups and Duration:

The study has a duration of 5 months of participant participation and consists of up to 7-days screening, up to 1-month HK Treatment Phase (all participants take SZC with standard dietary advice), 4-month Diet Comparison Phase (participants are randomised to SoC arm with standard dietary advice or to SZC arm with enhanced dietary advice), and ends with a follow-up visit (2 weeks [14 ± 3 days] to match dialysis schedule).

Data Monitoring Committee: No

Statistical Methods

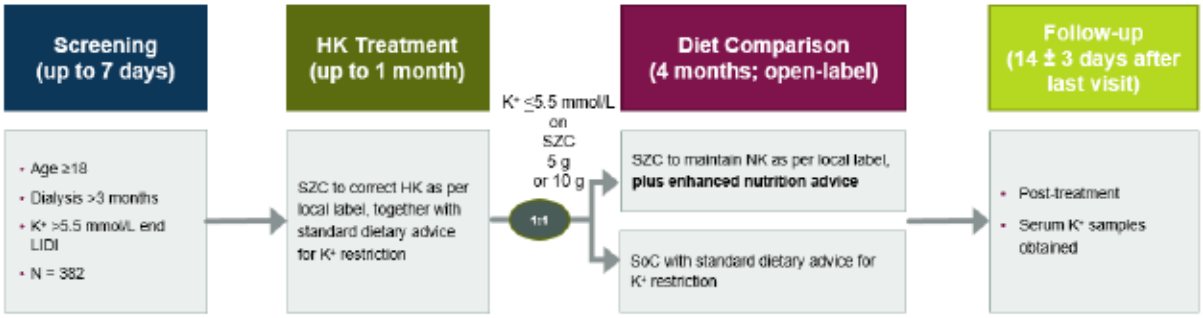
Sample size determination is based upon the primary objective of the primary estimand, ie, *To evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in reducing S-K^+*. With 80% power to reject the primary hypothesis, 81 randomised participants per treatment arm (162 in total) would be required with a 1-sided alpha of 0.025, assuming a common standard deviation across treatment groups of 0.45 and a non-inferiority margin of 0.2. It is expected that 15% of participants who enter the HK Treatment Phase will not continue to the Diet Comparison Phase, and consequently it is anticipated that approximately 191 participants will enter the HK Treatment Phase in order to achieve 162 randomised. Further, the screening failure rate is estimated to be 50%, meaning 382 participants will be enrolled. Participants will be randomised into the 4-month Diet Comparison Phase until the required number of randomised participants is reached, at which point the recruitment will stop.

Analysis populations are as follows: All-participants analysis set, HK treatment safety analysis set, full analysis set (FAS), and safety analysis set (SAS).

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

1.2 Schema

Figure 1 Study Design



Abbreviations: HK = hyperkalaemia; K^+ = potassium; LIDI = long interdialytic-dialysis interval; N = number of participants; NK = normokalaemia; SoC = standard of care; SZC = sodium zirconium cyclosilicate.

Note: Only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC at end of HK Treatment Phase will be randomised.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening/ Enrollment[a]	HK Treatment Phase[b]				Diet Comparison Phase							Follow-up[c]	ED[d]	Details in Clinical Study Protocol (CSP) Section or Appendix
		Month 1				Month 2				M3	M4	M5			
Visit[e]	1	2	3	4[f]	5[f]	6[g]	7	8	9	10	11	12	13		
Visit Window (Days)	-7 to -1	0	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3			
Electronic informed consent[h] (via e-device at site)	X														Section 5.1
Eligibility criteria	X														Sections 5.1 and 5.2
Demography	X														
Physical examination[i]		X				X						X		X	Section 8.2.1
Height		X													Section 8.2.1
Lean weight, triceps skin-fold thickness[i]		X				X						X		X	Section 8.2.1
Medical history[j]	X														
Serum pregnancy test (WOCBP only)	X														Section 8.3.7
Serum K^+ measurement[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Clinical safety laboratory assessments[i]	X					X						X		X	Section 8.2.4
ECG[i]	X	X				X						X	X	X	Section 8.2.3
Vital signs[d, i]		X				X						X	X	X	Section 8.2.2
IDWG[k]		X				X						X		X	Section 8.2.5.3
Drug dispensation/Drug accountability		X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[m]		X[m]	Sections 6.1 and 6.2
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Prior/Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5

Procedure	Screening/ Enrollment[a]	HK Treatment Phase[b]				Diet Comparison Phase							Follow-up[c]	ED[d]	Details in Clinical Study Protocol (CSP) Section or Appendix
		Month 1				Month 2				M3	M4	M5			
Visit[e]	1	2	3	4[f]	5[f]	6[g]	7	8	9	10	11	12	13		
Dialysate K^+ prescription	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5.2
Dialysis prescription[n]	X					X	X	X	X	X	X	X			Section 8.2.5.1
Dialysis adequacy[o]	X											X			Section 8.2.5.2
PROs (KDQOL-36, EQ-5D-5L, TSQM-9, PGIC) via e-device at site[p]		X				X						X		X	Section 8.1.2
Noom app[q]		X													Sections 6.1.2, 6.1.3 and 6.1.4
Standard diet advice		X	X	X	X									X[r]	Section 6.1.2
Standard diet advice (SoC arm in Diet Comparison Phase)						X	X	X	X	X	X	X			Section 6.1.2
Enhanced diet advice (SZC arm in Diet Comparison Phase)						X	X	X	X	X	X	X			Section 6.1.3

Abbreviations: AE = adverse event; ECG = electrocardiogram; ED = Early Discontinuation; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; HK = hyperkalaemia; IDWG = interdialytic weight gain; K^+ = potassium; KDQOL-36 = Kidney Disease and Quality of Life-36 item; M = month; PGIC = Patients' Global Impression of Change; PRO = patient-reported outcome; SAE = serious adverse event; SoC = standard of care; SZC = sodium zirconium cyclosilicate; TSQM-9 = Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items); WOCBP = woman of childbearing potential.

a Screening Phase duration: Up to 7 days before Day 0.
b HK Treatment Phase duration: Up to 1 month.
c Follow-up Phase duration: 14±3 days after previous visit. Includes participants who have been enrolled into the HK Treatment Phase but not been randomised into the Diet Comparison Phase.
d Applicable for ED prior to the end of study treatment.
e Visits 1 to 12 required to be performed at a long interdialytic-dialysis interval visit.
f Visits 4 and 5 if needed; participants with controlled S-K^+ levels can be randomised earlier.
g Randomisation occurs at Visit 6. Only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC will be randomised.
h ICF can be obtained up to 7 days prior to study specific assessments.

i Procedure to be performed before dialysis.
j COVID-19 vaccination before enrolment should be captured under "medical history" and under "prior medication".
k Current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the study visit) in Kg.
l Drug dispensation in SZC arm only.
m Only drug accountability at Visit 12 and at ED.
n Blood flow (Qb, mL/min), time on dialysis (minutes).
o spKt/V and/or urea reduction ratio; record the most recent value but this should be no older than 5 weeks.
p PROs are to be collected before treatment initiation on Visits 2 and 6. PGIC to be collected at Visit 6, 12, and ED visits only.
q Create the Noom account and train the participants on Noom application. Participants are expected to track their daily food intake via the Noom app until Visit 12.
r In case of early discontinuation, all participants will be provided with standard diet advice.

2 INTRODUCTION

Sodium zirconium cyclosilicate (SZC) is a novel non-absorbed zirconium silicate that preferentially captures potassium (K^+) in exchange for hydrogen and sodium that is being developed for the treatment of hyperkalaemia (HK) in adult patients. SZC (brand name LOKELMA®) is approved in the United States (US), European Union, Canada, Japan, China, and Brazil.

2.1 Study Rationale

Prescribing SZC with enhanced nutritional advice to participants with hyperkalaemia on haemodialysis will reduce serum K^+ ($S\text{-}K^+$) and enable the consumption of more fruit and vegetables and more satisfying diet. The study aims to show that participants using SZC achieve $S\text{-}K^+$ reduction as well as participants on SoC (other than K^+ binders), without the need for restricting K^+ in the diet.

2.2 Background

There is growing evidence supporting the positive effects of plant-based dietary patterns. Dietary advice that encourages increased fruit and vegetable intake could be an effective tool to reduce morbidity and mortality in people with kidney disease (Wai et al. 2017). This study aims to show that for haemodialysis patients with HK, treatment with SZC together with enhanced nutritional advice encouraging the consumption of fruit and vegetables is as effective as SoC, which includes dietary restriction of K^+-containing foods, in maintaining $S\text{-}K^+$ in the range 3.5–5.5 mmol/L.

Healthy diet patterns have been widely linked to better health and health outcomes.

Diets rich in vegetables and fruits, while low in fats, meats, and sweetened products, have been identified as healthy dietary patterns and have shown protective associations with morbidity and mortality. Such diets have been shown to lower blood pressure in prehypertensive and hypertensive adults, and have been associated with lower risks of cardiovascular and cerebrovascular disease in observational studies (Liu et al. 2017).

Among kidney outcomes examined, a healthier fruit and vegetable rich diet has been associated with slower estimated glomerular filtration rate decline (Kim et al. 2019) and with lower odds of incident chronic kidney disease (CKD). In addition, an interventional study found that a dietary pattern, rich in fruits and vegetables, attenuated markers of kidney injury among persons with macroalbuminuria (Goraya et al. 2019).

The main source of renal acid load comes from diet, and the main source of dietary balance is provided by K^+-containing amino acids principally found in fruits and vegetables

(Siener 2018). It has been shown that fruits and vegetables have a similar effect on metabolic acidosis as sodium bicarbonate tablets (Goraya et al. 2014).

One of the main ways of excreting K^+ once the kidney is impaired is by excretion in the stool. K^+ excretion in the stool is proportional to the amount of stool produced (Hayes et al. 1967), and dialysis patients with constipation have significantly higher S-K^+ than those without constipation (El-Sharkawy et al. 2009).

A detailed description of the chemistry, pharmacology, efficacy, and safety of SZC is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

The primary benefit for participants randomised to SZC treatment is expected to be the maintenance of normokalaemia during the long interdialytic-dialysis interval (LIDI), in line with what was observed in the DIALIZE study. Further, should the study hypothesis prove true, participants taking SZC will be able to consume a healthy diet including more fruit and vegetables. Such dietary changes are expected to have participant benefits including improved quality of life and satisfaction with treatment.

Participants treated with SoC may not obtain any benefit in terms of hyperkalaemia correction and maintenance but may benefit from a closer follow-up. Participants will receive alternative therapies whenever clinically indicated.

An established dose adjustment algorithm will be used during the study to titrate SZC doses to enable participants to achieve and maintain pre-dialysis normokalaemia after the LIDI. In accordance with the algorithm, the dose may be increased, reduced, or kept unchanged, depending on the current K^+ concentration, adapting the dosing regimen to each participant and preventing unnecessarily high exposure to the product.

The risks identified with SZC treatment include hypokalaemia and oedema-related events (includes fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, peripheral oedema, peripheral swelling). In this study, the risk for hypokalaemia is mitigated by periodic monitoring of S-K^+ and adjustment of the SZC dose as necessary. Oedema can be managed by conservative measures in line with standard clinical practice. No additional safety risks were identified in the DIALIZE study.

In conclusion, the favourable benefit-risk ratio that has been established for SZC in the clinical development program remains positive when SZC is used to treat hyperkalaemia in participants on chronic haemodialysis, as shown in the DIALIZE study.

More detailed information about the known and expected benefits and potential risks of SZC may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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^+	• Change in S-K^+ taken at 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 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 [PCS] and Mental Component Summary [MCS], Burden of Kidney Disease and Effects of Kidney Disease) (Cohen et al. 2019) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) (Herdman et al. 2011) • Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items) (TSQM-9) (Atkinson et al. 2004) • 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 3.5–5.5 mmol/L, without requiring rescue therapy for 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 will 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 will be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory, interdialytic weight gain (IDWG), and electrocardiogram (ECG) • Assessments related to AEs cover: o Occurrence/frequency

	○ Relationship to SZC as assessed by investigator ○ Intensity ○ Seriousness ○ Death ○ AEs leading to discontinuation of SZC
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.1 Estimands for Primary Objective

In line with the ICH E9 (R1) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population level summary) have been specified to translate the primary and secondary efficacy objectives into treatment effects that are to be estimated (estimands).

- The treatment condition of interest is:
  - SZC dosed as per local label to control HK and maintain normokalaemia in addition to SoC dietary advice for the up to 1-month HK Treatment Phase followed by the 4-month Diet Comparison Phase (SZC with enhanced nutrition advice versus SoC, including standard dietary advice) for the full 5-month treatment duration.
- The treatment effect is assessed by the primary efficacy endpoint of change from baseline in S-K^+ levels over the M3, M4, and M5 visits.
- The population of participants targeted is adults with HK as defined by the inclusion/exclusion criteria who are able to complete the HK Treatment Phase.
- Intercurrent events are handled through a combination of a treatment policy strategy and a composite strategy. Specifically, the following events which preclude the collection of data for the primary estimand as defined in Section 9.4.3.1 will be handled according to the table below:

Intercurrent event	Data collection and analysis
Premature treatment discontinuation due to lack of efficacy or physician's decision	Subjects will be followed and data collected will be analysed after the intercurrent event in line with a treatment policy strategy. In the case of missing data after treatment discontinuation, values will be imputed through a multiple imputation (MI) procedure.
Premature treatment discontinuation due to reasons other than lack of efficacy or physician's decision	Subjects will be followed and data collected after the intercurrent event in line with a treatment policy strategy. In the case of missing data after treatment discontinuation, values will be imputed through a MI procedure.
Introduction of rescue therapy of a K^+ binder for HK	Subjects will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for the primary analysis of the primary estimand. All values after introduction of rescue medication will be imputed using a composite policy through a MI procedure.

- The treatment effect will be quantified by via recombination of the least squares (LS) mean of the change from baseline in S-K^+ levels across the M3, M4, and M5 visits, obtained from a repeated measures analysis of covariance (ANCOVA) performed multiple times on MI data as outlined in Section 9.4.3.1.

Details regarding sensitivity estimands for the primary objective and estimands for the secondary objective will be included within the Statistical Analysis Plan (SAP).

4 STUDY DESIGN

4.1 Overall Design

This is 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 hyperkalaemia on haemodialysis.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this Clinical Study Protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with COVID-19 or similar pandemic infection) that would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider (HCP) guidelines (eg, hospital policies), or local government, these changes may include the following options:

- Obtaining consent for the mitigation procedures and documenting this in the source data
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix D.

4.1.2 Up to 1-month HK Treatment Phase (all participants)

Participants will follow labelled instructions for dosing dialysis participants, starting at 5 g on non-dialysis days. At weekly intervals participants can be titrated up or down in 5-g steps to a maximum of 15 g on non-dialysis days and a minimum of 5 g on non-dialysis days, to keep S-K^+ in the range of 3.5-5.5 mmol/L.

K^+ will be corrected with SZC as per local label. Participants will receive dietary advice consistent with SoC at that site, including K^+ restriction. Dietary advice will be given by dietitians at study visits.

4.1.3 4-month Diet Comparison Phase (2 arms)

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

SZC arm: Participants will continue taking SZC, which can be titrated up or down as described in Section 4.1.2 to maintain S-K^+ in the range 3.5-5.5 mmol/L; participants will also receive enhanced nutritional advice to consume fruit and vegetables. Advice will be provided by dietitians at study visits and by Noom app between visits.

SoC arm: SZC will be withdrawn and participants will receive SoC as per site practice, including dietary K^+ restriction. Dietary advice will be given by dietitians at study visits and by Noom app between study visits.

4.1.4 Follow-up Phase (all participants)

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

4.2 Scientific Rationale for Study Design

For the purposes of this study, the accepted range for normokalaemia of 3.5–5.5 mmol/L has been selected following advice from the steering committee to align with nephrologist perceptions of HK in dialysis patients and to closely reflect the range commonly regarded as acceptable in these patients.

4.3 Justification for Dose

For patients on dialysis, SZC should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily. To establish normokalaemia (in the range commonly regarded as acceptable in these patients [3.5-5.5 mmol/L]), the dose may be titrated up or down weekly based on the pre-dialysis S-K^+ value after the LIDI. The dose can be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days. It is recommended to monitor S-K^+ weekly while the dose is adjusted; once normokalaemia is established, S-K^+ should be monitored regularly (eg, monthly, or more frequently based on clinical judgement including changes in dietary K^+ or medication affecting S-K^+).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

End of treatment is defined as the date of the last visit in the Diet Comparison Phase (Visit 12).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with prevalent HK ($S\text{-}K^+$ >5.5 mmol/L at the end of LIDI) not requiring acute treatment.

3 Receiving haemodialysis 3 times a week with stable vascular access for at least 3 months before screening visit.

4 Participants who have and are able and willing to use smart phone (android or iOS) nutrition app.

Sex

5 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Female participants of childbearing potential must have a negative pregnancy test (see Section 8.3.7).
- Female participants must be 1 year post-menopausal, surgically sterile, or using 1 highly effective form of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and willing to remain on the birth control until 12 weeks after the last dose.

For women of childbearing potential (WOCBP; ie, those who are not chemically or surgically sterilised or who are not post-menopausal) included in United-Kingdom sites, highly effective forms of birth control are defined as follows:

a) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
b) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
c) Intrauterine device (IUD)
d) Intrauterine hormone-releasing system (IUS)
e) Bilateral tubal occlusion
f) Vasectomised partner (vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success
g) Sexual abstinence: it is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Informed Consent

6 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 As judged by the investigator or sponsor, any medical condition (including active, clinically significant infection) that may pose a safety risk to the participant in this study, may confound safety or efficacy assessments and jeopardise the quality of data, or may interfere with study participation.

2 Myocardial infarction, acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina), stroke, seizure, thrombotic/thromboembolic event (eg, deep vein thrombosis or pulmonary embolism, but excluding vascular access thrombosis), percutaneous transluminal coronary angioplasty, or coronary artery bypass graft within 12 weeks prior to screening visit.

3 Severe leucocytosis (>20 × 10^9/L) or thrombocytosis (≥450 × 10^9/L) during screening.

4 Polycythaemia (haemoglobin >14 g/dL) during screening.

5 Severe constipation, bowel obstruction, post-operative motility disorders.

6 Scheduled date for living donor kidney transplant.

7 Participants with a life expectancy of less than 6 months.

8 Females of childbearing potential, unless using contraception as detailed in the protocol or sexually abstinent.

9 Currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

10 Presence of cardiac arrhythmias or conduction defects that require immediate treatment at HCP discretion.

11 History of alcohol or drug abuse within 2 years prior to screening visit.

12 History of QT prolongation associated with other medications that required discontinuation of that medication.

13 Congenital long QT syndrome or QT interval corrected for heart rate (QTc) using Fridericia's method (QTcF) >550 ms.

14 Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.

15 If the participant has evidence of Coronavirus disease 2019 (COVID-19) within 2 weeks prior to screening (see Appendix D), the participant cannot be enrolled in the study.

Prior/Concomitant Therapy

16 Participants treated with SZC, sodium polystyrene sulfonate (SPS: Kayexalate™; Resonium™ A), calcium polystyrene sulfonate (CPS: Calcium Resonium™), or patiromer (Veltassa™)[1] within 4 weeks before screening.

17 Participants with a known hypersensitivity or previous anaphylaxis to SZC or any of the excipients of the product.

18 Participants unable to take oral SZC.

Prior/Concurrent Clinical Study Experience

19 Participation in another clinical study with an investigational product administered during the month before screening[2].

[1] As approved and available locally

[2] Participants vaccinated with COVID-19 vaccine whilst still under Emergency Use Utilisation will not be excluded from the study

20 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

22 Previous enrolment in the present study.

5.3 Lifestyle Considerations

There are no project-specific safety requirements or restrictions for SZC.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only 1 rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening.

At Visit 6, only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC will be randomised. Participants on 15 g SZC are randomisation failures.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study participant according to the CSP.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 3 Investigational Product

Intervention Name	SZC
Dose Formulation/Unit Dose Strength	White to grey crystalline powder for oral suspension in 5- and 10-g sachets
Dosage Level(s)	Participants in the active arm will receive SZC dosed as per the local label to control HK and maintain normokalaemia. Any decision to discontinue SZC will be up to the treating physician's judgement and as advised by the label. Per the label, SZC should only be dosed on non-dialysis days. The

	recommended starting dose is 5 g once daily. To establish normokalaemia (in the range commonly regarded as acceptable in these patients [3.5-5.5 mmol/L]), the dose may be titrated up or down weekly based on the pre-dialysis S-K^+ value after LIDI. The dose can be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days.
Route of Administration	Oral
Use	Investigational product
IMP and NIMP	Sodium zirconium cyclosilicate
Sourcing	Provided centrally by the sponsor
Packaging and Labelling	Study intervention will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.

Abbreviations: GMP = Good Manufacturing Practice; HK = hyperkalaemia; IMP = investigational medicinal product; LIDI = long interdialytic-dialysis interval; NIMP = non-IMP; SZC = sodium zirconium cyclosilicate.

6.1.2 SoC Dietary Advice

All participants during the HK Treatment Phase, and participants randomised to the SoC arm of the Diet Comparison Phase will receive standard dietary advice including K^+ restriction. This advice will be provided by dietitians at study visits and will be consistent with SoC at that site and will use a mobile app (Noom, described below) to track food intake only. Participants will be encouraged to consume less than 50 mmol K^+ per day.

6.1.3 Enhanced Dietary Advice

Upon randomisation to the SZC arm of the Diet Comparison Phase, participants will receive enhanced dietary advice in addition to taking SZC. This will include advice from dietitians at study visits to consume fruit and vegetables. Participants will receive dietary support from the Noom app between visits. Participants will be encouraged to consume up to 70 mmol K^+ per day.

6.1.4 Diet Mobile App (Noom)

In order to track dietary changes, participants in both arms will be supported by a mobile app (Noom) between study visits. Participants will be required to enter information daily on their food intake. This app will (a) track food intake, including K^+, fruit and vegetables, and fibre, (b) provide feedback regarding an estimate of daily K^+ consumption, and (c) provide live guidance on food consumption by human coaches.

Noom is a commercially available mobile app (android and iOS) that has been in use for over 7 years and currently has more than 50 million users worldwide. The app allows participants to enter and track their food intake and has a 3.7 million-item predictive food database backend, which includes food item K^+ content. There are 15 published studies (including

Nature and BMJ) describing use of the app, and Noom has received 4 National Institutes of Health (NIH) grants.

6.2 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorised staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study; however, the specific intervention to be taken by a participant will be randomly assigned using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log-in information and directions for the RTSM will be provided to each site. The site will contact the IRT/RTSM prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable electronic Case Report Form (eCRF), if required. Potential bias will be reduced by central randomisation.

6.4 Study Intervention Compliance

When participants are dosed at the site, which will occur on non-dialysis days and should be kept to a minimum, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned sachets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of SZC sachets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Concomitant Therapy

SZC can transiently increase gastric pH by absorbing hydrogen ions that can lead to changes in solubility and absorption kinetics for co-administrated drugs with pH-dependent bioavailability. Therefore, SZC should be administered at least 2 hours before or 2 hours after oral medications with gastric pH-dependent bioavailability.

Examples of drugs that should be taken 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are listed below:

Class of Drug	Drugs
Azole antifungals	Ketoconazole, itraconazole, posaconazole
Anti-HIV drugs	Atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine
Tyrosine kinase inhibitors	Erlotinib, dasatinib, nilotinib

SZC can be co-administered with oral medications that do not exhibit pH-dependent bioavailability without spacing of dosing times.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

However, if the participant received one (or more) COVID-19 vaccination(s) prior to enrolment then this needs to be recorded in the eCRF.

The investigator should be contacted if there are any questions regarding concomitant or prior therapy.

Table 4 Restricted Medications

Type of Medication/Treatment	Timeline/Instructions
K^+ binders including SPS, CPS, patiromer	Only permitted to be used as rescue therapy to treat severe HK (S-K^+ >6.0 mmol/L) after IMP has been discontinued
K^+ supplements or other drugs administered to raise S-K^+ (eg, potassium chloride)	Except if used to treat hypokalaemia (S-K^+ <3.5 mmol/L) according to medical judgement

Abbreviations: CPS = Good Manufacturing Practice; HK = hyperkalaemia; IMP = investigational medicinal product; S-K^+ = serum potassium; SPS = sodium polystyrene sulfonate.

6.5.1 Rescue Medicine

For both arms, rescue therapy is defined as any therapeutic intervention considered necessary in accordance with local practice patterns to reduce S-K^+ in the setting of severe HK as defined by physician and site.

Treatments considered rescue may include:

- Intravenous insulin/glucose or dextrose, beta adrenergic agonists, intravenous sodium bicarbonate, and any additional dialysis or other forms of renal-replacement treatments when used specifically for the treatment of severe HK as defined locally at site.
- In addition, reduction in the dialysate K^+ concentration that is prescribed for the treatment of severe HK during the study is also considered rescue therapy. Investigators may change dialysate bath as needed.
- Use of other K^+ binders including SPS, CPS, and patiromer.

Rescue therapy should be followed by the appropriate SZC dose adjustment if appropriate and proper documentation of the event. Use of rescue therapy will be treated statistically as described in the SAP.

See Statistical Considerations, Section 9, for implications of the use of rescue therapy and/or other K^+ binders to the analysis of endpoints.

6.5.2 Dialysate Potassium Concentration Prescription

The dialysate K^+ concentration prescription should be recorded at the times indicated in the Schedule of Activities (SoA; see Table 1).

For pre-dialysis S-K^+ concentrations <3.5 mmol/L, subsequent adjustments will be made in accordance to locally accepted clinical practice patterns and guided by the investigator's clinical judgment.

For centres that adopt the clinical practice of modifying the prescribed dialysate potassium

concentration when the pre-dialysis serum potassium concentration decreases, if pre-dialysis S-K^+ is below 3.5 mmol/L the dialysate K^+ concentration should be increased by 0.5 or 1 mmol/L according to SoC, eg, increase dialysate K^+ from $1K^+$ to 1.5 or $2K^+$, from $2K^+$ to 2.5 or $3K^+$, or from $3K^+$ to 3.5 or $4K^+$.

6.6 Dose Modification

The recommended starting dose is 5 g once daily on non-dialysis days. To establish normokalaemia (in the range commonly regarded as acceptable in these patients [3.5-5.5 mmol/L]), the dose may be titrated up or down weekly based on the pre-dialysis S-K^+ value after the 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.

6.7 Intervention After the End of the Study

No intervention will follow the end of the study. Decision to continue on SZC treatment or SoC will be at investigator's discretion.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study and complete all end-of-treatment procedures. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

To minimise risk for events related to prolongation of QTc, the following discontinuation criteria will be followed:

- If an absolute QTcF >550 ms or an increase in QTcF interval >60 ms from enrolment to more than 500 ms is reached, the subject should immediately receive appropriate medical intervention and be discontinued from the study drug treatment.
- All participants meeting the QTcF >500 ms criterion should immediately have K^+ assessed, if not already done within 1 hour of performing the ECG.

Other reasons for discontinuation of study intervention may include:

- Participant decision: The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Incorrectly randomised participant in whom the inclusion/exclusion criteria violation would put the participant at undue risk.
- Adverse event for which the investigator judges continued treatment may put the participant at undue risk.
- Severe noncompliance with the CSP.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

In haemodialysis patients, if S-K^+ is <3.0 mmol/L on any non-dialysis day or pre-dialysis, SZC administration should be withheld and hypokalaemia should be managed as per standard practice. The participant should be evaluated for any intercurrent illness or comorbidity that may increase the risk of hypokalaemia. SZC administration can be resumed if indicated but only after the intercurrent medical condition that precipitated the hypokalaemia has improved and S-K^+ has returned to the target range of normal levels (3.5–5.5 mmol/L).

If participant temporarily discontinue study intervention for reasons other than hypokalaemia, SZC administration can be resumed once participant condition is stabilised according to investigator judgement, and if the participant is willing to take treatment.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Discontinuation visit should be conducted, as shown in the SoA (Table 1) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or as per locally allowed regulations). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

8.1 Efficacy Assessments

8.1.1 Potassium

Potassium will be measured after LIDI and after vital signs, ECG, and physical examination. Serum samples will be analysed using local laboratory for the purposes of study inclusion and monitoring.

All serum samples should be examined and any overtly haemolysed samples must be redrawn.

See the laboratory manual for details on drawing, preparation, and analysis of blood samples.

8.1.2 Patient-Reported Outcomes (PROs)

PROs refer to all outcomes and symptoms that are directly reported by the participant. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating effectiveness of treatments in clinical trials.

The following PROs will be administered in the study: KDQOL-36, EQ-5D-5L, TSQM-9, and PGIC (refer to Appendix C). Participants will be asked to complete the questionnaires in an electronic device at site visits specified in the SoA (Table 1).

8.1.2.1 KDQOL™-36

The KDQOL-36 is a validated, self-reported questionnaire that combines generic and disease-specific components for assessing symptoms and health-related quality of life (HRQoL) of patients with CKD, see Appendix C 1 (Ricardo et al. 2013). The KDQOL-36 comprises a PCS (12 items), MCS (12 items), Symptoms/Problems (12 items), Burden of Kidney Disease (4 items), and Effects of Kidney Disease (8 items). Higher scores indicate better health/HRQol.

8.1.2.2 EQ-5D-5L

The EQ-5D-5L is a self-reported questionnaire that is used to derive a standardised measure of health status, also referred to as a utility score (refer to Appendix C 2 [Herdman et al. 2011]). EQ-5D-5L utility scores are widely accepted by reimbursement authorities and will be used to support health economic evaluations.

8.1.2.3 TSQM-9

The TSQM-9 is a patient-reported instrument to assess patients' satisfaction with medication, providing scores on 3 scales: effectiveness (3 items), convenience (3 items), and global

satisfaction (3 items) (see Appendix C 3). The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain. TSQM-9 is an abbreviated version derived from the TSQM version 1.4 and has shown good psychometric properties (Bharmal et al. 2009).

8.1.2.4 PGIC

The PGIC will be included to assess how a patient perceives his/her change in activity limitations, symptoms, emotions, and overall HRQoL since the start of study treatment (see Appendix C 4).

8.1.2.5 Administration of Electronic Patient-Reported Outcomes (ePROs)

The following best practice should be followed:

- All PRO questionnaires must be completed by participants at site using an electronic device; paper questionnaires are not allowed in this study.
- Each site must allocate the responsibility for the administration of the ePROs to a specific individual and, if possible, assign a backup person to cover if that individual is absent.
- A key aspect of study success is to have high PRO compliance. Therefore, it is essential that site personnel follow the SoA (Table 1) and ensure that the device is charged and set up properly before the first participant attends visit 1, in order to minimise missing data.
- It is recommended that the ePRO questionnaires are completed before any other study procedures are conducted, including being seen by the investigator.
- To avoid bias participants must not receive help from relatives, friends, or site staff to answer or to clarify the ePRO questionnaires and must be completed by the participant in private.
- The appointed site personnel should explain to participants the value and relevance of ePRO assessments and inform that these questions are being asked to find out, directly from participants, how he/she feels.
- The appointed site personnel must show participants how to use the ePRO device, in accordance with the instructions provided.
- If the participant is unable to read the questionnaire (eg, is blind or illiterate), the participant is exempted from completing the ePRO questionnaires but may still participate in the study. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in eCRF.
- If a participant uses visual aids (eg, spectacles or contact lenses) for reading and does not have them at hand, the participant will be exempted from completing the PROs questionnaires on that visit. Participants exempted in this regard should be flagged appropriately by site the staff in source documents and in the eCRF.

- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- Site staff must administer questionnaires available in the language that the participant speaks and understands. Questions should not be read in an available language and translated into another language for the participant.
- On completion of the questionnaires, the tablet should be handed back to the designated responsible person who should check that all questionnaires relevant for the specific visit were completed. If any PRO questionnaire was not completed, the site personnel must document the reason why a participant could not complete assessments in source documents and the REVPRDI module in the eCRF.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Height, lean weight, and triceps skin-fold thickness assessments will also be made at the times specified in the SoA (Table 1).

Physical examination will be performed at timepoints as specified in the SoA (Table 1).

8.2.2 Vital Signs

Vital signs (blood pressure, pulse rate, and oral temperature) will be performed at timepoints as specified in the SoA (Table 1), after 5 min of lying or sitting down without any distractions.

8.2.3 Electrocardiograms

An ECG will be performed at timepoints specified in the SoA (Table 1). QTc(F) should be recorded at each ECG measurement. ECG data and S-K^+ values should be collected and recorded in the eCRF in connection with reporting AEs of S-K^+ below 3.0 mmol/L.

Study subjects with pacemakers:

- All ECG variables, including QT/QTc(F), should be read manually and recorded in the eCRF.

- If not fulfilling the inclusion/exclusion criteria or fulfilling the discontinuation criteria, pacemaker participants should be managed as recommended by protocol (without exceptions).

8.2.4 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken before dialysis at the visits indicated in the SoA (Table 1).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured.

Table 5 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	Blood urea nitrogen (BUN)
B-Leukocyte differential count (absolute count)	S/P-Bilirubin, total
B-Platelet count	S/P-Alkaline phosphatase (ALP)
	S/P-Aspartate transaminase (AST)
	S/P Gamma-glutamyl transferase (GGT)
	S/P-Albumin
	S/P-Lactate dehydrogenase
	S-K^+
	S-calcium
	S-magnesium
	S-sodium
	S-phosphate
	S-bicarbonate
	S/P-Chloride
	S/P-Glucose
	S/P-Creatine kinase (CK)
	S/P-Total protein
	S-Pregnancy test (serum hCG)

Abbreviations: B = blood; hCG = human chorionic gonadotropin; P = plasma; S = serum.

8.2.5 Other Assessments

8.2.5.1 Dialysis Prescription

Dialysis prescription parameters including blood flow (Qb, mL/min) and time on dialysis (minutes) should be recorded at the times specified in Table 1.

8.2.5.2 Dialysis Adequacy

Dialysis adequacy indices including spKt/V and/or urea reduction ratio (URR) should be recorded at the times specified in Table 1. Investigators should record the most recent values but these should be no older than 5 weeks. If no values within 5 weeks are available, a new assessment of spKt/V and/or URR should be performed on the next weekly visit. Sites should consistently use either spKt/V or URR in determining dialysis adequacy. A combination of both is not acceptable.

8.2.5.3 Interdialytic Weight Gain (IDWG)

IDWG will be calculated as the difference between current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the visit) in kilograms. In order to obtain all required measurements of IDWG the investigators must make sure that a post-dialysis weight is available for the immediate dialysis session (as per usual schedule) prior to the visit.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the first dose of SZC, throughout the study, and during the follow-up period, described earlier.

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant

treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the follow-up visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum AE intensity (mild, moderate, severe)
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
    - Results in death
    - Is immediately life-threatening
    - Requires in-patient hospitalisation or prolongation of existing hospitalisation
    - Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
    - Is or results in a congenital anomaly or birth defect
    - Is an important medical event that may jeopardise the participant or may require medical intervention to prevent one of the outcomes listed above
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed

- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication.

8.3.3 Causality Collection

The investigator will assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report.

Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.7 Pregnancy

A serum pregnancy test in dialysis patients can result in false positive or indeterminate outcomes, likely due to clearance of the hormone human chorionic gonadotropin (hCG). In a

real pregnancy, hCG levels usual double every 2-3 days. A repeat hCG test will be required ±1-2 weeks after the 1st assessment to observe the trend. A false-positive 1st result will yield similar results in the 2nd test. In case of doubt an ultrasound should be considered to exclude any pregnancy, per the discretion of the investigator.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants.

If any pregnancy occurs in the course of the study (participant-reported), then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

8.3.7.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study unless using acceptable methods of contraception. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca within **1 day**, ie, immediately but **no later than 24 hour**s of when he or she becomes aware of it.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.6) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module is used to report the pregnancy and the PREGOUT module is used to report the outcome of the pregnancy.

8.3.7.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

8.3.8 Medication Error

For the purposes of reporting in AstraZeneca clinical studies, a medication error is an unintended deviation from the allowable schedule as per protocol in administering any study drug that either causes harm to the participant or has the potential to cause harm to the participant.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.6) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of SZC greater than 15 g per day on non-dialysis days will be considered an overdose. Treatment with SZC on dialysis days should be judged as a medication error and reported in the eCRF.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.6) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study, nor is immunogenicity.

8.6 Human Biological Sample Biomarkers

Samples for biomarker research are not required in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical hypothesis of the study is that prescribing SZC with enhanced nutritional advice to participants with hyperkalaemia on haemodialysis will show a non-inferior difference in the change from baseline in S-K^+ taken at LIDI visits M3, M4, and M5 when compared to participants on SoC (other than K^+ binders).

9.2 Sample Size Determination

Sample size determination is based upon the primary objective of the primary estimand, ie, *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) would be required using a 2-group t-test with equal n's with a 1-sided alpha of 0.025, assuming a common standard deviation across treatment groups of 0.45 and a non-inferiority margin of 0.2 (defined as clinically meaningful by scientific committee). It is expected that 15% of participants who enter the HK Treatment Phase will not continue to the Diet Comparison Phase, and consequently it is anticipated that approximately 191 participants will enter the HK Treatment Phase in order to achieve 162 randomised. Further, the screening failure rate is estimated to be 50%, meaning 382 participants will be enrolled.

Participants will be randomised into the 4-month Diet Comparison Phase until the required number of randomised participants is reached, at which point the recruitment will stop.

9.3 Populations for Analyses

The analysis of data will be based on different analysis sets according to the purpose of analysis, i.e. for efficacy and safety.

Table 6 Populations for Analysis

Population	Description
All-participants analysis set	The all-participants analysis set will consist of all participants who are screened for the study.

Population	Description
HK treatment safety analysis set (HKS)	The HKS will include all participants who receive at least 1 dose of SZC during the HK Treatment Phase.
Full analysis set (FAS)	The FAS, the primary efficacy analysis set, will include all randomised participants, with participants being analysed as randomised, rather than as treated.
Safety analysis set (SAS)	The SAS will include all randomised participants receiving at least 1 dose of study treatment during the Diet Comparison Phase, for the SZC arm, and all randomised participants completing visit 5 for the SoC arm.

Abbreviations: HK = hyperkalaemia; SoC = standard of care; SZC = sodium zirconium cyclosilicate.

The number of participants in each analysis set, and the number excluded and associated reasons will be summarised by treatment group and overall. In addition, the following periods will be defined for the purpose of reporting.

Table 7 Analysis Periods

Period	Description
Screening Phase	Screening refers to the period from the first study specific assessment to the first dose of SZC during the HK Treatment Phase or screen failure, whichever occurs first
HK Treatment Phase	The HK Treatment Phase (open-label period) refers to the period from the date of first dose of SZC during the HK Treatment Phase until the date of randomisation at the start of the Diet Comparison Phase
Diet Comparison Phase	The Diet Comparison Phase refers to the period from the date of randomisation until the earliest date of last assessment during the follow-up period, withdrawal of consent, last contact with the participant, or death

Abbreviations: HK = hyperkalaemia; SZC = sodium zirconium cyclosilicate.

9.4 Statistical Analyses

The SAP will be drafted and approved within 90 days of the date of the first participant enrolled, and any further changes during the course of the study will be finalised prior to Data Base Lock. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

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

Intercurrent events are handled as outlined within each section for the primary and secondary

endpoints below. For the primary endpoint, missing data will occur in the case where participants are lost to follow-up, provide insufficient evaluable data, withdraw consent, or die during the study. The proportion of participants missing data for the primary endpoint will be presented alongside the number of responses and non-responses.

Baseline is defined as the last available assessment prior to or on the date of the randomisation visit for all participants, unless otherwise specified.

In general terms, the full analysis set (FAS) will be used for the efficacy analyses, while the HK safety analysis set (HKS) and safety analysis set (SAS) will be used for the safety reporting.

In general, all baseline characteristics and efficacy and safety variables will be summarised using descriptive statistics as appropriate. Continuous variables will be summarised by descriptive statistics (including number of participants [n], mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarised using frequencies and percentages, where the denominator of calculation is the underlying analysis set population unless stated.

Descriptive statistics of quantitative efficacy and safety parameters by scheduled visits will be provided on observed cases (ie, including only participants who have non-missing assessments at a given visit).

9.4.2 COVID-19 Considerations

It is anticipated that additional sensitivity and supplementary analyses will be required to determine the impact of the COVID-19 pandemic on this trial and its endpoints. Planned sensitivity analyses will distinguish between pandemic and non-pandemic-related intercurrent events in terms of the approach taken for sensitivity analyses. Further details will be included within the SAP.

9.4.3 Efficacy

All efficacy endpoints will be analysed using the FAS.

9.4.3.1 Primary Endpoint

The primary endpoint will be defined as the change in the serum K^+ taken at LIDI visits M3, M4, and M5 compared to the serum K+ taken at baseline.

The primary objective will test the null hypothesis of [S-K^+ for SZC participants] – [S-K^+ for SoC participants] >= 0.2 mmol/L against the alternative hypothesis that [S-K^+ for SZC participants] – [S-K^+ for SoC participants] <0.2 mmol/L at the 1-sided 0.025 significance level.

The primary analysis will account for missing values and values recorded for participants after commencement of rescue therapy of a K^+ binder for hyperkalaemia through a MI method. Any assessments performed after the introduction of rescue therapy of a K^+ binder for HK will not be used as inputs for the MI procedure. Precise details of the MI process will be defined within the SAP.

All scheduled assessments during the Diet Comparison Phase will be used for imputation and analysis. Intermittent observed values will be used to generate a full set of imputed values up to and including M5.

A repeated-measures ANCOVA model will be used for each of the completed datasets, with fixed terms for the treatment groups for SZC and SoC, timepoint, baseline S-K^+ as a covariate, treatment by timepoint as an interaction. Additional model terms may be included, details of which will be described in the SAP. The results from each model will be recombined to provide the estimated change from baseline in S-K^+ for each treatment group over the period of M3 to M5, as well as the between group difference and the 95% confidence interval (CI) for the between group difference. The null hypothesis will be rejected if the upper bound of the CI is below 0.2.

9.4.3.2 Secondary Endpoints

A multiplicity correction procedure that covers the primary and the secondary endpoints will be applied, with the method being a fixed-sequence hierarchical testing procedure where the primary hypothesis is tested first. If the primary endpoint or any of the secondary endpoints listed in the order of importance are negative, then all endpoints beneath them in the hierarchy are then reduced to being exploratory endpoints. The order of importance for the secondary endpoints is as follows:

- Maintaining S-K^+ levels within a range of 3.5–5.5 mmol/L without requiring rescue therapy for HK
- Consumption of fruit and vegetables
- EQ-5D-5L score
- KDQOL-36 PCS
- KDQOL-36 MCS
- TSQM-9
- PGIC.

The secondary endpoint of maintaining S-K^+ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK will be assessed as a binary (responder/non-responder) variable, with participants being deemed responders if all of the following are true:

1. The participant provides 2 or more non-missing S-K^+ assessments during the period from M3 to M5, inclusive.

2. At least 66% of their non-missing S-K^+ assessments between the M3 and M5 visits, inclusive, show values within the normokalaemic range.

3. The participant does not receive rescue therapy or a K^+ binder for HK at any point between the M3 and M5 visits, inclusive.

Participants will be deemed non-responders if point 3 is not true, or if point 1 is true and point 2 is not true.

Participants will be excluded from the secondary analysis if point 1 is not true and point 3 is true.

This secondary objective will test the null hypothesis of [Proportion of SZC responders] – [Proportion of SoC responders] < -0.1 against the alternative hypothesis that [Proportion of SZC responders] – [Proportion of SoC responders] ≥ -0.1 at the 1-sided 0.025 significance level.

The proportions of responders and non-responders will be calculated for each treatment arm, and a difference in proportions (SZC - SoC) constructed. A 95% 2-sided CI for the difference will be created, and the null hypothesis will be rejected if the lower bound of the CI is greater or equal to - 0.1.

A sensitivity analyses will be performed where participants who discontinued study prior to providing a response for this secondary endpoint will be treated as non-responders. Details regarding sensitivity analyses will be included in the SAP.

Consumption of fruit and vegetables will be tracked within the Noom app. Details regarding the analysis and presentation of data from this source, including how missing/incomplete data is to be handled, will be described in the SAP.

The average daily fruit and vegetable consumption per 28 days will be analysed using a repeated-measures ANCOVA model with fixed terms for treatment, 28-day period, baseline average daily consumption, and treatment by 28-day period interaction. The comparison between treatment groups will be assessed based upon the p-value associated with the treatment by 28-day period interaction term at M5, which will be presented alongside the LS mean of the M5 treatment difference and its associated 95% CI. Further, descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided per each 28-day period.

The EQ-5D-5L questionnaire score change from study baseline at M2 and M5 will be analysed using a repeated-measures ANCOVA model with fixed terms for treatment, visit, baseline EQ-5D-5L, and treatment by visit interaction. The comparison between treatment groups will be assessed based upon the p-value associated with the treatment by visit

interaction term at the M5 visit, which will be presented alongside the LS mean of the overall treatment difference and its associated 95% CI. Further, descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided per visit.

The KDQOL-36 scores for symptoms, PCS, and MCS will be analysed and summarised using the same ANCOVA approach as for the EQ-5D-5L.

9.4.3.3 Exploratory Endpoints

CCI

9.4.4 Safety

Safety will be assessed in terms of AEs, SAEs, AEs leading to treatment discontinuation, clinical laboratory data, vital signs, and ECG. Appropriate summaries of these data will be presented by treatment group.

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). A treatment-emergent AE (TEAE) is defined as an AE with the start date on or after the first dose date and up to (and including) 14 days after the last dose date. Only TEAEs will be included in table summaries.

The number and percentage of participants experiencing AEs, SAEs, AEs that led to withdrawal, AEs that led to death, and the number of such events, will be summarised by SOC, PT, and treatment group. The number and percentage of participants experiencing AEs will further be summarised by intensity, and will be presented with the number of events at each level of intensity.

Additionally, for participants in the SZC treatment arm, the number and percentage of participants with AEs leading to discontinuation of SZC will be presented by SOC and PT, and the number and percentage of participants with any AE will be presented by SOC, PT, and relationship to SZC as assessed by the investigator. Each of these SZC summaries will additionally include the number of such events.

An overview of IDWG and instances of S-K^+ <3.5 will be presented.

All AE data will be listed for all participants. In addition, SAEs and AEs that led to withdrawal or death and treatment-related AEs will be listed.

Clinical safety laboratory assessments will be summarised and listed. Shift tables will be provided for select tests, where shift from screening baseline to the worst value within each part of the study and overall will be summarised. Laboratory data outside the reference ranges will be indicated in all listings.

All safety analyses will be performed on the Safety Set. In general, safety assessments will be reported descriptively by treatment group. Full details on safety analyses will be provided in the SAP.

9.5 Interim Analyses

Not applicable.

9.6 Data Monitoring Committee

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies, except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- The first study specific assessment has to be performed within 7 days after the ICF has been signed, allowing the screening phase to start at the first study specific assessment.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 7 days from the previous ICF signature date.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A Steering Committee consisting of members independent of AstraZeneca will be engaged during the development and conduct of this study to provide scientific advice on the study design and objectives.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the

summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment in the first site activated will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Results in congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events (AEs) for **malignant tumour**s reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if, following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or SoC medication in open-label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Electronic Patient-Reported Outcomes

C 1 KDQOL™-36

Your Health
– and –
Well-Being

Kidney Disease and Quality of Life (KDQOL™-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Thank you for completing these questions!

Study of Quality of Life For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

Page 1

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
4. Accomplished less than you would like	☐ 1	☐ 2
5. Were limited in the kind of work or other activities	☐ 1	☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
6. Accomplished less than you would like	☐ 1	☐ 2
7. Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 2

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 3

Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 4

During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
	▼	▼	▼	▼	▼
17. Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23. Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[a]. (Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[b]. (Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 5

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease bother you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
29. Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Page 6

C 2 EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

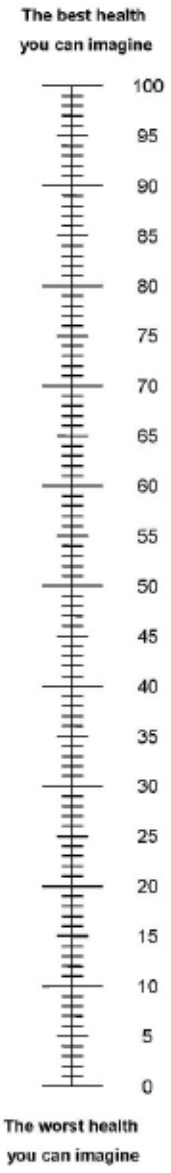
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

C 3 TSMQ-9

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial.

We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it.*

For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. **How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?**

   □1 Extremely Dissatisfied
   □2 Very Dissatisfied
   □3 Dissatisfied
   □4 Somewhat Satisfied
   □5 Satisfied
   □6 Very Satisfied
   □7 Extremely Satisfied

2. **How satisfied or dissatisfied are you with the way the medication relieves your symptoms?**

   □1 Extremely Dissatisfied
   □2 Very Dissatisfied
   □3 Dissatisfied
   □4 Somewhat Satisfied
   □5 Satisfied
   □6 Very Satisfied
   □7 Extremely Satisfied

3. **How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?**

   □1 Extremely Dissatisfied
   □2 Very Dissatisfied
   □3 Dissatisfied
   □4 Somewhat Satisfied
   □5 Satisfied
   □6 Very Satisfied
   □7 Extremely Satisfied

4. **How easy or difficult is it to use the medication in its current form?**

   □1 Extremely Difficult
   □2 Very Difficult
   □3 Difficult
   □4 Somewhat Easy
   □5 Easy
   □6 Very Easy
   □7 Extremely Easy

5. **How easy or difficult is it to plan when you will use the medication each time?**

   □1 Extremely Difficult
   □2 Very Difficult
   □3 Difficult
   □4 Somewhat Easy
   □5 Easy
   □6 Very Easy
   □7 Extremely Easy

6. **How convenient or inconvenient is it to take the medication as instructed?**

   □1 Extremely Inconvenient
   □2 Very Inconvenient
   □3 Inconvenient
   □4 Somewhat Convenient
   □5 Convenient
   □6 Very Convenient
   □7 Extremely Convenient

7. **Overall, how confident are you that taking this medication is a good thing for you?**

   □1 Not at All Confident
   □2 A Little Confident
   □3 Somewhat Confident
   □4 Very Confident
   □5 Extremely Confident

8. **How certain are you that the good things about your medication outweigh the bad things?**

   □1 Not at All Certain
   □2 A Little Certain
   □3 Somewhat Certain
   □4 Very Certain
   □5 Extremely Certain

9. **Taking all things into account, how satisfied or dissatisfied are you with this medication?**

   □1 Extremely Dissatisfied
   □2 Very Dissatisfied
   □3 Dissatisfied
   □4 Somewhat Satisfied
   □5 Satisfied
   □6 Very Satisfied
   □7 Extremely Satisfied

C 4 PATIENT GLOBAL IMPRESSION OF CHANGE - PGIC

Overall, how would you rate the change in your activity limitations (eg, cooking and eating, doing household chores or climbing stairs) since starting this study?

Please select one response only

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

Overall, how would you rate the change in your Kidney Disease symptoms (eg, lack of appetite or feeling tired) since starting this study?

Please select one response only

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

Overall, how would you rate the change in your emotions (eg, feeling overwhelmed or depressed) since starting this study?

Please select one response only

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

Overall, how would you rate the change in your overall quality of life (eg, satisfaction with life, or sense of wellbeing) since starting this study?

Please select one response only

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

Appendix D Management of Study Procedures During the COVID-19 Pandemic

D 1 Introduction

Safeguarding the health and wellbeing of our participants and ensuring the continued supply of our medicines to participants remains of paramount importance for AstraZeneca through the ongoing COVID-19 outbreak.

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

D 2 Risk Assessment for COVID-19 Pandemic

Sodium Zirconium Cyclosilicate (SZC) is a K^+ binder acting in the gastrointestinal tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC.

However, the risk of exposure to infected people cannot be completely excluded during study participation as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff).

D 2.1 Measures to Mitigate the Risks Associated with COVID-19

- This study will start or resume enrolment only when the sponsor and investigator deem it appropriate. In addition, the enrolment at a site level will only start or resume when local regulations and guidelines allow.
- National laws and local recommendations regarding the pandemic will be strictly adhered to.
- Site is encouraged to contact the participant within 1 day prior to a study visit to ask for signs and symptoms related to COVID-19.

D 3 COVID-19 Prior to Screening

It is important that participants with possible ongoing or not completely resolved COVID-19 infection are not to be enrolled in the study. If the participant has evidence of COVID-19 within 2 weeks prior to screening (eg, a positive COVID-19 test or a clinical risk that has not been satisfactorily excluded), the participant cannot be screened and will be treated according to SoC.

D 4 Suspected COVID-19 After Screening

D 4.1 Participant is Severely Ill or Hospitalised

If the participant becomes symptomatic after screening and has suspected COVID-19 (regardless of any SARS-CoV-2 test results that may be available), and is severely ill and/or hospitalised, the participant may temporarily or permanently discontinue study intervention at the discretion of the site investigator.

D 4.2 Participant is NOT Severely Ill or Hospitalised

If the participant becomes symptomatic after screening and has suspected COVID-19 (regardless of whether any SARS-CoV-2 test results are available or not), and is NOT severely ill and/or hospitalised, the investigator should determine if continuation of treatment with study intervention is in the best interest of the participant.

Regardless if study intervention is continued or not, the participant is encouraged to attend the study visits according to schedule.

D 5 COVID-19 During the Study

D 5.1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete on-site study visits and assessments and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the SoA (Section 1.3). Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed.

Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

D 5.2 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the study participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits that are scheduled to be on site may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medications to be reported and documented.

D 5.3 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified HCP from the study site.

Appendix E Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ANCOVA	analysis of covariance
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CPS	calcium polystyrene sulfonate
CSP	Clinical Study Protocol
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcomes
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
FAS	full analysis set
GCP	Good Clinical Practice
HCP	healthcare provider
HK	hyperkalaemia
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDWG	interdialytic weight gain
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
K^+	potassium
KDQOL-36	Kidney Disease and Quality of Life-36 item
LIDI	long interdialytic-dialysis interval
LS	least squares
M	Month
MCS	Mental Component Summary
MI	multiple imputation
PCS	Physical Component Summary
PGIC	Patients' Global Impression of Change

Abbreviation or special term	Explanation
PRO	patient-reported outcome
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
RAASi	renin-angiotensin-aldosterone system inhibitor
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
$S\text{-}K^+$	serum potassium
SoA	Schedule of Activities
SoC	standard of care
SOC	system organ class
SPS	sodium polystyrene sulfonate
SZC	sodium zirconium cyclosilicate
TEAE	treatment-emergent adverse event
TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items)
URR	urea reduction ratio
US	United States
VAS	visual analogue scale
WOCBP	Woman of childbearing potential

Appendix F Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 05-May-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 Schedule of Activities and Section 6.5 Concomitant Therapy	Collection of information on COVID-19 vaccination has been clarified	To specify that COVID-19 vaccination at any time prior to enrolment should be recorded in the eCRF	Non-Substantial
Appendix C 4 Patient Global Impression of Change - PGIC	Previous version of the questionnaire was replaced by a new one	PGIC questionnaire has been updated	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

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